Int. J. Pharm. Investigation, 2025; 15(2):313-324.
https://www.jpionline.org

Review Article

# A Comparative Review of 3D Printing Technologies and their Applications: A Systematic Review for Future of Medicine Fabrication

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## ABSTRACT

This review explores the role of additive manufacturing, particularly 3D printing, as an innovative approach in targeted drug delivery. It effectively addresses the limitations of traditional methods, such as high costs, complex geometrics and difficulties in individualized medications. The advent of 3D printing offers a modern solution, enabling the manufacturing of customized 3D objects from digital models. The approval of Spritam® (levetiracetam) by the FDA, the first additive manufacturing tablet, is a clear indication of the demand for 3D printing. This technique, which creates products layer-by-layer through a two-step process of data transfer and print head movement in all three dimensions, is gaining popularity. The review explores the diverse additive manufacturing methods applicable to drug delivery systems, including Fused Deposition Modeling (FDM), Stereo Lithography (SLA) and others. FDM, in particular, stands out for its creativity and cost-effectiveness. Beyond drug delivery, additive manufacturing has found applications in tissue engineering, manufacturing of complicated geometries, controlled-release systems and individualized medication for specific patient needs. The technology empowers the creation of intricate, customized structures loaded with drugs, demonstrating great potential for targeted therapies and personalized medicine.

**Keywords:** Modern Fabrication, Individualized Medicine, Dosage form printing, Nanotechnology, FDA Approved.

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**Received:** 24-07-2024;
**Revised:** 02-09-2024;
**Accepted:** 05-11-2024.

## INTRODUCTION

The pharmaceutical field is constantly exploring new approaches to drug delivery, with a particular focus on targeted delivery methods. Targeted delivery enhances patient safety and medication compliance. However, the conventional method is unable to fulfill individual patient needs due to their focus on mass production (Gaurkhede *et al*., 2021). Traditional methods, including encapsulation and compression, are expensive and struggle to produce highly complex medications. Additionally, they are ineffective in manufacturing personalized products (Tan *et al*., 2019). For this purpose, 3D printing, a rapidly expanding and revolutionary technology, can be employed to make additive items from electronic models (Glukhova *et al*., 2022). The 3D printing process involves two key steps: (1) transferring data from software to the 3D printer and (2) using the print head to repeatedly deposit material in layers, building the object one layer at a time (Ramya and Vanapalli, 2016). 3D printing technology gained significant attention in August 2015 when the FDA approved Spritam® (levetiracetam) as the first additive manufacturing tablet (Samiei, 2020). The pharmaceutical industry has recently shown a surge of interest in additive printing. This is due to 3D printing's unique capabilities, such as creating complex drug release patterns, intricate drug shapes and customized medications. Additionally, it enhances the effectiveness of drug loading into pharmaceutical products (Sen *et al*., 2020). 3D printing possesses several key features, including affordability, accessibility and the ability to produce objects in any conceivable shape. These potential positions 3D printing as a technology with significant probability for advancements in both the pharmaceutical and biomedical fields.[2] Three-dimensional printing is a rapid prototyping technique that creates products layer by layer. This enables the production of complex internal structures, such as hollow channels, internal walls and areas with varying materials and porosities. Besides, additive manufacturing allows the dispensation of multiple drugs within a single object, a capacity beyond the reach of traditional pharmaceutical manufacturing methods (Li *et al*., 2018). Contemporary advancements in 3D printing technology

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**DOI:** 10.5530/ijpi.20250024



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have extended implementation in oral drug administration. This is notable because successful drug delivery requires leveraging modern technologies like 3D printing and nanotechnology while ensuring safe medication delivery (Pandey *et al.*, 2020). In tissue engineering and drug delivery, additive printing enables the creation of intricate and personalized structures infused with medication, which is especially advantageous for pediatric and geriatric patients (Jamróz *et al.*, 2018). 3D printing encompasses various techniques, such as Stereolithography (SLA), Fused Deposition Modeling (FDM), Powder Bed Fusion, Binder Jetting and Material Jetting. FDM is particularly notable for its versatility and affordability, making it the most commonly utilized method.

Several techniques are employed in the creation of 3D-printed objects, including Fused Deposition Modeling (FDM) (Nober *et al.*, 2019), Binder jet 3D printers (Sen *et al.*, 2020) Stereolithography (SLA) (Wang *et al.*, 2016), Extrusion-based modelling (Gaurkhede *et al.*, 2021). This review article examines how 3D printing has transformed the development of various Drug Delivery Systems (DDS), such as tablets, capsules, gels, novel dosage forms and transdermal patches. Additionally, 3D printing provides a unique capability to tackle the challenge of creating complex multi-drug tablets, where each drug is released according to a customized release profile (Khaled *et al.*, 2015).

Current research aims to provide a comprehensive review of 3D printing technologies used in drug delivery systems. This review will cover various 3D printing methods, including Fused Deposition Modeling (FDM), Stereo Lithography (SLA) and Digital Light Processing (DLP), among others. It will delve into how these techniques are applied to develop a range of drug delivery systems, such as multi-layered tablets, hydrogels, nanoparticles, liposomes, niosomes and transdermal patches. Additionally, the review will discuss the specific functionalities and practical applications of each 3D printing method in this context.

## MATERIALS AND METHODS

The study took place over four months, from February 10, 2024, to June 10, 2024. Ethical approval was granted by the Research Ethics Committee at the University of Biological and Applied Sciences (UBAS) in Lahore, Pakistan, under reference number RMEC/AM/09791, ensuring adherence to ethical standards and guidelines. This review primarily utilized PubMed and Cochrane databases. The study protocols followed the PRISMA flow statement guidelines. Research studies were identified using keywords such as '3D Printing,' 'Future Fabrication,' 3D Printing Applications'' and '2010-2024'. Additionally, various electronic databases and manual searches on Google Scholar were conducted to collect relevant studies for this review. The inclusion criteria focused on studies conducted in English and studies on 3d printing, modern dosage form fabrication and its applications between 2010 and 2024 in different world regions. Only studies published in English were considered. The Prisma flow chart and appraisal tool for systematic review are given in Figure 1 and Table 1, respectively.

### Exclusion Criteria

The exclusion criteria included:

- Conventional dosage form design.
- Traditional methods of formulation development.
- Research articles written in languages other than English.
- Studies conducted before 2010.

### Data Extraction

The extracted data from the included studies comprised author details, the year of the study, the 3D printing device, its history, construction, fabrication procedure and application.

The PRISMA 2020 statement: an updated guideline for reporting systematic reviews.

For more information, visit:http://www.prisma-statement.org/

### 3D printing devices

#### *Fused Deposition Modeling (FDM)*

In 1988, Steven Scott Crump developed the Fused Deposition Modeling (FDM) method, later founding Stratasys and commercializing the process in the following year (Günaydın and Süleyman Türkmen, 2018). FDM has since become a widely used 3D printing technique for drug delivery systems (Goyanes *et al.*, 2015).

FDM facilitates the creation of hollow objects and dosage forms with varied drug release profiles, offering high-resolution and precise dosage control through computer settings (Goyanes *et al.*, 2015). The components of fused deposition modeling include a Filament roll from where the filament holds drug and polymer passes towards heated rollers. The heated material is released from the nozzle to a moveable base/platform, where 3D objects are prepared. The graphical representation of fused deposition modeling is shown in Figure 2.

Fused Deposition Modeling (FDM) operates by passing an extruded polymer filament through a heated coil, melting the polymer, which is then deposited onto a platform where it solidifies. By relying on these solidified layers, a 3D object is formed. FDM enables the creation of hollow objects and dosage forms with varying drug release profiles by adjusting the formulation's infill density or surface area-to-volume ratio. This technique, known as Hot-Melt Extrusion (HME), is commonly used in the pharmaceutical industry to integrate drugs within a carrier matrix at the molecular level, allowing for

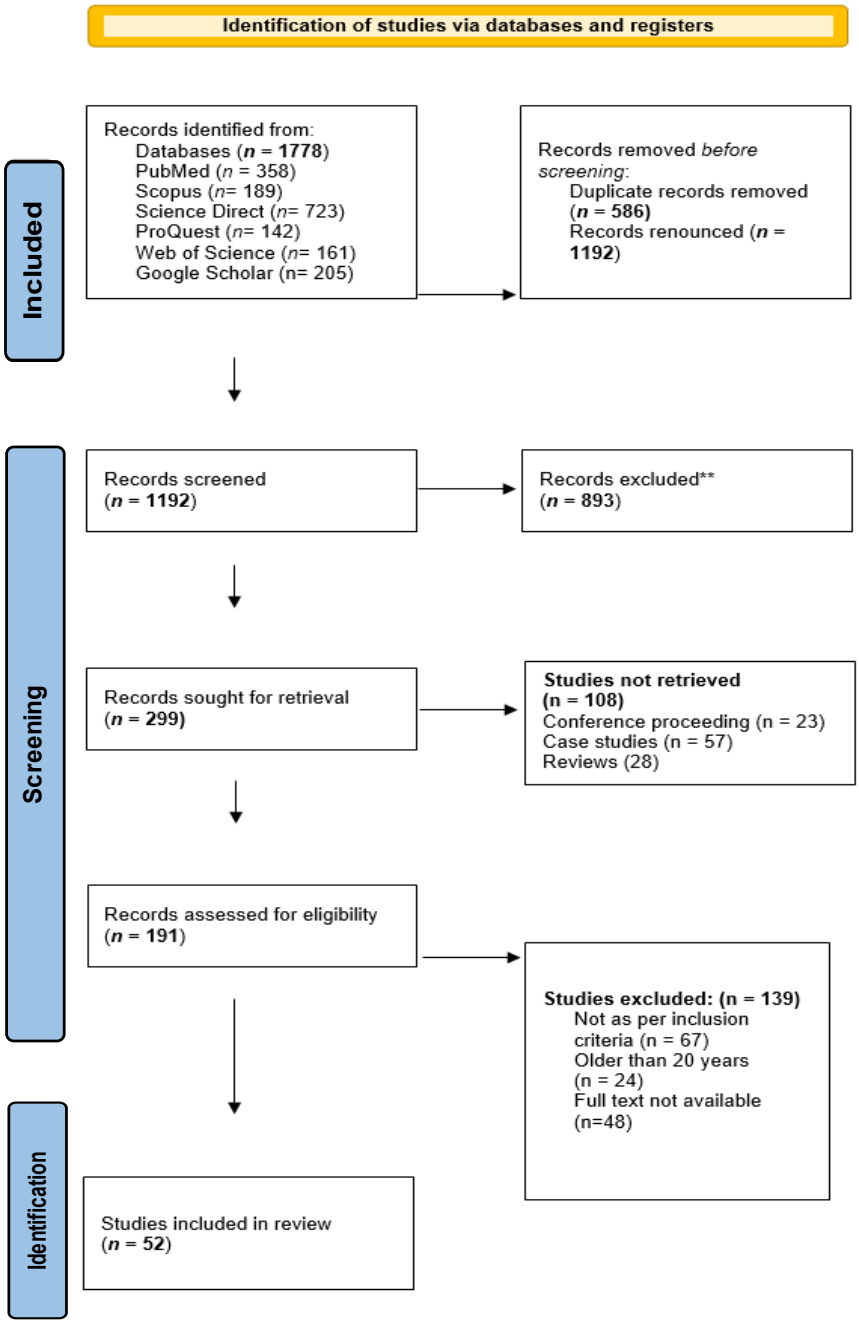


**Figure 1:** PRISMA flow diagram for systematic review.

the development of solid solutions for drug delivery systems with higher drug-loading capacity (Goyanes *et al.*, 2015).

Microfluidics is used for nanoparticles, with reactors essentially made from conventional materials. 3D printing is being used, with fused deposition modeling being a less expensive option (Bressan *et al.*, 2019). Fused deposition modeling, in which an extruded polymer crosses through a heating coil. The polymer softens by heat and then is placed onto a plate to solidify. Then, layers of hardened polymer are deposited and form a 3D object. This printing method can form hollow objects and dosage forms in different drug release profiles. The final step involves adjusting the surface area-to-volume ratio or infill density of the formulation. Compared to earlier printing methods, FDM 3D printing provides higher resolution and allows for improved dosage precision, which can be readily adjusted by modifying computer settings (Goyanes *et al.*, 2015).

## Selective Laser Sintering technique (SLS)

SLS, a 3D printing technique, is utilized for the development of innovative solid dosage forms (Fina *et al.*, 2018). At room temperature, this method is advantageous for producing objects with good resolution (Fina *et al.*, 2017).

The study's objective is to show that SLS is easy to use to form novel solid dosage forms with instant drug release qualities to

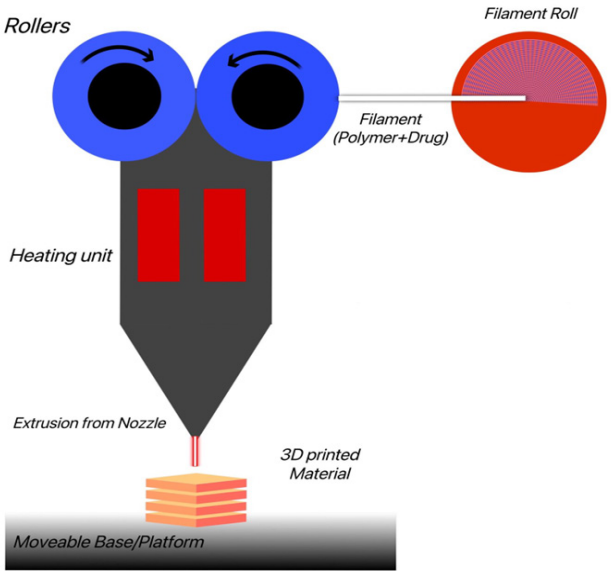


**Figure 2:** Fused Deposition Modelling.

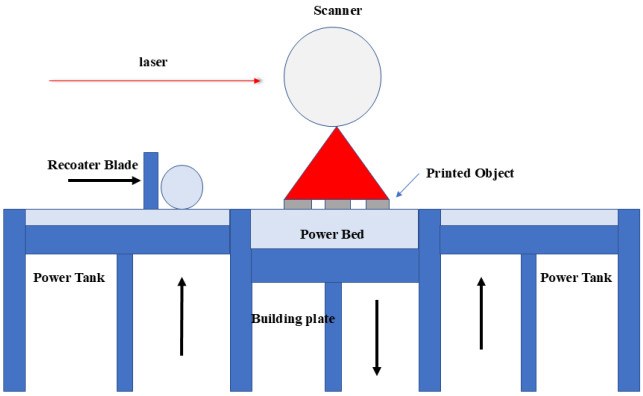


**Figure 3:** Selective Laser Sintering.

make the oral disintegrating formulations (Fina *et al.*, 2018). The components of SLS are a Laser, scanner, recoated blade, power bed, power tank and building plate as shown in Figure 3 (Fina *et al.*, 2017).

Copolymers and polymers were combined individually with colorant and 5% active ingredient. The powder mixtures were then printed using SLS technology to form printlet. Printlets hold active ingredients, which have recently been produced by using various 3-D printing processes called stereolithography. Drug-containing photopolymerizable polymer solution is solidified using a laser with SLA technology. At room temperature, this method has the advantage of forming objects with good resolution (Fina *et al.*, 2017).

## Stereolithography (SLA)

Stereolithography is a fast, economical, one-step method for producing multi-scale aspects and combining them with

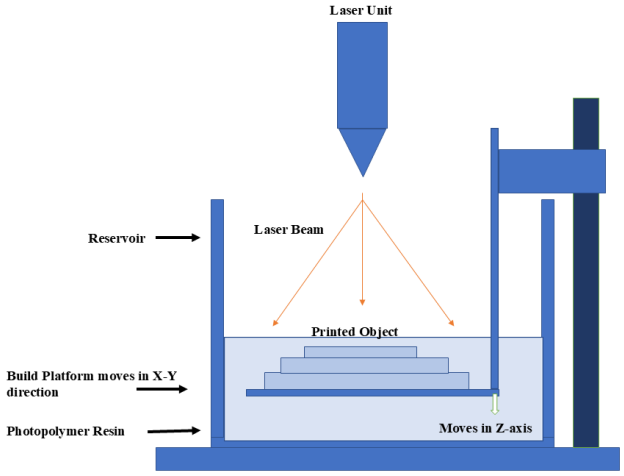


**Figure 4:** Stereo Lithography (SLA).

microfluidic-microneedle devices at the same time (Yeung *et al.*, 2019). Among the various forms of 3D printing, Stereo Lithography (SLA) stands out for its capability to create objects through the formation of interconnected polymer matrices via resin cross-linking (Cho *et al.*, 2018).

3D printing has emerged as a powerful technique for fabricating 3D nanogels. Nanogels are hydrogels formed by cross-linking nanoscopic micelles dispersed in a liquid medium. Most nanogels are produced by incorporating drug(s) or photo-initiator-loaded nanoparticles, liposomes, or nano-emulsions into hydrogels using 3D printing methods (Cho *et al.*, 2018). To enhance the capabilities of Stereo Lithography (SLA), components typically include a resin vat, UV chamber, biocompatible resins and composite materials, as illustrated in Figure 4 (Yeung *et al.*, 2019).

Stereolithography exhibits a vat polymerization process. In resin vat, the laser is directed to a certain depth, resulting in localized polymerization and consequent solidification. The intensity of the light source, scanning speed, exposure time, quantity of polymer and photo-initiator employed and various other factors collectively determine the energy imparted by the laser during SLA printing. Layer-by-layer solidification proceeds until a complete, three-dimensional object is produced (Wang *et al.*, 2016). A new composite substance with added metal is necessary to enhance the SLA application and mechanical properties. Ag nanoparticles are a promising class of nanofillers for obtaining composites with optical and electrical properties, hence expanding the range of applications for SLA into domains such as biomedical or electronic.

In the manufacturing of patches, the solidification of liquid resin to obtain the desired object in the SLA method relies on photopolymerization. Solidification is continued until solid; the 3D object is manufactured (Wang *et al.*, 2016). An SLA printer and Class IIa biocompatible resin were utilized to create a microfluidic-enabled microneedle device. The product

**Table 1: ZEE tool for studies assessment (Appraisal tool).**

| Parameters | Study 1 (Gaurkhede *et al.*, 2021) | Study 2 (Tan and Maniruzzaman, 2019) | Study 3 (Glukhova *et al.*, 2022) | Study 4 (Li *et al.*,2018) | Study 5 (Sen *et al.*, 2020) | Study 6 (Nober et l.,2019) | Study 7 (Wang *et al.*, 2016) | Study 8 (Khaled *et al.*, 2015) | Study 9 (Erkus *et al.*, 2023) | Study 10(Petrová *et al.*, 2024) | Study 11(Yeung *et al.*, 2019) | Study 12 (Chen *et al.*, 2022) | Study 13 (Bressan *et al.*, 2019) | Study 14(Valencia *et al.*, 2022) | Study 15 (Sharma *et al.*, 2022) | Study 16 (Goyanes *et al.*, 2015) | Study 17 (Pereira *et al.*, 2019) | Study 18 (Fina *et al.*, 2018) | Study 19 (Fina *et al.*, 2017) | Study 20 (Cho and Jammalamadaka, 2018) | Study21 (Chan *et al.*, 2024) | Study 22 (He *et al.*, 2023) | Study 23 (Ballacchino *et al.*, 2021) | Study 24 (Wang *et al.*, 2016) | Study 25 (Arcaute and Mann, 2010) | Study 26 (Curti and Kirby, 2024) | Study 27 (Xu *et al.*, 2020) | Study 28 (Linares *et al.*, 2023) | Study 29 (Eosoly *et al.*, 2010) | Study 30 (Pandav and Karanwad, 2024) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Are study objectives specific? | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Is the study design suitable for aims? | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Was the basic data adequately described? | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Were results internally consistent? | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Were the results presented for all the analyses described in the methods? | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Are discussion and conclusions justified by results? | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Were the limitations of the study discussed? | × | ✓ | ✓ | ✓ | ✓ | × | × | × | × | × | × | × | × | × | ✓ | × | × | × | × | × | × | × | × | × | ✓ | × | × | × | × | × |
| Is there any conflict of interest that might affect study findings? | × | × | × | × | × | × | × | × | × | × | × | × | × | × | × | × | × | × | × | × | × | × | × | × | × | × | × | × | × | × |

| Parameters | Study 31 (Fina *et al.*, 2017) (Fina *et al.*, 2017) | Study 32 (Lekurwale and Karanwad, 2022) | Study 33 (Fina *et al.*, 2018) | Study 34 (Adamov *et al.*, 2022) | Study 35(Kadry *et al.*, 2019) | Study36 (Xu *et al.*, 2021) | Study 37 (Wu *et al.*, 2019) | Study 38 (Yang *et al.*,2020) | Study 39 (Madžarević, 2021) | Study 40 (Xu *et al.*, 2021) | Study 41 (Li *et al.*, 2022) | Study 42 (Papadimitriou *et al.*, 2022) | Study 43 (Xenikakis and Tsongas, 2021) | Study 44 (Cristaldi *et al.*, 2021) | Study 45 (Cristaldi, 2020) | Study 46 (De Grandi *et al.*, 2022) | Study 47 (He *et al.*, 2023) | Study 48 (Tan and Maniruzzaman, 2018) | Study 49 (Cailleaux and Sanchez-Ballester, 2021) | Study 50 (Mathew *et al.*, 2020) | Study51 (Pires *et al.*, 2020) | Study 52(Khalid, 2022) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Are study objectives specific? | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ |
| Is the study design suitable for aims? | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ |
| Was the basic data adequately described? | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ |
| Were results internally consistent? | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ |
| Were the results presented for all the analyses described in the methods? | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ |
| Are discussion and conclusions justified by results? | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ |
| Were the limitations of the study discussed? | × | × | × | × | × | × | × | × | × | × | × | × | × | × | × | × | × | × | × | × | × | × |
| Is there any conflict of interest that might affect study findings? | × | × | × | × | × | × | × | × | × | × | × | × | × | × | × | × | × | × | × | × | × | × |

underwent preprocessing using 3D printer preparation software and was designed using Computer-Aided Design (CAD) software. To enhance productivity and quality, the object was positioned at a 45º angle. To optimize the stiffness and strength of the microneedle patch, SLA-printed components were cleaned in isopropyl alcohol for 5 min and then cured in a UV chamber with a 405nm wavelength at 80ºC for 20 min. A single-piece, three-dimensional microfluidic device with a multi-inlet and integrated hollow microneedle array was produced using SLA 3D printing. Underneath the construction platform is an optical window through which the printer in use applies UV light, enabling additive manufacturing of the intended model through the layer-after-layer curing of photopolymer resin inside the resin tank (Yeung *et al.*, 2019).

## Digital Light Processing (DLP)

It is a 3D printing technique based on photopolymerization. By this technique, irradiation photopolymer hardens layer by layer as the sections of the model are stick out onto the liquid photopolymer's surface by the digital micromirror element (Erkus *et al.*, 2023).

Digital light processing is a helpful technique for producing a digital workflow for personalized medicine. There is evidence of its effectiveness in applications in biomedical areas such as dental prostheses and tissue engineering (Yang *et al.*, 2020). The initial functional component is a digital micromirror device made of several adjustable mirror sizes of microns, as shown in Figure 5.

This method employs light sources that direct light onto photosensitive material using an array of chipsets based on optical microelectromechanical technology. A rotating mirror controls the path of light, projecting it onto photosensitive resins. The resolution of digital light processing-based 3D printing is determined by the projection plane, which is modified by the DMD (Digital Micromirror Device) and lens. Ultimately, digital

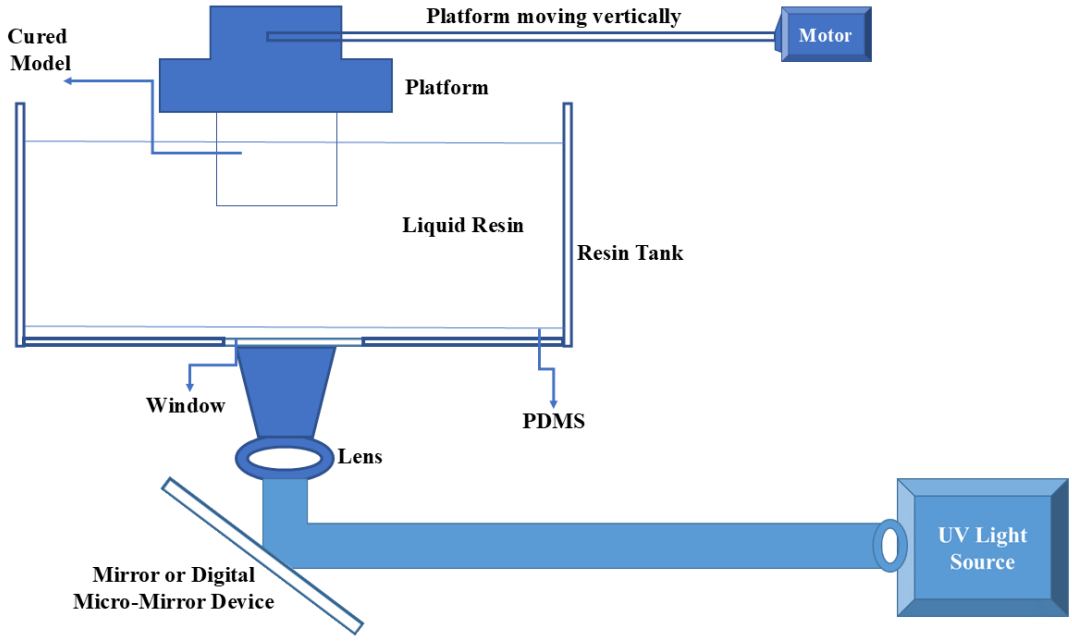


**Figure 5:** Digital Light Processing.

light processing achieves high-resolution (Zhang *et al.*, 2020). Microneedles were prepared with the help of a computer-aided program named Tinker CAD. After printing, every patch consisted of 36 conical microneedles measuring 1mm in diameter and 1.5 mm in height. After being changed to STL format, the design was connected to the Lumen X 3D printer. In the printing process, a solvent and resin are utilized. Following printing, the patch was gently removed, rinsed in 70% ethanol and then exposed to a UV chamber for 1 min (Petrová *et al.*, 2024). In contrast to other techniques, DLP is less susceptible to oxygen inhibition. As compared to the rest of the 3D printing techniques, DLP provides higher resolution and faster printing (Erkus *et al.*, 2023). Rapid modifications to the final patch's size and shape are another merit of employing DLP printing, contrary to the conventional method (Petrová *et al.*, 2024).

## LCD-printed microfluidic devices

LCD 3D printing, combined with specially formulated ink, paves the way for anyone, anywhere, to access high-resolution formulating of ready-to-use microfluidic and organ-on-a-chip devices. This technology even holds promise for the preparation of liposomes (He *et al.*, 2023).

The liposomes made with microfluidics have better encapsulation efficiency than other techniques (Ballacchino *et al.*, 2021). Printer platform, printed object, resin vat, power switch, USB port, LED source, touch screen and platform securing knob as shown in Figure 6 (Ballacchino *et al.*, 2021).

The designed microfluidic devices were used in this work to manufacture liposomes. It entails the fabrication of various microfluidic structures, particularly Y-shaped mixers, featuring different configurations with two inlets and one outlet. A continuous flow of lipids in an alcohol solution and another in a wet solution pass through separate channels. Liposome production is achieved by merging these two channels where the streams converge. Therefore, the mixing is determined by the diffusion process occurring at the boundary between liquids, resulting in the formation of micelles as the lipids precipitate in the wet solutions, followed by the formation of liposomes (Ballacchino *et al.*, 2021).

## 3D-printed Reactor-in-a-Centrifuge (RIAC) device

RIAC is a simple, pump-free technique that requires a 3D-printed flow-through reactor and is powered by a standard centrifuge (Andrea *et al.*, 2021).

The RIAC device is used to formulate liposomes and silver nanospheres, which are used in the production of nanoparticles (Andrea *et al.*, 2021). The components used in the formulation of liposomes are the reservoir, centrifuge tube, polymer stabilizer and test tube, as shown in Figure 7 (He *et al.*, 2023).

Another device is a 3D-printed RIAC device in which a single reservoir was pipetted with a lipid solution of 2 mL, which contained different molar ratios of stabilizer, solubilizer, surfactant, polymer stabilizer and membrane stabilizer to produce liposomes and optimize the formulation parameters. After being preheated to the appropriate temperature, Deionized water was transferred into the second reservoir. Additionally, 6 mL of water was added to the bottom of a 50 mL centrifuge tube containing the RIAC. This water addition was aimed at reducing

the tendency of liposomes to aggregate. Increasing this volume beyond 6 mL would not significantly alter the properties of the liposomes. However, modifying production parameters such as time (between 1000 and 2000 cf) and centrifugal force would further decrease the concentration of liposomes in the final product (He *et al.*, 2023).

## Applications of 3d Printed Devices

### *Fused Deposition Modelling (FDM)*

FDM provides cost-effectiveness, design flexibility and exceptional reproducibility in pharmaceutical production procedures (Tan *et al.*, 2018). This technology aids the production of complicated geometries swiftly from digital design without any necessity of moulds or other traditional industrial procedures (Cailleaux *et al.*, 2021). FDM printing technology can be utilized in the development of Controlled-release and floating gastroretentive tablets. Due to its accuracy, versatility and ease of use in producing various dosage forms, including implants, capsules, films and adhesives, 3D printing by fused deposition modeling contains great potential for therapeutic customization (Pires *et al.*, 2020). Solid dispersions can enhance the solubility of APIs by utilizing suitable polymers. Combining solid dispersions with FDM offers new technological possibilities that address the challenge of low API solubility (Khalid and Billa, 2022).

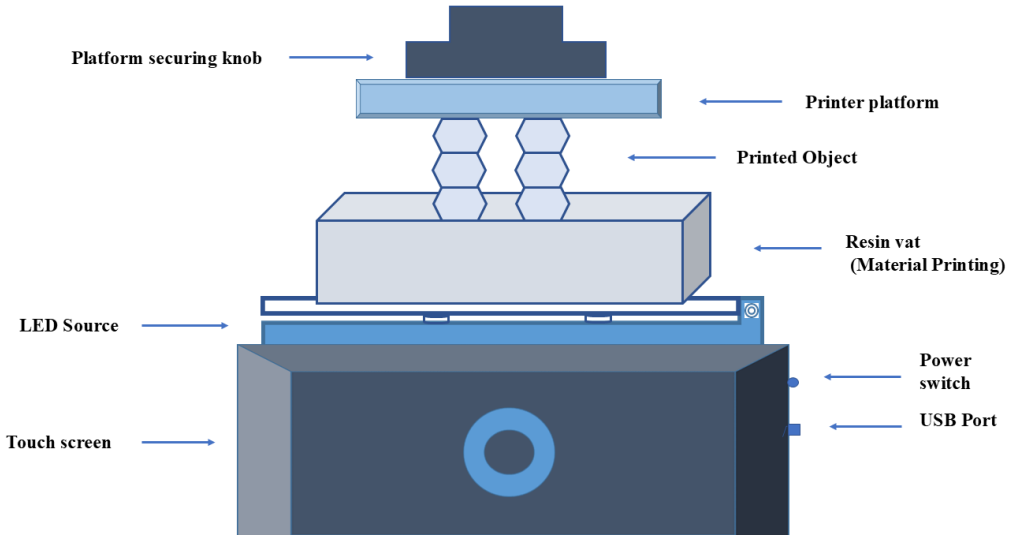


**Figure 6:** LCD Printed Microfluidic Device.

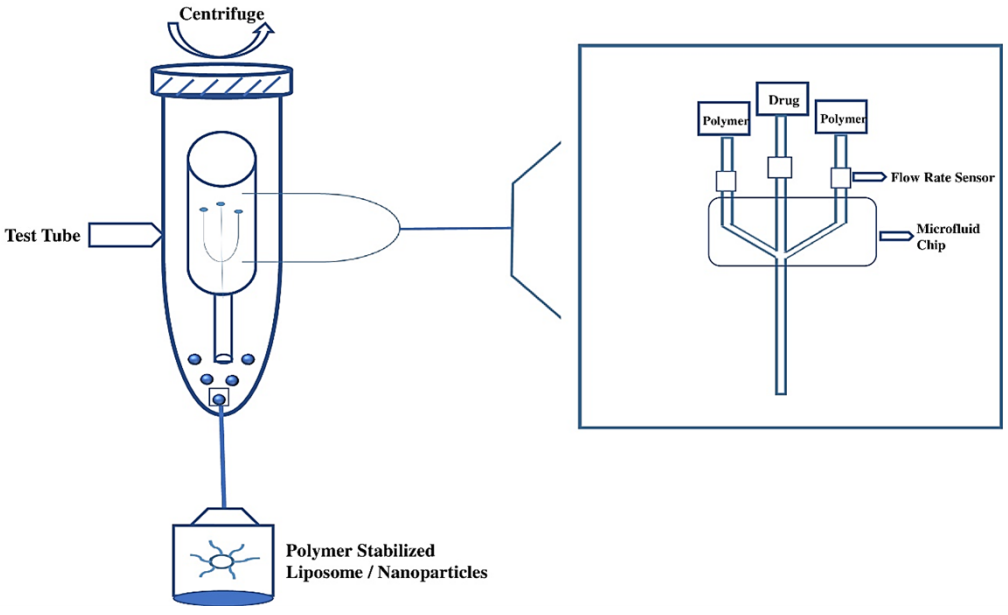


**Figure 7:** Reactor in a centrifuge (RIAC) Device.

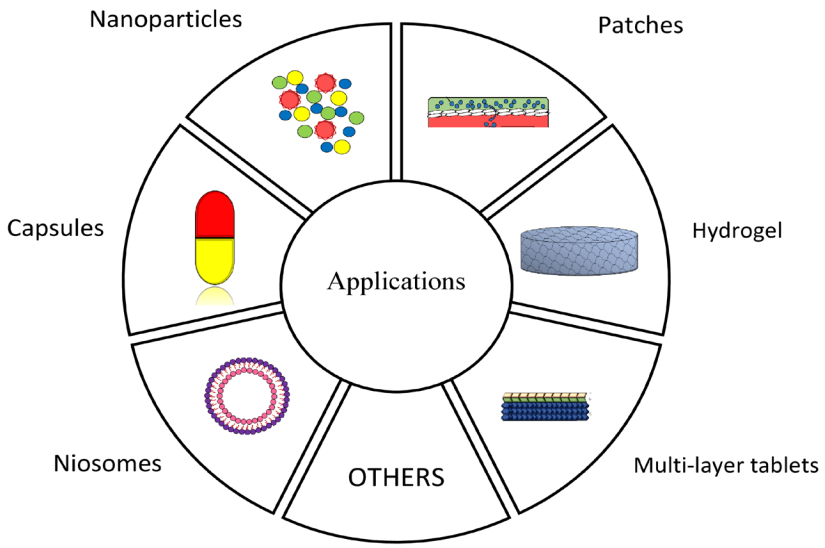


**Figure 8:** Application of 3D Printing Devices.

## Stereolithography (SLA)

SLA is used for the development of controlled-release drug delivery (Xu *et al*., 2020). It finds applications in the field of tissue engineering. SLA is used to develop multi-material 3-D structures with specified characteristics (Arcaute and Mann, 2010). SLA is also used for thermolabile drugs and avoids flowability issues (Arcaute *et al*., 2010). SLA can form printable resins (Linares *et al*., 2023).

## Selective Laser Sintering (SLS)

SLS printers are capable of producing bilayer objects. In industries, SLS is used for different manufacturing processes, such as plastic, metallic and ceramic products. The necessity of excipients and solvents can be minimized. Also, it recycles and reprocesses feedstock. SLS is used to form porous scaffolds with intricate geometries both internally and externally. SLS devices produce SLS-mediated hollow capsular shells (Linares *et al*., 2023).

## Digital Light Processing (DLP)

DLP is effective for establishing a digital workflow in personalized medicine, as evidenced by its applications in biomedical fields such as dental prostheses and tissue engineering. Hydrogel, microneedles and dental models can be manufactured (Pandav *et al*., 2024). Drug delivery systems such as nose patches, intravaginal rings, oral dosage forms, bladder devices, microneedles and dental implants can be produced with the help of DLP (Adamov *et al*., 2022). It is also used in computational imaging, multiplexing and hyperspectral imaging (Xu *et al*., 2021). Designing acrylate-based photosensitive resin through 4D printing can be done through DLP (Kadry *et al*., 2019).

## LCD 3D Printer

Liquid Crystal Display (LCD) technology is utilized to manufacture solid oral dosage forms, where active substances can be blended with photopolymer before printing and encapsulated within solidified matrices (Wu *et al*., 2019). In mobile-based pharmaceutical supply systems it is clearly advantageous for patients who live far away, as it improves access to healthcare by allowing them to receive their medications directly (Madžarević and Ibrić, 2021). Liquid crystal display 3D printing helps in the formulation of different placebo moulds of VOR tablets (Xu *et al*., 2021). Microneedle arrays are successfully constructed employing 3D printing methods such as liquid crystal display (Papadimitriou *et al*., 2022). By using a liquid crystal display, the human microneedles were fabricated, which provides the accuracy that is essential for microstructures like human Microneedles (Papadimitriou *et al*., 2022).

## Reactor in a Centrifuge (RIAC)

The efficacy and accuracy of the reactors were demonstrated through the production of inorganic and organic nanoparticles. It is used in the formulation of nanoscale liposomes within the required size range, that is, diameter (80-300 nm). It is also used to produce silver nanospheres at selected operational settings, which have significance in drug delivery for infectious and cancerous disease treatment and imaging techniques. Cationic liposomes have become a necessary DDS due to the advancement in the fields of gene therapy and mRNA-based vaccines. Due to their compatibility and effectual transfection, results have led to the development of functionalized liposomal formulation through RIAC. RIAC is used to formulate liposomes and silver nanospheres (Andrea *et al*., 2021). The graphical representation of the 3d printing application is illustrated in Figure 8.

## CONCLUSION

This review comprehensively explored the development procedures and diverse applications of 3D printing technologies in fabricating a range of drug delivery systems. From FDM-printed controlled-release tablets to DLP-manufactured microneedles, 3D printing offers unparalleled flexibility and customization compared to traditional methods. Notably, 3D printing empowers the creation of personalized medicine, a prospect previously limited by conventional manufacturing. While challenges like high costs and complex material requirements remain, 3D printing undoubtedly presents a transformative platform for the pharmaceutical industry, paving the way for more precise, patient-centric and on-demand drug delivery systems.

## ACKNOWLEDGEMENT

We want to extend our sincere gratitude to the Deanship of the Faculty of Pharmaceutical Sciences at Lahore University of Biological and Applied Sciences (UBAS) for providing the necessary resources and support that made this research possible. Their commitment to fostering academic excellence has been invaluable.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## ABBREVIATIONS

**FDM:** Fused Deposition Modeling; **RIAC:** Reactor in a centrifuge; **SLA:** Stereo lithography; **DLP:** Digital Light Processing; **HME:** Hot-melt extrusion; **DDS:** Drug delivery system; **LCD:** Liquid Crystal Display; **CAD:** Computer-Aided Design; **DMD:** Digital Micromirror Device; **FDA:** Food and drug administration; **Ag:** Silver.

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**Cite this article:** Mustafa MA, Malik A, Javed E, Amjad A, Iqbal S, Mustafa E. A Comparative Review of 3D Printing Technologies and their Applications: A Systematic Review for Future of Medicine Fabrication. Int. J. Pharm. Investigation. 2025;15(2):313-24.

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Review Article

# Precision Medicine in Diabetes Management: From Theory to Clinical Practice

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**ABSTRACT**

Precision medicine in diabetes management is a groundbreaking approach that tailors treatment strategies to individual patients, moving beyond the one-size-fits-all model. It leverages genetic, molecular and lifestyle data to personalize care. The complex interactions between genetics, the environment and lifestyle decisions that lead to diabetes growth and progression are understood through the theoretical framework. Numerous susceptibility genes have been identified thanks to genomic research, which facilitates risk assessment and customized therapies. Early disease identification has been made easier to detect biomarker. The integration of many data sources for accurate patient profile is possible by cutting-edge technologies like machine learning and data analytics. A thorough understanding of disease mechanisms has been made possible by the inclusion of omics data, genomics and metabolomics, paving the way for the creation of tailored treatments. This involves identifying the precise diabetes subtype of a patient, predicting how they will react to certain drugs and creating a specialized diet and exercise regimen. Wearable technologies and continuous glucose monitoring improve real-time data collecting, enabling quick modifications. Pharmacogenomics also aids in selecting the best treatments while reducing adverse effects. Precision medicine gives medical professionals the ability to improve outcomes and avoid problems, eventually raising the quality of life for diabetics. It represents a paradigm change in the treatment of diabetes, allowing for more focused therapies and effective control.

**Keywords:** Precision medicine, Diabetes mellitus, Biomarkers, Machine Learning, Wearable devices, Patient empowerment.

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**Received:** 08-08-2024;
**Revised:** 31-10-2024;
**Accepted:** 17-12-2024.

## INTRODUCTION

The classification of patients into categories based on clinical criteria, molecular and hereditary biomarkers and other factors in order to optimize therapeutic results is known as precision medicine. The focus of precision medicine has been expanded to encompass environmental and behavioural elements in addition to genetics, with suggestions focusing on populations instead of single patients (Gloyn and Drucker, 2018). The use of data-driven healthcare can be seen as the future of medicine; however, the practice of individualized medicine is not new. Precision medicine is a movement that takes account of each person's unique genetic makeup when determining the best course of treatment and/or prevention. Pharmaceutical specialists can forecast a person's response to a specific drug and/or treatment through the study of the human genome and its environmental factors, enhancing the standard of care given to patients. Diabetes is notoriously difficult to prevent and cure because of its complexity (Ni Ki *et al*., 2022). The specialized and intensive treatment that helps diabetic expecting mothers achieve glycaemic objectives and optimize pregnancy outcomes may be jeopardized by COVID-19-induced restrictions that prevent face-to-face patient-provider conversation. Maintaining an emphasis on patient-centered patient-provider communication therefore becomes crucial during this period of transition from face-to-face ambulatory care to virtual care (Sushko *et al*., 2023). Dealing with data in medicine presents many difficult problems, privacy being one of them. Another important challenge and usually the biggest one in the situation is data collection. Privacy is a serious issue that arises with the adoption of big data techniques or systems. Medical data are much more sensitive than data from other sources. The accessibility of information is a key factor in machine learning algorithms. Without openly accessible data, it is difficult for researchers to conduct analysis to boost the effectiveness of the present and future healthcare systems (Ni Ki *et al*., 2022). Individuals have particular physical qualities, emotional demands and problems and environmental factors that affect their capacity for and desire to carry out a variety of everyday chores to regulate their blood sugar levels and enhance their general health. When there were few medications and tools available, it was acceptable for practitioners to use a "one size fits all" approach to patient

**DOI:** 10.5530/ijpi.20250047

care. This strategy has long since lost its value. In addition to improving glycemia management and multiple complications of diabetes, new drugs and cutting-edge technology also offer chances to tailor treatment to the unique demands and circumstances of each patient (Midyett, 2023). Different people present with T2D in different ways; some present with the disease for a short period, some for a long time and some present with additional comorbidities. Therefore, "a single size does not fit all" when it comes to therapy. More recently, the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) have suggested creating treatment to be more or less strict depending on the mindsets of individuals, the risk of hypoglycemia, the length of the illness, lifespan, complications and resources. The development of a therapeutic plan that is specific to the patient is the basis of individualized diabetes care. Along with social, medical (including comorbidities), clinical and phenotypic factors, they also included biochemical, genetic and phenotypic elements (Williams *et al*., 2022).

## Precision Medicine Foundations

A report by the US National Research Council that attempted to establish an innovative taxonomy for illness identification using a knowledge network is where the phrase "precision medicine" first gained notoriety (Ashley, 2016). Subgroups and categorisation have long been fundamental to the study of medicine. The ancient Greeks believed that certain factors, including gender, location, social status, humour's, nutrition, trauma, beliefs and attitude, had an impact on both health ("a gift from the gods") and disease ("divine punishment") (Merino and Florez, 2018). Medical information, genomic information and environmental data are the three main types of data used in PM. On the other hand, the following is a short and straightforward explanation of how an IoT-based healthcare system functions. First, the patient's body of interest is directly connected to the IoT health sensors and gadgets. Sensors gather a range of physiological information including signs of life (Afzal *et al*., 2020). Genome-guided medical treatment places an emphasis on a patient's unique genomic characteristics to determine if they are likely to benefit from a particular treatment, avoid harsh adverse reactions from drugs that are unlikely to work and change prescription dosages to maximize their efficacy and safety. Drug reaction variable in humans is known to be significantly influenced by genetic variants (Tremblay and Hamet, 2013). The most popular genetic testing in the USA are prenatal screenings, which include sequencing paternal blood-derived neonatal fragments of DNA for genetic disorders. Another exciting new subject that is essential to modern genomics is pharmacogenomics, which optimizes drug response in relation to genetics (Mar *et al*., 2019) . These innovations will thus be a component of the omics pipelines, which also includes methods for supporting PM such as microbiomics, transcriptomics, interactomics, transcriptomics, proteomics and peptidomics. Numerous current studies have shown that such a PM strategy is both feasible and efficient. The integrated Private Omics Profile, an extensive individual omics characterization that combined an individual person's genomic, transcriptomic, proteomic, metabolomic and autoantibody profiles over a 14-month period, revealed dynamic molecular and medical phenotypes including a risk for type 2 diabetes (Nice, 2018).

## Genetics and Genomics in Diabetes

Biomedical research has a primary focus on identifying and characterizing the genetic variations that either cause or predispose to diabetes. A variety of monogenic and syndromic types of diabetes have been developed during the last fifteen years and the utilization of standard directional cloning and candidate gene techniques has been successful in generating increasingly thorough inventories of the genes that are causally linked in these developments (Owen and McCarthy, 2007). The potential of personalized medicine is being realized by scientific and technological advancements in genomics, which are transforming our approaches to genetic counselling and examination, specific therapy and cancer diagnosis and prevention (Weitzel *et al*., 2011). In the pathophysiology of T2D, concurrent or interdependent abnormalities of peripheral tissues' (liver, muscle in the skeleton and adipose tissue) insulin sensitivity and pancreatic β-cells' insulin secretion led to the decompensation of β-cell functioning and persistent hyperglycemia. T2D is recognized as a medically heterogeneous metabolic condition made up of numerous subtypes, including common polygenic forms of T2D in adults where genetic susceptibility strongly correlates with environmental factors and monogenic diabetes, which has greater penetrant genetic forms in young people (Vaxillaire and Froguel, 2008). We have made significant progress over the past ten years in understanding the genetic causes of diabetes. The clinical community has come to assume that with this advancement, our capacity to identify, classify and treat individuals with diabetes will change. This notion is understandable given the well-documented success in the quick transformation of gene finding efforts for monogenic variants of diabetes into modifications in clinical care pathways. Monogenic diabetes can account for up to 3% of cases in children, with alterations in the transcription factors gene HNF1A being the most frequent culprit. Rare penetrant HNF1A mutant carriers generally develop non-insulin-dependent diabetes before the age of 25, are thin and have a longstanding family history of the disease. Clinical evaluation typically indicates that these people are C-peptide positive but autoantibody negative (Gloyn and Drucker, 2018). In genomic epidemiology, study of associations looks at whether certain genetic variations (polymorphisms) in the studied population are linked to a particular phenotype. This trait might be quantitative (such as blood glucose levels) or qualitative (such as diabetes mellitus). The foundation of numerous approaches used in the investigation of diseases

involving multiple, genetically and environmentally influenced components is the polygenic additive model. Genome-Wide Association Studies (GWAS) which examine hundreds of thousands of gene variants throughout the whole human genome to see if they are related with phenotype are a novel and effective method. The main issue with a GWAS looking at, say, 500,000 SNPs is that 25,000 false positive associations will be found if the standard significance level of p 0.05 is used.

## Type 2 diabetes mellitus GWAS

The geneticist's worst nightmare is Type 2 Diabetes Mellitus (T2DM). Yet, current GWAS developments revealed some unexpected findings that led to a significant advancement. Six GWAS found six additional gene regions in addition to the five already known gene regions, bringing the total number of proven areas to 11 (Kronenberg, 2008).

## Biomarkers for Personalized Diabetes Care

"A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention" is the definition of a biomarker. The decision-making process involving drug discovery, preclinical pharmacological and toxicological investigations, clinical trials and even after marketing investigations is significantly influenced by biomarkers. Knowledge gains in the fields of molecular biology, genomics, transcriptomics, lipid omics, glycomics and proteomics have resulted in the discovery of a number of biomarkers that may one day be used in therapeutic settings. The treatment should be based on clinical observations in addition to the study of the biomarkers and the biomarkers should not be misconstrued for clinical end points. Genetics, proteomics, metabolomics and imaging can all be used to predict biomarkers and some of these methods are already being used in clinical settings (Figure 1) (Pichu *et al.*, 2017). Many biological indicators or biomarkers, including C-reactive protein, gamma-glutamyl transpeptidase, or adiponectin, have been linked to the likelihood of developing T2D, according to a substantial body of observational research conducted over the past ten years. Due to the chronic and variable character of diabetes, the utilization using biomarkers may aid in better defining diabetes risk and guiding medical judgment. The usefulness of a novel biomarker in this situation depends on whether it enhances prediction beyond straightforward clinical data. Yet, biomarkers can also be useful in identifying the underlying mechanisms that increase the risk of diabetes, which might afterwards help design new pharmacological targets for curative or preventive therapies (Abbasi *et al.*, 2016).

## miRNAs as biomarkers in diabetic complications

A recently identified class of non-coding RNAs called miRNAs is essential for controlling the expression of genes. They alter the post-transcriptional pathways, which in turn suppress the expression of the target genes which play a variety of roles in cellular function. miRNAs play a variety of roles in numerous biological processes including division, proliferation, cell death and growth, which are all supported by a large body of research. miRNAs can be targeted for many diseases, including diabetes and its consequences, because they have unique properties that allow them to regulate important pathways in a variety of physiological and pathophysiological circumstances. Dysregulation of miRNAs has been linked to an increasing number of illnesses. miRNA expression changes that occur as diabetes progresses

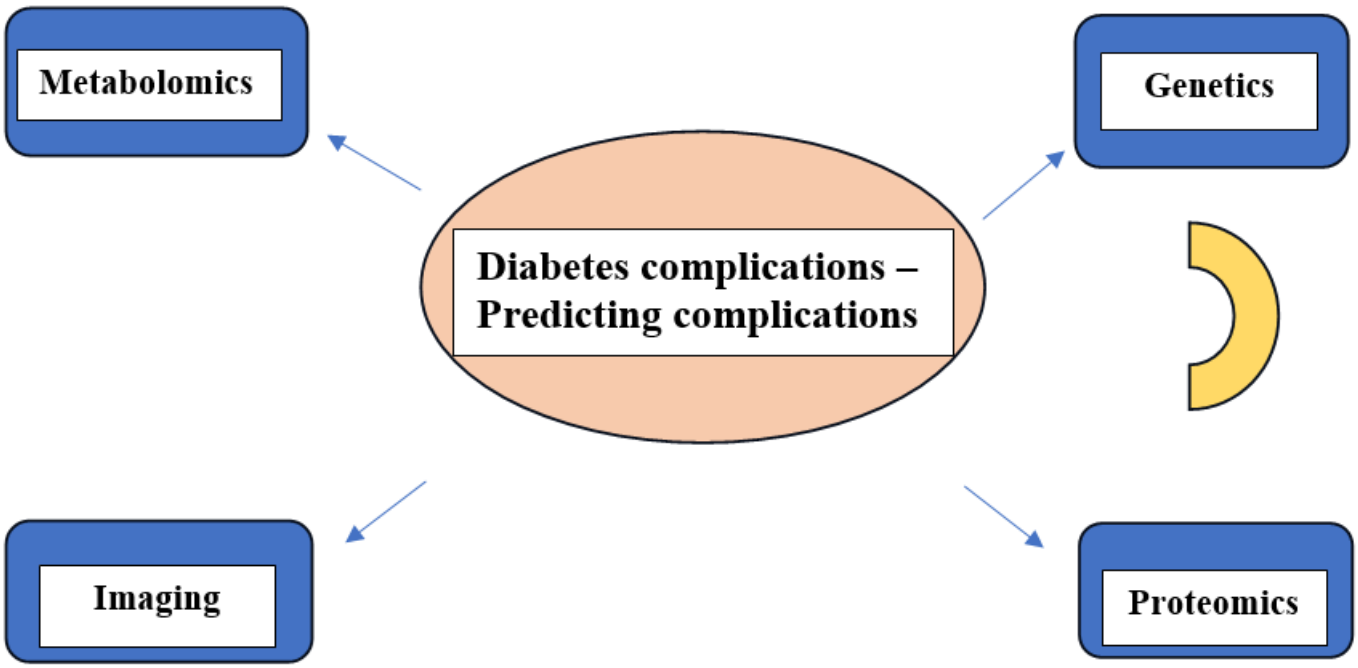


**Figure 1:** Identification of biomarkers for diabetics and its complication using advanced techniques.

have been linked to a number of diabetic problems, including cardiomyopathy, nephropathy, retinopathy, neuropathy and several. New research has established a direct connection between changed miRNA expression and its effects on diabetic complications (Pichu *et al*., 2017).

## Genetic Biomarkers

Studies of large cohorts have identified over 50 loci that influence the chance of developing type 1 diabetes and genetic indicators are used to determine type 1 diabetes propensity. But routine HLA typing is used to test for genetic risk for type 1 diabetes, similar to the way it is carried out for other autoimmune conditions. There is currently no widely acknowledged link with any risk variants despite estimates of the heritability of DR and proliferative DR being as high as 27 and 52%, respectively. Despite a sizable number of genes and genetic variations that have been demonstrated to be significantly linked with DR, none of these relationships have been repeated consistently across numerous populations (Ting *et al*., 2016).

## Emerging biomarkers: omics

It has become possible to track the changes that take place when type 1 diabetes develops using a variety of omics technologies. Changes linked with the onset of type 1 diabetes can be identified early in the course of the disease, according to the study of long-term data from people at elevated risk for the condition and samples from properly matched controls. Additionally, recent research has shown that serum proteomes can be used to track the development of the disease in people with type 1 diabetes at several phases, including early childhood, seroconversion and diagnosis. When it comes to the pathophysiology of type 1 diabetes, metabolomic and lipidomic markers are likely to indicate alterations in immunological and metabolic state. They'll probably produce a brand-new class of immunological indicators as well. Awareness on how surroundings and antibodies may influence one another may be gained from metabolomic investigations, which are also just beginning to take off. The recognition of relevant indicators, such as those for patient classification and inquiries for patients to gauge their reaction to therapy, may then result from tailored analysis of particular analytes (Mathieu *et al*., 2018). The accessibility of big data with the growth of technologies to mine these data are two significant factors in the recent explosive growth of precision medicine. Traditional medical data sources like patient history, physical exam and lab workup are thought to be more accurate when combined with deep phenotypic data mining, genomic analyses, epigenetic, metabolomic, proteomic and transcriptomic data to help individual patients receive precision medicine as showed in Figure 2 (Mohan and Radha, 2019).

## Diabetes Subtyping: Moving Beyond Type 1 and Type 2

More accurate categorizations can be made using genotypic and phenotypic data, with the goal of illuminating the various biological pathways that contribute to the development of hyperglycemia in a particular individual. A precise medical approach to managing diabetes may be made possible by such patient stratification, which would highlight subgroups of clients who are: (1) most at threat for progression of the disease and/or (2) more likely to benefit from specific management regimens. While they were recognized as separate entities long before these words were developed, in the past, a large percentage (>95%) of people who developed hyperglycemia outside of pregnancies have been divided into two subtypes known as type 1 and type 2. Clinical traits have been used to categorize these subtypes, which have been revised throughout time to reflect new information, such as the 1970s discovery of autoantibodies against islet cells in the pancreas in type 1 diabetes. The error of the present medical classifications of diabetes has led to the development of a number of algorithms to more objectively divide the disease into subtype based on phenotypic characteristics. These algorithms take into account the presence or absence of self-antibodies along with unaltered β cell function in diabetes involving ketoacidosis (the "AB classification"), blood-based predictors of insulin secretion ability and diabetes-related insulin resistance, enormous scale study of networks of phenotypes from electronic health records and more. All of these methods have shown that there is variation within the various diabetes subtypes, but they only applied to a tiny portion of all diabetes cases or haven't been widely duplicated (Deutsch *et al*., 2022).

## Tailoring Pharmacotherapy

The avoidance of DM, early identification and slowing the disease's course are essential steps to take in order to prevent potentially fatal consequences. The use of patient-specific pharmacological methods to treat is encouraged by current guidelines, which emphasize the value of individualized care for individuals with DM. Personalized therapy for diabetes management also includes treating cardiovascular disease complications and educating patients on adopting a healthy lifestyle. The notion of patient-specific therapy can be expanded in light of genetic information in DM risk evaluation, pathogenesis, disposition and therapeutic efficacy (Elk and Iwuchukwu, 2017). Pharmacogenomics is an investigation of the genetic underpinnings of individual medication response variations. It is a young and difficult therapeutic discipline with little clinical value and application. There are a lot of factors that might affect a medicine's efficacy, such as the environment, weight, age, gender and digestion. Patient's privacy must be protected and everyone should be given the same chance to benefit from individualized therapy. Pharmacogenomics has the potential to significantly solve problems with medication safety and

## The Impact of Pharmacogenomics in Personalized

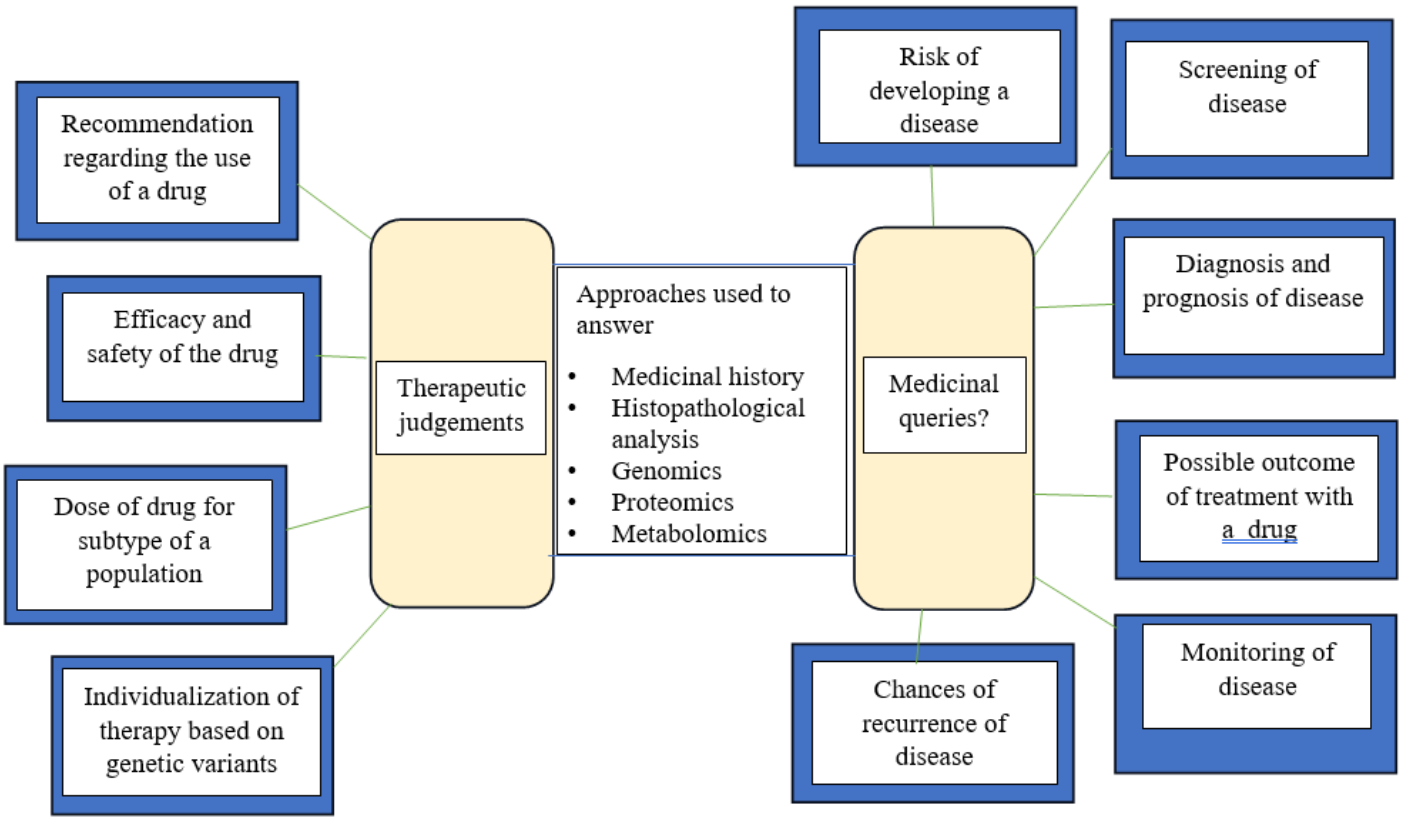


**Figure 2:** For improved therapeutic judgments and individualization of therapy, medical queries and the use of omics and other techniques are also used.

effectiveness. Pharmacogenomics' long-term objective is to assist physicians in making diagnoses and prescribing medications and dosages depending on the genetic composition of the patient. Pharmacogenomics' main goal is to investigate and compile all the genetic and epigenetic variations that influence medication response. For medications used for the avoidance and treatment of diseases like cancer, diabetes, mood disorders, vaccinations, anticonvulsant, anti-infective, cardiovascular and psychiatric treatments and also for various other therapies, studies relating to pharmacogenomics have been carried out. Several people pass away as a result of the drug's side effects (Singh, 2020).

## Personalized Nutritional Interventions

According to current nutritional suggestions aimed at enhancing the general quality of food are crucial for the avoidance and management of diabetes. These recommendations include eating a diet high in veggies, whole grains, fruits, nuts, legumes and marine while consuming fewer refined and highly processed foods. Particularly regarding the health benefits of dairy, meat and drinks, as well as dietary trends such as ketogenic eating habits, there is less agreement among experts. The disparity about the health benefits of particular nutrients, food items, or diets also stems from inter-individual variances. Previous research has demonstrated that there is a significant interindividual variation in how people react to the same meals due to variations in demographic, medical, genetic, gut microbiota and lifestyle factors (Singh, 2020).

Nutrigenomics investigates the interactions between genetics and foodstuffs or food bioactive and their impact on human health. It tries to determine the effects of various nutrients, especially micronutrients as well as macronutrients, on the genome. The term "Nutrigenomics" also refers to the study of how nutrients affect gene expression, transcriptional activity and the diverse responses of gene variations. The relationship between diet and the human body is extremely complex, encompassing the physiology of several organs as well as molecular mechanisms at every regulatory level, including genes, gene expression, proteins and metabolites. To investigate the intricate relationship between dietary phytochemical consumption and human health, metabolomics methods are applied. The term "nutrigenomics" also refers to the study of biological systems using functional genomic methods to understand how dietary components influence metabolic processes and homeostatic regulation. Human behaviour and metabolic functions are influenced by the regulation and gene expression brought on by eating. The power of precision nutrition to improve human health is great. Technologies used in nutrigenomics research include

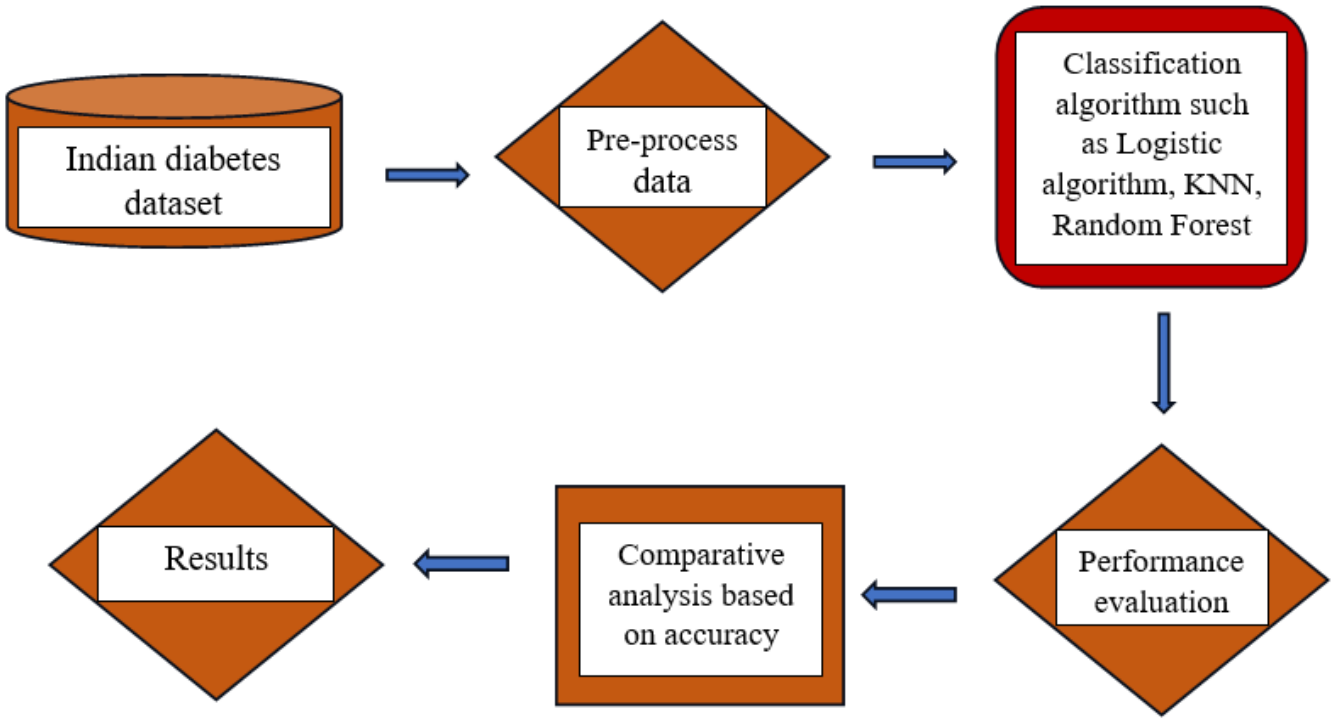


**Figure 3:** Framework of Monitor Learning techniques.

transcriptomics, proteomics and metabolomics (Farhud *et al.*, 2010).

## Wearable Devices and Continuous Monitoring

In the last 10 years, customers have spent a lot more time dealing with technology and machine learning. In four crucial areas of diabetes care, including computerized retinal testing, support for clinical decisions, predictive risk population stratification and self-management for patients' tools, Artificial Intelligence (AI) is widely used. Artificial Intelligence (AI), a branch of computer science, works to create systems or procedures that can analyse data and control complexity in a range of applications. The application of AI is both desirable and practicable for effective data analysis and the development of tools and technology for treating diabetes. To produce safer technology utilizing AI, it is suggested that there should be safer designs, safe reservations and production safeguards with all hazards outlined for all potential technological systems. Wearables, cell phones and other devices have been made possible by technological advancements and they can help with ongoing symptom monitoring and illness status tracking. To treat diabetes effectively, doctors and other healthcare providers should let patients select AI-assisted care. The three main components of diabetes treatment that AI may influence and improve patients with the disease, medical professionals and healthcare systems (Ellahham, 2020). The current technological revolution includes consumer acceptance of wearable technologies. Wearable electronics, also known as wearables, are defined by Wright *et al.* as smart computers incorporated into a range of accessories, such as clothing, trendy accessories, smart watches and other common consumer goods. There are more and more ways than ever before that these advances in technology are being applied in healthcare. This is brought on by the numerous sensors that have been incorporated into these gadgets, including those that detect sound, images, human body gestures and light levels. The development and roll out of better chronic illness management services may be made possible by the fusion of cutting-edge technologies, such as sensor technologies, wearable technology and artificial intelligence approaches. The body of research on managing diabetes with various AI-based solutions is extensive and difficult to understand (Makroum *et al.*, 2022).

## Data Analytics and Machine Learning: Enhancing Precision

Several investigators are carrying out experiments for identifying illnesses using various algorithms for classifying artificial intelligence techniques like J48, SVM, Naive Bayes, Decision Tree, Decisions Table, etc., as showed in the Figure 3. Since research studies indicate that machine-learning algorithms perform better in diagnosing a variety of diseases. The power of information gathering and learning algorithms comes from their ability to handle enormous amounts of data, combine data from multiple sources and incorporate background knowledge into the research (Makroum *et al.*, 2022).

## Challenges and Ethical Considerations

The implementation of personalized medicine in diabetes management gives rise to ethical considerations concerning the

acquisition of informed consent from patients. It is imperative for patients to possess a comprehensive understanding of the advantages, drawbacks and potential ramifications associated with the disclosure of their genetic and personal information for making personalized treatment decisions (Ellahham, 2020). The use of precision medicine in the management of diabetes raises ethical questions about how to obtain patients' informed permission. In order to make informed decisions about their own care, patients must have a thorough awareness of the benefits, risks and other implications of disclosing their family history and personal information. In the area of personalized medicine, the gathering and storage of patient genetic and medical data may pose possible privacy problems. To protect confidential information from unauthorized access and breaches, it is essential to put into place strong data security measures and rigorously adhere to patient privacy requirements. Patients may raise worries about who will hold their data, who will use it for research and how it will be shared with outside parties (Sugandh *et al*., 2023; Golledge *et al*., 2020). The collection and storage of patients' genetic and health-related data in the field of personalized medicine may present potential privacy risks. It is imperative to implement robust data security measures and strictly adhere to patient privacy standards to safeguard sensitive information from unauthorized access and breaches. Patients may express concerns regarding the ownership of their data and the manner in which their information will be utilized in research or disclosed to third parties. Research, healthcare and regulatory science have entered a new frontier as a result of recent advancements in digital technology (such as sensors, software and algorithms) and their increasing pervasiveness in daily life (Coravos *et al*., 2019; Sim, 2019). Patient participation in research, the creation of new types of scientific data to support regulatory conclusions and the potential fulfilment of prior "bigdata" objectives in areas like post-approval surveillance of medical goods are all examples of these unique techniques. More generally, it's possible that we're only beginning to see a paradigm change in the divisions and connections between biomedical research, health care and regular activities. Technologies that will enable continuous tracking of health markers from diverse sources are being developed for the initial time in human history. This has the great potential to improve precision medicine at both population- and individual-levels. Additionally, this offers chances to improve healthcare delivery models for patients, providers and systems (Adamo *et al*., 2020). The sources, categories and amount of data that may be gathered on health are all changing quickly as a result of technological advancements. These data may contain important information about a person's health condition, needs, illness load, relative value of outcomes and outcomes in a longitudinal picture of a person's health and the efficacy of interventions or treatments. Such information and insights can then support a variety of stages in the life cycle of developing a medical device. As a result, these data have the potential to be a substantial and crucial source of knowledge that not only helps assess the effectiveness of medications but also increases their value by managing care pathways. However, the quality, quantity and type of data generated and continuously gathered in real-world scenarios (such as at-home monitoring, wearable technology and other IoT-connected devices) may differ significantly from those generated in conventional healthcare or controlled research settings (Beeson *et al*., 2020).

## Clinical Implementation and Translational Research

Similar significant growth is being seen in the area of precision medicine. The National Research Council at first referred to its establishment of "a New Taxonomy of diseases in humans based on cellular biology" as precision medicine. Another way to put it is that precision medicine is a movement in health care that was sparked by information learned from arranging the human genome. Since then, the discipline has advanced to understand how the convergence of multiomic data with medical history, social and behavioural variables and environmental knowledge properly describes medical conditions, disease states and treatment alternatives for afflicted individuals. With the help of precise medicine, healthcare professionals now have the opportunity to collect and disseminate information that either supports or alters a clinical decision, changing from one that is based upon the evidence for the typical patient to a choice that is dependent on the individual's specific features. It makes it simpler for physicians to give each patient tailored care. Early illness identification and the creation of individualized therapies are just a couple of the practical advantages that precision medicine advancements have to offer. Several data collecting and analytics technologies provide the ability of personalized medicine to tailor care (Johnson *et al*., 2021).

Barack Obama, who was president at the time, unveiled a brand-new healthcare project in 2015 called precision medicine. The project uses genetic diversity to categorize people and target illnesses and preventative therapy. This effort uses the constantly expanding library of human genetic sequences in conjunction with improved computer intelligence to target oncology as its initial area of focus. This results in an educated basis for treatment choices. Since then, several organizations, like Intermountain Health Care (Levit *et al.*, 2019), have adopted precision medicine. An integrative healthcare delivery organization called Intermountain Health Care provides patients with genetic testing as part of their program. Informed treatment plans may be given to patients thanks to the physicians' prior understanding of the patient's needs. The outcomes of this initiative have given patients better clinical benefits for comparable, if not less, money. Intermountain has changed its own policy in favor of this new endeavour due to the program's results, putting greater faith in it as its success increases (Ni Ki *et al*., 2022).

## Patient Empowerment and Shared Decision-Making

An individual gains more control over their choices and self-care practices via the process of empowerment. Having enough knowledge about diabetes is crucial for DM patients in order to improve patient empowerment. According to several researches, empowerment can improve psychological well-being, encourage behavioural changes, reduce HbA1c levels and increase understanding of health issues, as well as self-care and self-control. The self-determination method, which attempts to enhance a person's ability for autonomous care decision-making and critical thought, mainly focuses on shared engagement, awareness-raising, the provision of required information, taking into consideration linguistic and cultural variations and open communication. The World Health Organization, also known as the WHO, says that treating chronic diseases and preserving or improving the individual's quality of life depend on doing this. People with poorly managed DM may see an improvement in their quality of life through a patient-centered empowerment-based approach. According to Chan *et al.*'s study, those who participated in the person-centered empowerment-based program showed a decrease in blood sugar level of 0.476%, which is on the edge of becoming a clinically significant improvement in glycaemic control (Lambrinou *et al.*, 2019). The ability of everyone to decide if there are hazards to their own health or well-being has long been acknowledged by biomedical ethics. Patient preferences are an individual's assessment of the relative importance of things, such as health conditions, treatments, treatment outcomes, or other elements of health or medical care. The idea of patient preferences takes advantage of the requirement to adapt therapy and care to the unique personality and beliefs of the person. Patient safety is related to the ideas of patient preference and joint decision-making. These three ideas centre on obtaining the best outcomes for patients with the fewest harms. Shared decision-making and patient preferences give a greater emphasis on attaining desired results from the standpoint of patients, whereas research on patient safety places a greater emphasis on eliminating medical mistakes. A failure to attain an anticipated consequence in an anticipated order of operations that is not attributable to chance is referred to as an error, according to reason. According to the evidence, a lack of pertinent data, incorrect data interpretation and inefficient communication are some of the main causes of inaccuracy. Patient preferences are significant pieces of information for decision-making with unclear, value-sensitive outcomes and doctors' failure to gather this information may compromise their ability to provide the optimal results (Ruland, 2004).

## Future Directions

The delivery of healthcare services, notably in the area of diabetes management, has been profoundly changed by the use of telemedicine and remote patient surveillance, which have emerged as important tools in modern medicine. Telemedicine enables healthcare professionals to undertake remote evaluations, diagnoses and treatments with the aid of technology, providing personalised care and improving patient outcomes. By enabling people to take an active role in their own diabetes selfcare, the combination of remote patient surveillance and virtual consultations significantly improves patient engagement. Nevertheless, telemedicine offers considerable potential for managing diabetes, but in order to fully realize these advantages, it is imperative to recognize and address the difficulties it faces. By removing accessibility barriers and helping patients to get quick, convenient medical help, the deployment of telemedicine has significantly impacted the provision of tailored diabetic care. Healthcare professionals can remotely check blood sugar levels, modify treatment plans as needed and send prompt feedback thanks to telemedicine, which allows them to tailor interventions to each patient's particular needs. Data privacy and security concerns are raised by the transfer and preservation of patient data on telemedicine platforms. To ensure the confidentiality and safeguarding of patient information, it is crucial to employ strong data protection mechanisms. To effectively use telemedicine tools and provide excellent virtual care services, healthcare providers must undergo in-depth training (White *et al.*, 2000). Due to the various laws and reimbursement practices that exist in various regions, telemedicine faces regulatory and reimbursement problems. To encourage widespread adoption of telemedicine services, it is essential to simplify the current rules and create fair reimbursement procedures (Tesfaye and Selvarajah, 2012; Golledge *et al.*, 2020).

## CONCLUSION

In conclusion, the transition of precision medicine in the management of diabetes from theory to clinical application has enormous promise. Personalized techniques, cutting-edge technologies and the incorporation of genetic markers have made diagnosis and therapy more precise. Personalized treatment plans have been made possible by theoretical underpinnings, including developments in genomes, metabolomics and artificial intelligence. Clinicians may now customize therapies to match the particular needs of each patient because of the discovery of genetic variations, biomarkers and lifestyle variables. A major focus is on empowering patients via individualized therapies and lifestyle changes. But resolving difficulties with pricing and accessibility is essential for fair implementation. The use of precision medicine has an opportunity to transform diabetes care as research advances, lessening the financial burden of this chronic illness and enhancing patient outcomes. This development is a key step in providing people with diabetes with healthcare that is more effective and individualized.

## CONFLICT OF INTEREST

We have no conflicts of interest related to this work. We affirm that the research, authorship and publication of this article have not been influenced by any personal or financial relationships. Kindly provide the competing interest if any or declare none.

## ABBREVIATIONS

**DM:** Diabetes mellitus; **T2DM:** Type 2 Diabetes mellitus; **GWAS:** Genome Wide Association Studies; **AI:** Artificial Intelligence; **SVM:** Support Vector Machine.

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**Cite this article:** Pooja K N, Bharathi D R, Ahmed SS, Jayanth B M, Chandan K. Precision Medicine in Diabetes Management: From Theory to Clinical Practice. Int. J. Pharm. Investigation. 2025;15(2):325-33.

Int. J. Pharm. Investigation, 2025; 15(2):334-343.
https://www.jpionline.org

Review Article

# Revolutionizing Healthcare: The Impact of AI on Precision Medicine

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**ABSTRACT**

Artificial Intelligence (AI) is ushering in a transformative era for personalized medicine by customizing therapeutic interventions based on individual patient profiles, including genetic information and environmental influences. Through the analysis of intricate biological datasets, AI significantly improves diagnostic accuracy, prognostic assessments and therapeutic planning, thereby enabling more precise patient stratification and enhanced clinical outcomes. This advancement is particularly evident in the realms of genomic analysis and pharmacogenomics. Nonetheless, the integration of AI into healthcare introduces substantial legal and ethical considerations. Foremost among these are concerns related to data privacy, security and equitable access to treatment. It is imperative to address these issues to effectively leverage the full potential of AI. Achieving this requires a reevaluation of regulatory frameworks and an enhancement of training programs for healthcare professionals. As AI continues to advance within the healthcare sector, it promises to fundamentally redefine disease management and prevention, heralding a new epoch of medical innovation.

**Keywords:** Personalized medicine, Artificial intelligence, Pharmacogenomics, Regulatory framework, Diagnosis.

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**Received:** 11-09-2024;
**Revised:** 05-11-2024;
**Accepted:** 12-01-2025.

## INTRODUCTION

Self-healing medicine powered by artificial intelligence is gaining acceptance from the medical industry, policymakers and regulators. The integration of AI and personalized medicine is expected to improve treatment and patient safety while reducing healthcare costs. In oncology, AI-informed molecular diagnostics are guiding treatment options, giving each patient the best chance of survival. AI is also enhancing the accuracy of HLA genotyping, leading to better transplant outcomes and more accurate predictions of high antibody levels. Additionally, intelligent genotyping of drug-metabolizing enzymes can increase the understanding of genetic variation, thereby providing better treatment for patients while reducing side effects.

AI also enables the analysis of individual and environmental differences, offering new insights for medical treatments and prevention models. There is a shift from a one-size-fits-all approach to treatments tailored to the specific needs of each patient. Background information plays a crucial role in distinguishing personalized medicine from standard prevention and treatment guidelines. The emergence of new genetic testing technologies and molecular diagnostics has further stimulated the development of personalized medicine. By using the molecular uniqueness of each patient, AI can predict whether a patient will benefit from a particular treatment or whether they might experience adverse reactions. The success of AI-driven personalized medicine requires collaboration among researchers, AI developers, analysts, regulators, healthcare professionals, physicians and patients (Jiang & Zhang, 2023).

### Understanding Personalized Medicine

The concept of self-medication has gained popularity in recent years, driven by the recognition that conventional treatments can often be ineffective or unsafe and by advances such as the Human Genome Project. These advances facilitate the identification of disease subtypes based on genetic data and other methods like histology, which many believe will enhance disease prevention and pain management. For instance, genetic studies can reveal that patients with certain conditions are more likely to benefit from specific new or existing drugs. Artificial Intelligence (AI) plays a crucial role in analyzing data, drawing conclusions, identifying new relationships and supporting doctors in their decision-making. Companies have demonstrated that

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**DOI:** 10.5530/ijpi.20250100



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supercomputers, deep learning and AI can significantly enhance the accuracy of personalized medicine.

This article focuses on creating universal solutions for treating patients with similar symptoms while incorporating evidence-based practices. The evolution of medicine from Hippocrates to the twentieth century highlights a shift from acquiring knowledge to relying on evidence. Technological advancements and treatment innovations are transforming how doctors diagnose and treat patients. Modern medical decisions are increasingly based on research and clinical trials, offering access to advanced treatments and necessitating thorough research on potential side effects. Innovations such as affordable genome sequencing, advanced biotechnology and health sensors integrated into daily life are accelerating this change. However, the influx of information and the digital health revolution driven by smartphones and healthcare providers have introduced data analysis and interpretation challenges (Redekop & Mladsi, 2013).

According to the National Institutes of Health, personalized medicine develops disease and prevention strategies based on an individual's genetics, environment and bioactivity. This approach enhances the ability of doctors and researchers to predict the most effective treatments and preventive measures for individuals (Redekop & Mladsi, 2013; Collins & Varmus, 2015). AI functions similarly to a supercomputer, utilizing fast-learning algorithms like deep learning to achieve high accuracy in treating diseases, often matching, or surpassing human expertise in fields such as cardiology, dermatology and oncology (Gilvary *et al.*, 2019).

Nevertheless, it is crucial to emphasize the integration of intelligent algorithms with human expertise. While AI can provide accurate diagnoses, combining its capabilities with doctors' knowledge and experience is essential for optimal patient care (Johnson *et al.*, 2021). For instance, at the World Biomedical Imaging Symposium, a computational model for identifying metastatic breast cancer in lymph node images achieved a success rate of 92.5% in a competition. This rate increased to 96.6% with the addition of doctors' evaluations and combining AI predictions with human diagnoses raised the success rate to 99.5%, reducing human error by approximately 85% (Johnson *et al.*, 2021).

In personalized medicine, AI serves as a powerful tool for accurate diagnosis and reduced human error, especially when complemented by clinical expertise. The shift from traditional methods to personalized medicine exemplifies the transition to more precise, data-driven healthcare. This evolution underscores the need to balance technological advancements with clinical knowledge to uphold high standards in patient care. As the field progresses, it presents both unprecedented opportunities and challenges that require ongoing collaboration among experts, practitioners and policymakers to fully realize its potential (Davenport & Kalakota, 2019).

## Current Technologies and Methodologies

The growth of AI-driven personalized medicine is propelled by several key technological advancements:

1. Genomic Sequencing: Advanced sequencing technologies have made it possible to quickly and affordably decode genetic information. This enables the detection of genetic variations linked to diseases and treatment responses, allowing for more personalized medical care.
2. Bioinformatics: By applying powerful computational methods, bioinformatics helps analyze large-scale biological data, uncovering disease-related genes and pathways. This deepens our understanding of disease mechanisms and Aids in the development of targeted therapies.
3. Machine Learning and Predictive Analytics: These tools use algorithms to analyse data from various sources, predicting disease risks and treatment outcomes. Their ability to process extensive datasets enhances clinical decision-making and supports the creation of personalized treatment plans.
4. Wearable Health Devices: These devices offer continuous monitoring of vital signs and lifestyle habits, providing real-time data that can be used to tailor medical treatments. They are crucial in the proactive management and prevention of diseases by delivering insights into a patient's daily health.
5. Electronic Health Records (EHRs): EHRs serve as digital repositories that consolidate patient data, making it easier to incorporate personalized medicine into routine clinical practice. They offer a valuable source of information that can be analyzed with AI to improve patient care and treatment outcomes.

## AI and the Future of Personalized Medicine

The combination of AI and Personalized medicine has the potential to revolutionize healthcare. Personalized medicine focuses on identifying patient phenotypes with poor clinical response or specific treatment needs. AI uses computation and reasoning to understand and empower healthcare professionals through artificial intelligence. Recent studies suggest that research on the integration of intelligence with personalized medicine can solve important problems, especially the integration of genomic and non-genomic markers with patients' symptoms, clinical history and lifestyle to facilitate individual diagnosis and prognosis (Greenberg *et al.*, 2020). The report emphasizes the need for caution when using these technologies, but also recognizes their significant promise. The digitalization of health information and the rapid use of technology are accelerating progress in

**Table 1: Applications of AI in Healthcare.**

| Sl. No. | Applications of AI in Healthcare | Impact of artificial intelligence in different sectors within healthcare |
|---|---|---|
| 1 | AI for Drug Discovery | AI accelerates the drug discovery process by automating the identification of drug targets and assessing potential compounds. Leading pharmaceutical companies like Pfizer and Sanofi are incorporating AI tools to streamline the development of new treatments. AI is anticipated to transform drug development by making it faster, more cost-effective and more efficient. |
| 1.1 | AI for Clinical Trials | AI enhances the clinical trial process by automating data monitoring and improving the accuracy of results. Key applications of AI in clinical trials include: |
| 1.2 | Intelligent Clinical Trials | AI helps to optimize clinical trials by analyzing Real-World Data (RWD) and employing predictive models. These advancements enable researchers to gain deeper insights into diseases, identify suitable patients and design innovative trial protocols. AI also aids in data management, reducing human error and ensuring more reliable results. |
| 1.21 | Clinical Trial Cooperation and Model Sharing | Effective global collaboration and data sharing are crucial for advancing AI applications in clinical trials. Initiatives for scalable data-sharing and open science contribute to the rapid development and deployment of AI solutions. Projects like EIOS leverage open-source data to improve public health responses and early detection of health threats. |
| 1.3 | Patient Care | AI contributes to enhanced patient care by providing systems that generate valuable insights and improve the quality of life. These AI-driven systems support various aspects of patient care. |
| 1.31 | Maternal Care | AI aids in predicting risks for pregnant women and improves access to both routine and specialized care. This can lead to a reduction in complications and mortality for high-risk pregnancies by delivering timely and precise care recommendations. |
| 1.32 | Healthcare Robotics | Medical robots, including exoskeletons and advanced prosthetics, assist with rehabilitation and surgical procedures. For instance, Cyberdyne's HAL exoskeleton helps individuals with lower limb disorders by detecting electrical signals and enabling joint movement, thus supporting recovery from conditions like spinal cord injuries and strokes. |
| 1.33 | Genetics AI Data-Driven Medicine | The integration of AI and extensive data collection enhances the detection of genetic diseases and facilitates personalized medical treatments. This approach boosts the precision and adaptability of healthcare by utilizing comprehensive data from diverse sources. |
| 1.34 | AI-powered Stethoscope | AI-enabled stethoscopes provide accurate readings even in noisy environments and are easy to use. They improve medical care in remote areas and for patients with chronic conditions, while also reducing the risk of COVID-19 transmission. AI can analyze large volumes of clinical data to identify disease patterns and abnormalities, enhancing diagnostic accuracy. |

the use of AI in healthcare. However, integrating multiple data sources, ensuring security and overcoming challenges related to government training, performance standards and biases are important issues that need to be addressed (Holzinger *et al.*, 2017). The use of AI is essential: data security and transparency, analysis and visualization and integration. While data security provides transparency and trust in AI systems, analytics and insights provide support to healthcare professionals. Experts share the collaboration between humans and AI that supports the development of new skills and the need for cutting-edge AI models and effective business practices (Holzinger *et al.*, 2017).

A vast amount of data influencing our health exists outside traditional medical systems. Factors such as lifestyle, diet, environmental factors, healthcare accessibility and access to care significantly impact our health. These behavioral and social determinants can be tracked through wearables and medical devices. Over our lifetimes, we generate extensive Individual and health data that could offer insights for a longer, healthier life.

Large-scale data analysis and AI are progressively prevalent in healthcare, impacting payers, providers, policymakers, patients and product manufacturers. AI-powered tools assist in reducing fraud, waste and abuse in payer programs, saving significant amounts of money, time and effort. For instance, IBM's AI-based tool, Data Probe, detected and recovered substantial funds in medical fraud cases. In the healthcare sector, AI is in evidence-based clinical decision-making and forecasts patient readmission risks. Policymakers and governments leverage AI to manage and predict infections and outbreaks, exemplified by the FINDER model for detecting foodborne illnesses. During crises, AI-enabled solutions have integrated data and services to streamline care coordination, as seen in Sonoma County's response to wildfires. AI is not the only data-driven field influencing health care. Personalized medicine, with its goal of personalizing care for every individual, also plays a significant role. Personalized medicine relies on extensive data, such as that collected through biobanks and health projects and a healthcare ecosystem willing to adopt personalized strategies. The integration of AI and Personalized medicine is anticipated to accelerate the achievement of personalized care goals. As already discussed, the digitalization of health information and the rapid use of technology are accelerating progress in the use of AI in healthcare.

## AI in Healthcare

The acceptance of AI has increased in many areas, especially healthcare, in the last decade. While AI offers the opportunity to create smart products, create new services and create new business models, it also brings with it social and ethical issues related to security, privacy and human rights. AI technologies range from virtual machines such as deep-learning information for the management of health to cyber-physical systems such as surgical robots and nanorobots for drug delivery. AI's ability to recognize complex patterns makes image-based diagnosis as effective as or better than doctors. AI-based medical decision-making processes can reduce misdiagnoses and support decision-making by processing EHR data. Advances in computing resources such as natural language processing and pattern recognition will empower AI to solve complex problems.

AI supports and enhances human capabilities, making the role of AI in healthcare clearer. AI systems; provide skills such as perception, reasoning, learning and motivation that support human skills such as understanding, reasoning and creativity. Insights can be developed in oncology, imaging and primary care. For example, AI algorithms trained on mammogram images and EHR data can predict breast cancer with higher accuracy than radiologists, potentially reducing the number of diagnoses. Personalized medicine is a rapidly growing field that focuses on personalized medicine based on individual characteristics. Initially characterized as the development of a novel theory of human disease grounded in molecular biology, this theory now combines multidisciplinary data with clinical history, social decision-making/behavior and environmental factors to determine health and disease states. Personalized medicine

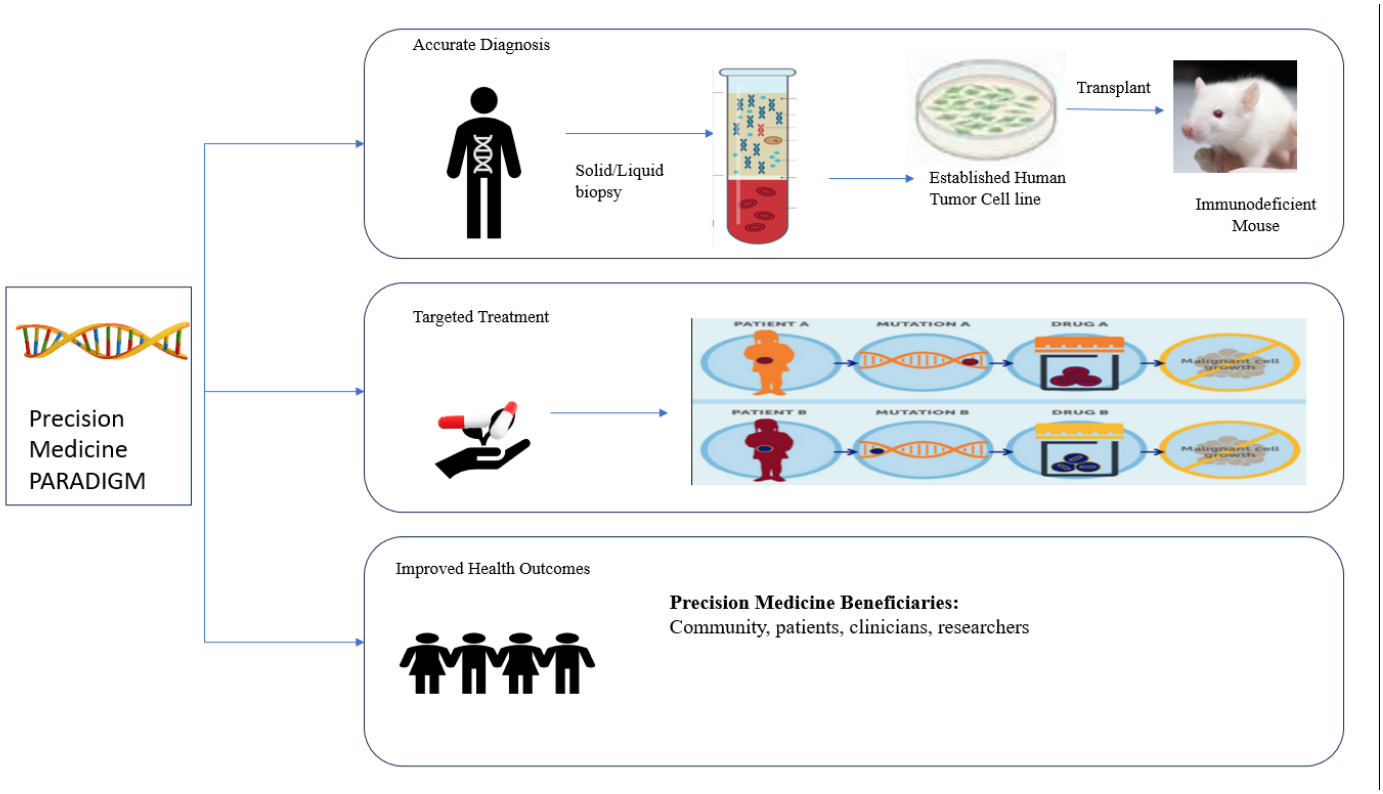


**Figure 1:** Personalized medicine Data quality relevance.

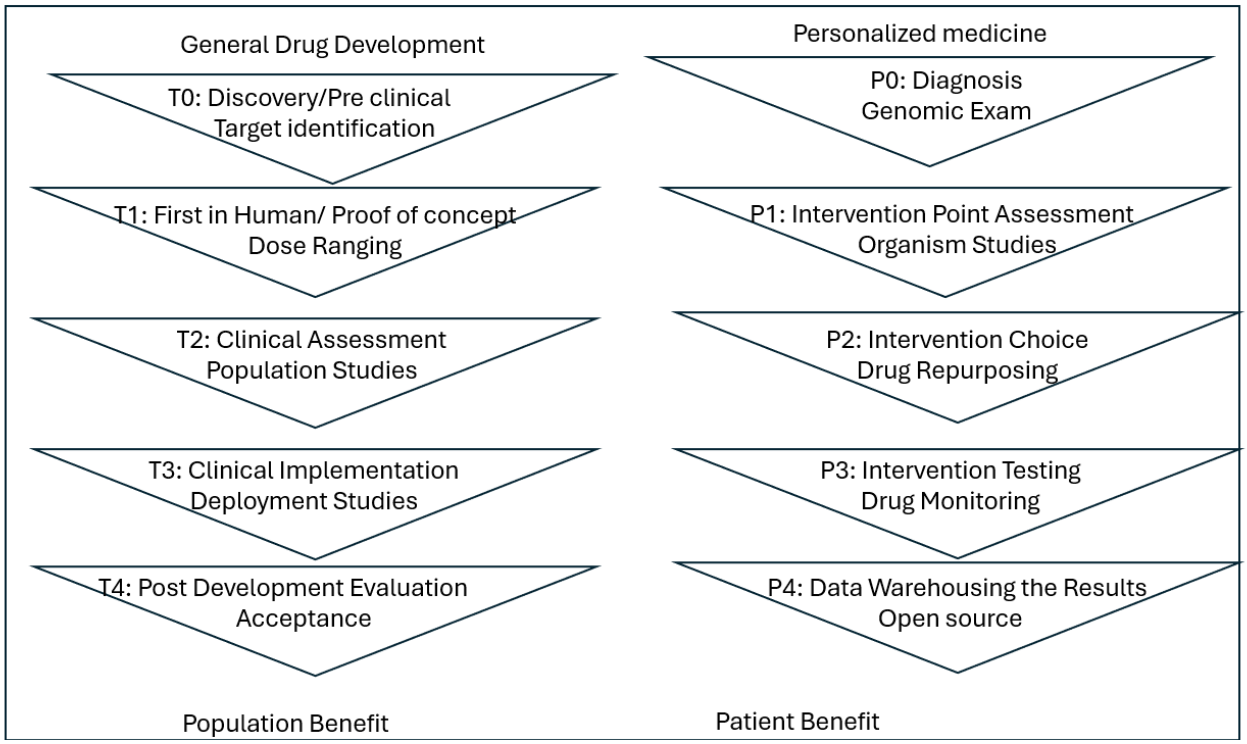


**Figure 2:** Work flow in the personalized medicine Federal Policies Shaping AI-Driven Personalized Medicine.

enables doctors to deliver personalized care based on individual characteristics. The adoption of genotyping and electronic health records allows researchers to derive new phenotypes from clinical data, thereby improving diagnosis and treatment planning. A great work in personalized medicine that helps determine the accuracy of medicine and provides treatment plans for cancer patients. Integration of Personalised medicine into healthcare promises to provide more accurate diagnosis, disease risk prediction and treatment plans. The creation of data repositories such as biobanks supports a different world of personalized medicine training algorithms and addressing governance, privacy and governance.

## Applications for AI in Healthcare

AI is rapidly transforming healthcare by addressing critical challenges such as rising costs, limited access and the need for more efficient processes. AI's ability to analyze vast data sets allows for enhanced diagnostics, personalized treatments and streamlined operations. The following Table 1 outlines key applications of AI in healthcare, showcasing how this technology is being utilized to improve patient outcomes and operational efficiency.

## AI for Personalized Medicine: Data Accuracy and Applicability

Although AI has made significant strides in recent times, its potential in clinical research, gaps and opportunities for improvement remain. Highlights the need for either more data or improved algorithms to further enhance AI capabilities. Currently, AI focuses on developing algorithms that require large amounts of data to optimize. This is because current machine learning methods are too data-intensive. Comprehensive data combined with simple algorithms have been shown to provide better results compared to complex algorithms using limited data. This means that advanced AI systems work best when variability is low, which is usually not a problem in clinical practice. It plays an important role in thinking about reality. The quality of the predictions made by the model cannot exceed the quality of the data used for training. Although traditional statistical methods can filter data by removing outliers, their effectiveness is limited because they cannot measure the quality and accuracy of the data. Therefore, inaccuracies in the data content can introduce bias and affect the study sample. To overcome these challenges in AI, particularly when handling complex data, researchers leverage data analysis, including sensitive analysis, feature selection and model reduction. Relationships are also important for specific diseases. Most recent efforts to apply ML techniques are based on complex tools that have been studied without appropriate analysis for many diseases as depicted in Figure 1 (Gulshan *et al.*, 2016).

## AI-driven personalized Medicine in Practice

AI technologies are revolutionizing healthcare by providing innovative solutions for personalized medicine, drug discovery, diagnostics and treatment optimization. Below are some key examples of how AI is being harnessed in these areas:

- **Curate. AI: Dose Recommendation Platform:** CURATE.AI is a pioneering AI-driven platform designed to optimize drug dosing for individual patients. By mapping the relationship between drug dose (input) and patient response (output), it creates a personalized profile for each patient based on their unique data. This profile dynamically adjusts as the patient's condition changes over time, recommending the most effective dosing strategies to achieve the best possible therapeutic outcomes. Unlike traditional methods, it incorporates complex biological phenomena without explicitly modelling them, making it a robust and mechanism-independent tool for personalized treatment (Blasiak *et al.*, 2020).
- **Quadratic Phenotypic Optimization Platform (QPOP):** QPOP is another innovative AI technology focused on optimizing combination therapies. It utilizes a quadratic phenotypic optimization model to determine the most effective drug combinations and their initial doses. By analyzing how different drug combinations affect phenotypic outcomes, QPOP helps in selecting the best therapeutic strategies, especially in complex diseases where multi-drug regimens are necessary. This platform minimizes the trial-and-error approach traditionally associated with drug combination therapy, improving both efficacy and safety (Lin & Ho, 2018).
- **IBM Watson for Oncology:** IBM Watson for Oncology is an AI-powered decision-support system that assists oncologists in selecting the most appropriate cancer treatments. By analyzing vast amounts of medical literature, clinical trial data and patient records, Watson provides evidence-based treatment recommendations tailored to individual patients. This system enhances the decision-making process, helping clinicians choose the most effective therapies based on the latest research and patient-specific factors (Ferrucci *et al.*, 2010).
- **Path AI: AI-Powered Pathology:** Path AI is an AI-driven platform that improves the accuracy and efficiency of pathology diagnostics. Using machine learning algorithms, Path AI analyzes medical images, such as tissue biopsies, to identify patterns and diagnose diseases with high precision. This technology is particularly valuable in cancer diagnostics, where early and accurate detection is critical for effective treatment. Path AI not only assists pathologists in making more accurate diagnoses but also reduces the time required for analysis, enabling faster clinical decision-making (Howard *et al.*, 2021).
- **DeepMind's AlphaFold:** AlphaFold, developed by DeepMind, is an AI system that predicts the 3D structures of proteins based on their amino acid sequences. This breakthrough technology has significant implications for drug discovery and development, as understanding protein structures is key to identifying how drugs interact with their targets. AlphaFold's ability to accurately predict protein folding has accelerated research in various biomedical fields, opening new avenues for the development of targeted therapies (Jumper *et al.*, 2021).

## Integrating Personalized Medicine into the Workflow

To ensure seamless integration, the concept of personalized medicine must extend beyond isolated innovations and into the broader healthcare workflow. By combining individual and collaborative drug activity within a unified process, personalized medicine can transform patient care across all levels, from diagnosis to treatment and monitoring. This holistic approach is vital for realizing the full potential of AI-driven solutions in enhancing patient outcomes and enabling more precise, tailored therapies. Combined and individual drug activity: P0-P4 Individual Drug Activity is like the T0-T4 Drug and Medical Equipment Development Study. For these projects to work effectively, change needs to be achieved at all levels, although different elements require different skills and ideas. Traditionally these differences have led to differences, but emerging ideas in personalized medicine, particularly cognitive, promise to enable integration and shared efficiency of patient care across the P0-P4 workflow. Ideal scenario Personalized medicine enables the transformation of all levels by integrating diagnosis, treatment and monitoring into an integrated process. An important example is the development of cell transplantation for various diseases. For example, in some cancer immunoassays, a patient's tumor may be analyzed for specific neoantigens, or mutations, that trigger the body's immune response against cancer cells. If neoantigens are identified, the immune system can be harvested from the donor (allogeneic transplant) or the patient (autologous transplant) and then trained to recognize the neoantigens. The aim is for the sensitized cells to cause the patient's immune system to attack the tumor cells. This approach, called controlled production, suits the immediate needs of patients, unlike pharmaceutical production, which the medical center reserves for future use. The management approach will become more common in personalized medicine than in cancer treatment because it is not good to plan all treatment options. Production management, artificial intelligence-supported robots and 3D printers can be used for quality production. The FDA approved the first 3D-printed drugs in 2015, demonstrating the potential of point-of-care manufacturing in medical care. AI can also instantly support N-of-1 testing, where treatments are personalized and their results carefully monitored using advanced technology. AI-based simulations can also help predict possible treatment

strategies, further improving patient care as depicted in Figure 2 (Keerthana *et al*., 2020).

Federal policies play a fundamental role in guiding the development and implementation of AI-driven personalized medicine, ensuring that the balance between encouraging innovation and protecting patient safety is maintained. These policies set the groundwork for a healthcare landscape that is increasingly tailored to individual patient needs, driven by advancements in technology and data science.

## Key Federal Initiatives and Regulations

- ***Personalzsed Medicine Initiative (PMI)*:** In 2015, PMI sought to advance personalized medicine by tailoring treatments to individual genetic, environmental and lifestyle factors, thereby enhancing therapeutic outcomes
- ***HIPAA Privacy Rule and GINA:*** These regulations protect patient privacy and genetic information, building trust and ensuring ethical practices in applying personalized medicine.
- ***21st Century Cures Act:*** Enacted in 2016, this legislation accelerates the development and approval of medical products, emphasizing the integration of real-world evidence and advanced biomarkers critical for personalized medicine strategies.
- ***FDA Personalized Medicine Framework:*** The FDA has developed a regulatory framework.
- ***FDA's Role:*** The Food and Drug Administration (FDA) is actively adapting its regulatory practices to accommodate the advancements in AI and personalized medicine. This includes creating new approval pathways and establishing specific guidelines for AI-driven technologies, ensuring that they meet rigorous safety and effectiveness standards before they can be widely implemented.
- ***NIH's Contribution*:** The National Institutes of Health (NIH) is a key player in promoting the development of personalized medicine, particularly through initiatives like the All of Us Research Program. This program seeks to collect various health data from diverse populations to drive research and ultimately improve healthcare outcomes. By supporting such initiatives, the NIH is helping lay the groundwork for more effective and personalized treatment options.

## Supportive Aspects

Federal initiatives like the Personalized Medicine Initiative (PMI) and the 21st Century Cures Act have significantly propelled research and development in personalized medicine by providing essential funding and streamlining regulatory pathways. These efforts have accelerated innovation and ensured that new treatments can reach patients more efficiently. Furthermore, regulations such as the Health Insurance Portability and Accountability Act (HIPAA) and the Genetic Information Non-discrimination Act (GINA) are crucial in safeguarding patient data. This protection is vital for maintaining ethical standards in the application of AI technologies in medicine, where data privacy and security are paramount (Magrabi *et al*., 2019).

## Analysis of AI-driven Personalized Medicine and Federal Policies

The convergence of AI with personalized medicine marks a significant evolution in patient care, offering the potential for more tailored and effective treatments. Federal policies and regulations are critical in shaping this field, ensuring that technological progress occurs responsibly and ethically. This analysis examines the interplay between federal policies and AI advancements, addressing both the challenges and opportunities of integrating these technologies within existing regulatory frameworks. It also presents case studies showcasing how these policies have influenced the development of AI-driven solutions. Federal policies are integral in promoting AI innovation within personalized medicine, providing a regulatory backbone while encouraging advancements. Initiatives like the Personalized Medicine Initiative (PMI) and the 21st Century Cures Act are pivotal in supporting AI's integration into healthcare, ensuring that patient safety remains a top priority. These programs enable the responsible application of AI in personalized medicine by balancing innovation with stringent safety standards. However, aligning AI developments with current regulations presents several hurdles. These include modernizing outdated policies to account for new technologies and tackling issues related to proprietary algorithms and data privacy. Despite these difficulties, there are opportunities for regulatory adaptation, as seen in the FDA's Digital Health Innovation Action Plan. This initiative represents a proactive effort to update regulatory approaches in line with rapid technological advances, ensuring that AI-based solutions are evaluated ethically and efficiently (Amnesty International, 2024).

## Regulatory Power and Epistemic Authority in AI-Driven Personalized Medicine

The FDA's role is crucial in asserting regulatory authority and setting scientific standards for AI-driven personalized medicine. As Carpenter (2010) describes, the FDA's influence spans three main areas: directive, conceptual power and gatekeeping.

## Directive Power

The FDA exercises directive power by enforcing regulations on AI technologies used in personalized medicine. This can involve requiring modifications to AI algorithms or mandating

transparency in how these systems are validated and monitored, ensuring they meet safety and efficacy standards.

## Conceptual Power

The FDA's conceptual power helps shape the regulatory landscape for AI in personalized medicine. This authority builds on the legacy of past regulations, such as the 1962 Kefauver Amendments, which set high standards for drug approvals. Similarly, the FDA is now developing guidelines to ensure AI systems used in personalized medicine meet rigorous evidence and validation requirements.

## Gatekeeping Power

The FDA acts as a gatekeeper by evaluating and approving AI tools for personalized medicine before they enter the market. This role is essential for maintaining high standards between the development and clinical application stages. However, the FDA's oversight diminishes post-market, making it harder to monitor performance and address issues that arise after these AI systems are deployed. Post-market oversight of AI tools in personalized medicine remains a challenge. While the FDA can revise product labeling or require post-market studies, monitoring the ongoing effectiveness of AI systems in diverse clinical environments is complex. Additionally, the use of AI tools beyond their approved purposes often goes unregulated, creating gaps in oversight. The regulatory landscape for AI in personalized medicine involves not just the FDA, but also a range of stakeholders and mechanisms. This results in a polycentric regulatory approach, where multiple entities contribute to the oversight and governance of AI technologies (Timmermans & Berg, 2010).

## Challenges and Future Directions

The rapid pace of innovation in AI often surpasses the capacity of existing regulatory frameworks to keep up, posing significant challenges in maintaining the safety and efficacy of new technologies. Additionally, issues related to data sharing and system interoperability remain substantial obstacles. The integration of AI systems across different platforms and institutions can be hindered by these challenges, slowing down the potential benefits of personalized medicine. AI holds undeniable potential to enhance cancer patient care and significantly impact cancer outcomes. In clinical settings, its success has been so profound that it is altering practices in nearly every phase of cancer research and treatment. In healthcare, gathering sufficient data from the entire population is crucial for building robust AI models. It appears that differences in race, gender and socioeconomic status influence the occurrence and recurrence of diseases. For instance, there are ethnic disparities in the occurrence and frequency of genomic abnormalities in cancer. Research by Bhargava and colleagues even revealed racial disparities in bacterial aggression between Caucasian and African American women suffering from breast cancer. However, existing data used to train and diagnose cancer AI models often lack representation from certain groups and races. For instance, the largest database, TCGA, predominantly comprises individuals of European descent. Moreover, biases exist in large datasets, for example, the TCGA dataset has a higher prevalence of solid tumors and a low incidence of metastatic tumors. While cell lines populate huge genomic datasets, they fail to capture real scenarios due to issues like genetic drift. Apart from unbiased information, there is a disparity between the ease of accessing information from various platforms and the ease of independent usage, particularly concerning personal information or access control. As prospective clinical trials and interventional data become more integrated and validated, the clinical efficacy of AI will continue to improve, alongside addressing disparate data influencing practice. Sharing coded cognitive models is another way to ensure transparency, reproducibility and suitability for clinical use. However, universal methods for sharing complex model code effectively are still lacking.

Fortunately, most reputable journals now mandate detailed explanations of the reporting process, enhancing clarity and sharing. Although the model emphasizes imaging and omics data, one of the richest resources, Electronic Health Records (EHRs), remains largely untapped due to its unstructured nature, noise, sparsity, inconsistency and the need for special management and data cleansing. Models like the Healthcare Outcomes-partnership Common Profile model Aim to address these issues, supported by client software enabling visibility into long-term patient information. Establishing trust in artificial intelligence-supported decision-making among physicians is crucial in integration into hospitals. To this end, Begoli and colleagues recommend developing a measure of uncertainty in cognitive models. Model uncertainty can arise from data selection, accuracy, completeness, biases, artifacts and inaccurate models.

Estimating uncertainty in driven data forecasting models is an active research area that will improve model robustness and increase confidence in information, thereby enhancing future decisions. Although deep learning is often termed a "black box," preserving data relationships is vital. Further research to improve model interpretation and understanding of cellular and molecular mechanisms is crucial. Ground research has led to the compilation of cancer risk factors and technological advancements offer various ways to collect patient information, including genetic testing, EHRs and smartphone sensors. AI systems can improve diagnostic accuracy, enhance self-care, remotely monitor cancer patients and provide personalized options for prevention, early intervention and management of critical situations (Ideker *et al.*, 2011).

## Limitations of AI in the Promotion of Personalized Medicine

Despite the potential of AI, the field of personalized medicine still faces some challenges. A major problem is the lack of ergodicity, meaning that models based on big data will not reflect the relationship between individuals. If the model prioritizes public disclosure of the patient's data, this will make the treatment decision impossible. Some AI tools, such as IBM's Watson, have shown inconsistent results, underscoring the importance of quality analysis from clinical trials. If an AI system is trained with biased or incomplete data, its recommendations will be unreliable, just like Google's flu predictions. Additionally, the SHIVA comparative medicine study showed no benefit compared to conventional treatment, raising questions about the effectiveness of the matching algorithm. Use them in learning whose algorithms are constantly updated. This approach requires initially conflicting data to provide reliable results and takes a lot of time for the system to develop high accuracy. AI-based tools that can provide accurate predictions suffer from a black box problem where the connection between inputs and outputs is invisible. This lack of explanation reduces confidence in AI predictions. Additionally, many AI methods focus on correlation rather than causation; this is not enough to identify drug targets that directly address the need. Understanding the relationship and impact is important for effective design (Schmidt, 2017).

**Case Studies:** The Influence of Federal Policies on AI-Driven Innovation.

- ***Oncology Personalized medicine:*** Federal regulations have played a significant role in advancing personalized cancer treatments. For example, the FDA's expedited approval of AI-powered diagnostic tools demonstrates how supportive policies can accelerate the use of innovative technology in oncology, leading to more precise and individualized cancer care.
- ***AI in Drug Discovery:*** Legislation such as the 21st Century Cures Act has been vital in incorporating AI into drug discovery. By fostering the use of AI, this act has sped up the development of new drugs and enhanced the success of clinical trials, contributing to the advancement of personalized medicine.
- ***Wearable Health Technologies*:** Federal backing for digital health has fueled the rise of AI-driven wearable devices. These devices provide personalized health insights and early warnings through real-time data, empowering individuals to control their health proactively (Shortliffe, 2019).

## AI Employment in Investigation of TNBC

Triple-NEGATIVE BREAST CANCER (TNBC) is an aggressive type of breast cancer that lacks the three main receptors (estrogen, progesterone and HER2), making it harder to treat. This case study explores the spread of cancer (metastasis) and survival rates in patients diagnosed with TNBC. Metastasis in TNBC Metastasis is when cancer cells move from the original tumor to other areas of the body. In TNBC, this process tends to happen more quickly compared to other breast cancer types. TNBC often spreads to distant organs like the lungs, liver and brain. Detecting metastasis early is crucial, as it greatly impacts a patient's chances of survival. Survival Rates in TNBC Patients TNBC patients generally have lower survival rates than those with other breast cancer types, due to the aggressive nature of the disease and limited treatment options. Early-stage TNBC can often be managed with surgery and chemotherapy, but once the cancer has spread to other parts of the body, treatment becomes more difficult. The five-year survival rate is relatively good for patients without metastasis but drops significantly if the cancer spreads. Factors Affecting Survival The survival of TNBC patients is influenced by factors such as the stage of cancer at diagnosis, the patient's age, overall health and how well they respond to treatment. Younger patients and those diagnosed earlier typically have better survival outcomes. Research and Treatment Advances Current research is focused on developing new treatments for TNBC, including immunotherapy and targeted therapies. These advancements aim to increase survival rates and reduce the risk of metastasis in those diagnosed with this aggressive cancer. In summary, TNBC is a challenging cancer to treat due to its aggressive nature and tendency to spread. However, ongoing research efforts involving AI offer hope for better treatment options and improved survival outcomes in the future (Cernea *et al*., 2019; Shortliffe, 2019).

## CONCLUSION

The integration of Artificial Intelligence (AI) into personalized medicine marks a monumental advancement in healthcare, offering extraordinary potential for customized treatment and enhanced patient outcomes. Through the application of advanced technologies such as genomic sequencing, bioinformatics and machine learning, AI significantly augments our capacity to interpret complex biological data and forecast individual responses to therapies. Moreover, the utilization of wearable health devices and Electronic Health Records (EHRs) provides a continuous influx of real-time data, further refining treatment strategies and enabling proactive care. Nevertheless, the adoption of AI in personalized medicine introduces formidable legal and ethical challenges. Critical issues related to data privacy, security and equitable access must be meticulously addressed to fully unlock the transformative potential of these technologies. The establishment of robust regulatory frameworks and the provision of thorough training for healthcare professionals are essential to navigating these challenges and ensuring the judicious application of AI. As this field continues to evolve, the collaboration among researchers, developers, regulators and clinicians will be essential in shaping the future trajectory of personalized medicine. By

achieving a balance between technological innovation and clinical expertise, we can usher in an era of healthcare that not only advances precision in treatment but also fosters a more equitable and effective healthcare system for all individuals.

## ACKNOWLEDGEMENT

The authors are thankful to Shri Vishnu College of Pharmacy, Bhimavaram for providing the necessary facilities.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## ABBREVIATIONS

**PMI:** Personalized Medicine Initiative; **EHR:** Electronic Health Records; **FDA:** Food and Drug Administration; **NIH:** National Institutes of Health; **HIPAA:** Health Insurance Portability and Accountability Act; **GINA:** Genetic Information Non-discrimination Act; **QPOP:** Quadratic Phenotypic Optimization Platform; **HLA:** Human Leukocyte Antigen; **TNBC:** Triple-Negative Breast Cancer; **IBM:** International Business Machines; **FDA:** Food and Drug Administration.

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**Cite this article:** Nori LP, Lohitha M, Vadapalli RR, Bonthagarala B, Nagineni SR, Kalidindi VR. Revolutionizing Healthcare: The Impact of AI on Precision Medicine. Int. J. Pharm. Investigation. 2025;15(2):334-43.

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https://www.jpionline.org

Review Article

# Review on Soluplus®: Pharmaceuticals Revolutionizing Drug Delivery and Formulation Strategies

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**ABSTRACT**

Solubility enhancers are one way to get around the difficulties with medication absorption and dissolution in oral drug delivery, since many novel active pharmaceutical components are not well soluble in water. The efficacy of a novel solubility-enhancing excipient (Soluplus) to enhance intestinal medication absorption. Improved drug release from poorly soluble pharmaceuticals can be achieved via polymer-based solid dispersions, such as Amorphous Solid Dispersions (ASD). Drug release and the rate of precipitation are directly influenced by the polymer concentration in dissolving fluid as well as the polymer and drug release occurring simultaneously. Investigating the polymer's release in addition to the drug's release is crucial, in addition to emphasizing the simultaneous measurement of both polymer and drug in the dissolution media, the goal of this critical systematic review was to provide an overview of the existing quantification techniques for commonly used water-soluble polymers, such as Soluplus®.

**Keywords:** Amorphous solid dispersions, Graft copolymer, Oral drug delivery soluplus, Polymer-based drug release, Solubility enhancers, Soluplus.

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**Received:** 09-10-2024;
**Revised:** 05-11-2024;
**Accepted:** 22-12-2024.

## INTRODUCTION

Soluplus is a trademarked name for a graft copolymer composed of Polyvinyl Acetate (PVAc), Polyethylene Glycol (PEG) and Polycaprolactone (PCL). This copolymer is primarily used as a carrier polymer in pharmaceutical formulations due to its unique properties, including its solubility in water, compatibility with a wide range of drugs and ability to enhance drug solubility and bioavailability. A commercial graft copolymer that belongs to the amphiphilic polymer class is called Soluplus. Because of its special qualities, it is frequently employed in biological and pharmacological applications. Vinyl caprolactam, vinyl acetate and Polyethylene Glycol (PEG) combine to form Soluplus, a copolymer. These monomers are copolymerized to produce a polymer that is both lipophilic (attractive to fat) and hydrophilic (attractive to water). A growing number of recently developed Active Pharmaceutical Ingredients (APIs) have strong lipophilic characteristics, which limits their oral bioavailability. The breakdown of medications that are not very water soluble in gastrointestinal media is the limiting stage for the drug's penetration and absorption through the intestinal system, according to the Biopharmaceutical Classification System (BCS). Consequently, the goal of many formulation attempts is to use surface-active excipients, which can function as both wetting agents and solubilizers, to increase drug solubility in physiological fluids. Utilizing cyclodextrin complexes or nanosizing are two further techniques for increasing oral medication solubility (BASF, 2010).

### Structure

Soluplus is synthesized by grafting PEG and PCL chains onto the PVAc backbone through covalent bonding, resulting in a copolymer with both hydrophilic and hydrophobic segments (Figure 1). This unique structure imparts amphiphilic properties to Soluplus, allowing it to interact with both water and lipids, which is advantageous for drug delivery applications.[2] See the polymer profile in Table 1.

Soluplus is an appealing carrier polymer for pharmaceutical formulations because of several of its attributes: (Figure 2). It is easier to formulate aqueous-based drug delivery systems, such as oral solutions, suspensions and emulsions, because Soluplus is soluble in water. This feature facilitates better patient compliance and ease of administration (BASF, 2010; Paaver *et al*, 2014).

### Applications

Soluplus has been extensively investigated and utilized in various pharmaceutical applications (Figure 3).

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**DOI:** 10.5530/ijpi.20250146

## Significance of SOL in improving the dissolution rate and bioavailability of poorly water-soluble drugs

Lipophilic APIs are more orally bioavailable when formulated with surface-active excipients such as cyclodextrin complexes or nanosizing. Solid solutions are made possible by hot melt extrusion with Soluplus, which enhances solubility in polymer matrices. This technique increases drug flow by dispersing medication molecularly, which upon disintegration forms supersaturated solutions. Soluplus considerably increases solubility in aqueous media, which may increase the oral bioavailability of poorly soluble medications. It is especially effective for BCS class II substances. Soluplus (SOL) plays a crucial role in improving the dissolution rate and bioavailability of poorly water-soluble drugs, addressing a significant challenge in pharmaceutical development. The incorporation of SOL into drug formulations enhances the solubility and dissolution kinetics of hydrophobic compounds, thereby improving their absorption and therapeutic efficacy (Kumari *et al*., 2023).

Several factors contribute to the significance of SOL (Figure 4):

## SOL - Based Formulation Strategies

### *Solid Dispersions (SDs)*

Solid dispersion enhances drug solubility and dissolution, crucial for improving bioavailability. However, its main drawback is the thermodynamic instability of amorphous pharmaceuticals, prone to recrystallization during storage, especially if residual crystalline drugs are present. Complete transformation of crystalline drugs into amorphous form is vital for stability and dissolution improvement. Modern solid dispersion focuses on glass solutions of poorly soluble compounds using amorphous carriers with high glass transition temperatures, ensuring enhanced physical stability and dissolution capacity.

Resveratrol is a very promising antioxidant drug candidate with low oral bioavailability due to its intrinsic poor water solubility, intestinal efflux and metabolization mechanisms. Resveratrol solubility high-throughput screening with different carriers was performed showing an enhancement above 2000-fold with Soluplus® and Tween® 80 (Figure 5). The former was selected as a carrier at the ratio of resveratrol: Soluplus® (1:2) (Kumari *et al*., 2023).

Mahbubur Rahman *et al*. (2020) examined the effects of Sodium Dodecyl Sulfate (SDS), Hydroxypropyl Cellulose (HPC) and Soluplus (Sol) on the release of Griseofulvin (GF) from Amorphous Solid Dispersions (ASDs). The ASDs included 2.5% GF, different HPC/Sol (2.5%-12.5%) and either 0.125% SDS or none. Due to their better miscibility, Sol-based ASDs displayed XRPD-amorphous GF, whereas HPC-based ASDs displayed crystalline GF. While HPC caused GF recrystallization, Sol alone showed only moderate supersaturation. Retaining Sol's inhibitory effect on recrystallization, SDS enhanced the wettability of Sol-based ASD without causing recrystallization. In GF-Sol-SDS ASDs, low SDS concentrations improved wettability without causing recrystallization. Higher supersaturation was correlated with increasing Sol loading; for example, after 30 min with 0.83% SDS, a 1:5:0.05 GF:Sol:SDS ASD retained ~500% GF supersaturation (~430%) (Rahman *et al*., 2020).

Liu *et al*. (2015) sought to improve a poorly water-soluble adjuvant's physicochemical characteristics and oral bioavailability using solid dispersion formulations. They considerably increased the rate of aprepitant dissolving by using Soluplus®. The persistence of the amorphous form was confirmed by XRD, DSC and SEM and FTIR revealed intermolecular hydrogen bonding between the aprepitant and Soluplus®. $AUC_{0-t}$ increased by 2.4 times as compared to aprepitant alone in rat pharmacokinetic trials, indicating improved solubility and bioavailability and absorption comparable to Emend®. With a potentially improved medication solubility and absorption, this effective method highlights the effectiveness of Soluplus® in solid dispersion formulation and characterization (Liu *et al*., 2015).

Shuyu Jia *et al*. (2022) investigated the usage of Soluplus (SOL) to improve Erlotinib (ERL) Solid Dispersions (SDs) and Microparticles (MPs) for drug dissolution. SOL inhibited crystallization while promoting ERL solubility. DSC, PXRD, SEM and FT-IR indicated that ERL MPs, which were created via bottom-up and solvent evaporation techniques, displayed metastable crystal form A, but ERL SDs stayed amorphous. More stability in ERL MPs was found by accelerated testing, which

**Table 1: Polymer Profile.**

| Parameter | Description |
|---|---|
| Structural Formula | PEG 6000/vinylcaprolactam/vinyl acetate 13/57/30. |
| Appearance | White to yellowish free flowing granules. |
| Molecular weight | Nominally in the range of 90 000-140 000 g/mol. |
| Critical Micelle Concentration | Micelles are typically 70-100 nm in diameter (pH 7 buffer). |
| HLB | Approximately ~14. |
| Solubility | It is soluble in water. Furthermore, it is soluble in acetone (up to 50%), methanol (up to 45%), ethanol (up to 25%), dimethylformamide (up to 50%) and in mixtures of (1:1 m/m) methanol/ acetone (up to 50%) and (1:1 m/m) ethanol/acetone (up to 45%). |
| Density | 1.082 g/cm$^3$. |
| Angle of Repose | 27.5° |
| Particle Size | Approximately 340 microns in diameter. |

provided insight into drug solubilization and post-recrystallization stability. The solubility of both formulations was greatly increased. Because SOL is hygroscopic, stability was affected differently in MPs and SDs, requiring specific tactics. Because of its ability to stop crystallization, SOL may be used as an MP stabilizer under the direction of its molecular interactions with the medication. The understanding of stabilizing amorphous and metastable drug states is improved by this work (Jia *et al.*, 2022).

## Nanosuspensions

Drugs in pharmaceutical nanosuspensions are insoluble drug particles dispersed in aqueous solutions at nanoscale, stabilized by surfactants. Nanoparticles, on the other hand, are lipid or polymeric colloidal drug carriers. The only choice available when a medication molecule has numerous drawbacks that prevent them from creating appropriate formulations, such as the inability to produce salt, huge molecular weight and dose, high log P and melting point, is the nanosuspension approach (Baumgartner *et al.*, 2016).

Different manufacturing procedures generate homogeneous particle sizes, which are primarily responsible for the submicron particle stability attained in the nanosuspension. Throughout their shelf life, nanosuspensions' particles must not fluctuate in size to prevent spontaneous crystal development. As a result, the Oswald ripening effect can prevent any crystal development by preventing the presence of variable saturation solubility by preserving the uniform particle size distribution (Patel and Agrawal, 2011).

Anjani, Qonita Kurnia *et al.* (2022) studied the use of Metronidazole (MTZ) Nanosuspensions (MTZ-NS) in dissolving Microarray Patches (MAPs) to treat Skin and Soft Tissue

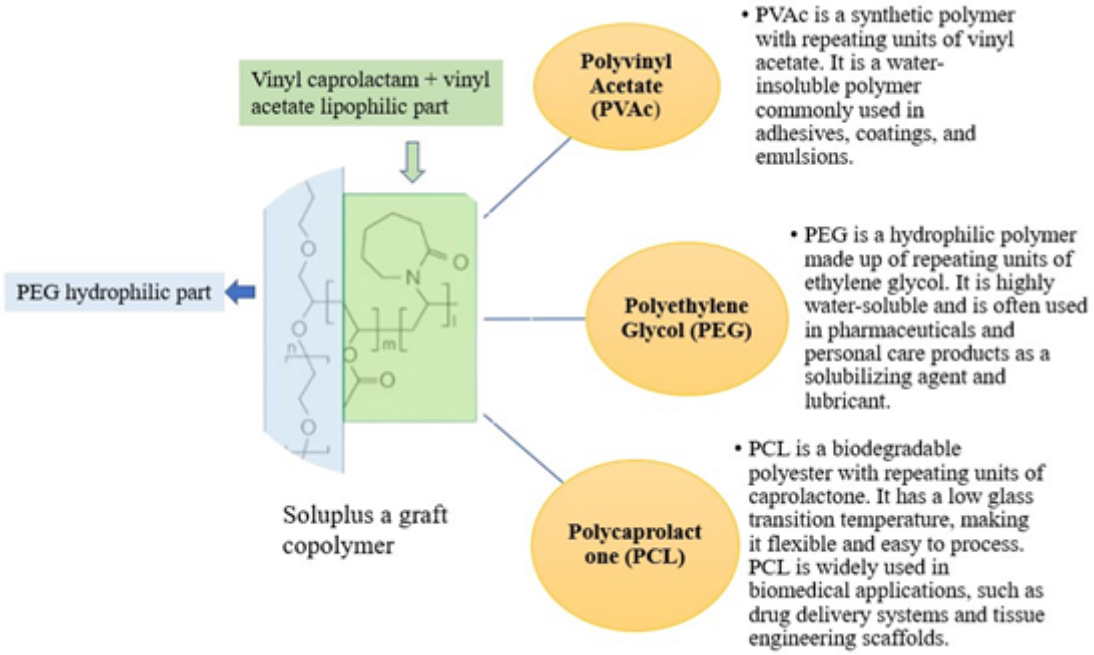


**Figure 1:** Structure of Soluplus with components.

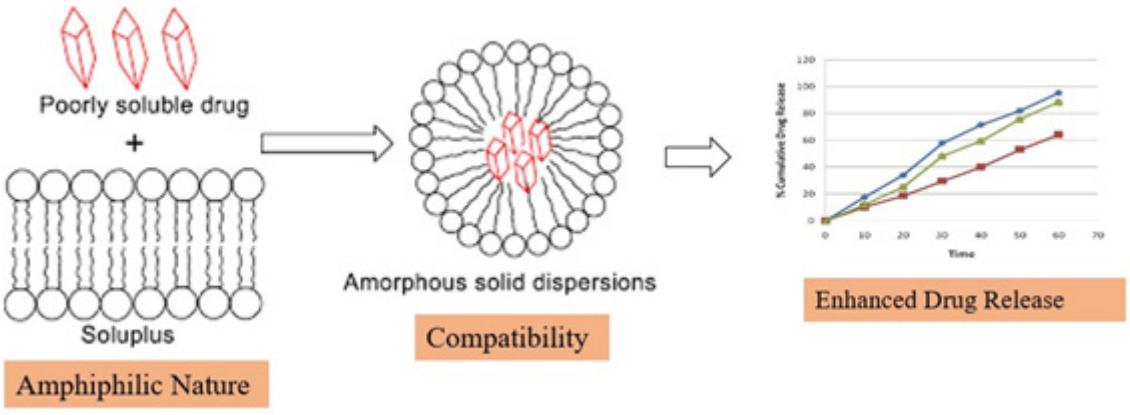


**Figure 2:** Soluplus feature.

Infections (SSTIs) caused by Bacteroides fragilis (Figure 6). The 115 nm particle size and 0.27 PDI of MTZ-NS was made possible by Soluplus®. The optimized MTZ-NS loaded MAPs completely reduced B. fragilis and exhibited no toxicity, achieving 95% skin penetration through all layers. Dermatokinetic studies on swine skin exhibited 95% transport efficiency across all layers over a 24 hr period, whereas biocompatibility testing on 3T3L1 cells showed low toxicity. Total bacterial inhibition was verified by agar plating experiments. By treating deeply embedded SSTIs with this innovative delivery system, less intrusive treatment options may be available, possibly eliminating the need for intravenous or oral antibiotics. *In vivo* efficacy studies ought to be a part of future research to its ability to treat in animal models (Anjani *et al*., 2022).

Itraconazole (ITZ) extrudates and nanosuspensions were compared *in vitro* and *in vivo* profiles by Keru Zhang *et al*. (2013). ITZ that was both amorphous and nanocrystalline was verified. *In vitro* release using amorphous ITZ/Soluplus demonstrated 100% release, whereas ITZ nanocrystals only achieved 40%. With a relative bioavailability of 98.3%, ITZ/Soluplus exhibited 6.9- and 11.6-fold greater $AUC_{(0-t)}$ and Cmax *in vivo* when compared to pure ITZ. Extrudates demonstrated a relative bioavailability of 101.3% and $AUC_{(0-t)}$ that were comparable to Sporanox®. There was stability for a minimum of three months. The study highlights increased amorphous ITZ/Soluplus solubility and bioavailability, with extrudates performing comparably to the commercial product and indicating potential as a stable substitute for improved ITZ oral delivery (Zhang *et al*., 2013).

Xing you Ye *et al*. (2016) presented a unique technique for creating Efavirenz (EFZ) Nanocrystal Solid Dispersions (NCSDs) by combining Hot-Melt Extrusion (HME) with High-Pressure Homogenization (HPH) (Figure 7). HPH first created a Nanosuspension (NS) using Kollidon® 30 and Sodium Lauryl Sulfate (SLS). The extruder barrel was then filled with Soluplus® and water was allowed to evaporate. By decreasing the size of EFZ particles, as demonstrated by zeta particle size analysis and scanning electron microscopy, this method increased the rate of dissolution. For six months, EFZ NCSD stability was guaranteed. This new strategy solves problems with traditional approaches and offers great opportunities to improve drug delivery systems (Ye *et al*., 2016).

Ramona Baumgartner *et al*., (2014) This paper introduces NANEX, a novel continuous process converting stabilized aqueous


**Figure 3:** Pharmaceutical applications of Soluplus.

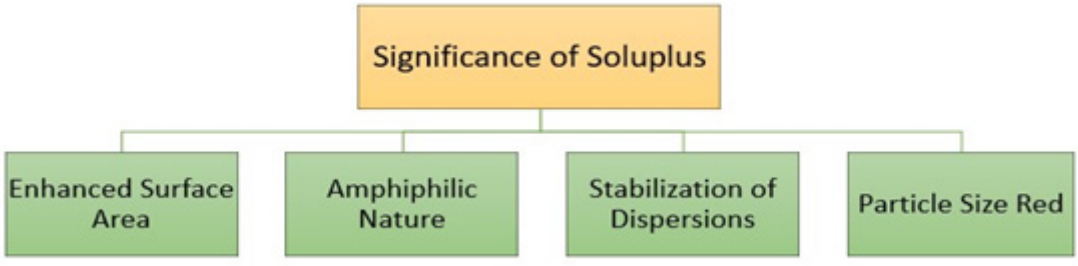


**Figure 4:** Significance of Soluplus.

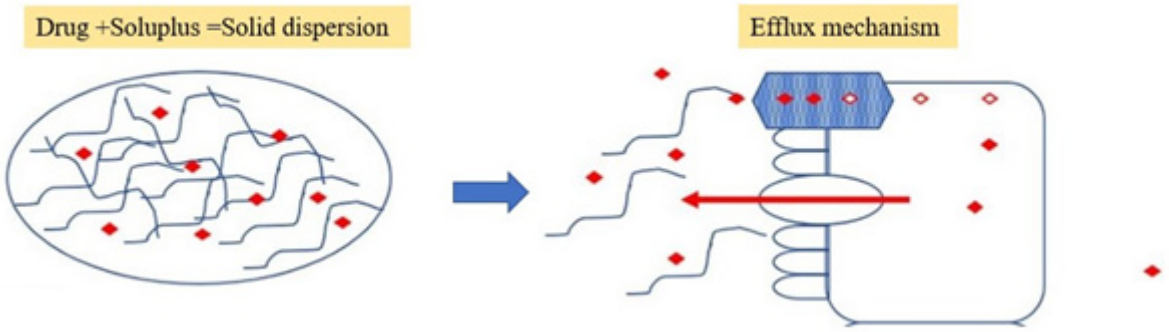


**Figure 5:** solid dispersion combining Soluplus enhances the oral bioavailability of resveratrol.

nano-suspensions into solid oral formulations in a single step, aiming to enhance drug solubility. Phenytoin nano-suspensions, stabilized with Tween® 80, were prepared via media milling. Using a hot melt extruder, the suspension was mixed with Soluplus® polymer, instantly removing water and dispersing nanocrystals in the molten polymer matrix. Transmission electron microscopy confirmed de-aggregated nanocrystals evenly dispersed in the extrudates, with no crystallinity changes observed. Dissolution studies demonstrated increased solubility of nano-crystalline phenytoin, regardless of the polymer used. This innovative approach offers a promising platform for designing advanced drug delivery systems to address challenges associated with drug stability, solubility and biological barrier crossing (Khinast *et al.*, 2013).

## Soluplus Mixed Nano micelles

The FDA's 2007 clearance of the paclitaxel micelle formulation Genexol®PM for the treatment of breast, ovarian and lung cancer highlights the growing interest in nanomicelles for a variety of diseases. Nanomicelles, which are made of amphiphilic polymers, self-assemble in water to create hydrophobic core-hydrophilic shell nanostructures that are larger than 20-200 nm. By insulating the drug from plasma components, this structure improves solubility, controlled drug release and *in vivo* circulation. Small particle size promotes barrier traversal and cellular absorption, extending circulation and preventing filtration. Together, these characteristics increase the bioavailability of drugs, indicating the potential of nanomicelles for improvements in diagnostics and therapy (Hwang *et al.*, 2020).

The study conducted by Ezequiel Bernabeu *et al.* (2016) aimed to increase the solubility of Paclitaxel (PTX) by creating mixed micelles using Soluplus® and TPGS. The results showed an increase of 38,000-fold in mixed micelles and 60,000-fold in pure Soluplus®. Stable release of PTX was shown by *in vitro* release investigations. In comparison to the PTX solution and single Soluplus® micelles, mixed micelles showed better anti-tumor activity against the cancer cell lines SKOV-3, MCF-7 and MDA-MB-231, along with increased cellular uptake. Via the induction of apoptosis by TPGS, blank mixed micelles produced cytotoxicity. Emphasizing their therapeutic potential, these results point to the potential of Soluplus®:TPGS mixed micelles as a promising nano-drug delivery method for cancer treatment (Bernabeu *et al.*, 2016).

Pervez *et al.* (2023) used Microneedles (MNs) and nanomicelles to improve the solubility and bioavailability of Glimepiride (GM) by Transdermal Drug Delivery (TDD) (Figure 8). The zeta potential of the 10% Soluplus® and 40% GM nanomicelles was -16.2 mV, resulting in a 250-fold improvement in solubility. Dissolving Microneedles (DMNs) loaded with GM demonstrated concentration-independent release by non-Fickian transport, guaranteeing mechanical stability and drug release. When compared to oral tablets, pharmacokinetic tests in healthy volunteers revealed better values (Cmax: 1.56 µg/mL, $T_{max}$: 4 hr, MRT: 40.04 hr). Microneedle shape, drug distribution and excipient compatibility were verified by SEM and FTIR. Studies conducted *in vivo* revealed sustained transdermal administration, which offers a novel approach to treating diabetes and promises improved glycemic control without side effects (Pervez *et al.*, 2023).

Paclitaxel hybrid nanomicelles were developed by Ling-Hui Dian *et al.* (2018) as an oral chemotherapy target for resistant breast cancer. Soluplus, TPGS1000 and DQA (molar ratio 1/0.8/0.4) were combined to create nanomicelles, which have a diameter of around 65 nm, through solvent evaporation and hydration (Figure 9). In drug-resistant breast cancer cells, they demonstrated improved cellular uptake and strong anticancer activity, causing death via protein regulation and mitochondrial co-localization. In mice with resistant breast cancer, oral delivery equalled intravenous taxol effectiveness, underscoring the critical function of soluplus. These results indicate that paclitaxel hybrid nanomicelles represent a viable oral chemotherapy option for patients with drug-resistant breast cancer, providing enhanced therapeutic results and convenience (Khong, 2011).

Yoshiki Kojo *et al.* (2017) investigated the use of Soluplus®-based Self-Micellizing Solid Dispersion (SMSD) in hypochlorhydric

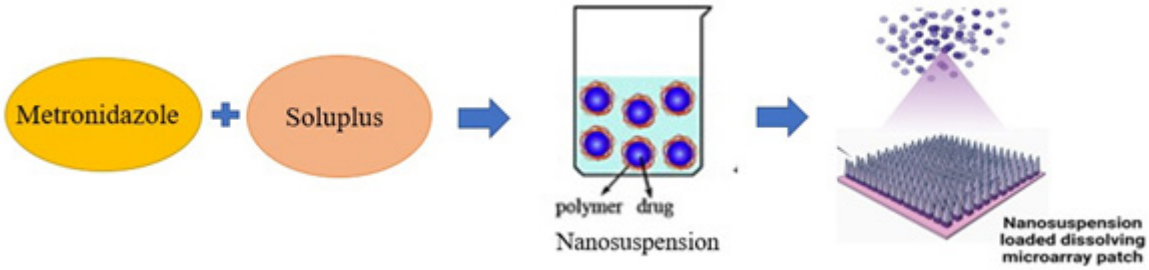


**Figure 6:** Metronidazole nanosuspensions in dissolving Microarray Patches (MAPs).

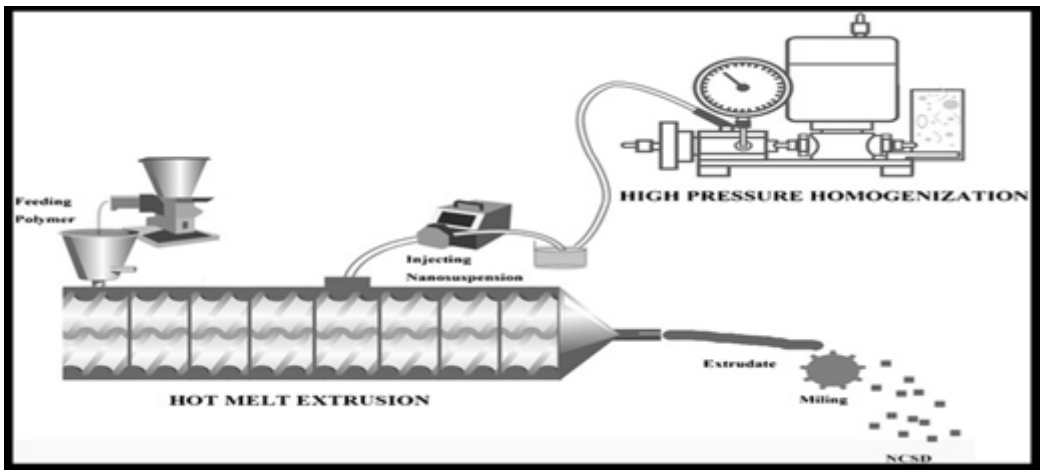


**Figure 7:** Hot-Melt Extrusion (HME) with high-pressure homogenization.

environments to improve oral absorption and Itraconazole (ITZ) dissolution. SMSD showed an amorphous shape, better dissolving at neutral and acidic pH and insignificant degradation under rapid storage; however, exposure to light increased degradation by around 33%, emphasizing the necessity of light protection during storage. Pharmacokinetic analyses showed that SMSD/ITZ had a far higher oral bioavailability than crystalline ITZ, with absolute bioavailability values in the hypochlorhydric model being 6.3% and in normal rats being 2.9%. The potential of SMSD to enhance drug absorption is highlighted in this study, which is especially helpful for those with hypochlorhydria (Kojo *et al.*, 2017).

Hongxue Shen *et al.*, (2018) A novel Genistein-Loaded Mixed Micelles (GEN-M) system composed of Soluplus® and TPGS was developed to address the poor solubility and bioavailability of genistein. The optimized GEN-M exhibited spherical morphology with a mean particle size of 184.7±2.8 nm and a narrow PDI of 0.162±0.002. It displayed high entrapment efficiency (97.12±2.11%) and drug loading (3.87±1.26%). GEN-M demonstrated sustained release behavior and increased the solubility of GEN in water to 1.53±0.04 mg/mL. Permeability across Caco-2 cell monolayers was enhanced and pharmacokinetic studies showed a 2.42-fold increase in relative oral bioavailability compared to free GEN. This novel nanomicelles system holds promise for delivering hydrophobic drugs efficiently (Shen *et al.*, 2018).

Jaleh Varshosaz *et.al* (2017) aimed to develop polymeric micelles loaded with Docetaxel (DCT) and Fe3O4 Magnetic Nanoparticles (MNPs) for targeted delivery. MNPs were prepared with oleic acid coating. The micelles were characterized for size, zeta potential, drug loading and release. Fe loading was determined by atomic absorption. Characterization included FT-IR, TGA, TEM and VSM. The optimized formulation had 70% drug loading, zeta potential of -2.58 mV and a size of 144.3 nm. Drug release efficiency at pH 5.5 was 68.9% in 24 hr. MNPs were coated and showed superparamagnetic properties. DCT-loaded micelles exhibited higher cytotoxicity against breast cancer cells compared to free drug, with no significant cytotoxicity on fibroblast cells (Varshosaz *et al.*, 2017).

## Self-Nanoemulsions

The study conducted by Tamer H. Hassan *et al.*, (2014) examined semisolid Self-Nanoemulsifying Drug Delivery Systems (SNEDDS) that comprised PEG-30-dipolyhydroxystearate, also known as Cithrol® DPHS, Capmul® MCM and Kolliphor® HS 15. Mixtures showed a hydrodynamic diameter of less than 25 nm, solidifying at ambient temperature and melting at body temperature. The stability of the dispersion was greatly affected by the DPHS:MCM ratio, with a 2:1 ratio being ideal for the size, dispersibility and stability of the nanoemulsion. The mono-modal volume distributions of formulas F2 and F3 have an average diameter of less than 25 nm. For *in vivo* performance,

the presence of excipients was established by 1H NMR. To evaluate the influence of biofate and digestibility, especially with medications that are poorly soluble in water, more research is necessary (Hassan *et al.*, 2014).

Han *et al.*, (2020) developed a precipitation inhibitor-based Self-Nanoemulsifying Drug Delivery System (PI-SNEDDS) using Soluplus and Poloxamer 407 to enhance the dissolution and oral bioavailability of pH-dependent soluble Carvedilol (CAR) (Figure 10). The PI-SNEDDS significantly increased CAR content in the oil phase of nanoemulsions in the stomach and inhibited subsequent precipitation in the intestine compared to CAR SNEDDS and tablets. Relative bioavailability of CAR PI-SNEDDS (397.41%) was 1.56-fold higher than CAR SNEDDS (254.09%). Preparation involved mixing the oil phase, surfactant and cosurfactant, dissolving CAR in the blank emulsion to form CAR SNEDDS, then adding precipitation inhibitors (PVP K30, PVP K90, HPMC E5, Poloxamer 407 and Soluplus) to obtain CAR PI-SNEDDS. This approach enhances drug dissolution and offers potential for improving oral bioavailability of poorly soluble drugs with pH-dependent solubility (Han *et al.*, 2020).

Hakan Nazlı *et al.* (2021) was to use Self-Nanoemulsifying Drug Delivery Systems (SNEDDS) to increase the water solubility of Aprepitant (APR). A number of formulations, including solid formulations using Soluplus® as a Polymeric Precipitation Inhibitor (PPI) and supersaturated (super-SNEDDS) and conventional SNEDDS, were developed. Neusilin® US2 was used as a porous carrier for solid formulations and optimization produced a combination of 20% Imwitor® 988, 60% Kolliphor® RH40 and 20% Transcutol® P. Improved solubility and dissolving rate of APR were found during characterization and Soluplus® played a critical role in avoiding drug precipitation. These SNEDDS formulations demonstrate the efficacy of lipid-based drug administration and show promise as a substitute for micronized APR or commercialized capsules (Nazlı *et al.*, 2021).

Three different nanocarriers loaded with lidocaine were characterized by Aikaterini Lalatsa *et al.* (2016). Customized Franz cells were utilized for diffusion tests via cellulose membranes. Among the nanocarriers were Polymeric Micelles (PMs) (Soluplus), solid lipid nanoparticles (SLNs) (Tripalmitin: Lecithin: Labrasol: polysorbate-20: water; 3.33:1:40:1:4.67 w/w) and Self-Nanoemulsifying Drug Delivery Systems (SNEDDS) (Capryol-90: Transcutol: Labrasol; 1:3:6 w/w). Zeta-potential, size and form of the particles were all described. At a significance threshold of $p<0.05$, the study used one-way Analysis of Variance (ANOVA) in conjunction with post hoc Tukey's tests to assess permeation differences. With an eye toward future eyelid surgery, the purpose of this work was to explore the viability of delivering

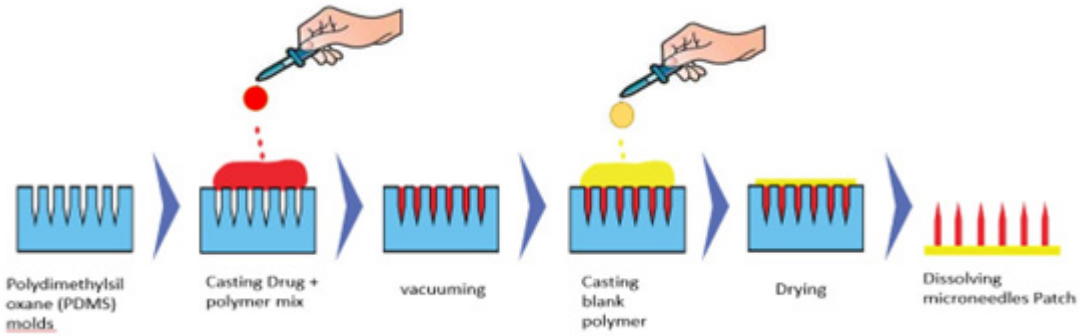


**Figure 8:** Microneedles patch preparation.

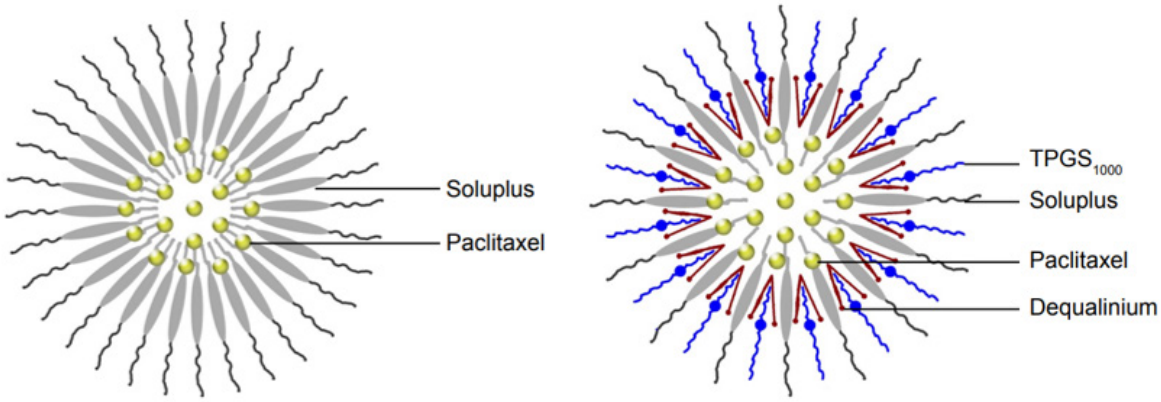


**Figure 9:** Hybrid nanomicelles.

lidocaine via nanotechnology across an artificial skin equivalent. Solid Lipid Nanoparticles (SLNs), Soluplus®-based Polymeric Micelles (PMs) and other lidocaine-loaded nanocarriers (Lalatsa *et al*., 2016).

## Drug Formulation Strategies with SOL

### *Hot-Melt Extrusion Technique*

Hot-Melt Extrusion (HME) is a continuous manufacturing process used in the pharmaceutical industry for the preparation of solid dosage forms. In HME, (see Figure 11) a blend of drug, polymer (such as Soluplus), plasticizers and other excipients is fed into the extruder, where it is subjected to controlled heating and mixing. The heat softens the components, forming a molten mass that is forced through a die to obtain a desired shape, such as pellets, granules, or extrudates. As the material exits the die, it undergoes cooling and solidification, resulting in the formation of solid dosage forms with uniform drug distribution and controlled release properties. HME offers several advantages over conventional manufacturing methods, including improved product quality, reduced manufacturing costs, enhanced process efficiency and scalability (Patil *et al*., 2016; Repka *et al*., 2008).

## Advantages of Using Hot-Melt Extrusion in Soluplus-Based Formulations

There are benefits to using Soluplus in Hot-Melt Extrusion (HME) for pharmaceutical applications. It makes it possible to create Amorphous Solid Dispersions (ASDs) with medications that are not very soluble in water, which improves the drug's solubility and rate of dissolution for increased bioavailability. HME ensures uniform dispersion within the polymer matrix by fostering close drug-polymer interactions. This technique makes it easier to incorporate Soluplus into different dosage forms, giving pharmacists exact control over the kinetics of drug release and loading in tablets, capsules and films. The continuous process of HME guarantees effective and consistent production at an industrial level, which is why pharmaceutical manufacture uses it. To summarize, HME offers a flexible and effective method for Soluplus-based formulations, resolving issues with poorly water-soluble medications and improving drug performance (Li *et al*., 2024).

In their 2015 study, Ritesh Fule *et al.* sought to improve the solubility and dissolution rates of Artesunate (ARS) by generating Solid Solutions (SSL) with Kollidon VA64 (VA64) or Soluplus (SOL) in addition to surfactants or plasticizers. The uniform distribution and amorphous drug states were validated by analytical methods. With F1 SSL (Soluplus-based) having 66.44 times higher $AUC_{(0\text{-}72)}$ and 16.60 times higher $C_{max}$ and K1 SSL (Kollidon VA64-based) having 62.20 times higher $AUC_{(0\text{-}72)}$ and 13.40 times higher $C_{max}$ than pure ARS, SSL formulations showed significantly quicker ARS release than pure ARS (Fule *et al*., 2013).

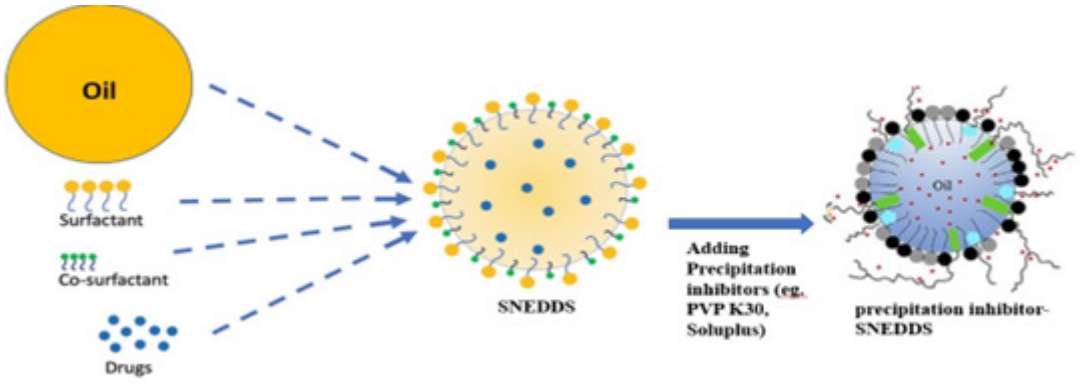


**Figure 10:** Precipitation inhibitor-based Self-Nanoemulsifying Drug Delivery System (PI-SNEDDS).

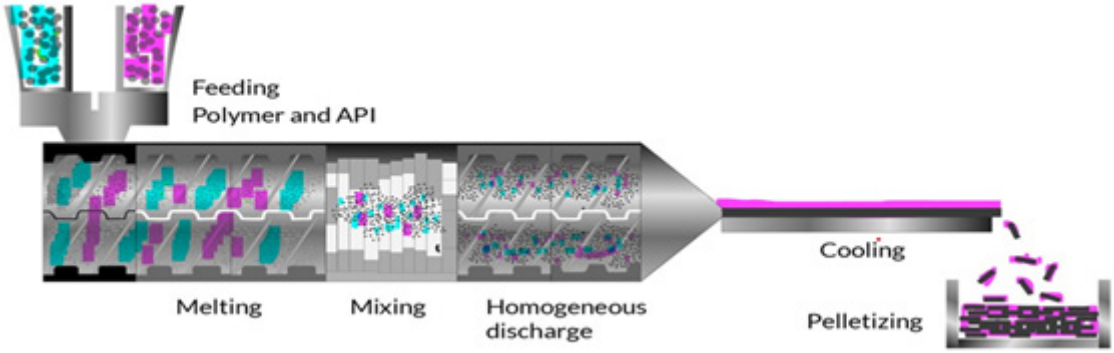


**Figure 11:** Hot Melt Extrusion Process.

Saad M. Alshahrani *et al.* (2015) investigated the use of a unique combination of Soluplus® and Hypromellose Acetate Succinate (HPMCAS-HF) polymers in Hot-Melt Extrusion (HME) to improve the solubility and stability of Carbamazepine (CBZ) in amorphous solid dispersions. A range of Soluplus® and HPMCAS-HF ratios were used to produce the best CBZ dissolving rates, which showed full miscibility and 40% drug loading. By using FTIR spectroscopy, DSC, XRD and dissolution investigations, characterization verified the production of an amorphous solid dispersion. With Soluplus® as the main matrix polymer, especially at 7-21% (w/w) HPMCAS-HF, favorable results, such as increased drug loading and release, were noted. A year of stability under severe conditions was demonstrated by the polymer mix, indicating its promise for stable formulations with enhanced release profiles and solubility through HME (Alshahrani *et al.*, 2015).

Jelena Djuris *et al.* (2013) investigated the viability of using Hot-Melt Extrusion (HME) to create solid dispersions of Carbamazepine (CBZ) in the copolymer (Soluplus®) grafted with polyethylene glycol, polyvinyl caprolactam and polyvinyl acetate. Differential Scanning Calorimetry (DSC), ATR-FTIR spectroscopy, Thermogravimetric Analysis (TGA) and Hot Stage Microscopy (HSM) were used to evaluate miscibility. Soluplus® and plasticizer-free HME of CBZ were able to produce microcrystalline dispersion at greater levels of molecular dispersion, up to 5% w/w CBZ. The temperature at which the extrusion was carried out had an impact on dispersion; higher temperatures promoted both molecule dispersion and the creation of CBZ form I. These results provide credence to the optimization of HME processes by thermodynamic model use (Djuris *et al.*, 2013).

## Nano extrusion

Nanoextrusion, a variation of Hot-Melt Extrusion (HME), offers superior advantages in Soluplus (SOL)-based formulations due to its ability to produce nanoscale drug delivery systems. Nanoextrusion enables precise control over particle size, morphology and drug distribution, resulting in enhanced drug solubility, dissolution rate and bioavailability. By reducing drug particle size to the nanometer range, nanoextrusion maximizes drug surface area, facilitating rapid dissolution and absorption. Moreover, nanoextrusion promotes homogeneous drug-polymer interactions, ensuring uniform dispersion and stability of SOL-based nanoparticles. This enables tailored drug release profiles and improved therapeutic outcomes, making nanoextrusion a superior choice for SOL-based formulations (Khinast, *et al.*, 2013).

Grizeofulvin (GF) extrudates were made by means of nanoextrusion with HPC and Soluplus® polymers: micro/nanocomposites with crystalline GF in HPC and amorphous GF in Soluplus® (ASD). The wet medium milling process's GF particle size had an impact on composites' dissolution. Since GF in HPC degrades more quickly and is enhanced in wettability more than GF nanocrystals, amorphous GF in Soluplus® dissolves more slowly than GF nanocrystals. ASD used high medication dosages to produce higher supersaturation. Fast-dissolving HPC-based nanocomposites and Soluplus®-based ASDs may enhance the solubility of low-dose BCS Class II drugs (Li *et al.*, 2021).

Meng Li *et al.* (2017) looked at how the size of the polymeric matrix and the drug particle affected the drug's inability to dissolve griseofulvin extrudates, a medication that is not very water soluble. Using Soluplus® stabilized wet-milled solutions and Hydroxypropyl Cellulose (HPC), nanoextrusion generated extrudates that were then dried and pulverized. In example, amorphous medicines with smaller extrudate particles showed delayed release from Soluplus®-based Amorphous Solid Dispersions (ASDs). Particle size effects were not as noticeable in nano/microcomposites using HPC. The investigation illustrated the impact of temperature-regulated regions with different polymer-drug ratios during the extrusion process. Increasing drug solubility using nanoextrusion is a promising approach that

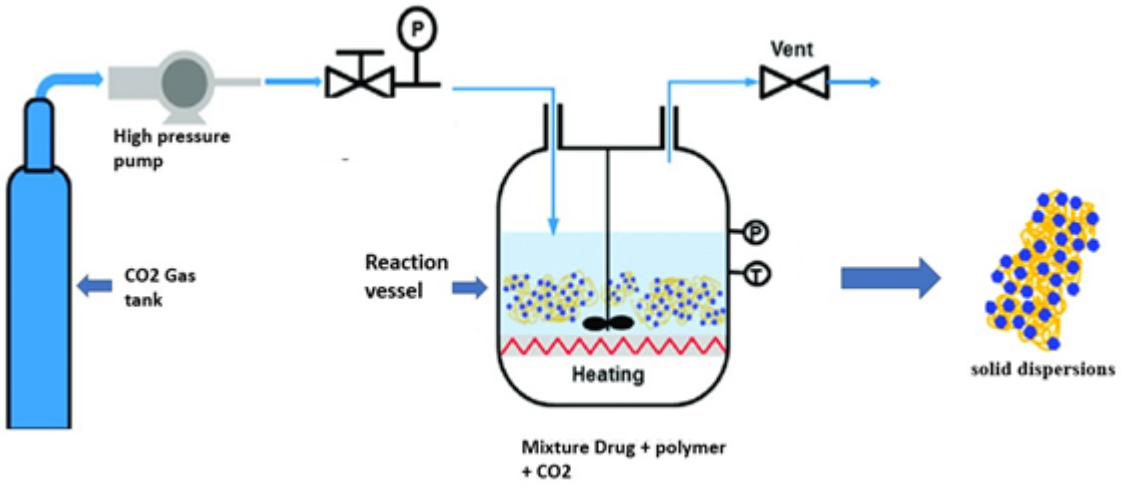


**Figure 12:** Supercritical Fluid Processing.

highlights the role of particle size and matrix composition on drug release kinetics (Li *et al*., 2017).

Stoja Milovanovic *et al*., (2022) This study specifically addresses the pharmaceutical sector and concentrates on producing novel materials using environmentally friendly methods. The potential application of supercritical $CO_2$ ($scCO_2$), both alone and in combination with the cardiovascular drug carvedilol, is being studied in the manufacturing of medical polymers such as Eudragit®, Soluplus® and hydroxypropyl methylcellulose acetate succinate. Solvent-free polymeric foams and Carvedilol solid dispersions with a controlled microstructure and pore width (101-257 μm) suitable for pharmaceutical applications were created in two hours at 30 MPa and 100°C using a single-step static $scCO_2$ technique. The $scCO_2$ treatment had no effect on the polymer composition of the post-processing foams. Carvedilol dispersed molecularly and changed from a crystalline to an amorphous state in the solid dispersions because of hydrogen bonds it established with the polymers. Carvedilol dissolution from these solid dispersions was well-represented by the Korsmeyer-Peppas model, which demonstrated a markedly increased dissolution rate in acidic conditions. All things considered, the high-pressure technique that uses $scCO_2$ appears to have potential for increasing drug dissolving rates and producing customized pharmaceutical materials (Milovanovicć and Lukić, 2022).

K. Eggenreich *et al*. sought to streamline the tablet production process in their 2016 work by employing Injection Molding (IM) straight from primary powder to create solid-dispersion-based tablets with fenofibrate as the model API. The graft co-polymer matrix approach and state-of-the-art IM equipment were employed to manufacture and characterize tablets both chemically and physically. The 10%, 20% and 30% (w/w) fenofibrate found in both powder- and pellet-based IM tablets showed consistent drug dispersion across formulations. Regardless of the processing method, a constant 60% drug release was seen after 120 min for both kinds of tablets. This work shows that it is possible to make tablets from compounded primary material that contain both fenofibrate and a solid dispersion base via IM, especially for formulations where the drug loading is less than 10%. These results are a first step in improving the efficiency of tablet production procedures (Eggenreich *et al*., 2016).

## Supercritical Fluid Processing

Soluplus (SOL) improves the solubility and dispersion of weakly water-soluble pharmaceuticals, showing potential in supercritical fluid processing (Figure 12). Its ability to interact with supercritical fluids and medicinal molecules facilitates homogenous particle formation and drug solubilization. By adjusting parameters, Soluplus provides control over medication release kinetics, particle size and shape, enabling customized formulations. However, depending on the drug and processing circumstances, effectiveness may differ; therefore, optimization for the optimum drug loading and release profiles is required. Overall, Soluplus advances medication delivery applications by improving yield and efficiency in supercritical fluid-based processes such as Supercritical Antisolvent Precipitation (SAS) and Supercritical Fluid Extraction (SFE) (Misra and Pathak, 2020).

To accelerate the rate of dissolution of Simvastatin (SIM), Uttom Nandi *et al*. (2021) used Supercritical Carbon Dioxide ($scCO_2$) to prepare SIM Solid Dispersions (SDs) with Soluplus® (SOL). Despite the crystallinity of SIM, amorphous SDs were revealed via physicochemical investigation (XRD, DSC, ATR-FTIR, SEM) when different SIM-SOL ratios (10%, 20% and 30%) were investigated. The results of the dissolution trials showed that SIM-SOL SDs displayed significantly higher rates of full release within 45 min when compared to physical mixtures. For medications that are sensitive to temperature, our solvent-free approach improved solubility without sacrificing stability, even at greater SIM loadings. An effective method for creating amorphous SDs is the $scCO_2$-based approach, particularly when combined with supercritical fluid and Soluplus procedures (Nandi *et al*., 2021).

Rana M. Obaidat *et al*. (2017) looked at the use of Supercritical Fluid Technology (SFT) for solid dispersions to improve the solubility

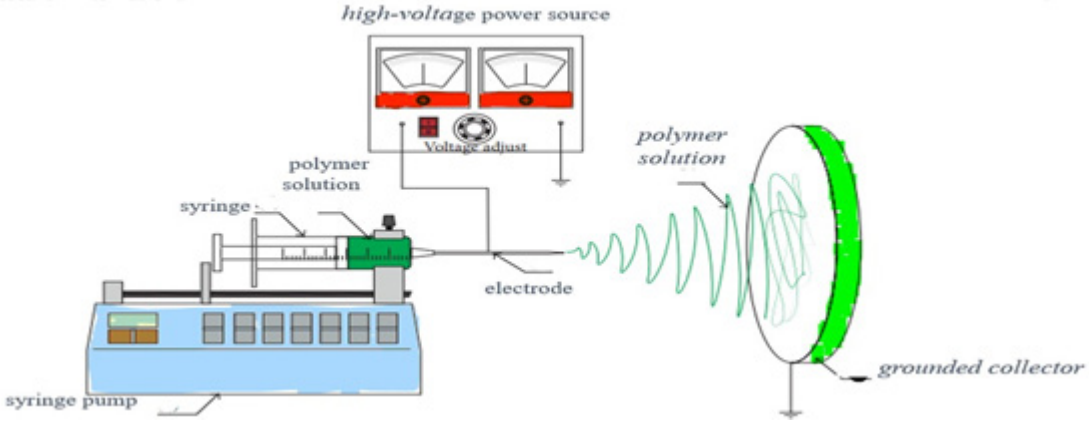


**Figure 13:** illustrates the use of an electrospinning apparatus.

of tacrolimus, an immunosuppressant with low bioavailability. A variety of polymers were used, such as porous chitosan, PVP, Soluplus and HPMC. Chitosan, HPMC and PVP were added together with TPGS surfactant. The Loading Efficiency (LE) and dissolution of Soluplus dispersions were adjusted for processing parameters (time, temperature and pressure). *In vitro* release tests, DSC, XRD, FTIR and SEM were all used in the physicochemical analysis. After three months of stability testing, release profiles improved, with Soluplus achieving a cumulative release of 98.76% in just 24 hr. All dispersions, except for those based on chitosan, had amorphous drug precipitation. After a month, PVP formulations including TPGS displayed recrystallization, demonstrating the considerable impact of processing conditions on dispersion properties (Obaidat *et al*., 2017).

Catherine Potter *et al*., (2015) explores Supercritical Fluid Impregnation (SFI) and Hot Melt Extrusion (HME) for producing Amorphous Solid Dispersions (ASDs) of Indomethacin (INM). Both methods avoid toxic solvents and achieve lower temperatures than HME. INM dispersions at 50% w/w loading were amorphous via HME and 30% w/w via SFI. SFI showed γ-INM crystallinity, unlike HME. INM-PVP formulations exhibited higher dissolution rates, with PVP enhancing solubility 4-4.5 times over crystalline state compared to 2 times for Soluplus. HME produced more homogeneous dispersions, while SFI had challenges with high-viscosity polymers without surfactants. SFI formulations with Soluplus showed similar amorphous stability to HME. HME offers high throughput, but SFI is promising for thermally labile compounds or high Tg polymers. Different processing methods suit different drug formulations. Overall, considering multiple methods for poorly soluble drug formulations is essential for optimal outcomes (Potter *et al*., 2015).

## Electrospinning

Electrospinning is a versatile technique used to produce nanofibrous materials from polymer solutions or melts. In this process, a high voltage is applied to a polymer solution or melts, causing the formation of a charged jet that is stretched and elongated as it travels towards a collector (Figure 13). The solvent evaporates during flight, leaving behind ultrafine fibers with diameters ranging from nanometers to micrometers. Electrospun nanofibers offer a high surface area-to-volume ratio and a porous structure, making them suitable for various applications such as drug delivery, tissue engineering, filtration and wound dressing. The morphology and properties of electrospun fibers can be tailored by adjusting parameters such as polymer concentration, solution viscosity, applied voltage and collector configuration. Despite its versatility, electrospinning has limitations such as low production rates, difficulty in scaling up and potential polymer degradation during processing (Xue *et al*., 2019).

Urve Paaver *et al*. (2014) used the synthetic graft copolymer Soluplus (PCL-PVAc-PEG) to study electrospun nanofibrous Drug Delivery Systems (DDSs) loaded with Piroxicam (PRX). Upon examination using Raman spectroscopy, X-ray powder diffraction, differential scanning calorimetry and scanning electron microscopy, circular nanofibers with diameters varying between 500 nm and 2 µm were identified. Inside the nanofibers, PRX stayed amorphous. These DDSs showed consistent, extended PRX release that was appropriate for wound healing treatment. To produce stable DDSs for poorly water-soluble drugs like PRX, the study proposes electrospinning using Soluplus. This technique may find use in advanced wound healing formulations (Paaver *et al*, 2014).

Using electrospinning, Olivera Kaljević *et al.* (2017) methodically produced Soluplus nanofibers laden with carvedilol. A miscibility investigation showed that carvedilol and Soluplus were compatible. Acetone: chloroform (90:10; w/w) as a solvent combination improved electrospinning. At lower drug concentrations, smooth nanofibers with fewer beads were observed using scanning electron microscopy. Through differential scanning calorimetry, it was determined that carvingilol had taken on an amorphous state within the nanofibers. Carvedilol and Soluplus interacted, as seen by the infrared spectra. In contrast to 20% from pure material, almost 85% of the drug was released in 15 min during dissolution studies. This technique demonstrates how studies of miscibility and solubility deal with weakly water-soluble drug dissolution (Kaljević *et al*., 2017).

Ahmad Salawi *et al.* (2018) used solvent casting to examine the effect of vitamin E as a plasticizer on Soluplus® films. Various amounts of vitamin E (0-75% w/w) were used to cast the films. Reduced tensile strength and Young's modulus, together with greater flexibility and higher elongation, were the results of the texture examination. Vitamin E improved Soluplus® compatibility by decreasing film crystallinity. Increased water contact angle and reduced swelling were indicative of improved hydrophobicity and adhesion with higher vitamin E concentration. While films with ≥65% may function as pressure-sensitive adhesive films, those with 30-50% vitamin E demonstrated great pliability. Using mixes of vitamin E and Soluplus®, this study suggests customized mechanical and adhesive qualities for flexible film compositions (Salawi and Nazzal, 2018).

The process of electrospinning nanofibrous DDSs. Figure 13 illustrates the electrospinning apparatus and experimental conditions utilized in the creation of the nanofibrous DDSs.

Suyeong Nam *et al*., (2017) An electrospinning technique was used to create a Poly (Vinyl Alcohol) (PVA) and Soluplus (SP)-based Nanofiber (NF) mat that would be used to administer Angelica Gigas Nakai (AGN) extract (ext) to oral malignancies. Electrospinning was used to construct AGN/SP NF (mean diameter: 75±26 nm; entrapment efficiency: 84.6±18.6%) and AGN/PVA/SP NF (mean diameter: 170±35 nm; entrapment efficiency: 81.0±10.1%). X-ray Diffractometry (XRD) analysis

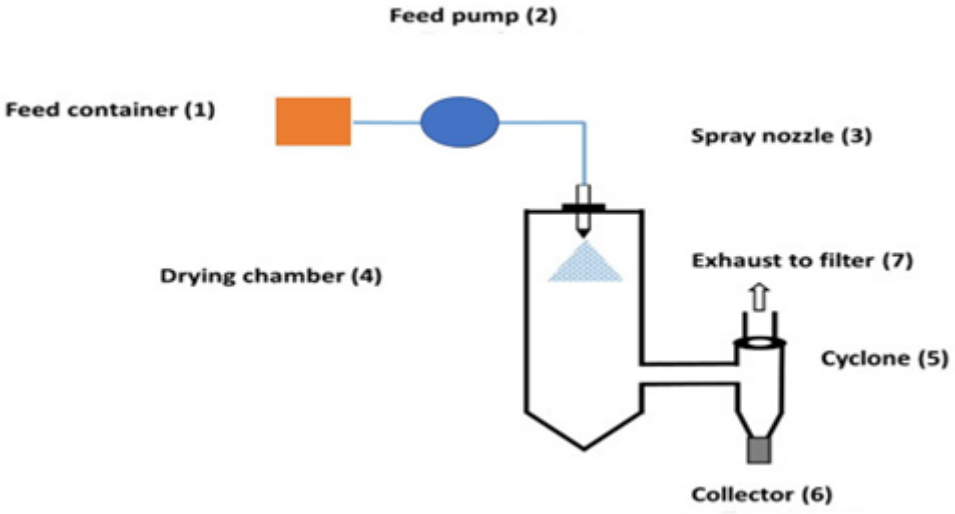


**Figure 14:** Spray-drying.

was used to confirm that AGN EtOH ext had become amorphous throughout the electrospinning procedure used to create NF structures. When compared to the AGN/PVA NF group, the AGN/PVA/SP NF group demonstrated faster disintegration (within 3 min) and quick wetting (within 2 sec), ensuring the successful and traditional administration of AGN/PVA/SP NF film in the oral cavity without the need for beverage consumption (Nam *et al*., 2017).

Zsombor K Nagy *et al*. (2012) improved the solubility of spironolactone by using Soluplus® as a carrier and solubilizer. To make solid solutions, extrusion and Electrospinning (ES) techniques were used. Particularly in ES-generated fibers, Raman microscopy showed negligible crystalline spironolactone. Better dissolving and a larger surface area were produced by ES as opposed to extrusion. Effective amorphization and solid solution production were enhanced by ES, especially once the process was refined. These results demonstrate the potential of ES and extrusion to enhance the solubility of pharmaceuticals that are not very soluble in water, providing pharmaceutical formulations with promising solutions (Nagy *et al*., 2012).

In their 2018 study, Eniko Borbas *et al*. investigated size-exclusion membranes as a potential lipid membrane replacement for Amorphous Solid Dispersions (ASDs). Soluplus and Vinylpyrrolidone-vinyl acetate copolymer (PVPVA64) ASDs loaded with carvedilol were electrospun. The study assessed the load-dependent effects of additives on cellulose membrane regeneration and permeation using a µFLUX diffusion cell. The Supersaturation Ratio (SSR) drove membrane transit by representing the dissolution of medicine in relation to its solubility. Polymer additives demonstrated comparable membrane transport behavior despite different methods. This proposes size-exclusion membranes as workable substitutes for lipid membranes in formulations for ASD, helping to improve medication solubility and bioavailability (Borbás *et al*., 2018).

Polyvinylpyrrolidone (PVP) was used in the Formulations of Fenofibrate (FF) Electrospun (ES) nanofiber compositions by Peter Belton *et al*. (2021) to improve physical stability. High humidity did not stabilize FF-PVP ES dispersions, despite their propensity to increase drug solubility. PVP was used in conjunction with Eudragit E, Soluplus and Hypromellose Acetate Succinate (HPMCAS) to address moisture sorption problems. According to miscibility tests, phase separation is influenced by FF's compatibility with Eudragit E and Soluplus over PVP and HPMCAS. While PVP-Eudragit E maintained its ability to increase disintegration, PVP-Soluplus reduced the release of the medication. Phase separation led to formulation deformation in polymer blends, but it also decreased water absorption. With a focus on phase separation and polymer miscibility's roles in ES nanofiber formulation stability and dissolution enhancement, our findings inform the creation of balanced drug delivery systems (Tipduangta *et al*., 2021).

The solubility and dissolution enhancement of lovastatin were studied by Sasa Kajdic *et al*. (2020) using poloxamer 188/poly (ethylene oxide) and Soluplus/poly(ethylene oxide) nanofibers. Lower starting concentrations and different nanofiber morphologies were the results of lovastatin's breakdown during electrospinning. To increase lovastatin's chemical stability within the nanofibers, antioxidants were added. With no crystalline lovastatin visible, Soluplus-based nanofibers had the best rate of lovastatin dissolving and solubility, suggesting enhanced drug release. In an expedited stability examination, poloxamer-based nanofibers including antioxidants showed improved lovastatin stability, while soluplus-based nanofibers showed only marginal lovastatin retention. For formulation stability, appropriate packaging and storage conditions are essential. Antioxidant-enriched Soluplus-based nanofibers present a viable method for improving the solubility and dissolution rates of chemically unstable and poorly soluble medications such as lovastatin (Kajdič *et al*., 2020).

Borbas E *et al.* (2016) used solvent-based electrospinning to assess the effects of formulation additives on meloxicam dissolution, supersaturation and membrane transport. Soluplus, 2-hydroxypropyl)-β-cyclodextrin and Polyvinylpyrrolidone (PVP) derivatives (K30, K90, VA 64) were used as solubilizing agents to generate five Amorphous Solid Dispersions (ASDs). While the dissolving characteristics of the formulations were similar, the formulations that included Soluplus showed better flow. The study created a mathematical model based on Fick's first rule and showed how important it is to take supersaturation gradients into account when optimizing drug delivery methods for APIs that are poorly soluble in water (Borbás *et al.*, 2016).

## Spray-Drying

Spray-drying is a widely used technique for converting liquid formulations into dry powders by atomizing the feed solution into droplets and drying them rapidly in a heated chamber. The droplets are dispersed in a hot gas stream, where solvent evaporation occurs, resulting in the formation of solid particles (Figure 14). Spray-drying offers several advantages, including high efficiency, reproducibility and scalability. It is commonly employed in the pharmaceutical industry to produce inhalable powders, solid dispersions and amorphous formulations. The process parameters such as inlet temperature, feed rate and atomization pressure can be adjusted to control particle size, morphology and drug encapsulation efficiency. Despite its widespread use, spray-drying may lead to issues such as particle aggregation, loss of bioactivity and residual solvent content in the final product (Santos *et al.*, 2017).

Lucas *et al.* (2022) explored the use of Spray Freeze Drying (SFD) to create amorphous celecoxib spheres that would improve solubility. Stable porous particles were produced by freeze-drying tertiary butyl alcohol solutions of celecoxib with excipients (povidone, HPMC-AS, Soluplus®). The amorphous form of celecoxib was verified by XRPD research. Kollidon 25 and HPMC-AS combinations demonstrated better drug concentrations and rates of dissolution; lower $T_{max}$ values suggested faster *in vivo* drug absorption. AUC values continued to be like formulations that were amorphous. SFD particles' high porosity allowed for quick disintegration and absorption, providing a viable method to improve the oral bioavailability of weakly water-soluble drugs like celecoxib (Lucas *et al.*, 2022).

Desai *et al.* (2023) investigated the use of Soluplus or Kollicoat IR in solid dispersion to increase the solubility and bioavailability of Arteether (ART), a BCS class II antimalarial with limited oral bioavailability. Three solvent-based methods were used: aqueous freeze-drying, hydro-alcoholic spray drying and ethanol rotary evaporation. The ART-polymer miscibility was enhanced by a 4-6% increase in polymer content. The maximum ART saturation solubility (476.01 mg/L with Soluplus) was obtained by spray drying. The formulations that were spray-dried demonstrated exceptional flow properties (Carr index: 21.27) and accomplished 88.88% drug release in a pH 6.8 buffer. As a carrier, Soluplus fared better than Kollicoat IR, producing a stable, somewhat amorphous ART solid dispersion with improved oral bioavailability (Desai and Chatterjee, 2023).

Koch *et al.* (2020) used three methods to increase the solubility of Cannabidiol (CBD). While amorphous CBD was more soluble and dissolved more quickly than its crystalline counterpart, it was also more prone to recrystallization. Using water-soluble polymers (Kollidon® VA64, Kollidon® 12PF, Soluplus®), mesoporous silicas (Silsol®, Syloid® AL-1FP) and cyclodextrins (CH3αCD, HPβCD, HPγCD) by freeze-drying, spray-drying, subcritical CO2 impregnation, or hot-melt extrusion, full amorphous CBD was obtained. Formulations including cyclodextrin and CBD showed notable improvements in solubility, especially when freeze- or spray-dried. Among water-soluble polymers, Kollidon® VA64 demonstrated the largest solubility increase. For at least two

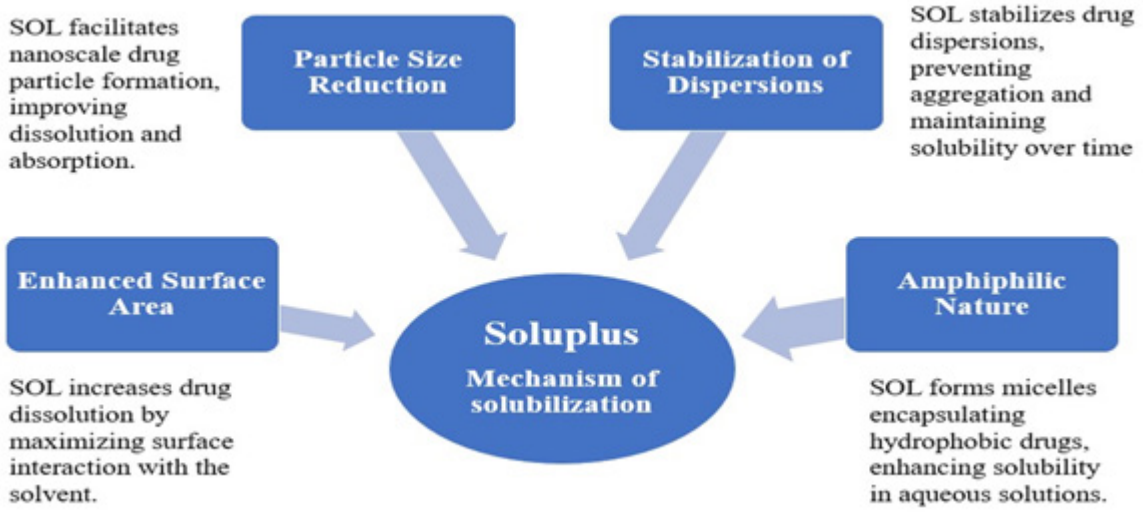


**Figure 15:** Soluplus-Mechanism of solubilization.

months, the majority of formulations remained stable, providing important information on the potential medical uses of CBD (Koch *et al.*, 2020).

## Freeze-Drying

Freeze-drying, also known as lyophilization, is a low-temperature dehydration technique that involves freezing and then vacuum-removing the solvent. It maintains the structure and activity of meals, medications and biomolecules by stabilizing them. Superior stability, extended shelf life and preserved bioactivity are among the benefits. It consists of desorption (secondary drying), freezing and primary drying (sublimation). Ice crystals are directly sublimated during primary drying and any remaining moisture is removed during secondary drying. The end products include low density, good reconstitution characteristics and have a porous structure. Notwithstanding its advantages, freeze-drying is an expensive and time-consuming process that requires specialized equipment and optimization to ensure consistency and quality (Roy and Gupta, 2004).

Rehab Shamma *et al.* (2014) used solvent-casting to improve the solubility of Spirolactone (SL) for usage in pediatric applications utilizing freeze-dried oral thin films. Maximum desirability (0.836) was attained by the improved formulation (0.33:0.66 Soluplus:PVA ratio, 30% PEG 400, 10% polymer concentration). Improved porosity structure in the freeze-dried films facilitated the dissolving of SL. User satisfaction and residue-free dissolution were validated by *in vivo* studies. After five and fifteen min, this formulation demonstrated the best mechanical qualities and maximum drug release, making it appropriate for freeze-drying. The research highlights the potential of freeze-dried Soluplus/PVA-based oral thin films as a means of improving the oral dispersion of poorly soluble medications, particularly in the case of young patients (Shamma and Elkasabgy, 2016).

Pozzoli *et al.* (2017) used Soluplus® to create an Amorphous Solid Dispersion/solution (ASD) through freeze-drying to improve Budesonide (BUD) absorption and dissolution via nasal delivery. The porosity structure and specific surface area of the freeze-dried Soluplus-BUD formulation (LYO) demonstrated enhanced solubility and X-ray diffraction verified the drug's amorphous nature. Comparing LYO to commercial goods that were based on water, such as dry powder and suspension, LYO showed faster release rates. With a greater transfer in permeability tests using RPMI 2650 nasal cells than commercial BUD solution, LYO-Ca, bulked with calcium carbonate, demonstrated appropriate aerodynamic qualities for nasal distribution. The nasal administration of poorly soluble medications appears to be improved by Soluplus (Pozzoli *et al.*, 2017).

Soluplus(®) nanomicelles were created by Fernando Alvarez-Rivera *et al.* (2016) to improve the solubility, stability and ocular permeability of α-Lipoic Acid (ALA). Soluplus increased ALA solubility by over 10 times and formed micelles that were smaller (70-80 nm) than those produced by conventional surfactants. After being freeze-dried, membrane-sterilized and diluted in lachrymal fluid, these nanomicelles showed stability. They demonstrated the ability to gel in situ at doses of 1 or 2 mM, which may extend the corneal residence period. Soluplus nanomicelles markedly enhanced ALA build-up and flow toward the receptor chamber in cow ocular permeability experiments. Comparing Soluplus nanomicelles to traditional eye drops, the results point to them as potentially effective ALA carriers due to their superior stability, solubility and corneal permeability (Alvarez-Rivera *et al.*, 2016).

## Improvements in Physical Stability and Solubility

The lipophilic qualities of a growing number of newly developed Active Pharmaceutical Ingredients (APIs) cause them to have low oral bioavailability. The breakdown of weakly water-soluble medications in gastrointestinal medium is the limiting stage for their penetration and absorption through the intestinal system, according to the Biopharmaceutical Categorization System (BCS).

Hua Yang (2014) investigated the stabilization of Fenofibrate (FBT) nanosuspensions using Soluplus® and HPMC. The study found that nanosuspensions stabilized by Soluplus® (344 nm) and HPMC (642 nm) significantly reduced particle size compared to coarse FBT. Soluplus® provided superior stability by minimizing Ostwald ripening due to its micelle formation, which slowed the diffusion of dissolved FBT. This stabilization resulted in better dissolution and bioavailability. The *in vivo* study showed higher AUC, $C_{max}$ and shorter $T_{max}$ for the nanosuspensions (Yang *et al.*, 2014).

Jian Guan *et al.* (2019) explored how hyaluronic acid and Soluplus® work together to preserve the supersaturation and enhance the physical stability of lovastatin. As a crystal growth inhibitor, HA was included into the structure of Soluplus® to provide steric and electrostatic stability, improving performance both *in vitro* and *in vivo*. A potential strategy for supersaturated drug delivery systems, the combination of Soluplus® and hyaluronic acid effectively preserved supersaturation while enhancing moisture uptake and physical stability (Guan *et al.*, 2019).

Sumit Kumar Saha (2023) applied the Amorphous Solid Dispersion (ASD) technique to study the solubility and dissolution enhancement of Alectinib hydrochloride (ALB). Solubility was greatly improved by using Soluplus in a 1:5 ratio with ALB and it was further enhanced by adding 5% P407 in the third-generation ASD. The formulation maintained stability for a full year and demonstrated a two-fold increase in FaSSIF dissolution (Saha *et al.*, 2023).

Rosario Pignatello (2022) demonstrated that Soluplus® nanomicelles, with a size of 60-70 nm, effectively enhance the solubility of BCS class II drugs like ibuprofen, idebenone

**Table 2: Following is the table that showing patent related to soluplus formulation.**

| Applicant | Application Number and Status | Outcome |
|---|---|---|
| Zhejiang University of Technology ZJUT. | CN201610243442. 8A Granted (Active). | Temperature-sensitive gel matrix using Soluplus, providing extended drug slow release for 7 days, superior to Poloxamer 407. |
| Allergan Inc. | EP12808637. 8A Granted (Active). | Ophthalmic compositions using Soluplus for enhancing solubility and bioavailability of therapeutic agents. |
| Sanovel Ilac Sanayi Ve Ticaret Anonim Sirketi. | WO2013191668A1 Published. | Compositions using Soluplus for hypertension, enhancing solubility in solid formulations. |
| Allergan Inc. | EP2790673B1 Granted (Active). | Ophthalmic compositions with Soluplus graft copolymers, enhancing drug delivery for eye applications. |
| European Patent Office. | 20902732.5 Published. | Solid oral composition of Olaparib with enhanced solubility and bioavailability. |

and miconazole. Solubility increased linearly with Soluplus® concentration. The nanomicelles remained stable after freeze-drying and reconstitution, showing potential for bioadhesive applications like ocular drug delivery (Pignatello *et al.*, 2022).

Memoona Ishtiaq *et al.* (2024) created Ternary Solid Dispersions (TSDs) of curcumin with Soluplus® (20%), which considerably improved its solubility and dissolution. The modified formulation, F3, improved curcumin solubility to 186 µg/mL (3100-fold) and dissolution to 91% (9-fold). FTIR, SEM, XRD and DSC corroborated the increased solubility. When compared to pure curcumin, F3 demonstrated improved biological activities such as antibacterial, antioxidant (93%) and anti-inflammatory properties (Ishtiaq *et al.*, 2024).

Iskra Z. Koleva *et al.* (2024) significantly improved eugenol's water solubility by encapsulating it with Soluplus® and Lutrol F 127 using spray drying. The optimized formulations achieved high encapsulation efficiencies of 97.9-98.2% for 5% eugenol and around 90% for 15% eugenol. The addition of Lutrol F 127 improved particle shape and flowability, enhancing the solubility and usability in various dosage forms (Koleva and Tzachev, 2024).

## Soluplus-Mechanism of solubilization

Soluplus® improves drugs solubility through various vital mechanisms (Figure 15). It decreases drugs particle size to the nanoscale, resulting in better solubility and absorption. Soluplus stabilizes dispersions by preventing particle aggregation, resulting in sustained solubility. Its amphiphilic nature enables it to create micelles that encapsulate hydrophobic drugs, improving their solubility in aqueous solutions. Furthermore, Soluplus improves the drug's surface area by optimizing interaction with the solvent, resulting in faster dissolving. These mechanisms work together to greatly increase the solubility and bioavailability of medicines that are poorly water soluble (Figure 15).

## Patent

Table 2 summarizes key patents involving Soluplus® formulations, highlighting innovative applications.

# CONCLUSION

In conclusion, the use of solubility enhancers like Soluplus is a viable solution to the problems posed by the insufficient solubility of Active Pharmaceutical Ingredients (APIs) in oral drug delivery. By using methods such as solid dispersions and especially Amorphous Solid Dispersions (ASD), Soluplus improves drug absorption and release in the intestines, increasing bioavailability. The thorough analysis highlights the significance of measuring drug release and polymer simultaneously in dissolving media, highlighting the need for reliable quantification methods tailored to water-soluble polymers like Soluplus®. Several manufacturing approaches have been investigated to successfully incorporate Soluplus into therapeutic formulations, including as hot-melt extrusion, nanoextrusion, supercritical fluid processing, electrospinning, spray-drying and freeze-drying. Improved physical stability, regulated release and increased drug solubility are some benefits of these techniques. Also, Soluplus amphiphilic nature, increased surface area, particle size reduction and stabilization of dispersions all contribute to its capacity to improve the physical stability, dissolving rate and bioavailability of poorly water-soluble medications. The performance of poorly soluble medications can be greatly improved by Soluplus, which also advances pharmaceutical formulations for better therapeutic outcomes. All things considered, Soluplus proves to be a flexible and effective solubility enhancer. Leveraging the full potential of Soluplus in medication delivery applications requires ongoing study and development of formulation and processing procedures.

## ACKNOWLEDGEMENT

We thank R. C. Patel Institute of Pharmaceutical Education and Research (RCPIPER) and R. C. Patel Institute of Pharmacy (RCPIOP), Shirpur, for their support and resources in facilitating this work.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## ABBREVIATIONS

**SOL:** Soluplus; **SD:** Solid Dispersion; **HME:** Hot Melt Extrusion; **ASD:** Amorphous Solid Dispersion; **BCS:** Biopharmaceutics Classification System; **FDT:** Fast Disintegrating Tablet; **ART:** Arteether; **SFD:** Spray freeze drying; **NCSDs:** Nanocrystal solid dispersions; **HME:** Hot-melt extrusion; **HPH:** High-pressure homogenization; **MTZ-NS:** Metronidazole nanosuspensions; **SMSD:** Self-micellizing solid dispersion; **TGA:** Thermogravimetric analysis; **CBD:** Cannabidiol; **HSM:** Hot stage microscopy; **SFD:** Spray Freeze Drying; **BUD:** Budesonide.

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**Cite this article:** Shinde DT, Patil KR, Mali KD. Review on Soluplus®: Pharmaceuticals Revolutionizing Drug Delivery and Formulation Strategies. Int. J. Pharm. Investigation. 2025;15(2):344-60.

Int. J. Pharm. Investigation, 2025; 15(2):361-376.
https://www.jpionline.org

Review Article

# Pharmaceutical Excipients: Functions, Selection Criteria, and Emerging Trends

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**ABSTRACT**

Pharmaceutical excipients are integral to therapeutic formulations; their importance has grown from inert and economical materials to components that make up 80-90% of the finished product. This review examines the excipient classification scheme developed by the International Pharmaceutical Excipient Council (IPEC) and the process by which safety evaluation criteria are set for newly suggested excipients. It also highlights how excipients impact the price, effectiveness, and stability of medications, especially when used in solid dosage forms. The study also addresses new developments in excipient functionality and utilization, highlighting the need for multifunctional excipients to improve pharmacological efficacy, stability, and affordability. The purpose of this article is to shed light on the roles that pharmaceutical excipients play in the efficacy of medication formulations by examining their functions, selection criteria, and developing trends.

**Keywords:** Pharmaceutical Excipients, Formulations, Active pharmaceutical ingredient (API), Excipient selection, Interactions.

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**Received:** 21-03-2024;
**Revised:** 05-06-2024;
**Accepted:** 18-08-2024.

## INTRODUCTION

Pharmaceutical excipients are crucial parts of medicine formulations and are important to the creation and production of drugs. They are described as ingredients added to the formulation to ensure the quality, safety, and efficacy of formulations, aside from the Active Pharmaceutical Ingredient (API). Excipients have the potential to facilitate drugs solubility, increase stability, boost bioavailability, and maintain dose homogeneity. Additionally, they support the drug delivery system's general efficacy and safety. As a matter of fact, 90% of recently identified therapeutic compounds and 40% of currently available pharmaceuticals have low water solubility, emphasizing the critical role that functional excipients play in addressing these barriers (Van der Merwe J *et al.*, 2020). Excipients are crucial in many aspects of the production of pharmaceuticals. ensuring the security, efficacy, and caliber of pharmaceuticals is their primary responsibility. Excipients help to increase the quantity of medication that is bioavailable and improve the solubility of pharmaceuticals that are not highly soluble in water, all while aiding in the delivery mechanism for APIs. They also have an important part to play in the manufacturing process, helping to identify the drug product and disintegrate the drugs (Available from). Excipients can be added to the formulation to improve the drug's physico-chemical qualities or to aid in its dissolution. Additionally, they can be utilized to re-formulate already-existing drugs to create more potent medications and to create dosage forms that can decrease the number of doses by enhancing drug delivery. Excipients are typically added to dosage forms in larger amounts than the Active Pharmaceutical Ingredient (API) and are involved in every facet of the finished product, such as the API's stability, dose consistency, efficient delivery to the systemic circulation following administration, and appropriate patient compliance (Patel R *et al.*, 2020).

### Functions

Pharmaceutical excipients play several crucial roles in drug formulations. Keeping liquid formulations at the proper pH and/or osmolarity is just one of these responsibilities; additional responsibilities include regulating the solubility and bioavailability of APIs, stabilizing APIs in the dosage form, encouraging patient acceptability, helping with product identification, and improving the overall safety and efficacy of the drug delivery system. Excipients play a crucial role in the manufacturing process and the efficacy of drugs, making them necessary components in contemporary pharmaceutical supplies. They can be used as preservatives, coloring agents, lubricants, binders, disintegrants, and diluents. Excipients can also help to facilitate formulations and improve the functionality of products. As these functions demonstrate, excipients play a crucial role in providing the

**DOI:** 10.5530/ijpi.20251676

effectiveness, safety, and overall quality of pharmaceutical formulations (Elder DP *et al.*, 2016).

**Increasing Stability:** Excipients contribute to the shelf life of a drug product by assisting to keep Active Pharmaceutical Ingredients (APIs) stable in the dosage form.

**Modulating Bioavailability and Solubility:** Excipients can improve the body's solubility and bioavailability of APIs.

**Preserving Osmolarity and pH:** Excipients assist in maintaining liquid formulations' pH and osmolarity, ensuring their compatibility with the physiological conditions of the body.

**Improving Patient Acceptability:** By making the drug product taste better and look better overall, they increase patient acceptability and encourage compliance, especially in younger patients.

**Helping with Product Identification:** A few excipients facilitate the drug product's identification.

**Ensuring Safety and Effectiveness:** To improve the formulation's overall safety and effectiveness, excipients are added to drug delivery systems (Van der Merwe J *et al.*, 2020).

Excipients are inert materials that are added to drugs to facilitate drug dissolution, absorption and delivery. They can be introduced to the formulation in order to assist the drug dissolution, or specific dosage forms that increase the rate of dissolution through different methods can be created. Excipients can influence how quickly a solid dosage form dissolves, and some can even adsorb Active Pharmaceutical Ingredients (APIs), improving bioavailability in the process. Pharmaceutical excipients have a variety of functional roles, such as regulating bioavailability and solubility, boosting API stability in the dosage form, preserving the liquid formulations' osmolarity and/or pH, averting dissociation and aggregation, etc, (Li Z *et al.*, 2021).

## Classification of Excipients

### *Based on their origin*

- Animal source- Beeswax, honey, lanolin, stearic acid, lactose.
- Vegetable source- Starch, acacia, peppermint, turmeric, and guar gum.
- Mineral source- Calcium phosphate, kaolin, asbestos, silica, calamine, talc, paraffin.
- Synthetic source- Polyethylene glycols, polysorbates, lactic acid, boric acid, and saccharin.

## Based on Function

Binders, Surfactants, Emulsifying agents, Disintegrants, Lubricants, Cosolvents, Fillers Sweeteners, Flavors, Glidants, Colors, Preservatives, Film coatings, Dispersing agents, Printing inks, Compression aids.

## Based on Role in Pharmaceutical Formulation

Antioxidants, Coating materials, Emulgents, Taste and smell improvers, Ointment bases, Conserving agent, Consistency improvers.

## Selection criteria of excipients

The ideal properties of pharmaceutical excipients are critical for ensuring the effectiveness and purity of pharmaceutical dosage forms, and they perform a significant role in drug formulations. Excipients should ideally modulate bioavailability and solubility, prevent aggregation and dissociation, maintain the pH and osmolarity of liquid formulations, and improve the stability of APIs in the dosage form. Furthermore, excipients should overcome low drug bioavailability, promote drug dissolution, and improve wettability. The stability and efficacy of the medicinal product might be significantly affected by the excipients' properties and concentration (Patel R *et al.*, 2020). High-functionality excipients are especially useful since they are capable of performing a variety of tasks, including enhancing flow, serving as a disintegrant, and enabling an increased drug loading. Pharmaceutical technology is also focusing on the creation of multifunctional excipients, or substances that can operate as both a binder and a direct-compressible filler material at the same time. Excipient stability is a crucial factor to take into account since it affects the quality and performance characteristics of pharmaceutical dosage forms. In order to ensure the dosage form's physical and chemical integrity as well as the packaging's integrity, excipient stability is crucial (Pockle RD *et al.*, 2023).

Excipients should be studied in terms of interactions and possible ways to mitigate instabilities, in addition to their direct impacts. Excipients are vital for the preservation of products because they protect the Active Pharmaceutical Ingredient (API) from external influences and alter sensory attributes like appearance, texture, taste, and smell. Comprehending the fundamental standards of excipients, the rationale behind the creation of novel excipients, and the varieties of excipients that are now in use are essential for the continuous progression of pharmaceutical compositions (Pockle RD *et al.*, 2023).

Drug development logically depends on the selection of excipients, that serve as essential components of pharmaceutical formulations. Excipient selection involves a number of considerations, such as functionality, compatibility, safety, and regulatory requirements. Dosage forms consist of excipients to improve the solubility, stability, efficacy, and safety of drug, Additionally, they can be utilised as tonicity or bulking agents, or they can assist in the controlled delivery of drugs. It is critical that excipients be thoroughly proven safe before being used in pharmaceutical formulations. The target population, mode of

**Table 1: Excipients used in tablets.**

| Excipient | Use | Examples | References |
|---|---|---|---|
| Diluents | These are fillers that are added to tablets to increase their volume.<br>They can also modify the release rate of the drug. | Calcium carbonate, dibasic calcium phosphate, Calcium sulfate, dextrose, lactose, mannitol, starch etc. | (Van der Merwe J *et al.*, 2020) |
| Binders | They give powdered materials cohesive strength and serve as binding agents in tablets. | Acacia, carbomer, gelatin starch, cellulose, Hydroxypropyl cellulose, Povidone etc. | (Van der Merwe J *et al.*, 2020) |
| Disintegrants | These facilitate the tablet's disintegration into smaller components | Alginic acid, cellulose, guar gum, Sodium alginate, sodium starch glycolate etc. | (Available from) |
| Lubricants | Used to reduce the friction that presses the tablet against the die wall, keeping it from adhering to dies and punches. | Calcium stearate, Fumaric acid, Sodium lauryl sulfate, magnesium stearate and stearic acid. | (Patel R *et al.*, 2020) |
| Glidants | Used to enhance the flowability of powder or granules. | Calcium silicate, Magnesium oxide, Magnesium carbonate, Starch, Talc etc. | (Available from) |
| Preservatives | They prolong the product's shelf life and prevent microbiological growth. | Benzalkonium chloride, propyl paraben, methylparaben etc. | (Elder DP *et al.*, 2016) |

**Table 2: Excipients used in liquid dosage forms.**

| Excipient | Use | Examples | References |
|---|---|---|---|
| Solvents | For dissolution of API or other excipients. | Alcohol, water, syrups, ethyl acetates, acetone, acetic acid, etc. | (Elder DP *et al.*, 2016) |
| Cosolvent | Increases the solubility of drugs in solvents. | Propylene glycol, glycerin, ethanol etc. | (Li Z *et al.*, 2021) |
| Buffering agents | Maintain the pH of the formulations. | Citric acid, phosphate buffers, and acetate buffers etc | (Li Z *et al.*, 2021) |
| Preservatives | Prevent the growth of microbes in formulations. | Benzyl alcohol, phenol, thiomersal, butyl paraben, etc. | (Chaudhari SP & Patil PS, 2012) |
| Antioxidants | Delays or inhibit the oxidation of the drug molecules. | Sodium bisulphate, ascorbic acid, thiourea, Butyl Hydroxy Toluene (BHT), tocopherols, etc. | (Chaudhari SP & Patil PS, 2012) |
| Wetting agent | Lowers the surface tension of water. | Lecithins, Spans, Tween 80, Sodium Lauryl Sulphate (SLS), etc. | (Liberman HA *et al*,) |
| Thickening agents | Increases the viscosity of a liquid. | Microcrystalline cellulose, hydroxyethyl cellulose, methyl cellulose etc. | (Chaudhari SP & Patil PS, 2012) |
| Humectants | Minimizes the water loss thus control water content. | Glycerol, polyethylene glycol, propylene glycols, etc. | (Pockle RD *et al.*, 2023) |

administration, dosage form, type of active ingredient and local regulatory requirements also influence excipient choosing. For instance, the Japanese Pharmaceutics Excipients Council (JPEC) in Japan assembles excipients in approved products; the FDA in the US offers a searchable list of approved inactive ingredients; and Health Canada in Canada publishes a list of acceptable non-medicinal agents (Rayaprolu BM *et al.*, 2018).

Additionally, a crucial factor in the selection of excipients is their functionality. The selection of excipients is dependent upon their capacity to carry out particular tasks within a reasonable range for a specific composition. It is interesting that an excipient may play different roles in different formulations or more than one role in a single formulation. As a result, excipients' suitability and functionality in a given medicinal product should be carefully considered. To further add to the complexity of their selection, excipients must be categorized. The International Pharmaceutical Excipient Council (IPEC) provides a framework for classifying

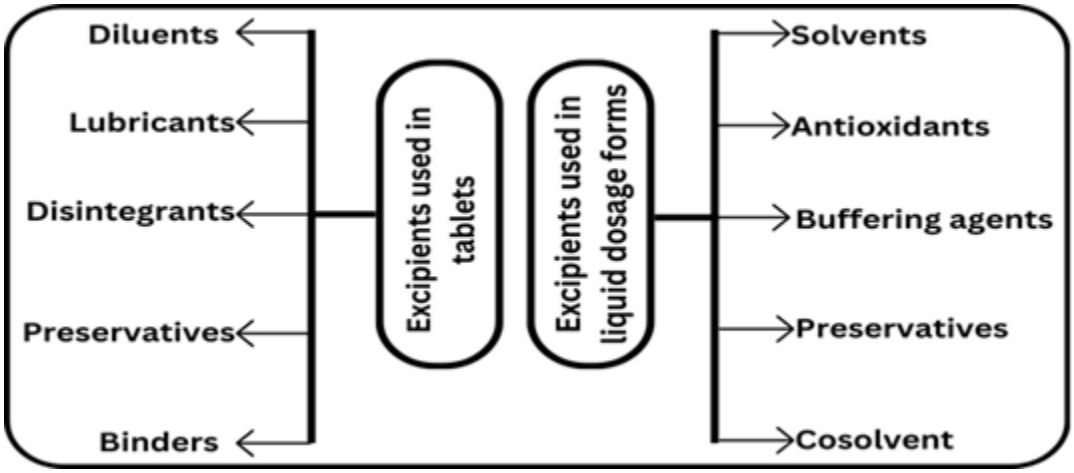


**Figure 1:** Excipients used in tablets and liquid dosage forms (Liberman HA *et al*,).

excipients so that their roles and functions can be better understood (Medi MB *et al*., 2014).

With their multifunctional nature and potential effects on the overall stability and cost of the medication, these categories help ensure that the appropriate excipients are selected for particular drug formulations. To sum up, the process of choosing excipients for pharmaceutical formulations is complex and requires a thorough evaluation of factors such as functionality, safety, compatibility, and regulatory compliance. Pharmaceutical scientists have more information to choose excipients for the creation of safe, efficient, and effective drug products by considering these variables and using the resources that are available for excipient classification (Medi MB *et al*., 2014).

## Based on Safety and Toxicity

Concerning the development of safe and effective medications, the toxicity and safety of pharmaceutical excipients are crucial factors, as they are an essential component of drug formulations. A risk-based assessment that takes into account the possible risks and benefits of each excipient is part of the selection criteria for excipients based on safety and toxicity analysis. Excipients' potential toxicity, pharmacokinetics, and pharmacodynamics are all assessed as part of their safety evaluation. When assessing an excipient's risk/benefit ratio, it's important to consider both its intended use and the possibility of unforeseen consequences. After reviewing the safety and biopharmaceutical issues surrounding common excipients used in off-label pediatric formulations, recommendations were made to minimize the quantity of excipients used in a formulation. Pediatric patients may have an increased vulnerability to excipient-related adverse reactions because of their developing metabolism, elimination, absorption, and distribution pathways. Drugs designed for elderly patients are still frequently utilized off-label because few clinical studies have received regulatory approval. Excipients can be hazardous even if they are safe for adults because there is no evidence that they are safe for use in pediatric populations. Excipient toxicity is not related to dose, age, or route (Abrantes CG *et al*., 2016).

To summarize, the criteria for choosing excipients based on safety and toxicity involve a risk-based evaluation that takes into account the benefits as well as drawbacks of each excipient. The evaluation of excipient safety necessitates considering their intended purpose, possibility for unforeseen consequences, and the existing safety evidence. Excipients can be harmful due to several reasons, such as their chemical structure, impurities, and interactions with co-excipients or active pharmaceutical ingredients. Excipient safety is a crucial concern, and it is important to thoroughly assess how toxic they are (Belayneh A *et al*., 2020).

## On the basis of compatibility with other active ingredients

A crucial part of developing pharmaceutical formulations involves selecting excipients that combine well with the active ingredient. A variety of methods, such as Nuclear Magnetic Resonance (NMR), Fourier Transform Infrared Spectroscopy (FTIR), and Differential Scanning Calorimetry (DSC), are typically used to assess compatibility. Because drug-excipient interactions are so complex, there are no universal standards for the evaluation methodology; however, more individual studies are reporting the use of different screening techniques. Studies on drug-excipient compatibility are conducted to evaluate possible interactions between the drug and excipients, which may affect the final drug product's performance, stability, and quality (Dave VS *et al*., 2015).

The International Council on Harmonisation (ICH) and the U.S. Food and Drug Administration (USFDA) have established the Q8 guidelines and the 21$^{st}$-century Current Good Manufacturing Practices (cGMP) initiative, which both support the application of Quality by Design (QbD) principles in the drug development process, to ensure a logical selection of excipients. A thorough grasp of the physico-chemical characteristics and processes of

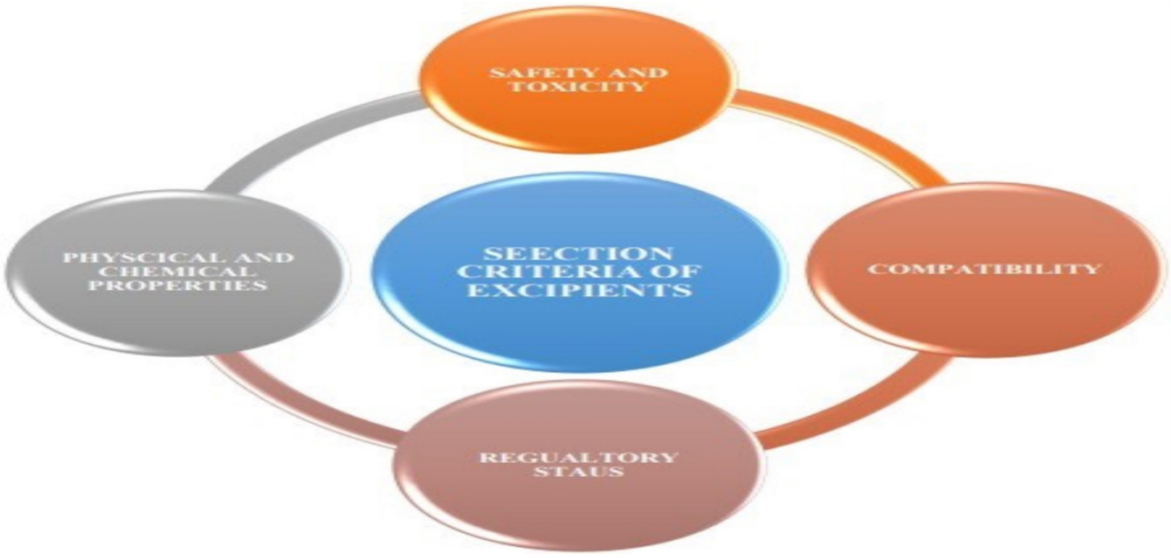


**Figure 2:** Selection criteria of excipients (Rayaprolu BM *et al*., 2018).

the drug and excipients is necessary to comprehend the direct interactions and potential impacts of these components on the final drug product. By identifying variations in heat flow values and changes in the endothermic or exothermic peaks, thermal techniques like DSC are especially helpful for evaluating incompatibilities. Regarding the drug's stability in both its pure form and at the prescribed dosage, these studies offer invaluable information. Although there are no set standards for carrying out drug-excipient compatibility studies, the pharmaceutical industry is aware of the importance of excipients for drug stability and the necessity of thorough evaluation. A key component of formulation development is choosing excipients that work harmoniously with the active ingredient. Using a variety of analytical techniques is also essential to ensure the effectiveness and quality of the finished drug products. When choosing excipients rationally, it's crucial to take compatibility assessment into account and apply QbD principles and thermal techniques (Omari D *et al*., 2023).

## On the basis of Regulatory Status

Drug products require excipients as an essential ingredient, and the regulatory status of these ingredients determines how they are chosen. Excipients are reviewed by the FDA in relation to drug products when they are submitted as a Biological License Application (BLA), New Drug Application (NDA), or Investigational New Drug application (IND). Currently, there isn't a distinct review procedure in place for excipients. Stated differently, excipients are not reviewed by the FDA outside of the framework of an IND, NDA, or BLA. Both Japan and the European Union are in comparable situations. The FDA recognizes excipients found in drug products with its approval, and the industry views these excipients as permitted or allowed. Drug products require excipients as an essential ingredient, and the regulatory status of these ingredients determines how they are chosen. Excipients are reviewed by the FDA in relation to drug products when they are submitted as a Biological License Application (BLA), New Drug Application (NDA), or Investigational New Drug application (IND). Currently, there isn't a distinct review procedure in place for excipients. Stated differently, excipients are not reviewed by the FDA outside of the framework of an IND, NDA, or BLA. Both Japan and the European Union are in comparable situations (Yu YB *et al*., 2021).

Excipients are not approved or licensed on their own; instead, they are evaluated in conjunction with drug products. Rather, excipients found in pharmaceuticals with FDA approval are considered to be approved by the FDA. Flavoring agents undergo independent evaluation by FEMA. On September 7, 2021, the programme was implemented voluntarily, and the FDA urged excipient manufacturers to submit applications for FDA assessment of novel excipients prior to their duration of exposure or mode of administration.

Excipients are selected according to their efficacy, safety, and intended use. The European Medicines Agency (EMA), the FDA, and other regulatory bodies set the regulatory status of excipients, which forms the basis of the selection criteria. Excipients have different regulatory statuses in various countries and regions. For instance, in December 2017, the co-review procedure for excipients was enacted in China. All domestic and foreign manufacturers and owners of pharmaceutical excipients are required to submit their dossiers to the CDE in accordance with CFDA announcement No. 146.

The excipients' intended use influences the selection criteria as well. The Active Pharmaceutical Ingredient (API) compatibility, stability, and capacity to improve drug delivery are the three main factors considered when choosing excipients. Excipients are chosen in accordance with their efficacy and safety. Excipients need to be safe for ingestion by humans and shouldn't affect the drug product's therapeutic effect.

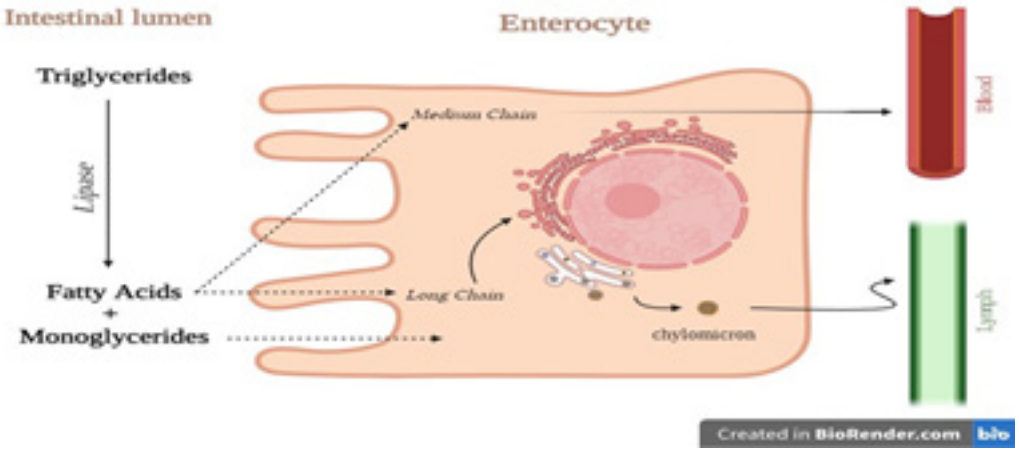


**Figure 3:** Lipid-based excipients facilitating drug absorption.

To sum up, the criteria used to select excipients are determined by their intended use, safety, and efficacy. Excipients are regulated differently in each country and area, and their status is assessed when they are used in pharmaceutical products. The FDA recognizes excipients found in drug products that have received FDA approval, and the industry views these excipients as permitted or allowed. On September 7, 2021, the FDA announced the opening of a voluntary Novel Excipient Review Pilot Program (Pilot Program), asking excipient manufacturers to submit proposals for FDA review of novel excipients before their length of exposure or mode of administration (Yu YB *et al.*, 2021; Saito J *et al.*, 2022).

### On the basis of Physical and Chemical Properties

Excipients are typically regarded as inert additives added to drug formulation to aid in delivery or absorption, product differentiation, enhance appearance, or preservation of quality. Excipients are chosen according to their chemical and physical characteristics, which have an impact on the end product's efficacy, safety, and quality. Particle size, shape, density, and flowability are examples of physical characteristics that can impact the way an excipient processes and performs as well as the end product. Chemical properties such as solubility, stability, and reactivity can have an impact on the stability and compatibility of an excipient with an Active Pharmaceutical Ingredient (API).

High-resolution analytical methods on the molecular, particulate, and bulk levels can be used to assess the quality and functionality of excipients. Pharmacological excipients were categorized by the International Pharmaceutical Excipient Council (IPEC) according to their regulatory status and track record of human use. The category of excipients known as "new chemical excipients" can be further separated into "modified excipients" and "new chemical entities" that are incorporated into pharmaceutical products for the first time. The latter category may contain excipients that are already well-known. More advanced excipients are required to impart specific properties into the finished product as innovative drug delivery systems continue to advance (Felton LA, 2005; Pifferi G *et al.*, 1999).

Excipients with more than one purpose, such as a filler substance that is directly compressible and can also serve as a disintegrant or binder, are referred to as multifunctional excipients. A single excipient that serves multiple purposes, such as improving flow, acting as a disintegrant, and concurrently permitting a larger drug loading in the dosage form, is referred to as a high-functionality excipient.

Excipients can cause disruptions to the quality or efficacy of a drug by reacting chemically or physically with an active ingredient. Every incompatibility has the potential to manifest itself either overtly or covertly, and destabilization scenarios are real and should be looked into.

Excipients are selected depending on their chemical and physical characteristics, which have an impact on the end product's efficacy, safety, and quality. High-resolution analytical techniques can be used to characterize the molecular, particulate, and bulk levels of an excipient's quality and functionality. Pharmaceutical excipients were categorized by the International Pharmaceutical Excipient Council (IPEC) according to their regulatory status and history of human use. Excipients with high and multifunctionality can, respectively, carry out several tasks and offer extra functions. A detailed understanding of the chemical and physical properties of excipients, as well as any related impurities or residues, and how they may interact with other materials or with one another, can alert the pharmaceutical technologist to potential undesirable consequences (Felton LA, 2005; Pifferi G *et al.*, 1999).

## INTERACTIONS

The quality or efficacy of the medication may be harmed by excipients' tendency to interact chemically or physically with the active ingredient. Drug molecules may adsorb to the surface of the excipient as part of these interactions, which may have an effect on absorption and particle size. The rate of dissolution and

bioavailability can also be impacted by finely divided excipients adhering to active components. Drug-excipient interactions can affect a number of physicochemical and physiological processes, which in turn might affect drug absorption. For example, a drug's action in the body may be altered by complexation agents interacting with the drug to produce a complex. Stabilizers may also influence the drug's recrystallization by lowering the dispersed drug's molecular mobility. These are only a few instances of how excipients might change a drug's efficacy and behavior. To ensure drug stability and bioavailability, it is crucial to comprehend the workings and implications of interactions between the drug and the excipient. Drug-excipient interactions of various kinds, as well as potential molecular explanations for these interactions, might result in incompatibilities that change the medication's intended characteristics. Pharmaceutical technologists need to know this information in order to foresee and minimize unfavorable developments in medication formulation (Rao VA *et al.*, 2020).

An important field of research is the relationship between pre-systemic medication metabolism and routinely used excipients. It has been discovered that excipients such fatty acids, solvents, polymers, and surfactants affect the expression of cytochrome P450 enzymes, which can change the rate of drug metabolism and bioavailability. When designing dosage forms, it is crucial to take the excipient's type, concentration, and other associated variables into account since they can have a substantial impact on the drug's metabolism (Patel R *et al.*, 2020).

In conclusion, complex interactions between excipients and drugs can have a big impact on the efficacy, performance, and quality of treatments. For the purpose of creating safe and effective medication formulations, it is imperative to comprehend these interactions. The numerous ways that excipients can affect drug behavior are still being investigated by researchers and pharmaceutical technologists in an effort to maximize drug stability, bioavailability, and overall therapeutic results (Rao VA *et al.*, 2020).

## Drug-Excipients Interactions

Drug-excipient interactions are an important part of drug formulation because excipients aren't just inert additives; they can interact chemically or physically with the active ingredient, which could affect the drug's efficacy and quality. These interactions may have an impact on the stability and bioavailability of drugs and may occur through a variety of mechanisms, including adsorption, complexation, or incompatibilities. For example, drug molecules may adsorb onto the surface of excipients, influencing drug absorption and particle size, or complexing agents may interact with a drug to form a complex, affecting the drug's behavior. Furthermore, depending on variables like the therapeutic window, the site of absorption, and rate-limiting factors in drug absorption, the degree to which these interactions impact drug bioavailability varies (Rao VA *et al.*, 2020).

Common excipient categories, such as buffering agents, surfactants, lyoprotectants, and tonicity agents, were identified through a thorough analysis of excipients utilized in pharmaceutical products derived from biotechnology. This survey offers important information on the frequency of excipients in various drug classes and how they interact with different formulation parameters like pH, dosage form, and administration route.

Studies on the compatibility of excipients are carried out to forecast possible physicochemical incompatibilities of the drug in its ultimate dosage form. The purpose of these studies is to identify interactions that might impact the dosage form's stability, chemical, physical, and bioavailability. A crucial factor in the selection of pharmaceutical excipients is their safety (Vranić E, 2004). New excipients for use in drug or biological product formulations must adhere to safety profile development guidelines. These guidelines offer strategies for safety evaluations as well as recommended excipient toxicity testing for various pharmaceutical types. An effective tablet formulation should consider a number of factors when selecting its excipients, such as the target formulation, the manufacturing process, the properties of the Active Pharmaceutical Ingredient (API), and any potential effects on the formulation. The selection process involves several crucial factors, including excipient quality, functionality, and safety. In order to determine possible interactions that might affect the effectiveness and caliber of pharmaceutical formulations, drug-excipient compatibility studies are crucial. Pre-formulation studies are an important part of drug development, focusing on the interactions between drugs and excipients and their effects on stability, bioavailability, chemistry, and physical properties.

In conclusion, interactions between drugs and excipients are a complicated and important part of pharmaceutical formulation. For the development of safe and effective pharmaceutical products, it is crucial to comprehend the nature of these interactions, carry out compatibility studies, and ensure the quality and safety of excipients (Abrantes CG *et al.*, 2016).

## Excipient-Excipient Interactions

Excipient-excipient interactions are important to understand in order to predict and prevent unfavorable developments in drug formulations. Excipient interactions have been found to have an impact on drug stability, bioavailability, and drug metabolism. For instance, excipients have been shown to alter drug bioavailability through their effects on cytochrome P450 enzyme expression. Excipients that have been found to influence drug metabolism include solvents, polymers, fatty acids, and surfactants. Excipient type, concentration, and other factors have been found to have an impact on the inhibition of CYP450 enzymes, emphasizing the significance of taking excipient effects into account when designing dosage form (Rao VA *et al.*, 2020).

Ensuring the safety, efficacy, and quality of the final product throughout the manufacturing of pharmaceutical formulations requires careful consideration of potential interactions between excipients. Comprehending the behavior of the excipients individually and collectively in the formulation requires an extensive understanding of their physical and chemical characteristics. Pharmaceutical technicians can maximize the efficacy and stability of a medicine by determining and evaluating excipient interactions (Patel R *et al.*, 2020).

To summarise, interactions between excipients can have noteworthy consequences for drug formulations, impacting elements like drug stability, bioavailability, and physicochemical results. For the purpose of minimizing potential side effects and designing pharmaceutical formulations logically, it is imperative to comprehend these interactions. Numerous studies have demonstrated how crucial it is to take excipient effects on drug metabolism into account when making formulation decisions, as well as how thorough understanding of excipient behavior is necessary.

## Co-processed Excipients

Co-processed excipients are mixtures of two or more separate excipients that are physically combined without undergoing a substantial chemical alteration. In the pharmaceutical industry, they are widely used to simplify formulation development, improve product performance, and improve drug processability. These excipients are made to require the fewest possible ingredients and processing steps, which speeds up development, lowers manufacturing complexity, and streamlines processing. They may have to do with the manufacturing of drug products, *in vitro* or *in vivo* drug performance, or both. They can enhance functionality over straightforward physical mixtures (Serrano-Mora LE *et al.*, 2021).

Co-processed excipients perform more effectively in terms of flowability, particle size distribution, blending behavior, compressibility, storage stability, and batch-to-batch consistency. They may also result in fewer manufacturing expenses, quicker drug development, reduced time to market, and easier formulation development. Co-processed excipients can also cut down on the number of excipients required to attain good product performance, which will shorten the time needed to develop new drug products and simplify their manufacturing. Co-processed excipient development entails selecting the necessary excipients, figuring out their ideal relative proportions, selecting the best co-processing method, and optimizing a number of process variables. The majority of co-processed excipients consist of a filler and either a binder or a glidant, or a binder and a glidant and a filler. The development of novel co-processed excipients has been made possible by the availability of nanotechnology. It has been demonstrated that using co-processed excipients results in more patient-friendly formulations, less need for damaged tablet inspection, and improved product robustness. Additionally, by increasing solubility, bioavailability, stability, and overall drug performance, these excipients may help. In conclusion, co-processed excipients are a significant advancement in the pharmaceutical sector that provide many advantages such as simplified manufacturing, enhanced product performance, and streamlined formulation development. The application of these could result in lower costs and quicker drug discovery (Garg N *et al.*, 2013).

## Excipients' effects on a drug's solubility and bioavailability

Drug-related dose forms and physiological features at the absorption site, as well as adjuvants that may impact oral bioavailability, can all have an impact on a drug's bioavailability. A complete understanding of the dependence on these interactions is required for the synthesis of complex molecules. Chemical excipients have the potential to increase emissions and waste associated with Active ingredients (APIs). Excipients that can be added to chemical formulations to aid in the dissolution of the chemicals or to provide variable degrees of improved water solubility by various ways include cyclodextrins, disintegrants, pH-modifying excipients, and surfactants (Sheikh M *et al.*, 2023).

Chemical and physical properties of drug formulations can be enhanced by the addition of excipients, which are inert substances. To increase the solubility of drugs that are poorly soluble, excipients play a critical role. A number of strategies, such as inclusion complexes, encapsulation, chemical modification of the API, physical modification, and dispersion, can be used to overcome solubility issues. For drugs with low solubility, excipients can help with numerous formulation techniques. For instance, for many years, drug particles have been maintained in Amorphous Solid Dispersions (ASDs) or the API has been solubilized in micellar structures, respectively, to improve the solubility of hydrophobic APIs. Polymers, surfactants, and lipids are the most often utilized excipients for improving solubility. Excipients with polymers are frequently utilized to improve solubility. When they combine with drugs, they can create inclusion complexes that improve the solubility of drug. Moreover, polymers can be utilized to create ASDs, which keep the medicine amorphous and inhibit crystallization, improving the drug's rate of solubility. Another family of excipients that can improve the solubility of poorly soluble drugs is surfactants. In aqueous solutions, they have the ability to create micelles that can solubilize the drug and boost its bioavailability. Additionally, lipids are employed as excipients to improve solubility. They have the ability to produce liposomes, which can encapsulate the medication and increase its bioavailability and solubility (Patel R *et al.*, 2020).

Naturally, lipid-based excipients facilitate drug absorption. Lipid-based formulations have the potential to increase API bioavailability through: promoting chylomicron production,

**Table 3: Various Aspects of Consideration for Pharmaceutical Excipients.**

| Aspects | Summary | References |
|---|---|---|
| Importance of Excipients | Excipients are crucial components in drug formulations, making up 80-90% of the finished product. They enhance drug solubility, stability, bioavailability, and overall efficacy. | (Patel R *et al.*, 2020) |
| Functions of Excipients | Excipients play various roles such as improving stability, modulating bioavailability, preserving osmolarity and pH, enhancing patient acceptability, aiding in product identification, and ensuring safety and effectiveness. | (Li Z *et al.*, 2021) |
| Classification of Excipients | Excipients are classified based on their origin, function, and role in pharmaceutical formulations. | (Liberman HA *et al*,) |
| Selection Criteria | Ideal excipients should modulate bioavailability, prevent aggregation, and improve stability. | (Pockle RD et al., 2023) |
| Standardization of Excipients | Organizations like IPEC and guidelines like ICH Q8 support Quality by Design principles in excipient selection. | (Peng Soh JL *et al.*, 2015) |
| Emerging Trends | Co-processing for multifunctional excipients and green chemistry approaches are emerging trends in excipient technology. | (Saha S and Shahiwala AF, 2009) |
| Drug-Excipient Interactions | Drug-excipient interactions can impact drug stability, bioavailability, and efficacy, necessitating compatibility studies. | (Rao VA *et al.*, 2020) |
| Challenges and Future Directions | Risks in the excipient supply chain include sourcing issues, supply disruptions, and regulatory complexities. Strategies like dual-sourcing and regulatory frameworks like ICH Q12 are essential for maintaining a robust pharmaceutical supply chain. | (Available from) |

which leads to increased drug absorption through the lymphatic channel and avoids the liver's first pass metabolism, and enhancing drug permeability through the intestinal epithelium. Medium chain lipids (C<12) permeate the enterocyte and enter blood arteries immediately. The lymphatic route facilitates the absorption of long unsaturated chain lipids (C18:1, C18:2).

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The drug's physicochemical characteristics and the desired formulation attributes influence the choice of excipient (Available from). To enhance a drug's solubility, for instance, salt production can frequently be explored if the molecule has an ionizable component. The stability of the drug may also be influenced by the application of excipients. Drug bioavailability can be affected by excipients that inhibit or increase the activity of cytochrome P450 enzymes, for instance, which can influence how quickly drugs are metabolized. As a result, it's critical to choose excipients carefully so that they don't interfere with the drug's stability or pharmacokinetics. The use of excipients is essential in improving the solubility of drugs that dissolve poorly. Excipients utilized most frequently for solubility enhancement are lipids, polymers, and surfactants. The pharmacological qualities and intended formulation features influence the excipient selection. The pharmacokinetics and stability of the drugs must be preserved while choosing excipients and therefore significant thought must be given to which ones work ideally (Available from).

## Standardization of Excipients

To ensure the safety and effectiveness of pharmaceutical products, standardization of excipients is essential. A number of groups and programs, including the International Pharmaceutical Excipients Council (IPEC), have been set up to promote standardization across various guidelines for the production and application of pharmaceutical excipients. Several investigations have examined excipient variability, with a focus on how it affects the performance and processing of drug products. The source of the raw materials, the synthesis/manufacturing procedure, and the ideal concentration to be used in the finished product can all contribute to this variability.

The advancement of excipient standardization is greatly assisted by the International Pharmaceutical Excipients Council (IPEC). It seeks to promote the harmonization of various standards for the production and application of pharmaceutical excipients, eventually leading to the advancement of enhanced product quality and consumer safety. The organization also offers the pharmaceutical industry helpful guidelines and resources to ensure the quality and safety of excipients used in drug products (Peng Soh JL *et al.*, 2015).

The pharmaceutical industry has shown interest in excipient variability, with research concentrating on how it affects the functionality of dosage forms and the performance of drug products. This variation may affect a blend's homogeneity and content uniformity as well as the impact of various pharmaceutical

processes on the finished product. Pharmaceutical product performance and quality must be maintained, and this requires an understanding of and approach to excipient variability.

To further revolutionize drug formulation, the development of novel excipients has been a major area of focus in recent years. Reviewing novel excipients can help you better understand the types and uses of these cutting-edge excipients and how they can improve the functionality and performance of pharmaceutical formulations. The focus on new excipients highlights the ongoing efforts to enhance and standardize the components used in the creation of new drugs.

In conclusion, IPEC and other organizations are instrumental in promoting harmonized standards for excipients, which is a crucial component of pharmaceutical development. The variability of excipients has been studied in extensive detail, and the development of new excipients keeps pushing the boundaries of innovation in medication formulation. To ensure the effectiveness, safety, and quality of pharmaceutical products, it is crucial to comprehend and take care of these factors (Dureja H & Kumar D, 2013).

## Excipient Stability Testing

Testing the stability of excipients is an important part of pharmaceutical formulation. A number of investigations have been carried out to assess the effects of excipients' chemical and physical instabilities on the finished product. The selection of excipients has a major impact on a number of formulation parameters, including shelf life, disintegration, and dissolution. To ensure the security and efficacy of oral solid dosage forms, excipient stability testing is crucial.

In excipient stability testing, the relationship between moisture and excipients and its effects on the stability of drugs that are sensitive to moisture are critical factors to take into account. The main goal of stability testing is to evaluate chemical deterioration in order to ensure that the product is safe for the duration of its shelf life. Chemical degradation is frequently studied through accelerated stability studies, and the results are frequently extrapolated for long-term storage. To assure product quality, pharmaceutical products, including directly compressed tablets, must also have their physical stability assessed in addition to their chemical stability (Darji MA *et al.*, 2018).

Planning and carrying out scientific studies to ascertain the stability of excipients is governed by guidelines provided by the International Pharmaceutical Excipients Council. These recommendations focus on the elements that should be taken into account when performing stability studies on excipients, such as the necessity of stability programs, the categorization of excipients according to stability, and the structure of stability studies. An excipient stability study's main goals are to demonstrate that the excipient will continue to fulfill the manufacturer's specifications, specify suitable storage settings, ascertain shelf life, and validate shelf-life claims.

Since forced degradation samples must include all potential degradation impurities, current regulatory requirements place a strong emphasis on the validation of stability indicating methods. Making sure the techniques utilized for stability testing are accurate and dependable is a crucial part of the validation process for pharmaceutical stability analysis (Chaudhari SP & Patil PS, 2012).

## Excipient safety evaluation

To ensure the safety and efficacy of the finished product, pharmaceutical excipients are a necessary component of drug products, and their safety evaluation is critical. Excipient safety evaluation is a multifaceted process that takes into account a number of variables, such as the intended use, the mode of administration, and any possible interactions with active pharmaceutical ingredients and other excipients.

## General status of pharmaceutical excipients

A review article states that one of the most important aspects of drug development is the safety of pharmaceutical excipients. According to the article, an excipient's efficacy, potential toxicity, and intended use should all be taken into consideration when calculating its risk/benefit ratio. In order to reduce the possibility of toxicity, the article also emphasizes how crucial it is to simplify the formulations as much as possible (Abrantes CG *et al.*, 2016).

## Safety Assessment of new Pharmaceutical Excipients

An article offered a set of suggested guidelines for the evaluation of new pharmaceutical excipients' safety. The International Pharmaceutical Excipients Council's Safety Committee created the guidelines, which are based on the most up-to-date toxicological research available. The guidelines offer a method for establishing safe usage conditions for suggested pharmaceutical excipients that is grounded in science.

## Toxicity testing of Excipients

Excipient toxicity testing is a crucial component of evaluating their safety; it should be carried out in compliance with good manufacturing practices, good distribution practices, good laboratory practices, and guiding principles in toxicology assessment. Genotoxicity and carcinogenicity studies should be included in the toxicity testing, in addition to acute, sub-acute, and chronic toxicity studies (Abrantes CG *et al.*, 2016).

## Excipient Safety Evaluation in Parenteral Formulations

One of the most important parts of drug development is evaluating the excipient safety in parenteral formulations. Testing for pyrogenicity, sterility, and compatibility with other formulation

ingredients should be part of the safety assessment of excipients used in parenteral formulations (Abrantes CG *et al.*, 2016).

## Excipient Safety Evaluation in Oral Formulations

The safety assessment of excipients used in oral formulations is one of the most significant parts of drug development. The Food and Drug Administration (FDA) of the United States provides guidelines for the safety assessment of prospective novel excipients intended for use in pharmaceutical products labelled for clinical use of longer than three months. This guideline describes testing procedures for drugs meant for short-, intermediate-, and long-term use as well as recommended excipient toxicity testing for pulmonary, injectable, and topical treatments. It emphasises how important it is to establish safe and appropriate limits for these compounds and do risk-benefit evaluations on proposed novel excipients.

## Excipient Safety Evaluation in Topical Formulations

Ensuring the quality and safety of pharmaceutical products involves evaluating the safety of excipients used in topical formulations. A number of resources offer direction on this subject. The FDA's "Guidance for Industry" discusses testing procedures for drugs meant for short-, intermediate-, and long-term use as well as recommended excipient toxicity testing for topical treatments. It also covers suggested safety assessments for excipients that are suggested for use in over-the-counter and generic drug products.

## Excipient Safety Evaluation in Ophthalmic Formulations

A critical component of drug development is the safety assessment of excipients used in ophthalmic formulations, especially given the sensitivity of ocular tissues. At the target site, ocular drug delivery systems need to maintain consistent, safe, and user-friendly concentrations. To satisfy the specifications of a certain medication formulation, excipients used in ophthalmic formulations go through particular processing and treatments. The necessity of evaluating the safety of ocular drug delivery formulations has become more pressing with the acceleration of the development of new drug candidates and innovative delivery methods for the treatment of ocular diseases. Furthermore, excipient safety and biopharmaceutical issues in off-label pediatric formulations have been examined, emphasizing the significance of using a risk-based assessment to support the use of excipients in pediatric formulations (Osterberg RE *et al.*, 2011).

## Excipient Safety Evaluation in Inhalation Formulations

Excipient selection for inhalation formulations must be done carefully because there are few FDA-approved options and new excipients must undergo rigorous toxicity testing. The workload and uncertainty in the development of new drug products are increased by the absence of regulatory guidance on excipient safety evaluation. Certain non-clinical safety data can be replaced by human data for some excipients; however, it is preferable to use an excipient that has been shown to have been exposed to humans in the past under conditions pertinent to the intended use. Excipients can change the characteristics of drug particles and their aerodynamic behavior in inhalation formulations. However, there is a limited number of excipients that have been approved for use in pulmonary delivery, and using an unapproved excipient comes with additional work, expense, time, and the possibility of rejection by regulatory bodies (Osterberg RE *et al.*, 2011).

## Nanotechnology based Excipients

Excipients based on nanotechnology are crucial for drug delivery systems because they provide benefits like enhanced solubility, stability, and targeted delivery. Polymers, targeting agents, coating agents, and lipids are examples of excipients for nanomedicines that are used to improve absorption or regulate the release of the drug substance. These excipients are necessary for stabilizing the finished pharmaceutical product and putting structures together. The categorization of excipients and pharmaceutical ingredients for nanomedicines, however, is up for debate, especially when it comes to regulatory review and product approval (Hemmrich E and McNeil S, 2023).

Drug delivery systems have been greatly improved by nanotechnology, making it possible to employ FDA-approved nanoparticle medications as adjuvants in combination cancer treatments. Because of their special qualities, drugs can be delivered to target sites with greater stability and specificity, increasing treatment efficacy. Additionally, nanotechnology has transformed imaging and diagnostic techniques, which has aided in the creation of precise and accurate drug delivery systems.

Drug delivery systems like nanoshells and nanobubbles are made from nanoparticles, which have special qualities that can be adjusted for different uses. While nanobubbles are formed at the nanoscale and can be stabilized at room temperature, offering opportunities for various medical applications, nanoshells, with a silica core and an outer layer of metal, are used for drug targeting. These nanostructures show how versatile and adaptable drug delivery systems based on nanotechnology can be (Mazayen ZM *et al.*, 2022).

Drug delivery systems based on nanotechnology have advanced significantly in the field of nanobiotechnology, with an emphasis on addressing the drawbacks of conventional delivery techniques. The delivery of medicinal drugs, biosensors, and tissue engineering applications may all be enhanced by nanoparticles because of their small size and special characteristics. It may be possible to get around current restrictions and improve the efficacy of drug delivery systems by using nanotechnology approaches in drug design (Serrano-Mora LE *et al.*, 2021).

Since they have special physical, electrical, magnetic, and optical properties, inorganic nanoparticles like gold, iron, and silica have been used in advanced nanoparticle designs for drug delivery. These engineered nanoparticles may increase the drugs' solubility and stability while also improving their transport and delivery properties. The goal of this field's continuing research and development is to produce precision nanoparticles for drug delivery applications that are both personalized and non-personalized (Yu YB *et al.*, 2021).

In conclusion, excipients and drug delivery systems based on nanotechnology have greatly advanced medicine and offered unique opportunities to raise the efficacy and accuracy of drug delivery. Because of their adaptability and variety of qualities, nanoparticles serve as helpful tools for the development of novel drug delivery systems that have the potential to overcome current constraints and improve patient outcomes (Sim S and Wong NK, 2021).

## Natural and biodegradable excipients

Because of their sustainability, lower environmental impact, and biocompatibility, natural and biodegradable excipients have drawn a lot of attention in the pharmaceutical and biomedical industries. Numerous natural polymers, including hyaluronic acid, alginate, chitosan, and albumin, have been thoroughly studied for their potential in drug delivery systems. These polymers can be used in targeted and customized drug delivery systems because of their benefits, which include enhanced bioavailability, biodegradability, and biocompatibility. Natural polymers have also been investigated for application in cardiac tissue engineering, where their biodegradability and capacity to retain mechanical qualities are very advantageous. Chitosan is a naturally occurring polymer that is biocompatible, biodegradable, and nontoxic. Its exceptional film-forming capacity has made it a viable excipient for a range of pharmaceutical compositions. Natural polymers are also well-known for their sustainability, renewability, and abundance, all of which are crucial for the development of formulations that are ecologically friendly and green (Idrees H *et al.*, 2020).

Natural and biodegradable polymers have certain drawbacks in addition to their numerous advantages, like rapid disintegration and limited electrical conductivity. Despite these obstacles, scientists are still investigating and creating novel biodegradable polymers to improve traditional dosing systems and reduce the adverse impacts of pharmaceutical formulations on the environment. Excipients are essential in the production of dosage forms because they enhance the physicochemical characteristics of the product. The use of natural and biodegradable excipients is consistent with the pharmaceutical industry's increasing focus on ecologically conscious and sustainable operations (Pockle RD *et al.*, 2023).

The general sustainability of pharmaceutical formulations, tissue engineering, and drug delivery systems could all be significantly affected by the study and development of natural and biodegradable excipients, especially polymers. A dedication toward creating biomedical innovations while reducing environmental harm is evident in the continuous investigation of these materials (Patel R *et al.*, 2020).

## Emerging Trends

### *Co-processing for Multifunctional Excipients*

The method of coprocessing multifunctional excipients involves mixing two or more existing excipients at the subparticle level in order to produce a single, enhanced multifunctional excipient. Enhanced flow, compressibility, compactibility, and disintegration ability are a few examples of these qualities. As tablet manufacturing techniques have advanced, so has the need for excipients with enhanced capabilities, which has raised interest in co-processed excipients (Saha S and Shahiwala AF, 2009).

Coprocessing requires certain material characteristics, such as the physicochemical and mechanical properties of the excipients. There are several ways to accomplish coprocessing, and the excipients that are produced minimize the disadvantages of the individual components, providing significant advantages.

Research has demonstrated the benefits of utilizing natural ingredients in coprocessing and the possibility of creating customized, designer excipients to satisfy specific formulation requirements. Given the rising cost of creating new chemical entities and the preference for direct compaction processes, the development of high-functionality coprocessed excipients is viewed as a significant opportunity (Serrano-Mora LE *et al.*, 2021).

In addition, coprocessed excipient regulations must be taken into account. A current and emerging trend in excipient technology is the development of single multifunctional excipients rather than utilizing multiple separate excipients in formulations. In a nutshell coprocessing multifunctional excipients presents a viable way to meet the growing need in tablet manufacturing for excipients with better qualities. Subparticle-level excipient combinations have the potential to reduce the need for numerous separate excipients in formulations by producing high-functionality excipients with improved performance. Nonetheless, it's crucial to take regulatory concerns into account and make sure the co-processed excipients that are produced fulfill the precise functionality needs of the intended applications (Garg N *et al.*, 2013).

## Excipient innovation for personalized medicine

A key factor in the advancement of personalized medicine is excipient innovation, especially when it comes to customized

pharmaceutical products and Personalized Drug Delivery Systems (PDDS). Drug formulations can be specific to each patient's unique needs by incorporating excipients, which are inactive ingredients, according to variables like age, sex, and genetic composition. This strategy may increase medication efficacy, lessen adverse effects, and improve patient outcomes. Moreover, excipient integration in personalized medicine may result in financial savings for insurers, healthcare providers, and patients. As the field of personalized medicine develops, the use of excipients is probably going to become more and more crucial for improving patient care.

The potential of 3D printing technology in the pharmaceutical industry has been suggested by recent advancements in personalized medicines that are 3D printed. Complex formulations can be created with 3D printing using straightforward methods, and they can be customized to meet each patient's unique needs. This technology can create precisely dosed medications and patient-tailored drug delivery systems, which could completely transform the pharmaceutical industry, especially in the context of personalized medicine. For widespread adoption, however, a number of technical, quality control, and regulatory issues still need to be resolved before 3D-printed personalized medications are practical (Omari D *et al.*, 2023).

The treatment of chronic diseases and the delivery of multiple drug doses customized for individual patients are made more difficult by the mass production-based structure of conventional pharmaceutical manufacturing today. As a crucial component of personalized medicine, Personalized Drug Delivery Systems (PDDS) aim to tailor the dosage form and drug release kinetics to each patient's specific requirements (Peng Soh JL *et al.*, 2015).

Bridging the gap between traditional pharmaceutical production and the demands of personalized medicine requires the integration of PDDS into digital health and the application of advanced manufacturing techniques. The role of excipients in customizing drugs for individual patients is becoming more widely acknowledged in the context of personalized medicine. Excipients can be modified to allow for the targeting specific tissues or cells, increasing drug efficacy and lowering side effects. They can also be used to improve the stability, safety, and efficacy of drug formulations. Everyone involved could potentially save cost if this customized approach to drug products can lower the quantity needed and increase the effectiveness of drug therapy (Vaz VM and Kumar L, 2021).

Excipient innovation has enormous potential to advance personalized medicine, especially in the areas of 3D printing and customized drug delivery systems. Excipients can help to increase drug efficacy, decrease side effects, and save costs by tailoring drug formulations and drug delivery methods to each patient's specific needs. To be widely adopted, these innovations in personalized medicine still face a number of technical and regulatory obstacles that must be overcome in order to be put into practice. The integration of excipients and advanced manufacturing techniques is anticipated to become more crucial as the field of personalized medicine develops in terms of enhancing patient care and treatment results (Vaz VM and Kumar L, 2021).

## Advances in taste-masking technologies

In particular, taste-masking technologies are essential for improving the palatability of drugs taken orally for elderly and pediatric patients. Various techniques, such as physical methods involving the use of sweeteners, microencapsulation, and the effervescent base in drug formulations, are used to mask the unpleasant taste of drugs. Furthermore, powders, chewable tablets, and liquid suspensions have had their tastes masked by specialized methods like microemulsion technology. Many taste-masking techniques have been developed in response to the need for better palatability, demonstrating the significance of this parameter in ensuring patient compliance and preference (Sohi H *et al.*, 2004).

The basis of taste-masking technologies is the variation in taste thresholds and the use of different techniques to select the masking technology that best suits the Active Pharmaceutical Ingredients (API) characteristics. These technologies solve a major formulation challenge, especially for pediatric patients, by enabling the oral administration of bitter drugs with a tolerable degree of palatability. Since it is commonly known that unpleasant tastes can have a substantial negative influence on patient acceptance, particularly in younger patients, taste-masking technologies are an important area of focus for pharmaceutical development (Sheikh M *et al.*, 2023).

Taste-masking technologies refer to a range of techniques and strategies intended to mask the disagreeable taste of pharmaceuticals, thereby improving patient acceptance and adherence. The significance of taste-masking technologies in pharmaceutical formulation and the need to evaluate their efficacy to ensure the development of palatable and effective drug products are highlighted by the ongoing advancements in this field (Sohi H *et al.*, 2004).

## Green chemistry approaches in Excipient Synthesis

Green chemistry techniques in excipient synthesis use non-toxic and sustainable solvents, raw materials, and reaction conditions in an effort to lessen the process's negative environmental effects. Natural products have been incorporated into topical green formulations as excipients. A review of using arginine as a building block to create environmentally friendly excipients has been conducted. The foundation of green chemistry, which aims to promote the use of environmentally friendly alternative reaction conditions and discourage the use of dangerous chemicals, is the 12 Principles of Green Chemistry. Green chemistry principles have been utilized in the synthesis of bio-based surfactants,

including sucrose esters and alkyl polyglucosides. The synthesis of pharmacologically active compounds can be complex, requiring multiple steps and harsh reaction conditions. This makes the synthesis of excipients using green chemistry approaches difficult.

In order to facilitate the sharing of best practices and knowledge, cooperation between industry, regulatory agencies, and researchers is required to fully apply green chemistry principles in excipient synthesis. Accurate control, selectivity, and resource efficiency can be made possible by continuous flow technologies, biocatalysts, and AI-driven methods. It is also necessary to have a deeper understanding of how the process affects the impurity profiles and products. Green and sustainable science is actively promoted in the pharmaceutical industry by groups like Merck (Rose HB *et al*., 2022).

## Characterization of Excipients

The compatibility of excipients with Active Pharmaceutical Ingredients (APIs) is determined through compatibility studies. The physical and chemical interactions between excipients and APIs are discussed in these studies. To identify drug-excipient interactions and optimize drug formulation, spectroscopic and thermal analysis techniques like FTIR, UV-vis, DSC, and TGA are crucial (Bugay DE, 2001).

An important component of drug development is the physical characterization of pharmaceutical solids. Characterizing excipients is essential to ensuring the final product's quality, safety, and efficacy because they are an essential component of drug formulation. Characterizing excipients is a common use for spectroscopic methods like Ultraviolet-visible (UV-vis) and Fourier-Transform Infrared (FTIR) spectroscopy. The functional groups, chemical makeup, and purity of the excipients are all disclosed by these procedures (Patel R *et al*., 2020).

The thermal behavior of excipients is investigated using thermal analysis methods such as Thermogravimetric Analysis (TGA) and Differential Scanning Calorimetry (DSC). These methods yield data regarding the excipients' melting point, glass transition temperature, and thermal stability. The optimization of the drug formulation and the choice of excipients depend on this information (Pockle RD *et al*., 2023).

To ascertain the particle size distribution of excipients, particle size analysis methods like laser diffraction and microscopy are employed. The excipients' surface area, shape, and particle size are all disclosed by these methods. This information is essential for developing drug delivery systems and optimizing drug formulation (Belayneh A *et al*., 2020).

Excipients' flow properties are ascertained through rheological studies. These investigations offer details regarding the excipients' viscosity, elasticity, and plasticity. The development of drug delivery systems like gels, emulsions, and suspensions requires this knowledge (Felton LA, 2005).

Determining the surface area and pore size distribution of excipients is performed through measurements of porosity and surface area. The surface area that can be used for drug adsorption and the distribution of pore sizes that influence drug release are indicated by these measurements. Drug delivery systems like porous matrices and sustained-release formulations require this information to be developed (Darji MA *et al*., 2018).

## Challenges and Future Directions

The manufacturing and distribution of safe and effective drugs are ensured by the intricate and strictly regulated pharmaceutical supply chain. It calls for meticulous care to detail, stringent quality assurance, and a steadfast dedication to the security and welfare of the patient. Every stage of the process is linked to the others, acting as an essential link in the chain, from sourcing raw materials to manufacturing, packaging, distribution, and final dispensing.

Specific risks pertaining to quality, regulatory compliance, and overall supply chain resilience are associated with the excipient supply chain. These risks include the requirement to assess and qualify both new and existing suppliers, as well as the interaction of performance, quality, testing, and compliance. Modern technologies, international cooperation between regulators and industry, and stakeholder collaboration on a global scale are necessary for ensuring high-quality excipients (Saito J *et al*., 2022).

The process of developing new drugs can be impacted by the sourcing of essential excipients, and supply chain disruptions can have serious repercussions. Critical excipient supply chains should be evaluated, and dual-sourcing tactics should be taken into account to reduce the risk of disruptions caused by things like shortages of raw materials, regulatory issues, and manufacturing difficulties (Rayaprolu BM *et al*., 2018).

Maintaining a robust pharmaceutical supply chain that can serve patients worldwide depends on the raw material regulatory environment. A consistent and flexible regulatory framework must be established due to a lack of resources and the complexity of regulations. Using guidelines such as ICH Q12 can help streamline the number of post approval submissions and make the supply chain more agile (Dave VS *et al*., 2015).

Pharmaceutical businesses must deal with issues related to regulatory compliance, supplier risk management, and supply chain continuity. By implementing digital technology and radically rethinking the procurement process, the crisis has presented an opportunity to enhance procurement capabilities. However, because of fixed costs and the difficulty of decentralized site-level purchasing, pharmaceutical companies have been hesitant to drastically improve procurement (Available from).

## CONCLUSION

Regulatory compliance, safety, toxicity, compatibility, and other important factors are highlighted in pharmaceutical excipients. In assessing the possible dangers and advantages of each excipient, especially in connection to safety and toxicity, the paper emphasizes the significance of a risk-based evaluation. The need to do extensive research on drug-excipient compatibility is also highlighted in order to guarantee the efficacy, stability, and quality of the finished pharmaceutical product. The article also addresses excipients' regulatory status and the procedures used by regulatory organizations like the FDA and the European Medicines Agency to evaluate them. The conclusion highlights the intricate process of selecting excipients and the need for thorough assessment to guarantee the effectiveness, safety, and conformity of pharmaceutical formulations with regulations.

## ACKNOWLEDGEMENT

I would like to extend my gratitude to Datta Meghe College of Pharmacy, DMIHER Wardha. I am deeply appreciative of the invaluable guidance and insightful feedback provided by Pranita Jirvankar ma'am. I also acknowledge the contributions of my colleagues Mujibullah Sheikh and Sanskruti Shende who assisted with analysis and manuscript preparation.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## ABBREVIATIONS

**API:** Active Pharmaceutical Ingredient; **IPEC:** International Pharmaceutical Excipient; Council; **FDA:** Food and Drug Administration; **EMA:** European Medicines Agency; **CFDA:** China Food and Drug Administration; **QbD:** Quality by Design; **DSC:** Differential Scanning Calorimetry; **FTIR:** Fourier Transform Infrared; **UV-vis:** Ultraviolet-visible; **TGA:** Thermogravimetric Analysis; **PDDS:** Personalized drug delivery systems; **BLA:** Biological license Application; **NDA:** New Drug Application; **IND:** Investigational New Drug Application.

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**Cite this article:** Makkad S, Sheikh M, Shende S, Jirvankar P. Pharmaceutical Excipients: Functions, Selection Criteria, and Emerging Trends. Int. J. Pharm. Investigation. 2025;15(2):361-76.

Int. J. Pharm. Investigation, 2025; 15(2):377-387.
https://www.jpionline.org

Review Article

# Review on Nanoemulsion Based Nanogel for Fungal Infection

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**ABSTRACT**

Nanoemulsion-based nanogels have emerged as a promising approach for treating fungal infections due to their unique properties. Nanoemulsions are fine oil-in-water or water-in-oil dispersions stabilized by surfactants, characterized by their small droplet size, which enhances the solubility and bioavailability of hydrophobic drugs. When integrated into nanogels, these nanoemulsions provide a stable, gel-like medium that ensures prolonged retention and controlled release of antifungal agents at the infection site. The nanogel matrix not only offers a localized treatment, reducing systemic side effects, but also protects the encapsulated drugs from degradation, enhancing their efficacy. Additionally, the high surface area and small size of nanoemulsion droplets facilitate better penetration into fungal biofilms and deeper layers of infected tissues, improving therapeutic outcomes. Recent studies have demonstrated the effectiveness of nanoemulsion-based nanogels in delivering antifungal agents like fluconazole, amphotericin B, and clotrimazole, showing enhanced antifungal activity compared to conventional formulations. These nanogels exhibit superior mucoadhesive properties, making them suitable for treating mucosal infections. In conclusion, nanoemulsion-based nanogels represent a significant advancement in antifungal therapy, offering improved drug delivery, enhanced antifungal efficacy, and reduced adverse effects, thus holding great potential for the effective management of fungal infections.

**Keywords:** Antifungal Agents, Hydrophobic Drugs, Mucoadhesive, Nanoemulsions.

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**Received:** 13-02-2024;
**Revised:** 16-04-2024;
**Accepted:** 28-06-2024.

## INTRODUCTION

Infections are increasing and are one of the most important factors in human health. The end of the last century and the beginning of the current one were marked by a decrease in the interest and number of new drugs resulting from their long development and high cost because many diseases had been eradicated anyway (Sousa *et al*., 2020). This changed in a dynamic and evolving way, with the resurgence of many viral, bacterial and especially fungal diseases, such as the well-known Acquired Immunodeficiency Syndrome (AIDS), by the Epstein-Barr virus, hepatitis, tuberculosis and others arose due to ura disease (Bongomin *et al*., 2022).

The return of fungal diseases on a large scale has brought difficulties and complications for medical treatment, since the agents causing these infections are difficult to treat. Advances in the development of new delivery systems aim to optimize therapy, focusing on targeting the therapeutic agent in infected areas, reducing dose intervals, side effects and improving bioavailability. Nanostructures, especially emulsions and hydrogels, are promising drug delivery systems and reduce the development time of the drug to market. In this manuscript, we developed and evaluated a nanoemulsion-based hydrogel for the treatment of fungal infections caused by the K. Sprengeri vegetable's essential oil (Rhijn and Bromley, 2021; Gupta *et al*., 2021; Wiederhold, 2022).

### Background and Rationale

Hence, the survey and assessment of nanoemulsion and nanogel-loaded drugs as antimycotic agents for the treatment of deep-seated fungal infections are essential. The efficacy of Chloramphenicol (CA), Clotrimazole (CT) and Itraconazole (IT) loaded Poly D, L-Lactide-co-Glycolide (PLGA) based nanogel was evaluated in our previous work and it revealed a profound and controlled capacity of the nanogel to deliver gene drugs at the site of infection (Aderibigbe, 2024). However, the retention of mature fungal infection to exert sustained drug release of gene drugs is needed. The development of polymeric or lipid-based nanoemulsions is reported to enhance thermodynamic stability and establish promising physicochemical and colloidal properties, respectively, that help protect antibiotics, antiviral and antifungal agents for inherently increased shelf life and provide sustained

**DOI:** 10.5530/ijpi.20251793

action with improved antifungal efficacy in the target tissue than conventional aqueous delivery (Choi and McClements, 2020).

The nanoemulsions, having a droplet size in the range of 10-100 nm, which provides a high surface area for delivering water-insoluble drugs in a solubilized form within an oil-in-water pre-concentrate. This results in enhancing drug permeation and retention within deep-seated fungal infections. The nanoemulsions, with a droplet diameter below 200 nm, typically protects the incorporated drug from degradation, enhances its uptake into the cell, favors controlled and sustained drug release and likely potentiates its retention within the deep-seated target niche. The nanogel, having a spongy and porous system, allows drug content to be loaded within the nanogel core. The nanogel network swells and disassociates in the presence of body physiological vaginal (acidic pH, high viscosity, increased temperature) and rectal (neutral pH, low viscosity, decreased temperature) triggering factors, promoting highly localized sustained drug delivery without systemic toxic side effects in treating deep-seated vaginal and rectal fungal infections (Sadeq, 2020; Ma *et al*., 2021; Malode *et al*., 2021).

## Scope and Objectives

The prepared nanoemulsions have been characterized and further developed into nanogel using a synthetic polymer. The formulation work encompasses tioconazole-loaded nanoemulsions preparation by ultrasonication method using soybean oil and cremophor ELP as oil and surfactant respectively.

Secondly, the existing work aims to evaluate the suitability of such optimized eudragit S100-based nanogel in a wound healing delivery strategy, using a standardized wound healing mouse model.

In this work, nanoemulsion-based nanogel systems are an attractive system for incorporating a drug, which can be used for treating various fungal skin infections, in a way facilitating the efficacy at affected sites, improving the localized sustained release of the drug, as well as reducing the side effects.

## Nanoemulsions and Nanogels

A nanogel-based nanoemulsions technique using the self-gelation of carbopol 940 polymers was also mentioned in detail, in which the manipulated polymer microstructure could give the formulated nanogels a unique organization and properties. The focus is on the interfacial nanogel layer that determines its controlled drug release.

Nanogels and nanoemulsions are potential drug delivery systems used to improve the therapeutic or toxic effects of drugs by either selective targeting or imaging of the site in the body or by controlling an *in situ* release. In addition, nanogels and nanoemulsions have full function in the optical properties of contrast agents, making them applicable to multiple imaging technologies compatible.

Nanogels are extensively used in the delivery of both hydrophilic and hydrophobic drugs to the site of action and they possess excellent properties like ease of administration, enhanced bioavailability and prolonged release. Due to improvements in the drug delivery route, nanogels and nanoemulsions can be used for both lipophilic and hydrophilic drugs that can extend half-life, slow down the clearance of the active component in the body, reduce the adverse effects of the drug and achieve an easy therapeutic concentration (Garg *et al*., 2020; (Patil and Kontamwar, 2021; Carvalho *et al*., 2021; Sindhu *et al*., 2022).

Nanogels based nanoemulsions are a less explored drug delivery system for the efficient delivery of antifungal drugs. In this probable work, an attempt was made to fabricate and evaluate the nanogels based nanoemulsions for prolonged and efficient delivery of amphotericin B. The formulation was optimized and *in vitro* drug release and *in vivo* antifungal testing had shown promising results. Its significant use lies in the proper administration of amphotericin B with the required concentrations for its efficient antifungal effect and also decreases the toxic nature caused by IV injection of amphotericin B (Li *et al*., 2021).

Nanoemulsions have been used extensively in agricultural, pharmaceutical and food products due to their unique properties. Nanoemulsions are prepared through different methods like high-pressure homogenization, microfluidization, ultrasonication and phase inversion composition. Among them, phase inversion composition is a simple, easy method that offers high drug encapsulation along with uniform size distribution at low energy (Zhang and Zhang, 2020).

## Nanoemulsions: Composition and Properties

The air-containing lipid droplets are coated with Polyethylene Glycol (PEG) and applicable targeting antibodies (e.g., transferrin), they can be precisely targeted to the vascular endothelia of the occlusion tissue. It could target the gas volume in the brain and diagnose brain lesions. PBio found that this type of nanoemulsions could be used in a mouse model of breast cancer. Animal experiments show that 5 to 20 min after the nanoemulsions containing macrophages that can bind to over expressed vascular endothelial cells accumulates in the mouse blood vessels, large embolisms are found in the corresponding opaque tissues. Such nanoemulsions provides a new possibility for the diagnosis, treatment and monitoring of vascular occlusion diseases (Zhang *et al*., 2021).

The nanostructure of emulsion is a novelty in emulsion droplets. The droplets in the emulsion could employ drug targeting to deliver hydrophobic drugs *in vivo*. We can obtain these favorable biological distribution characteristics by altering the hydrophobic structure of the nanoemulsions. Propranolol in nanoemulsions

was distributed in adipose tissue (rich in hydrophobic) more significantly than the conventional liquid particle emulsion. The size of the droplet is adjusted to the diameter of the capillary, thereby reducing non-specific drug deposition along the arteriole wall, thereby facilitating the targeted delivery of colloidal drug carriers to the hydrophobic site of action (Rajput *et al*., 2020).

## Nanogels: Structure and Functionality

Nanogels are highly swollen cross-linked polymeric networks dispersed in water. They are structurally similar to hydrogels but with dimensional reduction to the nanoscale size. Hydrogels are physically or covalently cross-linked polymeric three-dimensional networks that are capable of imbibing large amounts of water or biological fluids. The crosslinked networks in hydrogels vary according to the nature of monomers, repeating units and usually undergo swelling. If crosslinked polymers swell in a dispersed aqueous medium, those nanoscale gel structures are termed as 'nanogels' (Mauri *et al*., 2021; Scotti *et al*., 2022; Yin *et al*., 2020). The network structure and dimensional reduction to nanoscale are unique to nanogels, leading to the intriguing properties of nanogel resulting in considerable attention from scientific and industrial research. Owing to their characteristic range of particle sizes, nanogel formulations typically have low viscous liquids or soft solids properties. The nanoscaled size allows nanogels to permeate into tissues or efficiently uptake by a majority of the cells, which enables efficient penetration against biological barriers, such as the blood or intestinal barriers and also leads to rapid cellular internalization via endocytosis-mediated pathway such as clathrin-mediated endocytosis. Thus, nanogels are widely viewed as prescient multifunctional materials for medical delivery. Currently, some nanogels have inspired significant interest and have been chosen in other industrial applications of medical imaging, tissue engineering and designing enzyme immobilized supports and so on. The unique feature of the nanogel is discussed in brief (Cao *et al*., 2020; Dos Santos Matos *et al*., 2020).

## Fungal Infections

Researchers have encapsulated amphotericin B into a nanoemulsion which can be used orally. Especially in the Indian subcontinent, fungal infections are endemic and amphotericin B is the drug of choice for the treatment of visceral leishmaniasis. Treatment options include miltefosine, liposomal amphotericin B and combination therapy. After administration, amphotericin B is responsible for organ toxicity, producing both acute and chronic side effects. This is explained by the liposomal or lipid-related drug formulations available, including the high price of amphotericin B for the treatment of patients in developing countries. These formulations also appear to have some irreversible constructive effects (Fisher *et al*., 2022). Fungal infections are an emerging health problem and the increase in fungal infections is evident. The most commonly used antifungal drugs, azoles, mainly act on the cell membrane of fungi. The rise of resistance to these drugs has led to the urgent need for new therapeutic approaches. Recent conventional research has focused on the combination of two or more existing drugs with different mechanisms of action, instead of developing new molecules (Pathakumari *et al*., 2020). Alternative therapeutic approaches are being developed as well, in particular, the nanoencapsulation of existing antifungal drugs. Nanoscale technologies have enormous potential, particularly in offering an innovative approach for the formulation of poorly water-soluble drugs (Tirado-Sánchez *et al*., 2020).

## Types and Common Pathogens

There are different classes. Superficial mycoses are local infections of tissue or organ surfaces, where the pathogen proliferates without invading the subdermal tissues. They may be endemic or epidemic, clinical configurations resembling many other dermatoses. Or they can be the expression of more complex systems, including functional or metabolic alterations within the host that yield to imbalance of the biological relationship with the saprophyte microorganisms, which normally populate the corresponding sites and changes of the pathosphere by the action of one or more factors of charge. Cutaneous mycoses are a group of diseases with distinct clinical configurations or auxologic patterns, activated by the penetration, saprophyte invasion and proliferation in the stratum compactum of pathogens of a widespread mycetes sociologic, as clinically observable, mainly directly, with the appearance of colored macules, generally exercised with tests of virofteal findings (Mlynarczyk *et al*., 2021). Systemic mycoses are systemic generalized infectious syndromes determined by dimorphic micelles. The deep mycoses are thermonuclear diseases, occurring with important invasions to certain regions of the human organism, frequently reaching internal organs, presenting geographical distribution. They include lymphadenitis, paracoccidomycosis, histoplasmosis, blastomycosis, cryptococcosis and sporotrichosis. Deep Scopularioposis of Lymphatic System is due to the invasion of the lymphatic chain by a saprophyte basidiomycosis, but thermos de simulation profile, which extends to the subcutaneous cellular tissue, involving one or more lymphatic chains of the lateral cervical region, with exertion of several consultations; the lymphatic involvement only appears on MRI. Superficial mycoses usually include Pityriasis Chiracrai, white rot and black nail ringworm, hair infection, feet hyphae and scrotal tinea with the main pathogen of *Malassezia* sp (Renzi *et al*., 2021; Tragiannidis *et al*., 2021; McCarty *et al*., 2021).

## Current Treatment Challenges

Furthermore, the numbers of invasive fungal infections, along with the limited range of antifungal treatments available, make the development of new antifungal agents an essential part of the next phases of tackling these infections. Commercial antifungal drugs, although necessary for public health, have several issues, such as high cost, increasing resistance and limited range for

their use, being an impetus to develop new, effective and selective treatments for these agents.

In the last two decades, an exponentially increasing prevalence of invasive candidiasis and candidemia has been observed, indicating an urgent need for new and improved antifungal agents. Currently available drugs face serious challenges, such as the emergence of resistant strains caused by the widespread use of antifungal agents, high drug toxicity, limited spectrum of antimicrobial activity, insufficient solubility and tissue distribution, low selectivity toxicity to fungal cells and an increase in patients undergoing antitumor chemotherapy, organ transplants, or cardiac surgery. As a consequence, the treatment of fungal infections requires the patient to receive antifungals for an extended period of time, producing undesired side effects in patients and toxicity for the administration of antifungal treatment (Logan *et al*., 2020; Pandey *et al*., 2020).

## Combination Therapy Approach

Another research study from the Department of Pharmaceutics Andhra University, India formulated novel nanoparticles loaded gel for the treatment of vaginal fungal infections with butenafine HCl as the model drug. The *in vitro* VS-64 efflux pump inhibition in Candida species reduction was experimentally evidence for the higher accumulation of butenafine in nanoparticles compared to conventional topical formulation. The developed novel gel formulations loaded surface-modified nanoparticles improved the bioavailability of butenafine and efficient VS-64 efflux pump inhibiting action. The present minoxidil-loaded nanoemulgels can be used as a better and effective dosage form in the treatment of vaginal fungal infections (Kurakula and Naveen, 2020; Rial-Hermida *et al*., 2021).

Researchers have been turning their attention to combining several antifungal agents to treat severe fungal infections. Several reports suggest that there is a probability of interactions or a synergistic effect, which could be attributed to the increased clinical cure of fungi as different antifungal drugs. Nanogel with antifungal drugs such as itraconazole has been reported. It showed lower MIC and significantly higher antifungal activity against medically important Candida species, including some azole-resistant clinical strains. Due to its small particle size and high saturation solubility, it can penetrate the biofilm, resulting in the effective treatment of candidiasis (Yang *et al*., 2022).

## Rationale for Using Nanoemulsion-Based Nanogel

Hydrogels based on natural polysaccharides have become a versatile scaffold for therapeutic applications due to their nontoxic, biodegradable and biocompatible properties. However, to achieve the beneficial effects for topical or systemic drug delivery, nanogel formulations consisting of controllable nanoscale size and mechanical properties, high biocompatibility and loading efficiency, acceptable stability and desirable functions in release were widely studied and are still under development. Forming nanogels with nanoemulsions through physical or chemical cross-linking is one of the effective strategies for further obtaining hybrid materials with excellent characteristics and resolving the limitations that exist in nanoemulsions or nanogels, providing a promising prospect in therapeutic drug delivery (Manimaran *et al*., 2023; Golwala *et al*., 2020).

Nanogel is a combination of the nanosized materials of hydrogel and a nanoparticle, which has novel properties for various applications. Nanoemulsions are a thermodynamically stable and transparent dispersion of two immiscible liquids, typically water and oil (or any nonpolar liquid), stabilized by an interfacial film of surfactant molecules. They also satisfy the nanoscale structural criterion and usually possess some unique structural, optical and physicochemical properties. Modification in the conventional gels with nanoemulsions results in the formation of nanogels. Nanoemulsions can easily facilitate the formation of nanoemulsion-based nanogels. Furthermore, nanoemulsions refresh the polymer chain space, leading to the polymer chain conversion from hydrophobic to hydrophilic across the interface. It results in enhanced physical properties, i.e., elongation at break and tensile strength, due to covalent bonding between the gel and the nanoemulsions. Several studies utilizing emulsions with alginate and poly (N-isopropylacrylamide) (PNIPAAm) as a crosslinker to prepare alginate-based and PNIPAAM-based nanogels were reported (Rathod *et al*., 2024; Bhattacharya *et al*., 2020).

## Design and Formulation of Nanoemulsion-Based Nanogel

Nanoemulsions, with average particle sizes less than 100 nm, were formed under optimized processing conditions. The volume fraction of surfactant and co-surfactant influenced the formulation more significantly than homogenization speed. A Schematic Diagram of preparation of nanoemulsions is shown in Figure 1. The viscosity of nanogels, whose morphological measurement was recorded as good, was found to be well fitted with the power law. The released data of 78% from the nanoemulsions was the most suitable kinetic model, which suggested Fickian (anomalous diffusion) transport. The DoE-RSM used for the development of nanoemulsions in nanogel for antifungals with crab oil was found to provide positive and promising effects. The prepared formulation possessed excellent characteristics and had shown great potential for treating fungal infections in the future (Ahmad *et al*., 2022; Roselan *et al*., 2020).

Fungal infection is hard to treat because there are few antifungal active pharmaceutical ingredients, which restricts formulation development. And most of the available antifungals have significant drawbacks such as low solubility, poor permeability, multidrug resistance and low oral bioavailability. The objectives of this study are to develop a novel antifungal formulation, optimize

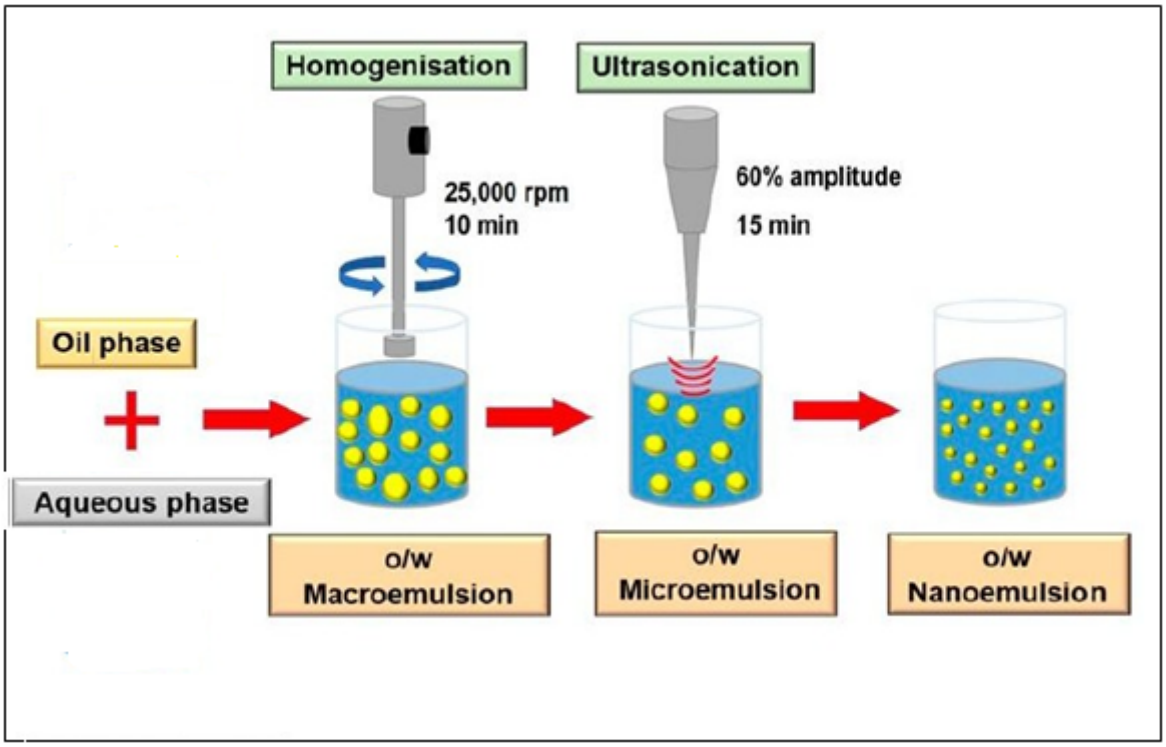


**Figure 1:** Schematic Diagram for the nanoemulsions preparation.

the preparation conditions and characterize the *in vitro* release behavior of the developed antifungals. The antifungal crab oil was taken as the oil phase for preparing nanoemulsions. Carbopol 940 was taken as the carrier for preparing nanogels and mixture design-response surface methodology was used to optimize the preparation conditions of nanoemulsion in nanogel (Roselan *et al*., 2020).

## Selection of Ingredients

Currently, fluconazole resistance continues to be the main obstacle to successful use, limited application, very high and inconsistent oral bioavailability, poor and variable topical permeation and solubility problems. The optimized nanogel was able to increase the antifungal activity upon bacterial strain accumulation loaded with 150 ppm G26 broth filtrate as an antidermatophytic agent. The purpose of this study is to overcome the instability and low entrapment effectiveness of the optimized nanogel by formulating a nanoemulsions base for nanoparticle encapsulation. The optimized nanoemulsion was mixed with a selected single-stabilizer hydroxypropyl methylcellulose that contains the loaded antidermatophytic agent and converted into a stable and monodispersed nanogel structure. The work study included antidermatophytic activity, rheology, *in vitro* release, physical appearance, centric ability, skin drying time and antifungal efficacy on an antifungal-treated rat model (Kotta *et al*., 2021).

Among all topical formulations, emulgel is affected as it can overcome the pharmacokinetic limitation of conventional gel without losing characteristics of easy and non-greasy application, as well as patient compliance. Developing a nanogel emulgel has a safe and efficacious site-specific drug delivery system that promises the accurate release of the incorporated agent it is intended. It is increasing drug bioavailability, decreasing systemic toxicity, improving the stability of volatile and photosensitive compounds, improving drug stability, enhancing drug permeation, sustaining drug release and improving patient compliance. In this study, we are trying to optimize the formulation that was previously studied by our team, encapsulating antifungal fluconazole nanogel from a nanoemulsions base. In our previous work, we successfully selected and optimized Streptomyces spp. G26 against *Candida albicans* (Elsewedy *et al*., 2021).

## Optimization of Formulation Parameters

In this approach, we studied the influence of independent formulation factors in nanoemulsions preparation and its effect on the dependent variables via response surface method. The experimental data were collected using a single-factor experimental procedure. Based on the preliminary experiments, the ranges and the levels for the three variables were selected. The design matrix was constructed based on the range of each factor and formulation runs were conducted according to the experimental design. After forming all the possible combinations of the formulation variables, the formulations of each combination were prepared according to the optimized method and the resultant nanogel was subjected to further investigations. As the factorial design matrix was created in order, a mathematical model was obtained and compatibility of the fitted model

was estimated in response Yates format. Finally, the resulting polynomial equations were expressed in mathematical mode and further analysis has been carried out in the form of 3D surface plots against the significant factors. The model was validated and the relationship between Z-potential versus different formulation parameters was established (Alam *et al*., 2022).

The 'Design of Experiments' is an appropriate tool to study and model the influence of formulation parameters used on the product quality. In the present research, we have used a 'Response Surface Methodology' in the form of a 'Central Composite Design' for the validation of the nanoemulsion-based nanogel. Three important factors including Na-caseinate, oil-surfactant and water ratios essential for the ocular nanogel have been studied. The influence of formulation parameters on the different responses has also been approached. A quadratic model was established within the ranges studied for analysis. To optimize the experimental conditions, constraint optimization method has also been applied. The compatibility of the fitted model has been evaluated by response Yates analysis (Gao *et al*., 2022).

## Characterization Techniques

Design and synthesis of core-shell (nanoemulsions) are very important as they are responsible for the drug entrapment into the polymeric shell of nanogel and also respond to different stimuli. Normally, various characterization techniques such as TEM and CLSM are necessary for the characterization of the core-shell structure of the nanoemulsions. To study the nanogels, a number of methods are needed to characterize different properties of the nanogels. The characterization techniques, once developed, can be extended to different applications depending on the requirements.

Various characterization techniques, including particle size, polydispersity index, core-shell structure of nanogel, zeta potential, morphology, solid-state behavior, *in vitro* drug release, *in vitro* and *in vivo* antifungal activity and cytotoxic effect on phagocytic cells, need to be carried out.

## Particle Size Analysis

The particle size distribution is important in the formulation of the nanogels, as it determines the physical properties of the nanogel. The size distribution of the nanogels was estimated using DLS. The selected nanogels were prepared and the particle sizes were calculated as a function of time. Initially, the nanogels were formed and the sizes were retarded. After a short incubation time, the size of the nanogels was increased and Z average of 594 nm was obtained. This effect signaled that the nanogels were swollen by the medium. With increased incubation time, aggregation was observed, due to the enhanced hydrophobic interaction driven by increased surfactant amounts. During the reaction, the distribution became broader, with the PDI higher than 0.5. This result indicates that the main part of the nanogels consisted of small-sized particles also produced with the light scattering effect and the aggregation degree was higher (He *et al*., 2023).

## Zeta Potential Measurement

In our study, magnetic nanogels with different storage times were measured using Zeta potential. The theoretical value of Zeta potential for the excellent stability of nanoparticles in liquid is not less than -30 mV or higher than +30 mV. The results showed that there was no significant potential change in the following 28 days, which may depend on their relatively higher absolute Zeta potential. The absolute value of nanogel Zeta potential is determined by the difference in O-Fe bond. Before storage, the calculated absolute Zeta potential showed a maximum and the potential is close to -41 mV and the potential remained relatively constant for 28 days, which may depend on their relatively higher absolute Zeta potential. The absolute potential value of particles stabilizes, but changes rapidly when the threshold is exceeded. Then, the potential of Zeta was calculated as 28.7, approximately -30 mV and +30 mV (Keskin *et al*., 2021).

## *In vitro* Evaluation

The nanogel was non-cytotoxic under an *in vitro* cytotoxicity study using Vero cells. Additionally, *in vitro* skin irritation studies demonstrated that the plain nanogel did not cause skin irritation, as evidenced by the histopathological evaluation after a 24 hr exposure time. Nanogels were prepared using carbopol 212 m (0.5% w/w) and hydroxypropyl methylcellulose (2% w/w) as the gelling agents. Clotrimazole was used as a model drug for minimum fungicidal concentration studies and was incorporated into the nanogel. The synthesized nanogels were characterized by the drug content, entrapment efficiency, pH, rheology, zeta potential, particle size distribution and polydispersity index. The physicochemical compatibility of the model drug with the components was evaluated by physical and chemical characterization. Cytotoxicity and skin irritation studies demonstrated that the developed clotrimazole-loaded HPMC K100 M nanogel was well tolerated. The present investigation was designed to develop clotrimazole nanogels and evaluate their suitability as a dermal nano-antifungal delivery system (Nnamani *et al*., 2021).

Nanogel prepared by the cold method was white and opaque with a smooth texture, whereas nanogel formulated by the hot method was transparent with a rubbery texture. The particle size and polydispersity index of carbopol 212 m/HPMC K100 M formulations were significantly affected by the selected gelling agent. The pH of the nanogel was within the acidic range, making it suitable for topical therapeutic application. Nanogels incorporating clotrimazole showed high drug entrapment efficiency in all formulations. Antifungal activity was evaluated against *Aspergillus flavus, Aspergillus niger, Penicillium chrysogenum* and *Candida albicans*. F1 4% HPMC K100 M nanogel formulated by the hot method was found to have a higher

antifungal effect against *A. niger* using an agar diffusion method (Arendrup *et al*., 2020).

## Antifungal Activity Assays

Minimum Inhibitory Concentration tests were commonly carried out for susceptibility testing of Candida. The technique was easy to perform and was used when a stock of a limited number of drugs was available, avoiding the need to perform all individual antifungal drugs to check their effectiveness. Four miconazole solutions of known activity with the same quality control values but about 20% of the miconazole content were used (range of 0.015 to 8 µg/mL for *C. albicans*) and found to be acceptable (Medina-Alarcón *et al*., 2021).

Any formulation becomes meaningful if it accomplishes the intended therapeutic action in an organism. Nanoemulgel would be required to release drugs slowly, to provide uniform drug concentration, reduce frequency of the drug administration and to improve patient compliance and tolerability and to increase the duration of treatment with reduced systemic toxicity. Formulations can be screened either by screening of nanogels for particle size diameter, zeta potential, polydispersity index, drug content, encapsulation efficiency, transmission electron micrographs and drug release and stability studies. However, they need to be evaluated by *in vitro* studies and drug release patterns. Finally, their therapeutic efficacy can be tested in *in vivo* experiments on different animal disease model (Pereira and Cotas, 2024).

## *In vivo* Studies

Antifungal LC2 NE2 treatment also did not promote any reduction in *C. gattii* CNS infection. However, NE3 antifungal therapy not only arrested the progression of the infection inhibiting main *C. gattii* interactions with the host but also reversed signs of illness and increased the activity of the infected animals.

The report of improved *in vitro* activity of NE3 against Cryptococcus spp. led to the necessity of examining whether it can also operate with the *in vitro* observed potential, in the *in vivo* model. Initially, a study was conducted involving both *in vivo* challenges using infected mice as well as antifungal treatment carried out using NE3. Overall, NE3 was found to be more efficacious in treating early-stage infections when testing against *C. gattii*, while having minimal toxicity toward mice. Interestingly, when tested against multidrug-resistant clinical *C. gattii* isolates, NE3 demonstrated a composition-dependent improved curative effect on infections caused by some Cryptococcus strains. After intranasal administration, NE3 performed well in both prophylactic and treatment experiments carried out using mice infected with *C. gattii*. When testing NE3 using a high mortality model, the average survival of the mice treated using NE3 was higher when compared with the mice treated with amphotericin B (Samson, 2020).

## Animal Models and Ethics Considerations

After infection, the animals were divided into four groups, I, II, III and IV and treated with PBS, natamycin, NE and NE/NG, respectively. An equal concentration of clotrimazole was added in the NE and NE/NG groups. At the end of the study, 30% of the animals in the PBS group had to be sacrificed due to irreversible keratitis, while 10% of the animals in the NE group (only reducing inflammation), 10% of the animals in the natamycin group and 70% of the NE/NG group completed the study with significant improvement in infection. Our results revealed that NE/NG significantly improved the ocular retention time and the antifungal efficacy of NE, which can be attributed to the mucoadhesive property of the gellan gum used in the synthesis of the nanogel. These results support NE/NG as a promising nanomedicine for the efficient treatment of fungal infection.

Both *in vitro* and *in vivo* models are necessary to assess the antifungal efficacy of nanoemulsion-based nanogel. *In vitro* antifungal efficacy assessment is helpful in determining the minimum inhibitory concentration of the nanogel. The antifungal efficacy of NE/NG was assessed against *F. solani* in an animal model of fungal keratitis. A total of twenty animals were used for the *in vivo* study. The animals were administered local anesthesia. For induction of fungal keratitis, 0.0186 mol/L of *F. solani* suspension cultures were injected into the corneal stroma using a 30-gauge needle. The infection was confirmed by 1% calcofluor white staining (McAleenan *et al*., 2020; Pereira *et al*., 2022).

## Pharmacokinetic and Pharmacodynamic Studies

PD efficacy is potent and critically dependent on the actual administered dose, such as the drug concentration at the site of infection. This drug concentration and the pharmacokinetic properties of a dosage regimen define the PK/PD index that correlates with drug efficacy. It is strictly applied for all known dosage forms. After collection of concentration-time data profiles, a calculation algorithm evaluates the PK-PD indices from temporal exposure-response dynamics (Pharmacobotanic bacterial killing of drug) required to produce selective endpoint action. Time-kill curve analysis is just one of several different *in vitro* exposure-response (time-kill-based) models used to define the relationship of drug concentration to inhibitory activity and a variety of alternate models (e.g., post-antibiotic, post-antifungal, post-antiviral, post-antimalarial and post-diagnosis effects) have been described to help explain the impact of chemotherapy on infecting microorganisms (Firacative, 2020; Jenks *et al*., 2020).

A limited number of reports are available on the pharmacokinetic and Pharmacokinetic-Pharmacodynamic (PK-PD) of NNGE and whether these dosage forms could offer healing with lower side effects remains unresolved. PK-PD is the scientific discipline involved in determining the relationships between drug dosage regimens and toxic effects. These studies have described the relationships of PK/PD index to the efficacy of NNGE. Usually,

determination of the standard PK/PD indices of NNGE is a crucial part of these studies.

## Safety and Toxicity Assessment

Fungal infections continue to cause significant morbidity and mortality despite an increasing number of antifungal agents. In therapy, there are various limitations of traditional fungicides, such as poor bioavailability, drug resistance and systemic side effects. In the present study, a propiconazole Nanoemulsions (RTM-NE), Nanostructured Lipid Carrier loaded with propiconazole (RTM-NLC) anda propiconazole nanogel; hydrogel loaded with RTM-NLC (RTM-NG) were designed for the skin delivery of a hydrophobic fungicide. The differences between the particle sizes through communication, zeta potential, morphological, entrapment efficiency, drug release profile, antifungal activity and safety profiles were examined.[60,61] The Minimum Inhibitory Concentration (MIC) of RTM-NE, RTM-NLC and RTM-NG against *M. canis* was 62.5 µg/mL, 15.63 µg/mL and 7.82 µg/mL, which were reduced by more than two-fold at each sample when compared to the free drug. An *in vitro* cytotoxicity test revealed that fresh and storage samples showed a particle size range of approximately 193 nm, a zeta potential of -9.60 mV and an entrapment efficiency of 92.53%. RTM-NE, RTM-NLC and RTM-NG had a slow-release profile in the sink condition. The safety evaluation of the prepared formulations revealed the safe and non-toxic nature of the nanoemulsions.

The therapeutic efficacy of and systemic side effects resulting from the administration of an antimicrobial drug are both important. An *in vitro* cytotoxicity study was performed using Vero cells and *in vivo* acute oral toxicity was performed in Balb/c mice. The cell viability of Vero cells treated with fresh and aged RTM-NLC and RTM-NG was above 80% at all concentrations, demonstrating the safety of the nanocarriers. An *in vivo* acute oral toxicity study showed no abnormalities in behavior or histopathological changes in all examined organs compared to the control. The non-irritating and non-toxic effects of the prepared nanocarriers in the host system displayed their potential future use as antifungal agents (Yang *et al*., 2021).

## *In vitro* Cytotoxicity Assays

### *Trypan Blue Exclusion Assay*

Media for mammalian cell culture must provide a variety of *in vivo* services and be capable of supporting the growth and viability throughout the life cycle of a given cell. Generally, media formulations consist of a source of energy for cellular processes (sugars); material for nucleic acid and phospholipid synthesis; a buffering system to maintain the physiological pH of the medium, which can be affected by the production of carbon dioxide, a byproduct of cellular respiration; ions and vitamins that are usually also provided as a mixture of fatty acids and protein, sterilized to avoid contamination. The main objective of the culture medium for *in vitro* assays is cytoprotection, which means maintenance of cell viability and its normal behavior. This is paramount to obtain biologically relevant and meaningful results in any experiment that aims to evaluate cell performance, due to pharmacological or toxicological studies, for example. Cell viability should also be an important parameter to be controlled in cell culture studies, as it affects the reliability, reproducibility and acceptability of the results. A number of methods can determine the viability density of the cells. A simple technique is the trypan blue exclusion test, which stains non-viable cells blue, allowing visualization under a light microscope. 0.05% trypan blue in phosphate-buffered saline was used to exclude dead cells for statistical analysis (Kamiloglu *et al*., 2020; Pintor *et al*., 2020).

## Chemicals and Reagents

All the chemicals, reagents and medium solutions used in the cytotoxic experiments were of analytical grade. They were purchased from closely located vendors. Their stock solutions were prepared in the laboratory and were kept in the dark at 4°C for a maximum of 8 weeks before use. In order to avoid evaporation of the solvents, the stock solutions were put in airtight vials. The contents of each vial were used only once. RPMI-1640 medium was supplemented with penicillin (100 U/mL), streptomycin (100 µg/mL) and 10% heat-inactivated fetal bovine serum. The compound (10 mM) was dissolved in DMSO and 20 or 50 µg/mL stock solutions were made prior to starting the experiments.

## *In vivo* Toxicity Studies

*In vivo* toxicity studies provide meaningful information regarding the hepatic and renal function of an organism. Evaluation of liver function was done by estimating the levels of liver enzymes like alanine aminotransferase, aspartate aminotransferase and alkaline phosphatase synthesized in liver and clearance of total bilirubin and albumin from liver. The estimation of serum alkaline phosphatase forms an early and sensitive test for hepatic damage. The level of serum albumin indirectly reflects the function of the liver. Serum bilirubin level provides information regarding liver cell necrosis and is raised in patients with hepatic or cholestatic disease (Makhdoumi *et al*., 2020).

The influence of TO-NE-NG and NP-NE-NG on liver and kidney function of both healthy and infected mice was investigated. The investigation revealed that a significant increase in liver enzymes, alanine aminotransferase, alkaline phosphatase and levels of bilirubin from liver, albumin and creatinine clearance from kidney were found in infected mice and treated with posaconazole. Treatment with NP-NE-NG and TO-NE-NG resulted in non-significant changes in liver enzymes and markers of liver function. A similar trend was observed for renal function in both healthy and infected mice and treated with NP-NE-NG and TO-NE-NG.

## Future Directions and Challenges

With respect to the evaluation of antifungal nanoemulsions, not many methods are available. The main problem lies in the growth of the fungi. Many antifungals are fungistatic, meaning they slow down or stop the growth of the fungal cells. This would lead to an inaccurate method being used. Currently, the half maximal Inhibitory Concentration ($IC_{50}$) is commonly used for the evaluation of antifungals. The time taken to reach the half maximal Inhibitory Concentration ($IC_{50}$) is assessed for each treatment and the faster the time required, the better the treatment. Is $IC_{50}$ the best method? Else, can other better methods be used for the evaluation of nanoemulsions as antifungal agents? More effective and selective assessment of the method should be developed (Miri *et al*., 2020; Trefzger *et al*., 2020).

The studies (*in vivo*) are yet to be conducted to prove the synergistic effect of essential oils, particularly in resistant strains. The failure of the most resistant strains in the clinical environment might be one of the potential problems in clinical therapy with diffusion therapy. However, history has shown the potential of essential oils as antifungals. Unrigging the bell, will the effort succeed in controlling the resistant strains as fast as the evolution of resistance? The usage of a larger amount of essential oils in the antifungal nanoemulsions should also be considered because there are no reports regarding the essential oil in monotherapy (Ju *et al*., 2022; Sharma *et al*., 2020).

## CONCLUSION

In summary, the results of the drug-gelatin combination mechanism study showed that there are good binding modes for the binding models in two nanogels, separated the different source of the drug particles in the nanogel and effectively increasing the probability of encouraging intermolecular interaction of Dexidin antifungal NAGs, revealing drug efficacy. The current comprehensive study highlighted the successful development of controlled drug delivery nanogel systems utilizing NAGs with Dexidin antifungal NAGs, which was fabricated by means of the nanoemulsions process by employing bio-ingredients-based biomaterial. Due to the small size and the oil-based membrane of the NAGs, these competitive drug-entrenched nanogels enhanced the local conditioning of the drugs. The drug-nanogel effectively controlled antifungal activity, as well as outstanding thermal stability. The biodegradation test recommends the potential application of the NAGs as a drug delivery agent. The *in vitro* and *in vivo* studies furnish drug efficacy and biocompatibility for further subungual delivery design preclinical and clinical studies.

## ACKNOWLEDGEMENT

We would like to thank to Dr. Mukesh Tiwari, Vice Chancellor, Dr. G. R. Selokar, Registrar and heartfelt thanks to Dr. Kanchan Shrivastava, Dy. Registrar from Sri Satya Sai University of Technology and Medical Science, Sehore, Madhya Pradesh, India for providing me all the support, facilities and resources for better accomplishment of this review in appropriate time.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## ABBREVIATIONS

**AIDS:** Acquired Immunodeficiency Syndrome; **CA:** Chloramphenicol; **CT:** Clotrimazole; **PIT:** Itraconazolec; **PLGA:** Poly D, L-lactide-co-glycolide; **PEG:** Polyethylene glycol; **PNIPAAm:** Poly N-isopropylacrylamide; **PK-PD:** Pharmacokinetic-Pharmacodynamic; **MIC:** Minimum inhibitory concentration.

## IMPLICATIONS

The Dexidin antifungal drug encapsulated oil-in-water nanoemulsions loaded nanogels have a particle size in the submicron range for fungal infection. The low concentration of efficient antifungal drug-loaded nanogels showed substantial mycological cure due to the direct application of the nanogel on subungual infection. The advantage of drug efficacy nanogel is beneficial for the treatment of subungual fungal infection, which contemplates developing a new drug delivery system for drug formulation with dexidin antifungal drug properties.

This delivery system also creates new dimensions for cosmetic application for nail care without the presence of harmful cocktail chemicals. The functional groups present in the drug-nanogels and drug-gelatin interactions in the biological/physiological medium were evaluated by ATR-FTIR and molecular docking. The results showed standard FT-IR results for the investigation of dexidin drug functional groups and docking outcomes were reflected for the drug-docking targets present in the nanogel. The docking analysis data has given an established structure of gelatin for NAGs. The average molecular distance between all possible pairs of the considered drug-nanogel was calculated and the dynamical behavior of the nanogel was studied using the radial distribution function.

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**Cite this article:** Gupta SK, Chaubey N. Review on Nanoemulsion Based Nanogel for Fungal Infection. Int. J. Pharm. Investigation. 2025;15(2):377-87.

Int. J. Pharm. Investigation, 2025; 15(2):388-396.
https://www.jpionline.org

Original Article

# Determination of Momelotinib in Rat Plasma by LC-MS/MS: Application to Pharmacokinetics Study

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## ABSTRACT

**Objectives:** This study describes developing and validating a novel method using LC-MS/MS to measure the concentration of Momelotinib in rat plasma. **Materials and Methods:** The pharmacokinetic applicability of the process was assessed in rats using a Symmetry $C_{18}$ column (250 mmx4.6 mm, 5 µm) at room temperature for separation. The mobile phase consisted of a mixture of acetonitrile and 0.1% formic acid (45:55) with a 1.0 mL/min flow rate and an injection volume of 10 µL. The Liquid Chromatography (LC) process was carried out over 5 min, with the mass spectrometer operating in positive ESI mode. The mass-to-charge ratio transitions for Momelotinib and Oclacitinib were determined as m/z 415.4285→160.4698 and 338.2142→266.9137, respectively. **Results and Discussion:** The concentration range for Momelotinib was established at 7.50-60.00 ng/mL, with a correlation coefficient of 0.9999. The precision and accuracy for High-Quality Control (HQC), Medium-Quality Control (MQC), Low-Quality Control (LQC) and Lower Limit of Quantification (LLQC) were 97.52%, 98.97%, 95.46% and 92.55%, respectively. The recovery accuracy for Momelotinib was found to be 97.29%. In pharmacokinetic studies, Momelotinib exhibited an average $AUC_{0-t}$ of 156 ng-hr/mL and a $C_{max}$ of 27.2 ng/mL in rats. **Conclusion:** In conclusion, this validated approach effectively demonstrates the determination of pharmacokinetic parameters following the oral administration of Momelotinib in Wistar rats.

**Keywords:** Momelotinib, Oclacitinib, Bioanalysis rat plasma, Pharmacokinetics.

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**Received:** 16-07-2024;
**Revised:** 25-10-2024;
**Accepted:** 19-12-2024.

## INTRODUCTION

Bioanalysis studies the presence of analytes in biological samples, such as biomarkers, drugs and metabolites (Meng & Bennett, 2012; Tasic, 2022). This process consists of several key steps: data reporting, sample collection and sample analysis. The first step involves obtaining samples from clinical or preclinical studies. These samples are then sent to a laboratory for analysis (Yin *et al*., 2015; Déglon *et al*., 2015; Mikkelsen and Cortón, 2004). Following this, the bioanalysis process includes sample clean-up, also known as sample preparation, which is essential for achieving accurate and reliable results. To ensure precision, it's vital to employ a sample preparation method that is both robust and stable, aimed at removing impurities from the sample matrix and optimizing the analytical system's performance (Tan & Shaw, 2014; Konatham *et al*., 2022).

Momelotinib is a Janus Kinase 1 (JAK1) and 2 (JAK2) inhibitors and competitively inhibits JAK ATP binding. It was approved by FDA on September 15, 2023 (Xu *et al*., 2019; Winton & Kota, 2017). Momelotinib is used to treat myelofibrosis. Myelofibrosis (MF) is a group of myeloproliferative neoplasms characterized by abnormal proliferative hematopoietic stem cells, leading to the release of cytokines and growth factors. MF includes Primary MF (PMF), Post-polycythemia Vera (PV) MF and post-Essential Thrombocythemia (ET) MF (Chifotides *et al*., 2022; Keam 2023). Clinical manifestations of MF include anemia and thrombocytosis. Momelotinib works by blocking the JAK-Signal Transducer and Activator of Transcription (STAT) signalling pathway, which is aberrant in MF (GlaxoSmithKline, 2023).

In November 2023, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) adopted a positive opinion, recommending the granting of a marketing authorization for the medicinal product Omjjara (GlaxoSmithKline Trading Services Limited) January 2024 (GlaxoSmithKline, 2023; European Medicines Agency, 2023). Intended for the treatment of disease-related splenomegaly or symptoms in adults with moderate-to-severe anemia who have primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis. The most common nonhematologic treatment-emergent Adverse Event

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**DOI:** 10.5530/ijpi.20250004



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(AE) occurring in ≥20% of patients was diarrhea (any grade, 27% and grade ≥3, 3%). Any-grade thrombocytopenia, anemia and neutropenia occurred in 25%, 23% and 7% of patients, respectively (Verstovsek *et al.*, 2023). The chemical formula of Momelotinib $C_{23}H_{22}N_6O_2$ and its Molecular weight is 414.469 and its structure is shown in Figure 1.

## MATERIALS AND METHODS

### Chemical and Reagents

Samples of Momelotinib and Oclacitinib were supplied as the reference material by Cipla Pharmaceuticals in Vijayawada. All compounds, including LCMS-grade acetonitrile and formic acid, were procured from the chemical division of Merck located in Mumbai. Purified water (Milli-Q water purification system, HPLC Quality) was utilized throughout the investigation.

### Instrumentation

Chromatography was carried out using a Waters 2695 HPLC equipped with a high-speed autosampler, column oven, degasser and a SCIEX QTRAP 5500 mass spectrometer using ABSCIEX software.

### Stock and working solutions

Momelotinib Stock Solution (120 ng/mL).

Stock solutions were prepared using the mobile phase as a diluent. Six milligrams of Momelotinib working standard were weighed and transferred into a 100 mL volumetric flask, then diluted to volume with the diluent. 0.2 mL of this solution was further diluted to 10 mL with the diluent. Finally, 1 mL of this diluted solution was transferred into a 10 mL volumetric flask and made up to the mark with the diluent.

### Preparation of Internal Standard Stock Solution (120 ng/mL)

Weigh 6 mg of Oclacitinib working standard and transfer it into a 100 mL volumetric flask diluted to volume with diluent. Further diluted 0.2 mL to 10 mL with diluent. Take 1 mL of the above solution into a 10 mL volumetric flask and make it up to the mark with diluents.

### Preparation of Standard Solution (30 ng/mL of Momelotinib)

Transferred 500 µL of the standard stock solution into a 2 mL centrifuge tube. To this, add 200 µL of plasma, 500 µL of internal standard stock, 300 µL of acetonitrile and 500 µL of diluent. Centrifuged at 4000 rpm it to 15 min. Filter the supernatant liquid and transfer it into an HPLC vial.

### Conditions of liquid chromatography and mass spectrometry

A Symmetry C18 analytical column (250 mmx4.6 mm, 5 µm) was employed for separation at room temperature. The mobile phase consisted of a mixture of acetonitrile and 0.1% formic acid in a 45:55 ratio, with a flow rate of 1.0 mL/min and an injection volume of 10 µL. The Liquid Chromatography (LC) process lasted 5 min, while the mass spectrometer operated in positive ESI mode. The mass-to-charge ratio transitions for Momelotinib and Oclacitinib (m/z 415.4285→160.4698 and 338.2142→266.9137, respectively) were determined using Multiple Reaction Monitoring (MRM), as shown in Figures 2 and 3.

### Preparations of Linearity solutions

Calibration curves were generated using standards at concentrations of 7.50, 15.00, 22.50, 30.00, 37.50, 45.00 and 60.00 ng/mL, which were centrifuged at 4000 rpm for 15 min. The supernatant was collected and transferred into the chromatograph using an HPLC container. Quality Control (QC) samples were prepared following the same procedure, with Momelotinib concentrations of LLOQQC at 3.00 ng/mL, LQC at 15.00 ng/mL, MQC at 30.00 ng/mL and HQC at 45.00 ng/mL.

### Extraction protocol

Rat plasma was subjected to protein precipitation to isolate Momelotinib. The plasma samples were centrifuged, treated and labeled according to the appropriate time intervals. 200 µL of processed plasma was mixed with 300 µL of diluent, followed by 500 µL of acetonitrile to precipitate proteins. The mixture was vortexed and centrifuged at 4000 rpm for 15 min. The supernatant was collected and injected into the chromatograph using an HPLC-specific container.

### Bio-analytical method validation

Following the FDA's bioanalytical method guidelines, the devised method underwent comprehensive validation by computing all validation parameters as detailed below:

### Selectivity

Selectivity refers to the ability of an analytical procedure to accurately distinguish and measure analytes even when interfering substances are present in the biological matrix. We utilize blank samples from at least six independent sources or lots to assess selectivity. These samples are processed without including any analyte or Internal Standard (IS).

### Linearity

The calibration curve illustrates the relationship between the reaction and the known concentration of the analyte. Preparing the calibration curve using the same biological matrix as the samples is essential. Furthermore, distinct calibration curves are

required for each analyte to be measured. The method's range denotes the concentration interval where accuracy, precision and linearity have been established.

## Accuracy and precision

During method development, verifying the technique's suitability for validation is crucial by evaluating replicate Quality Controls (QCs) at various concentrations across the assay range. This includes examining replicate QCs at multiple concentrations. Method validation studies should consist of at least 6 independent runs, each featuring a calibration curve and multiple sample concentrations measured in replicates to assess accuracy and precision.

## Recovery

The Six quality control samples (LQC, MQC and HQC) were either thawed or prepared fresh from the deep freezer. The IS was added to the quality control samples (extracted samples) prior to injection. A 100% extraction of the analyte was achieved by processing blank matrix samples sourced from a single lot. These samples were injected along with six sets of each quality control dilution at low, medium and high concentrations, with the IS included in the process. At each QC level and for the IS, the percent Coefficient of Variation (CV) of recovery should be less than 15.00%. The overall mean recovery percent CV should remain below 20.00% for all QC levels.

## Matrix effects

The matrix effect is a variation in analyte reactivity caused by interfering and sometimes undetectable components in the sample matrix. The matrix effect was assessed 8 times for each analyte and internal standard at LQC and HQC concentration levels. 2 replicates of blank plasma samples were prepared using eight different screened plasma batches. The LQC concentration was spiked with the IS using one set of eight independent blank matrices, while the HQC concentration was spiked with the IS using a separate set. The analysis utilized spiked analyte(s) and the IS to reconstitute the solution, creating one set of aqueous samples comparable to the final LQC and HQC concentrations.

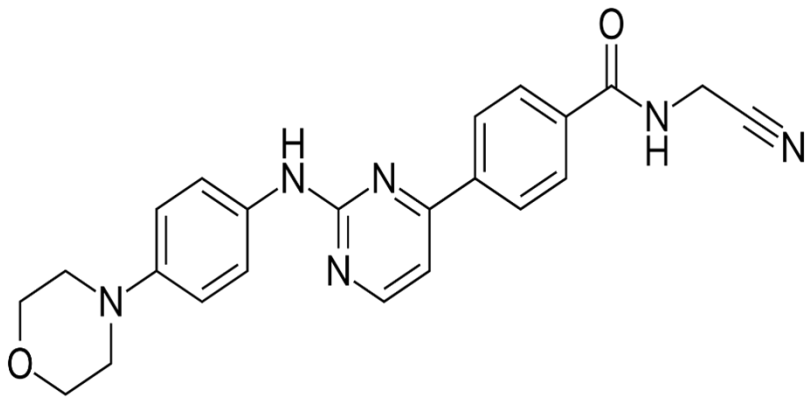


**Figure 1:** Structure of Momelotinib.

**Table 1: Linearity Results of Momelotinib.**

| Conc. (ng/mL) | Momelotinib Peak Response | Oclacitinib Peak Response | Ratio |
|---|---|---|---|
| 0 | 0 | 0 | 0 |
| 7.50 | 0.718 | 2.745 | 0.262 |
| 15.00 | 1.429 | 2.736 | 0.522 |
| 22.50 | 2.134 | 2.771 | 0.770 |
| 30.00 | 2.855 | 2.758 | 1.035 |
| 37.50 | 3.509 | 2.764 | 1.270 |
| 45.00 | 4.208 | 2.728 | 1.543 |
| 60.00 | 5.672 | 2.749 | 2.063 |
| Slope | | | 0.0341 |
| Intercept | | | 0.00628 |
| $R^2$ Value | | | 0.99982 |

## Stability experiments

Stability tests are essential to ensure that the concentration of the analyte remains unchanged throughout sample preparation, processing, analysis and storage conditions. Evaluating the analyte's stability within the matrix is under investigation by utilizing quality controls for stability, including low and high concentrations. Once the storage conditions have been implemented at time 0, we analyze aliquots of the quality controls with low and high stability. Conducting and assessing at least three stability tests for every concentration level, storage condition and time point is imperative. The FDA has advised the following stability measures for biological investigations. Changing the analyte in any way can impact chromatographic behavior, making the method development process more complex.

The above parameters can make the development and validation processes much more accessible to implement. The approach is unacceptable for its intended purpose if selectivity cannot be demonstrated. It will be difficult to develop the approach if recovery is uneven and the analytes are fractionated after being adjusted. Accuracy, precision, range and other qualities would be considerably altered under such circumstances.

## Application of the bio-analytical method to pharmacokinetics study

A cohort of six male Wistar rats weighing 180 and 220 g was utilized to conduct the pharmacokinetic experiments. The animals were accommodated in ventilated enclosures that were adequately supplied with food and water for seven days before the initiation of the experiments. The rats were fasted overnight before being given a dose. The animal study protocol has been approved by the Institute of Animal Ethics Committee (Registration Number: 1250/PO/RcBi/s/18/CPCSEA). A single dose of Momelotinib capsule (50 mg) was administered to rats; samples were collected at 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0 and 8.0 hr post-dose. An aliquot of 5 mL blood was collected at each time point in K2 EDTA vacutainer tubes. Additionally, a predose sample was collected to check the possible interferences from the plasma. The collected samples were centrifuged to obtain the

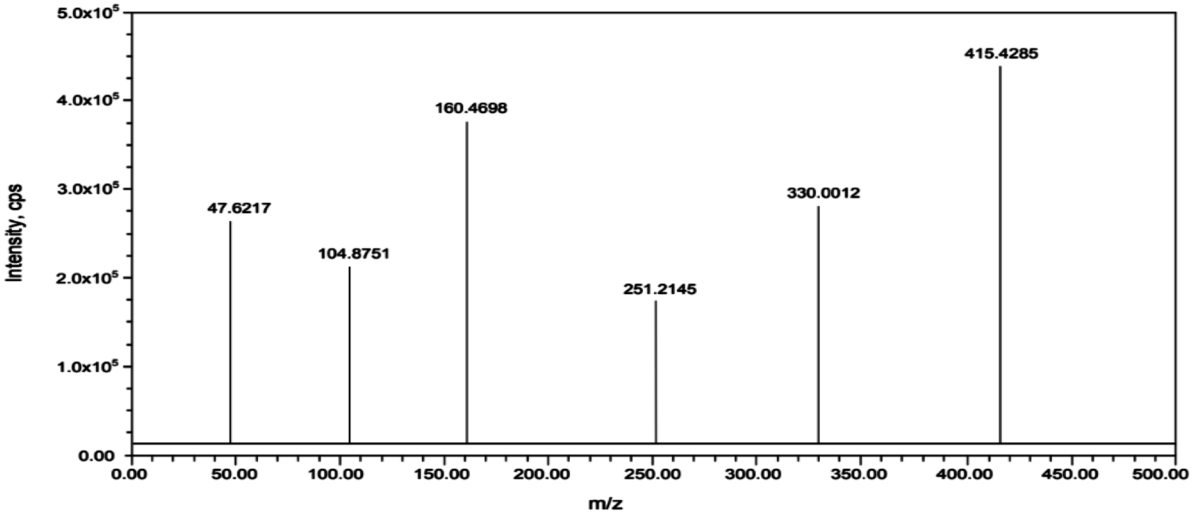


**Figure 2:** Mass spectrum of Momelotinib.

**Table 2: Calculated concentrations obtained for precision and accuracy batches.**

| Injections | HQC | MQC | LQC | LLQC |
|---|---|---|---|---|
| 1 | $4.121x10^5$ | $2.799x10^5$ | $1.344x10^5$ | $0.259x10^5$ |
| 2 | $4.125x10^5$ | $2.788x10^5$ | $1.348x10^5$ | $0.258x10^5$ |
| 3 | $4.126x10^5$ | $2.794x10^5$ | $1.346x10^5$ | $0.261x10^5$ |
| 4 | $4.129x10^5$ | $2.786x10^5$ | $1.347x10^5$ | $0.265x10^5$ |
| 5 | $4.123x10^5$ | $2.787x10^5$ | $1.349x10^5$ | $0.257x10^5$ |
| 6 | $4.128x10^5$ | $2.793x10^5$ | $1.341x10^5$ | $0.266x10^5$ |
| Mean | $4.125x10^5$ | $2.791x10^5$ | $1.346x10^5$ | $0.261x10^5$ |
| SD | 0.00301 | 0. 00598 | 0.00293 | 0.00374 |
| % CV | 0.17 | 0.20 | 0.22 | 1.43 |
| %Mean Accuracy | 97.52% | 98.97% | 95.46% | 92.55% |

**Table 3:** **Recovery of Momelotinib.**

| | Extracted LQC | Un extracted LQC | Extracted MQC | Un extracted MQC | Extracted HQC | Un extracted HQC |
|---|---|---|---|---|---|---|
| Mean | $1.340x10^5$ | $1.366x10^5$ | $2.766x10^5$ | $2.784x10^5$ | $4.111x10^5$ | $4.138x10^5$ |
| SD | 0.00380 | 0.00234 | 0.00339 | 0.00308 | 0.00434 | 0.00400 |
| %CV | 0.28 | 0.17 | 0.12 | 0.11 | 0.11 | 0.10 |
| %Mean Recovery | 95.04% | 96.88% | 98.09% | 98.72% | 97.19% | 97.83% |
| Overall Recovery | 97.29 | | | | | |

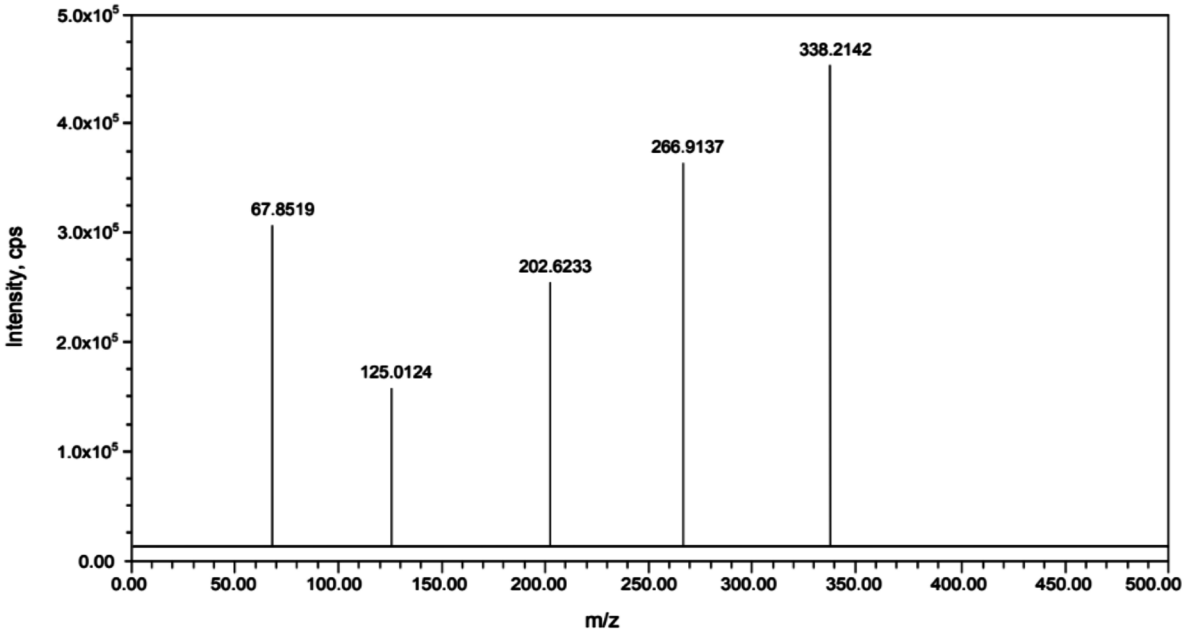


**Figure 3:** Mass spectrum of Oclacitinib.

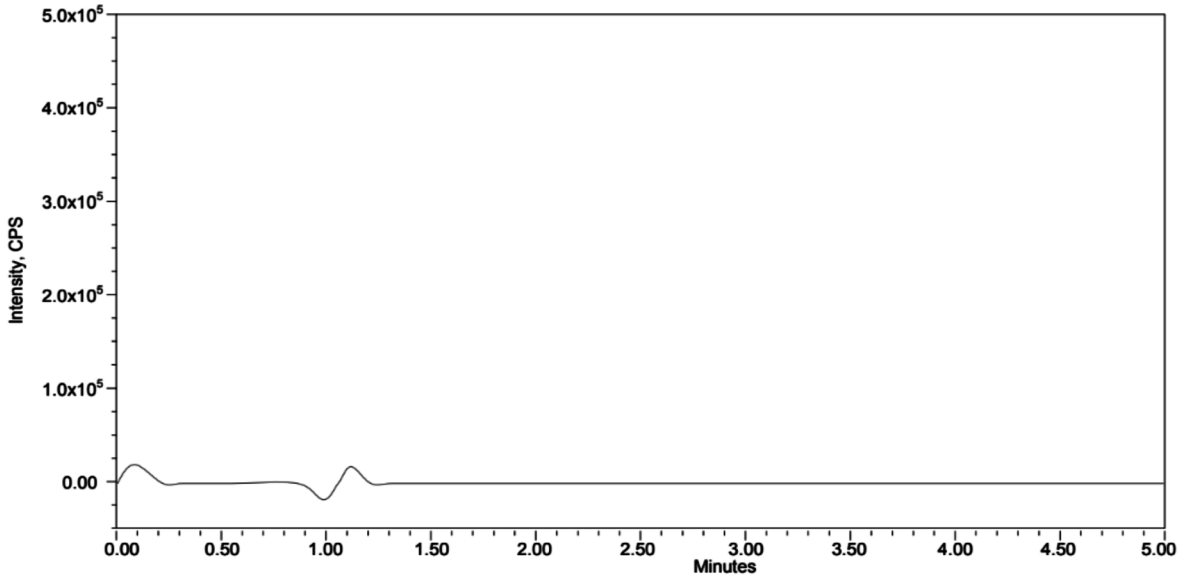


**Figure 4:** Chromatogram of Blank.

plasma and stored at -70 °C. Plasma samples were spiked with the IS and processed along with QC samples at four concentrations. Pharmacokinetic parameters of Momelotinib were calculated using WinNonlin (Version 5.2) software package. Stability of the study samples were established by Incurred Sample Reanalysis (ISR). For ISR two samples from each subject were selected near $C_{max}$ and the elimination phase in the pharmacokinetic profile. The samples were considered stable; the percent difference should not be more than 20%.

## RESULTS

### Mass spectrometry

To optimize the most sensitive ionization mode for Momelotinib and the Oclacitinib (IS), Electrospray Ionization (ESI) full scans were carried out both in positive and negative ion detection modes and it was found that both the analyte and the IS showed a better response in positive ion mode. At m/z 415.4285 and 338.2142, respectively, Momelotinib and Oclacitinib generated protonated [M+H]+ in positive ion mode. Figure 2 depicts the proposed Momelotinib fragmentation pattern. Momelotinib was quantified using the MRM reaction pair of the m/z 415.4285 precursor ion (Q1) to the m/z 160.4698 daughter ion (Q3) after the MS parameters were carefully optimized. The ideal option to be utilized as an IS is the deuterated analog of Momelotinib. Because deuterated Momelotinib was unavailable, we used a similar structurally and pKa value like a compound Oclacitinib chosen as an IS. This compound was the best for the current study based on chromatographic elution, ionization, reproducibility and good extraction efficiency. For the quantitation of IS, the MRM reaction pair of m/z 338.2142 precursor ion (Q1) to the m/z 266.9137 daughter ion (Q3) was used for the developed and validated optimized method.

**Table 4: Internal standard Results of Oclacitinib (30 ng/mL).**

| Sl. No. | Extracted Area Ratio | Un Extracted Area Ratio |
|---|---|---|
| 1. | $2.619x10^5$ | $2.652x10^5$ |
| 2. | $2.618x10^5$ | $2.654x10^5$ |
| 3. | $2.622x10^5$ | $2.659x10^5$ |
| 4. | $2.614x10^5$ | $2.657x10^5$ |
| 5. | $2.623x10^5$ | $2.653x10^5$ |
| 6. | $2.611x10^5$ | $2.661x10^5$ |
| Mean | $2.618x10^5$ | $2.656x10^5$ |
| SD | 0.00462 | 0.00358 |
| % CV | 0.18 | 0.13 |
| %Mean Recovery | 96.14% | 97.54% |

### Liquid Chromatography

The mobile phase choice significantly impacts the internal standard, analyte separation and ionization. To best achieve an effective chromatographic resolution of Momelotinib and the Oclacitinib (IS), a variety of mixtures of solvents, such as acetonitrile and methanol, with different buffers, such as formic acid, phosphate buffer, acetate buffer, ammonium acetate and ammonium formate, were tested. To optimize the separation of Momelotinib and Oclacitinib without any endogenous interference and to get a satisfactory and repeatable response with a short run time, many HPLC columns, including Inertsil, Atlantis, Zorbax, Gemini, C18 and C8, were investigated. The resolution of the analyte and the IS was best achieved with an isocratic mobile phase comprising Acetonitrile and 0.1% formic acid (45:55, v/v) at a flow rate of 1.0 mL/min. Symmetry C18 column, 250 mmx4.6 mm, 5µm, was found to be suitable with sharp and symmetric peak shapes. Momelotinib and Oclacitinib eluted at 2.524 and 3.567 min, respectively, in a total run time of 5.0 min.

### Selectivity

When comparing the peak response of blank samples with the response of spiked LLOQ samples containing IS mixtures, it was shown that the selectivity of the method demonstrated the absence of interference with Momelotinib of both the analyte and the IS (see Figures 4 and 5).

### Linearity

The linearity of the standard curves for Momelotinib was observed within the concentration range of 7.50 to 60.00 ng/mL, with an average correlation coefficient of 0.9998. Sample quantities were determined by calculating the ratio of the peak areas of the analyte to that of the IS. The peak area ratios corresponding to the plasma concentrations are presented graphically in Table 1 and Figure 6.

### Precision and accuracy

The Six duplicates of Momelotinib were analyzed at three distinct Quality Control (QC) levels to evaluate intra-assay precision and accuracy. Inter-assay precision was determined by analyzing the three levels of QC samples across independent runs. The proposed method demonstrated a percent mean accuracy ranging from 92.55% to 98.97%, with precision (% CV) for LQC, MQC and

**Table 5: Matrix effect results of Momelotinib (HQC-45 ng/mL and LQC-15 ng/mL).**

| Mean | $4.110x10^5$ | $1.360x10^5$ |
|---|---|---|
| SD | 0.00618 | 0.00539 |
| %CV | 0.15 | 0.40 |
| % Mean Accuracy | 97.16% | 96.45% |
| No. of QC Failed | 0 | 0 |

**Table 6:** **Momelotinib QC sample stability results using LC-MS/MS.**

| Stability Parameters | Spiked concentration | Mean±SD | %RSD | % Accuracy |
|---|---|---|---|---|
| Bench Top (8 hr) | 15 (ng/mL) | $1.343x10^5$±0.00407 | 0.30 | 95.25 |
| | 45 (ng/mL) | $4.148x10^5$±0.00410 | 0.25 | 98.06 |
| Freeze Thaw | | $1.352x10^5$±0.00718 | 0.53 | 95.89 |
| | | $4.145x10^5$±0.00460 | 0.11 | 97.99 |
| Wet extract (18 hr) | | $1.341x10^5$±0.00437 | 0.33 | 95.11 |
| | | $4.150x10^5$±0.00417 | 0.10 | 98.11 |
| Dry Extract (18 Hr) | | $1.347x10^5$±0.00649 | 0.48 | 95.53 |
| | | $4.130x10^5$±0.00564 | 0.14 | 97.64 |
| Autosampler (for 12 hr) | | $1.349x10^5$±0.00626 | 0.49 | 95.67 |
| | | $4.160x10^5$±0.00580 | 0.14 | 98.35 |
| Short Term (24 hr) | | $1.324x10^5$±0.00216 | 0.16 | 93.90 |
| | | $4.020x10^5$±0.00603 | 0.15 | 95.04 |
| Long Term (28 Days) | | $1.165x10^5$±0.00279 | 0.24 | 82.62 |
| | | $3.637x10^5$±0.00376 | 0..10 | 85.98 |

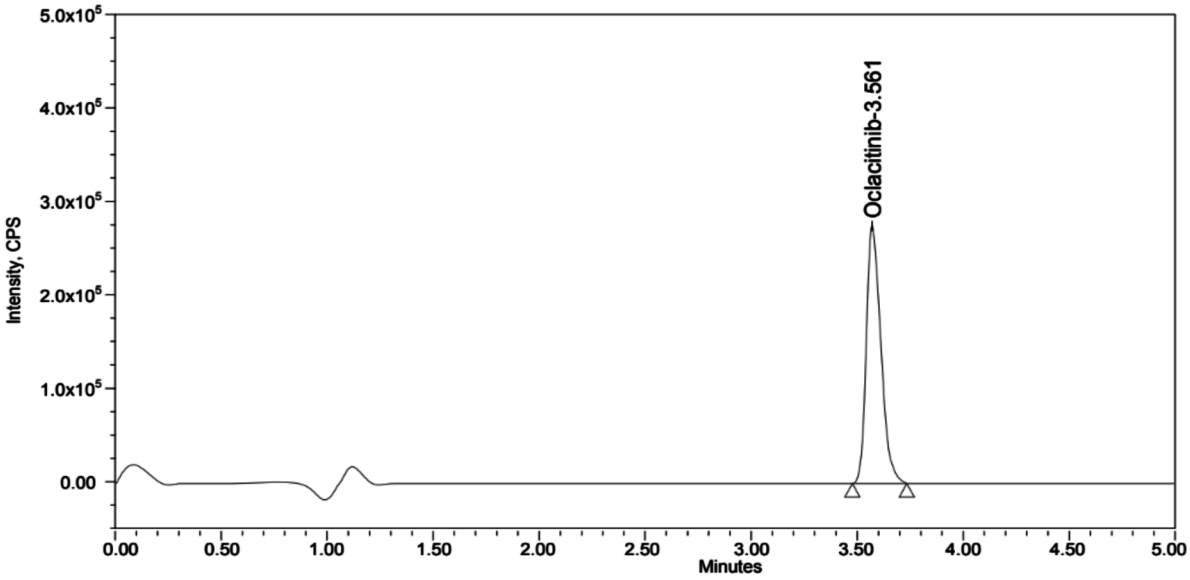


**Figure 5:** Blank chromatogram+IS.

HQC ranging from 0.17% to 1.43%. The findings are summarized in Table 2.

## Recovery

It was determined that the average recovery rate for Momelotinib was 97.29%, while the average recovery for the IS at the tested concentration was 96.84%. Tables 3 and 4 present the findings, which indicate that the extraction efficiency for Momelotinib was suitable, consistent and independent of concentration when using the liquid-liquid extraction technique.

## Matrix Effect

Back estimated concentrations of HQC and LQC levels had a mean percent accuracy of 97.16 and 96.45%, respectively. Because the results tabulated in Table 5 met the acceptance criterion of 85.00-115.00%, the present approach did not demonstrate any ionization effects.

## Stability

Momelotinib stability in plasma was assessed using 6 duplicate Quality Control (QC) samples at low and high concentrations. Momelotinib standard solutions were added in the appropriate volumes to generate drug-free plasma samples. The findings in Table 6 were determined to be within the acceptable range, suggesting that Momelotinib exhibits favorable stability.

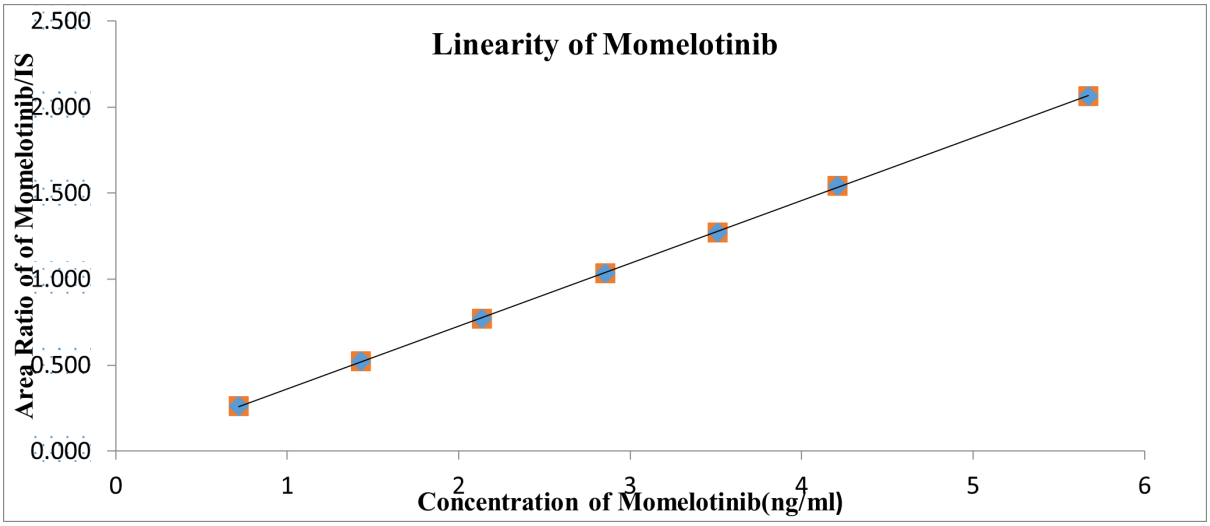


**Figure 6:** Calibration plot for concentration v/s Area ratio of Momelotinib.

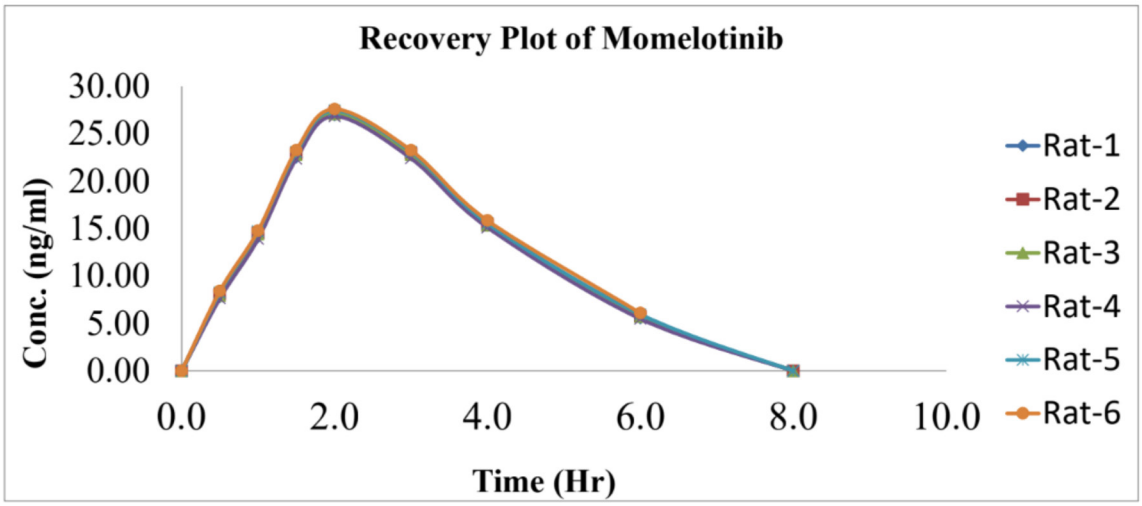


**Figure 7:** Mean plasma concentration-time profile Momelotinib in Rat plasma.

**Table 7: Mean plasma concentration-time curves of Momelotinib.**

| Pharmacokinetic parameters | Momelotinib |
|---|---|
| $AUC_{0-t}$ | 156 ng-hr/mL |
| $C_{max}$ | 27.2 ng/mL |
| $AUC_{0-\infty}$ | 156 ng-hr/mL |
| $t_{max}$ | 2.0 hr |
| $T_{1/2}$ | 6.0 hr |

## Pharmacokinetic application

The pharmacokinetic properties of Momelotinib were determined by calculation. The peak plasma Concentration ($C_{max}$) and time to reach peak plasma concentration ($T_{max}$) values were extracted directly from the plasma time profile curve shown in Figure 7. The pharmacokinetic characteristics of Momelotinib were determined using the WinNonlin software tool (Version 5.2). The stability of the research samples was determined using Incurred Sample Reanalysis (ISR). The linear trapezoidal method estimated several pharmacokinetic parameters such as AUC 0-t, $AUC_{0-\infty}$, $t_{1/2}$, $C_{max}$, $T_{max}$ and Clearance (CL). The above estimates were consolidated and presented in Table 7.

## DISCUSSION

The literature study ended with the non-availability of LC-MS/MS methods for determining Momelotinib. This method uses fewer toxic solvents and less solvent consumption. Overall extraction is conducted by a systematic pathway and bioanalytical methods guidelines. In this developed current study, the solvent used for the extraction procedure is entirely novel and new. Each parameter is well evaluated in the method validation and all data mentioned are within acceptable limits. The linearity study, at a low level of quantification to a high level of qualification with excellent correlation coefficient value, indicates the efficacy of the proposed method. By slight change, the parameters like mobile phase, flow rate and others are not affected by the quantification

of Momelotinib from the biological matrix and used of rat plasma for develop the proposed method and properly validated each parameter with the extracted Momelotinib and Oclacitinib (IS) sample from the rat plasma are help to get the novelty of proposed method and serves to supplement pivotal studies and aid in the decision-making process for approval, safety, labeling of a drug or biologic and, choice of the biomarker in biological fluids. In addition, a pharmacokinetic study of Momelotinib in rat plasma was successfully conducted using this optimized method, which is an added advantage.

## CONCLUSION

A method for accurately and precisely identifying Momelotinib using LC-MS/MS has been developed. This technique is also sensitive and allows for rapid analysis. Oclacitinib is used as the IS in this procedure. The total chromatography runtime is 5.00 min, with retention times of 2.524 min for Momelotinib and 3.567 min for Oclacitinib. Momelotinib has been validated over a dynamic linear range of 7.50 to 60.00 ng/mL, yielding a correlation coefficient ($r^2$) of 0.9999. The new bioanalytical method has been validated according to USFDA standards, with all validation parameters confirmed to be within acceptable limits. According to guidelines, precision (%CV) for both intra-batch and inter-batch measurements should be below 15% across LQC, MQC and HQC levels. Stability studies showed that results remained within assay variability limits at all stages. This optimized method successfully conducted a pharmacokinetic study of Momelotinib in rat plasma. Additionally, a simpler, more efficient and cost-effective protein precipitation method was developed for pre-treating biological samples, outperforming previously reported techniques. Plasma concentrations of Momelotinib were measured and key pharmacokinetic parameters were determined.

## ACKNOWLEDGEMENT

The authors would like to thank all faculty members and management of the GITAM Gandhi Nagar, Rushikonda, Visakhapatnam, Andhra Pradesh, for providing all necessary technical support and motivating us at every stage.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## ETHICAL APPROVAL

The Institutional Ethical Committee, Flair Labs, Surat, Gujarat, India reviewed and approved all experimental procedures and protocols. (Reg.No:1250/PO/RcBi/S/22/CPCSEA).

## ABBREVIATIONS

**FDA:** Food drug administration; **QC:** Quality control; **LQC:** Low-quality control; **MQC:** Medium Quality control; **HQC:** High-quality control; **Rt:** Retention time.

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**Cite this article:** Babu BS, Baby NR, Mondal S. Determination of Momelotinib in Rat Plasma by LC-MS/MS: Application to Pharmacokinetics Study. Int. J. Pharm. Investigation. 2025;15(2):388-96.

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Original Article

# Evaluation of the Multifaceted Impact of Hypothyroidism on Metabolic Components and Quality of Life

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## ABSTRACT

**Background:** Hypothyroidism is characterized by an underactive thyroid gland. As thyroid hormones are essential for regulating metabolism, disruptions in secretions can cause metabolic syndrome. This study is to assess the relationship of hypothyroidism with metabolic components and quality of life. **Materials and Methods:** A cross-sectional study was conducted over a year in the department of general medicine of a tertiary care hospital with 200 patients diagnosed with hypothyroidism with metabolic syndrome. Metabolic syndrome was determined using modified NCEP ATP III criteria (2005 revision). The study parameters were Thyroid Hormones (TSH, T3 and T4), metabolic components and quality of life (assessed using the WHOQOL BREF questionnaire). Spearman's correlation analysis was used to determine the relationship between TSH and metabolic components. **Results:** Thyroid Stimulating Hormone (TSH) exhibited a significant positive correlation with BMI (R: 0.07, p: 0.02), systolic blood pressure (R: 0.18, p: 0.008), triglycerides (R: 0.15, p: 0.03) and fasting blood sugar (R: 0.13, p: 0.05) and a negative correlation with High-Density Lipoprotein (R: -0.14, p: 0.04). Regarding quality-of-life domains, TSH has a significant negative correlation with the physical domain (R: -0.18, p: 0.08). **Conclusion:** Hypothyroidism is associated with body mass index, waist circumference, blood pressure and triglycerides but has a negative relationship with high-density lipoprotein. Patients with hypothyroidism with metabolic syndrome experience a poor quality of life, especially in the physical domain.

**Keywords:** Hypothyroidism, Metabolic syndrome, Thyroid stimulating hormone, Quality of life.

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**Received:** 22-07-2024;
**Revised:** 07-11-2024;
**Accepted:** 05-01-2025.

## INTRODUCTION

Thyroid hormones play a crucial role in metabolism (Mullur *et al.*, 2014). Disruptions in their secretion can lead to Metabolic Syndrome (MetS), characterized by insulin resistance, hypertension, hyperglycemia and abnormal cholesterol levels (Fahed *et al.*, 2022).

In the Western world, Hypothyroidism (HT) affects about 5% of its population, with another 5% potentially undiagnosed (Chiovato *et al.*, 2019; Garmendia *et al.*, 2014). In India, HT is the most prevalent thyroid disorder, affecting 10.9% of adults (Unnikrishnan *et al.*, 2013; (Kumar *et al.*, 2022).

HT is related to MetS, including dyslipidemia, hypertension, obesity and insulin resistance (Shaji and Joel, 2022; Mavromati and Jornayvaz, 2021). Studies indicate that 95% of newly detected hypothyroid cases exhibit elevated cholesterol levels, with 5% presenting with hypertriglyceridemia (Gluvic *et al.*, 2015).

HT can present with vague and nonspecific symptoms that often resemble those of other conditions, making diagnosis difficult. Weight gain results from decreased fat burning, while cold intolerance stems from reduced heat production. This affects the Quality of Life (QOL) (Chaker *et al.*, 2017).

The primary treatment for HT is levothyroxine, with dosage adjusted based on TSH levels and clinical symptoms (Razvi *et al.*, 2020). Special considerations are required for pregnant women, central hypothyroidism and those with alternative treatments such as liothyronine or supplements (Lee and Pearce, 2022; Jonklaas *et al.*, 2014). Regular monitoring and dosage adjustments are essential to prevent drug-related problems.

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**DOI:** 10.5530/ijpi.20250019



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Patients with HT experience poor QOL, particularly in the physical dimensions compared to social dimensions (Ghamr *et al.*, 2022). Physicians should regularly assess hypothyroid patients' QOL and prioritize improving it as part of their management plan (Shivaprasad *et al.*, 2018). With this background, the study assess the impact of hypothyroidism on metabolic components and QOL.

## MATERIALS AND METHODS

### Study design and setting

The study is part of a long-term study conducted in the Department of General Medicine of a tertiary care hospital, which analyses the impact of clinical pharmacy services in hypothyroid patients with MetS.

### Sample size

The sample size determination was based on a 5% level of significance, 80% power, a mean difference of 1.3 and an effect size of 0.435. The required sample size was calculated as 200, using nMaster software, version 2.0.

### Ethical Approval

The Central Ethics Committee, Nitte (Deemed to be University), approved the study (Ref. No: NU/CEC/2022/317), prior to initiation. The investigator explained the study to the participants and obtained their written informed consent. Participants who gave voluntary consent were enrolled in the study. Privacy and confidentiality were maintained throughout the study.

### Participant Enrollment

#### *Inclusion Criteria*

The study included patients aged 18 years and above diagnosed with hypothyroidism with metabolic syndrome. MetS was determined using the modified NCEP ATP III criteria (2005 revision) (National Cholesterol Education Program (NCEP), 2002). Both Inpatients and Outpatients were included in the study.

### Exclusion Criteria

Pediatric patients, Pregnant women, Patients who had undergone thyroid surgery, Type I Diabetic Mellitus, Psychiatric illness and Cancer patients were excluded from the study.

Based on the inclusion and exclusion criteria, eligible patients were enrolled randomly after obtaining written consent.

### Laboratory TESTS

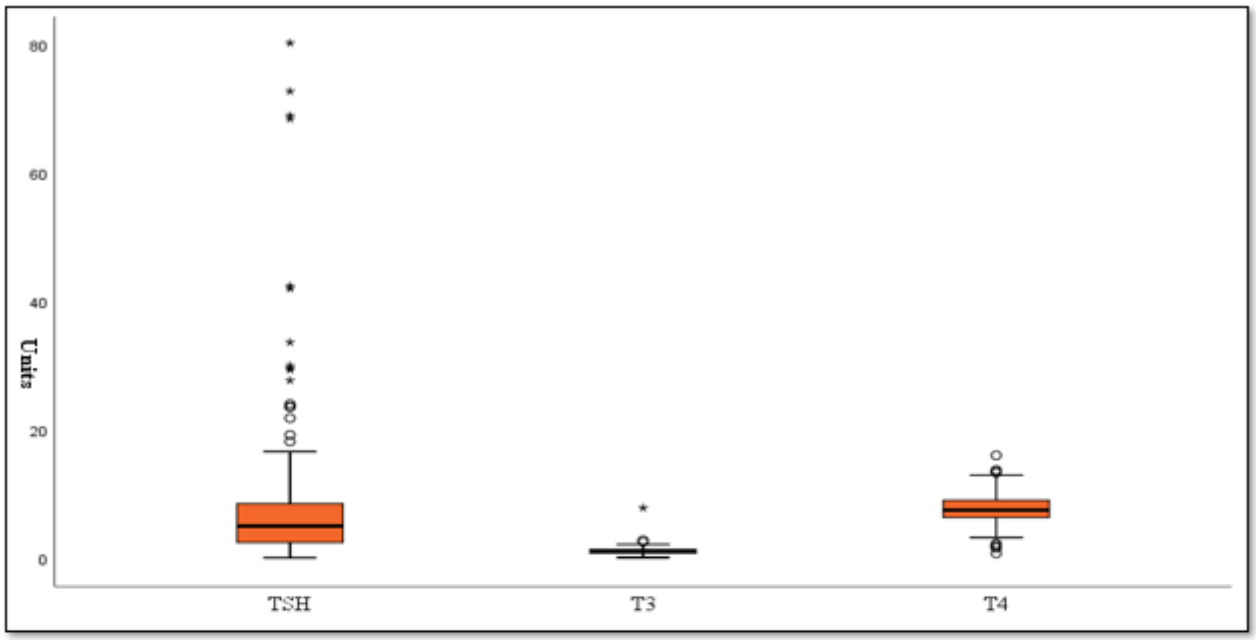
As part of their regular checkup, the patients gave their blood samples to the laboratory following the consultation with their physician. A qualified medical laboratory technician collects the blood sample and analyzes it for Thyroid function tests (TSH, T3, T4) and metabolic components (FBS, TG and HDL). A consultant pathologist verified the laboratory reports. The researcher collected the study subjects' laboratory data and documented it for data analysis.

**Table 1: Sociodemographics of the study population.**

| Characteristics | Frequency | Percentage (%) |
|---|---|---|
| **Age Group** | | |
| Less than 40 | 20 | 10 |
| 40 - 50 | 62 | 31 |
| 51 - 60 | 63 | 31.5 |
| 61 - 70 | 55 | 27.5 |
| **Gender wise Distribution** | | |
| Male | 48 | 24 |
| Female | 152 | 76 |
| **Body Mass Index** | | |
| Healthy (18.5-24.9) | 59 | 29.5 |
| Overweight (25.0-29.9) | 121 | 60.5 |
| Obese (30.0 and above) | 20 | 10 |
| **Educational Status** | | |
| Primary School | 117 | 58.5 |
| Middle School | 38 | 19 |
| Secondary School | 39 | 19.5 |
| Graduate | 6 | 3 |
| **Comorbid Conditions** | | |
| Diabetes Mellitus | 47 | 23.5 |
| Hypertension | 43 | 21.5 |
| Dyslipidemia | 21 | 10.5 |
| Diabetes Mellitus and Hypertension | 51 | 25.5 |
| Diabetes Mellitus and Dyslipidemia | 14 | 7 |
| Hypertension and Dyslipidemia | 13 | 6.5 |
| Hypertension, Diabetes Mellitus and Dyslipidemia | 11 | 5.5 |
| **Socio-economic Status** | | |
| Upper Lower | 66 | 33 |
| Lower Middle | 82 | 41 |
| Upper Middle | 52 | 26 |

### Definition of MetS

As per Modified NCEP ATP III (2005 revision) MetS is determined as the presence of three or more of the following five




**Metabolic Components and Quality of Life**

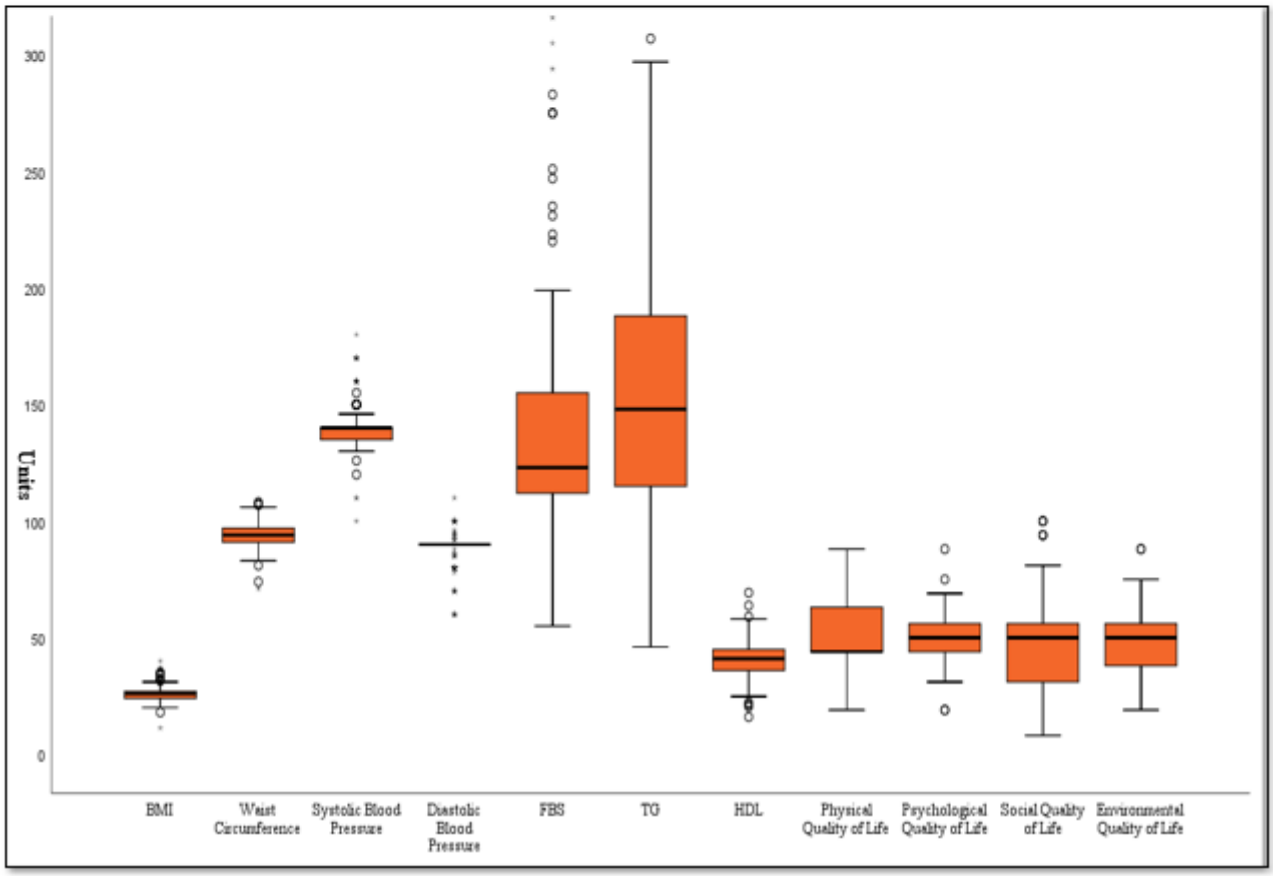



**Figure 1:** Levels of Thyroid Hormones, Metabolic Components and Quality of Life Metabolic Components and Quality of Life.

**Table 2: Thyroid Hormones and Metabolic Components.**

| Thyroid Hormones | Mean | Standard Deviation |
|---|---|---|
| TSH | 13.59 | 32.69 |
| T3 | 1.65 | 6.88 |
| T4 | 8.42 | 9.15 |
| **Metabolic Components** | | |
| BMI | 25.75 | 3.36 |
| Waist Circumference | 94.32 | 5.22 |
| Systolic Blood Pressure | 139.70 | 10.53 |
| Diastolic Blood Pressure | 88.07 | 6.88 |
| Fasting Blood Sugar | 139.26 | 43.72 |
| Triglycerides | 159.20 | 57.04 |
| **Quality of Life** | | |
| Physical Domain | 48.34 | 12.84 |
| Psychological Domain | 51.46 | 10.58 |
| Social Domain | 49.78 | 17.00 |
| Environmental Domain | 49.29 | 12.63 |

criteria: WC above 40 inches (men) or 35 inches (women), BP above 130/85 mmHg or on treatment, fasting TG above 150 mg/dL or on treatment, fasting HDL cholesterol levels less than 40 mg/dL (men) or 50 mg/dL (women) and FBS above 100 mg/dl or on treatment.

## Blood Pressure, Waist Circumference and Body Mass Index Measurements

The BP, WC and BMI were assessed as a part of the regular checkup. The data were documented by the researcher for analysis.

## Assessment of Quality of Life (QOL)

The QOL was assessed using the WHOQOL BREF, a short version of the WHOQOL questionnaire. The questionnaire was translated from English to regional languages (Kannada and Malayalam). The researchers requested the study participants to complete the WHOQOL BREF Questionnaire within 30 min and the responses were collected and documented. The scores were converted to the WHOQOL questionnaire format and analyzed.

## Statistical Analysis

The collected data were documented using Microsoft Excel 2021 and statistically analyzed with SPSS version 29. The categorical variables were presented as frequency and percentage. Mean and standard deviation were used to illustrate the thyroid hormones, metabolic components and quality of life. The relationship between TSH with Metabolic Components and QOL was analyzed using Spearman's Correlation. Multiple linear Regressions was used to analyze the effect of TSH on Metabolic Components and Quality of Life.

# RESULTS

## Sociodemographics of the Study Population

Among 200 study subjects, the majority of the patients were females. The mean age of the subjects were 51.93+10.09. The majority of the subjects (60.5%) were overweight. Based on the level of education, 58.5% had completed primary school, 19% middle school, 19.5% secondary school and 3% were graduates. Among the study subjects, Diabetes mellitus was present in 23.5% of the patients, hypertension in 21.5% and dyslipidemia in 10.5% of the patients. Moreover, 25.5% of patients have both diabetes mellitus and hypertension, 7% have diabetes mellitus and dyslipidemia, 6.5% have hypertension and dyslipidemia and 5.5% have all three disease conditions. Based on socioeconomic status, 33% of the patients were in the upper-lower class, 41% in the lower-middle class and 26% in the upper-middle class (Table 1).

## Thyroid Hormones, Metabolic Components and Quality of Life (QOL)

In the study subjects, the mean TSH, T3 and T4 were 13.59+32.69, 1.65+6.88 and 8.42+9.15, respectively. Among the metabolic components, the mean BMI, WC, SBP and DBP, TG, HDL and FBS were 25.75±3.36 kg/m$^2$, 94.32±5.22 cm, 139.70±10.53 mmHg, 88.07±6.88 mmHg, 159.20±57.04 mg/dL, 40.83±8.1 mg/dL, 139.26±43.72 mg/dL respectively.

Across the four domains of physical, psychological, social and environmental QOL, the mean scores were 48.34±12.84, 51.46±10.58, 49.78±17.00 and 49.29±12.63, respectively (Table 2), (Figure 1).

## Association between TSH and Metabolic Components

### *Association between TSH and BMI*

A significant weak positive correlation (R: 0.070, p: 0.02) was observed between TSH and BMI. This suggests that as the TSH levels increase, BMI also increases, indicates a direct potential relationship between TSH and BMI.

The linear regression analysis shows a weak, significant positive correlation between TSH and BMI (R: 0.070, p: 0.02). The $R^2$ value is 0.005, indicates that the 0.5% variation in TSH is contributed by the BMI. The F value is 0.948 and the *p*-value is 0.33, shows that the regression model is not significant. The beta coefficient for BMI indicates that as BMI increases, TSH increases by 0.010 units; however, this effect is not statistically significant (p: 0.331).

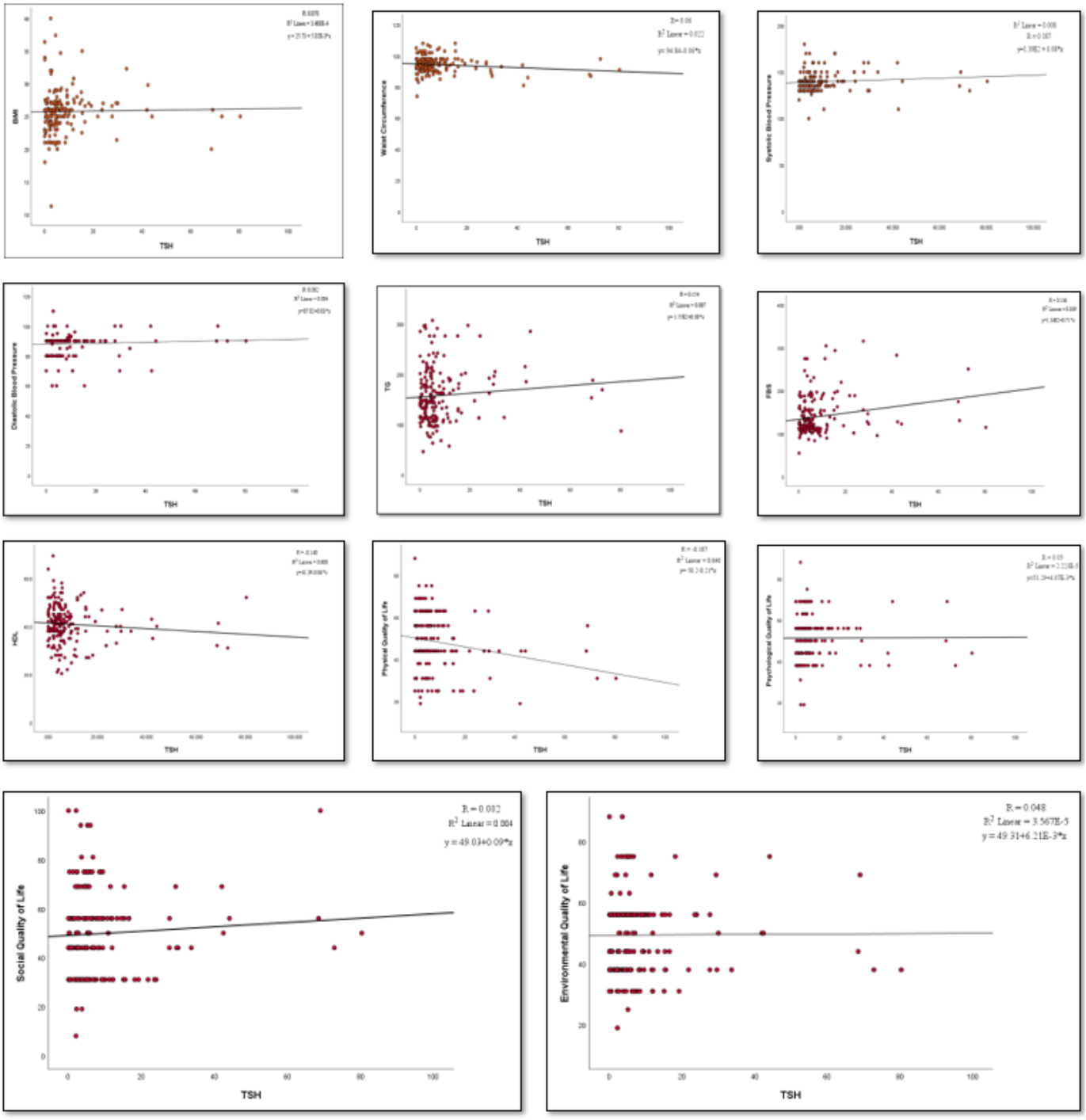



**Figure 2:** Association of TSH with Metabolic Components and Quality of Life.

## Association between TSH and Waist Circumference

A weak positive association was observed between TSH and WC (R: 0.068) but not statistically significant (p: 0.86). TSH may not be a direct factor affecting WC in this specific population.

The linear regression analysis shows a weak positive correlation between TSH and WC (R: 0.068) but not significant (p: 0.86). The $R^2$ value of 0.005 implies that the WC contributes to the 0.5% variation in TSH. The F-value of 0.922 and the *p*-value of 0.338 shows that the regression model is not significant. While the beta coefficient for WC suggests a potential increase in TSH by 0.006 units with increasing WC, but this trend is not statistically significant ($p$=0.338).

## Association between TSH and Systolic Blood Pressure

A significant positive association was found between TSH and SBP (R: 0.187, p: 0.008). This suggests that as the TSH increases,

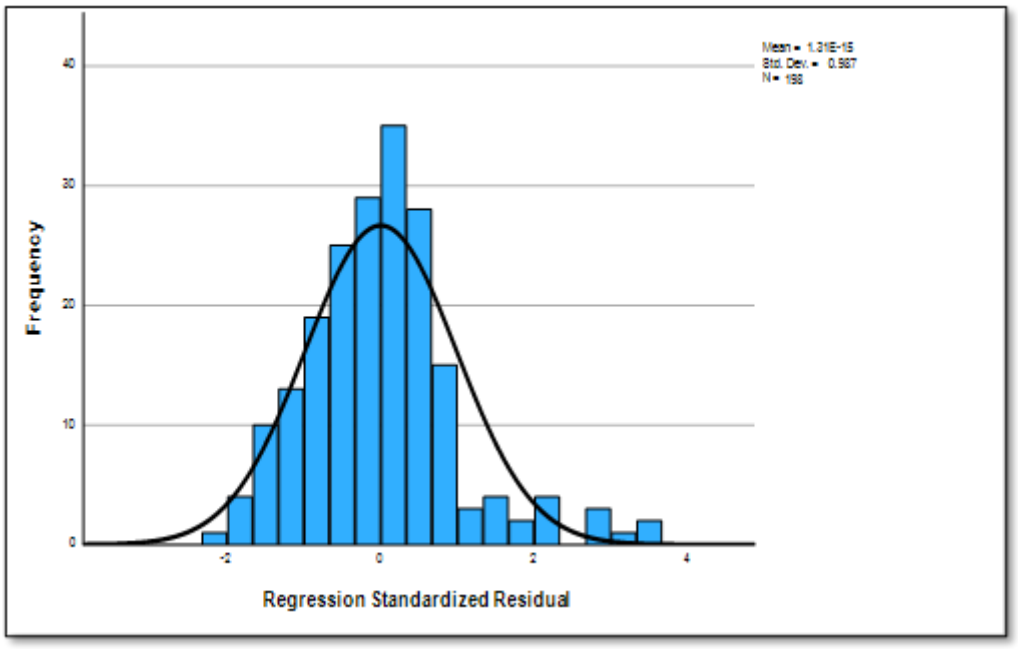



**Figure 3:** Regression Standardized Residual.

**Table 3: Association of Thyroid Hormones with Metabolic Components and Quality of Life.**

| Variables | R | Interpretation | *p* |
|---|---|---|---|
| TSH-BMI | 0.007 | Very weak positive correlation | 0.02 |
| TSH-Waist Circumference | 0.06 | Very weak positive correlation | 0.86 |
| TSH-Systolic Blood Pressure | 0.187 | Weak positive correlation | 0.008 |
| TSH-Diastolic Blood Pressure | 0.082 | Very weak positive correlation | 0.28 |
| TSH-Triglycerides | 0.154 | Weak positive correlation | 0.030 |
| TSH-High Density Lipoprotein | -0.140 | Weak negative correlation | 0.04 |
| TSH-Fasting Blood Sugar | 0.136 | Weak positive correlation | 0.05 |
| TSH-Physical Domain | -0.187 | Weak negative correlation | 0.008 |
| TSH-Psychological Domain | 0.05 | Very weak positive correlation | 0.172 |
| TSH-Social Domain | 0.002 | Very weak positive correlation | 0.98 |
| TSH-Environmental Domain | 0.04 | Very weak positive correlation | 0.49 |

* Spearman's Correlation.

SBP tends to increase, indicating a potential association between TSH levels and SBP.

The $R^2$ value of 0.040 implies that SBP contributes to 4% of the variation in TSH. The F value of 8.064 and the *p*-value of 0.005 imply that the regression model is statistically significant. The beta coefficient for SBP suggests that SBP increases, TSH increases by 0.009 units and this effect is statistically significant.

## Association between TSH and Diastolic Blood Pressure

TSH is weakly correlated with DBP (R: 0.082) but was not statistically significant (p: 0.28). The findings suggest that TSH levels do not significantly influence DBP.

The linear regression analysis shows a very weak, non-significant correlation between DBP and TSH (R: 0.082, p: 0.28). The $R^2$ value of 0.007 implies that DBP contributes to 0.7% of the variation in TSH. The F value of 1.409 and the *p*-value of 0.237 indicated that the regression model is not statistically significant. The beta coefficient for DBP suggests that as DBP increases, TSH increases by 0.006 units; but this effect is not statistically significant.

## Association between TSH and Triglycerides

A weak positive association was found between TSH and TG (R: 0.154), but the correlation was not significant (p: 0.030). There may be an association between TSH and TG, but it is not strong enough to be considered a reliable predictor of TG based on TSH.

**Table 4: Regression Analysis between TSH and Metabolic Components.**

| Dependent Variable | TSH | TSH | TSH | TSH | TSH | TSH | TSH | TSH | TSH | TSH | TSH |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Predictors | BMI | WC | SBP | DBP | FBS | TG | HDL | Physical QOL | Psychological QOL | Social QOL | Environmental QOL |
| R-value | 0.070 | 0.06 | 0.19 | 0.08 | 0.13 | 0.15 | -0.14 | 0.18 | 0.055 | 0.002 | 0.058 |
| R square value | 0.005 | 0.00 | 0.04 | 0.007 | 0.01 | 0.02 | 0.02 | 0.03 | 0.003 | 0.000 | 0.003 |
| Adjusted R square value | 0.000 | 0.00 | 0.03 | 0.002 | 0.01 | 0.01 | 0.01 | 0.03 | -0.002 | -0.005 | -0.002 |
| **ANOVA** | | | | | | | | | | | |
| Sum of Squares (Regression and Residual) | 0.206 | 0.19 | 1.68 | 0.30 | 0.78 | 1.00 | 0.83 | 1.49 | 0.12 | 0.000 | 0.023 |
| | 42.37 | 42.39 | 40.91 | 42.29 | 41.81 | 41.5 | 41.75 | 41.10 | 42.36 | 6.769 | 6.748 |
| Mean Square (Regression and Residual) | 0.206 | 0.19 | 1.68 | 0.30 | 0.78 | 1.00 | 0.83 | 1.49 | 0.12 | 0.000 | 0.023 |
| | 0.217 | 0.21 | 0.20 | 0.21 | 0.21 | 0.21 | 0.21 | 0.21 | 0.21 | 0.034 | 0.034 |
| F value | 0.948 | 0.92 | 8.06 | 1.40 | 3.67 | 4.75 | 3.93 | 7.14 | 0.59 | 0.001 | 0.676 |
| *P* value | 0.331 | 0.33 | 0.00 | 0.23 | 0.05 | 0.03 | 0.04 | 0.008 | 0.44 | 0.980 | 0.412 |
| **Coefficients** | | | | | | | | | | | |
| Beta ( Constant*, Variable) | 0.567 | 1.389 | -0.40 | 0.29 | 0.61 | 0.61 | 1.14 | 1.14 | 0.694 | .923 | .964 |
| | 0.10 | 0.006 | 0.00 | 0.006 | 0.001 | 0.001 | - 0.008 | - 0.007 | 0.002 | -1.98 | -.001 |
| Standard Error ( Constant*, Variable) | 0.258 | 0.596 | 0.43 | 0.44 | 0.11 | 0.097 | 0.16 | 0.127 | 0.694 | 0.041 | 0.053 |
| | 0.10 | 0.006 | 0.03 | 0.005 | 0.001 | 0.001 | 0.004 | 0.003 | 0.002 | 0.001 | 0.001 |
| Standardized Coefficients Beta | 0.070 | 0.068 | 0.19 | 0.08 | 0.13 | 0.154 | - 0.14 | -0.187 | 0.055 | -0.002 | -0.058 |
| *t* value ( Constant*, Variable) | 2.199 | 2.329 | - 0.93 | 0.66 | 5.61 | 6.373 | 6.80 | 9.02 | 4.198 | 22.66 | 18.215 |
| | 0.974 | 960 | 2.84 | 1.18 | 1.91 | 2.179 | -1.98 | - 2.67 | 0.769 | -0.026 | -0.822 |
| P value ( Constant*, Variable) | 0.029 | 0.021 | 0.34 | 0.50 | 0.001 | 0.001 | 0.001 | 0.001 | 0.001 | 0.001 | 0.001 |
| | 0.331 | 0.338 | 0.05 | 0.23 | 0.05 | 0.030 | 0.04 | 0.008 | 0.443 | 0.980 | 0.412 |
| 95% Confidence Interval (Constant*, Variable) | 0.05 - 1.07 | 0.21 - 2.56 | -1.25 - 0.44 | -0.57 - 1.16 | 0.400 - 0.833 | 0.427-0.809 | 0.812 - 1.475 | 0.894 - 1.394 | 0.368 - 1.020 | 0.843 - 1.004 | 0.860 - 1.069 |
| | - 0.10 - 0.02 | 0.01 - 0.02 | 0.00 - 0.01 | 0.000 - 0.01 | 0.000 - 0.003 | 0.000 - 0.002 | - 0.016 - 0.000 | -0.012 - -0.002 | -0.004 - 0.009 | -0.002 - 0.002 | -0.003 - 0.001 |

The $R^2$ value of 0.024 implies that TG contributes to 2.4% of the variation in TSH. The regression model is statistically significant, as indicated by the F value of 4.750 and the *p*-value of 0.030. The beta coefficient for TG suggests that as TG increase, TSH increases by 0.001 units, which is statistically significant.

## Association between TSH and Fasting Blood Sugar (FBS)

A positive correlation was obtained between TSH and FBS (R: 0.136) but not statistically significant (p: 0.05). The observation suggests that while there is a slight tendency for FBS to increase as TSH increases, the relationship is very weak.

The $R^2$ value of 0.018 implies that FBS contributes to 1.8% of the variation in TSH. The F value of 3.677 and the *p*-value of 0.05 indicated that the regression model is statistically significant. The beta coefficient for FBS suggests that as FBS increases, TSH increases by 0.001 units.

## Association between TSH and High-Density Lipoprotein (HDL)

A significant negative association was found between TSH and HDL levels (R:-0.140, p: 0.04). This suggests there is an inverse relationship between TSH and HDL

The $R^2$ value of 0.020 implies that HDL contributes to 2.0% of the variation in TSH. The regression model is statistically significant, as indicated by the F value of 3.933 and the *p*-value of 0.04. The beta coefficient for HDL suggests that as HDL increases, TSH decreases by 0.008 units.

## Association between TSH and the domains of Quality of Life (QOL)

### *Association between TSH and Physical domain of Quality of Life (QOL)*

A negative significant correlation was observed between TSH and Physical Domain of QOL (R: -0.187 p:0.008). This suggests an inverse relationship between TSH and Physical QOL domain. When the TSH levels increase, hypothyroid symptoms intensify and the patients become weaker physically.

The $R^2$ value of 0.035 implies that the physical domain of quality of life contributes to 3.5% of the variation in TSH. The regression model is statistically significant, as indicated by the F value of 7.141 and the *p*-value of 0.008. The beta coefficient for the physical domain of QOL suggests that as the physical domain of QOL increases, TSH decreases by 0.007 units.

## Association between TSH and Psychological domain of Quality of Life (QOL)

A weak positive correlation was observed between TSH and psychological Domain (R: 0.055) but not statistically significant (p: 0.172). Even though there is a weak positive relationship between TSH and the psychological domain, the data are not sufficient to substantiate a strong significant association between TSH and the psychological domain of QOL.

The linear regression analysis shows a very weak positive correlation between the psychological domain of QOL and TSH (R: 0.055), but not statistically significant (p: 0.443). The $R^2$ value of 0.003 implies that the psychological domain of quality of life contributes 0.3% of the variation in TSH. The F value is 0.591

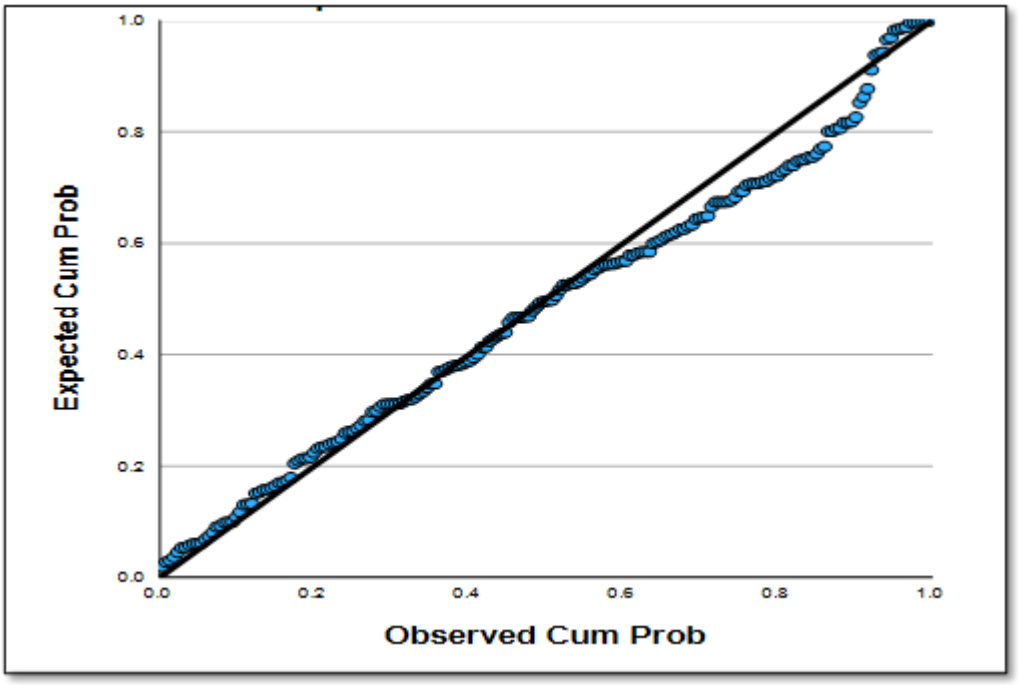



**Figure 4:** Normal *P*-Plot of Regression Standardized Residual.

and the *p*-value is 0.443 implies that the regression model is not significant.

### Association between TSH and Social domain of Quality of Life (QOL)

A weak positive correlation coefficient exists between TSH and the social domain of QOL (R: 0.002) but is not statistically significant (p: 0.98).

The regression analysis shows an extremely weak correlation between the social domain of quality of life and TSH levels (R: 0.002) but not statistically significant (p: 0.980). The F value of 0.001 and *p*-value of 0.980 imply that the regression model is not significant. The beta coefficient for the social domain of QOL suggests that the social domain of QOL increases, as the TSH decreases by 1.98 units.

### Association between TSH and Environmental domain of Quality of Life (QOL)

The correlation analysis of TSH and the Environmental Domain of QOL showed a very weak positive correlation (R: 0.048) but not statistically significant (*p*=0.49) (Table 3), (Figure 2).

The regression analysis shows a weak positive correlation between the environmental domain of QOL and TSH levels (R: 0.058) but is not statistically significant (p: 0.412). The $R^2$ value of 0.003 implies that the environmental domain of QOL contributes 0.3% of the variation in TSH. The F value of 0.676 and *p*-value of 0.412 indicate that the regression model is not significant. The beta coefficient for the environmental domain of QOL suggests that as the environmental domain of QOL increases, TSH decreases by 0.001 units (Table 4, Figures 3 and 4).

## DISCUSSION

Thyroid hormones play a critical role in regulating metabolism. Since thyroid hormones have an important role in metabolism, HT increases the risk for metabolic syndrome (Iwen *et al*., 2013).

In this study, TSH was found to have a significant positive correlation with BMI (R: 0.07, p: 0.02), SBP (R: 0.187, p: 0.008), TG (R: 0.154, p: 0.03) and FBS (R: 0.136, p: 0.05) and a negative significant correlation with HDL (R: -0.140, p: 0.04). These findings were similar to the study conducted by Khatiwada S *et al*. and Bensenor IM *et al*., where a positive correlation was observed for DBP, blood glucose and TG with TSH. However, HDL and TSH had a negative correlation (Khatiwada *et al*., 2016; Bensenñor *et al*., 2015). Similarly, a negative correlation between SBP and WC with TSH was observed in their study, but this correlation was not significant, which contradicts the findings of the present study. In contrast to the findings of this study, Huang CY *et al*. found no correlation between serum TSH levels and MetS, but strong correlations with high serum T3 levels and no clear correlations with low serum T4 (Huang and Hwang, 2016).

The current study found that females are at a greater risk of developing metabolic syndrome (76%). The findings can be compared with the study conducted by He J *et al*., where metabolic syndrome is more prevalent in women with hypothyroidism than in men (He *et al*., 2021).

Regarding QOL, hypothyroid patients with MetS experience poor QOL, with the psychological domain better than the physical, social and environmental domains. A negative correlation was observed between TSH and the physical domain of QOL, indicating that higher TSH levels are associated with a decline in QOL. These findings are comparable to studies by Ghamri R *et al*. and Kelderman-Bolk *et al*., which also observed a decline in QOL with increasing TSH (Ghamr *et al*., 2022; Kelderman-Bolk *et al*., 2015).

The current study provides comprehensive insights into the impact of HT on metabolic diseases and overall QOL. Through a multifaceted analysis, the research highlights the association of hypothyroidism with metabolic components and QOL.

## CONCLUSION

Hypothyroidism is associated with BMI, WC, BP and TG; however, it has a negative relationship with HDL. Hypothyroidism patients with metabolic syndrome have a poor quality of life, particularly in the physical domain. Screening of MetS in hypothyroid patients is important for the early detection and prevention of disease-related complications.

## ACKNOWLEDGEMENT

We would like to thank the faculties of Department of Pharmacy Practice, NGSM Institute of Pharmaceutical Sciences and Department of General Medicine, KS Hegde Medical Academy, Justice K S Hegde Charitable Hospital for their valuable guidance throughout the research process. The authors would like to express their sincere gratitude to Nitte (Deemed to be University), Mangaluru, for providing the necessary facilities to carry out the research work.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## ABBREVIATIONS

**HT:** Hypothyroidism; **MetS:** Metabolic Syndrome; **QOL:** Quality of Life; **BP:** Blood Pressure; **NCEP ATP III:** National Cholesterol Education Program Adult Treatment Panel III; **T4:** Thyroxine; **TSH:** Thyroid Stimulating Hormone; **T3:** Triiodothyronine; **TG:** Triglycerides; **WC:** Waist Circumference; **HDL:** High-Density Lipoprotein; **FBS:** Fasting Blood Sugar; **BMI:** Body Mass Index; **SBP:** Systolic Blood Pressure; **DBP:** Diastolic Blood Pressure.

## ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Central Ethics Committee, Nitte (Deemed to be University), (Ref. No: NU/CEC/2022/317). Informed consent was obtained from every subject involved in the study.

## AUTHOR CONTRIBUTIONS

Bipin Shaji: Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Data Interpretation, Visualization, Writing-original draft, Writing-review and editing, Project administration. Juno Jerold Joel: Conceptualization, Methodology, Project administration, Writing-review and editing, Supervision. Raghava Sharma: Conceptualization, Methodology, Project administration, Writing-review and editing, Supervision. Shraddha Shetty: Methodology, Data Curation, Formal Analysis, Data Interpretation, Visualization, Writing-review and editing.

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**Cite this article:** Shaji B, Joel JJ,Sharma R, Shetty S.Evaluation of the Multifaceted Impact of Hypothyroidism on Metabolic Components and Quality of Life. Int. J. Pharm. Investigation. 2025;15(2):397-406.

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https://www.jpionline.org

Original Article

# KAP Analysis of the Materiovigilance Programme: A Comparative Study between M.Pharm and D.Pharm Students

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## ABSTRACT

**Background:** Materiovigilance is important for checking the safety and effectiveness of medical devices. There isn't much research on how pharmacy students understand and perceive about materiovigilance. To understand this study was conducted among M Pharm and D.Pharm students at KLE College of Pharmacy, Hubballi. **Materials and Methods:** A cross sectional self-developed questionnaire-based study was conducted by using a set of 15 questions about knowledge, attitudes and perceptions of materiovigilance. The questionnaire was given to 183 students before and after an educational session. SPSS software was used to analyse the results. **Results:** Both groups improved their knowledge after the session. D.Pharm students knew more initially, but M Pharm students caught up. In the view of attitude factor both groups felt more positive about materiovigilance after the session whereas D.Pharm students were more positive to start with. M Pharm students had a better view initially and their perception improved more after the session whereas D.Pharm students' perception slightly went low. **Conclusion:** The educational session successfully enhanced both D.Pharm and M Pharm students' knowledge about materiovigilance. Initially, D.Pharm students had more knowledge and a more positive attitude, while M Pharm students showed a more favourable perception. However, after the session, M Pharm students' knowledge and perception improved significantly, catching up with their peers. In contrast, although D.Pharm students remained positive, their perception slightly decreased. This indicates that while the educational intervention was beneficial for both groups, there is a need for continued focus on improving perceptions among D.Pharm students.

**Keywords:** Educational session, M Pharm, D.Pharm, factor, Materiovigilance.

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**Received:** 30-07-2024;
**Revised:** 22-10-2024;
**Accepted:** 09-12-2024.

## INTRODUCTION

Materiovigilance aims to monitor and investigate incidents that may arise from the use of medical devices. It facilitates the recall of hazardous or unsafe devices and helps eliminate defects in the manufacturing processes of medical devices, thereby ensuring patient safety (Indushree *et al*., 2022).

Not only medicines, but medical devices also pose risks to patient safety, security and can potentially cause harm. The devices used in routine practice aid in the detection, diagnosis, prevention and management of various illnesses and disease conditions (Gagliardi *et al*., 2018). Those of higher risk, or those related with more prominent probability of causing serious or untoward health consequences may sometimes lead to death, involve orthopaedic implants that is of hip or knee joints, also cardiovascular implants used as pacemakers or Implantable Cardioverter Defibrillators (ICDs) (Pane *et al*., 2017).

Medical devices present significant challenges in ensuring their safe and effective use compared to drugs. In fact, implantable devices often exhibit higher effectiveness than drugs because they are not affected by patient non-adherence. The size, complexity and functionality of medical devices vary greatly, ranging from bandages, disposable gloves and wheelchairs to more complex structures such as active implants (e.g., pacemakers) and automated systems used in cataract surgery (Abhima *et al*., 2023).

The theoretical framework of materiovigilance is similar to that of pharmacovigilance, which focuses on the safety of medicines. Just as pharmacovigilance involves the collection, assessment, analysis and interpretation of data on Adverse Drug Reactions (ADRs), materiovigilance is concerned with gathering and

**DOI:** 10.5530/ijpi.20250035

evaluating data on medical device incidents, problems and Adverse Events (AEs) (Selvam *et al.*, 2024).

As there is smaller number of studies done with respect to responsiveness of materiovigilance, in this way the current study is embraced to survey the knowledge and attitude toward materiovigilance by healthcare specialists in a healthcare sector (Rehman *et al.*, 2022).

## MATERIALS AND METHODS

### Study Site

The research was carried out at KLE College of Pharmacy, Vidyanagar, Hubballi.

### Study Design

This was a cross-sectional study employing a self-developed questionnaire to assess the knowledge, attitude and perception of materiovigilance among students enrolled in the M.Pharm and D.Pharm programs at KLE College of Pharmacy, Vidyanagar, Hubballi. A set of 15 questions were provided as a part of pre-test to the study participants and were instructed to fill the form (Google form). After the completion of pre-test, participants were exposed to an educational session which covered all the information related to the questions provided with the help of power point presentation. The same set of 15 questions was sent to the participants after the educational session for collecting the responses of post-test.

### Ethical Approval

Ethical clearance was granted by the Institutional Ethical Committee of KLE College of Pharmacy, Hubballi. The approval reference number KLECOPH/IEC/2023-24/01.

### Study Period

The study was conducted over a period of six months at KLE College of Pharmacy, Vidyanagar, Hubballi, Karnataka. The study involved planning of one month, data collection and interpretation for three months and result analysis two months.

### Study Criteria

Inclusion Criteria: Students enrolled in the M.Pharm and D.Pharm programs at KLE College of Pharmacy, Hubballi. Exclusion Criteria: Participants of the pilot study who were already provided with the educational session and students unwilling to participate in the study were excluded.

### Study Procedure

15 questionnaires, each containing five questions, were developed by the faculty of the Department of Pharmacy Practice to assess three factors: knowledge, attitude and perception. The knowledge domain employed a binary response format, with "Yes" assigned a value of 1 and "No" assigned a value of 0. The attitude and perception domains utilized a 5-point Likert scale, ranging from 'Strongly Agree' (5) to 'Strongly Disagree' (1).

Internal consistency was evaluated using Cronbach's alpha (α) via IBM SPSS 27.0, with values ranging from 0 to 1. A higher alpha value indicates stronger internal consistency, with values between 0.8 and 0.9 signifying good internal consistency. The pilot survey, conducted with 21 participants, yielded a Cronbach's alpha of 0.827, indicating a respectable level of internal consistency for the MvPI questions.

Participants initially completed a pre-test questionnaire. Subsequently, they attended an educational session on materiovigilance, which included a PowerPoint presentation covering the definition, objectives, regulatory bodies, history, reporting procedures and safety monitoring of medical devices. After the educational session, the same set of 15 questions was administered again via Google Forms to assess post-test responses.

### Statistical Analysis

Data were entered into a Microsoft Excel spreadsheet and continuous variables were presented as mean±standard deviation. Group differences were analysed using a t-test and appropriate descriptive and inferential statistical analyses were conducted using Excel and SPSS version 27.

### Sample size

Sample size is calculated using the formula;

$$N = \frac{[Z_{1-\alpha/2}]2\ p\ (1-p)}{d2}$$

N=183

Where, Z is critical value,

d is allowable error,

p is sample proportion,

α is level of significance.

## RESULTS

### Demographic details

The study involved 183 participants, with a higher proportion of females (56.83%) compared to males (43.16%). Participants' ages ranged from 18 to 25 years, with the largest groups being 18-year-olds (19.12%) and 19-year-olds (18.57%). Most participants were D.Pharm students (67.21%), while the rest were M.Pharm students (32.78%). A significant majority of the participants came from non-medical backgrounds (85.24%). In terms of socioeconomic status, a large portion belonged to the lower class, earning less than 1 lakh Rupees per year (42.07%), while others were distributed among lower middle class (16.93%), upper lower class (12.02%), upper middle class (22.40%) and upper class (6.55%). Additionally, the study had more urban residents

**Table 1: Demographic details of M.Pharm and D.Pharm.**

| Demographics | Characteristics | *N*=183 (%) |
|---|---|---|
| Gender | Female | 104 (56.83) |
| | Male | 79 (43.16) |
| Age in years | 18 | 35 (19.12) |
| | 19 | 34 (18.57) |
| | 20 | 22 (12.02) |
| | 21 | 26 (14.20) |
| | 22 | 14 (7.65) |
| | 23 | 29 (15.84) |
| | 24 | 15 (8.19) |
| | 25 | 08 (4.37) |
| Study group | M.Pharm | 60 (32.78) |
| | D.Pharm | 123 (67.21) |
| Parents profession | Non-medical background. | 156 (85.24) |
| | Medical background. | 27 (14.75) |
| Socioeconomic status | Lower class (<1 lakh Rupees per year). | 77 (42.07) |
| | Lower middle class (2-5 lakh Rupees per year). | 31 (16.93) |
| | Upper class (>10 lakh Rupees per year). | 12 (6.55) |
| | Upper lower class (1-2 lakh Rupees per year). | 22 (12.02) |
| | Upper middle (5-15 lakh Rupees per year). | 41 (22.40) |
| Residence | Rural | 71(38.79) |
| | Urban | 112(61.20) |

(61.20%) than rural residents (38.79%), reflecting a greater urban representation (Table 1).

## Knowledge factor Assessment of Knowledge regarding MvPI among M.Pharm and D.Pharm students

The Figures 1 and 2 shows the comparison of knowledge between M.Pharm and D.Pharm students about the Materiovigilance Programme of India and medical device reporting showed different results in various areas. For awareness of the Materiovigilance Programme, D.Pharm students did better in the post-test, scoring 95.12% correct answers compared to 90% for M.Pharm students. In understanding medical device classification, D.Pharm students had a higher pre-test score (71.54%) than M.Pharm (48.33%). Although M.Pharm students improved to a slightly higher post-test score (96.67% vs. 94.31%), both groups showed significant progress. When it came to knowing how to report adverse events, M.Pharm students excelled in the post-test with 96.67%, while D.Pharm students scored 91.06%. For exposure to reporting forms for adverse events, D.Pharm students scored higher in the pre-test (60.16%) compared to M.Pharm (43.33%) and after training, D.Pharm maintained a slight lead (90.24% vs. 85%). Lastly, both groups scored the same in the post-test for awareness of alerts or recalls about medical devices (90.24%), but D.Pharm had a higher pre-test score (59.35% vs. 45%). Overall, both groups improved significantly after training, but their performances varied depending on the specific topics, so it's hard to say that one group was better than the other overall.

The Table 2 presents the mean scores and standard deviations of M.Pharm and D.Pharm students in pre-test and post-test assessments related to their knowledge about the Materiovigilance Programme of India and medical device reporting. For M.Pharm students, the mean pre-test score was 2.48±1.867, which significantly increased to 4.58±1.030 in the post-test ($p$<0.001). Similarly, D.Pharm students showed a significant improvement from a mean pre-test score of 39±1.867 to 3.40±1.949 in the post-test ($p$<0.001). These results indicate that both groups benefited from the training intervention, with statistically significant increases in their knowledge scores.

## Attitude factor Assessment of Attitude regarding MvPI among M.Pharm and D.Pharm Students

The Figures 3 and 4 compares the attitudes of M.Pharm and D.Pharm students regarding medical device adverse event reporting before and after a training session. In the pre-test, 54.17% of M.Pharm and 56.91% of D.Pharm students agreed that medical devices can cause adverse events, which increased to 68.33% and 70.73%, respectively, after training. Regarding the importance of reporting adverse events, agreement was 68.34% for M.Pharm and 76.42% for D.Pharm in the pre-test, rising to 71.66% and 74.39% post-training. For the necessity of materiovigilance training, 61.67% of M.Pharm and 79.68% of D.Pharm students agreed in the pre-test, with post-training agreement at 75% and 79.67%. When asked if reporting enhances patient safety, 71.67% of M.Pharm and 84.55% of D.Pharm students agreed before training, increasing to 80% and 80.49% afterward. Finally, 71.66% of M.Pharm and 59.35% of D.Pharm students indicated they would report adverse events in the pre-test, which rose to 80% and 73.98% post-training. Overall, both groups exhibited positive attitudes towards adverse event reporting, with D.Pharm students generally showing higher agreement percentages in the pre-test and both groups demonstrating increased agreement across all questions after the training.

The Table 3 presents the mean scores and standard deviations of M.Pharm and D.Pharm students in pre-test and post-test assessments related to their attitude on the Materiovigilance Programme of India and medical device reporting. For M.Pharm students, the mean pre-test score was 17.28±5.428, which increased to 18.58±6.614 in the post-test, with a $p$-value of 0.261, indicating no statistically significant change. In contrast, D.Pharm students had a pre-test mean score of 17.14±1.892, which significantly

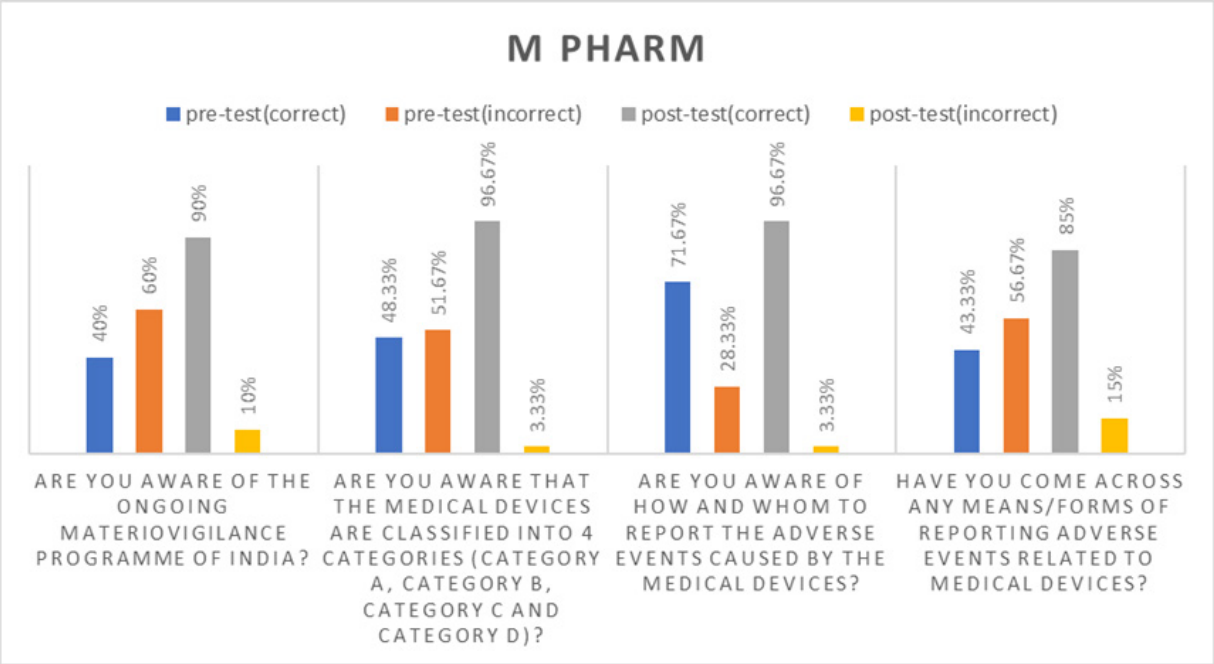


**Figure 1:** Knowledge assessment of M.Pharm.

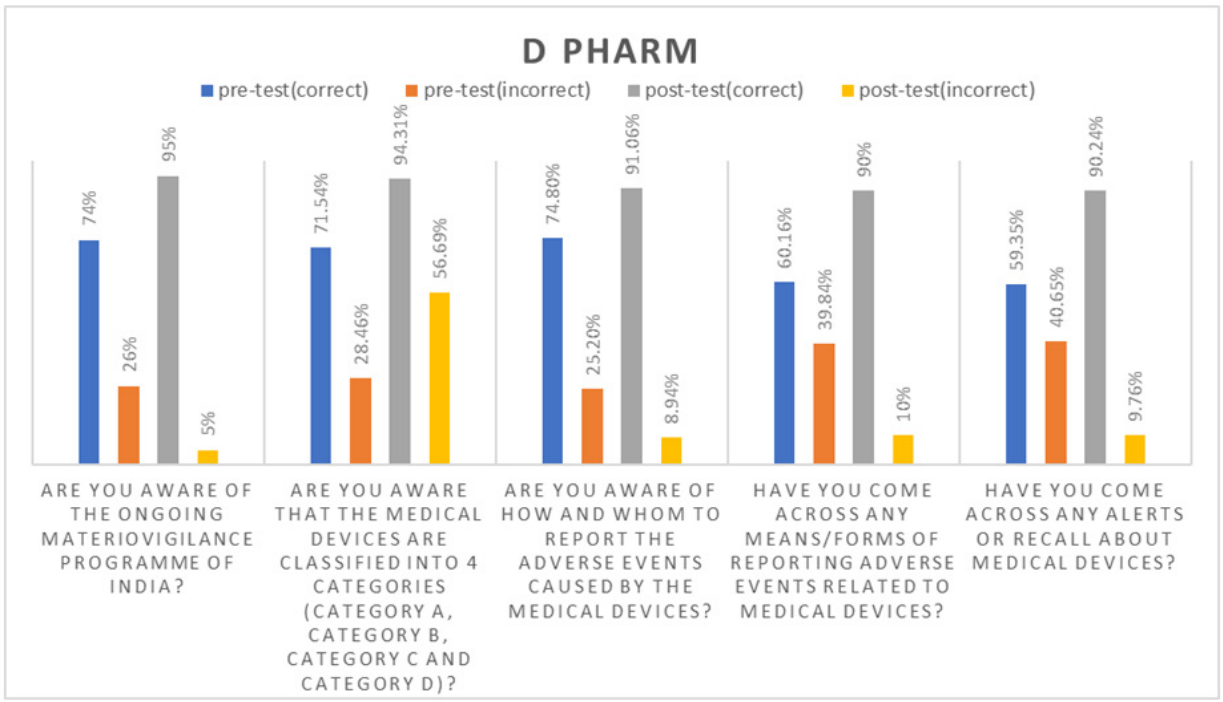


**Figure 2:** Knowledge assessment of D.Pharm.

improved to 19.19±2.979 post-test, with a *p*-value of less than 0.001, indicating a statistically significant increase in knowledge. Overall, while both groups showed improvement, only the D.Pharm students demonstrated a significant enhancement in their attitude scores after the training.

## Perception factor Assessment of Perception regarding MvPI among M.Pharm and D.Pharm student

The Figures 5 and 6 presents the perceptions of M.Pharm and D.Pharm students regarding various aspects of the Materiovigilance Programme before and after a training session. Initially, 61.67% of M.Pharm students believed that India's materiovigilance programme can generate evidence-based data

**Table 2: *T*-Test Analysis of Knowledge scores in M.Pharm and D.Pharm students regarding MvPI.**

| Sl. No. | Stream | N | Mean±Sd. Dev | | *p*-value |
|---|---|---|---|---|---|
| | | | Pre | Post | |
| 01 | M.Pharm | 60 | 2.48±1.867 | 4.58±1.030 | <0.001* |
| 02 | D.Pharm | 123 | .39±1.867 | 3.40±1.949 | <0.001* |

*Significantly significant $p<0.05$.

**Table 3: *T*-Test Analysis of Attitude scores in M.Pharm and D.Pharm students towards MvPI.**

| Sl. No. | Stream | N | Mean±Sd. Dev | | *p*-value |
|---|---|---|---|---|---|
| | | | Pre | Post | |
| 01 | M.Pharm | 60 | 17.28±5.428 | 18.58±6.614 | .261 |
| 02 | D.Pharm | 123 | 17.14±1.892 | 19.19±2.979 | <0.001 |

*Significantly significant $p<0.05$.

on medical device safety, which increased to 79.17% post-test. For D.Pharm students, the pre-test agreement was 52.85%, rising to 90.24% post-test. Regarding the impact of reporting adverse events, 69.99% of M.Pharm students thought one report could make a difference, increasing to 83.33% post-training, while D.Pharm students showed a similar trend, with pre-test agreement at 72.36% and post-test at 83.74%. Awareness of the potential consequences of not reporting adverse events was 60% for M.Pharm students pre-test, increasing to 86.67% post-test and 63.41% for D.Pharm students pre-test, rising to 86.59% post-test. Initially, 60% of M.Pharm students viewed materiovigilance reporting as beneficial for their professional development, which rose to 85.71% post-test and for D.Pharm students, the pre-test agreement was 58.54%, increasing to 84.55% post-test. Finally, 68.33% of M.Pharm students felt there was a need for greater awareness of materiovigilance among pharmacy students, which increased to 83.33% post-test, while D.Pharm students showed similar results, with pre-test agreement at 65.04% and post-test at 89.43%. Overall, both groups demonstrated enhanced positive perceptions regarding the Materiovigilance Programme after the training.

The Table 4 presents the results of a *t*-test analysis comparing the perception factor between M.Pharm and D.Pharm students regarding the Materiovigilance Programme of India and medical device reporting. For M.Pharm students, the mean pre-test perception score was 17.20 (SD=5.784), which significantly increased to 19.75 (SD=5.461) in the post-test, with a *p*-value of 0.019, indicating a statistically significant improvement. In contrast, D.Pharm students had a mean pre-test perception score of 19.16 (SD=2.732), which decreased to 18.24 (SD=2.722) post-test, with a *p*-value of 0.004, also statistically significant. This suggests that while M.Pharm students benefited from the training, enhancing their perceptions, D.Pharm students experienced a decline in their perception scores despite the intervention. These findings highlight a noteworthy difference in the impact of the training on the two groups, warranting further investigation to understand the reasons behind the decrease in D.Pharm students' perceptions.

## Comparative analysis of Knowledge, Attitude and Perception (KAP) factors between M.Pharm and D.Pharm students regarding MvPI

The participants responses were categorised into three levels based on their total scores in each domain namely Poor, Moderate and Good. The Table 5 summarizes the structure and scoring for three assessment domains: Knowledge, Attitude and Perception.

The Table 6 compares the Knowledge, Attitude and Perception (KAP) factors between M.Pharm and D.Pharm students, categorized as poor, moderate and good as mentioned in Table 5. In terms of knowledge, D.Pharm students had more participants in the good category, with 76 compared to 53 for M.Pharm. Similarly, for attitude, D.Pharm students had a higher number of participants (88) in the good category than M.Pharm students (42), suggesting that D.Pharm students had a better overall understanding of the Materiovigilance Programme and medical device reporting. However, when it comes to perception, M.Pharm students had more participants (47) in the good category compared to D.Pharm students (65), indicating that M.Pharm students had a better understanding of the consequences and benefits of the Materiovigilance Programme. While the table provides a clear comparison of the KAP factors between the two groups, further analysis would be needed to determine if these differences are statistically significant (Figures 7 and 8).

## DISCUSSION

In this study we discuss the Knowledge, Attitude and Perception among the M.Pharm and D.Pharm students in which they were assessed with Pre-test and Post-test respectively. Both the streams had positive impact in all aspects which signifies the importance of educational intervention. The results also showcase the differences in both the streams as seen in KAP of Materiovigilance between the groups where D.Pharm students had an overall

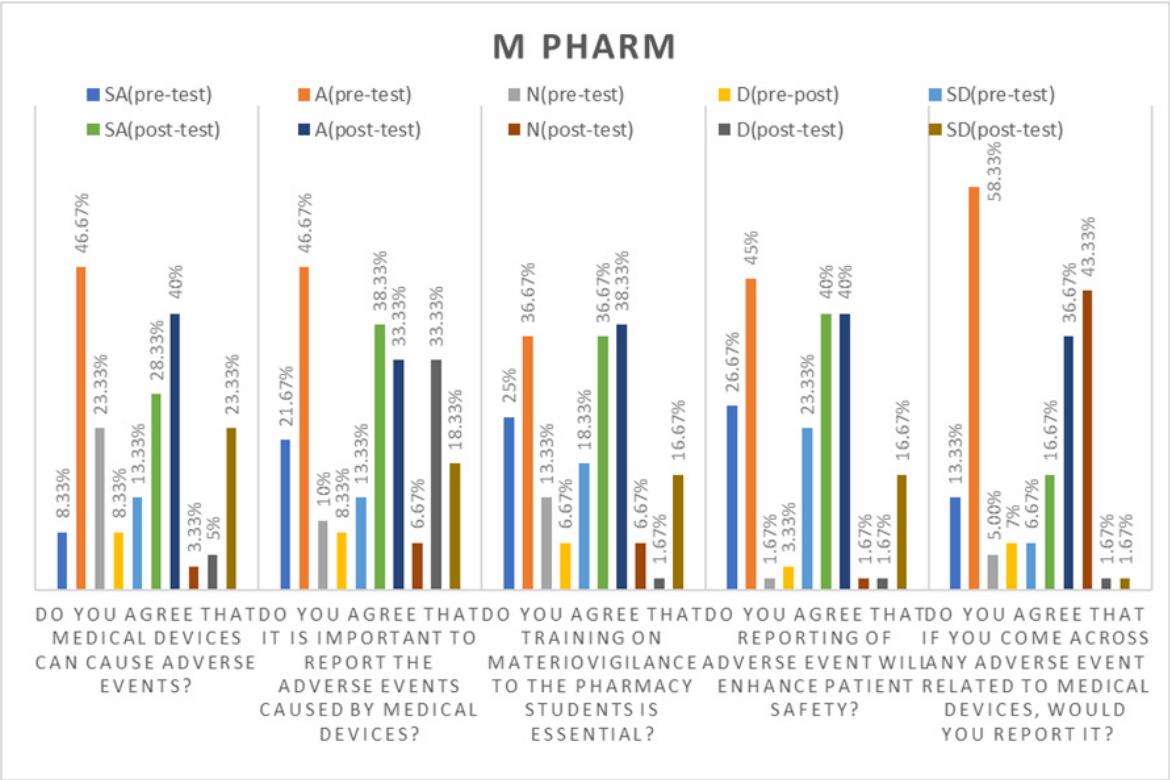


**Figure 3:** Attitude assessment of M.Pharm.

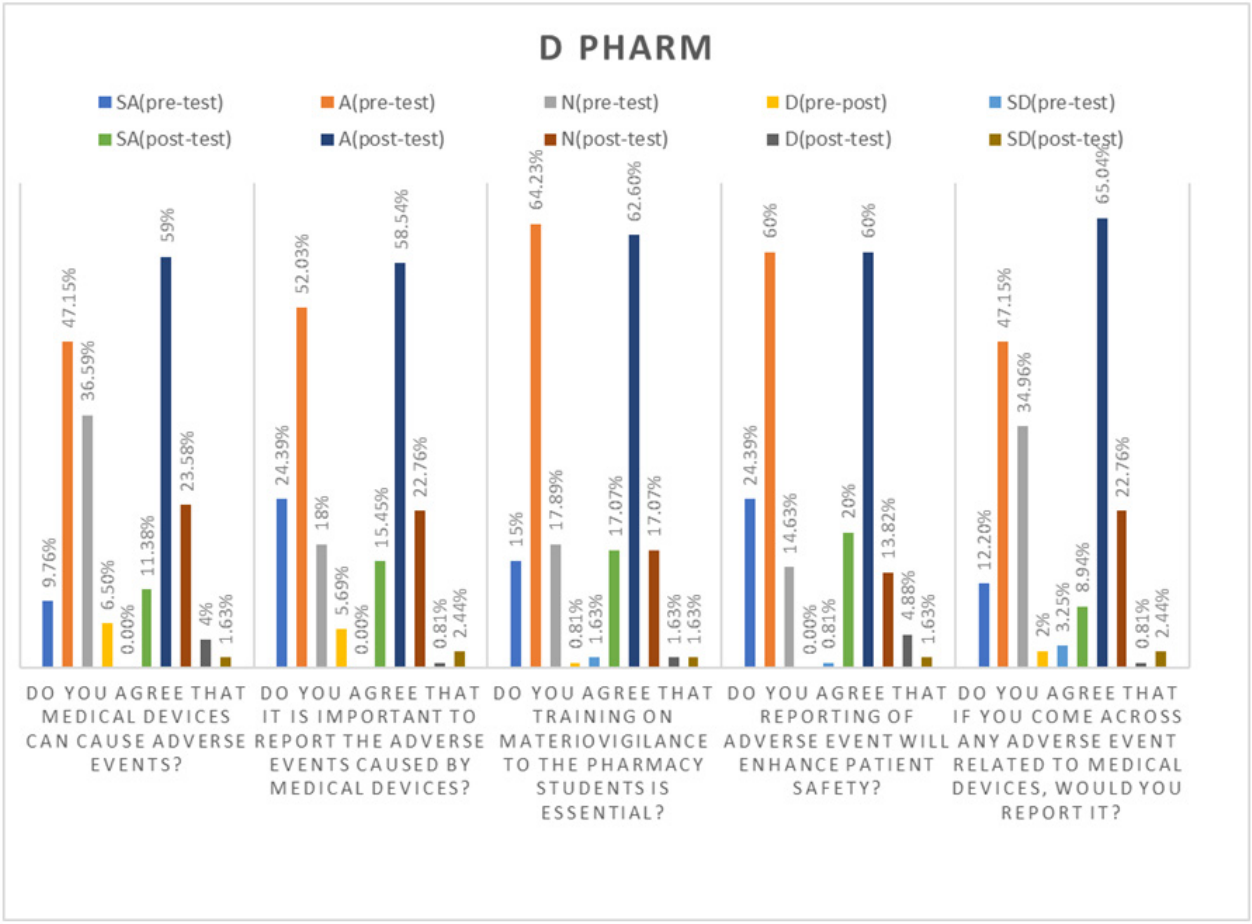


**Figure 4:** Attitude assessment of D.Pharm.

**Table 4: Test Analysis of Perception scores in M.Pharm and D.Pharm students regarding MvPI.**

| Sl. No. | Stream | N | Mean±Sd. Dev | | *p*-value |
|---|---|---|---|---|---|
| | | | Pre | Post | |
| 01 | M.Pharm | 60 | 17.20 ±5.784 | 19.75 ±5.461 | .019* |
| 02 | D.Pharm | 123 | 19.16 ±2.732 | 18.24 ±2.722 | 0.004* |

*Significantly significant $p<0.05$.

**Table 5: Scoring and categorization of KAP.**

| Domain | Question format | Scoring | Poor category | Moderate category | Good category |
|---|---|---|---|---|---|
| Knowledge | Yes/No (2 options). | Yes=1, No=0 | 0-2 points | 3 points | 4-5 points |
| Attitude | SA, A, N, D, SD (5 options). | 5,4,3,2,1 | 0-16 points | 17-18 points | 19-25 points |
| Perception | SA, A, N, D, SD (5 options). | 5,4,3,2,1 | 0-16 points | 17-18 points | 19-25 points |

**Table 6: Comparison of KAP factors between M.Pharm and D.Pharm.**

| Stream | M.Pharm | | | D.Pharm | | |
|---|---|---|---|---|---|---|
| Criteria | Poor | Moderate | Good | Poor | Moderate | Good |
| Knowledge | 03 | 04 | 53 | 32 | 15 | 76 |
| Attitude | 12 | 06 | 42 | 23 | 12 | 88 |
| Perception | 10 | 03 | 47 | 36 | 22 | 65 |

higher level of understanding as compared to M.Pharm towards MvPI from the on set.

The analysis of Knowledge tells us that both the groups had significant improvement in the knowledge after the training, in which D.Pharm had outclassed M.Pharm in the post-test by scoring 95.12% correct answers as compared to M.Pharm 90% respectively. In case of reporting of adverse events M.Pharm had more positive knowledge 96.67% as compared to D.Pharm students 91.06%. A comparable study was done by Sivagourounadin *et al.* in which nurses were found to have adequate knowledge regarding MvPI and NCC but had slightly poor knowledge regarding the functioning of MDAEs 61% which also resulted in lack of reporting of adverse events (Sivagourounadin *et al.*, 2022).

The assessment of attitude showed positive trend of response in both the groups from pre-test to post-test respectively. In this D.Pharm had shown profound attitude in the pre-test as compared to M.Pharm which justifies that D.Pharm had a higher agreement in understanding the reporting of adverse events and the necessity of Materiovigilance program. Thus, both the groups had exhibited positive attitude and approach of adverse event reporting after the training. The study led by Bikash Ranjan *et al.* in Bhubaneswar had a significant majority in reporting of ADRs (84.4% of medical faculty and 90% of resident doctors) and they believed that medical devices can cause adverse events. Also, 93.3% of resident doctors felt the necessity and were obliged to report the adverse events in a responsible manner (Meher *et al.*, 2022).

These outcomes were found to be consistent in various studies such as study conducted by Panchal *et al.* which revealed high level of interest in reporting MDAEs 77.6% and the significance of establishing of Materiovigilance by educational intervention had an overall response of 94.8% (Panchal *et al.*, 2022). Hence, these studies describe us that positive Attitude regarding Materiovigilance is necessary for reporting of adverse events associated with medical devices and to enhance the patient's safety and HRQOL.

The perception-based analysis tells us that in both the groups M.Pharm and D.Pharm there was significant improvement in post-test scores resulting in positive perception of Materiovigilance program. In this study D.Pharm students had shown higher agreement of percentages in several areas, particularly in recognizing the importance of reporting adverse events and the potential for professional growth through materiovigilance. This indicates both had an overall positive perception of Materiovigilance in which their score had climbed to 83.74% as compared to M.Pharm post-test score of 83.33% respectively. In the study conducted by Mangala *et al.* 71% of health-care practitioners observe patients for MDAEs out of which 38% had actually encountered MDAEs. This study shows doctors had advanced practice as compared to other medical professionals and majority of medical professionals 82% did not

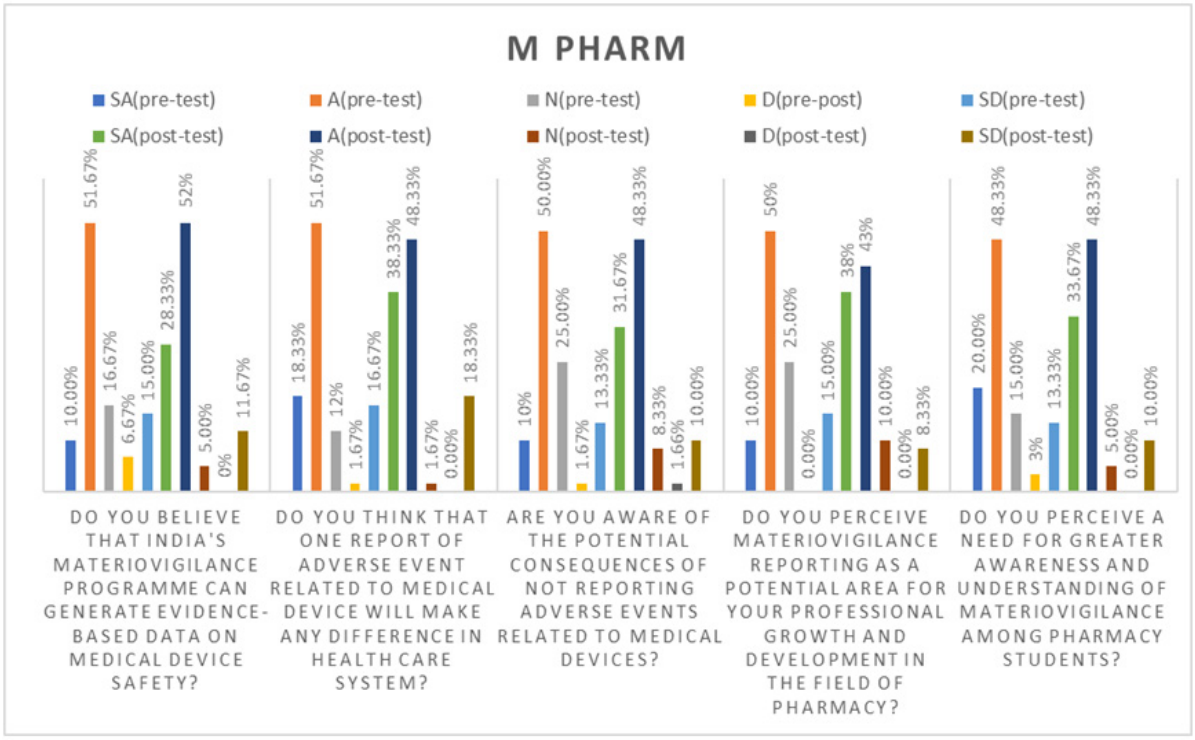


**Figure 5:** Perception assessment of M.Pharm.

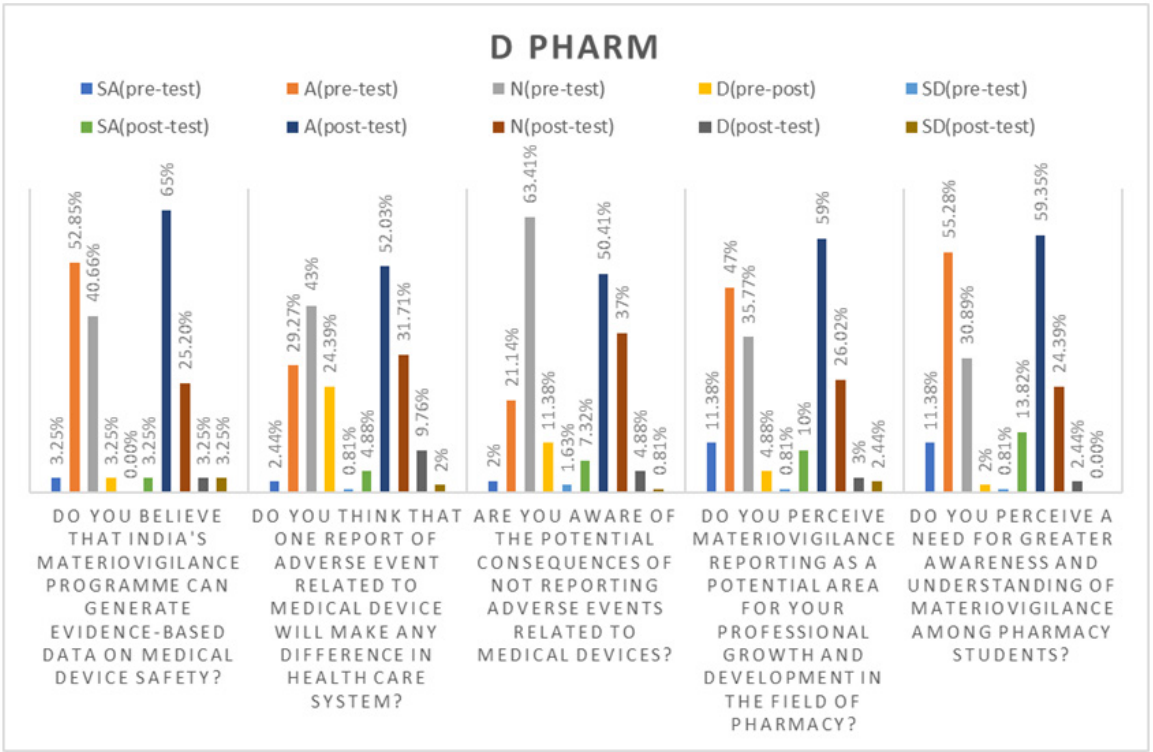


**Figure 6:** Perception assessment of D.Pharm.

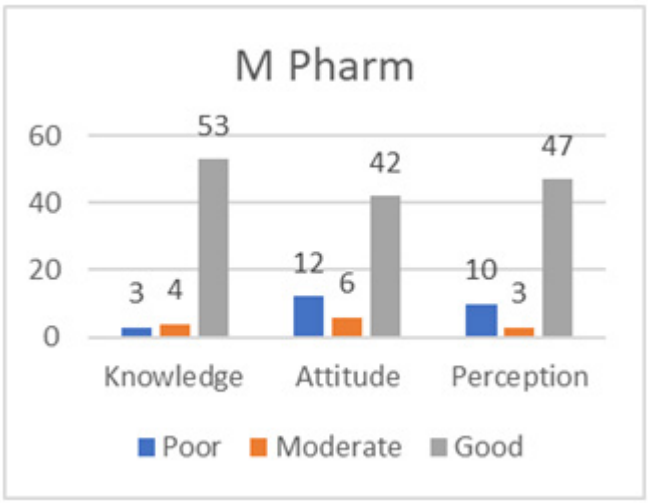


**Figure 7:** Post-test KAP of M.Pharm.

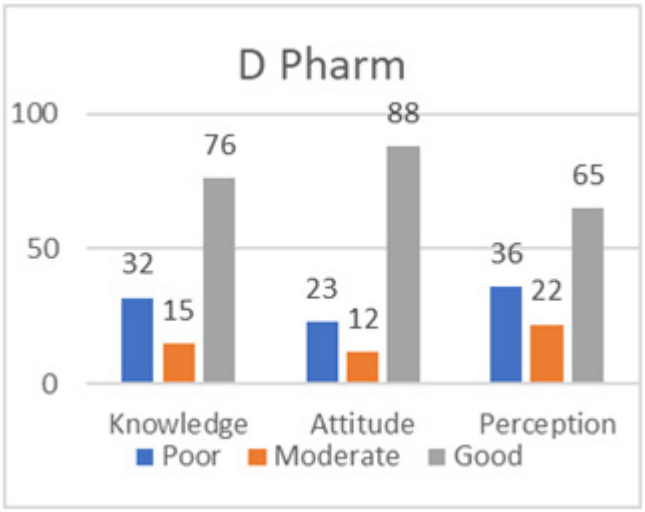


**Figure 8:** Post-test KAP of D.Pharm.

receive training on reporting of MDAEs (Srinivas *et al.*, 2023). These studies show marked importance in improving the positive perception about Materiovigilance programme and a need for better training to report adverse events.

Lastly, this study marks that both the groups had significantly improved in all the aspects knowledge, attitude and perception showing positive results in post-test which marks the importance of educational intervention regarding Materiovigilance. The study also reveals that D.Pharm students had consistently performed better than M.Pharm students in overall KAP assessments. A study conducted by Nirmalya *et al.* states that training regarding MDAEs reporting and its promotion can be done by posting posters with instructions. Also, by implementing training, workshops and CME (continuing medical education) Materiovigilance awareness can be improved among the health-care professionals. Strategies to include medical device surveillance and Materiovigilance in the curriculum can definitely workout towards early awareness among all HCPs (Manna *et al.*, 2023).

## CONCLUSION

The comparison of Materiovigilance (Mv) performance between D.Pharm and M.Pharm graduates using Knowledge, Attitude and Perception (KAP) factors reveals that D.Pharm students exhibit superior knowledge, attitudes and perceptions regarding medical device safety and reporting compared to M.Pharm students. D.Pharm students demonstrated higher initial and post-intervention awareness of the Materiovigilance Programme of India, medical device classifications and reporting procedures. They also showed a stronger belief in the importance of reporting adverse events and the need for materiovigilance training. In contrast, M.Pharm students, while improving post-intervention, initially had lower levels of awareness and less belief about the impact of reporting on healthcare systems. Both groups acknowledged the importance of materiovigilance for professional growth and emphasized the need for greater awareness among pharmacy students, marking the necessity for enhanced training across all pharmacy education levels to ensure improved patient safety and healthcare outcomes.

## CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

## ABBREVIATIONS

**KAP:** Knowledge Attitude Perception; **SPSS:** Statistical Package of Social Sciences; **M.Pharm:** Master of Pharmacy; **D.Pharm:** Diploma in Pharmacy; **ICD:** Implantable cardioverter defibrillators; **ADRs:** Adverse drug reactions; **AEs:** Adverse events; **SD:** Strongly disagree, **D:** Disagree; **N:** Neutral; **A:** Agree; **SA:** Strongly agree; **MvPI:** Materiovigilance Programme of India; **Sd. Dev:** Standard Deviation; **NCC:** National Coordinating Centres; **MDAEs:** Medical device related adverse events; **HRQOL:** Health related quality of life; **CME:** Continuing medical education; **HCPs:** Health care professionals; **Mv:** Materiovigilance.

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**Cite this article:** Sail SS, Gore A, Sayed AA, Khan MR, Swamy AHMV, Dayana BM, *et al*. KAP Analysis of the Materiovigilance Programme: A Comparative Study between M Pharm and D Pharm Students. Int. J. Pharm. Investigation. 2025;15(2):407-16.