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Cubosomes in Transdermal Drug Delivery System

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Abstract:

Cubosomes are spherical, cubic particles characterized by an internal cubic lattice. Cubosomes possess an extensive interfacial area and feature two internal aqueous channels divided by honeycombed features. They exhibit thermodynamic stability. The cubic liquid crystalline particles are known as cubosomes. These particles consist of particular surfactants, which have a unique microstructure, making them useful and possessing an ideal water content ratio. The cubic liquid crystalline phase is transparent, highly viscous, and features a distinctive nanoscopic structure. "Bicontinuous" indicates a lipid bilayer assembled in a space-filling system separating two continuously existing but not overlapping aqueous regions. Cubosomes are usually created through hydration of either a polar lipid or a surfactant, generating the cubic phase and dispersing the solid-like phase into tiny particles. From the time of their discovery and naming, cubosomes self-assembled have attracted considerable attention as potent drug delivery systems. They have distinct drug-loading mechanisms and different cubic shapes and composition inside. Their properties include high internal surface area, cubic crystalline structures, lipids' biodegradability, encapsulation of hydrophobic, hydrophilic, and amphiphilic compounds, targeted delivery, and bioactive substance release. Cubosomes can be classified using several evaluation parameters and have broad applications in diverse fields. Cubosomes are consequently garnering heightened interest within the pharmaceutical sector.

Keywords: amphiphilic, hydrophilic, hydrophobic, drug-loading, liquid crystal, cubosomes.

Introduction

Transdermal drug delivery systems (TDDS) represent one of the most significant advancements in contemporary pharmaceutical sciences since they offer a painless and regulated means for introducing the drugs through the skin layer into the bloodstream. The increasing need for a more secure, efficient, and patient-friendly approach to drug administration has led to an increase in scientific studies on transdermal drug administration. Traditional methods of administering drugs like oral and parenteral routes have been known to pose some drawbacks like gastric irritation, enzymatic breakdown, first-pass effect, inconsistent plasma concentrations, and lack of compliance by the patients because of continuous dosing schedules. Transdermal drug delivery systems were introduced to alleviate most of these problems (Pastor et al., 2020).

Skin is the largest organ in the body, acting as an obstacle to prevent harmful contaminants from entering the body, microorganisms from invading it, and ultraviolet rays from damaging it. Although skin acts as an effective barrier, it can serve as a medium for administering drugs under specific conditions. The stratum corneum is the outermost layer of the skin that prevents foreign matter from penetrating into it. Stratum corneum consists of dead keratinized cells in a structured arrangement of lipids. The structure of stratum corneum is typically referred to using the "brick and mortar" analogy, where corneocytes are bricks and intercellular lipids are mortar. Drug molecules applied to the skin surface must penetrate this highly resistant barrier before reaching deeper skin layers and systemic circulation (Benson et al., 2019).

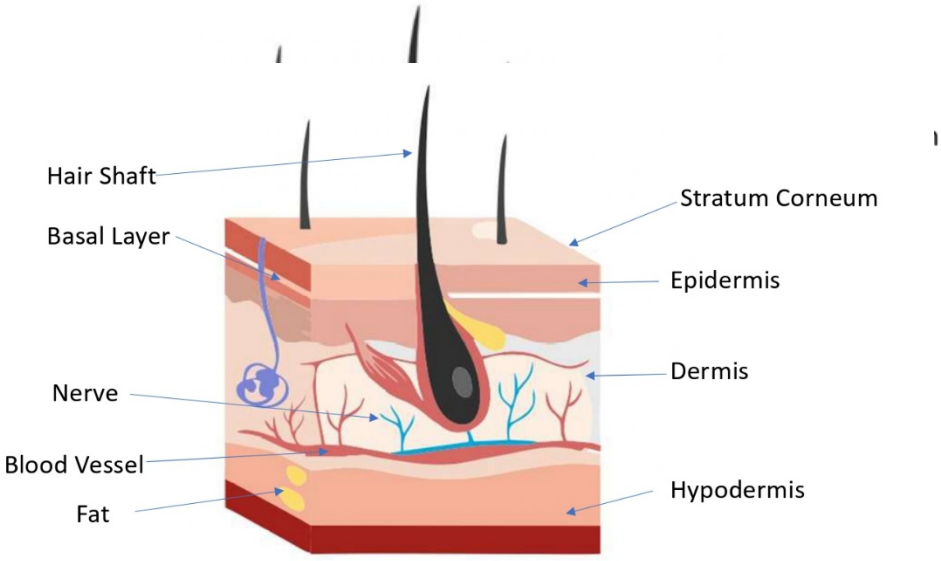

Figure 1 Human Skin and its layers

The anatomy of human skin is very significant for identifying how effective the process of transdermal drug delivery would be. The human skin is composed of three basic layers, which are the epidermis, dermis, and hypodermis. The epidermis is the top layer of the skin and is made up of Stratum corneum, viable epidermis, and basement membrane. On the other hand, the dermis is made up of many blood capillaries, lymph vessels, connective tissues, hair follicles, and sweat glands. Out of these layers, Stratum Corneum is the one through which drug is supposed to pass in order to reach its target destination site. Hence, transdermal drug delivery will be effective only when it passes through this layer. (Nguyen et al., 2018).

Permeation of drugs through the skin is usually through three pathways; the transcellular pathway, the intercellular pathway, and appendageal pathway. In the transcellular pathway, the molecules cross corneocytes and lipid lamellae. Drugs passing through the intercellular pathway have to diffuse through the lipid bilayer surrounding corneocytes, and it is considered that the intercellular pathway is the most efficient route for lipophilic drugs to permeate. The appendageal pathway is the transport of drugs through the sweat glands and hair follicles, and this plays a

very minor role in drug permeation, except for ions, nanoparticles, and macromolecules. (Brown et al., 2017).

The ideal candidate for transdermal delivery would have the optimal physicochemical properties, which allow efficient partitioning into the SC as well as diffusion through aqueous tissue fluids. The general criteria for drug candidates include having molecular weight below 500 Daltons, moderate hydrophobicity, low melting point, and sufficient pharmacological potency. Highly hydrophilic compounds often fail to penetrate the lipid-rich stratum corneum, whereas extremely lipophilic molecules may remain trapped within skin layers. Therefore, successful transdermal therapy requires careful optimization of both drug properties and formulation components (Kumar et al., 2021).

There are various medical and pharmaceutical merits of transdermal drug delivery systems. The first advantage of TDDS is that it enables the maintenance of constant plasma levels of drugs over an extended period of time, thus avoiding any variations in plasma drug levels compared to other methods of administration. In addition, transdermal systems avoid hepatic first-pass metabolism and gastrointestinal degradation, which may significantly improve bioavailability of certain drugs. These systems are non-invasive, painless, and easy to discontinue simply by removing the patch from the skin surface in case of adverse effects or toxicity (Patel et al., 2020).

However, transdermal administration is not without its own drawbacks. The highly impermeable nature of the stratum corneum is a major constraint on the delivery of hydrophilic drugs and large molecules. Only highly potent drugs that require relatively smaller dosages can be administered via this route. Skin irritation, erythema, itching, and sensitization caused by adhesives, excipients, or penetration enhancers may affect patient acceptability. Furthermore, interindividual variations in skin permeability may lead to differences in drug absorption and therapeutic response. But the process of transdermal delivery does come with some limitations. The very high impermeability of the stratum corneum becomes a limitation for the delivery of hydrophilic drugs and molecules of larger molecular weight. Transdermal delivery can only be done with drugs that are very potent in small dosages. (Ita et al., 2017).

Transdermal patches are among the most widely investigated and commercially successful dosage forms used in TDDS. These patches have been developed in such a way that they can stick to the skin and deliver medicines at certain rates for a prolonged period of time. Transdermal patches are usually classified based on their mode of functioning into four types, which are reservoir systems, matrix systems, drug-in-adhesive systems, and microreservoir systems. In the reservoir systems, the medicine is present in a chamber which is surrounded by a rate controlling membrane. Drug-in-adhesive systems integrate the drug within the adhesive layer itself, simplifying patch construction. Microreservoir systems combine characteristics of both matrix and reservoir systems to provide controlled release properties (Bhowmik et al., 2018).

The use of polymers is essential in transdermal patch development, as it controls drug release, strength, flexibility, stability, and adhesive properties. Several natural and synthetic polymers have been investigated for transdermal applications. Some of the most commonly employed polymers include hydroxypropyl methylcellulose, polyvinyl alcohol, ethyl cellulose, carbopol, Eudragit, chitosan, and polyvinyl pyrrolidone. The choice of a suitable polymer is based on its

compatibility with the active pharmaceutical ingredient, film-forming properties, and required release rate. Plasticizers like propylene glycol, glycerol, polyethylene glycol, and dibutyl phthalate may be included to increase flexibility and avoid brittleness of patches (Singh et al., 2018).

The use of penetration enhancers is essential in most transdermal dosage forms due to their ability to facilitate the absorption of drugs across the skin. They temporarily change the skin barrier structure, thus enhancing permeation without causing any permanent skin injuries. Oleic acid, which belongs to the fatty acid family, acts by disrupting the lipid arrangement in the stratum corneum, thus making the membranes more fluid. Alcohol increases the solubility of drugs in the skin. Surfactants interact with both proteins and lipids, thereby increasing permeability. Terpenes obtained from natural essential oils are also widely used due to their effectiveness and relatively low toxicity. An ideal penetration enhancer should produce reversible enhancement, possess minimal irritancy, and be pharmacologically inert (Williams and Barry, 2016).

The development in the field of nanotechnology has paved the way for a revolutionary approach to transdermal drug delivery with respect to the ability to produce nanocarriers which can improve the efficacy of absorption, stability, and delivery of drugs. Some of the technologies of nanocarrier include liposomes, niosomes, ethosomes, transferosomes, nanoemulsion, solid lipid nanoparticles, nanostructured lipid carriers, dendrimers, and cubosomes. The main advantage associated with these nanocarriers when used for transdermal delivery is the small size and large surface area that facilitate the interaction of the drug with the layers of skin. (Mishra et al., 2022).

liposomes

Liposomes can be defined as vesicular carriers which consist of a bilayer phospholipids and are able to encapsulate not only hydrophilic but also lipophilic drugs. These vehicles enhance the stability and localization of drugs inside the skin; yet, traditional liposomes have poor ability to penetrate through the skin. In order to address this problem, transferosomes and ethosomes were created. Transferosomes possess elastic membranes that enable them to squeeze through narrow pores within the skin under hydration gradients. Ethosomes contain high concentrations of ethanol, which fluidize both vesicular and skin lipids, thereby improving penetration. These advanced vesicular carriers have demonstrated superior transdermal performance compared with conventional liposomes (Touitou et al., 2016).

Cubosomes

Cubosomes are yet another class of nano-carriers that have been widely studied for their suitability in transdermal applications. Cubosomes are nano-particles formed from bicontinuous cubic liquid crystal phases stabilized with surfactants. It has a distinct structure, which includes curved lipid bilayer sheets that are formed in three-dimensional periodic lattice arrangements. It is known to have a high drug carrying capacity, controlled release ability, and biocompatibility. Common lipids that may be utilized for the formation of such phase include glyceryl monooleate and phytantriol; Poloxamer 407 is used as the stabilizer. The top-down approach refers to the breaking down of an existing cubic phase to nanoparticles through mechanical force application (Garg et al., 2007). More recently, bottom-up methods based on self-assembly and solvent dilution have also been explored for preparation of cubosomes

with improved particle size control and stability (Esposito et al., 2018).

Nanoemulsions

Nanoemulsions have also been widely studied for transdermal delivery due to their capacity to increase the solubility and permeability of drugs with poor aqueous solubility. Nanoemulsions consist of an oil-water mixture that is stabilized using surfactants and cosurfactants, with the droplets typically having a diameter in the nanoscale range. The smaller droplet size and larger interfacial surface area of nanoemulsions increase the thermodynamic potential and diffusion across the skin Moreover, the constituents like oil and surfactants of nanoemulsions may serve to fluidize the lipid layer in the stratum corneum. The potential benefits of using nanoemulsion-based gels and transdermal delivery systems in anti-inflammatory, antihypertensive, analgesic, and antifungal drug delivery have already been confirmed. (Shakeel et al., 2019).

Microneedle

Microneedle technology has emerged as one of the most innovative approaches for overcoming the barrier properties of the skin. These needles are small projections that can create microchannels temporarily on the surface of the stratum corneum without penetrating the nerve endings present deeper in the skin. Various types of microneedles such as solid, coated, hollow, dissolvable, and hydrogel-forming microneedles have been created. Microneedles have shown remarkable potential for the delivery of peptides, proteins, insulin, vaccines, and nucleic acids that cannot easily permeate intact skin through passive diffusion (Kim et al., 2020).

Iontophoresis and sonophoresis

Iontophoresis and sonophoresis are physically assisted enhancement techniques employed to improve transdermal transport of drugs. Iontophoresis utilizes a low electrical current to facilitate migration of charged molecules across the skin through electrorepulsion and electroosmosis. Sonophoresis uses ultrasound waves to disrupt lipid organization within the stratum corneum and improve permeability. Electroporation, thermal ablation, laser-assisted delivery, and jet injectors are additional techniques investigated for transdermal administration of macromolecules and hydrophilic compounds. These technologies have significantly broadened the scope of transdermal therapy beyond traditional small lipophilic drugs (Mitragotri et al., 2018).

Hydrogels

The second type of formulation classification that has a key role in topical and transdermal drug delivery includes hydrogels. Hydrogels consist of hydrophilic polymer matrices which are three dimensional and can absorb large amounts of water without being structurally unstable. Hydrogels offer many benefits, among which are: biocompatibility; cool feeling; good spreadability; and drug release control. Smart or stimuli-responsive hydrogels capable of responding to pH, temperature, electrical signals, or light have expanded the possibilities of personalized and on-demand drug delivery systems (Li et al., 2021).

Evaluation of transdermal formulation

Evaluation of transdermal dosage form is important to guarantee quality, stability, safety, and effectiveness. Physicochemical evaluation normally comprises testing for appearance, thickness, weight variation, moisture content, water uptake, pH of the surface, tensile strength, folding endurance, and uniformity of drug content. Folding endurance indicates flexibility and mechanical resistance of the patch, whereas tensile strength reflects the ability of the film

to withstand stress. Surface pH close to skin pH is important to minimize irritation and improve patient comfort (Khalid et al., 2021).

The process of in vitro release testing often involves the use of Franz diffusion cells that incorporate artificial or dialysis membranes. In such cases, a barrier exists between the test sample and receptor fluid, and samples are taken from the system periodically. Ex vivo permeation studies involving animal or human skin provide additional information regarding drug flux, permeability coefficient, and skin retention. Such studies are valuable for predicting in vivo transdermal behavior of formulations (Dash et al., 2017).

Highly advanced methods of characterization are extensively utilized while developing transdermal drug formulations. Fourier transform infrared spectroscopy can be applied for investigating the compatibility of drugs with excipients. Information about crystallinity and thermal behavior of the formulation can be obtained using differential scanning calorimetry and X-ray diffraction techniques. Surface morphological studies can be performed using scanning electron microscope while particle size measurement can be done using dynamic light scattering and zeta potential determination techniques. (Khalid et al., 2021).

Mathematical modeling of drug release kinetics is useful for understanding release mechanisms from transdermal systems. Zero-order kinetics indicates constant release independent of concentration, whereas first-order kinetics suggests concentration-dependent release behavior. Higuchi kinetics is associated with diffusion-controlled release from matrix systems. The Korsmeyer–Peppas model is widely used to identify Fickian or non-Fickian diffusion mechanisms. Such kinetic studies are important for optimization and prediction of therapeutic performance (Dash et al., 2017).

Transdermal drug delivery Targets

The transdermal system has been tested on many kinds of medicinal substances like cardiovascular preparations, anti-inflammatory preparations, analgesic preparations, hormones, anti-diabetics, antiviral drugs, and CNS drugs. Nitroglycerin, clonidine, propranolol, and nifedipine are some cardiovascular drugs that have been used for research through the transdermal route owing to their extensive first-pass effect and short biological half-life when taken orally. Non-steroidal anti-inflammatory drugs such as diclofenac, ketoprofen, ibuprofen, and meloxicam are examples of drugs tested in the transdermal dosage form. (Verma et al., 2020).

Hormone replacement therapy

Hormone replacement therapy represents another important application of transdermal delivery. Estradiol and testosterone patches provide sustained hormone release while avoiding hepatic metabolism and reducing plasma concentration fluctuations. Nicotine patches remain among the most successful examples of commercial transdermal systems used in smoking cessation therapy. Similarly, fentanyl and buprenorphine patches are widely used in chronic pain management due to their ability to provide continuous analgesia over extended periods (Alexander et al., 2019).

Transdermal vaccine delivery

Transdermal vaccine delivery has become an area of growing interest because conventional needle-based vaccination is associated with pain, needle phobia, and risk of needle-stick injuries. Microneedle vaccine patches offer a less invasive option that is able to target antigen presenting cells in the skin. This method could increase the

effectiveness of vaccinations while decreasing the need for cold chain transport and medical professionals. (Kim et al., 2021).

Advancements made in wearable technology also had an effect on the field of transdermal drug delivery systems. Patches utilizing biosensors and processors for monitoring the physiological status can be programmed to provide drugs depending on this information. These devices could potentially lead to personalized medicine, where medications would be adjusted to patient's needs instantly. The combination of digital technology with pharmacological formulas will likely become a cornerstone in the future of medicine. (Lee et al., 2022).

Artificial intelligence and computational modeling are increasingly being utilized to optimize transdermal formulations. Machine learning algorithms can predict skin permeability, evaluate formulation variables, and analyze release kinetics using large experimental datasets. Such computational tools may accelerate formulation development and reduce the need for extensive experimental trials. Predictive modeling may also facilitate identification of suitable drug candidates for transdermal delivery (Patel et al., 2022).

The safety and regulatory aspects of transdermal systems are extremely important during formulation development and commercialization. Regulatory agencies require detailed evaluation of adhesion properties, dose uniformity, skin irritation, sensitization, stability, and pharmacokinetic performance before approval of transdermal products. Stability studies conducted under accelerated environmental conditions are necessary to ensure long-term product quality and efficacy. Clinical studies are essential for establishing therapeutic effectiveness and patient acceptability (US FDA, 2019).

Sustainability and environmental concerns have also become important considerations in pharmaceutical manufacturing. Researchers are increasingly investigating biodegradable polymers, renewable biomaterials, and environmentally friendly solvents for formulation development. Biopolymers like chitosan, alginate, gelatin, and cellulose-based products have been receiving increasing attention due to their natural biodegradable and biocompatible properties. The use of green processing methods might ensure safer pharmaceutical manufacturing processes in the coming days. (Raghav et al., 2021).

Table 1. Various drugs utilizing transdermal drug delivery system

Drug	Therapeutic Category	Disease/Disorder	Transdermal Drug Delivery system type	Functional Benefit of the drug delivery system	Reference
Meloxicam	NSAID	Rheumatoid arthritis	Cubosome-loaded gel	Provides sustained drug release and prolonged analgesic effect	(Modi et al., 2024)
Ketoprofen	Anti-	Joint pain and	Adhesive	Improves	(Liu et al.,

	inflammatory analgesic	arthritis	transdermal patch	penetration through the skin barrier and prolongs therapeutic activity	2020)
Lidocaine	Local anesthetic	Neuropathic pain and post-herpetic neuralgia	Transdermal therapeutic patch	Delivers continuous local anesthesia with controlled release	(Lee et al., 2021)
Nitroglycerin	Vasodilator	Angina pectoris	Reservoir-type patch	Maintains consistent plasma concentration and prevents chest pain episodes	(Lee et al., 2021)
Nicotine	Smoking cessation agent	Nicotine dependence	Drug-in-adhesive patch	Supplies controlled nicotine release to minimize withdrawal symptoms	(Zhou et al., 2020)
Fentanyl	Opioid analgesic	Chronic cancer pain	Reservoir transdermal patch	Offers long-duration systemic analgesia with reduced dosing frequency	(Sharma et al., 2020)
Clonidine	Antihypertensive agent	Hypertension	Matrix patch	Supports prolonged blood pressure management	(Lee et al., 2021)
Scopolamine	Anticholinergic drug	Motion sickness	Membrane-controlled patch	Prevents nausea and vomiting by sustained systemic absorption	(Zhou et al., 2020)
Salbutamol	Bronchodilator	Asthma	Transdermal	Maintains	(Lee et

			therapeutic system	prolonged bronchodilator activity and minimizes dosing frequency	al., 2021)
Tacrine	Cholinesterase inhibitor	Alzheimer's disease	Transdermal patch	Improves sustained neurological drug release and patient adherence	(Sharma et al., 2020)
Phycocyanin	Antioxidant and anti-inflammatory agent	Oxidative stress and skin aging	Cubosomal carrier system	Enhances stability and transdermal permeation of antioxidant compounds	(Zhu et al., 2024)
Indomethacin	NSAID	Inflammatory disorders and arthritis	Cubosomal gel and patch	Improves controlled release and anti-inflammatory efficiency	(Modi et al., 2024)

Transdermal drug delivery & Cubosomes

Cubosomes are a sophisticated category of nanostructured lipid carriers used for drug delivery. Cubosomes have recently gained much interest due to their ability to increase the solubility, stability, permeability, and targeting capability of drugs. The delivery vehicle is made up of bicontinuous liquid crystalline phases that are produced using amphiphilic lipids and aqueous phases. This special characteristic of the drug delivery vehicle enables it to encapsulate both hydrophilic and hydrophobic drugs together with having high surface area and drug loading capability. These properties make cubosomes highly suitable for transdermal drug delivery applications. In recent years, researchers have increasingly focused on cubosome-based systems for enhancing dermal and transdermal transport of therapeutic agents because conventional topical formulations often suffer from poor skin penetration, limited drug retention, and inadequate bioavailability (Sivadasan et al., 2023).

The concept of transdermal administration of drugs entails the transport of the active components across the skin into the bloodstream. The use of this mode of administration is associated with numerous benefits over others, including circumventing the first-pass effect, reduced risk of side effects on the gastrointestinal tract, sustained delivery, better patient compliance, and non-invasive application. Despite these benefits, several challenges exist in transdermal administration, including the inability of the active components to cross the stratum corneum barrier and diffuse past it. To address this challenge, new transport carriers like liposomes, ethosomes, transferosomes, solid

lipid nanoparticles, nanostructured lipid carriers, and cubosomes have been developed. Cubosomes, among all the carriers mentioned, are very promising due to their high stability and excellent penetration properties. (Bhatt et al., 2025).

Cubosomes are generally prepared using lipids such as glyceryl monooleate (GMO) or phytantriol combined with stabilizers like poloxamer 407. These lipids self-assemble in aqueous environments to form thermodynamically stable cubic phases characterized by a three-dimensional periodic arrangement of lipid bilayers and aqueous channels. The intricate internal structure of cubosomes resembles a honeycomb network, enabling efficient entrapment and sustained release of drugs. Their nanosized dimensions further enhance interaction with the skin surface and facilitate deeper penetration through the epidermal layers (Modi et al., 2024).

The increasing interest in cubosomes for transdermal delivery is associated with their ability to improve permeation through biological membranes. Cubosomes are capable of interfering with the lipid matrix present in the stratum corneum, thus leading to a disruption in the organization of this layer, which increases skin permeation. Furthermore, their bioadhesive nature enhances the retention period on the site of application, which improves drug absorption. Several studies have demonstrated that cubosomal formulations provide higher transdermal flux and better skin retention compared to conventional creams, gels, and ointments (Chandrakala et al., 2025).

Cubosome Structure and Composition

The cubosome is an example of a nanoparticle synthesized from the bicontinuous cubic liquid crystalline phase. Cubosomes have a unique interior architecture with curved lipid bilayers organized in a three-dimensional lattice network separating two aqueous phases that do not intersect each other. The result is a large interfacial area, which enhances the efficiency of drug loading and its controlled delivery features. The liquid crystalline cubic phase is thermodynamically stable and very viscous as a bulk sample, but when converted into nanoparticles using surfactants, it becomes cubosomes. (Karami and Hamidi, 2016).

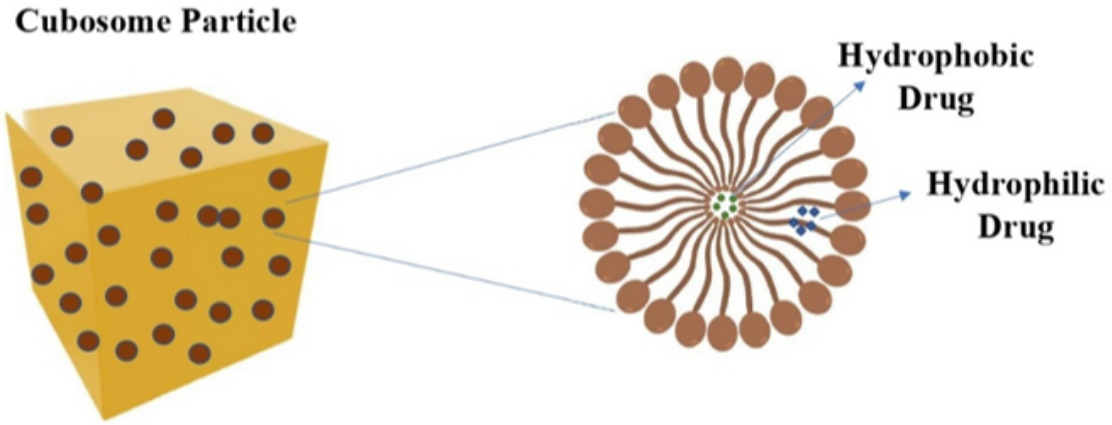

Figure 2 Structure of Cubosome particle

The primary components used in cubosome preparation are amphiphilic lipids and stabilizers. Glyceryl monooleate is one of the most commonly used lipids because of its biodegradability, biocompatibility, and ability to form cubic phases upon hydration. Phytantriol is another important lipid used in cubosome formulation due to its chemical stability and resistance to enzymatic degradation. Stabilizing agents like poloxamer 407 are used to inhibit agglomeration and stabilize nanoparticle suspension. Other additives, like surfactants and co-surfactants, can be added to achieve optimal particle size, zeta potential, drug entrapment efficiency, and controlled drug release. (Garg et al., 2021).

The nanoscale dimensions of cubosomes generally range from 100 to 500 nm. Their small size enhances surface contact with the skin and promotes efficient drug penetration. Moreover, cubosomes possess both hydrophilic aqueous channels and hydrophobic lipid bilayers, enabling simultaneous incorporation of drugs with varying physicochemical properties. This dual drug-loading capability represents a major advantage over many conventional nanocarriers (Gaballa et al., 2020).

Mechanism of Transdermal Drug Delivery Using Cubosomes

The process through which the use of cubosomes helps improve transdermal drug delivery is rather complicated, as there exist several mechanisms for the same purpose. One of the most significant ones is the interaction between cubosomes and stratum corneum lipids. Lipids of cubosomes could interact with the lipids present in the skin and lead to the disruption of their tight arrangement. (Zhu et al., 2024).

Another mechanism involves the bioadhesive properties of cubosomes. Their lipidic composition enables prolonged retention on the skin surface, increasing the duration of contact between the formulation and the skin. Prolonged contact time allows sustained drug release and enhanced penetration. Moreover, the nanostructure of cubosomes enables controlled release properties, ensuring therapeutic levels of drugs for prolonged durations (Bhatt et al., 2025).

Cubosomes may also facilitate transappendageal transport through hair follicles and sweat glands. Since nanoparticles can accumulate in follicular openings, cubosomal systems may serve as reservoirs for sustained drug release. Moreover, the high surface area and aqueous channels of cubosomes increase drug solubility, thus boosting the thermodynamic activity for skin penetration (Sivadasan et al., 2023).

Methods of Preparation of Cubosomes

There have been various approaches used for preparing cubosomes; these include the top-down and bottom-up method. In the top-down approach, the bulk cubic phase is first created, followed by breaking up of the bulk phase into nano-scale particles through high energy. The top-down approach entails the use of high energy in breaking up the bulk phase into nano-scale particles. (Garg et al., 2021).

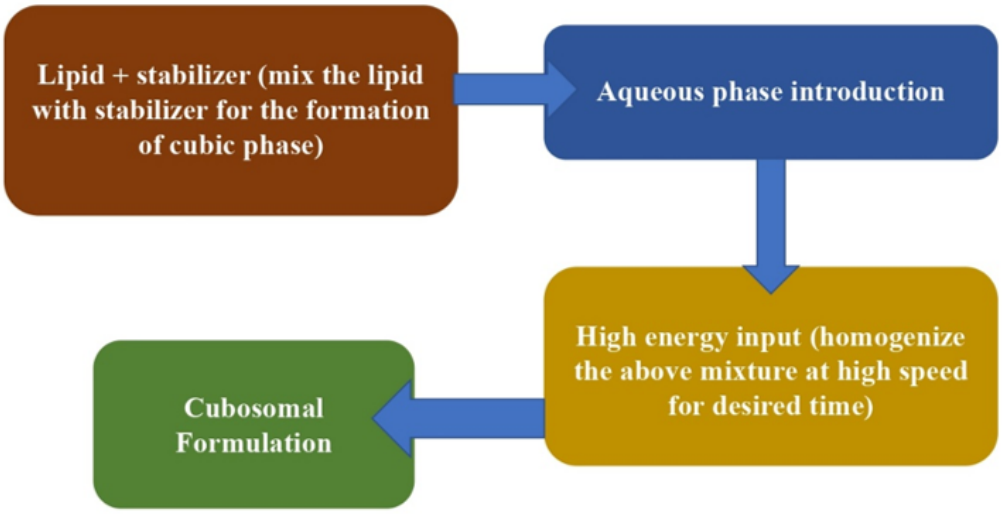

Figure 3 Top Down method of cubosome formulation

In the bottom-up approach, cubosomes are formed by controlled self-assembly of molecular precursors. This method generally requires lower energy input and produces smaller particles with narrower size distribution. Solvent dilution, hydrotrope dilution, and spontaneous emulsification are examples of bottom-up techniques. These methods are increasingly preferred because they minimize thermal and mechanical stress on sensitive drug molecules (Mishra et al., 2023).

One such process that has been frequently used for the commercial manufacture of cubosomes is high pressure homogenization. This involves subjecting the bulk cubic phase to very strong shear stress conditions brought about by pumping the system through narrow channels at high pressure. Ultrasonication is another widely used method where ultrasonic energy reduces particle size and forms stable nanoparticle dispersions. Spray drying and solvent evaporation techniques have also been explored for cubosome production (Singh et al., 2021).

Benefits of Cubosomes in Transdermal Drug Delivery

There are many benefits associated with cubosomes, which make them better than other options for use in transdermal drug delivery. The first benefit relates to the ability of these nanoparticles to incorporate drugs with diverse solubility properties. Hydrophilic drugs can be encapsulated within the aqueous channels, whereas lipophilic drugs can be encapsulated within the lipid bilayers. (Modi et al., 2024).

A notable benefit is increased skin permeability. The interaction between cubosomes and lipids in the stratum corneum enhances drug penetration. The small size of cubosomes is another factor contributing to better transport through biological membranes. Research indicates that the transdermal flux of cubosomal formulations is higher than traditional formulations. (Chandrakala et al., 2025).

Controlled and sustained drug release is another important benefit of cubosomes. The highly ordered cubic structure acts as a diffusion barrier that regulates drug release

over prolonged durations. It also leads to an increased patient compliance as the dosing frequency is reduced. Moreover, cubosomes provide protection to the drug molecules from degradation by chemicals and enzymes (Sivadasan et al., 2023).

Cubosomes are also biocompatible and biodegradable because they are composed mainly of physiological lipids. Their non-toxic nature minimizes irritation and adverse skin reactions. Moreover, cubosomal formulations exhibit high bioadhesion, ensuring prolonged residence time at the application site and improved therapeutic outcomes. (Gaballa et al.,2020)

Cubosomes preparation of Transdermal dosage forms

It should be noted that cubosomes have attracted substantial attention as regards the use of these nanosystems for the transdermal delivery of anti-inflammatory drugs, antifungal drugs, anticancer drugs, peptides, proteins, and other components of cosmetics. Such anti-inflammatory drugs as diclofenac sodium, indomethacin, and meloxicam were efficiently loaded into cubosomes and exhibited improved skin permeability and extended release in addition to increased anti-inflammatory properties in comparison with traditional transdermal drugs. (Hundekar et al., 2014).

Cubosomes have also shown promise in antifungal therapy. Drugs such as clotrimazole, ketoconazole, and miconazole nitrate have been formulated into cubosomes for treatment of fungal skin infections. The enhanced penetration and retention properties of cubosomes improve local drug concentration and therapeutic efficacy (Chandrakala et al., 2025).

Cubosomes, as a type of novel carrier, have been explored in anticancer therapy for delivering chemotherapeutic drugs to skin tumors and melanomas. Their small size and controlled release characteristics enable effective drug targeting while reducing systemic side effects. Researchers have also explored cubosomes for transdermal administration of insulin and peptide-based therapeutics, which traditionally face challenges due to poor skin permeability (Zhang et al., 2020).

Evaluation Parameters of Cubosomes

Characterization and evaluation of cubosomes are important to guarantee their formulation quality, stability, and efficacy. The determination of particle size is usually done by dynamic light scattering methods. Reduced particle size is positively related to skin permeability and formulation stability.

Zeta potential testing helps determine the surface charges and the stability of the colloids. The higher absolute zeta potential values imply better physical stability because of the electrostatic repulsion among particles. The determination of the cubic structure is done through morphological characterization using both TEM and SEM. (Singh et al., 2020).

Entrapment efficiency is another critical parameter that determines the amount of drug successfully incorporated within cubosomes. High entrapment efficiency contributes to improved therapeutic performance and sustained release characteristics. Drug release studies are conducted in vitro for the release kinetics and ex vivo using Franz diffusion cells for the transdermal flux. (Zhu et al., 2024).

The other methods used in the assessment include rheological measurements, differential scanning calorimetry, X-ray diffraction, and small angle X-ray scattering. These help to confirm the presence of the cubic phase, its thermal behavior, and internal structures. (Sivadasan et al., 2023).

Challenges Associated with Cubosomes

Despite numerous advantages, cubosomes also face certain limitations and challenges. One major issue is the complexity of large-scale manufacturing. Preparation methods such as high-pressure homogenization require specialized equipment and high energy input, which may increase production costs.

Drug leakage during storage and transportation is another challenge associated with cubosomal systems. Since cubosomes contain internal aqueous channels, hydrophilic drugs may diffuse out over time, affecting formulation stability. In addition, maintaining long-term physical stability without particle aggregation remains difficult in some formulations (Mishra et al., 2023).

Another concern is the limited availability of comprehensive toxicity and safety data. Although cubosomes are generally considered biocompatible, extensive clinical investigations are still needed to establish their long-term safety profiles. Regulatory challenges also exist because standardized guidelines for characterization and evaluation of cubosomal formulations are still evolving (Bhatt et al., 2025).

Furthermore, incorporation of highly hydrophilic macromolecules into cubosomes may sometimes result in lower encapsulation efficiency. Stability issues may also arise when sensitive biomolecules are exposed to mechanical stress during preparation processes such as ultrasonication and homogenization (Gaballa et al., 2020).

Future Perspectives of Cubosomes in Transdermal Delivery

The prospects of utilizing cubosomes for transdermal drug delivery technology appear highly promising due to advancements made in the areas of nanotechnology, lipids, and drug delivery science. Research has been carried out in stimulated release systems, wherein drugs were delivered in response to stimuli such as pH, temperature, enzymatic reaction, or external factors such as magnetic field or sound waves. (Singh et al., 2021).

Surface modification and ligand conjugation techniques are also being investigated to enhance targeting efficiency and cellular uptake. Functionalized cubosomes may enable selective delivery of drugs to diseased tissues while reducing off-target effects. Combination approaches involving cubosomes with microneedles, hydrogels, iontophoresis, and patches may further enhance transdermal drug delivery efficiency (Sivadasan et al., 2023).

Advances in microfluidic technology and continuous manufacturing techniques are expected to simplify large-scale production and improve formulation reproducibility. Additionally, increasing interest in personalized medicine and biologics may drive further development of cubosome-based delivery systems for peptides, proteins, vaccines, and gene therapy agents (Bhatt et al., 2025).

The integration of cubosomes into cosmeceutical formulations is another rapidly growing area. Cubosome-based products for anti-aging, antioxidant delivery, wound healing, and skin regeneration are likely to gain commercial importance in the coming years. Their ability to improve stability and penetration of active compounds makes them attractive carriers for pharmaceutical and cosmetic industries alike (Innovare Academics, 2022).

References

1. Benson HAE, Grice JE, Mohammed Y, Namjoshi S, Roberts MS. Topical and transdermal drug delivery: From simple potions to smart technologies. Curr Drug Deliv. 2019;16(5):444-460.

2. Pastor M, Moreno A, Esquisabel A, Pedraz JL. Current advances in transdermal drug delivery systems. Pharmaceutics. 2020;12(6):1-25.
3. Nguyen HX, Banga AK. Delivery of biologics by transdermal route. Int J Pharm. 2018;547(1-2):431-447.
4. Brown MB, Martin GP, Jones SA, Akomeah FK. Dermal and transdermal drug delivery systems: Current and future prospects. Drug Deliv Transl Res. 2017;7(3):463-489.
5. Kumar R, Philip A. Modified transdermal technologies: Breaking the barriers of drug permeation via the skin. Trop J Pharm Res. 2021;20(2):437-449.
6. Patel D, Chaudhuri S, Kumar V, Dwivedi J, Das S. Transdermal drug delivery systems: An overview of formulation strategies and current advances. Pharmaceutics. 2020;12(9):1-29.
7. Ita K. Transdermal drug delivery: Progress and challenges. J Drug Deliv Sci Technol. 2017;41:124-132.
8. Singh S, Gupta A, Kaur CD. Bioadhesive polymers in transdermal drug delivery systems. Int J Biol Macromol. 2018;107:192-203.
9. Li J, Mooney DJ. Designing hydrogels for controlled drug delivery. Nat Rev Mater. 2021;6(2):1-18.
10. Mishra V, Bansal KK, Verma A, Yadav N, Thakur S. Solid lipid nanoparticles and nanostructured lipid carriers for transdermal drug delivery. Colloids Surf B Biointerfaces. 2022;213:112435.
11. Touitou E, Dayan N, Bergelson L, Godin B. Ethosomes and transferosomes for transdermal delivery. J Liposome Res. 2016;26(4):1-13.
12. Esposito E, Drechsler M, Cortesi R. Cubosomes in drug delivery: Recent developments and applications. Nanomedicine. 2018;13(3):345-362.
13. Shakeel F, Ramadan W, Ahmed MA. Investigation of transdermal nanoemulsion systems for improved drug delivery. Drug Dev Ind Pharm. 2019;45(3):1-10.
14. Kim YC, Park JH, Prausnitz MR. Microneedles for drug and vaccine delivery. Adv Drug Deliv Rev. 2020;153:1-19.
15. Mitragotri S, Burke PA, Langer R. Overcoming the challenges in administering biopharmaceuticals through skin. Nat Rev Drug Discov. 2018;13(9):655-672.
16. Khalid N, Rahman M, Ullah I, Khan IU, Khan GM. Characterization and evaluation techniques for transdermal patches. Drug Dev Ind Pharm. 2021;47(9):1450-1464.
17. Dash S, Murthy PN, Nath L, Chowdhury P. Kinetic modeling on drug release from controlled drug delivery systems. Acta Pol Pharm. 2017;74(3):739-748.
18. Verma P, Pathak K. Therapeutic and clinical applications of transdermal systems. Drug Dev Ind Pharm. 2020;46(6):857-871.
19. Kim M, Jung H, Kim H. Microneedle-mediated vaccine delivery for infectious diseases. Expert Opin Drug Deliv. 2021;18(7):929-943.
20. Lee H, Song C, Baik S, Kim D, Hyeon T, Kim DH. Device-assisted transdermal drug delivery. Adv Drug Deliv Rev. 2022;127:35-45.
21. Patel A, Cholkar K, Agrahari V, Mitra AK. Nanocarrier systems in advanced transdermal delivery. Nanomedicine. 2022;17(4):267-285.
22. Raghav PK, Agarwal N, Saini M. Sustainable approaches in pharmaceutical formulation development. J Clean Prod. 2021;278:123456.
23. US Food and Drug Administration. Transdermal and topical delivery

systems—Product development and quality considerations. FDA Guidance Document. Silver Spring (MD): US Food and Drug Administration; 2019.
24. Sivadasan D, et al. Cubosomes in drug delivery—A comprehensive review on mechanisms and applications. Pharmaceutics. 2023;15(4):1123-1145.
25. Bhatt AH, Patel HP, Patel PR, Rathod HG, Hirawala JH, Shaikh PS, et al. Cubosomes in non-oral drug delivery: Advancing precision therapeutics from bench to bedside. Int J Pharm. 2025;648:126108.
26. Zhu C, Duan W, Jing H, Long J, Huang Y, Huang D, et al. Improving the stability and transdermal permeability of phycocyanin loaded cubosomes. Front Nanotechnol. 2024;6:1359219.
27. Modi P, Patel H, Vaghela N, Patel U, Naik P. Review of the innovative medication delivery system: The cubosome. Res J Pharm Technol. 2024;17(8):4063-4067.
28. Garg M, Goyal A, Kumari S. An update on the recent advances in cubosome: A novel drug delivery system. Curr Drug Metab. 2021;22(6):441-450.
29. Gaballa SA, El Garhy OH, Abdelkader H. Cubosomes: Composition, preparation, and drug delivery applications. J Adv Biomed Pharm Sci. 2020;3(1):1-9.
30. Mishra R, Aher A, Nandgude T, More K, Kolsure A. Cubosomes: Recent developments and applications from a global perspective. Int J Drug Deliv Technol. 2023;13(4):1591-1599.
31. Chandrakala V, et al. Cubosomes for rheumatoid arthritis: Enhancing anti-inflammatory therapy through advanced nanocarriers. Discov Nano. 2025;20:317.
32. Singh A, et al. Smart cubosomes: Responsive carriers for personalized medicine. Int J Pharm. 2021;593:117-126.
33. Zhang H, et al. Formulation and evaluation of cubosomes for transdermal delivery of insulin. Eur J Pharm Sci. 2020;149:105329.
34. Lee W, et al. Transdermal delivery systems: Prospects and challenges. J Control Release. 2021;334:345-354.
35. Sharma S, et al. Cubosome-based drug delivery systems: Potential for transdermal applications. Nanomedicine. 2020;21:102169.
36. Jadhav S, et al. Cubosome and its potential in dermatological drug delivery. Dermatol Ther. 2020;33(2):e13502.
37. Liu Z, et al. Advances in cubosomes for transdermal drug delivery. Int J Nanomedicine. 2020;15:497-509.
38. Zhou Q, et al. Nanocarriers in transdermal drug delivery: Present and future perspectives. Nanomedicine. 2020;21:102286.
39. Bhatt AH, Patel HP, Patel PR, Rathod HG, Hirawala JH, Shaikh PS, et al. Cubosomes in non-oral drug delivery: Advancing precision therapeutics from bench to bedside. Int J Pharm. 2025;648:126108.
40. Chandrakala V, et al. Cubosomes for rheumatoid arthritis: Enhancing anti-inflammatory therapy through advanced nanocarriers. Discov Nano. 2025;20:317.
41. Gaballa SA, El Garhy OH, Abdelkader H. Cubosomes: Composition, preparation, and drug delivery applications. J Adv Biomed Pharm Sci. 2020;3(1):1-9.
42. Hundekar C, et al. Cubosomal formulations for enhanced topical anti-inflammatory activity. Int J Pharm Sci Res. 2016;7(9):3721-3728.
43. Lee W, et al. Transdermal delivery systems: Prospects and challenges. J Control Release. 2021;334:345-354.

44. Liu Z, et al. Advances in cubosomes for transdermal drug delivery. Int J Nanomedicine. 2020;15:497-509.
45. Modi P, Patel H, Vaghela N, Patel U, Naik P. Review of the innovative medication delivery system: The cubosome. Res J Pharm Technol. 2024;17(8):4063-4067.
46. Sharma S, et al. Cubosome-based drug delivery systems: Potential for transdermal applications. Nanomedicine. 2020;21:102169.
47. Sivadasan D, et al. Cubosomes in drug delivery—A comprehensive review on mechanisms and applications. Pharmaceutics. 2023;15(4):1123-1145.
48. Zhang H, et al. Formulation and evaluation of cubosomes for transdermal delivery of insulin. Eur J Pharm Sci. 2020;149:105329.
49. Zhou Q, et al. Nanocarriers in transdermal drug delivery: Present and future perspectives. Nanomedicine. 2020;21:102286.
50. Zhu C, Duan W, Jing H, Long J, Huang Y, Huang D, et al. Improving the stability and transdermal permeability of phycocyanin loaded cubosomes. Front Nanotechnol. 2024;6:1359219.