EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 10
Issue: 8
114-121
Year: 2023

CUBOSOME AS DRUG DELIVERY SYSTEM: A REVIEW ARTICLE

Divyanshi Prakash* and Dr. Sunil K. Batra

Innovative College of Pharmacy, Greater Noida, UP.

***Corresponding Author: Divyanshi Prakash**
Innovative College of Pharmacy, Greater Noida, UP.

Article Received on 06/06/2023 **Article Revised on 27/06/2023** **Article Accepted on 17/07/2023**

ABSTRACT
Cubosomes, unique cubic-shaped particles formed by dispersing liquid crystalline clusters in water, offer a promising approach for drug delivery and have attracted significant interest in the field of pharmaceutical nanotechnology. This review creatively highlights the structural characteristics, merits and demerits of cubosomes. It discusses the use of amphiphilic lipids such as glycerol monooleate (GMO) and phytantriol in cubosome manufacturing, as well as the role of stabilizing agents in maintaining the stability of dispersed particles. The article further explores the two main approaches for cubosome preparation, namely the top-down and bottom-up methodologies, along with techniques such as high-pressure homogenization, probe sonication, spray drying, and heat treatment. Lastly, it introduces the concept of cubosomal precursor forms, which offer an alternative method for cubosome generation. This review is an attempt to provide a comprehensive overview of cubosomes and their potential applications in drug delivery systems.

KEYWORDS: Cubosomes, Glycerol monooleate (GMO), Phytantriol (PHYT), Poloxamer 407, Top down method, Bottom up method.

INTRODUCTION

Cubosomes are unique, tiny particles of bicontinuous cubic shapes created by dispersing liquid crystalline cubic clusters in aqueous environments. They share the same microstructure as their parent cubic clusters and have a large surface area.[1]

Cubosomes are peculiar physicochemical phases that are inverted bicontinuous cubic phases. The distribution of diverse hydrophilic, hydrophobic and amphiphilic medicines with increased bioavailability and high capacity for loading is attracting a lot of interest using these specialized systems. The cubosome formulation is adaptable to a wide range of medications and delivery methods. Because they are more stable, the lipids utilized in cubosome formulation provide sustainability to the formulation throughout its shelf life.

There have been various studies on the utilization of these systems as alternative medication delivery systems as a result of a growing interest in pharmaceutical nanotechnology. As a result, they have been thoroughly examined and explored for various therapeutic uses (peptides, enzymes, antimuscarinic medications, antibiotics, analgesic administration). A bicontinuous liquid cubic crystal phase may be formed by self-associating cubosomes, which are hydrated surfactant structures that can preserve their thermodynamic stability.[2]

The cubosome design had been presented with improved effectiveness, protein and vitamin stability. The long-term stability of the colloidal dispersions had been maintained by the inclusion of lipid polymers and polymers are in charge of regulating drug distribution in which the active moiety would permeate all the way through the channels that are present in the cubical phases.[3]

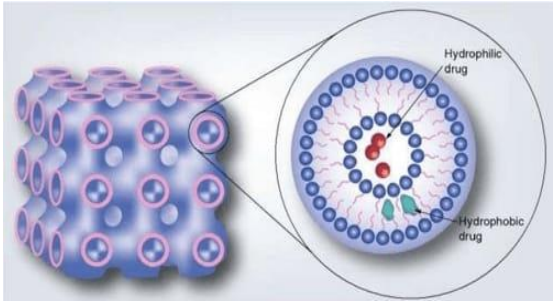

Figure 1: Cubosomes presenting its cavernous internal and cubic structure and its membrane composition.[9]

Merits

1. An absorption enhancer is provided by the nanovesicles formed by the lipid (GMO) while

cubosomes are penetrating the corneal and skin layers.[2]
2. They may be produced by using easy approaches.
3. They can encapsulate various drug molecules with hydrophobic, hydrophilic and amphiphilic features, offering a hopeful method for improving the bioavailability of medications that are poorly water-soluble.[2]
4. They are made of lipid that degrades quickly in biological fluid. Prevent the medicine from deterioration both physically and chemically.
5. Due of their high interior surface area, they entrap drug loading in higher amount.
6. They enable targeted and controlled release of the bioactive medication molecules.
7. They are flammable-free and stable in temperature.

Demerits

However, cubosomes also have a few noteworthy limitations that are worth mentioning.

1. Due to the high water content inside of their structure, they have low entrapment effectiveness for drug molecules that are solubility in water.[1]
2. A problem in large-scale manufacturing because of the cubic phase's excessive viscosity.

COMPONENTS FOR MANUFACTURING OF CUBOSOMES

Kåre Larsson originally made reference to the cubosome in his study of cubic lipid/water phases in the 1980s.[4] Larsson was followed by Patton and Carey in describing their discovery in fat digestion research that the interaction of lipase and bile salts with simulated stomach contents produced distributed particles of the bicontinuous cubic shapes. Larsson, however, launched the field of cubic structures when he showed that cubosomes, submicron-sized particles with the same internal structures as the parent cubic structure, may be generated from the bulk cubic structure. Cubosomes are three-dimensionally organized as a "honeycomb" framework, and the majority of their constituent parts are amphiphilic lipids distributed in water in the presence of appropriate stabilisers.[5] The primary goal of the cubosome formulation was to deliver lipophilic medications including diazepam, griseofulvin, propofol and rifampicin to the specific location body organ. The phospholipid layer boosts permeability by reducing the lipophilic moiety's solubility issue. The permeability across the biomembrane is restricted for hydrophilic glucose and insulin moieties, however this may be satisfactorily circumvented by integrating them in lipid constituents. Therefore, both types of medications can be integrated into cubosomes, albeit up until now it has been noted that lipophilic drug encapsulation is more frequent. Peptide stability was improved by cubosomes by limiting them susceptibility to various pH conditions in the environment. Therefore, by carefully choosing a cubosome carrier that permits the efficient delivery of the drug moiety at the specified tissue/organs, the drawbacks of other site-specific/targeted drug delivery methods might be minimized.[6]

Glycerol Monooleate

The most frequently used amphiphilic lipid in the production of cubosomes is glyceryl monooleate (GMO), also known as monoolein. GMO is a transparent, colourless polar unsaturated monoglyceride with a melting point of 35–37 °C and a storage temperature of 20 °C. It has an HLB value of 3.[7] It is a chemical mixture of oleic acid and glycerides ester and other fatty acids, with the primary component being monooleate, which is able to self-assemble in water to form bicontinuous cubical structures.[8] The chemical composition of GMOs demonstrates that they have both hydrophilic and hydrophobic properties simultaneously (amphiphilic molecule). This is due to the existence of hydrocarbon chains in the tail and hydroxyl groups in the head part, which are both responsible for the formation of H-bonds with water.[1] It is a frequent emulsifier in the food company and is a safe, non-hazardous, biodegradable, and biocompatible material.

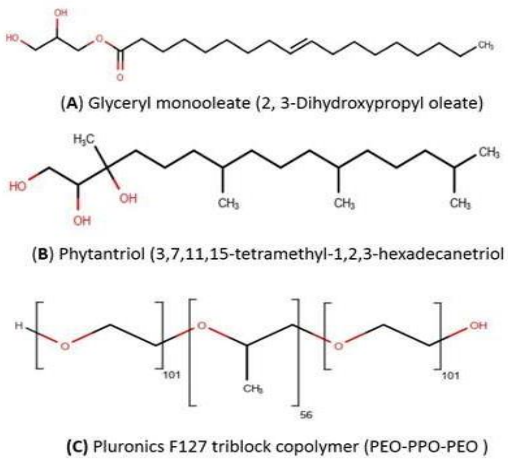

Figure 2:- Molecular structure of cubosomes forming lipid (A) glyceryl monooleate, (B) phytantriol, and (C) stabilizer (poloxamer 407)9.

Phytantriol

A excellent substitute for GMO in the manufacture of cubosomes is phytotanol, a popular ingredient in cosmetic goods. Under physiological circumstances and temperature, phytanatriol (3, 7, 11, 15-tetramethyl-1, 2, 3-hexadecantriol) can form a bicontinuous cubic structure in aqueous fluids. Due to its higher chemical stability than monoglycerides due to the absence of an ester group, its improved skin penetration properties, improved retention of humidity, and the fact that it is accessible to consumers with high quality (95%), whereas monoglycerides are with different levels of purity as they are created from multiple sources, it has recently attracted more interest in the biomedical field than monoglycerides.[9] The prolonged release of many drug molecules, particularly those with hydrophilic qualities, was discovered to be possible using PHYT-

based liquid crystalline matrices, which is why it is regarded as an exceptional sustained drug delivery method.

Sustainin Agent

Although the bulk cubic aggregates are thermodynamically stable, using stabilizing agents becomes a crucial step in the preparation of cubosomes to prevent re-coalescence of the dispersed particles into the parent bulk cubic structure when dispersed in water.[10] This is because the hydrophobic portions of the dispersed particles tend to aggregate as a result of exposure to the external hydrophilic aqueous media.[11] The stabilizer's primary purpose is to act as an electrostatic barrier between particulates, preventing intimate particle interaction and maintaining the consistency of the particles that are dispersed. The selection of the proper stabiliser is an important stage since it contributes to the lipid water assembly and produces this effect without interfering with the cubic liquid crystallinity. Pluronics are the stabilising agents that are most frequently utilised, specifically F127 (Poloxamer 407), which is regarded as the "gold standard". Pluronics are assembled itself triblock copolymers made of polyethylene oxide (PEO) and polypropylene (PPO) that are structured in a PEO-PPO-PEO configuration and are soluble in water.[12] The PPO and PEO sections are responsible for the materials' respective hydrophobic and hydrophilic qualities. When applied to cubosomes, the hydrophobic (PPO) component of F127 is assumed to adhere to the surface of the particles and stabilise them, while the water-loving (PPO) portion extends into the aqueous medium to provide steric shielding. GMO-polymer mixture is often used with a concentration between 2.5% (w/w) and 10% depending on the total weight of the dispersion, while stabiliser is typically employed with a concentration up to 20% w/w relying on the dispersed particles.[13]

PREPARATION OF CUBOSOMES

The Top-Down Approach

The most popular way for cubosome preparation is the top down approach. There are two key phases to it. First, to create the bulk viscous cubic coalscence by combining the lipid that forms cubosomes with an appropriate stabilizer. The second step involves the use of high energy homogenizer with high pressure or sonication to the created viscous cubic aggregates in aqueous environment which ultimately leads to the development of cubosomes.[14] Fortunately, it has been discovered that cubosomes made by the top-down approach are stable against aggregation for as long as a year. Unfortunately, these may present a problem when incorporating temperature-dependent bioactive agents, specifically peptides and protein, as this method has drawbacks in large-scale production as the formation of viscous cubic aggregates requires high energy input to be dispersed into cubosomes.[1]

Bottom-Up Methodology

This method, also known as a solvent dilution strategy, entails dispersing a combination made up of cubosomes producing lipid, a stabilizer and a hydrotrope in excess water while using a minimum amount of energy.

The fundamental component of the bottom-up method is hydrotrope, which is used to disintegrate water-insoluble lipids in order to create lipid precursors and avoid the development of liquid crystals at high concentrations.[15] A molecule known as a hydrotrope is capable of enhancing the solubility of one solute by the inclusion of another solute, which allows it to dissolve difficult to dissolve substances in aqueous conditions. The most often employed hydrotropes include sodium benzoate urea, sodium alginate, and. The complex that forms between the hydrotrope and the hydrophobic substance is the solubilizing mechanism of the hydrotrope.[16] Since it requires less energy input than the top-down method, the bottom-up method has more benefits. As a result, cubosomes that are loaded with temperature-sensitive compounds may be made safely using the bottom-up method. Because stabilisers were evenly distributed throughout the surface of the created nanovesicles, the obtained cubosomes also exhibit long-term stability.[17]

Pseudo-Binary Systems' Cubosomes

The initial creation of cubosomes involved the traditional method of energetically dispersing a mass cubic gel within a pseudo-binary solution of monoolein and water, with the addition of a low concentration of polymer.[10] The process entailed the following steps.

a) **Uniform Solution:** A mixture was prepared by combining monoolein (92% w/w) and melted Polyoxamer 407 (8% w/w) to create a homogeneous solution. This solution served as the base for further steps.
b) **Dilution with Deionized Water:** The monoolein-polymer solution was then mixed with deionized water, resulting in a mixture containing 1.8% monoolein. The composition of this mixture was 99.6% aqueous water and 0.2% Poloxamer 407.
c) **Sonication:** The mixture was subjected to ultrasonic sonication for a duration of 60 minutes, maintaining a constant temperature of 25°C. This process aimed to disperse the cubic liquid crystalline gel form, resulting in the formation of cubosomes.

Analysis using cryo-TEM (cryogenic transmission electron microscopy) revealed that the majority of the observed cubosomes exhibited a square shape, with each side measuring between 100 and 300 nm. This method allowed for the successful creation of cubosomes with the desired characteristics and dimensions, providing a foundation for further research and applications.

Homogenization under High Pressure

Achieving exceptional stability and extended shelf life for low-polydispersity index cubosomes requires the implementation of high-pressure homogenization, the

optimal processing method. This technique involves three fundamental steps.

a) Gel Preparation: To initiate the process, lipids and surfactants are meticulously dissolved in an appropriate organic solvent. Through thorough blending, the mixture attains a state of homogeneity.[18] Subsequently, the organic solvent is eliminated using a rotary evaporator, resulting in the formation of a gel phase.

b) Shearing: The gel is subjected to shearing by introducing an aqueous solvent. This crucial step facilitates the creation of a microdispersion, breaking down the gel into smaller particles or droplets, enabling the formation of cubosomes.

c) High-Pressure Homogenization: The sheared dispersion is then treated within a homogenizer, utilizing high pressure. This stage is highly sensitive to temperature, necessitating precise regulation based on the thermal characteristics of the selected lipid formulation. The homogenization process achieves a further reduction in particle size and ensures uniform distribution of cubosomes within the dispersion. Particularly suited for large-volume sample systems that effectively preserve the cubic structure, this technique leverages the use of an amphiphile and specific storage conditions. Prior to implementation, the quality of cubosomes is thoroughly evaluated through established procedures.[19] However, it is important to note that this preparative strategy may not yield satisfactory results when applied to sample systems with limited volumes.

Probe Sonication

Traditionally, the production of Solid Lipid Nanoparticles (SLNs) involved the use of high shear homogenizers and ultrasonicators. However, these methods often yielded particles in the micron size range.[20] The Ultra-Turrax T25 has been used to stir a combination of molten lipid, surfactant, and water in order to get around this constraint. Subsequently, probe sonication is employed, resulting in the formation of a nanoemulsion.[21] Upon cooling to room temperature, the nanoemulsion undergoes a transformation, forming cubosomes.

Spray Drying

In the work conducted by Spicer *et al*, the spray drying technique was employed to produce dry powder precursors. Two types of dry powder precursors were formulated. The first method involved spray drying a monoolein encapsulated dispersion using an aqueous starch solution, leading to the production of nanostructured particles.[22,23] The second method involved spray drying an emulsion of dextran-monoolein-ethanol-water system, which circumvented the need for high shear pressure prior to spray drying. The study concluded that dry powder precursors formulated through the spray drying technique could achieve desirable colloidal and functional efficacy upon reconstitution with water during the manufacturing process.

Heat Treatment

In the formulation of cubosomes, the coexistence of vesicles can affect the sustained release behavior. Eliminating these vesicles can restore the desired activity, which can be achieved through heat treatment. It is important to note that heat treatment is not an integrated method within the cubosomal formulation process. By applying heat treatment, well-ordered cubosomal particles can be obtained by transforming non-cubic vesicles.[24,25] This method involves standard processing techniques such as homogenization followed by heat treatment. Studies have shown that this approach yields cubosomes with narrow particle size distribution and improved colloidal stability. However, it may not be suitable for thermo-sensitive drugs such as proteins, as the loaded drugs could lose their stability during storage, resulting in diminished product efficacy.

CUBOSOMAL PRECURSOR FORMS

The development of in-situ cubosomes from cubosomal precursors prevents high energy procedures, which are costly and challenging to scale up, while also preserving temperature-sensitive components like proteins.

Liquid Precursors

Cubosome formation from liquid phase precursors needs a powerful driving force. Liquid precursors can be diluted to form more stable cubosomes of the required size.

Cubosomal particles are created by a nucleation and growth mechanism identical to the crystallisation and precipitation process in the hydrotrope dilution method.[26] In mouth washes and hand washes, where cubosomes might develop while rinsing and washing, respectively, liquid phase precursors are frequently employed. Since this approach does not need significant shear, the amount of active moiety degradation in cubic crystals can be reduced. The handling of bulk materials and the avoidance of high energy process procedures that damage the medicine are therefore reduced when using liquid precursors, which also provide a simple scale-up method for the manufacturing of cubosomes.

Powdered Precursors

Dehydrated surfactants coated with the appropriate polymer make up powdered cubosomal precursors. According to characterisation investigations using methods like cryo-TEM and the light scattering technique, cubosomes with an average particle size of 600 nm are created when powdered precursors are reconstituted with water. An efficient method for creating cubosomal powdered precursors is spray drying. It entails the creation of encapsulated particles from scattered solid particles in concentrated aqueous polymer solution as well as from liquid droplets in an emulsion. To scale up the manufacturing of consumer items like food and detergents, spray drying is a great option. Additionally, this method makes it simple to preload potent medications into cubosomes prior to drying.

These powdered precursors provide benefits over liquid phase cubosomal precursors in terms of processes and performance.

CAPACITY OF DRUG LOADING IN CUBOSOMES

Cubosomes exhibit diverse internal cubic structures, presenting a range of arrangements within their lipid bilayer network. Coupled with their variant composition, cubosomes offer a versatile platform for drug loading modalities. Researchers can customize the lipid components and incorporate appropriate surfactants to optimize the interaction between the drug and the cubosomal matrix.[2] This flexibility enables efficient entrapment and retention of drugs within the cubosomes, enhancing their drug loading capacity. The substantial drug loading potential of cubosomes holds great promise for drug nano formulations in melanoma therapy. Melanoma, being a highly aggressive form of cancer, often requires potent and targeted drug delivery to achieve optimal therapeutic outcomes. Cubosomes, with their ability to accommodate high drug payloads, offer a favorable solution. They provide a conductive environment for the encapsulation of a significant quantity of drugs, enabling the delivery of concentrated doses specifically to melanoma cells.

MECHANISM OF DRUG RELEASE FROM CUBOSOMES

The mechanism of drug release from cubosomes involves the release of hydrophobic and hydrophilic molecules. Factors such as size, charge, temperature, pressure, and pH affect the release kinetics. Although the precise mechanisms for the release of hydrophobic molecules are not fully understood, the partition coefficient, diffusion within the lipid bilayer, and diffusion into the surrounding water are important factors. Understanding and manipulating these mechanisms are crucial for optimizing drug release.[27] By selecting appropriate lipid composition, modifying cubosome properties, and controlling environmental conditions, researchers can influence the release rate and duration of drugs. This knowledge enables the design of precise and controlled drug delivery systems using cubosomes. Further research is needed to uncover more details about drug release mechanisms, particularly for hydrophobic molecules. Deeper insights will lead to the development of advanced strategies for efficient and predictable drug release from cubosome systems, resulting in improved therapeutic outcomes and patient care.

APPLICATION OF CUBOSOMES AS A DRUG DELIVERY SYSTEM

Ocular Drug Delivery System

Recent studies have focused on utilizing cubosomes for ocular drug delivery, taking advantage of their biodegradability and ability to encapsulate hydrophilic, hydrophobic, and amphiphilic drugs. Cubosomes offer targeted and controlled release of bioactive agents, leading to improved ocular bioavailability. Their long residence time on the corneal surface and mucoadhesive properties, attributed to GMO presence, enhance corneal permeability and increase the bioavailability of incorporated drugs.[28] Promising results have been obtained in the use of cubosomes as topical ocular drug delivery systems. *In vitro* permeation studies using cubosomes loaded with dexamethasone on excised rabbit corneas demonstrated an increase in the apparent permeability coefficient.[29] Pharmacokinetic studies and precorneal residence time tests using aqueous humor samples revealed that cubosomes formulations extended the retention time and resulted in higher dexamethasone concentrations compared to conventional eye drops. Similarly, when tropicamide, a mydriatic agent, was delivered using cubosomes, comparative evaluation studies showed no significant difference in in-vitro corneal permeation but a faster onset and higher intensity of mydriatic action in vivo compared to commercial ophthalmic solutions. Overall, cubosomes have shown great potential for ocular drug delivery, prolonging precorneal residence time, improving ocular bioavailability, and demonstrating safety and non-irritating properties based on histopathology studies.

Anticancer Drugs

Cubosomes offer a solution to the challenges encountered in oral drug delivery, particularly for compounds with poor aqueous solubility, absorption issues, and large molecular size. Moreover, they find application in local treatment within the gastrointestinal tract, even accommodating large proteins.[30] By incorporating controlled release and targeting functionalities, these liquid crystalline nanoparticles provide a versatile platform. The particles are designed to form in a controlled manner, ensuring optimal in vivo distribution of the drug. Additionally, cubosomes enable targeted release at specific absorption sites, such as the upper or lower intestine, which is crucial for drugs with narrow regional absorption windows. This technology holds promise for enhancing the effectiveness of oral drug delivery systems.

Applications in Dermatology

Due to their greater bioadhesiveness, cubic phases are ideal for the administration of many medications to the skin and mucous membranes. The foundation of topical delivery systems is the utilisation of the special characteristics of liquid crystal (LC) and liquid crystal nanoparticle (LCNP) technologies.[2] Topical drug delivery systems are distinct because they establish bioadhesive LC systems in situ, allowing for precise and efficient drug administration to mucosal surfaces (including buccal, ocular, vaginal, and others). This intriguing method creates a thin liquid crystal surface coating at mucosal surfaces, and its controllable nanostructure allows for the establishment of an appropriate delivery profile as well as effective short-term protection for sensitive and painful skin. Additionally, it provides temporary protection for

irritated and sensitive skin. The combination of bioadhesion and controlled drug release makes these topical drug delivery systems highly promising in the field of pharmaceutical research and development.

Application in Oral

Cubosomes offer a solution to the challenges encountered in oral drug delivery, particularly for compounds with poor aqueous solubility, absorption issues, and large molecular size. Moreover, they find application in local treatment within the gastrointestinal tract, even accommodating large proteins. By incorporating controlled release and targeting functionalities, these liquid crystalline nanoparticles provide a versatile platform. The particles are designed to form in a controlled manner, ensuring optimal *in vivo* distribution of the drug.[2] Additionally, cubosomes enable targeted release at specific absorption sites, such as the upper or lower intestine, which is crucial for drugs with narrow regional absorption windows. This technology holds promise for enhancing the effectiveness of oral drug delivery systems.

Applications of Cubosomes in Intravenous

The field of topical drug delivery systems has seen significant advancements through the utilization of cubic phases, which possess enhanced bioadhesive properties. These phases are particularly suitable for topical and mucosal applications, allowing for the deposition and delivery of various drugs. Topical delivery systems make use of the unique properties offered by liquid crystal (LC) and liquid crystal nanoparticle (LCNP) technologies.[2] These in situ forming bioadhesive LC systems enable controlled and effective drug delivery to mucosal surfaces such as buccal, ophthalmic, and vaginal areas, among others. This intriguing system forms a thin film on mucosal surfaces, comprising a liquid crystal matrix with controllable nanostructure, thereby achieving an optimal delivery profile. Additionally, it provides temporary protection for irritated and sensitive skin. The combination of bioadhesion and controlled drug release makes these topical drug delivery systems highly promising in the field of pharmaceutical research and development.

Table 1: In current studies cubosomes as a drug carrier.[31]

Drug	Lipid	Stabilizer	Use	Author
Dexamethasone	GMO	Poloxamer 407	Anterior ocular inflammation	Gan L *et al.*[31]
Ketorolac	GMO	Poloxamer 407	Itchy eyes	Maheshwari R *et al.*[17]
Capaicin	GMO	Poloxamer 407	Psoriasis	Bouwstra, J.A., *et al.*[32]
Indomethacin	GMO	Poloxamer 407	Antiinflammatory	Esposito E *et al.*[33]
Ibuprofen	PYT	Poloxamer 407	Analgesic	Longer M *et al.*[34]
5-fluorouracil (5 FU)	GMO	Poloxamer 407	GIT cancer therapy	Thomson A *et al.*[35]
Piperine	GMO	Poloxamer 407 -Tween 80 - Cremophor RH 40	Alzheimer's Disease	Dian L *et al.*[36]
Dacarbazine	GMO	Poloxamer 407	First- line melanoma therapy	Cheng, MR *et al.*[37]
Amphotericin B	PYT	Poloxamer 407	fungal infections like histoplasmosis	Lai J *et al.*[38]
Hydroxypropyl β cyclodextin / minoxidil complex	GMO	Poloxamer 407	Hair growth	Peng X *et al.*[39]

CONCLUSION

In conclusion, cubosomes are unique bicontinuous cubic particles formed by dispersing liquid crystalline cubic clusters in aqueous environments. They have gained significant attention in the field of pharmaceutical nanotechnology due to their ability to encapsulate a wide range of drug molecules and enhance drug bioavailability. Cubosomes offer several advantages, including improved absorption, easy production, high drug-loading capacity, stability, controlled release, and safety. However, they also have limitations such as low entrapment effectiveness for water-soluble drugs and challenges in large-scale manufacturing. The main component for manufacturing cubosomes is glyceryl monooleate (GMO), although phytantriol has emerged as a promising alternative. Stabilizing agents, particularly Pluronics, play a crucial role in preventing particle aggregation and maintaining dispersion consistency. Cubosomes can be prepared using top-down or bottom-up approaches, with each method offering specific benefits and considerations. Additionally, alternative techniques such as pseudo-binary systems, high-pressure homogenization, probe sonication, spray drying, and heat treatment have been explored for cubosome production. Overall, cubosomes show great potential as drug delivery systems, and further research and development are warranted to optimize their formulation and application in various therapeutic area.

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