Multidisciplinary Reviews

REVIEW ARTICLE
Published Online: March 18, 2025
https://doi.org/10.31893/multirev.2025269

Literature review: The role of particle size distribution in drug delivery

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Abstract Pharmaceutical formulations' particle size distribution (PSD) has a significant impact on the stability, bioavailability, and effectiveness of medications. In various delivery systems, such as oral, inhalation, transdermal and parenteral, the distribution of particle sizes can impact a drug's absorption, release rate, and therapeutic efficacy. This review presents the role of PSD in improvingdrug delivery quality through various methods. In respiratory formulations, for example, particles of a certain size more easily reach the lower respiratory tract, while in transdermal and ophthalmic systems, smaller particle sizes aid more controlled drug penetration and release. With attention to particle sizing techniques, more stable and safe formulations can be developed, enabling improved therapy and reduced side effects. The study's findings highlight how crucial it is to comprehend PSD during the medication development process, particularly in regard to promoting the best formulations for therapeutic efficacy and safety**.** In addition, the role of particle size (PSD) in various drug delivery system is now becoming more significant with advances in pharmaceutical technology. In inhalation formulations, PSD enables improved drug delivery efficiency by more accurately directing particles to target locations, such as the lower respiratory tract. On the other hand, in transdermal and ophthalmic delivery system, the use of nano-sized particles can enhance penetration into tissues and ensure controlled drug release, thereby minimizing systemic side effects. The study also discusses modern approaches, such as PSD measurement techniques that include laser diffraction analysis and cascade impactor methodes, which provide real-time and in-depth data to ensure formulation quality. With the implementation of these technologies, the development of more stable, safe and effective drug delivery system becomes possible. A deep understanding of PSD can help optimize drug therapy for various conditions, whether conventional pharmaceutical approaches or nanotechnologies.

Keywords: particle size distribution, pharmaceutical formulation, bioavailability, drug delivery system, therapeutic efficacy

1. Introduction

In today's pharmaceutical landscape, drug delivery systems (DDSs) have emerged as a crucial element in enhancing the efficacy and efficiency of drug treatments. A range of physicochemical technologies comprise DDSs, which are engineered to manage the release and distribution of pharmacologically active compounds into cells, tissues, and organs, thereby maximizing their therapeutic effects. These technologies encompass both drug formulations and delivery techniques that seek to enhance bioavailability, minimize side effects, and provide controlled drug release tailored to the therapeutic requirements of the patient (Jeong et al., 2021). A key factor influencing the effectiveness of DDSs is the particle size distribution (PSD). PSD refers to a set of numerical values or mathematical functions that characterize the distribution of particle numbers according to size within a formulation, whether in the form of powders, granules, or particles suspended in a liquid. This parameter is essential for defining the physicochemical characteristics of a substance, such as its stability, solubility, and the rate at which active ingredients are released. Consequently, PSD frequently serves as a critical element in the design and development of various pharmaceutical dosage forms (Nijhu et al., 2024). In the pharmaceutical sector, controlling particle size distribution (PSD) is crucial for manufacturing different dosage forms, including solid forms like tablets and capsules, semi-solid forms such as creams and ointments, and liquid forms like suspensions and emulsions. In tablets and capsules, which are solid preparations, PSD influences the mixing of ingredients, the characteristics of powder flow, and the tablet compression process, all of which ultimately impact the quality and consistency of the final product (Ainurofiq et al., 2020). For semi-solid formulations like creams, ointments, and suspensions, PSD is crucial for maintaining the physical stability of the preparation, preventing phase separation during storage or use (Lau, 2001). In pharmaceutical formulation

 Received: December 13, 2024 | Accepted: January 21, 2025

development, control of PDS is critical to ensure consistency and effectiveness of the final product. Particles with a narrow size distribution and regular shape are easier to produce and provide a more predictable release profile (Göke et al., 2016).

The impact of PSD on drug therapy effectiveness Changes in particle size distribution can influence multiple facets of pharmacokinetics, such as the rate of dissolution, absorption, and distribution within the body. PSD also affects the flow properties and bulk density of active pharmaceutical ingredients (APIs), which are important in manufacturing processes. Particles that are too large or non-uniform can cause problems in processing processes such as blending and packaging, which can ultimately affect the quality of the final product (C. C. Sun & Davé, 2022). Therefore, a deep understanding of how DUP affects these properties is essential for researchers and developers in the pharmaceutical industry. In pharmaceutical formulations, PSD plays a crucial role in a drug's bioavailability, particularly for those with low solubility. For instance, smaller particle forms of drugs possess an increased surface area, which enhances the speed of dissolution and facilitates quicker absorption in the gastrointestinal system. On the contrary, particles that are too large may slow down the dissolution rate and reduce the therapeutic effect. Therefore, particle size control becomes a key strategy to improve the therapeutic effect and overcome formulation problems in various drug delivery routes such as oral, inhalation and transdermal (Lau, 2001).

In addition, the use of nanotechnology in DDS is increasing, especially in nanoparticle-based formulations and targeted drug delivery systems. Particle size distribution (PSD) in nanoparticles plays a crucial role in drug delivery systems, especially in the context of cancer therapy. The particle size and distribution of nanoparticles can affect the biodistribution, tissue penetration, and therapeutic efficacy of the delivered drug. Research shows that nanoparticles with smaller sizes tend to have better penetration capabilities into tumor tissues, thanks to the enhanced permeability and retention (EPR) effects that occur in the tumor environment (Xu et al., 2020). By utilizing these characteristics, nanoparticles can be designed to enhance drug accumulation at the target site, thereby increasing therapeutic effectiveness and reducing systemic side effects. Nanoparticles of a certain size can improve the efficiency of drug delivery to targets such as cancer cells or inflammatory tissues and reduce systemic toxicity. In modern medicine, drug delivery based on small particles and nanoparticles has become an important method to improve the therapeutic effect and prolong the duration of drug action in the body (Nijhu et al., 2024).

The aim of this literature review is to analyze the impact of particle size distribution (PSD) on various drug delivery systems, including respiratory, oral, ophthalmic, transdermal, and parenteral. During inhalation therapy, PSD determines drug deposition in the respiratory tract, while during oral administration, it affects solubility and absorption in the gastrointestinal tract. In ophthalmic applications, smaller particles improve corneal permeability and therapeutic efficacy. In transdermal and topical formulations, PSD affects the penetration of active ingredients into the skin and hair follicles. During parenteral administration, precise particle size control is essential to prevent embolic risks and ensure efficient drug distribution. By studying these aspects, this review provides insights into the latest pharmaceutical technologies and highlights their role in improving drug stability, efficacy, and safety.

2. Particle Size Distribution in Respiratory Drug Delivery

The effectiveness of inhaled and intranasal drug delivery is significantly influenced by the particle size distribution. The size of the particles determines where the drug is deposited within the respiratory tract, subsequently affecting both its bioavailability and therapeutic results (Ainurofiq, et al., 2023a). Particles measuring less than 5 µm can access the deepest regions of the lungs, whereas those measuring less than 2 µm tend to gather in the alveoli. For the best distribution within the lungs, particle sizes ranging from 2–5 µm are regarded as the best (Dudhat & Patel, 2022a). One of the widely used dosage forms is dry powder, as it has advantages such as stability at room temperature compared with the liquid form. This formulation is highly advantageous for intranasal administration because of the extensive surface area and high permeability of the nasal cavity. Additionally, micro- and nanosized particles offer further advantages, including the extension of drug stability, regulation of drug release, and improved adherence to the nasal mucosa, which ultimately boosts drug absorption (Chang & Chan, 2022).

However, the particle size also presents challenges. Very small particles more easily penetrate biological barriers and are taken up by the body but tend to be more quickly eliminated by natural clearance systems. In contrast, larger particles have more difficulty crossing the body's barrier but have the advantage of better size control, which favors specific targeting and stable drug release (Mok, 2024). Particle size also affects the physicochemical stability of drug formulations and may pose a risk of side effects, such as mouth or throat irritation. Therefore, an understanding of the particle size distribution is essential when designing suitable drug formulations and inhaler devices. To guarantee that inhalation products adhere to safety and efficacy standards, stringent regulations concerning particle size distribution have been established. Various methods are employed for determining particle size, such as laser diffraction, which provides real-time measurements, and cascade impactors, which assess the aerodynamic diameter. The importance of reliable particle size data is underscored by regulatory bodies such as the FDA to ensure the safety and effectiveness of drugs administered (Kumar et al., 2022).

A size between 1 and 5 microns is the ideal particle size to reach the lower airway and alveoli. Larger particles are usually trapped in the upper airway, whereas smaller particles target areas affected by biofilm-forming pathogens, where antibiotics need to penetrate the mucus layer and biofilm to reach bacterial colonies. In these situations, it is also important to measure

size fractions finer than 10 µm in aerodynamic diameter. This is because these particles may enter the nasal cavity and enter the ducts that lead to the oropharynx or lower respiratory tract (Mitchell & Nagel, 2004).

The optimal particles for lung penetration range from 1 to 5 micrometres, as particles in this range can reach the alveoli, whereas larger particles tend to remain inthe upper airway, and smaller particles may be inhaled out before they have a chance to stick. As a result, methods such as cascade impactors and laser diffraction are crucial for determining particle size, which in turn affects how well inhaled medications work. Because it influences drug deposition in the lungs and ultimately affects treatment efficacy, particle size measurement is an essential component of respiratory drug delivery. Increasing the intended particle size can increase the effectiveness and safety of a medication when it is taken as prescribed (Sangolkar et al., 2012).

Drug particles less than 5 µm in size have a high chance of being deposited in the lungs, with particles smaller than 2 µm tending to reach the alveoli. Particles in the 2–5 µm range usually predominate in inhaled doses, providing an even distribution throughout the lungs. The success of inhalation therapy depends largely on the method of drug delivery as well as the patient's ability to use the inhaler correctly. Various types of inhalers are available on the market, each having advantages and disadvantages.Inhalers allow for lower drug doses, faster action, and fewer side effects. The effectiveness of drug deposition in the lungs is influenced by the particle size, inhalation technique, and type of inhaler used. In the treatment of lung illnesses, nano- and microsized particles are crucial because they enable direct medication administration to the required location with a low dosage and few adverse effects (Dudhat & Patel, 2022b).

There are several methods for measuring particle size distributions relevant to aerosol treatment. One well-established technique is laser diffraction, which uses the principle of light scattering; the star-like patterns produced by dispersed particles can be analyzed to determine their size with good precision. Furthermore, cascade pulverizationserves as another method where aerosol particles are separated on the basis of their aerodynamic diameter through a series of increasingly finer collection stages. Each technique has different benefits and drawbacks on the basis of the type of sample and resolution needed (Mitchell & Nagel, 2004).

Researchers can also examine individual aerosol particles at high magnification by imaging methods such as scanning electron microscopy (SEM). This technique provides detailed information about particle shape, which can influence performance aspects such as flowability and ease of use in inhaler systems. A comparison of these various approaches highlights that no single method can adequately capture complex particle behavior across multiple formulations; instead, the use of complementary methodologies often results in a more comprehensive dataset that is required when new formulations intended for patient use are evaluated (Mitchell & Nagel, 2004).

The implications around accurate particle size determination cannot beoverstated, as effectively targeting specific lung regions will have a direct effect onlocal treatment efficacy (such as reducing inflammation) alongside the risk of systemic absorption stemming from inappropriate deposition causing side effects instead of the desired outcome being achieved; improving overall patient compliance—inhaling the drug requires less effort if accurately sized dosage forms can be optimally maneuvered through the airway efficiently without burdening them with unnecessarily large aggregates that create discomfort (Shekunov et al., 2007).

Determining particle size is essential for successful drug delivery via metered dose inhalers (MDIs), particularly for managing respiratory conditions such as asthma and chronic obstructive pulmonary disease (COPD) (Kumar et al., 2022). Particles smaller than 5 microns are likely to settle in the lungs, whereas particles smaller than 2 microns are more likely to concentrate in the alveoli, the deepest part of the respiratory tract (Dudhat & Patel, 2022a).

Advances in nanotechnology have led to significant improvements in the formulation of MDIs, with nanoparticles providing advantages in terms of more accurate targeting and better drug retention in the lungs (Kumar et al., 2022). One promising innovation is the use of crosslinked chitosan nanoparticles, especially those containing PEG 1000, which have been shown to be effective for drug delivery to deep lungs via MDIs (Sharma et al., 2012). The aerodynamic particle size distribution, which is generally measured via devicecascade impactors, becomes an important factor in determining the effectiveness of MDIs and dry powder inhalers (DPIs) (Nayak et al., 2020). The efficiency of particle distribution in the lungs is influenced by various parameters, such as the nozzle size, jet length, and patient respiratory flow rate (Kumar et al., 2022).

The use of polymers in inhaler formulations aims to improve the effectiveness of drug delivery through stable and controllable aerosols to the respiratory tract. In metered dose inhalers (MDIs), polymer-based nanocarriers such as polymer nanoparticles and polymer micelles are often used. Polymers such as poly(lactic-co-glycolic acid) (PLGA) and chitosan are common examples, as they canbe molded into a nanoparticle matrix that allows gradual and targeted release of the drug until it reaches deep into the lungs. These nanoparticles are small in size and able to penetrate deeper, thus increasing the effectiveness of drug deposition in the target lung area without causing significant toxic effects. These polymers enable the regulation of the physicochemical characteristics of nanoparticles, such as their release rate and stability, which is particularly important in the treatment of chronic diseases such as asthma or COPD. Polymer micelles, for example, have a hydrophobic core that can store drugs and release them gradually, while ahydrophobic outer layer improves stability for long-term use. Polymer-based nanoparticles can be produced by various methods, such as direct dissolution or emulsion techniques, and

provide benefits in precise and sustained drug delivery toareas of the lung that require intensive therapy, as well as reducing the required drug dosage (Kumar et al., 2022).

To achieve optimal drug distribution, proper techniques are essential for using pressurized metered-dose inhalers (pMDIs) and softist inhalers (SMIs). Therapy effectiveness is often diminished by usage mistakes, such as inadequate coordination between inhalation and device activation. In contrast, nebulizers provide convenience, particularly for patients with physical limitations, acute conditions, or young children. Nevertheless, their bulkiness and lack of portability present challenges for users seeking high flexibility. While dry powder inhalers (DPIs) do not require propellants and offer improved stability in storage, their effectiveness is significantly reliant on the patient's ability to create a sufficiently strong inspiratory flow to trigger drug release. (Sorino et al., 2020).

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3. Particle Size Distribution in Oral Drug Delivery

3.1. Nanoemulsion

Emulsions characterized by droplet sizes ranging from 10 to 1000 nm are known as nanoemulsions. Generally, these nanoemulsions are composed of oil, water, and surfactants. The selection of surfactant plays a vital role in both the formation and stability of nanoemulsions. While they are thermodynamically unstable, nanoemulsions exhibit kinetic stability, indicating that if they are left undisturbed for an extended period, phase separation is likely to occur. Nanoemulsions have been developed for various uses in the pharmaceutical, food, and cosmetic fields, so they must be biocompatible and nontoxic. Therefore, the selection of safe oils and surfactants, such as vegetable oils or those that comply with pharmaceutical standards, is essential. Proteins and lipids are frequently employed as surfactants to maintain the stability of nanoemulsions (Leister & Karbstein, 2020).

Surfactant particles are increasingly popular because they can form stable, multifunctional, and economical emulsions. Various types of particles, such as silica, oxidized iron, hydroxyapatite, and graphene oxygen, are known to have surface activity (Jiang et al., 2020). Particle opacity can be regulated through surface modification in certain systems. Pickering emulsions have attracted attention as substitutes for small-molecule surfactants, particularly in drug delivery applications, because of their enhanced stability and biocompatibility. By adsorbing at the interface between oil and water, the particles create a barrier that inhibits coalescence, thereby stabilizing the emulsion. The degree of wettability of the particles affects emulsion stability; more water-wettable particles typically form oil-in-water (O/W) emulsions, whereas more oil-wettable particles create water-in-oil (W/O) emulsions. The stability of the emulsion is also affected by the morphology of the particles, such as spheres, sheets, or rods. The long-term stability and droplet size of these materials are also influenced by the particle concentration (Jiang et al., 2020).

3.2. Tablet

Tablets are solid drug preparations that are generally made by adding an appropriate pharmaceutical ingredient. Depending on their intended function and manufacturing process, tablets can have different dimensions, shapes, weights, hardnesses, thicknesses, and crushabilities (Ainurofiq et al., 2018).

In (Špaglová et al., 2023), the sieve method was used to examine the granule particle size in a study comparing the impact of particle size on tablet formulations using lactose (LAC) and microcrystalline cellulose (MCC) fillers, as well as rosehip powder and L-ascorbic acid. The results showed that larger granules had better flow characteristics, which is important for the tablet compression process (Ainurofiq, et al., 2023b). Significant differences were found in tablet size between tablets with LAC and those with MCC fillers. The tablets with LAC filler had an average mass of approximately 0.320 g and a height of 4.37 mm, whereas the tablets with MCC had an average mass of 0.285 g and a height of 4.10 mm. In addition, the LAC tablets had a greater hardness (64.8 N) than did the MCC tablets (27.8 N). These differences in mass and size affect the compactness and strength of the tablets, where tablets with LAC are considered more compact and have a better visual appearance (Špaglová et al., 2023).

3.3. Pellets

Pellets are spherical preparations that typically have a diameter of 0.5 to 1.5 mm and a limited particle size distribution. Pellet formulations have various advantages, such as maintaining stable drug levels in plasma, reducing the risk of adverse side effects, minimizing irritation, having good flow properties and simplifying the coating process. Pellets are made by converting

active substances into spherical solids 500–1500 µm in size via the use of appropriate additives. Some sources mention that the maximum size of pellets reaches 2000 µm, whereas that of micropellets is less than 500 µm. There are various technological methods used to produce pellets and micropipettes. The pelletization process produces nearly spherical kerign particles with good flow characteristics (Kállai-Szabó et al., 2024).

In a study by (Sarkar et al., 2014), pellets formulated through an extrusion process before spheronization had a surface that tended to be smooth compared with pellets made through granulation followed by direct spheronization. Additionally, pellets with smoother surfaces are produced by longer spheronization times. The impact of the amount of water used as a moisturizing liquid on the surface hardness of pellets made of microcrystalline cellulose (MCC) was examined quantitatively via laser profilometry and qualitatively via a scanning electron microscope. According to the qualitative study, pellets with smoother surfaces were created from formulations that contained more water. Nevertheless, the quantitative investigation revealed that the amount of water had no discernible effect on the surface hardness of the pellets. Since starting materials are used to make pellets, the size of the starting material particles is believed to have a significant effect on the surface hardness of the pellets. By determining how the initial material particle size affects the surface hardness of pellets, formulation scientists can choose the best material to create pellets with a specific surface hardness. Nevertheless, there has not been any research on how the particle size of the starting material affects the surface hardness of the pellet (Kállai-Szabó et al., 2024).

3.4. Nano spray-dried drugs for oral use

Spray drying is a crucial technology because of its rapid, straightforward, and consistent process, as well as its ability to support scalable production. This technology is widely utilized in various fields, such as food, chemical, and drug encapsulation. Conventional and nanospray drying techniques are two types of spray drying. The primary benefit of nanospray drying is its ability to create drug-containing nanoscale particles, which makes it appropriate for a range of drug delivery systems. Submicron-sized particle production is supported by recent advancements in this technology, such as Büchi Labortechnik AG's 2009 introduction of the Nano Spray Dryer B-90 (Ozturk & Arpagaus, 2021).

Several changes must be made to standard spray drying equipment to produce nanoscale particles via spray drying technology. The inability of cyclones to effectively separate and collect submicron particles, which are usually insufficiently inertial to absorb particles smaller than 2 microns, is a major challenge. Particles smaller than approximately 1.4 microns are difficult to separate from the gas stream even when sophisticated glass cyclones are used (Ozturk & Arpagaus, 2021). Electrostatic particle collectors are capable of collecting nanoscale particles, as described in various studies. Another option is to use gas flow in the drying chamber to prevent particle collection on the chamber walls and spray nozzles that create tiny droplets to catch dry particles in the submicron range (Ozturk & Arpagaus, 2021).

Spray manufacturing, laminar drying, and electrostatic powder collection procedures are all included in the technology referred to as nanospray drying. By using vibrating mesh technology derived from a nebulizer designed for inhaled drug delivery, droplets are produced. The spray nozzles are activated via ultrasonic frequencies ranging from 80 to 140 kHz. Tiny droplets are released from a perforated metal mesh by a small, replaceable spray cap that is attached to the nozzle. Millions of precisely sized droplets are produced with this technique; the droplet sizes are determined by the mesh size as well as the liquid characteristics, including surface tension and viscosity. For example, the use of a 4.0 micron spray mesh with water results in droplets that are approximately 3 to 8 microns in size (Ozturk & Arpagaus, 2021).

The laminar and unidirectional flow of drying gas allows for the slow drying of goods that are susceptible to heat, such as peptides or proteins. At a drying temperature of 75°C and a drying air flow rate of 100 L/min, 7-micron water droplets take approximately 10 milliseconds to dry. High-efficiency, electrostatic collecting electrodes are used to collect dried samples. For tiny powder batches ranging from 10 mg to 2.7 g, the submicron particle separation rate is greater than 99%. This electrostatic precipitation is also ableto collect porous and walled particles without damaging them (Ozturk & Arpagaus, 2021).

3.6. Pulveres

Pulveres are powdered preparations that are the drug's own concoction or the product of tablet pulverization. It is given to patients through pulverization or reduction of tablet particle size. This method is used because pure powder that can be formulated into pulverized preparations is unavailable. Pulverization and particle size reduction can be performed manually by grinding in a mortar or by using a milling device, such as a ball mill, grinder, or blender, depending on the material used. The dissolution speed, bioavailability, stability, and even product flavor are affected by this particle size. The pharmacopoeia divides pulveres into several size classes.

The coarse powder has the largest particle size, passes through sieve number 20 with a size of 800 microns and is retained on sieve number 40 with a size of 425 microns. The semifine powder was smaller in size, passed through sieve number 40 and was retained on sieve number 60, with a size of 250 microns. The fine powder also had a relatively small size, passed through sieve number 60 and stuck to sieve number 80 with a size of 180 microns. The smallest powder is very large (Nadya Bestari et al., 2017).

A higher dissolving speed means that the drug dissolves in the body more quickly since a smaller particle size has a larger

surface area. Since the body easily absorbs finer particles, this can also improve bioavailability. However, fine powders more easily absorb moisture and should be properly stored because it may impact the stability of the active components. Powders with fine particles do not leave a harsh taste in the mouth, which makes them more convenient to consume. To achieve the desired particle size, the particle reduction process is carried out via tools such as a ball mill, jet mill, or disk mill. These tools can produce very fine powders according to pharmaceutical formulation requirements (Nadya Bestari et al., 2017).

4. Particle Size Distribution in Ophtalmic Drug Delivery

In addition to the skin, the eye is the most accessible organ for topical treatment (Figure 1). Ocular insertion preparations are sterile solid and semisolid preparations of appropriate size and shape that are designed to be inserted behind the eyelid or placed over the eye to achieve topical or systemic drug effects. The treatment of eye diseases is localized and cannot be used as an entry point for drugs into the systemic circulation. Local administration of drugs in the workplace is a form of treatment that reduces the dose required to achieve pharmacological effects and minimizes side effects. In addition, advances in the optimization of ocular drug delivery systems are such that the pathways are associated with highly sophisticated drug delivery techniques (Yuniarsih et al., 2023).

Eye drops are a common preparation used to treat the eye. Eye drops are used to treat anterior segment diseases, such as infections, inflammatory conditions and glaucoma. Physicochemical attributes such as particle size and particle size distribution, in particular, are two dominant factors that influence drug absorption and the extent to which the active pharmaceutical ingredient (API) reaches the intended eye segment. For example, more dilute formulations may drain from theeye before being absorbed, reducing bioavailability to as little as 5%. As the particle size decreases, particle–particle interactions increase, leading to increased flow resistance or viscosity. Similarly, when similar-sized particles are combined to create a homogeneous and narrow particle size distribution, the viscosity usually increases. Owing to these properties, API and/or emulsion drop sizes are often manipulated to smaller particle sizes to improve bioavailability. Nonetheless, the bioavailability of ophthalmic drugs after eye drop administration in rabbits is limited to less than 5% of the dripped dose, often less than 1%. There are several influencing factors, namely, the corneal epithelial permeation barrier, rapid drainage of the dripped drug from the ocular surface, the blink rate and drainage of the solution from the ocular surface are also rapid, and the tight corneal barrier of the eye indicates low ocular bioavailability and effective transconjunctival absorption of the drug into the systemic blood circulation.

Ophthalmic drug administration methods are divided into topical, local, and systemic methods. Topical drug delivery methods include solutions, suspensions, ointments and gels. Local eye medications can be administered through periocular and intraocular injections. Periocular injections include subconjunctival, subtenon, and retrobulbar injections. Intraocular injections are via intracameral injection in the front eye chamber and via intravitreal injection in the vitreous cavity. Systemic ophthalmic medications are administered viaoral and intravenous routes (Souza et al., 2014).

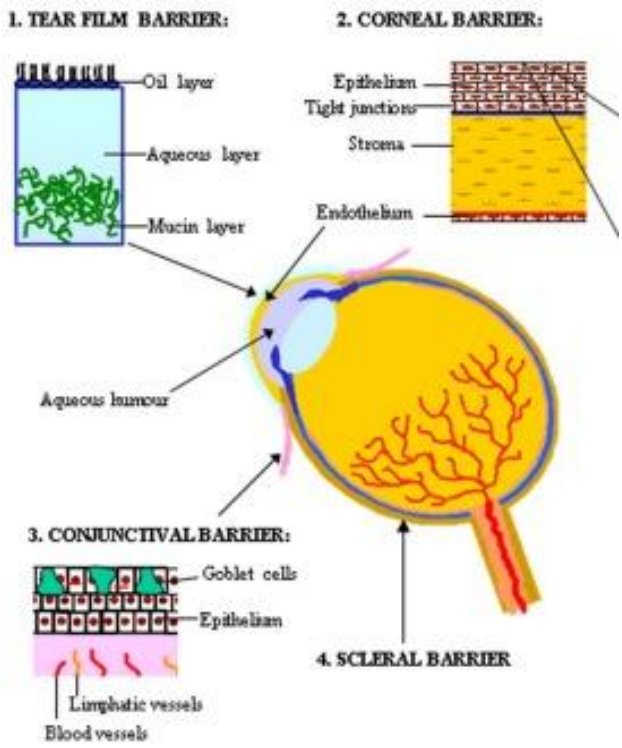

Figure 1 Anatomical blades of the eye. *Source:* de la Fuente et al., (2010).

A previous study (Santonocito et al., 2022) revealed that the natural compound mangiferin has anti-inflammatory and antioxidant activities and has potential for eye treatment. Owing to the poor physicochemical features of low solubility and high instability of mangiferin, it can be nanoencapsulated into a nanostructured lipid carrier, increasing its ocular bioavailability. In another study conducted by(Vo et al., 2020), a suspension-based topical preparation or gel was used in situ for the eye. The use of topical eye drops is the most common form used for eye care; however, in this form, there are challenges, namely, the continuous secretion of tears can cause the drug to dissolve with eye fluid very quickly. Therefore, various formulation strategies have been investigated to improve ocular drug retention, including in situ gel formation with addedviscosity and mucoadhesives (Ainurofiq, et al., 2023c). Ophthalmic medicinal products such as ointments, emulsions and suspensions are often used to prolong drug retention on the corneal surface. Suspensions are a popular choice for ophthalmic formulations containing poorly soluble active pharmaceutical ingredients (APIs). This dosage improves drug delivery by extending the residence time of the drug in the eye. As a suspension, API particles tend to stay in the cul de sac of the eye (conjunctiva between the sclera and eyelid) and dissolve gradually over a longer period of time, resulting in increased ocular bioavailability. Particle size is an important attribute of ophthalmic suspensions that affects the physical stability of the dosage form and treatment efficiency. The particle size ofophthalmic suspensions usually does not exceed 25 µm to avoid eye irritation (Uddin et al., 2017).

Although not commonly used, the literature suggests that nanosuspensions can improve the ocular bioavailability of dosage forms. Drug particles can be generated through bottom-up (e.g., precipitation of supersaturated solutions) or top-down approaches.) In general, the appropriate particle size and extentof distribution vary on the basis of the scale of the process, choice of size reduction method, energy input, processing time, etc., and require thorough evaluation during product development. In this study, several ways to modify the particle size of the active ingredients to achieve their effectiveness are discussed, and the results indicate that centrifugal planetary milling was found to be capable of producing the desired average particle size with distribution simply by optimizing process parameters such as bead size, milling speed and milling time. Regression equations were developed to relate these process parameters and to predict the desired particle size. These equations can be used to guide the optimization of the suspension process with a predetermined PSD.

Research conducted by (Toropainen et al., 2021) on ophthalmic topical suspension biopharmaceuticals involving indomethacin revealed that particle size plays an important role in drug absorption in the eye. Smaller particles have a greater surface-to-volume ratio, which increases the rate of drug dissolution. Consequently, compared with larger particles (3.12–3.50 µm), smaller particles (approximately 0.37–1.33 µm in diameter) enhance the absorption of indomethacin in rabbit aquatic humor. Smaller particles, although more rapidly eliminated from the tear fluid, resulted in higher concentrations of indomethacin in the cornea and aquatic humor. In contrast, larger particles had a greater AUC in tear fluid but lower absorption into the eye, indicating that small particles are more effective in increasing ocular bioavailability.

Particle distribution can also influence ophthalmic liposome delivery system technology. Research has been conducted by (Ferreira et al., 2018), namely, the ocular delivery of moxifloxacin-loaded liposomes. This study discusses the formulation of moxifloxacin in a liposome preparation that is given via the intracameral route through the eye. Moxifloxacin is often used as an intraocular ophthalmic drug to prevent these infections, but the limitation of aqueous humor (AH) turnover reduces its effectiveness. Therefore, liposomes have been proposed as a drug delivery system that can prolong the availability of moxifloxacin in the eye (Figure 2). The liposomes were prepared via the lipid layer hydration method, resulting in particles with an average size of 60.5 ± 0.72 nm. These preparations were then injected intracamerally (into the anterior chamber of the eye) into rabbits to study the drug release profile of moxifloxacin in the aqueous humor of the eye. The liposomal formulation was found to be stable and homogeneous. The size distribution and polydispersity index of liposomal vesicles are important parameters that indicate the uniformity and homogeneity of the formulation. In addition, these parameters can affect drug loading, release and bioavailability distribution. The liposomal formulations used for intraocular administration have average diameters of 100 to 400 nm. In this study, the particle size of the liposomes was very small, at 60.5 ± 0.72 nm.

In this study, the particle distribution in an ophthalmic liposome preparation containing moxifloxacin played an important role in the effectiveness of drug release. The liposomes had an average size of approximately 60.5 ± 0.72 nm with a polydispersity index of 0.307, indicating a relatively uniform particle size distribution and good formulation stability. The homogeneity of the particle size improved the encapsulation efficiency of moxifloxacin, which was 92.24%.

A uniform particle size distribution helps maintain more consistent drug release, which is crucial in intraocular applications. In addition, the small size of the liposomes allows for effective penetration and distribution within the eye while lowering the chances of ocular complications. This distribution also impacts the drug release profile, where rapid release occurs within the first 2 hours after application, followed by a gradual decrease in concentration for up to 24 hours. This favorable particle distribution enables controlled and efficient drug release, which is expected to increase the bioavailability of moxifloxacin in the targeted eye area.

5. Particle Size Distribution In Topical and Transdermal Drug Delivery

A delivery system called the transdermal drug delivery system (TDDS) is a system that can be used to control drug release on the basis of usage restrictions. TDDS methods are popular in the field of oral and postinjection pharmaceuticals

because they are noninvasive and easy to use. Through this route, drugs can escape the digestive environment, including enzymes, pH, and drug–food interactions that interfere with drug efficacy, and avoid the "first effect" through the liver. TDDS helps reduce fluctuationsin blood concentrations of drugs or active substances, resulting in more stable plasma levels and a lower risk of overdose (Zhou et al., 2018). This noninvasive method of administration also causes minimal painful effects on patients so that drugs can be administered safely and comfortably to children or the elderly (Jeong et al., 2021).

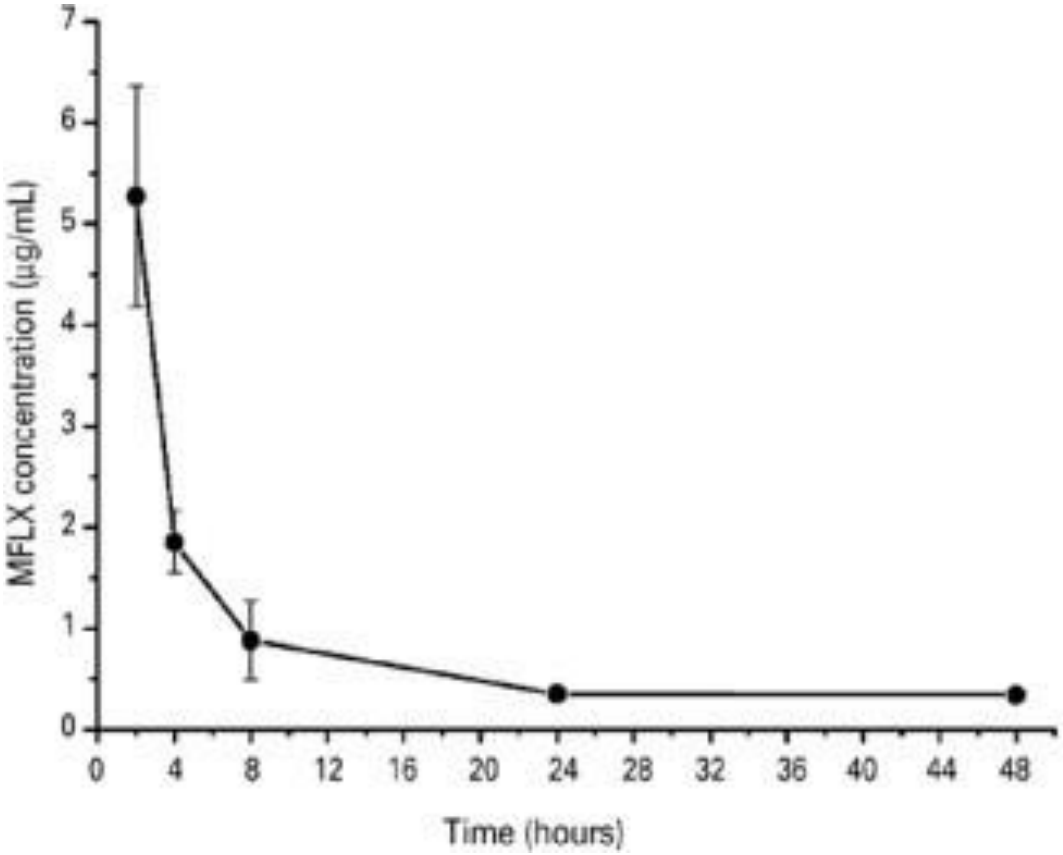

Figure 2 Concentration release graph of moxifloxacin encapsulated in liposomes in aqueous humor (AH) samples. *Source:* Ferreira et al., (2018).

Drug absorption through the skin can occur through two main pathways, namely, transepidermal and transappendage. The transepidermal pathway is the main pathway and can be further divided into two subpathways, namely, transcellular and intercellular.In the transcellular pathway, the drug diffuses through the cells of the stratum corneum, which requires the drug to pass through a membrane consisting of a lipid bilayer. This pathway is generally activated by hydrophobic drugs due to the hydrophobic nature of the lipid complex in the cell membrane of the stratum corneum. In contrast, the intercellular pathway involves drug diffusion through the lipid matrix between the cells of thestratum corneum. This pathway is more predominant for drug absorption and relies on a specific balance of drug molecules to be sufficiently soluble in lipids and water. The second pathway is transappendageal; this pathway involves drug delivery through hair follicles or sweat glands in the skin. This pathway is important for the transport of polar or ionized compounds and is useful for large macromolecules that are difficult to pass through epidermal cells because of their different molecular sizes and partitioning properties. However, the use of this pathway is limited by the smaller absorption area than that of the transepidermal pathway (Ramadon et al., 2022).

The particle size and particle size distribution influence the physical appearance of creams, ointments, and pastes (Hussein et al., n.d.). In addition, careful selection of particle size in topical formulations can minimize the potential for adverse systemic reactions while optimizing local efficacy within the skin area. Particle size is an important flux regulator if the drug is suspended in a carrier, such as a cream or gel, because it will interact with the solubility of the carrier to determine the dissolution rate. Particle size measurement can facilitate drug delivery in cases where the drug is poorly soluble in the medium by accelerating the dissolution rate of the particles. Skin penetration pathways are also significantly affected by particle size, with particles >10 µm remaining on the skin surface; particles between 3–10 µm concentrated in hair follicles; and particles <3 µm having the ability to penetrate the stratum corneum and follicles. The follicular route accounts for most of the percutaneous absorption of particles smaller than 3 µm, including nanoparticles. Follicular localization is the method by which polymeric polystyrene nanoparticles (20 and 200 nm) penetrate the skin, but there is no alternative nonfollicular penetration pathway(Shekunov et al., 2007).

One of the major challenges in designing topical drug products is achieving adequate drug penetration through the skin. The stratum corneum, epidermis, dermis,and hypodermis constitute most of the skin. The stratum corneum layer allows only small molecules (<500 Da) and molecules that are sufficiently lipophilic(log P 1--3) to penetrate. Owing to the presence of such a barrier layer, the penetration of poorly soluble drugs into the skin is hindered. Various techniques, including chemical penetration enhancers and physical techniques such as electroporation, iontophoresis, and sonophoresis, have been used to improve skin permeability. Nanocarrier-based topical formulations, such as nanoemulsions, lipid nanoparticles (NPs), polymeric NPs, and solid lipid NPs, have been used in recent years for transdermal delivery of insoluble drugs(Xiang et al., 2022). Zhou et al., (2018) described the classification and implementation of nanoformulations for transdermal delivery as follows:

5.1. Vesicles

Particles that are colloidal and filled with water are called vesicles. The walls of these capsules are made of amphiphilic molecules arranged in a bilayer structure. These amphiphilic molecules create one (unilamellar vesicle) or many (multilamellar vesicle) concentric bilayers when excess water is present. Water-soluble and fat-soluble drugs can be carried through vesicles to facilitate transdermal absorption, with the aim of enhancing the penetration function of the constituents. Vesicles can be used for drug storage to enhance sustained release when applied topically. Vesicles can control the rate of TDDS absorption by manipulating the multilayered structure (Zhou et al., 2018).

5.2. Liposomes

Coiled soft matter vesicles known as liposomes are created when one or more bilayer membranes are used to separate an aqueous medium from another. Usually, phospholipids—with or without cholesterol—formtheir main constituents. Two hydrophobic hydrocarbon chains and several polar head groups make up the bulk of a phospholipid molecule. The polar groups are potentially negatively charged or zwitterionic. The molecular length of the hydrocarbon chains and their degree of unsaturation vary. When dry lipid sheets are reconstituted in an aqueous solution, liposomes are naturally formed (Mezei & Gulasekharam, 1980). The unique structure of liposomes allows them to encapsulate water-soluble and fat-soluble compounds while maintaining their hydrophilicity and hydrophobicity (Eloy et al., 2014).

5.3. Transfersomes

Transfersomes are another name for elastic, highly flexible, or soft liposomes (Zhou et al., 2018). The elasticity caused by the addition of single-chain surfactants—also referred to as edge activators—such as sodium cholate, Tween®, Span®, polysorbic acid, and dipotassium glycyrrhizinate, is the most significant characteristic of vesicles. These surfactants give vesicles enormous deformation capabilities by weakening the phospholipid bilayer (Ashtikar et al., 2016; Honeywell-Nguyen & Bouwstra, 2005). The relative molecular mass limit of drugs that penetrate the skin can now reach up to 1 million owing to the invention of transfersomes, which have the potential to deform and enter through skin pores that are 5–10 times smaller than their own size. In addition, this enables the use of TDDSs to distribute macromolecular drugs such as proteins or peptides (Aggarwal & Goindi, 2012).

5.4. Ethosomes

Ethosomes are vesicles composed of phospholipids, alcohol and water. Ethosomes differ from liposomes in that they contain more alcohol. The flexibility and fluidity of ethosomes increase when alcohol molecules replace water molecules near the head of the lipid layer. Drug release can be delayed by etherosomes because the particle size is small, the structure is stable, and the binding efficiency is excellent (Mbah et al., 2014).

5.5. Niosomes

Niosomes, also known as nonionic surfactant-based elastic vesicles, are molecular clusters formed when nonionic surfactants self-associate in the aqueous phase. Cholesterol or its derivatives are also often present in these clusters (Moghassemi & Hadjizadeh, 2014). These are second-generation elastic vesicles that fall into three sizes, namely, multilamellar vesicles (MLVs), which include several double layers; small unilamellar vesicles (SUVs) (10–100 nm); and large unilamellar vesicles (LUVs) (100–3000 nm) (Kaur et al., 2004). Proniosomes (Ahmad et al., 2017), surfactant ethosomes (Meng et al., 2013), elastic niosomes (Manosroi et al., 2013), polyhedral niosomes Arunothayanun et al., 2010), discomes (disk-shaped vesicles) (Abdelkader et al., 2012), and aspasomes (ascorbyl palmitate vesicles) (Ghosh et al., 2018) are examples of niosomes that do not take size into account. Simvastatin-loaded niosomal gels were made by (Zidan et al., 2016) to increase their hypolipidemic effectiveness. When compared to oral drug suspension, the transdermal niosomal preparations of simvastatin increased its bioavailability by almost three times, according to in vivo pharmacokinetic studies conducted on rats. An examination of the accompanying hypolipidemic effects demonstrated a notable increase in biological activity, which corroborated the results. Because of this, simvastatin niosomal gels may be a promising treatment for TDDS, especially for children with hyperlipidemia.

5.6. Invasomes

The components of invasomes include phosphatidylcholine (also known as soy-phosphatidylcholine or lysophosphatidylcholine), ethanol, and a combination of terpenes (Dragicevic-Curic et al., 2009). Soy-phosphatidylcholine forms the invasomal bilayer matrix, whereas lysophosphatidylcholine acts as an edge activator that provides flexibility to the phosphatidylcholine bilayer. Terpenes and ethanol both enhance drug penetration while increasing the flexibility (Shah et al., 2015) of the phospholipid bilayer. Invasomes are effective drug delivery vehicles for both lipophilic and hydrophilic substances (Dragicevic-Curic et al., 2009; Dwivedi et al., 2017). A new vesicular nano-invasome carrying an anti-hypertensive drug was developed, improved, and tested for transdermal potential. Using a rat model, they contrasted an invasomal gel containing olmesartan with BENICAR®, a commercially available tablet formulation of the drug. The pharmacokinetic analysis showed that the transdermal nano-invasome formulation increased the bioavailability of olmesartan in Wistar rats 1.15 times more than the control formulation (Kamran et al., 2016).

5.7. Nanoparticles

The term 'nanomaterial' or 'nanoscale' refers to objects with sizes in the range of 1–100 nm. However, particles measuring 1–1000 nm have been approved for use as nanocarriers. When a drug is administered as a nanoparticle, it can exert a targeted and controlled release effect, change the dynamics of the drug in vivo, and prolong the duration of the drug being in the blood, all of which can increase the bioavailability of the drug, reduce its toxic profile and side effects, and improve its efficacy (Zhou et al., 2018).

5.8. Lipid nanocarriers

Lipid nanocarrier drug delivery systems use lipids as carriers or substances (Pardeike et al., 2009). The earliest lipid nanocarriers were liposomes and later evolved into solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and certain polymeric nanoparticles made from a combination of lipids (Teixeira et al., 2017). Membrane formation on the skin surface occurs when lipid nanoparticles attach to the skin surface and accumulate there. The particles then coalesce and deform as a result of capillary action. This membrane improves skin penetration by reducing moisture loss on the skin surface and increasing skin hydration. Lipid nanocarriers also improve drug stability and encapsulation (Siafaka et al., 2015).

5.9. Solid lipid nanoparticles (SLNs)

After the development of polymeric nanoparticles, liposomes, and microemulsions, the first lipid nanoparticle drug delivery system introduced was solid lipid nanoparticles (Wissing et al., 2004). This system is a lipid or lipid mixture with good physiological compatibility and remains in solid form at room temperature or body temperature. Solid lipid nanoparticles adsorb on the particlesurface or encapsulate the drug in a lipid core with an average diameter of <1000 nm (Winter et al., 2016). In the formulation of solid lipid nanoparticles, emulsifiers, coemulsifiers, and water are also frequently used as excipients. Like traditional liposomes, solid lipid nanoparticles are safe, exhibit biocompatibility and have stability comparable to that of polymer nanoparticles (J. Sun et al., 2016). In order to enhance the safety and permeability of aconitine, (Zhang et al., 2015) created SLN, an oil-in-water microemulsion, for transdermal administration. When compared to an ethanol tincture, the evaluated SLN formulations produced better transdermal fluxes and drug deposition in skin in vitro, and their drug encapsulation efficiencies above 85%.

5.10. Nanostructured lipid carriers (NLCs)

Nanostructured lipid carriers have an internal structure that is different from that of solid lipid nanoparticles. In addition to solid lipids, a certain amount of oil—usually up to 30%—is present in the structure of nanostructured lipid carriers (Doktorovova & Souto, 2009). By reducing the densityof keratinocytes and enlarging the interkeratinocyte gap, nanostructured lipid carriers attached to the skin surface increase skin moisture and facilitate drug deposition (Aliasgharlou et al., 2016). Compared with solid lipid nanoparticles, this system can reduce drug leakage during storage and improve drug encapsulation and the drug loading rate. Nanostructured lipid carriers are suitable for long-term administration to the skin because of their chemical similarity to skin lipids, the presence of a solid matrix, the highly specific surface area associated with the nanoscale size, and their biocompatibility (Aliasgharlou et al., 2016).

5.11. Polymeric nanoparticles (NPs)

Polymeric nanoparticles, whose sizes range from 10 nm to 1000 nm, are solid colloidal carriers made of a polymer matrix that resembles synthetic, semisynthetic, or natural polymers (Vrignaud et al., 2011). This form of formulation can protect unstable drugs from degradation and denaturation, release them continuously to reduce the side effects of toxic drugs, and increase the concentration gradient to improve percutaneous drug permeation (Zhu et al., 2017). Polymeric nanoparticles can be categorized as polymeric micelles, nanospheres, or nanocapsules on the basis of their architecture and preparation methods

(Santos et al., 2008). To improve the material's absorption into the skin, (Shetty et al., 2015). created innovative sunscreen lotions with polymeric NP of morin, a significant plant flavonoid with antioxidant and UVR protective qualities. After 12 hours, a significantly greater amount of morin had permeated from the nanoparticulate suspension than had been seen with the morin plain suspension.

5.12. Nanoemulsion (NE)

Nanoemulsions are low-viscosity mixtures that are isotropic, thermodynamically stable, kinetically stable, and thermodynamically stable (i.e., they do not appear to agglomerate or coalesce during long-term storage). A very thin droplet-sized layer of surfactant or cosurfactant molecules stabilizes the combination of transparent or translucent oil globules dispersed in the aqueous phase (the average droplet diameter achieved is often <500 nm). The particle size of nanoemulsions has long been a subject of discussion, but the suggested upper limits are 1000 nm, 500 nm, 200 nm, and 100 nm. Although the droplet size range, content, and appearance of nanoemulsions are almost identical to those of microemulsions, their structural features and long-term thermodynamic stability are quite different (Zhou et al., 2018).

The large specific surface area, low surface tension, and small particle size of the nanoemulsion provide good wetting power, which allows it to remain in close contact with the skin. In addition, nanoemulsions have a longer shelf life, greater solubilization ability, physical stability, better bioavailability, ease of preparation, and lower energy input during production. Compared with other common topical skin preparations, nanoemulsions have a shorter transdermal duration and a superior percutaneous absorption effect. Three types of nanoemulsions can be distinguished on the basis of their constituent parts: bicontinuous emulsions (microdomains of the oil and water phases mutuallydispersed in the system), water-in-oil emulsions (W/O: water phase dispersed in a continuous oil phase), and oil-in-water emulsions (O/W: oil phase dispersed in a continuouswater phase) (Zhou et al., 2018).

Nanoliposomes (lipid nanovesicles or nanometric versions of liposomes) are colloidal nanostructured systems consisting of a lipid/phospholipid bilayer. The particle size distribution and polydispersity index (PDI) of lipid-based nanocarriers are important physical characteristics to consider, as they can affect bulk properties, productperformance, processability, stability, and product appearance. Determination of the average diameter and size distribution of lipid nanocarriers are also fundamental quality control tests for a product. In general, vesicles with a diameter ≥600 nm are not able to deliver the encapsulated material to the deeper layers of the skin, as they tend to remain in or above the stratum corneum and may form a lipid film on the skin after drying. Nanovesicles with a diameter of ≤300 nm are able to deliver their contents to some extent into deeper layers of the skin. However, nanovesicles with diameters ≤70 nm show maximum deposition of contents in the living layers of the dermis and epidermis. NPs smaller than 6–7 nm can be absorbed through transepidermal lipids, whereas NPs smaller than 36 nm can be absorbed by aqueous pores. Nevertheless, particles between 10 and 210 nm in size prefer to penetrate thetransfollicular pathway (Danaei et al., 2018).

Microemulsions are prepared on the basis of their low interfacial tension. Lowinterfacial tension is achieved by the addition of a cosurfactant to form a thermodynamically stable microemulsion. As transparent liquids, microemulsions have very small droplets in their dispersed phase, i.e., those less than 200 nm in diameter. The preparation of itraconazole microemulsion-based gels for transdermal administration resulted in droplet sizes ranging from 19–100 nm, which corresponds to the droplet size distribution measured via photon correlation spectroscopy. The average droplet size ofthe microemulsion was 78.03±2.36 nm, with a low polydispersity indexvalue of 0.392, indicating the uniformity of droplet size in the microemulsion formulation (Figure 3) (Chudasama et al., 2011).

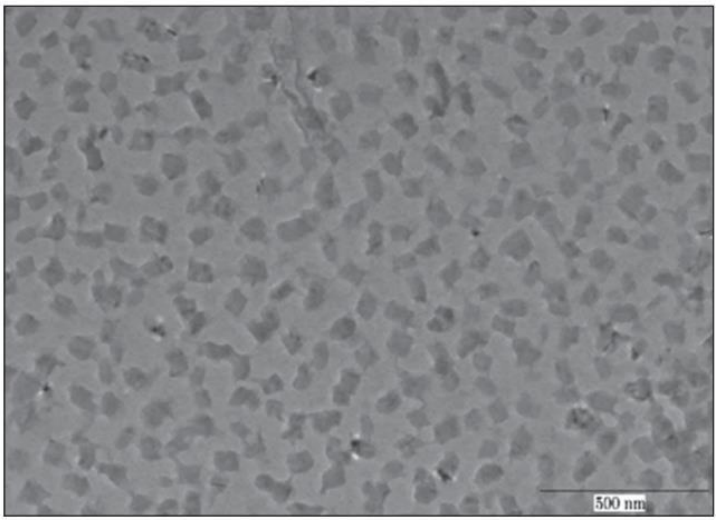

Figure 3 Transmission electron microscopy (TEM)-positive image of the itraconazole microemulsion. *Source:* Chudasama et al., (2011).

Agboola et al., (2023) developed a semisolid formulation in the form of (micro)emulsion-based gel (MEG) containing ibuprofen and its derivatives, namely, sodium ibuprofenate (IBUNa) and L-phenylalanine ethyl ester of ibuprofenate ([PheOEt][IBU]) (Figure 4). Particle size analysis was performed via Mastersizer 3000 laser diffraction, and the results are presented as a single curve as the volume fraction (%). The study revealed that MEGs with and without an API had very small globule sizes. Moreover, the addition of IBU, IBUNa, or [PheOEt][IBU] affects the size and distribution of droplets or particles in emulsion-based gels, which indicates a narrower size distribution because the droplets or particles tend not to aggregate and form larger sizes.

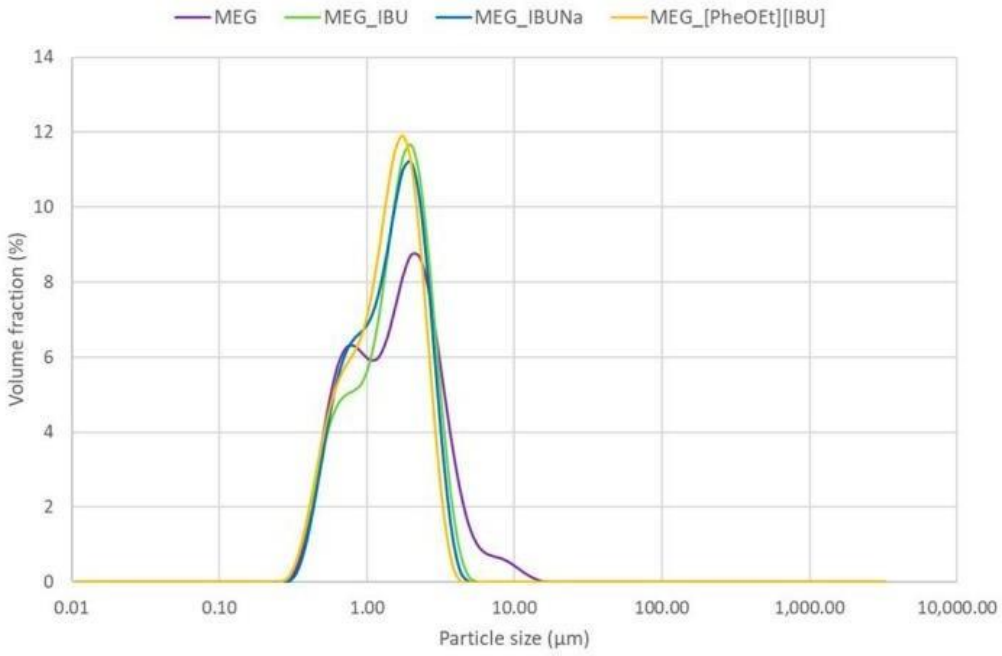

Figure 4 The MEG_[PheOEt][IBU], MEG_IBU, and MEG_IBUNa particle size profiles. *Source:* Agboola et al., (2023).

This study suggests that structural modifications to active ingredients and careful selection of formulation bases can regulate the permeability of active chemical substances through the skin.

Research by (Parveen et al., 2023) discussed the development of chaulmoogra oil-loaded solid lipid nanoparticle (SLN)-based gels. The average particle size and polydispersity index (PDI) of various SLN formulations were measured via photon correlation spectroscopy. The results showed that the average particle size varies depending on the concentration of Tween 80 as a surfactant and PVA as a stabilizer used in the formulation. Formulations with lower concentrations of Tween 80 resulted in smaller average particle sizes and more uniform particle size distributions, as indicated by lower PDI values. When the polydispersity value is lower, the particle size distributionis lower, and the particle size uniformity is greater. Furthermore, this developed SLN formulation had the highest cumulative release percentage of 80.89% in the in vitro study and showed a sustained release pattern, making it suitable for improving patient compliance.

Research by (Runnsjö et al., 2022) revealed that micronization of particles <10 µm in size, accompanied by optimization of formulation compatibility via the use of sebum in thedelivery of the pharmaceutical peptide FOL-005 into the skin, can improve follicular permeability and peptide dissolution after skin contact. Micronization was performed via the wet-milling technique, and the particle size was measured via a Malvern Mastersizer 2000 (Figure 5). The penetration and distribution test results revealed that all the tested FOL-005 formulations were able to penetrate the stratum corneum barrier, although with numerical differences.

Şenyiğit et al., (2016) formulated clobetasol propionate (CP)-loaded lecithin/chitosan nanoparticles and incorporated them into a chitosan gel for topical application (CP 0.005%). This study characterized the particle size via two methods, namely, dynamic light scattering (DLS) and scanning electron microscopy (SEM). The average particle size obtained via DLS was 248 ± 15 nm, whereas SEM revealed particles 100–150 nm in diameter with a rigid shell surface (Figure 6). The difference in the SEM and DLS measurement results can be attributed to the fact that DLS measures the hydrodynamic diameter on the basis of the diffusion coefficient of the nanoparticles, thus also considering the hydration layer surrounding the particles.

Xiang et al., (2022) explored CUR-NCs (curcumin nanocrystals) with sizes of 60, 120, and 480 nm that were incorporated into hyaluronic acid (HA) MNs through topical drug delivery (Figure 7). Three particle sizes of CUR-NCs were prepared via the antisolvent precipitation method, and the size of the CUR-NCs embedded on the tips of the MNs was analyzed via Nano Measure software. The study revealed that 60-nm CUR-NCs permeated the skin layer faster and accumulated in hair follicles.

The smaller the size of the nanocrystals was, the greater the concentration gradient formed and the faster and deeper the drug diffusion, which further improved the drug distribution.

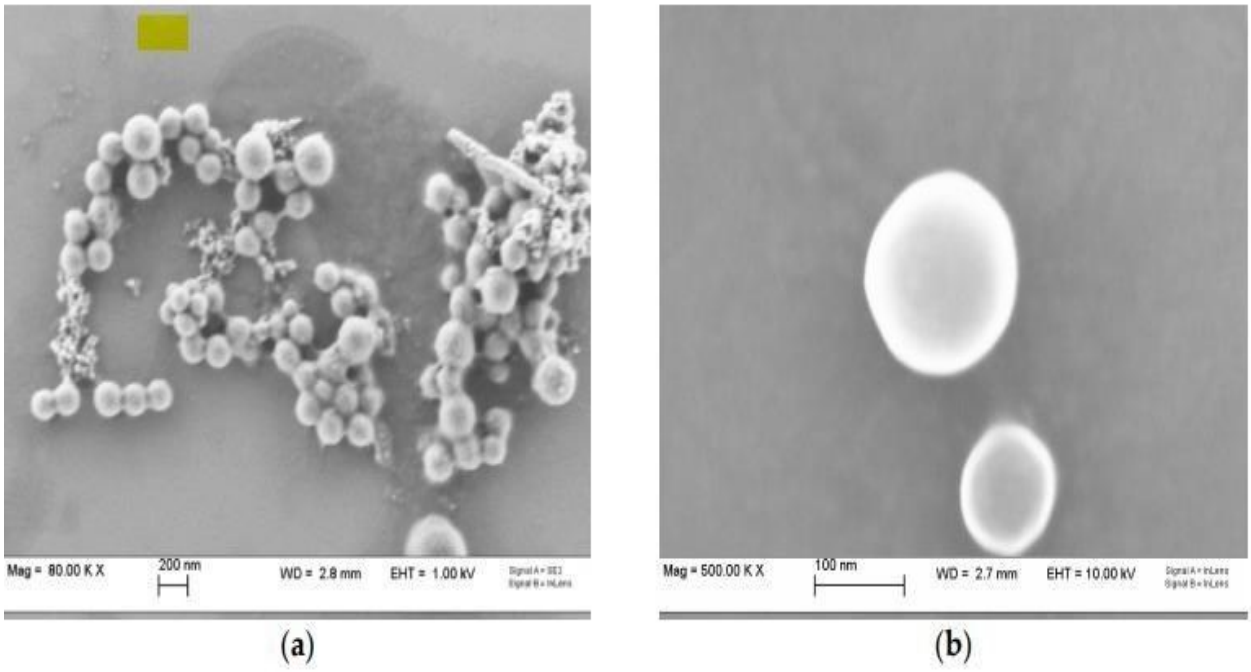

Figure 5 PSD measured with a Malvern Mastersizer 2000 before and after wet milling. *Source:* Runnsjö et al., (2022).

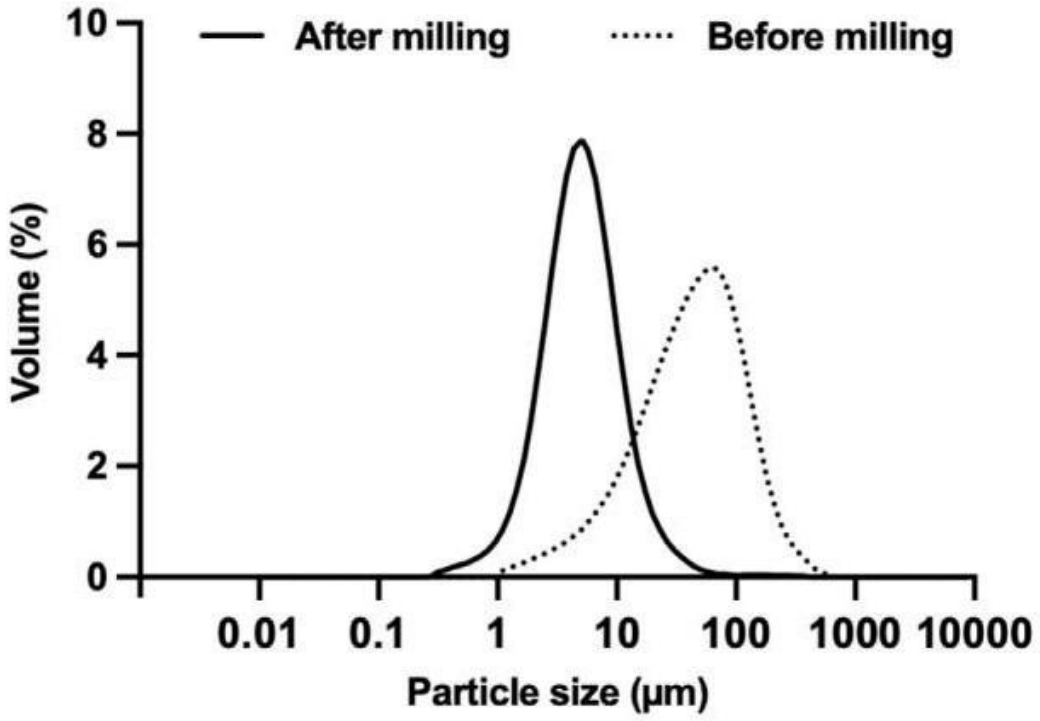

Figure 6 Scanning electron microscopy (SEM) images showing the chitosan/lecithin nanoparticles at two different magnifications: 80 K× (a) and 500 K× (b). *Source:* Şenyiğit et al., (2016).

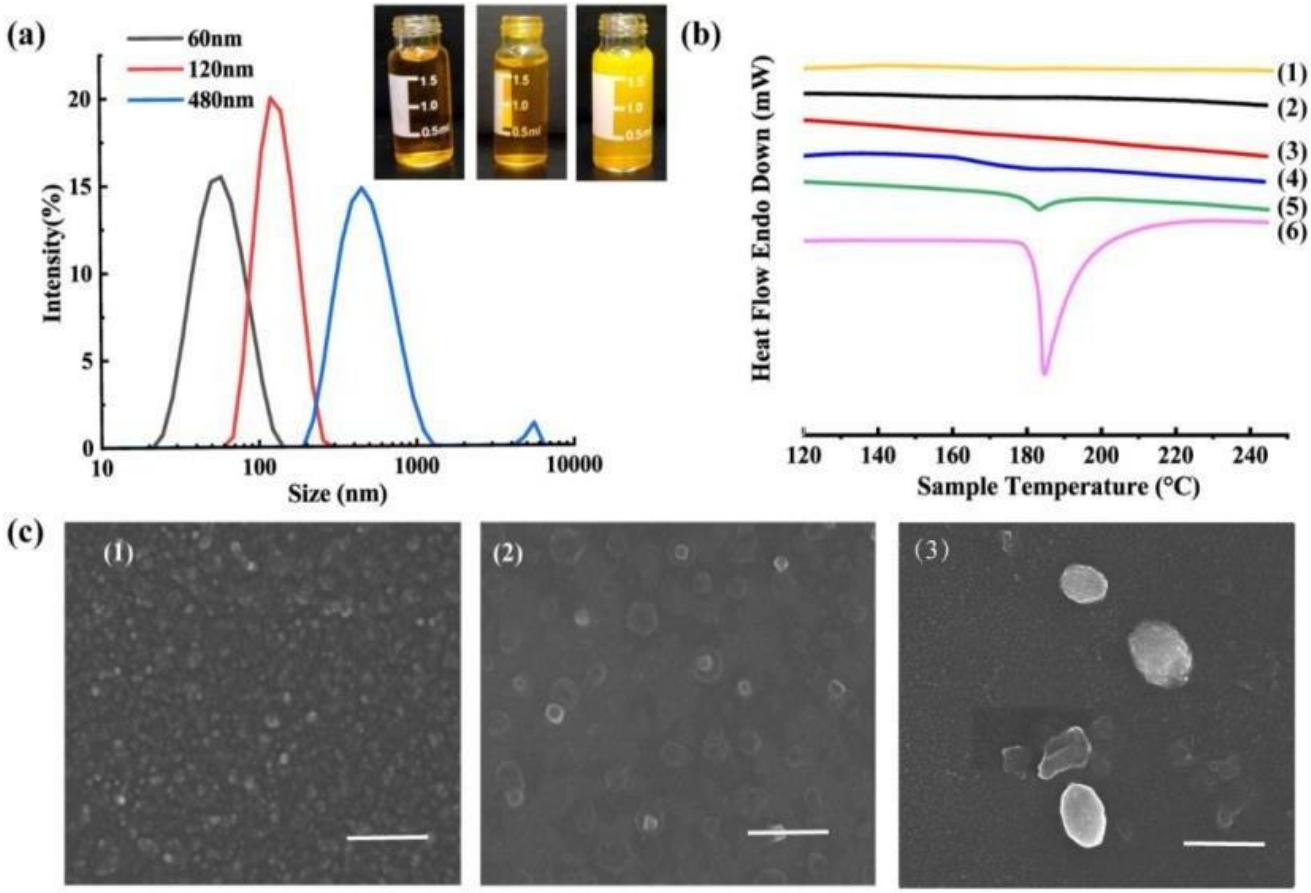

Figure 7 (a) Size distribution and photographs of three CUR-NC suspensions; (b) DSC profiles; (c) SEM morphologies of 60-nm CUR-NCs (1), 120-nm CUR-NCs (2), and 480-nm CUR-NCs (3) (scale: 500 nm). *Source:* Xiang et al., (2022).

6. Particle Size Distribution in Parenteral Drug Delivery

Over the years, the presence of particles in parenteral drugs has been a persistent problem and an intense topic of conversation within global regulatory bodies and the pharmaceutical industry. The latest state-of-the-art manufacturing capabilities cannot guarantee the absence of particles. This is true with today's well-controlled manufacturing processes and well-regulated and practiced particle detection technologies through 100% inspection programs. Particles in parenteral drugs can be caused by the manufacturing process and manufacturing environment (design, qualification, validation, and execution), as well as postproduction care, storage conditions, transportation, and end-user care. The particle occurrence can also be affected by the formulation properties. In addition, as drug parenteral container closure systems become more complex, techniques to identify visible materials may be more difficult than when drug parenterals are packaged in simple glass vials.

According to USP, EP, and JP, particles in parenteral injections and infusions consist of insoluble and mobile foreign particles and gas bubbles that occur accidentally in the solution (Bukofzer et al., 2015). Particles can be classified differently on the basis of their source or size. Particles can be categorized as inherent, intrinsic, or extrinsic depending on their source. Small particles that are common to certain high-concentration protein formulations (such as human serum albumin as an excipient,therapeutic proteins, etc.) and other common delivery forms (such as emulsions, lipids, etc.) are known as inherent particles. Therapeutic proteins are the most obvious exampleof inherent particles. Source-derived particles that are generated through formulation, packaging, or assembly processes.

Parenteral drug delivery, which includes methods such as intravenous, intramuscular, and subcutaneous administration, is essential in modern medicine because of its rapid onset of action and avoidance of first-pass metabolism. One important factor that affects the efficacy, safety, and stability of parenteral formulations is the particle size distribution (PSD). Particle size in parenteral formulations plays an important role in thebioavailability, therapeutic response, and immunogenicity of drugs.

Understanding PSD is critical for ensuring consistent drug performance, patient safety, and regulatory compliance. The particle size in parenteral formulations affects various properties, including drug solubility, stability and bioavailability. Smaller particles often dissolve faster and provide better bioavailability, whereas larger particles can cause side effects such as embolism or irritation at the injection site. Particle size analysis usually focuses on detecting particle contamination. Possible

causes of particle contamination are exposure of the drug by foreign substances or formulation incompatibility. Contamination of these particles can lead to blockage of blood vessels and pulmonary embolism and, at the same time, mustbe strictly controlled. For safety reasons, the particle size range (>1 μm) should be excluded from IV nanosuspension formulations. Not only will the particle size increase, but the injectability and injectability may also decrease.

Particle contamination of drug parenteral preparations is considered an indicator of overall product quality, as it can affect patient safety and product benefits. This is because particles are unintended and technically unavoidable contaminants. In 2014, the US FDA reported that 16 injectable parenteral drugs were recalled due to particle contamination. Particle occurrence is one of the most common causes of drug parenteral deficiencies. Owing to their significant effects, the US FDA has authorized the distribution of drugs containing particles found during inspection, with the requirement of using filters before administration to avoid exposing patients to particles. In general, these particles are nonreactive and inert to parenteral drugs in nature and are expected to have a lower risk of not reacting, adding, or absorbing. Glass particles are one example of intrinsic particles. Extrinsic particles can also be defined as particles that enter the container or solution during the production process; alternatively, they can be considered additive, extraneous, and immutable particles that are not included in the formulation, packaging, or assembly process. Flakes of clothing or skin are examples of extrinsic particles. Compared with intrinsic or intrinsic particles, these particles may be more vulnerable.

The particle size should be smaller than the inner diameter of the needle, as needle blockage can occur through single particle blockage or cross-linking of multiple particles. Parenteral suspensions are directly related to solute particle size due to their specific surface area, which is important for determining the in vivo drug release pattern. Nanosized particles are important for all IV applications, ID, SC, and IM, as well as the intrathecal delivery of anticancer drugs and many air-insoluble nanosuspensions (cumulative PSD 99%) (Journals & Articles, 2023). Therefore, control of PSD is essential to achieve optimal therapeutic outcomes and avoid complications such as drug aggregation, which can lead to blockage of the circulatory system (Mazaheri et al., 2024).

Animal models have been used to study particle safety after excessive clinical exposure; however, limited data are available for more important clinical exposure scenarios. According to (Barber, 1999), many animal studies have been conducted to study the effects and fate of intravenously administered visible light and SVPs invarious forms. For example, Spasoff conducted research on particles in injections by measuring and classifying particles present in intravenous solutions. They did this via their study of human and rabbit lung tissue taken at autopsy (Spasoff et al., 2018). The results of animal studies have shown that great attention has been given to the safety of patient particles. Many particles were infused in these studies. These observations included histological evidence of injury to lung capillary endothelial cells, microscopic thrombi in lung capillaries, microscopic lung granulomas, and inflammatory effects in the liver (Liu et al., 1992).

The particle size distribution affects several aspects of drug delivery. For example, drugs with a narrow particle size distribution provide a consistent absorption profile, thereby reducing pharmacokinetic variability (F. Liu & Hutchinson, 2024). Conversely, a broad distribution may result in inconsistent drug release, leading to variations in therapeutic efficacy. Interactions between particles and the biological environment, such as uptake by the reticuloendothelial system (RES), also depend on particle size, with larger particles being more likely to be cleared by macrophages (Perez et al., 2018). Various techniques are used to measure PSD in parenteral formulations. These methods include laser diffraction, dynamic light scattering, and microscopy (Borchert et al., 1986). Each method has its own advantages and limitations, with laser diffraction being widely used because of its ability to measure a wide range of particle sizes. The choice of the appropriate technique depends on the type of formulation and the precision needed.

Regulatory agencies, such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), mandate strict controls on size particles in parenteral formulations. These guidelines emphasize that particles larger than 5 microns should be minimized in intravenous formulations to prevent adverse events such as embolism (Sastry, n.d.). Furthermore, the International Council for Harmonization (ICH) guidelines require robust PSD characterization during drug development to ensure interbatch consistency ICH Topic Q 6 A (2000). To achieve an ideal PSD, several size reduction techniques, such as milling, high-pressure homogenization, and ultrasonic emulsification, are commonly used. Nanoparticle technology has attracted attention because of its ability to increase drug solubility andimprove drug delivery through biological barriers (Kesisoglou et al., 2007). These advanced techniques have contributed to the development of more stable and effective parenteral formulations.

7. Conclusion

Particle size distribution (PSD) plays an important role in the effectiveness of drug delivery in various pharmaceutical formulations, including parenteral, ophthalmic, and transdermal formulations. A narrow distribution results in consistent absorption and decreased pharmacokinetic variability, whereas a wider distribution can result in inconsistentdrug release, affecting therapeutic efficacy. By optimizing the particle size according to the type of formulation and intended delivery route, the efficacy, stability, and safety of drug formulations can be improved.

Acknowledgments

We would like to thank Universitas Sebelas Maret for supporting this work.

Ethical Considerations

Not applicable.

Conflict of Interest

All the authors declare that there are no conflicts of interest.

Funding

This research was funded by Universitas Sebelas Maret (Riset Kolaborasi Indonesia (RKI)) No. 590.1/UN27.22/HK.07.00/2023.

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