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Research Article

Enhancing paracetamol compressibility using the co-drying technique: Impact on tablet release profile from direct compression

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Abstract

Direct compression is the most acceptable and preferred method for manufacturing tablets. However, the poor flow property and lack of the required compressibility of most active ingredients preclude the direct compression technique. Paracetamol is a widely used analgesic drug, usually formulated in compressed tablet dosage forms. It is a poorly compressible drug with a hefty dose, usually 300 to 500 mg. In addition, Paracetamol exhibits poor flowability and shows the tendency to cap on tableting due to its poor plasticity and compatibility. The present research work developed Paracetamol DC (Directly Compressible) by co-processing with a mixture of Potato starch and Silicon Dioxide in various ratios using co-freezing and co-drying techniques. Paracetamol DC was assessed for multiple pre-compression and post-compression tableting parameters. The marked improvement in flow behavior and compressibility of co-processed Paracetamol was observed. Results of studies showed that Paracetamol DC developed with a 10% mixture containing Potato Starch and Silicon Dioxide in a ratio of 7:3 exhibited better disintegration properties and released more than 50% of the drug within 30 min. The study concluded that the technique of coprocessing poorly compressible drugs such as Paracetamol with starch and silicon dioxide using the co-freezing co-drying technique could enhance the compressibility and flowability of active pharmaceutical ingredients.

Keywords: Poor compressibility; co-processing; flow ability; direct compression; paracetamol

Introduction

Tablets are the most preferred dosage form due to their high dosing precision, compactness, manufacturing efficiency, stability, and patient compliance. Tablets are manufactured using techniques like direct compressing, wet granulation, or dry granulation. The method selection depends upon the drug's physicochemical properties and excipients [1,2]. Paracetamol, an active pharmaceutical ingredient, presents challenges due to its poor plasticity and compactability [3,4]. Strategies such as altering the crystal lattice or changing the crystal shape have been successful in enhancing its compression behavior, but stability issues with its crystalline structure have been reported [5]. Another major challenge is the poor flowability of paracetamol, which can be overcome by suitable granulation methods [6]. However, these methods are multi-step and involve various complex processes [7].

Direct compression is usually preferred over other tableting techniques due to its simplicity, cost-effectiveness, and less processing time with fewer manufacturing steps. Direct compression is also advantageous as it is suitable for thermolabile and moisture-sensitive active pharmaceutical ingredients. However, poor flow properties and lack of the required compressibility of most of the active ingredients preclude the use of direct compression. This creates the need to incorporate a number of excipients, such as fillers, binders, lubricating agents, and flow promoters [7,8]. An Increase in excipients in the formulation blend may increase the incidence of drug-excipient and excipient-excipient interactions. It may also affect the cost of manufacture. In the case of a potent drug, improper mixing of formulation blend may result in poor content uniformity [9,10]. Although multi-functionality excipients such as starch 1500, Micro Crystalline cellulose, and Lactose DC can be used to improve the

compressibility and tablet-forming ability of the drug, improper mixing, cost of excipient development and variability in excipients may create challenges for the manufacturing of tablets [11,12]. Co-processing is a technique for the development of a multifunctional, directly compressible excipient system consisting of a combination of brittle and plastic material in a suitable ratio, which is intermixed with one another by physical processing [13,14]. Co-processing of excipients improves dilution potential, improves compressibility, and reduces lubricant sensitivity and acceptable flow properties [15].

Starch is one of the most traditional excipients of natural origin used for manufacturing compressed solid dosage forms such as tablets due to its non-toxicity, economy, ease of modification, and versatile pharmaceutical applications. Depending on the type and proportion in the formulation, Starch acts as a diluent, binder, disintegrating agent, and lubricating agent [16,17]. Potato starch is an inert, odorless, and white multifunctional excipient. Usually modified physiochemically to improve its processability [18]. Alexiou G and Itiola OA reported that the use of pre-gelatinized Starch as a binder could improve the mechanical strength of Paracetamol tablets [19]. Potato starch can be gelatinized at a lower temperature (62°C) than other Starch [20]. Gelatinization of starch results in the breakdown of hydrogen bonds between the molecules of Starch [21], and Amylose will leak [22]. Deshkar *et al.* reported increased swelling and decreased crystallinity of Native Starch on hydrothermal treatment due to the leaching of Amylose [23]. Trisopon K and Kittipongpatana OS reported that crosslinking of Starch with 10% Sodium Silicate resulted in increased flowability; however, a negative effect on swelling behavior was observed at higher concentrations of Sodium Silicate. Adsorption of Sodium Silicate on the surface of Starch resulted in increased flowability but also led to inhibition of particle binding and structural irregularities [22]. Apeji YE and co-workers observed improved mechanical strength with the rapid disintegration of tablet-compressed tablets using Starch co-processed with silicon dioxide [24,25]. Rojas J and Kumar V showed that silicification of excipients (Cellulose Microcrystalline) can help reduce lubricant sensitivity, improve flowability, and increase brittleness behavior [26]. Rashid I and co-workers also reported similar results. Improvement in mechanical strength with reduced lubricant sensitivity was observed for excipients developed by coprocessing of Starch with Magnesium Silicate [27].

Although co-processed or particle-engineered excipients offer several advantages, developing excipients separately and processing them with active ingredients is costly and time-consuming. To overcome these challenges, an attempt has been made to develop a directly compressible Active Pharmaceutical Ingredient by physical modification using the technique of co-processing.

The objective of the current research was to develop a directly compressible active ingredient using the co-processing technique. In this study, the compressibility of a poorly compressible drug, viz., paracetamol, was enhanced by co-processing it with excipients such as potato starch and silicon dioxide using a co-freezing co-drying technique. The developed Paracetamol DC (Direct Compressible) exhibited improved tableting properties.

Materials

The Paracetamol was received as a gift sample from Wallace Pharmaceuticals Pvt Ltd, located in Goa, India. The potato starch was procured from Priti Trade MEX Private Ltd in Kalol, Gujarat, India, and the silicon dioxide was obtained from Chemi Enterprises Ltd in Mumbai, India.

Development of Paracetamol DC

Paracetamol was sifted through sieve no. 80 and blended with a mixture of potato starch and silicon dioxide in varying ratios, as in Table 1. Physical Blends were dispersed in purified water to prepare 50% w/v aqueous dispersion and refrigerated for 120 min in a deep freezer. The frozen dispersion was heated at 65 ºC for 30 min and dried in a tray dryer maintained at 60 ºC. The composite obtained after drying was pulverized and then sifted through sieve no. 80. The developed paracetamol DC is assessed for pre-compression and post-compression parameters [14,15,24-27].

Table 1. Formulation table for development of Paracetamol DC.

Ingredients	PDC 1	PDC 2	PDC 3	PDC 4	PDC 5
Paracetamol	500 mg	500 mg	500 mg	500 mg	500 mg
Potato starch	45 mg	40 mg	35 mg	30 mg	25 mg
Silicon dioxide	5 mg	10 mg	15 mg	20 mg	25 mg
Final weight	550 mg	550 mg	550 mg	550 mg	550 mg

Evaluation of pre-compression parameters of developed paracetamol DC

Angle of repose

The flow rate of developed Paracetamol DC was determined as the Angle of Repose by a fixed funnel method with a constant pressure head [28-30].

Hausner's ratio

The flow behavior of Paracetamol DC was determined as Hausner's ratio using tapped and untapped density. A tapped density apparatus was used to measure the untapped and tapped volume of Paracetamol DC. The apparatus was set for 50 tapings with a time interval of 2 seconds. Untapped Densities, Tapped Densities, and Hausner's ratio were calculated using formulas as mentioned below [28-30].

$$Untapped\ Density = \frac{Weight\ of\ Sample}{Untapped\ Volume},\quad Tapped\ Density = \frac{Weight\ of\ Sample}{Tapped\ Volume},\quad Housner's\ Ratio = \frac{Tapped\ Density}{Untapped\ Density}$$

Carr's index

Compressibility of developed Paracetamol DC was determined as Carr's Index using following formula [28-30].

$$Compressibility\ Index = \frac{Tapped\ Density - Untapped\ Density}{Tapped\ Density}$$

Preparation of tablets by direct compression

The Paracetamol DC composites (PDC1 to PDC5) have been meticulously formulated and compressed using a 12-station Karnavati tablet compression machine (Table 2) (F1 to F5) with uniform concentrations of Magnesium stearate and purified talc. The speed of the turret was carefully maintained within the range of 4 to 5 rpm. A total of 300 tablets for each batch, coded from F1 to F5, were meticulously compressed and evaluated for post-compression parameters [29,31].

Table 2. Content of the Paracetamol DC (in mg), in five different formulations of tablets 570 mg.

Composition	F1	F2	F3	F4	F5
Paracetamol DC *	PDC1	PDC2	PDC3	PDC4	PDC5
	550 mg (500:45:5)	550 mg (500:40:10)	550 mg (500:35:15)	550 mg (500:30:20)	550 mg (500:25:25)
Magnesium Stearate	10 mg	10 mg	10 mg	10 mg	10 mg
Purified Talc	10 mg	10 mg	10 mg	10 mg	10 mg

* Paracetamol DC: (Paracetamol: Potato Starch: Silicon Dioxide)

Evaluation of post-compression parameters of developed paracetamol DC

Determination of tensile strength

The mechanical strength of compressed tablets of Paracetamol DC was determined by using a Monsanto Hardness tester. The compact density of tablets was determined from the thickness and radius of the tablet using vernier calipers. The tablets' thickness, diameter, and diametral crushing strength were used to calculate the tensile strength [31-34].

$$Tensile\ Strength = \frac{2F}{\pi dt}$$

Where F is the crushing strength, d is the diameter, and t is the thickness of tablets.

Test for friability

Tablets of Paracetamol DC were subjected to a friability test per Indian Pharmacopoeial specifications using a Roche Friability tester. Since the weight of each tablet (570 mg) was less than 650 mg, a random sample of whole tablets corresponding to 6.5 gm was subjected to the testing. The test was carried out at 25 rpm for 4 min, and percent friability was calculated [35].

Determination of drug content

Test for uniformity of drug content was performed as per Indian Pharmacopoeial Specifications. Randomly selected 20 tablets from each batch of Paracetamol DC were crushed and powder equivalent to 500 mg of Paracetamol was dissolved in 100 ml of distilled water. Sample was analyzed UV spectroscopically and amount of drug was calculated [35].

Disintegration test

The disintegration test was carried out as per Pharmacopoeial specifications. Randomly selected 6 tablets of Paracetamol DC from each batch were subjected to a disintegration test using distilled water as media maintained at 37 ± 20 ºC. The time required for complete disintegration was recorded [35].

In-vitro drug release studies

The in-vitro drug release studies were conducted according to the USP specifications using the USP type II paddle apparatus. The study took place in Acid Buffer with a pH of 1.2. The temperature of the dissolution medium was meticulously maintained at 37 ± 0.5 ºC, while the rotation of the paddle was kept at 50 rpm. At various time intervals, samples were withdrawn and passed through a Whatman filter, with the same volume of fresh media being replaced to ensure sink conditions. The withdrawn samples were then analyzed using a UV Visible Spectrophotometer at 243 nm [36].

Results and discussion

Pre-compression parameters

The results of precompression parameters are given in Table 3. All the composites of Paracetamol DC showed better flowability and good compressibility compared to that of untreated paracetamol. An increase in flowability could be due to the adherence of silicon dioxide onto the surface of paracetamol particles, which could result in an increased distance between two adjutant host particles. In aqueous dispersion, silicon dioxide will be rendered nonporous to form large agglomerates. During pulverization and blending, large agglomerates break down into smaller particles, possibly due to the shear force that is distributed on the surface of paracetamol [37]. Composite PDC2 and PDC3 exhibited better flowability, which could be due to the optimum proportion of glidant. At lower concentrations, the amount of glidant is insufficient to cover the surface of host particles; at higher concentrations, glidant may spread out [38]. Better compressibility was observed for Paracetamol DC, possibly due to partial pre-gelatinization of Potato starch during the co-drying step [39].

Table 3. Evaluation of pre-compression parameters.

Formulation	Untapped Density (gm/cc^3)	Tapped density (gm/cc^3)	Angle of Repose (^{o})	Compressibility Index (%)	Hausner's ratio
Untreated Paracetamol	0.40 ± 0.04	0.55 ± 0.05	35.00 ± 2.22	27.27 ± 2.33	1.38 ± 0.03
PDC 1	0.53 ± 0.07	0.58 ± 0.05	20.50 ± 3.07	8.62 ± 1.54	1.09 ± 0.05
PDC 2	0.52 ± 0.05	0.56 ± 0.04	19.66 ± 2.33	7.14 ± 1.03	1.08 ± 0.03
PDC 3	0.57 ± 0.05	0.62 ± 0.04	18.68 ± 1.63	8.06 ± 1.23	1.09 ± 0.06
PDC 4	0.55 ± 0.06	0.60 ± 0.04	21.66 ± 2.24	8.33 ± 1.45	1.09 ± 0.03
PDC 5	0.58 ± 0.03	0.64 ± 0.03	22.98 ± 1.32	9.375 ± 1.78	1.10 ± 0.02

SD: n = 3

Post compression parameters

The findings of post-compression parameters for developed Paracetamol DC are tabulated in Table 4. Tablets of Paracetamol DC showed a bonding index of less than 0.4, indicating the formation of a strong compact [40].

Table 4. Evaluation of post-compression parameters.

Average	Formulations				
	F1	F2	F3	F4	F5
Compact density (g/cm²)	0.39 ± 0.02	0.40 ± 0.04	0.39 ± 0.03	0.39 ± 0.05	0.39 ± 0.04
Tensile strength (g/cm²)	2.59 ± 0.34	2.48 ± 0.54	2.43 ± 0.47	2.26± 0.30	1.95± 0.73
Bonding index	0.32± 0.06	0.33± 0.04	0.32± 0.05	0.32± 0.06	0.32± 0.04
Tablet porosity	0.60± 0.04	0.59± 0.05	0.60± 0.06	0.60± 0.05	0.60± 0.07
Percent friability (%)	0.31 ± 0.05	0.42 ± 0.07	0.49 ± 0.05	0.53 ±0.06	0.59 ±0.04
Percent drug content (%)	98.24 ±1.53	97.36 ± 1.44	99.56 ± 0.99	98.68 ± 1.11	99.66 ±1.05
Disintegration time (seconds)	15 ± 2	27 ± 4	28 ± 3	35 ± 5	49 ± 4

SD: n=3

All formulations' tensile strength, friability, and compact density were found to be in an acceptable range, which confirmed the mechanical strength of tablets of Paracetamol DC [41]. Improvement in mechanical strength was observed, possibly due to the formation of porous agglomerates due to the pre-gelatinization of potato starch and the vaporization of water during the drying stage. Porous agglomerates of Paracetamol DC could result in better fragmentation during compression. Pre-gelatinization of potato starch could also contribute to the prepared tablets' rapid disintegration [42]. Tablets of Paracetamol DC containing higher concentrations of Potato starch disintegrated rapidly.

The results of in-vitro drug release studies are presented in Table 5 and Figure 1. More than 50% of the drug was released within the first 40 min from all the formulations. An increase in the rate of drug release was observed with an increase in the proportion of potato starch in Paracetamol DC. However, further release of the drug was negatively affected by an increased proportion of potato starch. The initial release of the drug could be due to better disintegration of the tablet, and a further decrease in release rate could be due to the formation of a swollen layer of starch [43].

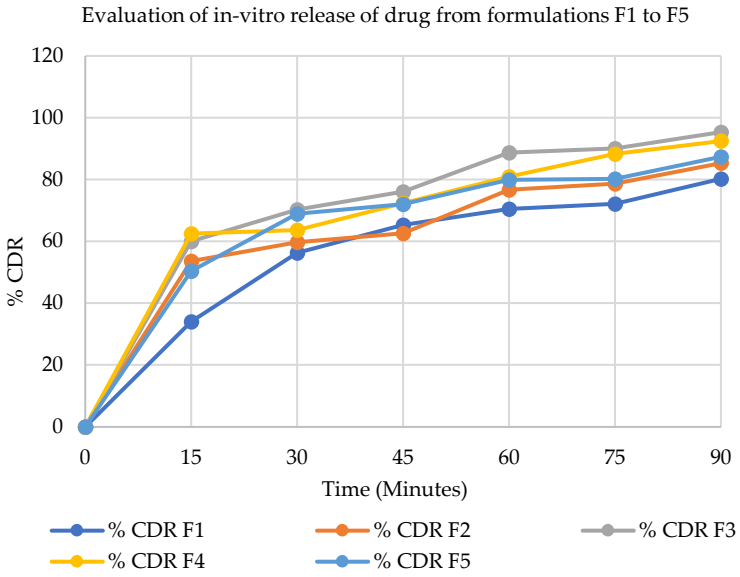

Figure 1. Evaluation of *in-vitro* release of drug from formulations F1 to F5.

Table 5. Evaluation of in-vitro release of drug from formulations F1 to F5.

Time (mins)	Cumulative % drug release				
	F1	F2	F3	F4	F5
15	34.02 ± 2.34	53.64 ± 2.33	60.02 ± 3.42	62.5 ± 2.45	50.4 ± 3.11
30	56.3 ± 2.55	59.66 ± 3.21	70.24 ± 3.21	63.66 ± 3.21	68.87 ± 4.22
45	65.31 ± 3.54	62.59 ± 2.55	76.02 ± 3.76	72.3 ± 3.46	72.02 ± 2.65
60	70.46 ± 2.21	76.66 ± 3.42	88.66 ± 2.44	80.88 ± 3.28	79.92 ± 3.42
75	72.09 ± 3.33	78.66 ± 2.63	90.08 ± 2.56	88.3 ± 3.76	80.24 ± 2.54
90	80.24 ± 3.32	85.34 ± 2.46	95.33 ± 2.11	92.52 ± 2.55	87.39 ± 3.56

SD: n=3

Based on the results of the assessment of precompression and post-compression parameters, it was observed that the Paracetamol DC (PDC3) developed with a 10% mixture containing Potato Starch and Silicon Dioxide in a ratio of 7:3 exhibited excellent flow behavior, good compaction properties, and better disintegration properties and released more than 50% of the drug within the first 30 min.

Stability studies of paracetamol DC

A stability study for PDC 3 was carried out according to ICH guidelines. The results of the study are tabulated in Table 6. No significant differences were observed in the precompression and post-compression parameters of PDC3. This indicates that the developed PDC3 exhibits satisfactory stability.

Table 6. Stability study of developed PDC 3.

Period	Angle of repose	Tensile strength	Disintegration time	% CDR at 30 min	% CDR at 60 min	% CDR at 90 min
1st Month	18.79 ± 1.25	2.44 ± 0.66	29 ± 1.64	68.34 ± 2.33	87.86 ± 1.42	93.35 ± 1.77
2nd Month	18.92 ± 1.56	2.44 ± 0.36	29 ± 1.44	67.44 ± 2.46	86.46 ± 1.67	93.37 ± 1.43
3rd Month	19.28 ± 1.22	2.43 ± 0.46	30 ± 1.57	66.27 ± 2.42	86.62 ± 1.83	92.28 ± 1.63

*Mean ± SD (n= 3)

Conclusion

Paracetamol DC was developed by co-processing Paracetamol with a blend of Potato starch and silicon dioxide using a co-freezing co-drying technique. Results showed marked improvement in flowability, possibly due to silicon dioxide's adherence onto the surface of paracetamol particles. Enhancement of compressibility with good compaction behavior of Paracetamol DC was observed. This could be due to the formation of porous agglomerates because of the pre-gelatinization of potato starch and vaporization of water during drying. An increased concentration of Potato starch showed better disintegration of the tablet; however, it hindered the drug release at higher concentrations.

The results of the studies showed that Paracetamol DC (PDC3) developed with a 10% mixture containing Potato Starch and Silicon Dioxide in a ratio of 7:3 exhibited excellent flow behavior, good compaction properties, and better disintegration properties and released more than 50% of the drug within the first 30 min. The results of accelerated stability studies on PDC3 confirmed the stability of the developed composite.

In conclusion, co-processing of poorly compressible API (Paracetamol) with Potato starch and silicon dioxide using a co-freezing co-drying technique can develop direct compressible active pharmaceutical ingredients.

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Declaration of interest

The authors declare no conflict of interest.

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Research Article

Statistical analysis of the critical quality attributes of 1,2-dihydroxypropane as a pharmaceutical excipient

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Abstract

The constituting ingredients, either active or inactive, directly influence the quality and efficacy of the pharmaceutical medicinal product. One of the most common and versatile excipients used in various industries, including pharmaceuticals, is 1,2-propanediol, propylene glycol, or methyl ethyl glycol. The present work aims to trend the quality characteristics of Methyl ethyl glycol using exploratory process-behavior plots, which are graphical tools for monitoring and improving process performance. This study focused on the assay and water content tests of the initial 34 batches of the manufactured 1,2-Propanediol using a standard analysis method according to the British Pharmacopoeia (BP), which specifies this excipient's quality requirements and limits. Exploratory Shewhart charts, the simplest and most widely used control charts, were plotted using Statistical Process Control (SPC) software. The results showed that the data did not follow a normal distribution, and there were several out-of-control signals from both quality aspects, indicating that the process was unstable and unpredictable even if no results exceeded the specifications criteria. The study suggests that the supplier needs to improve the process control and the quality limits of Methylethylene glycol to ensure its consistency and reliability. The application of SPC techniques is essential for the modern, competitive chemical industry, as they help to reduce variability, enhance quality, and optimize resources. Trending charts provide a quantitative estimation of the current situation and the actions needed for the future improvement of the quality control tests. Future research could explore the impact of the quality variation of 1,2-Propanediol on the performance and stability of the final dosage forms, as well as the potential risks and benefits of using alternative excipients with similar properties.

Keywords: Normal distribution; out-of-control; statistical process control; trending chart; Propane-1,2-diol

Introduction

Statistical Process Control (SPC) is a quality control technique that uses statistical methods to monitor and control the inspection characteristics of products or processes. Inspection characteristics are the features that are measured and inspected to verify that they meet the specification limits [1]. SPC is widely used in the manufacturing industry, especially in the chemical and pharmaceutical sectors, where the quality and consistency of the products are vital for the safety and efficacy of the medication [2-5]. SPC provides a systematic approach to process control by analyzing data and identifying process variations that can affect the quality of the products [6]. SPC also helps improve product quality and customer satisfaction by reducing defects, rework, and costs.

SPC's main principles and tools include defining the critical process parameters, collecting and analyzing data, and using control charts and process capability analysis to monitor and control the process [7]. Control charts are graphical tools that display the process performance over time and detect any out-of-control signals that indicate process instability or unpredictability [8]. Process capability analysis is a statistical tool that evaluates the ability of the process to meet the specification limits and indicates the potential for improvement.

SPC has been applied in various fields and industries to monitor and control inspection characteristics and improve quality control [9]. Other studies showed that SPC has proven to be effective in reducing defects, improving process efficiency, and increasing customer satisfaction [8]. However, the previous studies also reveal some limitations and gaps in the current research, such as the need for more empirical studies and the need to explore the application of SPC in different industries and analyses [9]. It is crucial that future research addresses these limitations and gaps, as this will provide a more comprehensive understanding of the role of SPC in improving quality control in manufacturing.

While SPC's effectiveness in reducing defects and improving quality is well documented [8,9], previous research also highlights limitations [9]. More empirical studies are needed to explore SPC implementation in under-researched industries, such as chemical industries of medicinal compounds. Additionally, research on integrating advanced data analysis techniques with SPC could offer a more comprehensive understanding of its role in quality control.

Propylene glycol, also known as 1,2-dihydroxypropane, functions as a crucial pharmaceutical excipient. Excipients are inactive ingredients that play essential roles in delivering drugs effectively. In the case of propylene glycol, it serves as a solvent, humectant, and plasticizer in various pharmaceutical formulations [10]. These functionalities directly impact medications' stability, shelf life, and efficacy. Even minor variations in the purity of propylene glycol can significantly affect drug performance, potentially leading to reduced effectiveness or even adverse reactions.

To ensure patient safety and drug efficacy, strict regulations govern the quality control of pharmaceutical excipients. Regulatory bodies like the United States Pharmacopeia (USP) and European Pharmacopoeia (Ph. Eur.) set forth specific quality standards for propylene glycol, including limits for assay (purity) and water content. Manufacturers must adhere to these stringent requirements to guarantee the quality and safety of their products. Statistical Process Control (SPC) is a powerful tool for pharmaceutical manufacturers to produce high-quality propylene glycol consistently. By continuously monitoring the critical quality attributes (CQAs) of assay and water content through control charts, SPC enables [7,8] **Early detection of deviations:** SPC charts can identify trends or unusual variations in the assay or water content before they reach critical levels. This allows for prompt intervention and corrective actions, preventing the production of non-conforming batches. **Improved process consistency:** SPC helps pinpoint and address assignable causes of variation in the manufacturing process. By minimizing these variations, manufacturers can achieve greater consistency, ensuring that every batch of propylene glycol meets the required quality specifications. **Reduced risk of product failures:** Early detection of potential issues through SPC allows corrective actions to be taken promptly. This minimizes the risk of producing batches that fail quality-control tests and potentially need to be discarded, leading to significant time and resource losses.

This research paper presents a case study of propylene glycol, a common pharmaceutical excipient, and two of its quality control tests that use trending charts in the chemical pharmaceutical industry. The paper will analyze quality control data from previous batches and apply SPC to monitor and control inspection characteristics. The paper will then report SPC's main findings and insights, including control charts and data patterns. Finally, the paper will justify the research objective and scope in the context of the pharmaceutical-grade excipient compound model in the chemical industry.

Materials and Methods

Materials

A new pharmaceutical-grade raw material from an Asian chemical manufacturer was imported. The market retailer provided samples of propylene glycol or α-propylene glycol (propane-1,2-diol in IUPAC) from sequential batches [10]. 1,2-dihydroxypropane which is colorless and odorless liquid with molecular formula CH3CH(OH)CH2OH has a molar mass of 76.095 $g \cdot mol^{-1}$. The raw chemical compound was analyzed using standard methods of the official compendia for the assay and water content [11,12]. Quality datasets of the testing were collected and stored in an electronic storage database.

Methods

The data analysis and visualization were performed using Statistical Process Control (SPC) techniques. Following the general approach for exploratory purposes, process-behavior charts, also known as control charts, were created [3,13]. The data first underwent normality testing using the Anderson-Darling (AD) test at a 95% confidence interval (CI) and α 0.05 [14,15]. If the data exhibited a non-normal distribution, normalization techniques were applied using either the Johnson family of transformations or the Box-Cox transformation, depending on the data characteristics [15,16]. These transformations mathematically modify the data to achieve a more symmetrical and normal distribution, making it suitable for control chart analysis. In cases where the data could not be normalized using these techniques, the capability analysis was excluded [15]. Software like Minitab can be utilized for these analyses and control chart generation.

Data analysis and visualization

The data analysis and visualization were performed using Statistical Process Control (SPC) techniques. SPC is a quality control technique that uses statistical methods to monitor and control the inspection characteristics of products or processes [13]. The steps of the data analysis and visualization for the assay and water content tests were as follows [14-16]:

- The distribution of the data was identified at a 95% confidence interval (CI) and α 0.05 using the Anderson-Darling (AD) method [15,16]. The AD method is a statistical test that evaluates how well the data fit a certain distribution.
- The Johnson family or Box-Cox transformation techniques were used to normalize the raw data, which did not follow any clear trend [9]. These mathematical methods transform the data to make them more symmetric and normal-like.
- The capability analysis was excluded if the data did not fit any definite distribution even after the transformation [15]. Capability analysis is a statistical tool that evaluates the ability of the process to meet the specification limits and indicates the potential for improvement.
- The process-behavior charts were created using the general approach for exploratory purposes [3]. Process-behavior charts, also known as control charts, are graphical tools that display the process performance over time and detect any out-of-control signals that indicate process instability or unpredictability.
- The control limits and the specification limits for each test were meticulously compared and investigated. The control limits are the boundaries of the natural variation of the process, while the specification limits are the requirements or standards for the product or process quality. The comparison and investigation were thorough, aiming to identify any abnormal patterns or sources of variation that could affect the quality of the product.

Results and Discussion

Propylene glycol is a diol with a sweet taste and a colorless and odorless appearance [11]. It can mix well with many solvents, such as water, acetone, and chloroform, and has a high boiling point of 188.2 °C [12]. It is widely used in the manufacture of polymers and as a humectant, emulsifier, and preservative in various sectors, such as food, cosmetics, pharmaceuticals, and electronics [13]. It is generally considered safe for specific uses by the US FDA and the EU, but it may cause harm to some people or animals if consumed or exposed excessively [14].

Quality is crucial in the manufacturing industry, and various methods and tools are required to ensure and maintain it [15]. One of these tools is Statistical Process Control (SPC), a statistical technique that helps to analyze and control processes [16]. SPC is especially useful in manufacturing chemical compounds, as it can verify that the final product conforms to the specifications [17,18]. SPC can monitor two essential parameters of chemical compounds: water content and assay. The water content is the amount in a compound, measured as a percentage. The assay is the percentage of the active ingredient in a compound, measured quantitatively [11,12]. Control charts are indispensable for monitoring and

controlling the water content and assay of chemical compounds [19]. A Shewhart chart is a control chart that plots process data over time to detect any variation or deviation from the target [20]. In this case, the control limits of the water content and assay results were based on the standard reference.

Distribution identification for assay

The test is about finding the distribution type for the assay data (Table 1). Minitab®v17.1.0 tries different distribution types and gives some notes and warnings [21]. The first part of the test says that a Johnson transformation function is not used because the p-value is more than 0.1. This means that the data are close to normal without transformation [22]. The second part of the test says that a 2-parameter exponential distribution has a warning about the variance/covariance matrix of the estimated parameters. This means that the parameter estimates may not be good, which can make the confidence intervals wrong [21]. The third part of the test says that a 3-parameter Weibull distribution has alarms about the algorithm's convergence and log-likelihood criterion.

Table 1. Distribution fit results for assay of propylene glycol.

Distribution	Location	Shape	Scale	Threshold	AD	P	LRT P
Normal	99.83824		0.24620		3.777	<0.005	
Lognormal	4.60355		0.00247		3.780	<0.005	
2-Parameter Exponential			0.86364	98.97460	9.013	<0.010	0.000
3-Parameter Weibull		3.60577E+05	50689.13304	-5.05892E+04	4.111	<0.005	0.772
Gamma		1.68968E+05	0.00059		3.815	<0.005	
3-Parameter Gamma		24104.01042	0.00157	61.66851	50.215	*	1.000

- Pooled sample is obtained from each batch manufactured lot of the raw chemical compound after manufacturing.
- The table only includes the distributions that have a P-value less than 0.01 for the Anderson-Darling (AD) test, which measures how well the data fit the distribution.
- The table also includes the likelihood ratio test (LRT) P-value for the distributions that have an extra parameter (threshold), which measures how much the extra parameter improves the fit.
- The table is sorted by the AD P-value in ascending order, so the distributions with the lowest P-value are at the top.
- The table uses scientific notation (E) for very large or small numbers, such as 3.60577E+05, which means 3.60577 x 10^5.
- The table uses an asterisk (*) to indicate that the P-value is not available or not applicable.

These alarms mean that the algorithm cannot find the best parameter estimates, which can be because the data do not fit the distribution or the starting parameter values are wrong. Also, the variance/covariance matrix of the estimated parameters does not exist, which can make the confidence intervals wrong. The last part of the test says that a 3-parameter Gamma distribution has the same alarms as the Weibull distribution [21]. These alarms mean that the parameter estimates may not be reasonable, and the confidence intervals may not be correct. The test also gives the goodness-of-fit test results for different distributions and the maximum likelihood estimates of the distribution parameters. The descriptive statistics and Box-Cox transformation are also given for the data [22]. The test shows that the data do not match well with any distribution type.

Distribution identification for water content

Minitab®v17.1.0 results show the distribution type for the water content (Table 2). The data have zero or negative values, so some distribution types, such as Exponential, Lognormal, Weibull, Gamma, and Log logistic, cannot be used. Also, Box-Cox transformation cannot be done because of the zero or negative values [22]. The Johnson transformation function cannot be chosen because the P-value is more than 0.1, so no transformation is done [21]. Three-parameter Lognormal, three-parameter Weibull, three-parameter Gamma, and three-parameter Log logistic distributions cannot make the variance/covariance matrix of estimated parameters, so the threshold parameter is fixed when finding confidence intervals.

Minitab® v17.1.0 also gives the Maximum Likelihood (ML) estimates of distribution parameters for each distribution type. ML estimates of distribution parameters are the values of the parameters that make the distribution model fit the data best [21]. They are found using a method called maximum likelihood, which tries to maximize the probability of the data given the model. The goodness of fit test

shows that the normal and logistic distributions have the smallest AD P-values. In contrast, the three-parameter Lognormal and three-parameter Gamma distributions have the biggest AD P-values. This means that the data do not match well with any distribution type.

Table 2. Distribution fit results for water content of propylene glycol.

Distribution	Location	Shape	Scale	Threshold	AD	P
Normal	0.02206		0.02129		1.210	<0.005
Logistic	0.02038		0.01202		1.152	<0.005
Largest Extreme Value	0.01244		0.01595		1.407	<0.010
Smallest Extreme Value	0.03327		0.02395		1.808	<0.010
2-Parameter Exponential			0.02273	-0.00067	4.816	<0.010
3-Parameter Weibull		0.29207	0.00825	-0.00000	5.691	<0.005
3-Parameter Loglogistic	-7.13290		4.01357	-0.00000	5.505	*
3-Parameter Lognormal	-14.07563		15.19920	-0.00000	6.606	*
3-Parameter Gamma		0.08116	0.27181	-0.00000	10.253	*

- Pooled sample is obtained from each batch manufactured lot of the raw chemical compound after manufacturing.
- The table only includes the distributions that can be fitted to the data, as some distributions cannot be used because the data contain non-positive values.
- The table is sorted by the Anderson-Darling (AD) statistic in ascending order, so the distributions with the lowest AD statistic are at the top.
- The table uses scientific notation (E) for very large or small numbers, such as 0.29207E+05, which means 0.29207 x 105.
- The table uses an asterisk (*) to indicate that the P-value is not available or not applicable.

Trending charts examination of inspection aspects

The following analysis shows the test results for modified U charts and the conventional Individual (I) charts created using Minitab software in Figures 1 and 2. The tests check the stability of the process-behavior chart for assay and moisture content [23]. The test results show the points that cross the control limits of the chart. These points are signals that the process is out of control. The processes are unstable and have variations. The users should examine the points that failed the tests and find the causes of the problems. The users should take action to fix the problems and make the process stable and quality-oriented.

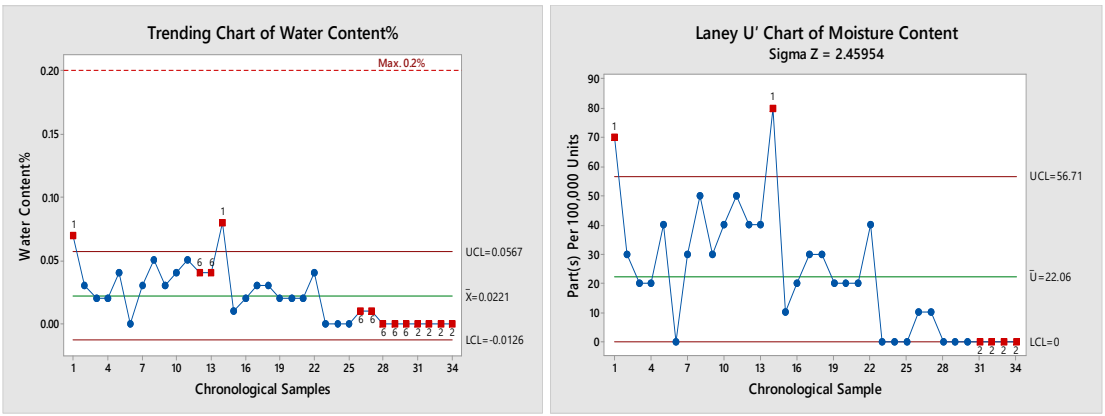

Figure 1. Process-behavior plot of the water content test for 1,2-Dihydroxypropane 34 chronological samples showing out-of-control points, the mean (X), Upper Control Limit (UCL) and Lower Control Limit (LCL).

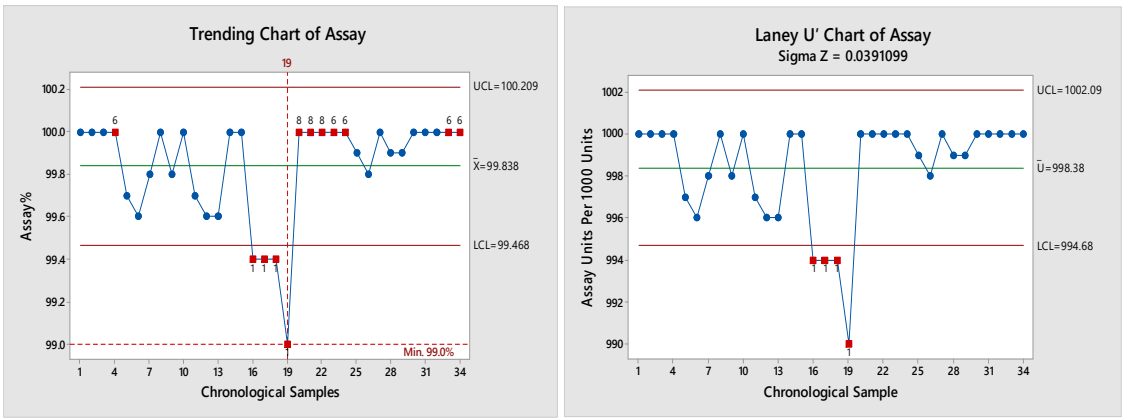

Figure 2. Process-behavior plot of the assay test for 1,2-Dihydroxypropane 34 chronological samples showing out-of-control points, the mean (X), Upper Control Limit (UCL) and Lower Control Limit (LCL).

Trending chart of inspection characteristics of the raw chemical material

Essential information about the control charts for the assay of 1,2-Dihydroxypropane:

- *I-Chart of assay:*
  - This chart shows the individual values of the assay over 34 batches.
  - The center line is the average of the assay values, which is 99.84%.
  - The upper control limit (UCL) is 100.209%, and the lower control limit (LCL) is 99.468%, calculated using the average moving range method.
  - There are four points that fall below the LCL, indicating a possible out-of-control condition in the process.
- *Laney U' Chart of assay:*
  - This chart shows the standardized units per thousand of the assay over 34 batches.
  - The center line is the average of the standardized units, which is 998.38.
  - The UCL is 1002.09, and the LCL is 994.68, calculated using the Laney method, which adjusts for under-dispersion in the data.
  - Four points also fall below the LCL, indicating a possible out-of-control condition in the process.
- *Comparison and conclusion:*
  - Both charts show similar trends and identify the same out-of-control points, batches between 16 and 19.
  - These batches have significantly lower assay values than the rest of the data, suggesting a problem in the process or measurement system.
  - The Laney U chart is more appropriate for this data, as it accounts for the non-normal distribution and the data's over- or under-dispersion.
  - The process needs to be investigated and improved to ensure the quality and consistency of the assay.
  - Key information about the control charts for the water content of 1,2-Dihydroxypropane.
- *I-Chart of water content*

  This chart shows the individual values of the water content over 34 batches. The center line is the average of the water content values, which is 0.0221%. The upper control limit (UCL) is 0.0567%, and the lower control limit (LCL) is -0.0126%, calculated using the average moving range method. Several points exceed the UCL, indicating variability in the process. While this might seem like an error, it can occur due to the nature of the control chart calculation procedure, specifically when using it for inherently positive data like percentages. In such cases, the negative LCL should be set to 0%, as a percentage cannot be negative. Several points exceed the UCL, indicating assignable cause(s) of variability in the process.
- *Laney U' chart of water content*

  This chart shows the standardized units per thousand water content over 34 batches. The center line is the average of the standardized units, which is 22.06. The UCL is 56.71, and the LCL is 00.00, calculated using the Laney method, which adjusts for over-dispersion in the data. A significant spike around batches 1 and 14 exceeds the UCL, indicating an anomaly or outlier in the data.
- *Comparison*

  Given that no distinct distribution could be identified due to the non-normal distribution of assay results, both charts might offer insights. However, the Laney approach might be preferable as it is designed for data that does not follow a normal distribution. Both charts show variability prominently. The process needs to be investigated and improved to ensure the quality and consistency of the water content.

Water content

Test 1: One point more than 3.00 standard deviations from center line. This test checks if any data point is more than 3.00 standard deviations away from the centerline. As per the given results, this test has failed at points 1 and 14. **Test 2:** 9 points in a row on the same side of the centerline. This test checks

if nine consecutive data points are above or below the centerline [19]. As per the results, this test has failed at points 31, 32, 33, and 34. **Test 6:** 4 out of 5 points more than 1 standard deviation from center line (on one side of CL). Figure 1 describes the fining.

This test checks if four out of five consecutive data points are more than 1 standard deviation away from the centerline on one side. As per the given results, this test has failed at points 12, 13, 14, 26, 27, 28, 29, 30, 31, 32, 33, and 34. **Test 8:** 8 points in a row with more than 1 standard deviation from the center line (above and below CL) [19]. This test checks if eight consecutive data points are more than 1 standard deviation away from the centerline, either above or below the centerline. As per the given results, this test failed at points 29, 30, 31, 32, 33, and 34. Laney chart showed similar output but with fewer alarm types.

Assay

The first test performed is Test 1, which checks if any point exceeds 3.00 standard deviations from the centerline. The test failed at points 16, 17, 18, and 19, indicating that the process is out-of-control. The next test is Test 5, which checks if 2 out of 3 points are more than 2 standard deviations from the centerline on one side of the centerline. The test failed at points 17, 18, and 19, indicating that the process is unstable [19]. The third test is Test 6, which checks if 4 out of 5 points are more than 1 standard deviation from the centerline on one side of the centerline. The test failed at points 4, 19, 23, 24, 33, and 34, indicating that the process is unstable.

The final test is Test 8, which checks if 8 points in a row are more than 1 standard deviation from the centerline, above and below the centerline. The test failed at points 17, 18, 19, 20, 21, 22, 23, and 24, indicating that the process is not stable at these points. In summary, the results of the I Chart for Assay indicate that the process is not stable at multiple points. The tests performed have provided valuable information about the stability of the process, which can be used to identify and eliminate the causes of variation [19]. By doing so, the process can be improved, and the quality of the product can be increased. Again, the Laney-trending chart shows a similar pattern but with fewer varieties of alarming points. Control charts that show the output can be visualized in Figure 2 demonstrating two approaches that are almost equivalent with just a few differences in the alarms.

The assay and water content tests are essential for evaluating the quality and purity of propylene glycol, according to the British Pharmacopeia. These tests help detect any differences from the expected values, which may indicate impurities or variations in the composition of propylene glycol [24]. These impurities or variations can affect the safety and efficacy of propylene glycol in various applications, such as food, cosmetics, pharmaceuticals, and electronics [25]. Therefore, it is important to follow these standards and take corrective actions if needed. By keeping the assay and water content levels within the specified range, industries can ensure that their products meet the required standards and provide high-quality substances to consumers.

Using multiple control chart tests provides a more comprehensive picture of process stability. Focus beyond Random Variation: The 3 sigma test primarily identifies random variation inherent in any process. While necessary, it does not tell the whole story. Other tests can detect specific patterns in the data that might indicate special causes of variation, like shifts in the mean, trends, or recurring cycles. Targeted Detection: Different control chart tests have specific strengths. For example, the run test is sensitive to unusual patterns like points above or below the center line sequences. Reduced False Alarms: Relying solely on the 3 sigma test can sometimes lead to false alarms. If the data distribution is irregular, points outside the control limits might not necessarily indicate a problem. Additional tests can help confirm if these points indeed indicate a particular cause.

While using multiple alarm tests seems exhaustive, there are justifications for using multiple tests. Early Detection: Using a combination of control chart tests, the investigator can detect problems earlier. This allows for quicker intervention and minimizes potential product quality or process efficiency issues. Deeper Process Understanding: A more comprehensive range of tests provides a richer picture of process behavior. This helps identify specific types of variation and allows for more targeted adjustments to improve process stability. However, it is essential to consider other challenges. Balance:

While using multiple tests is beneficial, avoiding information overload is also essential. Choosing a focused set of tests relevant to the specific process and potential issues is critical. False Alarm Management: More tests increase the probability of encountering a false alarm. Having clear guidelines for interpreting chart signals and investigating potential issues becomes crucial. Using a combination of control chart tests offers a more comprehensive and nuanced view of process stability. This allows for earlier detection of problems and a deeper understanding of process behavior, ultimately leading to better process control and improved product quality.

SPC is a useful method for monitoring and controlling the assay and water content tests, especially in the manufacturing of propylene glycol [26]. By using control charts, such as the Laney and I-Charts, manufacturers can ensure that the assay and water content values are consistent and close to the target [27,28]. This improves the product quality and increases customer satisfaction [29,30]. As the manufacturing industry continues to develop, SPC will continue to be a valuable tool for maintaining quality standards and driving continuous improvement [31]. The I-Chart of the assay and water content tests is an effective tool for tracking the quality levels of propylene glycol. By performing various tests on the chart, manufacturers can identify and correct any deviations or patterns that may affect the quality of propylene glycol. SPC helps ensure that propylene glycol meets the desired quality standards, thus ensuring safety and efficacy in its applications.

Conclusion

The assay and moisture content tests are essential for evaluating the quality and purity of propylene glycol, which is used in various applications in the pharmaceutical chemical industry. SPC is a valuable quality control technique widely used in manufacturing to monitor and control these tests. SPC uses statistical methods to analyze data and detect variations in the process. By using SPC, manufacturers can improve the quality of propylene glycol, lower costs, and satisfy the customers. The existing studies on SPC in monitoring and controlling these tests show that SPC can improve process control and product quality. However, more research is needed to overcome the challenges and gaps in the current knowledge. Some challenges and gaps are related to the data distribution, which may not follow any known distribution type, such as the standard or Gaussian distribution. This can be because of the nature of the data, the outliers or extreme values, the small sample sizes, or the complex variables. The warnings in the distribution identification analysis show the difficulties and limitations of statistical modeling and the need for careful analysis and interpretation of the results.

Authors contribution

The work was done by a single contributing author.

Declaration of interest

The authors declare no conflict of interest.

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Review Article

Silver nanoparticles: A review of the production techniques to reduce toxicological risk in ecosystems and in human health

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Abstract

Silver nanoparticles (AgNPs) are being proposed as a new pharmaceutical product because of their antimicrobial properties and eco-toxicological profile. AgNPs can be synthesized by physical or chemical methods. However, green synthesis, the so-called biosynthesis in which organic or biological materials are used, is becoming even more popular as it is economically sustainable and non-toxic. The latter plays a significant role in loading important bioactives during the synthesis. This review discusses the state of the art of using AgNPs as antimicrobial agents and their green synthesis and environmental impact. It focuses on works published since 2019 using new molecules, e.g., plant extracts, acids, bacteria and fungi, as innovative pharmaceuticals against antimicrobial resistance. A bibliometric map of works published since 2022 indexed to the Scopus core collection is also discussed, highlighting the main research areas of this innovative topic. Their physicochemical properties strongly influence the use of AgNPs and impact ecosystems and human health. Several approaches are described for their synthesis, highlighting that the toxicological risk can be mitigated by adopting green-based methodologies.

Keywords: Silver nanoparticles; green synthesis; antimicrobial resistance; plant extracts; bibliometric map

Introduction

Nobel metals (e.g., gold and silver) are known for their resistance against corrosive and oxidative processes. They have also been proposed as materials for the synthesis of metal nanoparticles using either top-down processes (e.g., milling, lithography, laser) or bottom-up processes (e.g., chemical synthesis), which usually require the use of organic solvents [1]. The use of metal nanoparticles is extensive in diverse industrial sectors, including the pharmaceutical industry, especially in developing drug delivery systems [2].

Among commonly available metals with antimicrobial properties, silver has been known since ancient times to control infections [3]. It can be obtained by different methods. Figure 1 summarizes the commonly available processes used to produce AgNPs.

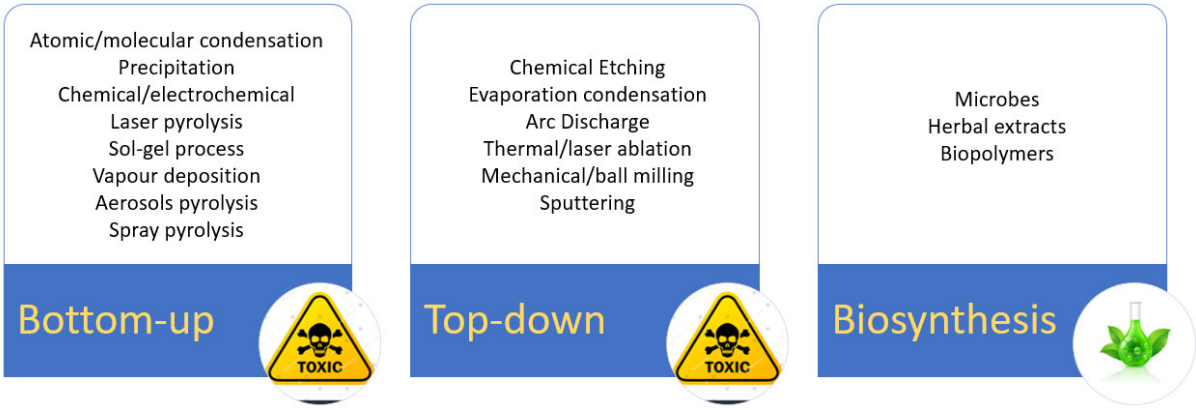

Figure 1. Commonly available methods used in the production of silver nanoparticles.

Bottom-up methods are based on molecular recognition or self-assembly, which means the combination of atoms or molecules, often needing an organic solvent, which could be environmentally friendlier. The results are influenced by temperature, pH, concentration, and covalent and ionic bonds. With the bottom-up approach, it is possible to obtain nanoparticles with better surface structure and smaller particle size compared to top-down approaches. The main techniques are colloidal precipitation, sol-gel synthesis and atomic condensation [4-6].

Top-down methods are more expensive and mainly based on grinding materials, which means that macroscopic structures are reduced to nanoparticles. This approach uses many thermal, chemical, and physical techniques to produce the energy needed to form nanoparticles. Mechanical milling can be used, including vibratory, planetary, and friction mills. Laser ablation, nanolithography, and sputtering can also downsize microparticles and turn them into nanoparticles. However, the top-down method is more used on laboratory scales [6-8].

In recent years, the use of biological methods in producing AgNPs has increased, mainly because it is an eco-friendlier method, not requiring expensive, toxic, or harmful materials, resulting in nanoparticles with good physicochemical characteristics, shapes, and sizes. Bacteria, fungi, algae, plants, and yeast are used in the green method.

To document the interest and relevance of "AgNPs" in scientific research, a quick search in the Scopus database on the 23rd of February 2024, combining "AgNPs" and "ecotoxicology" or "ecotoxicity" as keywords, resulting in a total of 25,002 documents indexed in the Scopus database since ever, out of which 3173 are published in the subject area of Pharmacology, Toxicology and Pharmaceutics. Refining our search to published works only in 2023 and 2024, a total of 288 manuscripts were retrieved. VOSviewer software was used for data analysis of these 288 papers, generating the bibliometric map shown in Figure 2 [9]. The outputs were six clusters, covering plant extracts and bioactivities, drug delivery, personalized medicine, antibacterial activity, animal experimentation and in vitro cell line studies as the major topics.

With the advance of antibiotic-resistant strains, silver has been proposed in different formulations for antibacterial treatments, thanks to its low trend of developing resistance [10]. This bactericidal activity is related to the size of the silver particles, with higher activity at smaller diameters, as the nanometric size allows them to cross the microbial membrane and cause intracellular damage.

AgNPs have been receiving attention for their diverse characteristics, which, in addition to antimicrobial properties [11-13], these particles promote wound healing [14,15]. More than half of the products available for wound healing are AgNP-based products using biomaterials (e.g., cotton, gauze, cellulose, alginate) in which these particles are incorporated [16]. Silver has been recognized for its active role in wound healing, particularly in preventing infection. When formulated as nanoparticles, AgNPs have the ability to promote the transformation of fibroblasts into myofibroblasts [17,18], and in this way, the particles promote proliferation and mobilization of keratinocytes [19,20].

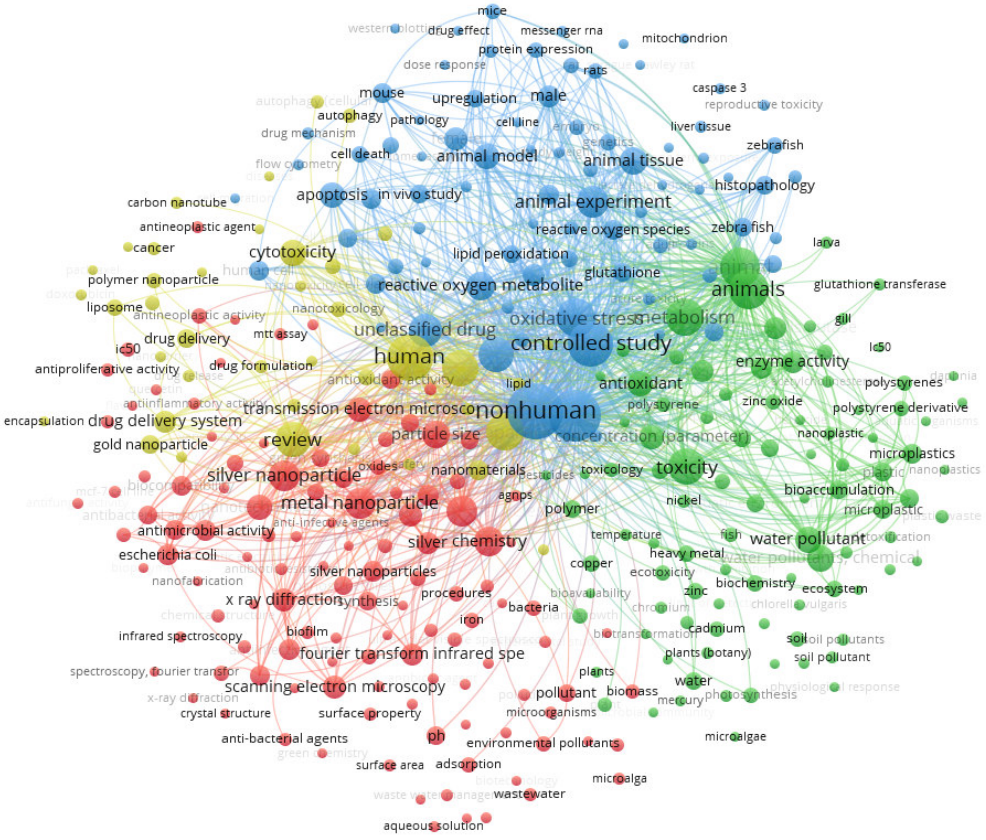

Figure 2. Bibliometric map obtained by VOSviewer software version 1.6.16 (https://www.vosviewer.com) [9], using "AgNPs" AND "ecotoxicology" OR “eco-toxicity” as keywords, recorded from Scopus database, limiting the search for publications in 2023 and 2024 in the subject area of Pharmacology, Toxicology and Pharmaceutics (search on 23rd February 2024).

The mechanism behind AgNPs' antibacterial action still needs to be fully disclosed. Various modes of action have been proposed, including the generation of reactive oxygen species (ROS), direct link to the cell membrane, and disrupting the membrane integrity, which increases cell permeability, interaction with proteins and disruption of their function, besides interfering with DNA replication causing DNA damage [21].

ROS are naturally produced by cells during normal oxygen metabolism and are typically eliminated by the cell's antioxidant defenses. However, when the production of ROS exceeds the cell's capacity to scavenge them, oxidative stress can occur due to the accumulation of excess ROS. These free radicals can attack cell membranes, react with lipids, proteins, and nucleic acids, and disrupt normal cellular processes [22].

While the mode of action of AgNPs is commonly described as governed by both Ag+ and AgNP-dependent mechanisms, van der Zende et al. (2016) [23] aimed to evaluate whether epithelial cells derived from different tissues would depict similar outcomes. The authors described distinct responses of Caco-2 and MCF-7 cell lines, with the former showing size-independent responses but a higher sensitivity and slower gene expression kinetics.

Męczyńska-Wielgosz et al. (2020) [24] evaluated the susceptibility of HepG2 cell lines to AgNPs when combined with other types of metallic nanoparticles (i.e., with AuNPs, CdTe quantum dot (QD) NPs, TiO_2NPs, or SiO_2NPs). The authors concluded that the type and ratio of nanoparticles influence the toxicity of the tested binary mixtures. The toxicity of binary mixtures was lower than the sum of toxicities determined for each tested nanoparticle type alone. It has already been documented that AgNPs produced through green synthesis may exhibit less toxicity and have a lower environmental impact [25,26].

For the green synthesis of AgNPs, bacteria, fungi, plant extracts, and even propolis have been used [11-13], as these are environmentally friendly, easy to handle, cost-effective and show greater efficiency compared to chemical synthesis [27]. To optimize this biogenic synthesis, some aspects need to be considered, namely, (i) the alkaline pH, because it promotes the ionization of hydroxyls and carboxyls of the biomaterials' molecules more efficiently, reducing Ag+ ions in AgNPs and stabilizing the particles formed [28,29]; (ii) the concentration of $AgNO_3$, because the relationship is inversely proportional, i.e. the higher the concentration of silver nitrate, the smaller the nanoparticles will be because of the formation of more generated nuclei [29,30]; (iii) the relatively high temperature, ranging from 25°C to 50°C, because increasing temperature provides the increase of silver reduction process [30-32]; and finally, (iv) the stirring speed of 200 rpm, as studies have proven that this rotation speed applied for one hour is sufficient to obtain smaller nanoparticles without the presence of aggregations [32].

Environmentally friendly synthesis of AgNPs

Plant extracts-based green synthesis

The synthesis of AgNPs through natural extracts has been commonly used thanks to their secondary metabolites, such as flavonoids, amides, phenols, amino acids and carbohydrates, capable of acting as stabilizers and reducing agents. Thus, this form of production is cost-effective due to its simplified methodology. In the literature, AgNPs in spherical shapes are frequently synthesized, with size dimensions occurring from 5-10 nm, 48-165 nm, 9-50 nm, 10-30 nm, 10-15 nm, 72-83 nm using *Selaginella bryopteris, Phyllanthus acidus, Corylus avellana, Senna alata* and *Nardostachys jatamansi, Trigonella foenum-graecum* extracts, respectively [33-37].

Some variations were observed according to the type of plant extraction, as observed us*ing Achillea millefolium* from aqueous, ethanol and methanol extracts were shown spherical, rectangular and cubical shapes, with an average diameter of 20.77, 18.53 and 14.27 nm, respectively. According to FTIR analysis, the formation of AgNPs is related to polyphenols, proteins, carboxylic acid, and alcohol. The antibacterial activity was observed against *Staphylococcus aureus*, *Bacillus subtilis*, *Salmonella enterica*, *Escherichia coli*, and *Pseudomonas aeruginosa* [38].

Spherical silver nanoparticle morphology was observed using *Mussaenda frondosa* leaf extract, with a 10 to 30 nm diameter and a crystalline nature. Increasing $AgNO_3$ concentrations also increase the inhibition of pathogens such as *E. coli* and *S. mutans* [39]. Through FTIR analysis, we can recognize the chemical composition of the extracts through the spectra so that this analysis can tell us the reducing and stabilizing agents of the AgNPs. The absorption bands belonging to polyphenolic chemical groups from *Petroselinum crispum* showed AgNPs in a spherical shape with sizes ranging from 25 to 90 nm, besides showing great activity against Gram-positive and Gram-negative bacteria [10].

Spherical AgNPs have also been synthesized using *Azadirachta indica*. Extract of this Neem tree has been associated with large amounts of bioactive compounds like alkaloids, leucoanthocyanins, coumarins, saponins, tannins, and terpenoids [40]. Acemannan participates as a reducing and stabilizing agent for AgNPs. This bioactive compound is Aloe vera's main polysaccharide and was effective against *Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa* and *Enterobacter* [41] and also, *Acinetobacter baumannii* [42] and *Candida albicans* [43].

Syzygium cumini was used to develop AgNPs of nearly spherical shape and of 47 nm in size. The secondary metabolites of *Syzygium cumini* were confirmed by FTIR spectroscopy [44]. AgNPs synthesized using *Withania coagulans* as reducing agent were spherical and with a size of 14 nm, in which flavonoids act as reducing agents and protein acts as a stabilizer during AgNP fabrication [45]. The phytochemical frankincense present in *Boswellia carterii* produced AgNPs of mean size of 14-85 nm. These compounds are capping and surface-attached components in the NPs, showing high antibacterial action against oral pathogens. This finding may promote the development of commercial products incorporating these NPs with antimicrobial activity, such as toothpaste and mouthwash [46].

In the search for new drugs using compounds of natural origin to decrease toxic side effects for the treatment of cancers, AgNPs are also being increasingly used, especially biosynthesized AgNPs [47].

With average sizes of 8-68 nm diameter, the green synthesis of nanoparticles showed activity against testicular, liver and ovarian cancer cells using extracts from *Camellia sinensis, corn silk*, and *Acacia nilotica*, respectively [48,49].

AgNPs synthesized from *Sophora pachycarpa* extract showed enhanced antibacterial, antifungal, antioxidant and antimicrobial properties, and cytotoxicity against tumor cell lines. They showed either spherical or oval-like morphology with sizes ranging from 30 to 40 nm [50].

The development of AgNPs using the methanolic extract of *Aegle marmelos* as a reducing agent generated average sizes of 15-37 nm in diameter, with spherical and hexagonal shapes. In addition to antitumor activity against cervical cancer, healing activity was evaluated [51]. The green production of AgNPs using *Piper longum* extract at a concentration of 1 mM $AgNO_3$ also acted as a strong larvicide against *Anopheles stephensi, Aedes aegypti* and *Culex quinquefasciatus* [52]. A mass remaining after extraction of the oils is called oil cake. The formation of spherical AgNPs by sesame oil cake resulted in diameters ranging from 6.6 nm to 14.8 nm. It was also observed to show antitumor activity against human breast cancer cells and antimicrobial activity against *P. aeruginosa, K. pneumoniae,* and *E. coli* [53]. The activity against breast cancer cells was also observed by AgNPs biosynthesized using *Heracleum persicum* extract [54].

In another study, the anticancer action of AgNPs biosynthesized using *Teucrium polium* was observed against human gastric cancer cell line. These studies may promote advancements in the production of effective anticancer drugs [47]. *Gloriosa superba* AgNPs showed a spherical morphology with an average size of 7 -14 nm and potent anticancer activity against a human lung cancer cell line [55].

Even using green synthesis, Ranoszek-Soliwoda et al. (2019) [56] observed that using the natural extracts of cocoa beans and grape seeds resulted in a colloidal suspension of unstable, polydisperse AgNPs. Then, it was proposed to add sodium citrate to the synthesis, resulting in stable and spherical monomodal particles [56].

Applying the best conditions to synthesize AgNPs using *Citrus limon* zest extract, 1 mM of $AgNO_3$ concentration, and a 4 h incubation period showed crystalline spherical AgNPs. In addition, these AgNPs showed excellent antipathogenic activity against *Escherichia coli, Staphylococcus aureus,* and *Candida albicans* [57]. Using the same concentration as in the previous study, AgNPs were biosynthesized using *Brassica oleracea* leaf extract. Different morphologies were found, rod-shaped and triangular, with sizes ranging from 20 nm to 40 nm [58].

For a long-term colloidal stability, the zeta potential of AgNPs should ideally be greater than +30 mV or lower than -30 mV. The zeta potential of AgNPs coated with curly kale leaf extract was determined to be -26.6 mV. This proves the particles were coated with various phytochemical compounds, leading to a highly negative zeta potential [59].

In another study, AgNPs biosynthesized with *Annona muricata* extract exhibited a crystalline nature with face-centred cubic phase particles, a mean size of approximately 87 nm, and a PDI of 0.329. The high negative charge of -27.2 mV may be related to the free amide and hydroxyl groups' [60].

Plant extracts' remarkable capability to create various silver nanostructures has led to their application in synthesizing antibacterial agents with diverse geometries, such as triangles, spheres, and cubes. AgNPs exhibit antimicrobial activity against *Escherichia coli, Staphylococcus aureus, Aspergillus flavus, Candida albicans, and Streptococcus mutans* using *Peganum harmala, Camellia sinensis, Pimpinella anisum, Rosa canina, Eucalyptus critriodora* [61-65]. AgNPs were also synthesized by *Ulva armoricana*, green algae, and showed antimicrobial activity toward both Gram-positive and Gram-negative bacteria [66].

Quercus coccifera extract was firstly analyzed for its content, and was used to synthesize AgNPs. The obtained AgNPs were spherical in shape, depicted a mean size range between 50-70 nm and were found active against several pathogens (*Escherichia coli, Staphylococcus aureus, Enterococcus faecium,*

Staphylococcus epidermidis, Salmonella enteritidis, Salmonella typhimurium, Listeria monocytogenes, Candida albicans) [67].

The polyphenols from the commercial green tea extract (Camellia sinensis) functioned as both reducing and stabilizing agents for the produced AgNPs. To improve the dispersion and biocompatibility of the obtained biogenic AgNPs, polyethylene glycol (PEG) was applied onto their surface. The results showed the formation of spherically shaped AgNPs coated with tea polyphenols yet with moderate polydispersity. Nevertheless, the produced AgNPs did not exhibit significant toxicity against human keratinocyte (HaCaT) cells. The antimicrobial efficacy of the biogenic nanoparticles was confirmed against *Staphylococcus*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Escherichia coli* and *Salmonella enterica* bacterial strains [68].

X-ray diffraction (XRD) analysis is an important aspect in the study of nanoparticles. It determines not only the size but also the shape of the unit cell. The XDR analysis of the biosynthesized AgNPs with Cissus quadrangularis extract confirmed the crystalline nature of the particles, which also showed spherical shape and anticancer properties [69].

The *Passiflora subpeltata* is a valuable source of secondary metabolites with diverse applications, particularly in addressing cancer and mosquito-related issues. Through XRD analysis, the crystalline nature of the plant material was revealed, while SEM images distinctly showcased the spherical shape of the nanoparticles. Notably, the plant extract demonstrated significant anti-proliferative activity on human colon cancer cell lines and exhibited larvicidal effects against *Culex quinquefasciatus* [70].

Spherical AgNPs using *Epipremnum aureum* leaf extract might open up new studies of unusual DNA binders, which can destabilize DNA and may further be used for various biomedical applications [71]. *Moringa Oleifera* AgNPs analysis gave a spherical morphology with particle sizes ranging between 4 and 12 nm. The XRD gave a face-centred cubic phase with the crystalline structure of Ag-NPs [72].

An extract of *Eugenia jambolana* was used to encapsulate AgNPs within the matrix of the biodegradable polymer PLGA and showed antibacterial activity against *Escherichia coli* and *Pseudomonas aeruginosa* [73].

The AgNPs from *Humulus lupulus* had an average hydrodynamic size of around 92.42 and a low polydispersity index. With TEM analysis, the nanoparticles were spherical, with an average size of 17.40 nm. They were lethal to both *E. coli* and *S. aureus* and exhibited an anti-cancer effect [59].

The Medicago sativa AgNPs' analyses confirmed the formation of a face-centred cubic crystalline structure, spherical morphology, an average particle size of 15-35 nm, and highly stable antimicrobial activities against *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Escherichia coli*, *Staphylococcus epidermidis*, *Enterococcus faecalis*, *Staphylococcus aureus*, and *Candida albicans* [74].

AgNPs were synthesized using the extract of *Caulerpa scalpelliformis* to analyze the wound healing potential. The results showed spherical AgNPs and uniform distribution with diameters ranging from 16 nm to approximately 48 nm. Furthermore, the possibility of applications for antitumor activities and chronic and diabetic skin wound healing was confirmed [75].

The synthesized *Gnaphalium polycaulon* AgNPs suppressed the growth of most dreadful pathogens associated with wound infections, such as *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans*, by *in vivo* studies [76].

Cotton fabrics coated with AgNPs from *Curcuma longa* extract were tested for their antimicrobial activity and wound healing potential. The analysis showed that the AgNPs, besides having high wound healing potential from the fibroblast test, they also showed a high activity against S. *aureus, P. aeruginosa, S. pyogenes,* and *C. albicans* [77]. The incorporation of biosynthesized silver nanoparticles into dressings is of great medical importance thanks to their antimicrobial and wound healing effects.

Acids-mediated green synthesis

Tannic acid and sodium alginate as reducing and stabilizing agents respectively, and the obtained particles were found to have remarkable antibacterial and antibiofilm properties. Studies showed that

optimal production resulted in spherical, stable, and monodispersed AgNPs with an average size of 18.52 nm. After exposure to the AgNPs, *S. aureus* showed irreversible cell membrane damage, changes in cellular morphology and increased cell death. In addition, the AgNPs significantly inhibited *S. aureus* biofilm formation [78]. Lignin is the most abundant, renewable and degradable biopolymer available in nature, and was used to synthesize AgNPs with face-centred cubic crystalline structure, and with a mean size between 15-20 nm. AgNPs were surface-coated with phenolic, hydroxyl and carboxylic groups of lignin. Li-AgNPs showed significant antimicrobial efficacy against several pathogens, *S. aureus* and *E. coli* and also anti-cancer effects against ovarian cancer cells [49].

These findings suggest that lignin-mediated AgNPs can find applications in different fields, including biomedical, drug delivery, biosensor, food packaging, and textile industries [79].

Algae-mediated green synthesis

In the last few years, studies on Cyanobacteria (Blue-green algae) mediated green synthesis have increased considerably, mainly due to their survival properties in acidic and basic environments, extreme temperatures, high metal content, and high salinity, besides showing antimicrobial and anticancer activity [80,81].

Oscillatoria sp. was used to form spherical AgNPs. Phosphate and amine were reported for the capping and stabilization of proteins in the AgNPs. The thermal analysis results confirmed the showed stability of the particles. The particle diameter of 558.1 nm with a polydispersity index of 0.580 had effective antibacterial activity against the tested bacterial pathogens [82].

A biomass parameter (80 µg/ml, pH 5.5, 60 °C, 60 min on UV light exposure and 1 mM $AgNO_3$ concentration) from Microchaete cell-free aqueous extract has been used to optimize the biosynthesis of spherical, polydispersed AgNPs of mean size between 60-80 nm [83].

Under the optimal *Microcystis aeruginosa* extraction conditions (57 °C, pH 4.9, and 30 min), spherical AgNPs were obtained with an average size of 6.80 nm. FTIR analysis showed that the functional groups from *Microcystis aeruginosa* extract participated in the synthesis of AgNPs. In addition, these biosynthesized AgNPs showed excellent antibacterial activity against gram-positive *Staphylococcus aureus* and gram-negative *Escherichia coli* [84].

Cyanobacteria-based AgNPs were developed using *Lyngbya majuscula* under the following conditions: pH 4, 1 mM, 72 h. As a result, the AgNP presented a mean particle size between 5 and 25 nm and a spherical but also irregular shape. The green production was shown to be an effective and low-cost technique that can be widely used [85].

Fungi-mediated green synthesis

Fungi secrete attractive agents for the biogenic synthesis of AgNPs because they offer high tolerance to metals and are easy to handle. They also secrete a massive amount of proteins that contribute to reducing and capping agents of the nanoparticles [86]. Many studies have shown that fungi-based AgNPs may be used as antibacterial, antifungal, anticancer, and antioxidant agents [87-90].

In synthesis using *Letendraea* sp., the authors revealed a diameter of 33.8 nm and face-centred cubic of crystalline nature. Furthermore, the synthesized AgNPs exhibited good antioxidant and antibacterial activities against Gram-positive and Gram-negative bacteria [91].

Using *Ganoderma applanatum, a* basidiomycete species, also displayed excellent antimicrobial properties against *Staphylococcus aureus*, *Escherichia coli*, and *in vivo* antifungal activity against *Botrytis cinerea* and *Colletotrichum gloeosporioides*. The spherical shape was observed with an average size of 20-25 nm [92].

The AgNPs from *Ganoderma lucidum*, a mushroom with many medicinal properties, such as antibacterial and antifungal, were developed to demonstrate their antimicrobial activity. The nanoparticles showed a spherical shape and a particle size of 25-150 nm, with the median size of 55 nm. These AgNPs showed high antibacterial activity against *Staphylococcus aureus*, *Escherichia coli*, and

Pseudomonas aeruginosa [93]. Table 1 summarizes some relevant applications of AgNPs obtained by different green synthesis approaches.

Table 1. Summary of relevant studies reporting the production of AgNPs by green synthesis.

Type of green synthesis	Material	Particle size	Applications	References
Plant extracts	*Achillea millefolium* from aqueous, ethanol and methanol extracts	20.77, 18.53 and 14.27 nm	Antibacterial activity (*Staphylococcus aureus, Bacillus subtilis, Salmonella enterica, Escherichia coli,* and *Pseudomonas aeruginosa*)	[38]
Plant extracts	*Mussaenda frondosa* leaf extract	10-30 nm	Antibacterial activity (*E. coli and S. mutans*)	[39]
Plant extracts	*Boswellia carterii*	14–85 nm	Antibacterial activity against oral pathogens	[46]
Plant extracts	Extracts *Camellia sinensis* and corn silk.	8-68 nm	Anticancer potential	[47,48]
Plant extracts	*Sophora pachycarpa* extract	30-40 nm	Antibacterial, antifungal, antioxidant, antimicrobial, and cytotoxicity against tumor cell lines	[50]
Plant extracts	*Humulus lupulus* extract	17.40 nm	Antibacterial (*E. coli* and *S. aureus*) and anticancer effect	[59]
Algae	*Oscillatoria sp*	558.1 nm	Antibacterial activity	[82]
Algae	*Microcystis aeruginosa.*	6.8 nm	Antibacterial activity (*E. coli* and *S. aureus*)	[84]
Fungi	*Letendraea sp*	33.8 nm	Antioxidant and Antibacterial activity	[91]
Fungi	*Ganoderma applanatum*	20-25 nm	Antibacterial properties against *S. aureus, E. coli,* and *in vivo* antifungal activity against *Botrytis cinerea* and *Colletotrichum gloeosporioides.*	[92]
Fungi	*Ganoderma lucidum*	25-150 nm	Antibacterial activity (*S. aureaus*, *P. aeruginosa* and *E. coli*)	[93]

Toxicological aspects and safety assessment of AgNPs

Since AgNPs exhibit potent antibacterial, antiviral, antifungal, and antimicrobial activities, they have been widely used for various biomedical and pharmaceutical applications. Nonetheless, there is ongoing discussion on their toxicity, demanding more research.

AgNP toxicity is dependent on size, shape, and surface modification; an investigation using alveolar macrophages revealed that AgNPs with an average size of 15 nm caused the highest reduction in mitochondrial activity [26,94]. The size of nanoparticles influences the binding and activation of membrane receptors and the subsequent production of proteins in cancer cells [95].

Sun et al. (2021) [96] ran a battery of cytotoxicity and genotoxicity tests, together with the analysis of the inflammatory responses in two human cell lines (HepG2 and A549), in order to clarify the distinct hazardous effects of polyvinylpyrrolidone-capped AgNPs with varying primary particle sizes (i.e., 5, 50, and 75 nm). AgNPs-induced cytotoxicity was shown to be primarily mediated by inflammation and disturbance of mitochondrial function, as evidenced by concentration-dependent decreases in cell proliferation and mitochondrial membrane potential and increases in cytokine excretion (i.e., interleukin-6 and interleukin-8). In HepG2 cells, a gradual rise in genotoxicity was observed as the diameter of AgNPs decreased. This was linked to the accumulation of S and G2/M and the transcriptional activation of the GADD45α promoter, as indicated by luciferase activity. In A549 cells, there was additional evidence of dose-related genetic damage as demonstrated by the development of micronuclei and the Olive tail moment; however, these effects and the cytotoxicity caused by AgNPs were mainly linked to the ionic Ag release from nanoparticles.

The mechanisms of action of AgNPs involved in their toxicological risk seem to be related to the production of reactive oxygen species (ROS) upon the uptake of particles by the cells, causing mitochondrial dysfunction [97]. ROS are known to promote cell death by mechanisms of apoptosis or necrosis [94]. Chang et al. (2021) [98] reported the cytotoxicity of AgNPs in a mouse hippocampal neuronal cell line (HT22 cells). The MTT and LDH experiment showed that AgNPs decreased cell

viability and caused membrane leakage in a dose-dependent manner. AgNPs induced oxidative stress and excessive generation of ROS in HT22 cells at dosages of 25, 50, and 100 μg/ml for 24 h.

Gurunathan et al. (2018) [99] prepared AgNPs using an anti-oxidant polyphenol (myricetin) and evaluated their effects on NIH3T3 mouse embryonic. AgNPs caused dose-dependent cell viability and proliferation loss, as demonstrated by increased lactate dehydrogenase (LDH) leakage from cells. One possible source of harm was ROS. Additionally, AgNPs decreased glutathione and superoxide dismutase, raised oxidative stress and malondialdehyde levels, decreased mitochondrial membrane potential and adenosine triphosphate (ATP), and damaged DNA in NIH3T3 cells by upregulating the expressions of the p53 and p21 genes and the level of 8-hydroxy-2′-deoxyguanosine. Asharani et al. (2023) [95] described the ability of AgNPs to adsorb cytosolic proteins onto their surface, which may have an impact on the activity of intracellular factors that control genes related to DNA damage response and repair in cancer cell lines, as well as cell cycle progression. On the other hand, the mechanisms that lead AgNPs to build up ROS and hyperpolarise the membrane potential in the mitochondria are also responsible for their effects on changing cell function or phenotype in a dose-dependent way. AgNPs can be used against single-cell biophysical features of colon cancer cells HCT-116, potentially advancing AgNP-based cancer therapy [97].

Studies in experimental animals document that AgNPs are absorbed in the gastrointestinal system [100], diffuse to numerous organs and tissues, and accumulate in several organs (primarily the colon, small intestine, kidney, and heart) [101].

Environmental impact of AgNPs

The behaviour of AgNPs in the environment is influenced by various factors, including their size and surface properties and the surrounding environmental conditions (Figure 3). AgNPs can exist as individual particles in suspension and be transported over long distances in aquatic environments governed by water flow rate, sedimentation, and interactions with other particles and surfaces. AgNPs may tend to aggregate in high ionic strength environments [102]. When the concentration of ions in the solution is high, such as in the presence of salts, the electrostatic repulsion between particles decreases, leading to aggregation. Aggregation can affect the behaviour and fate of AgNPs in the environment [103].

Upon contact with oxygen and other oxidants, AgNPs can undergo partial oxidation, resulting in the dissolution of Ag+ ions [104]. This process can occur at the nanoparticle surface, releasing silver ions into the surrounding environment. The extent of oxidation and dissolution depends on the reactivity of AgNPs and the availability of oxidants [105]. AgNPs can react with various natural substances present in the environment, such as sulphide and chloride ions [106]. These reactions can modify the original properties of AgNPs and lead to the formation of different silver-based compounds, which may influence their toxicity, stability, and bioavailability.

Capping agents, which are amphiphilic compounds used to prevent agglomeration during AgNP production, also affect their surface chemistry and, thus, their biological activity and influence nanoparticles' interaction with the environment. On the other hand, electrolyte composition, solution ionic strength, pH, and the presence of natural organic matter can all affect the stability, aggregation, and transformations of AgNPs in the environment. The pH of the suspension is another critical factor influencing the stability and aggregation of AgNPs. Nanoparticles exhibit different aggregation states across a wide pH range, with aggregate sizes increasing near the pH of the point of zero charge. The pH affects the surface potential of particles and dominates the risk of aggregation, which in turn affects the particle size [107]. Understanding these processes is crucial for assessing the potential environmental impact of AgNPs and developing appropriate strategies for green synthesis approaches to reduce toxicological concerns in ecosystems and human health.

AgNPs can escape into the air during various stages of manufacturing processes, such as drying, grinding, mixing, and packaging. Their use in disinfection and anti-odor sprays also contributes to their emission into the atmosphere.

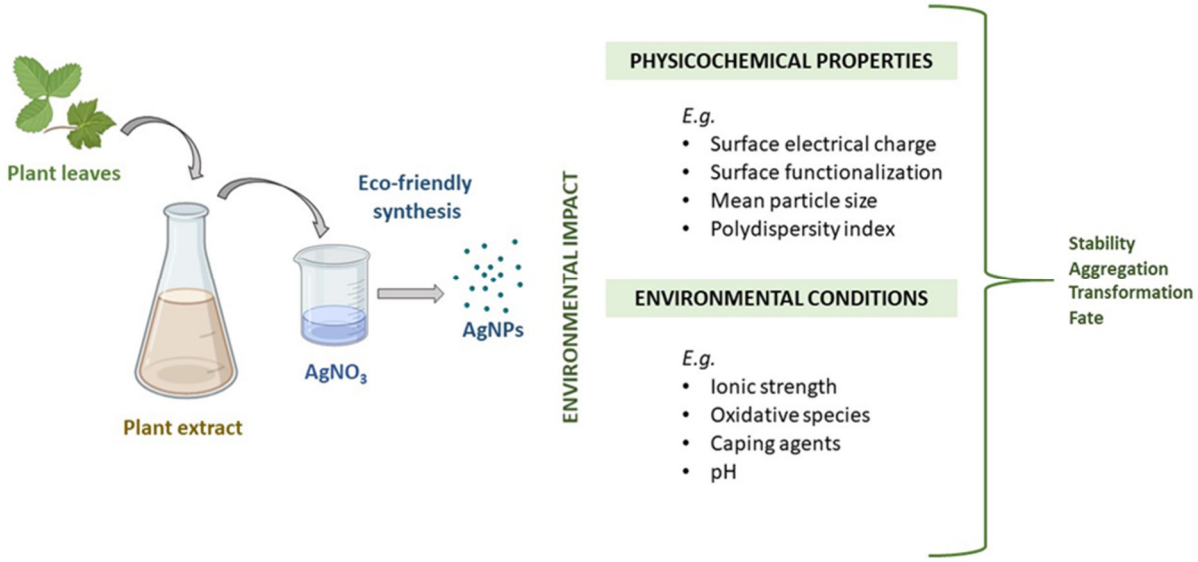

Figure 3. Schematic representation of the green synthesis process and the factors influencing the behaviour of AgNPs and their impact on the environment.

The small size of AgNPs allows for rapid diffusion in the air, potentially enabling long-distance mobility. Their large surface area makes them reactive and more toxic than larger particles. AgNPs can be deposited on surfaces and transferred through cleaning and laundering or transported through the air [108].

AgNPs can enter soils through direct disposal of AgNP products, such as their use as fertilizer in agriculture [109]. The fate and transport of AgNPs in soils depend on factors like particle size, surface charge, and soil characteristics. AgNPs may adsorb organic contaminants and serve as carriers for their transport. The interaction between AgNPs and different soil types, influenced by their surface charge, affects their mobility. AgNPs can strongly adsorb onto soils, reducing their availability in the environment.

Conclusion

In summary, the antibacterial activity of AgNPs involves complex processes, and multiple modes of action have been proposed. These include the generation of ROS, direct interaction with cell membranes, changes in membrane permeability, disruption of protein function, and interference with DNA replication. The specific mode of action may vary depending on the type of cell or organism being studied. On the other hand, the impact of AgNPs on ecosystems and human health is governed by the physicochemical properties of the obtained nanoparticles. The toxicological risk can be mitigated by adopting green synthesis approaches.

In this review, evidence is given that the synthesis of green AgNPs is expanding continuously. Nevertheless, careful considerations in the selection of green material for nanomaterial production, and more importantly, a comprehensive screening protocol for these green particles, are mandatory to predict the performance of nanoparticles on living cells and in the environment. Once the nanomaterial is produced, a thorough analysis of its structure and physicochemical properties must be conducted to determine the morphology, average size, surface chemistry, and other important parameters. This step in the development process is equally significant as the synthesis itself, as the results obtained can either suggest and recommend the use of the developed nanomaterials for further biological testing or demand additional refinements if nanoparticles with undesirable properties are produced. To enhance the biological characterisations of nanoparticle manufacturing processes, it is necessary to expand the scope by incorporating various cell types and strains and undertake *in vivo* studies.

Abbreviations

AgNO3: Silver nitrate; **AgNPs**: Silver nanoparticles; **AuNPs**: Gold nanoparticles; **CdTe**: Cadmium telluride; **DNA**: Deoxyribonucleic acid; **FTIR**: Fourier Transform Infrared; **PDI**: Polydispersity index; **PEG**: Polyethylene glycol; **ROS**: Reactive oxygen species; **TiO2NPs**: Titanium dioxide nanoparticles; **SiO2NPs**: Silicon dioxide nanoparticles.

Contributions

Conceptualization, writing—original draft preparation, ETSL, VLSS, PS and EBS; methodology, validation, formal analysis, visualization, CASV, SJ, JCC, RLCAJ, KK and AML; investigation, resources, data curation, writing—review and editing, supervision and project administration KK, PS and EBS; All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

The authors confirm that ethics approval and participation consent are not applicable to this work and that no ethics issues are raised in this manuscript.

Availability of data and material

The datasets generated during and analysed during the current study are available from the corresponding author upon reasonable request**.**

Declaration of interest

The authors declare no conflict of interest.

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Review Article

Ophthalmology: Navigating ocular barriers with advanced nanocarriers

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Abstract

The unique anatomy and physiology of the eye present significant challenges for effective drug delivery, necessitating innovative approaches to manage ocular diseases. This review examines the intricate structure of the eye and the barriers that impede drug penetration, including the corneal epithelium, conjunctival tissue, and blood-retinal barriers. Traditional ocular administration routes-topical, periocular, and intraocular-often face limitations in drug bioavailability and patient compliance. Recent advancements in nanotechnology offer promising solutions to these challenges. Nanocarriers such as nanoparticles, liposomes, nanosuspension, nanoemulsion, micelles, and dendrimers enhance drug delivery by improving bioavailability, controlling release rates, and minimizing systemic side effects. Factors influencing the efficacy of these nanocarriers include their size, surface charge, and hydrophilic-lipophilic balance. This review highlights the potential of these novel drug delivery systems in treating chronic ocular conditions such as glaucoma, age-related macular degeneration (AMD), and diabetic retinopathy. These advanced technologies are poised to significantly enhance the therapeutic management of ocular diseases by overcoming the inherent ocular barriers and optimizing drug delivery.

Keywords: Ophthalmology; ocular barriers/ ocular drug delivery; glaucoma; age-related macular degeneration; diabetic retinopathy; ocular diseases; nanocarriers

Introduction

Modern ocular illnesses have a devastating impact on patients' ability to see and ways of living in the modern day. According to the data in Figure 1, an estimated 1.1 billion individuals worldwide were visually impaired in 2020. There were 510 million people who lost near eyesight, 258 million who lost mild vision, 295 who lost moderate to severe vision, and 43 million who were blind. These figures add up to a significant amount. We may expect the total to have risen to over 1.8 billion by 2050, with 866 million people with near vision loss, 360 million with mild vision loss, 474 with moderate to severe vision loss, and 61 million cases of blindness [1].

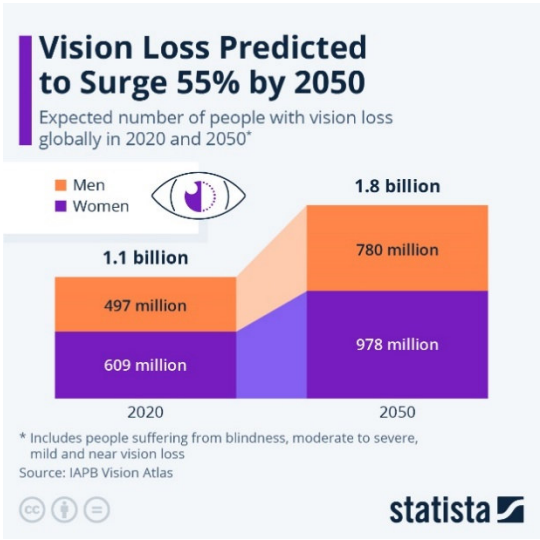

Figure 1. Chart shows the expected number of people with vision loss globally in 2020 and 2050. Reprinted under the terms of the Creative Commons Attribution 3.0 International (CC BY) license [1].

Drug delivery to the eye can be broadly classified into two main parts: anterior and posterior segments (Figure 2) [2]. The front part of the eye, about a third of the total, contains the ciliary body, cornea, iris, conjunctiva, aqueous humour, and crystalline lens [3]. In contrast, the back half of the eye

comprises the choroid, neural retina, sclera, optic nerve, vitreous humour, and retinal pigment epithelium (RPE) [4-6]. Both parts of the eye are vulnerable to various disorders that can cause permanent vision loss. The following conditions can affect the eye: uveitis, cataracts, choroiditis, retinitis, retinopathies, optic neuritis, retinal dystrophies, ectasia of the cornea, keratopathy, keratoconjunctivitis, scleritis, glaucoma, choroiditis, or retinopathy [7-11].

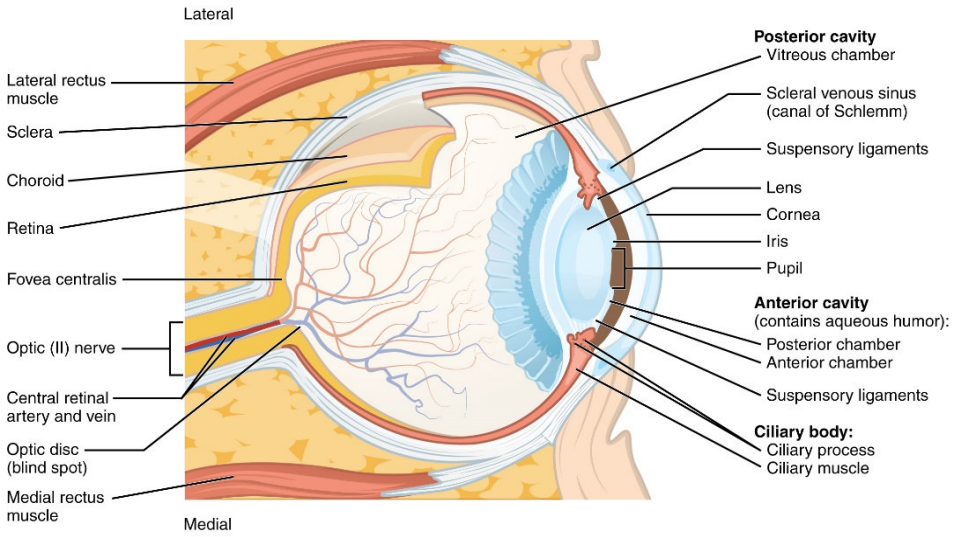

Figure 2. Structure of the eye. Reprinted under the terms of the Creative Commons Attribution 3.0 International (CC BY) license [2].

Even though the eyes are one of the body's most accessible organs, it is pretty challenging to administer medication to their tissues. Like the brain, the eye is considered "immune privileged" since it is part of the central nervous system protected from blood flow. An organ that is highly isolated from systemic circulation is the eye due to its complex ocular barriers and precise design. Thus, many obstacles can be overcome when treating eye illnesses, particularly those affecting the posterior region [12]. A non-invasive method widely used for administering drugs to the anterior portion of the eye is known as local instillation [13,14]. This method is popular since it is simple to use and patient-friendly. Following the administration of the drug, it quickly comes into contact with the mucus found on the eye's surface [15]. Lacrimal drainage, which travels through the upper and lower canaliculus and eventually reaches the lacrimal sac, which opens into the nasolacrimal duct, is responsible for quickly removing the dosage [16].

Additionally, the ocular bioavailability of topical eye drops could be improved. Several anatomical and physiological restrictions present hurdles and make it challenging to penetrate deeper ocular tissues. These limits include tear turnover, lacrimal drainage, blink reflex, and dynamic and static ocular barriers [17].

Barriers affecting ocular drug delivery

Tear film barrier

The initial permeability barrier that inhibits the transport of ocular drugs is tear film, a thin lipid layer covering the outside of the eye, a middle layer of aqueous fluid, and an innermost layer of mucous [12,18]. From an anatomical standpoint, the outer oil layer both keeps water from evaporating and decreases drug absorption into the sclera and cornea [19]. Reduced bioavailability can occur when specific endogenous proteins in the middle aqueous layer bind and metabolize the administered medicine. These proteins include lactoferrin, globulin, and albumin [20]. The mucus layer, located inside, is an intricate combination of many substances, such as water, lipids, salts, enzymes, and mucins [21]. The mucus layer is the most dense at the epithelial apex because of its pore structure, which contains negatively charged glycans and hydrophobic regions. It becomes more diluted as it extends outward into the tear fluid. It plays a significant role as a barrier in drug delivery because it can trap

and adhere to foreign particulates. Then, it is washed away by mucus turnover before it reaches the corneal surface [22,23]. After topical treatment, the average tear volume increases to 30 μL from 7 μL. This leads to the rapid drainage of excess fluid through the nasolacrimal duct and the loss of more than 85% of the drug dose before it reaches the corneal surface. The fast turnover of tears further dilutes the retained drugs, reducing the concentration gradient and diffusion rate. As a result, intraocular medicines often have limited bioavailability in aqueous humor, typically between 0.1% and 5% [24,25].

Regarding drug distribution, the most recommended and patient-friendly strategy is the topical administration of eye drops, instilled explicitly into the lower precorneal pocket. The blink reflex, however, renders this approach mostly ineffective since it causes the majority of the topical doses to be lost. Surprisingly, only approximately 20% of the amounts that are injected stay in the pocket long enough to have the desired impact [26]. For passive diffusion to occur across the corneal layers, the concentration of the medication in this lower precorneal area is a crucial factor. Nevertheless, the complicated task of achieving therapeutic medication concentrations for the posterior eye tissues persists. Topical drug use may be more effective in the conjunctiva and sclera due to their more excellent permeability than in the cornea; nevertheless, these posterior tissues have very poor drug absorption due to the fast circulation, making this treatment even more difficult [27]. Both static and dynamic barriers, such as the sclera, choroid, and RPE, and the passage of lymphatic and blood through the episcleral and conjunctiva, respectively, hamper the delivery of drugs to the eye [28,29]. Topical delivery requires a permeable cornea and prolonged corneal contact time, although other routes of administration, like intravitreal and periocular injections or systemic administration, have also been investigated. Because of the eye's tiny volume and the presence of the retinal blood barrier, which limits systemic administration, intravitreal injection is especially notable for its success in treating deep-seated ocular illnesses [30-32]. The transscleral route refers to the method of delivering therapeutic agents to the eye by passing them through the sclera, the tough, fibrous outer layer of the eye. This route is considered for delivering drugs directly to the posterior segment of the eye, such as the retina and choroid, which are otherwise challenging to reach via traditional topical or systemic routes [33].

Vitreal barrier

The anatomical and physiological features of the vitreous humor that restrict the penetration and diffusion of substances from the anterior segment (such as the aqueous humor) into the posterior segment (such as the retina and choroid) are collectively referred to as the vitreal barrier, which is also called the vitreoretinal barrier. This barrier is essential to stabilize the eye's internal environment and shield the retina from damaging substances. The vitreal barrier poses significant challenges to drug delivery to the posterior segment of the eye. The dense, gel-like nature of the vitreous humor impedes the free movement of substances. Large molecules and particles have difficulty diffusing through this matrix. The network of collagen fibers can trap and hinder the movement of therapeutic agents. Similar to the blood-brain barrier, the Blood-Retinal Barrier (BRB) is a physiological barrier that restricts the entry of substances from the bloodstream into the retinal tissue. It consists of tight junctions between retinal capillary endothelial cells and the RPE. Enzymes within the vitreous can degrade certain drugs before they reach their target. Larger molecules and those with specific charge properties may diffuse more slowly through the vitreous. Lipophilic (fat-soluble) substances often have better diffusion rates compared to hydrophilic (water-soluble) ones [34-36]. Specifically, negatively charged particles diffuse freely, while positively charged particles get trapped in the vitreous body [37]. As a result, the drug's vitreous dispersion and retinal bioavailability are significantly affected by its molecular weight and charge.

Blood-ocular barrier (BOB)

The eye is a highly specialized organ requiring precise regulation of its internal environment to maintain optimal function and protect delicate structures from potentially harmful substances. The BOB is a critical component in this regulatory system, comprising two main barriers: the blood-aqueous barrier (BAB) and the BRB. These barriers work in concert to control the exchange of substances between

the bloodstream and the ocular tissues, ensuring a stable environment for visual processes. The BAB primarily regulates the passage of substances into the anterior segment of the eye, particularly the aqueous humor. It consists of several anatomical components: Non-pigmented Ciliary Epithelium, Iris Vasculature, and Endothelial Cells of the Schlemm's Canal. However, The BRB is essential for protecting the neural retina and maintaining a controlled environment for photoreceptor function. It has two main components: the Inner Blood-Retinal Barrier and the Outer Blood-Retinal Barrier. Tight junctions between endothelial cells of retinal capillaries form the inner Blood-Retinal Barrier. These junctions restrict the passage of large molecules and ions from the bloodstream into the retinal tissue, ensuring the retina remains free from blood-borne toxins and pathogens. The outer blood-retinal barrier comprises the RPE, which forms tight junctions with adjacent RPE cells. The RPE regulates nutrient and waste exchange between the retina and the choroid, maintaining the subretinal space's homeostasis [5,18,38-43].

Furthermore, Ocular drug delivery presents unique challenges due to the eye's complex anatomy and protective barriers, which limit the bioavailability of therapeutic agents. Various advanced drug delivery systems have been developed to overcome these obstacles and enhance drug bioavailability, as shown in Figure 3 [44]. Nanotechnology has enabled rapid advancements in the ocular delivery of drugs, leading to novel therapeutic approaches for ocular disorders [45,46]. In comparison to conventional drug delivery methods, nanocarriers have many benefits, such as the ability to cross the ocular barrier, increase transcorneal permeability, decrease drug degradation, decrease dosage frequency, boost patient compliance, accomplish controlled release, target specific drugs, and deliver genes [47,48]. These systems aim to provide targeted, controlled, and sustained release of drugs to improve therapeutic outcomes while minimizing side effects.

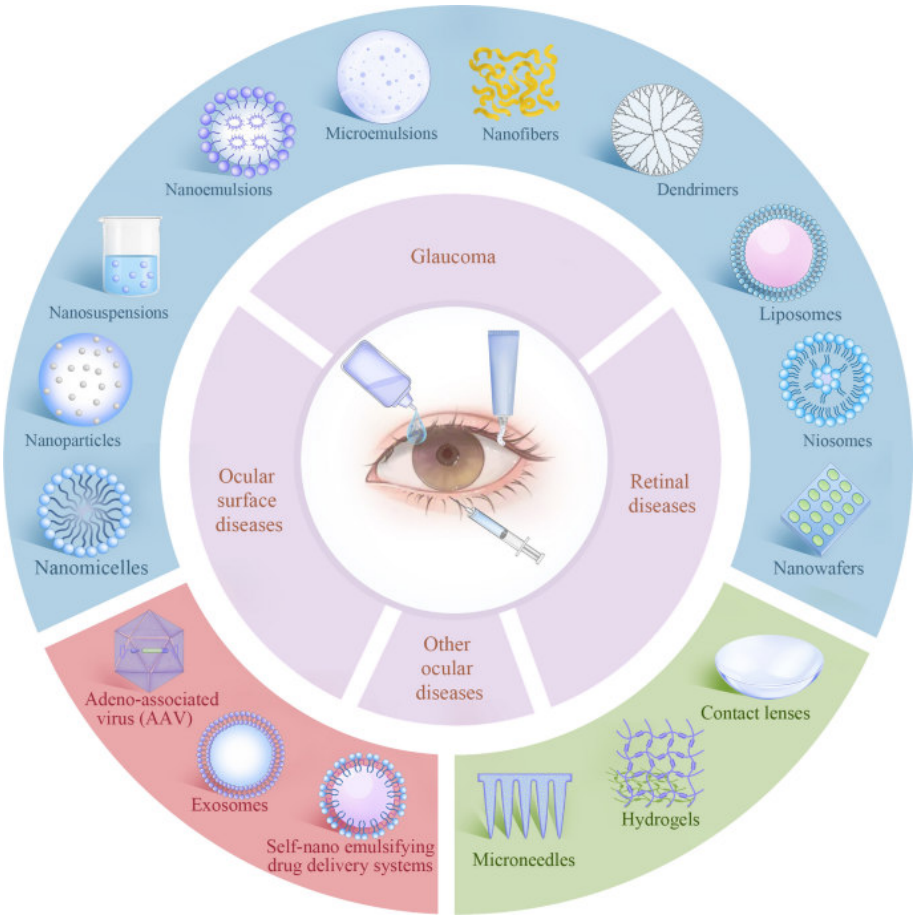

Figure 3. Advanced Ocular drug delivery systems. Reprinted under the terms of the Creative Commons Attribution 4.0 International (CC BY) license [44].

Ocular diseases

Ocular diseases encompass many conditions that affect the eyes, potentially leading to vision impairment or blindness if not properly managed. These diseases can affect different eye parts, including the cornea, lens, retina, optic nerve, and surrounding tissues. Understanding these conditions, their causes, symptoms, and treatment options is crucial for preserving eye health and preventing vision loss.

Glaucoma

Glaucoma is a group of eye conditions that cause damage to the optic nerve, which is vital for good vision. This damage is often caused by abnormally high pressure in the eye (intraocular pressure or IOP). Glaucoma is one of the leading causes of blindness for people over the age of 60, but it can occur at any age [49]. The presence of high IOP is an indication of glaucoma [50]. Corneal endothelial cells can be damaged due to increased intraocular pressure [51]. A further consequence of elevated IOP is the compression of the retinal blood vessels, which can harm the optic nerve and retinal ganglion cells [52].

The treatment of glaucoma focuses on lowering IOP to prevent damage to the optic nerve and preserve vision. Various treatment modalities are employed, tailored to the type and severity of glaucoma. The primary approach involves pharmacological therapy with eye drops, which aim to either decrease the production of aqueous humor or enhance its outflow. Common medications include prostaglandin analogs, beta-blockers, alpha agonists, and carbonic anhydrase inhibitors [49,53]. When medications fail to adequately control IOP or cause significant side effects, laser therapy or surgical interventions may be considered. Laser trabeculoplasty is a widely used procedure for open-angle glaucoma, improving the outflow of aqueous humor through the trabecular meshwork. For more severe cases or when laser therapy is ineffective, surgical options such as trabeculectomy or drainage implants are performed to create new pathways for fluid drainage, thereby lowering IOP [54,55]. Additionally, minimally invasive glaucoma surgeries (MIGS) have emerged as less invasive alternatives with fewer complications and quicker recovery times. Treatment choice depends on individual patient factors, disease progression, and response to initial therapies, underscoring the importance of personalized care in managing glaucoma effectively [56].

Age-related macular degeneration (AMD)

AMD is a leading cause of vision loss in older adults, characterized by the progressive deterioration of the macula, the central part of the retina responsible for sharp, detailed vision. AMD is classified into two main types: dry (atrophic) and wet (neovascular or exudative). Dry AMD, the more common form, involves the thinning of the macula and the accumulation of drusen, yellow deposits beneath the retina. Wet AMD, though less common, is more severe and occurs when abnormal blood vessels grow under the retina and leak fluid or blood, leading to rapid vision loss [57]. The pathogenesis of AMD is complex and involves a combination of genetic, environmental, and lifestyle factors. Key risk factors include advanced age, smoking, family history of AMD, and specific genetic variants, such as those in the complement factor H (CFH) gene [58]. Oxidative stress and chronic inflammation also play critical roles in disease [59]. Current treatments for dry AMD are limited, focusing primarily on nutritional supplements (AREDS2 formula) that may slow progression in intermediate stages.

In contrast, wet AMD is treated with anti-vascular endothelial growth factor (anti-VEGF) injections, which help reduce the growth of abnormal blood vessels and fluid leakage. Recent advances include the development of long-acting anti-VEGF agents and gene therapies aimed at providing sustained treatment effects with fewer injections [60]. Intravitreal injection (IVT) with anti-VEGF (including bevacizumab (Bev) and aflibercept, amongst others) is a successful treatment for neovascular age-related macular degeneration (AMD). However, it is still considered invasive [61]. Consequently, developing drug delivery technologies to achieve tailored drug delivery is of utmost significance.

Diabetic retinopathy

Diabetic retinopathy (DR) is a common complication of diabetes mellitus and a leading cause of vision impairment and blindness among working-age adults. It is characterized by damage to the retinal blood vessels due to chronic hyperglycemia. The disease progresses through two main stages: non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). In NPDR, early changes include microaneurysms, retinal hemorrhages, lipid exudates, capillary occlusion, and leakage. As the condition advances to PDR, there is an abnormal growth of new blood vessels (neovascularization) on the retina and vitreous humor, which can lead to severe complications such as vitreous hemorrhage and tractional retinal detachment [62]. Chronic hyperglycemia in diabetes leads to metabolic changes contributing to retinal vascular dysfunction, including oxidative stress, inflammation, and activating the protein kinase C pathway. These changes compromise the blood-retinal barrier, leading to vascular leakage and edema. Diabetic macular edema (DME) can occur at any stage and is a significant cause of vision loss in DR, characterized by fluid accumulation in the macula, the central part of the retina responsible for sharp vision [63].

Management of diabetic retinopathy involves tight glycemic control to slow disease progression and regular retinal screening to detect early changes. Treatment strategies for advanced stages include intravitreal injections of anti-VEGF agents, which inhibit abnormal blood vessel growth and reduce macular edema. Additionally, corticosteroids may be used to reduce inflammation and macular edema. Laser photocoagulation remains a cornerstone treatment for PDR, preventing further neovascularization and sealing leaking blood vessels. In severe cases, vitrectomy surgery removes vitreous hemorrhage or scar tissue that can cause retinal detachment [64]. Because drugs have a low bioavailability, the possibility of unwanted effects, and the inherent dangers associated with major surgery, it is necessary to develop new drug delivery systems to bring about new ideas for the treatment of DR.

Dry eye disease

Dry eye disease (DED) is a multifactorial condition characterized by a loss of homeostasis of the tear film, leading to ocular discomfort, visual disturbances, and potential damage to the ocular surface. It is associated with increased osmolarity of the tear film and inflammation of the ocular surface. DED can be broadly classified into two main types: aqueous-deficient dry eye, where the lacrimal glands fail to produce sufficient tear volume and evaporative dry eye, often due to meibomian gland dysfunction (MGD) leading to increased tear evaporation [65]. The pathophysiology of DED involves complex interactions between the tear film, ocular surface, and neural pathways. Inflammation plays a central role, with pro-inflammatory cytokines and matrix metalloproteinases contributing to ocular surface damage and a cycle of inflammation exacerbating the disease.

Additionally, environmental factors, systemic medications, and systemic diseases such as Sjögren's syndrome and rheumatoid arthritis can contribute to the development and severity of DED [66]. Management of DED focuses on a personalized approach tailored to the underlying cause and severity of the condition. Treatment strategies include artificial tears and lubricants to provide symptomatic relief and improve tear film stability. Anti-inflammatory therapies, such as cyclosporine A, lifitegrast, and corticosteroids, reduce ocular surface inflammation. For evaporative dry eye, warm compresses, lid hygiene, and medications like doxycycline or azithromycin are recommended to manage MGD. Advanced treatments include autologous serum eye drops and scleral contact lenses for severe cases. Lifestyle modifications, such as optimizing screen time, increasing ambient humidity, and ensuring adequate hydration, also play an essential role in managing DED [67]. Artificial tears, local secretagogues, corticosteroids, and immunosuppressants are standard drug therapies; nevertheless, they have adverse effects like glaucoma, raised intraocular pressure, ocular pain, and poor patient

compliance [68]. Employing novel drug delivery strategies is of the utmost importance to increase drug bioavailability and circumvent ocular barriers.

Traditional routes of ocular drug administration

Traditional routes of ocular drug administration aim to deliver therapeutic agents effectively to treat various ocular conditions. The most common methods include topical, periocular, intraocular, and systemic administration.

Topical administration

Topical administration of drugs to the eye is the most common method for treating various ocular conditions affecting the anterior segment, such as infections, inflammations, and glaucoma. This route is favored due to its ease of use, non-invasiveness, and patient compliance. The primary formulations used include eye drops and ointments, which offer localized treatment with minimal systemic side effects compared to systemic administration methods. Despite its advantages, topical administration faces significant challenges due to the eye's complex anatomical and physiological barriers. The cornea, tear film, and nasolacrimal drainage system are significant obstacles that limit drug absorption and retention on the ocular surface, often resulting in less than 5% of the administered dose reaching the target tissue [17,69,70]. When an eye drop is instilled, a substantial portion of the drug is rapidly drained through the nasolacrimal duct, leading to reduced drug availability at the target site. Additionally, the corneal epithelium's low permeability further restricts drug penetration into deeper ocular tissues [70,71].

Advancements in drug delivery systems have been explored to improve the efficacy of topical ocular therapies. Nanotechnology-based formulations, including nano micelles, nanoparticles, and liposomes, have shown promise in enhancing drug bioavailability. These nanocarrier systems increase the retention time of the drug on the ocular surface and enable controlled and sustained drug release, potentially overcoming the eye's natural barriers [70]. Despite these advances, achieving consistent and effective drug delivery remains challenging, necessitating ongoing research and development to optimize these innovative systems for clinical use [70,72].

Periocular administration

Periocular administration involves injections or depot systems around the eye, including subconjunctival, sub-Tenon, and peribulbar injections. This route provides higher drug concentrations to the posterior segment, making it suitable for treating posterior segment diseases like uveitis and macular edema. Despite its advantages, periocular administration can be invasive and cause discomfort or complications such as hemorrhage or infection [73]. This method includes several injection techniques: subconjunctival, sub-Tenon's, peribulbar, retrobulbar, and posterior juxta scleral routes. These approaches aim to circumvent the ocular barriers that impede drug delivery to the posterior eye, such as the corneal epithelium, conjunctival tissue, and blood-retinal barrier. Subconjunctival injection involves administering drugs beneath the conjunctiva, which allows for a slow release of medication over time and can be particularly effective for treating anterior segment diseases. However, its effectiveness in reaching the posterior segment is limited due to the multiple barriers the drug must traverse. Sub-Tenon's injection places the drug into the Tenon's capsule, a thin membrane surrounding the eyeball, offering a more direct route to the posterior segment but still facing significant diffusion barriers [74]. Peribulbar and retrobulbar injections target the space around and behind the eyeball. These techniques are often used for anesthesia in ophthalmic surgeries but have also been explored for drug delivery. Peribulbar injections deposit the drug in the adipose tissue surrounding the eyeball, allowing for slower systemic absorption and sustained local drug release. Retrobulbar injections place the drug closer to the optic nerve, potentially increasing the drug concentration in the posterior segment but posing risks such as optic nerve injury and hemorrhage [75]. Posterior juxta scleral injection delivers the drug near the sclera at the back of the eye, aiming for closer proximity to the retina and choroid.

This method can enhance drug penetration to the posterior segment but is technically challenging and can cause patient discomfort [74,76].

Despite these techniques, achieving therapeutic drug levels in the posterior segment remains challenging due to the eye's protective barriers. The drug's molecular size, lipophilicity, and formulation can significantly impact its ability to reach the posterior segment effectively. Research into advanced drug delivery systems aims to improve periocular administration's bioavailability and therapeutic efficacy. These systems can enhance drug retention, control release rates, and facilitate penetration through ocular barriers. For instance, nanoparticle-based delivery systems can encapsulate drugs, protecting them from degradation and enhancing their penetration through the ocular tissues [70].

Intraocular administration

Among the several intraocular delivery routes, the most common ones are intracameral, intravitreal, subretinal, intrastromal, suprachoroidal, and intrastromal. The intracameral injection approach is typically utilized after cataract surgery to treat anterior segment diseases such as bacterial and fungal keratitis. This technique includes the direct injection of the drugs into the anterior chamber. However, because the drug cannot penetrate the aqueous humor flow in the eye, this approach is not successful in delivering drugs to the posterior portion of the eye [77]. Because of this, intravitreal injection is utilized to achieve medication concentrations in the posterior region of the eye. Direct intravitreal injection and intravitreal implanted devices are the two components of this procedure, which has emerged as the most popular approach to treating vitreoretinal disorders in the past few decades [78]. Intravitreal injections of anti-VEGF agents [79], steroids [80], and genes [81] increase the drug concentration in the vitreous and retina. However, repeated injections can lead to complications like retinal toxicity, optic nerve damage, endophthalmitis, secondary glaucoma, cataracts, vitreous hemorrhage, excessive intraocular pressure, and bleeding [82,83]. Recent advancements in drug delivery systems aim to enhance the safety and efficacy of intraocular administration. For instance, liposomes and poly lactic-co-glycolic acid (PLGA) nanoparticles have been extensively studied for their potential to enhance drug retention and penetration within ocular tissues, offering promising avenues for long-term treatment of chronic eye diseases [84].

Systemic administration

Systemic administration of drugs, which reach the eye through the bloodstream, is vital for treating various ocular conditions, especially when localized administration is insufficient. Systemic delivery involves introducing a drug into the circulatory system via oral ingestion, intravenous injection, or other parenteral routes. Once in the bloodstream, the drug can traverse the blood-ocular barriers, including the blood-aqueous and blood-retinal barriers, to reach ocular tissues. The blood-ocular barriers, however, pose significant challenges for drug delivery. These barriers protect the eye from toxins and pathogens and limit therapeutic agent penetration. For example, the blood-aqueous barrier consists of tight junctions between endothelial cells of the iris and ciliary body capillaries, preventing many substances in the blood from entering the aqueous humor.

Similarly, the blood-retinal barrier restricts drug access to the retina and vitreous body, necessitating higher systemic drug concentrations to achieve therapeutic levels within the eye [85,86]. Systemically administered drugs can be crucial in managing conditions like uveitis, diabetic retinopathy, and age-related macular degeneration. For example, corticosteroids, commonly used for their anti-inflammatory properties, can be administered orally or intravenously to treat severe intraocular inflammation. Oral acetazolamide is used to lower intraocular pressure in glaucoma by decreasing aqueous humor production [85]. The systemic route is also beneficial when rapid and uniform drug distribution is required, as in the case of acute ocular infections. Intravenous antibiotics can quickly achieve therapeutic concentrations in ocular tissues, providing a more effective treatment than topical applications alone [87]. However, systemic drug administration is not without risks. High doses required to overcome the blood-ocular barriers can lead to systemic side effects, including gastrointestinal disturbances, cardiovascular issues, and potential toxicity.

Moreover, drugs eliminated via systemic circulation can cause unwanted effects in non-target tissues, emphasizing the need for careful dosing and monitoring [85,86]. While traditional routes of ocular drug administration have been essential in managing various eye conditions, each route has its own set of challenges and limitations. Ongoing research and development aim to enhance drug efficiency and patient outcomes through improved formulations and novel delivery systems.

Ocular drug kinetics

Ocular drug kinetics involves the study of the absorption, distribution, metabolism, and excretion (ADME) of drugs administered to the eye, as illustrated in Figure 4. Drug penetration tactics can be categorized into several routes: topical delivery through trans-corneal and non-corneal penetration (Routes 1 and 2), systemic administration via the blood-aqueous barrier (Route 3) and the blood-retinal barrier (Route 4), and direct injection through vitreous administration (Route 7). The main drug elimination strategies entail the movement of the drug through the trabecular meshwork and Schelemm's canal (Route 5), the drug entering the systemic circulation through the blood-aqueous barrier (Route 6), the drug crossing the blood-retinal barrier (Route 8), and the drug passing from the front to the back of the eye through the anterior route to the posterior chamber (Route 9) [12]. The eye's unique anatomical and physiological characteristics significantly influence these processes, presenting challenges and opportunities for effective therapeutic interventions.

Absorption

The primary routes for ocular drug delivery include topical, periocular, and intraocular methods. Topical administration is the most common due to its ease of use and non-invasiveness. However, it faces significant barriers, such as the corneal epithelium, which limits drug penetration. The cornea, comprising five layers, including the lipophilic epithelium and hydrophilic stroma, acts as a barrier to many drugs, restricting their bioavailability [88]. The tear film and nasolacrimal drainage further complicate absorption by rapidly diluting and removing the drug from the ocular surface [89].

Distribution

Once absorbed, the distribution of drugs within the eye is influenced by various factors, including molecular size, lipophilicity, and the presence of ocular barriers such as the BAB and the BRB. These barriers protect the eye from systemic toxins but also impede drug delivery. For example, the BAB limits the penetration of drugs from the systemic circulation into the aqueous humor, while the BRB restricts access to the retina and vitreous humor [90].

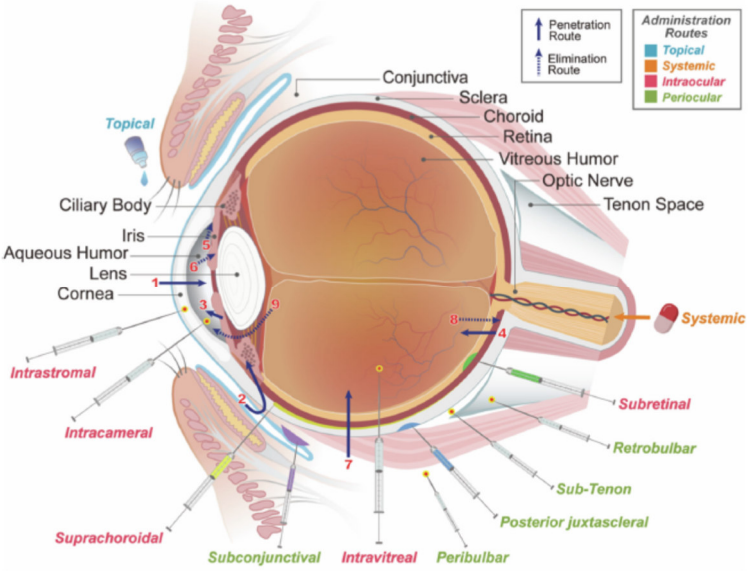

Figure 4. Approach of ocular administrations with different delivery routes. Reprinted under the terms of the Creative Commons Attribution 4.0 International (CC BY) license [12].

Factors influencing ocular drug kinetics

Several aspects, including drug formulation, delivery vehicle, and administration technique, influence the efficacy of ocular drug delivery systems. For instance, nanoparticles and liposomes can enhance drug penetration and retention in ocular tissues, providing sustained release and improved bioavailability [91]. Hydrogels and in situ gelling systems offer prolonged contact time on the ocular surface, enhancing drug absorption and therapeutic effects [92]. Understanding ocular drug kinetics is crucial for developing effective treatments for ocular diseases. Optimizing drug delivery systems to overcome ocular barriers and enhance drug absorption, distribution, and retention can improve therapeutic outcomes [93].

Nanocarrier-based ocular drug delivery systems

Nanotechnology-based ocular drug delivery systems are at the forefront of addressing the unique challenges of ocular drug delivery. Traditional methods often need better bioavailability and rapid clearance, but nanotechnology offers innovative solutions.

Enhanced penetration and retention

Nanoparticles, liposomes, dendrimers, and micelles are designed to improve drug penetration and retention in ocular tissues. Due to their small size and surface characteristics, nanoparticles can traverse the corneal barrier more effectively. For instance, chitosan-coated nanoparticles have shown enhanced mucoadhesive properties, prolonging the corneal surface's residence time and improving drug absorption [94]. PLGA nanoparticles have been extensively studied for their ability to provide sustained drug release, reducing the frequency of administration and improving patient compliance [95].

Targeted delivery

Nanocarriers can be engineered for targeted delivery, minimizing systemic side effects and enhancing therapeutic efficacy. Functionalizing nanocarriers with ligands, such as antibodies, peptides, or small molecules, enables specific targeting of ocular tissues or cells. Nanoparticles functionalized with transferrin have targeted the retina, providing localized treatment for retinal diseases [96]. This targeted approach allows for higher drug concentrations at the site of action, improving efficacy while reducing systemic exposure.

Overcoming ocular barriers

Nanotechnology helps overcome the physiological barriers of the eye, such as the BRB. With their highly branched structure, Dendrimers provide multiple sites for drug attachment and can penetrate the BRB effectively. This capability is particularly beneficial for treating posterior segment diseases like AMD and DR [97]. Moreover, micelles can solubilize poorly water-soluble drugs, enhancing their delivery across the ocular barriers [98].

Biocompatibility and Safety

The biocompatibility and safety of nanocarriers are paramount for their use in ocular applications. Materials like PLGA, chitosan, and polyethylene glycol (PEG) are commonly used due to their biocompatibility and biodegradability. These materials degrade into non-toxic byproducts, making them safe for ocular use. Additionally, surface modification of nanocarriers with PEG can reduce immunogenicity and prolong circulation time, further enhancing their efficacy [99].

Factors influences nanocarriers for ocular

Several factors influence the efficacy of nanocarriers in managing ocular diseases, including size, surface properties, drug loading capacity, release mechanisms, and biocompatibility.

Size of nanocarriers

The size of nanocarriers significantly impacts their distribution, penetration, and retention in ocular tissues. Nanocarriers typically range from 10 nm to 1 μm [100]. To ensure that medication is delivered

effectively, drug carriers must be sufficiently minuscule to pass through the ocular barriers and be well tolerated by the human eye when administered [101]. Nanoparticles that are smaller in size have the potential to provide improved stability and biodistribution, respectively. Smaller nanoparticles can penetrate deeper ocular tissues, including the retina, while larger particles may be more suitable for prolonged release in the anterior segment. Optimal size selection helps overcome barriers such as the corneal epithelium and BRB. Studies suggest that nanoparticles around 200 nm enhance permeation and retention in ocular tissues [100].

Surface properties

Surface charge and hydrophilicity/hydrophobicity balance are crucial in determining the interaction of nanocarriers with ocular tissues. Positively charged particles have higher mucoadhesion due to electrostatic interactions with the negatively charged mucin layer on the ocular surface, facilitating prolonged residence time [102]. Additionally, surface modification with hydrophilic polymers like PEG can enhance stability and reduce opsonization, prolonging systemic circulation time and improving ocular bioavailability [103].

Drug loading capacity and encapsulation efficiency

The drug loading capacity of nanocarriers determines the therapeutic dose that can be delivered. High encapsulation efficiency ensures that sufficient drug reaches the target site. For example, PLGA nanoparticles are well-known for their high encapsulation efficiency and controlled release properties [95].

Release mechanisms

Controlled and sustained drug release from nanocarriers is vital for maintaining therapeutic levels over extended periods, reducing dosing frequency, and improving patient compliance. Nanocarriers can be designed to release drugs through diffusion and degradation or are responsive to environmental stimuli such as pH and temperature. For instance, thermosensitive in situ gels that solidify at body temperature sustain drug release to the ocular surface [99].

Biocompatibility and Toxicity

The materials used in nanocarriers must be biocompatible and non-toxic to ocular tissues. Biodegradable polymers like PLGA, polycaprolactone (PCL), and chitosan are frequently used for their safety profiles and ability to degrade into non-toxic byproducts [104]. Additionally, the potential immunogenicity of nanocarriers must be considered, as ocular tissues are sensitive to inflammatory responses.

Specific targeting

Nanocarriers can be engineered to target specific ocular tissues or cells by modifying their surface with ligands such as antibodies, peptides, or small molecules. Targeted delivery enhances drug concentration at the disease site, minimizing systemic exposure and side effects. For example, nanoparticles functionalized with antibodies targeting vascular endothelial growth factor (VEGF) can provide targeted therapy for AMD [105].

Stability and Storage

The stability of nanocarriers during storage and upon administration is critical for maintaining their efficacy. Factors such as aggregation, degradation, and drug leakage can compromise their performance. Techniques like lyophilization and incorporation of stabilizing agents are employed to enhance the shelf-life of nanocarrier formulations [70,90,106,107].

Nanocarrier platforms

Nanoparticles

Nanoparticles are tiny particles that range in size from 1 to 1000 nm. Due to their small size and large surface area-to-volume ratio, nanoparticles possess unique physical and chemical properties that make them highly effective in various applications, including drug delivery, imaging, and diagnostics. In ocular drug delivery, nanoparticles offer several advantages over traditional drug delivery systems. They can enhance the solubility and stability of drugs, facilitate sustained and controlled release, and improve drug penetration across ocular barriers such as the cornea and BRB [88,90]. These nanoparticles can encapsulate hydrophilic and hydrophobic drugs, protecting them from degradation and enhancing their therapeutic efficacy. The targeting capability allows nanoparticles to deliver drugs directly to specific ocular tissues or cells, thereby increasing therapeutic efficacy and minimizing systemic side effects [96].

Yu et al. synthesized dexamethasone-glycol chitosan (Dex-GCS) conjugates with 277-289 nm particle sizes and a positive charge of approximately +15 mV. Dex-GCS nanoparticles caused slight cytotoxicity against L929, HCEC, and RAW 264.7 cells after 24 h incubation. They displayed a nearly identical anti-inflammatory efficacy to dexamethasone sodium phosphate (Dexp) in lipopolysaccharide (LPS)--activated RAW 264.7 macrophages. Overall, the results suggest that the Dex-GCS nanoparticles showed good ocular tolerance and provided a relatively longer precorneal duration compared with that of the aqueous solution formulation, which suggested that the self-assembled Dex-GCS nanoparticle might be a promising candidate for ophthalmic drug delivery [108]. Zein and PLGA nanoparticles embedded in bio-adhesive thermosensitive gel for the delivery of lutein via topical application were developed by Bodoki et al. Cataracts were induced in rats via selenite injection at 13 days post-partum, followed by 7 days of treatment with free lutein or lutein-loaded nanoparticles administered orally or topically. The authors concluded that Cataract severity was significantly reduced in rats treated with topical applications of lutein-loaded nanoparticles compared to the positive control [109]. Xing et al. formulated Triamcinolone acetonide (TA) in PLGA-chitosan (PLC) nanoparticles to treat ocular inflammatory diseases. When tested against human corneal epithelial (HCE) cells, TA-loaded polylactide nanoparticles (PLC NPs) showed remarkable anti-inflammatory properties. Furthermore, these nanoparticles dramatically decreased the release of interleukin (IL)-6 in cells stimulated by tumor necrosis factor (TNF)—α. Pharmacokinetic analysis of rabbit eyes revealed that TA-loaded PLC nanoparticles peaked at 6 h. Substantial concentrations of TA were observed until 24 h, indicating the superiority of this PLC-based nanocarrier system [110].

Liposomes

It was not until 1965 that liposomes were used for the first time as drug delivery vehicles. Liposomes have emerged as a significant advancement in ocular drug delivery due to their unique structural and functional characteristics, which enable efficient encapsulation and delivery of therapeutic agents to the eye. Liposomes are spherical vesicles composed of lipid bilayers that can encapsulate hydrophilic and hydrophobic drugs, thus protecting them from degradation and enhancing their bioavailability. This is particularly advantageous in ocular drug delivery, where the eye's complex anatomy and physiology pose significant challenges to conventional drug delivery systems. The ocular surface is protected by multiple barriers, including the tear film, corneal epithelium, and blood-ocular barriers, which limit drug penetration and absorption. Traditional methods like eye drops and ointments often suffer from low bioavailability and rapid drug clearance. Liposomes, however, can enhance drug retention time on the ocular surface and facilitate controlled and sustained release of the therapeutic agents, thus improving the efficacy of the treatment [111]. One of the critical advantages of liposomes in ocular drug delivery is their ability to improve drug penetration through the corneal and conjunctival epithelia. The lipid bilayer of liposomes can merge with the lipid layers of the ocular surface, facilitating drug release directly into the ocular tissues [112].

Additionally, liposome size and surface charge can be modified to optimize their interaction with ocular tissues and enhance drug absorption. Studies have demonstrated that positively charged liposomes show better adhesion to the negatively charged ocular surface, enhancing drug delivery efficiency [113]. Liposomes have also shown promise in delivering a wide range of drugs, including

anti-inflammatory agents, antibiotics, and anti-glaucoma medications. For instance, liposomal formulations of corticosteroids have been developed to treat inflammatory conditions of the eye, providing prolonged anti-inflammatory effects with reduced dosing frequency [114]. Similarly, liposomal antibiotics have been utilized to treat bacterial infections, achieving higher local drug concentrations and minimizing systemic side effects [115].

Moreover, liposomes can be engineered to deliver targeted drugs, further enhancing their therapeutic potential. Surface modification with ligands, such as antibodies or peptides, allows liposomes to specifically target diseased ocular tissues or cells, thereby increasing drug efficacy and reducing off-target effects [116]. This targeted approach is particularly beneficial in treating retinal diseases, where precise delivery of drugs to the retina is crucial. Despite the promising attributes of liposomes, some challenges need to be addressed for their widespread clinical application. The stability of liposomal formulations during storage, potential immunogenicity, and large-scale manufacturing are significant concerns. However, ongoing research and technological advancements are focused on overcoming these hurdles, making liposomes a viable option for ocular drug delivery shortly [117]. Zang et al. investigated the effects of the molecular weight (MW) and concentration of trimethyl chitosan (TMC) on the characteristics of Coenzyme Q10-loaded liposomes coated with trimethyl chitosan and the efficacy of the antioxidant Coenzyme Q10 in delaying selenite-induced cataract was assessed. Compared to the control group, the presence of TMC with a larger Mw increased in the precorneal residence period, which was nearly 4.8 times more than anticipated. Coenzyme Q10 demonstrated a significant anti-cataract effect, as evidenced by the fact that the percentage of lens opacity was approximately 53% after the study. It was concluded that the physical properties and precorneal retention time of liposomes could be modified with TMC, and ophthalmic instillation of Coenzyme Q10 can retard selenite-induced cataract formation [118]. Moiseev et al. developed Maleimide-Decorated PEGylated mucoadhesive liposomes for ocular drug delivery conventional, PEGylated, and maleimide-decorated PEGylated liposomes. The fluorescent flow-through approach was utilized to investigate the retention of these liposomes in the cornea and conjunctiva beyond the confines of the animals. Liposomes that were adorned with maleimide demonstrated superior retention performance on bovine conjunctiva when compared to other types of liposomes that were utilized in the research. On the bovine cornea, it was noted that all liposomal formulations retained themselves poorly [119].

Nanoemulsions

Nanoemulsions have gained considerable attention in the field of ocular drug delivery due to their unique properties that address the limitations of conventional ocular formulations. Nanoemulsions are submicron-sized emulsions with droplet sizes typically ranging from 20 to 200 nm. These systems consist of an oil phase, water phase, surfactant, and co-surfactant, creating a stable dispersion of oil droplets in water (O/W) or water droplets in oil (W/O). The small droplet size and high surface area of nanoemulsions enable enhanced drug solubilization, stability, and bioavailability, which are crucial for effective ocular drug delivery [120]. One of the significant advantages of nanoemulsions in ocular drug delivery is their ability to improve drug penetration and retention in ocular tissues. The tiny droplet size facilitates the interaction of the nanoemulsion with the corneal and conjunctival epithelium, promoting better drug absorption. Additionally, the surfactants in nanoemulsions can act as penetration enhancers, temporarily disrupting the tight junctions of the epithelial cells and thereby increasing drug permeability [121]. This property is particularly beneficial for delivering hydrophobic drugs with poor solubility in aqueous ocular environments. Nanoemulsions also offer the advantage of prolonged drug release, which can reduce the frequency of administration. The oil phase of the nanoemulsion acts as a reservoir for the drug, allowing a controlled and sustained release over time. This is particularly important in treating chronic ocular conditions, such as glaucoma and dry eye syndrome, where consistent therapeutic levels are required [122].

Furthermore, nanoemulsions can be easily sterilized and are generally well-tolerated, making them suitable for ocular applications. They are also versatile regarding the types of drugs that can be incorporated, ranging from anti-inflammatory agents and antibiotics to antifungal and antiviral drugs.

For example, a nanoemulsion formulation of cyclosporine A has been developed to treat dry eye disease, showing improved bioavailability and therapeutic efficacy compared to traditional formulations [123]. In addition to improving drug delivery to the anterior segment of the eye, nanoemulsions hold the potential for delivering drugs to the posterior segment, such as the retina. Due to their small size and ability to enhance drug permeability, nanoemulsions can potentially penetrate deeper into ocular tissues and reach the posterior segment, which is a significant challenge with conventional delivery systems [124]. The stability of nanoemulsions during storage is a critical issue, as phase separation and drug degradation can occur. Formulation strategies, such as using appropriate surfactants and co-surfactants, are essential to ensure the long-term stability of nanoemulsions.

Additionally, the potential toxicity of surfactants and other formulation components must be thoroughly evaluated to ensure safety for ocular use [125]. Nanoemulsions containing besifloxacin for ocular drug delivery were formulated by Kassaee and Mahboobian. In the ex vivo transcorneal permeation studies, the Nanoemulsions loaded with besifloxacin exhibited a sustained release pattern and 1.7-fold greater penetration than the solution that served as the control. According to the results of the HET-CAM test, there was no irritation, and the HL% test showed no damage to the tissue; hence, the eye tolerates the optimal Nanoemulsion well. In conclusion, besifloxacin-loaded Nanoemulsions have the potential to be considered an appropriate alternative to the suspension currently on the market for the treatment of bacterial eye infections [126]. Tang et al. fabricated stearoyl L-carnitine-modified nanoemulsions (SC-NEs). An improved corneal penetration, ocular surface retention ability, and ocular bioavailability were achieved as a result of the modified SC-NEs' capacity to target the new organic cation/carnitine transporter 2 (OCTN2) and amino acid transporter B (0+) (ATB0,+) on the corneal epithelium. Additionally, in a rabbit model of endotoxin-induced uveitis, SC-NEs demonstrated extremely high levels of anti-inflammatory activity in vivo. Based on the results of the ocular safety test, it was determined that the SC-NEs were biocompatible. According to the findings, OCTN2 and ATB0,+ -targeted nanoemulsions, were promising ophthalmologic drug delivery systems [127].

Nanosuspensions

Nanosuspensions have emerged as a promising formulation strategy in ocular drug delivery. A nanosuspension is a submicron colloidal dispersion of pure drug particles stabilized by surfactants or polymers [4,128]. One of the primary benefits of nanosuspensions in ocular drug delivery is their ability to enhance drug solubility and bioavailability. Poor water solubility is a common challenge with many ocular drugs, leading to inadequate therapeutic levels at the target site. Nanosuspensions address this issue by reducing the drug particle size, thereby increasing the surface area and improving the dissolution rate. This increases drug concentrations in the aqueous humor, enhancing the therapeutic efficacy [129]. Nanosuspensions also offer the advantage of prolonged drug retention on the ocular surface. The small particle size allows the drug to remain in the precorneal area for extended periods, crucial for maintaining therapeutic drug levels in the eye. Additionally, nanosuspensions can provide a controlled release of the drug, allowing for steady therapeutic effects over time [130]. The formulation flexibility of nanosuspensions is another significant advantage. They can be formulated with various stabilizers, including surfactants, polymers, and biopolymers, to enhance their stability and bioavailability. For instance, hydroxypropyl methylcellulose (HPMC), polyvinyl alcohol (PVA), and Pluronic F68 are commonly used stabilizers that improve the stability and ocular tolerability of nanosuspensions [131]. These stabilizers also help prevent particle aggregation, ensuring uniform distribution of drug particles.

Further, this system is particularly beneficial for delivering drugs to both the anterior and posterior segments of the eye. Drugs intended for the posterior segment, such as those for treating age-related macular degeneration or diabetic retinopathy, face significant delivery challenges due to the eye's anatomical barriers. Nanosuspensions, with their small particle size and enhanced penetration capabilities, can effectively traverse these barriers and deliver therapeutic concentrations of drugs to the posterior segment [132]. One primary concern is nanosuspension stability during storage, as particle aggregation and Ostwald ripening can occur, leading to a loss of efficacy. Formulation strategies, such

as using appropriate stabilizers and manufacturing techniques like high-pressure homogenization and media milling, are essential to ensure nanosuspension's long-term stability [133]. Using the quasi-emulsion solvent evaporation procedure, Qin et al. developed a voriconazole-loaded ophthalmic nanosuspension based on Eudragit RS 100 and Pharmasolve®. This nanosuspension was investigated for its potential ability to augment corneal permeability. The nanoparticle, which was well-discrete and had a size of 138 ± 1.3 nm, was created with a high entrapment efficiency of 98.6 ± 2.5%. Additionally, the nanoparticle exhibited a positive zeta potential in the 22.5-31.2 mV range, indicating its excellent physical stability. The nanosuspension that was loaded with voriconazole and contained the penetration enhancer demonstrated a high level of permeability in both in vitro and in vivo conditions. Furthermore, it demonstrated a high level of antifungal activity, significantly suppressing the growth of Candida albicans at a lower concentration of voriconazole (2.5μg/ml, $p < 0.05$) [134].

Micelles

Micelles have emerged as a highly promising platform for ocular drug delivery due to their unique structural characteristics and versatile functionality. Micelles are colloidal aggregates formed from amphiphilic molecules, typically surfactants or block copolymers, that self-assemble in aqueous environments. These structures have a hydrophobic core and a hydrophilic shell, which allows them to encapsulate hydrophobic drugs and enhance their solubility and stability in aqueous media [135]. One of the primary advantages of micelles in ocular drug delivery is their ability to improve the bioavailability of poorly water-soluble drugs. Many ocular therapeutics suffer low solubility, leading to inadequate drug levels at the target site. Micelles can encapsulate these hydrophobic drugs within their core, protecting them from the aqueous environment and enhancing their solubility. This encapsulation prevents premature degradation and extends the drug's half-life, improving therapeutic efficacy [136]. The small size of micelles, typically in the range of 10 to 100 nm, facilitates their penetration through the ocular barriers. The cornea and conjunctiva are significant barriers to drug delivery, but the nanoscale size of micelles enables them to traverse these barriers more effectively than larger particles. Furthermore, the hydrophilic shell of micelles can interact favorably with the tear film and mucosal surfaces, enhancing retention time on the ocular surface and improving drug absorption [137]. Micelles can also be functionalized to achieve targeted drug delivery. Modifying the micelles' surface with ligands such as antibodies, peptides, or small molecules can be directed to specific cells or tissues within the eye. This targeted approach ensures that higher drug concentrations reach the desired site of action, minimizing systemic exposure and potential side effects. For instance, micelles functionalized with hyaluronic acid have shown enhanced targeting of the ocular surface, providing more efficient treatment for dry eye disease [138].

Moreover, micelles exhibit excellent biocompatibility and safety profiles, essential for ocular applications. The materials used to form micelles, such as Pluronic block copolymers and phospholipids, are generally considered safe and have been extensively studied for their biocompatibility. These materials do not elicit significant inflammatory or immune responses, making them suitable for prolonged use in sensitive ocular tissues [135]. One of the primary challenges is the stability of micelles in the dynamic ocular environment. The presence of tears, blinking, and tear turnover can lead to the rapid clearance of micelles from the ocular surface. Formulation strategies, such as incorporating mucoadhesive polymers or developing in situ gelling systems, can enhance the retention and stability of micelles in the eye [139]. The formulation of Posaconazole (PSC) micelles for ocular delivery was carried out by Durgun et al., and in vitro permeability, ocular irritation, and anti-fungal activity investigations were evaluated. According to the findings, the micellar carrier system improved the permeability of PSC to the eye's tissues. Further, PSC-loaded micellar formulations' effectiveness against Candida albicans strains was confirmed through in vitro anti-fungal activity data. It was determined that micellar systems have the potential to be an effective and safe method of delivering PSC for the treatment of ocular fungal infections [140].

Dendrimers

Dendrimers, highly branched synthetic macromolecules, have shown significant promise in ocular drug delivery due to their unique architecture and versatile functionalization capabilities. These nanoscale structures comprise a central core, interior branching units, and peripheral functional groups, creating a globular, tree-like structure. Dendrimers' size, shape, surface functionality, and internal cavities can be precisely controlled during synthesis, making them highly customizable for drug delivery applications [141]. The hydrophobic core of dendrimers can encapsulate these drugs, increasing their solubility in aqueous environments. This encapsulation protects the drugs from enzymatic degradation, improving their stability and therapeutic efficacy. For instance, polyamidoamine (PAMAM) dendrimers have significantly enhanced the solubility and ocular bioavailability of various drugs, including anti-inflammatory and anti-glaucoma agents [142]. Dendrimers offer controlled and sustained drug release, crucial for treating chronic ocular diseases requiring prolonged medication. The release profile can be modulated by adjusting the generation and surface functionality of the dendrimers. High-generation dendrimers, with more branching and surface groups, tend to release drugs more slowly, providing a sustained therapeutic effect. This property is particularly beneficial for conditions such as glaucoma, where continuous drug administration is necessary to maintain intraocular pressure [143]. Dendrimers also enhance drug penetration through ocular barriers. The corneal epithelium is a significant barrier to drug delivery, but dendrimers can improve drug penetration through various mechanisms. For instance, surface modification with hydrophilic groups or targeting ligands can enhance interaction with the corneal surface and facilitate drug transport.

Additionally, the nanoscale size of dendrimers allows them to traverse the tight junctions of the corneal epithelium more effectively than larger particles [144]. Biocompatibility is another critical factor for ocular applications, and dendrimers have demonstrated favorable biocompatibility profiles. The surface chemistry of dendrimers can be tailored to reduce toxicity and enhance compatibility with ocular tissues. For example, dendrimers' PEGylation (attachment of polyethylene glycol chains) can reduce surface charge and decrease cytotoxicity, making them safer for ocular use. Studies have shown that PEGylated dendrimers exhibit minimal irritation and inflammation when applied to the eye, making them suitable for long-term use [145,146]. To determine the ocular cytotoxicity and biosafety of Poly(amidoamine) PAMAM dendrimers, Qin et al. researched ocular systems both in vitro and in vivo. According to the findings, the quantity of PAMAM below 50 μg/ml had a negligible effect on the ocular tissue. However, the concentration above 50 μg/ml severely damaged the ocular tissue in the evaluated circumstance. Furthermore, the results obtained from in vivo experiments indicated that a higher concentration of dendrimer, namely 100 μg/mL, was linked to functional impairment, as displayed by the utilization of optical coherence tomography and electroretinogram studies. Overall, it was determined that a higher concentration of PAMAM, precisely above 50 μg/ml, has the potential to cause harm to the functional aspects of the eye. On the other hand, PAMAM at concentrations lower than 50 μg/ml demonstrated a high level of biocompatibility and biosafety in human ocular cells and tissues [147].

Stability of nanocarriers in ocular drug delivery

The stability of nanocarriers in ocular drug delivery is a critical factor in determining their efficacy and safety in treating various eye diseases. Nanocarriers are designed to enhance drug solubility, bioavailability, and targeted delivery. However, their stability is influenced by several factors, including physicochemical properties, formulation composition, storage conditions, and biological environment interactions [148]. Physicochemical stability is a significant concern for nanocarriers in ocular drug delivery. Particle size, surface charge, and encapsulation efficiency are vital in maintaining stability. Nanocarriers must maintain a consistent particle size distribution to ensure uniform drug delivery and prevent aggregation or sedimentation. Surface charge, typically imparted by surfactants or polymers, affects the colloidal stability of nanocarriers by preventing particle agglomeration through electrostatic

repulsion. Encapsulation efficiency, the amount of drug encapsulated within the nanocarrier, must remain high to ensure therapeutic efficacy [149].

The choice of stabilizers and excipients in the formulation significantly impacts the stability of nanocarriers. Surfactants and polymers, such as polysorbates, Pluronic F68, and polyvinyl alcohol (PVA), are commonly used to stabilize nanocarriers. These stabilizers help to maintain particle size and prevent aggregation during storage and application. Additionally, using antioxidants and preservatives can enhance the stability of nanocarriers by preventing oxidative degradation and microbial contamination [150]. In addition, Storage conditions, such as temperature, light exposure, and humidity, also affect the stability of nanocarriers. Elevated temperatures can accelerate degradation processes, such as hydrolysis and oxidation, reducing drug potency and efficacy. Light exposure can cause photodegradation of both the nanocarrier and the encapsulated drug, while high humidity levels can lead to hydrolytic degradation. Therefore, proper storage conditions, such as refrigeration and protection from light and moisture, are essential to maintain the stability of nanocarriers [151].

Biological environment interactions pose another challenge to the stability of nanocarriers in ocular drug delivery. The ocular surface and internal eye structures present a dynamic and complex environment, with barriers such as the tear film, corneal epithelium, and BOB. Enzymatic degradation and interaction with tear proteins can destabilize nanocarriers, affecting drug release and bioavailability. Mucoadhesive polymers, such as chitosan and hyaluronic acid, can be incorporated into nanocarrier formulations to enhance retention time on the ocular surface and protect against enzymatic degradation [152]. Further, various strategies are employed to address stability challenges in designing and formulating nanocarriers. For example, using cross-linking agents in polymeric nanoparticles can improve structural integrity and resistance to degradation. Surface modification with polyethylene glycol (PEGylation) can enhance stability by providing a steric barrier against protein adsorption and enzymatic degradation. Additionally, advanced manufacturing techniques, such as high-pressure homogenization and freeze-drying, can enhance the stability and shelf-life of nanocarrier formulations [153].

Future prospects

Nanocarriers are revolutionizing ocular drug delivery, offering new strategies to overcome the anatomical and physiological barriers that limit the efficacy of conventional treatments. The prospects of nanocarriers in this field are promising, driven by advancements in nanotechnology, materials science, and biomedical engineering. These prospects include enhanced drug delivery efficiency, targeted therapy, sustained release, improved patient compliance, and innovative treatment modalities. Nanocarriers have shown potential in enhancing the bioavailability of ocular drugs. Their small size allows better penetration through ocular barriers like the corneal epithelium and the blood-retinal barrier. Future developments will optimize these nanocarriers' size, surface charge, and hydrophobicity to enhance further their penetration and retention in ocular tissues [154]. One of the most exciting prospects for nanocarriers is the ability to achieve targeted drug delivery. The precise targeting of diseased tissues can be accomplished by functionalizing nanocarriers with ligands, antibodies, or peptides that recognize specific cell types or receptors in the eye. This targeted approach increases therapeutic efficacy while minimizing systemic side effects and reducing the required dosage. For example, targeted nanocarriers could deliver drugs directly to the retina in AMD or the trabecular meshwork in glaucoma, enhancing treatment outcomes [155]. Nanocarriers can be engineered to provide sustained and controlled drug release, which is crucial for treating chronic ocular diseases that require prolonged medication. The release profile can be modulated by adjusting the generation and surface functionality of the nanocarriers. High-generation dendrimers, for instance, release drugs more slowly, providing a sustained therapeutic effect. This property is particularly beneficial for conditions such as glaucoma, where continuous drug administration is necessary to maintain intraocular pressure [143]. Moreover, improving patient compliance is critical in ocular drug delivery, particularly for

conditions like glaucoma, which require regular medication. Nanocarriers can be formulated into user-friendly delivery systems such as eye drops, contact lenses, or in situ gels that provide sustained drug release with fewer applications. Future advancements include the development of smart contact lenses or ocular inserts that can continuously monitor ocular conditions and release drugs as needed [156].

Further, Nanocarriers are opening up new possibilities for innovative treatment modalities. Gene therapy and RNA interference (RNAi) are promising approaches that nanocarriers can facilitate to deliver genetic material or siRNA directly to target cells. These therapies can potentially treat genetic ocular diseases or conditions like DR and AMD at the molecular level [157]. The development of multifunctional nanocarriers that can perform multiple roles, such as imaging, diagnosis, and therapy, is a promising area of research. These theranostic nanocarriers can deliver drugs while simultaneously allowing for real-time monitoring of treatment progress through imaging modalities. This dual functionality could lead to more personalized and effective treatment strategies [158]. Despite their advantages, overcoming biological barriers remains a challenge for nanocarriers. The research will focus on designing nanocarriers that can navigate the ocular environment more effectively. This includes developing strategies to prevent rapid clearance by tear turnover, blinking, and ocular surface mucins. Advances in surface engineering and bioadhesive materials will play a crucial role in addressing these challenges [36]. As research progresses, nanocarriers are expected to play an increasingly pivotal role in treating ocular diseases, offering improved therapeutic outcomes and better quality of life for patients.

Conclusions

The field of ophthalmology is witnessing a transformative shift with the advent of advanced nanocarriers, which offer unprecedented potential for navigating ocular barriers and enhancing drug delivery. Traditional ocular therapies have long struggled with the eye's complex anatomy and physiology, formidable barriers to effective drug absorption and retention. The cornea, conjunctiva, BRB, and tear turnover are just a few of the many obstacles that reduce the efficacy of conventional treatments. Nanocarriers represent a groundbreaking development in ophthalmology, offering solutions to the longstanding challenges of ocular drug delivery. However, advanced nanocarriers are overcoming these challenges, ushering in a new era of targeted and efficient ocular drug delivery. These nanocarriers can encapsulate such drugs, protecting them from enzymatic degradation and facilitating sustained release, crucial for treating chronic conditions like glaucoma and AMD. Researchers can precisely target diseased ocular tissues by functionalizing nanocarriers with specific ligands, antibodies, or peptides. This targeted approach increases the efficacy of the treatment by concentrating the drug where it is needed most. It also minimizes systemic side effects and reduces the overall dosage required. For instance, targeting the retina in AMD or the trabecular meshwork in glaucoma can significantly enhance therapeutic outcomes. Despite the significant progress, challenges remain in the clinical translation of nanocarrier-based therapies. Issues such as long-term safety, potential toxicity, and the complexity of large-scale manufacturing need to be addressed. Nonetheless, ongoing research and technological advancements are likely to overcome these hurdles, making nanocarriers an integral part of future ocular therapies. The future of ocular drug delivery lies in the continued exploration and optimization of these innovative nanotechnologies, heralding a new era in the management and treatment of ocular diseases.

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Declaration of interest

The authors declare no conflict of interest.

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