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Review Article

Exploring Cubosomes as an Emerging Approach of Novel Drug Delivery System: A Review

Amitha N[1], Sandeep DS[1,*], Rajanikant P[2], Gowrav MP[3], Kathirvel S[4], Pradeep HK[5], Jeyaprakash MR[6]

[1]Department of Pharmaceutics, NGSM Institute of Pharmaceutical Sciences (NGSMIPS), NITTE (Deeemed to be University), Mangalore, Karnataka, INDIA.
[2]Department of Pharmaceutical Formulation, Granules Pharmaceuticals Inc., Virginia, UNITED STATES OF AMERICA.
[3]Department of Pharmaceutics, JSS College of Pharmacy, Mysuru, JSS Academy of Higher Education and Research, Mysuru, Karnataka, INDIA.
[4]Department of Pharmaceutical Analysis, KMCT Institute of Pharmaceutical Education and Research, Kozhikode, Kerala, INDIA.
[5]Department of Pharmaceutics, GM Institute of Pharmaceutical Sciences and Research, Davangere, Karnataka, INDIA.
[6]Department of Pharmaceutical Analysis, MB School of Pharmaceutical Sciences, Mohan Babu University, Sree Sainath Nagar, Tirupati, Andhra Pradesh, INDIA.

ABSTRACT

Cubosomes are self-assembled nanostructures that exhibit a bicontinuous cubic phase. These nanoparticles can incorporate many drugs, including amphiphilic, hydrophilic, and lipophilic substances. The structure of cubosomes is typically analyzed using techniques such as NMR, electron microscopy, X-ray diffraction, and light scattering. Cubosomes, fabricated from biocompatible and biodegradable lipids such as phytantriol and monoolein, are considered safe drug delivery carriers. They are particularly effective in enhancing the solubility of poorly water-soluble drugs and offer site-specific drug delivery, a low dissociation rate, and improved drug retention. Common methods for preparing cubosomes include spray drying, ultrasonication, solvent evaporation, and hydrotrope. Cubosomes are widely used for ocular, transdermal, and oral drug delivery approaches as well as in cancer therapy.

Keywords: Cubosomes, Phytantriol, Spray drying, Particle size.

Correspondence:
Dr. Sandeep DS M. Pharm, Ph. D
Assistant Professor, Department of Pharmaceutics, NGSM Institute of Pharmaceutical Sciences, NITTE (Deemed to be University), Paneer, Deralakatte, Mangaluru-575018, Karnataka, INDIA.
Email: sandypharama@gmail.com

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INTRODUCTION

Cellular membranes consist of a combination of proteins and lipids. Non-lamellar phases, which have high membrane curvature, are crucial for processes such as fission, fusion, membrane remodeling, and transport. Vesicles, which are commonly used in cosmetics, biosensing applications, and drug delivery, are lipid assemblies where the aqueous internal volume is enclosed by a single bilayer leaflet. Although their size can vary from 10 to 1000 nm, this range influences the ratio of lipid membrane to encapsulated volume and the curvature of the membrane, which consequently restricts their potential applications. In complex lipid membrane systems, it is essential to regulate curvature at the nanoscale to harness and replicate the properties of highly curved structures (Yaghmur and Mu, 2021).

Recently, there has been growing interest in particles with diameters in 100 nm range, which are derived from more complex membrane phases. These include hexagonal, bi-continuous, and discontinuous micellar cubic phases. The bi-continuous cubic phases stand out for their ability to control membrane curvature over large length scales, irrespective of the nanoparticle diameter. This is due to their internal structure, which features a single membrane bilayer forming a lattice with two interwoven water channels that are not directly connected (Zhang *et al*., 2020).

Lipid-based nanoparticles are dispersions containing bulk lipid phases, with stabilizers such as PEG moieties or block copolymers on the outer surface. These stabilizers enable the targeting of specific cells, independent of the other lipid membrane assemblies, resulting in nanoparticles with high stability and biocompatible lipids. Nanoparticles that feature a lipid bicontinuous cubic phase are called cubosomes (Abourehab *et al*., 2022; Singhal *et al*., 2022).

The term "cubosomes" was first introduced by Larsson. These are discrete, nano-structured, sub-micron-sized particles that form from the bicontinuous cubic liquid crystalline phase. Cubosomes are derived from lyotropic liquid crystals, which exhibit cubic crystallographic symmetry and share characteristics with liquid crystalline substances, being optically isotropic and viscous in nature (Wakaskar, 2018; Almoshari, 2022).

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Unlike liposomes, cubosomes have a well-defined hydrophobic core and a higher capacity for drug accommodation, leading to a greater payload. The core of the cubosome is surrounded by bicontinuous water channels, enhancing their effectiveness in drug delivery. Additionally, cubosomes offer better stability than liposomes and are more efficient at encapsulating hydrophobic drugs, thanks to their liquid crystalline membrane structure (Azhari *et al.*, 2021).

A major drawback of cubic phases is their high viscosity, which cubosomes overcome compared to other nanomaterials. The colloidal stability of cubosome formulations is achieved through the use of stabilizers. These molecules adsorb to the particle surface, preventing aggregation. One commonly used stabilizer is Poloxamer 407, a surfactant that helps maintain the stability of cubosomes (Meikle *et al.*, 2020; Garg *et al.*, 2021; Aubine Molly and Prasanthi, 2019).

The high internal surface area, created by the curvature of the lipid bilayers separated by internalized water channels, allows for the encapsulation and release of complex biomolecules, as well as both polar and non-polar compounds (Kaur *et al.*, 2021).

Advantages

- They are non-irritating, bioadhesive, biodegradable, and biocompatible.
- They can encapsulate hydrophobic, hydrophilic, and amphiphilic substances.
- The encapsulated drug is protected from chemical and physical degradation.
- They offer sustained drug release.
- They exhibit enhanced thermodynamic stability (Karami and Hamidi, 2016; Chaudhary and Sharma, 2021).

Disadvantages

- Their high viscosity poses a challenge for large-scale production.
- The liquefied form is a limitation of cubosomes (Gaballa *et al.*, 2020).

CUBOSOME STRUCTURE

The structure of cubosomes resembles a honeycomb, dividing the ionic surfactant and two internal aqueous channels. These nanoparticles are formed through the self-assembly of amphiphilic molecules into liquid crystalline phases They are similar to round specks, where each dot represents a pore containing aqueous cubic phases. Three distinct cubosome structures have been identified based on variations in the nodal surface: Gyroid (G-surface), Diamond (D-surface), and Primitive (P-surface). Due to their unique bicontinuous architectures, which include two separate water areas divided by a controlled surfactant bilayer, cubic phases exhibit a high, solid-like viscosity. Amphiphilic molecules create bicontinuous oil and water channels, with "bicontinuous" indicating two hydrophilic regions separated by the bilayer. The interconnected structure leads to a viscous gel that exhibits rheological properties and an appearance akin to cross-linked polymer hydrogels (Deshpande and Singh, 2017).

Figure 1: Structure of Cubosome.

Cubosomes Precursors

Liquid Cubosome Precursors

These are smaller and more stable cubosomes produced using the hydrotrope dilution method. In this process, particles are formed through nucleation, followed by crystallization and precipitation. Monoolein is dissolved in ethanol, a hydrotrope, to prevent the formation of liquid crystals. The Quid precursor technique allows for faster scale-up of cubosome preparation, eliminating the need for potentially damaging high-energy processes and the handling of bulk solids (Dyett *et al.*, 2019).

Powdered Cubosome Precursor

Powdered cubosome precursors consist of dehydrated surfactants coated with a polymer, providing several advantages over liquid cubosome precursors. Upon hydration, these powders form cubosomes with a particle size of around 600 nm, which are confirmed through cryo-TEM and light scattering techniques. The resulting cubosomes are sticky, waxy solids composed of lipids. The lipid coating helps preserve the particle size and prevents agglomeration. Spray drying is an efficient method for producing these powdered precursors (Alvarez-Malmagro *et al.*, 2020).

COMPONENTS OF CUBOSOMES

Amphiphilic lipids

Glycerol Monooleate (GMO)

The most commonly used amphiphilic lipid for cubosome production is Glyceryl Monooleate (GMO), also known as monoolein. This polar, unsaturated monoglyceride is clear, colorless, and has an HLB value of 3 and a melting point between 35-37°C. GMO is a synthetic blend of glycerides derived from oleic acid and other fatty acids, predominantly containing monooleate, which can self-assemble in water to form bicontinuous cubic structures. The head group of GMOs features hydroxyl groups that form hydrogen bonds with water, while its tail consists of hydrocarbon chains. GMO is biodegradable, non-toxic, biocompatible, and safe, making them widely used as an emulsifier in the food industry (Varghese *et al.*, 2022).

The chemical structure of GMO is represented in Figure 1.

Phytantriol

Phytantriol is a suitable alternative to GMO in cubosome preparation and is frequently used in cosmetic products. At physiological temperatures, phytantriol can form a bicontinuous cubic structure in aqueous solutions. Unlike monoglycerides, it provides greater chemical stability due to the lack of an ester group. Phytantriol is commercially available in high purity and is known for its excellent moisture retention and enhanced skin penetration properties. Phyto-based liquid crystalline matrices are considered an excellent system for sustained drug delivery, particularly for hydrophilic drugs, as they can effectively release various drug molecules over time (Ahirrao and Shrotriya, 2017).

The Chemical structure of phytantriol is depicted in Figure 2.

Stabilizers

The internal structure of cubosomes must be preserved to effectively use cubosomes in biomedical applications. The primary role of a stabilizer is to create an electrostatic barrier that keeps the dispersed particles stable and prevents interactions between them. Pluronics, water-soluble triblock copolymers consisting of Polypropylene Oxide (PPO) and Polyethylene Oxide (PEO) in a PEO-PPO-PEO configuration, are commonly used as cubosome stabilizers. The PEO portion is hydrophilic, while the PPO portion is hydrophobic. The stability of cubosomes is influenced by the strength of the steric repulsion from the hydrophilic domain and the balance between the size of the hydrophobic domain. Recently, Pluronics have been replaced by alternatives like Tween 80, lipid-based polymers, and brush copolymers produced by Reversible Addition-Fragmentation Chain Transfer (RAFT) polymerization. These alternatives offer several advantages over Pluronics, including reduced toxicity, enhanced drug targeting capabilities, well-defined molecular weight, and the incorporation of biologically active diglycerides (Patel, Patel, and Thakkar, 2021).

FORMULATION APPROACHES

Top-down approach

The top-down approach is the most widely used method for preparing cubosomes, consisting of two main steps. In the first step, the lipid(s) are mixed with a stabilizer to form the bulk cubic phase. In the second step, this mixture is combined with an aqueous solution, followed by high-energy techniques such as sonication, high-pressure homogenization, or shearing, which results in the formation of cubosomes (Alvarez-Malmagro *et al.*, 2019).

Cubosomes produced using this method remain stable and resistant to aggregation for up to a year. However, incorporating temperature-sensitive ingredients such as proteins and peptides requires considerable energy to disperse the cubic phases into cubosomes, which presents a challenge for large-scale production. Moreover, although this method achieves higher encapsulation efficiency, the use of high temperatures can affect the quality of the cubosomes (Nielsen *et al.*, 2017).

The top-down method is depicted in Figure 3.

Bottom-up approach

In this method, cubosomes crystallize or form from precursors, which can be either liquid or powder. The liquid precursor consists of a solution of ethanol and monoolein. Ethanol (a hydrotrope) is added to molten monoolein at room temperature, leading to the formation of a viscous cubic liquid gel. This gel results from the emulsification of the monoolein-ethanol solution with a poloxamer 407 solution. The generated gel is then diluted with water and subjected to sonication for 5 min, resulting in the formation of cubosome nanoparticles. The powder precursor is made by coating monoolein powder with dextran or starch. In this case, the dehydrated surfactant with its polymer coating is hydrated to form a liquid droplet emulsion. From both types of precursors, cubosome nanoparticles are obtained through the spray drying technique (Bryant *et al.*, 2021; Mohammad *et al.*, 2022).

The bootom up method for formulation of cubosomes is depicted in Figure 4.

Spray drying

Due to the limited flexibility of liquid precursors for cubosome production, a dry powder precursor was introduced for cubosome preparation using the spray drying method. This process has been used to prepare dextran-encapsulated monoolein and starch-encapsulated monoolein precursors. However, the method is limited for use with vitamins and potent medications, as the encapsulation process, which involves high proportions of polymer (60% w/w for dextran and 75% w/w for starch), reduces the amount of active material that can be loaded. To form cubosomes, water, and monoolein are mixed at 40°C to create a cubic liquid crystalline gel, which is then dispersed into

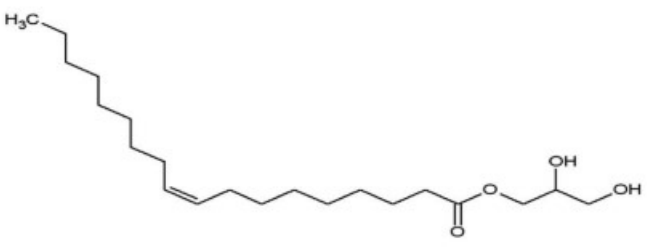

Figure 1: Chemical structure of GMO.

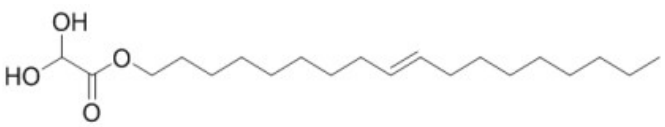

Figure 2: Chemical structure of phytantriol.

particles through ultrasonication. High-pressure homogenizers are commonly employed for the preparation of cubosomes (Mohsen *et al.*, 2021).

Melt Dispersion Emulsifying Method

In this method, stabilizers and amphiphilic lipids are melted on a hot plate magnetic stirrer. The drug is then added to the molten lipid-stabilizer mixture, which is either dissolved in the aqueous phase with a suitable surfactant or in ethanol or polyvinyl alcohol as a stabilizer. The molten lipid mixture is then introduced into the preheated aqueous phase while being stirred magnetically and emulsified using a homogenizer (Wei *et al.*, 2019).

EVALUATION OF CUBOSOMES

Cryo-Transmission Electron Microscopy

A cryo-TEM is employed to examine the morphology of cubosomes. This microscopy technique involves passing a beam of electrons through an ultrathin specimen, where the electrons interact with the sample. As the electrons travel through, they generate an image that can be magnified and focused onto an imaging device, such as photographic film, a fluorescent screen, or a sensor (Abo El-Enin, 2020).

Determination of drug loading and encapsulation efficiency

Gel permeation chromatography or ultrafiltration techniques are used to assess the drug loading and encapsulation efficiency of cubosomes. The drug content in the filtrate can be analyzed using a UV spectrophotometer or HPLC. Drug loading and encapsulation efficiency can then be calculated using specific equations (Abo El-Enin, 2020).

Drug loading = (Winitial-Wfree)/(Winitial-Wfree + Wexcipients) × 100%

Encapsulation efficiency (%) = (Winitial-Wfree/Winitial)× 100%

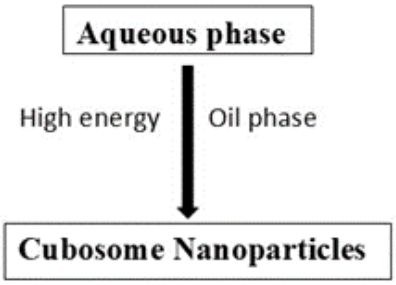

Figure 3: Top-down technique for cubosomes preparation.

Differential scanning calorimetry

Differential Scanning Calorimetry (DSC) is used to conduct the thermal analysis of cubosomes. Helium and nitrogen are used as purging gases. After weighing, the samples are placed in an aluminum crucible and introduced into the DSC under a nitrogen gas atmosphere. The samples are then heated at a constant rate, and the resulting thermogram peaks are compared with standard references (Younes *et al.*, 2018).

Zeta potential and particle size

Photon correlation spectroscopy with a ZetaSizer is used to determine the zeta potential and particle size of cubosomes. The data is presented as the average volume-weighted size, with samples taken in triplicate (Nasr and Dawoud, 2016).

Small angle X-ray scattering

Small-angle X-ray scattering is used to determine the spatial arrangement of groups within a sample. The setup includes a detector and a micro X-ray source. Peak positions are obtained from plots of intensity versus q value, and these peaks are subsequently converted into Miller indices. By matching the Miller indices with known values for various space groups and liquid crystalline structures, the dominant internal nanostructure of the sample can be identified (Ramalheiro *et al.*, 2020).

Stability studies

Physical stability can be assessed by examining the morphological and organoleptic characteristics over time. Changes in drug content and particle size distribution at specific time intervals can be used to evaluate any variations as time progresses (Victorelli *et al.*, 2022).

PHARMACEUTICAL APPLICATIONS OF CUBOSOMES

Anticancer formulations

Many anticancer drugs have been successfully encapsulated in cubosomes and characterized for their physicochemical properties. Cubosomes can directly target diseases at the site of injection within the body. This capability is particularly beneficial in cancer therapy, as the effectiveness of targeting cancer relies on the size of the delivery system, taking advantage of the enhanced permeability and retention effect. Cubosomes have been used to encapsulate various drugs, such as curcumin, paclitaxel, and doxorubicin (Cytryniak *et al.*, 2020).

Topical formulations

For topically applied drugs, the stratum corneum acts as a barrier to skin penetration. In transdermal drug delivery, cubosomes serve as an effective vehicle due to their unique properties and structure. Thanks to their bioadhesive nature, resulting from the presence of GMOs, cubosomes can be used for both mucosal and

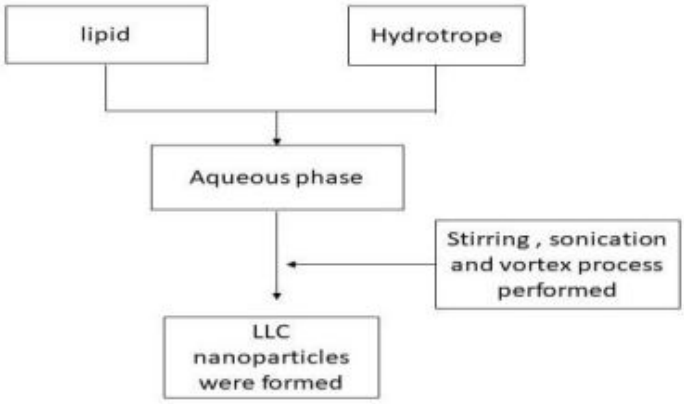

Figure 4: Bottom-up technique for cubosomes formulation.

topical delivery, adhering well to the stratum corneum (Nasr, Younes, and Abdel-Rashid, 2020).

Ocular drug delivery systems

Numerous studies have explored the use of cubosomes for ocular drug delivery, thanks to their ability to encapsulate amphiphilic, hydrophilic, and hydrophobic molecules. Cubosomes enhance the ocular bioavailability and corneal permeability of the incorporated drugs by providing prolonged residence time in the cornea and exhibiting mucoadhesive properties due to the presence of GMO (Eldeeb, Salah, and Ghorab, 2019).

Oral drug delivery systems

Cubosomes are used for the oral delivery of drugs with large molecular sizes, poor absorption, and low aqueous solubility. The bioavailability of tamoxifen citrate was enhanced by formulating sorbitol-based powder precursors of cubosomes. Studies aimed at improving the oral bioavailability of the poorly soluble tamoxifen involved both *in vitro* and *in vivo* evaluations in rats. The results from these evaluations demonstrated a higher rate and extent of drug absorption from the powder precursor (Chountoulesi *et al.*, 2022).

CONCLUSION

Cubosomes are nanoparticles derived from lipid bi-continuous cubic phases. Compared to liposomes, cubosomes offer a larger surface area, enabling more efficient loading of active substances. They are capable of encapsulating a broad range of compounds, including amphiphilic, hydrophobic, and hydrophilic substances, providing notable advantages over traditional emulsion systems and liposomes. With a honeycomb-like structure, cubosomes typically consist of glycerol monooleate, phytantriol, and a suitable stabilizer. Various methods, such as top-down, bottom-up, spray drying, and melt dispersion emulsification, are used to prepare cubosomes, with the top-down method being the most commonly employed. To evaluate cubosomes, parameters like particle size, zeta potential, drug loading, and encapsulation efficiency are analyzed. Additional characterization techniques, such as TEM, FTIR spectroscopy, differential scanning calorimetry, and small-angle X-ray scattering, are also used. Cubosomes have wide-ranging applications in cancer therapy, transdermal, ophthalmic, and oral drug delivery systems. Their excellent stability and mucoadhesive properties make them ideal for drug delivery, and their use in the pharmaceutical industry is growing.

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ABBREVIATIONS

GMO: Glyceryl Monooleate; **HLB:** Hydrophilic Lipophilic Balance; **TEM:** Transmission Electron Microscopy; **DSC:** Differential Scanning Calorimetry; **HPLC:** High-Performance Liquid Chromatography; **FTIR:** Fourier Transform Infrared; **NMR:** Nuclear Magnetic Resonance; **PPO:** Polypropylene Oxide; **PEO:** Polyethylene Oxide; **RAFT:** Reversible addition-fragmentation chain transfer; **PEG:** Polyethylene Glycol; **nm:** Nanometre; **UV:** Ultraviolet.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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