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Cubosomes as Versatile Nanocarriers: From Structure to Biomedical Applications

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A B S T R A C T

Cubosomes are single, sub-micron-sized entities with a characteristic internal structure referred to as the bicontinuous cubic liquid crystalline phase. In other words, they are a lipid bilayer that forms a periodic, continuous three-dimensional lattice with two distinct but interpenetrating channels of water, forming a tight honeycomb-like pattern. These nanostructures consist predominantly of amphiphilic lipids, which are molecules with both hydrophilic (water-attracting) and hydrophobic (water-repelling) regions; therefore, in aqueous solutions, they spontaneously self-assemble to produce stable cubic-phase particles. Cubosomes are unique among nanoparticles because of their ability to deliver and encapsulate an enormous range of substances, including hydrophilic, hydrophobic, and amphiphilic agents; thus, they are highly beneficial in drug delivery and other biomedical applications. Cubosomes have also been studied in the fields of pharmaceuticals, cosmetics, and biotechnology because of their ability to safely and effectively deliver drugs, genes, and vaccines. Cubosomes play a critical role in nanotechnology and drug delivery because they are versatile, stable, have high loading capacity, and can be delivered in a controlled and targeted manner, making them a promising platform for various therapeutic and biomedical applications.

Keywords: Cubosomes, Bicontinuous Cubic Phase, Lipid Nanoparticles, Controlled Release, Therapeutic Applications.

1. INTRODUCTION

Cubosomes are single, sub-micron-sized particles with a distinctive internal structure known as the bicontinuous cubic liquid crystalline phase. That is, they are a single lipid bilayer that creates a continuous, periodic three-dimensional lattice with two different but interpenetrating channels of water, which creates a dense honeycomb-like structure.[1]

These nanostructures are largely composed of amphiphilic lipids, molecules bearing both hydrophilic (water-attracting) and hydrophobic (water-repelling) domains, such that in aqueous solution, they self-assemble to form stable cubic-phase particles. Cubosomes are remarkable among other nanoparticles in that they can encapsulate and deliver a vast variety of substances, both hydrophilic, hydrophobic, and amphiphilic agents, and therefore are very useful in drug delivery as well as in other biomedical applications.[2]

The following are the key characteristics of cubosomes:

•High drug loading capability in internal surface area

•Aqueous stability

•Bioadhesiveness and biocompatibility

•Suitability for controlled and targeted delivery of the entrapped substance.[3]

Cubosomes have also been explored in pharmaceuticals, cosmetics, and biotechnology because they can efficiently and safely deliver drugs, genes, and vaccines. These are significant in nanotechnology and drug delivery because they combine versatility, stability, high loading capacity, and the ability to provide controlled and targeted delivery, making them a promising platform for a wide range of therapeutic and biomedical applications.[4]

2. STRUCTURAL FEATURES AND COMPOSITION

2.1. Structural Features

•Bicontinuous Cubic Structure:

Cubosomes are nanostructured particles with a three-dimensional bicontinuous cubic liquid crystalline structure. This refers to highly organized inner structure composed of twisted lipid bilayer that creates a repeating cubic lattice resulting in two distinct but continuous water channels within the particle.[5]

•Honeycomb-like Architecture

The internal structure is honeycomb- or labyrinth-like, with hydrophilic (water-loving) and hydrophobic (fat-loving) regions. This enables cubosomes to encapsulate a broad range of substances, such as hydrophilic, hydrophobic, and amphiphilic molecules.[1]

• Crystallographic Symmetry:

Cubosomes have cubic crystallographic symmetry and can exist in various cubic phases, primarily:

Pn3m (Diamond surface)

Ia3d (Gyroid surface)

Im3m (Primitive surface)

These phases are characterized by the geometric organization of the lipid bilayers and water channels.[6,7]

• Particle Size:

Cubosomes have diameters ranging from 10 to 500 nanometers and are suitable for drug delivery as they are small and have a high internal surface area.[1]

•Thermodynamic Stability:

They are also thermodynamically stable and they maintain their structure even after high dilution, which is not achievable in most other liquid crystalline systems.[1]

2.2. Composition

•Lipids:

The major constituent is an amphiphilic lipid, predominantly monoolein, but others, such as glyceryl monophosphate and phytantriol, have also been employed. These lipids spontaneously assemble in water to produce cubic-phase structures.

• Surfactants/Stabilizers:

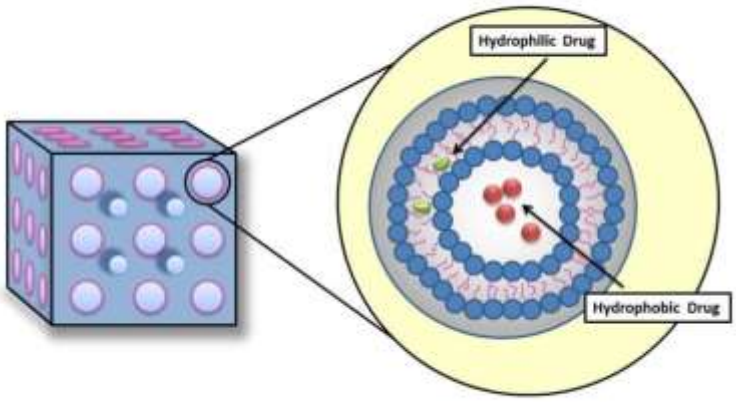
Surfactants such as Poloxamer 407 (PEO-PPO-PEO tri-block copolymer) are employed to stabilize cubosomes to prevent aggregation or fusion to form larger bulk phases34. The surfactant creates a layer on the cubosome surface, ensuring colloidal stability.

•Water:

Water is necessary for the formation of bicontinuous cubic phases, as it occupies the channels formed by the lipid bilayer and aids in self-assembly.

•Additional Polymers:

Occasionally, other polymers are added to further add stability or drug release modification properties.[8]



STRUCTURE OF CUBOSOMES

2.3. Summary Table

Component	**Role/Function**
Lipid	Formation of cubic lattice and bilayer structure
Surfactants	Particle stabilization, aggregation prevention
Water	Fills channels, allows self-assembly
Polymers	Optional, for increased stability or functionalization

3.PROPERTIES OF CUBOSOMES

Cubosomes possess unique properties that make them ideal for the delivery of drugs and other useful substances.

•**Different Internal Structure**

Lipids within cubosomes form a 3D cubic structure with two distinct water channels. This structure is similar to that of a miniature honeycomb.

•**Large Surface Area**:

Their internal structure gives them a large surface area, which enables them to hold many different kinds of drugs—whether they are hydrophilic, lipophilic, or both.

•**Robust Structure**:

Cubosomes are stable and maintain their shape even after dilution with water, unlike other particles of the same nature.

•**Stay Well Dispersed:**

They are kept apart and do not aggregate because of special stabilizers (such as Poloxamer 407) that coat their surface.

•**Tiny Size:**

They are very small—usually between 100 and 500 nanometers—because of which they can easily penetrate cells.

• **Effective for Poly-Drug Delivery**

They can simultaneously carry water-loving, fat-loving, or mixed-type medicines at the same time, which the majority of other carriers cannot do.

•**Controlled Drug Release:**

Their complex inner channels slow the rate at which medicines leave, thereby offering prolonged and sustained delivery.

•**Safe for the Body**:

Cubosomes are unlikely to induce immune reactions or toxicity because they are predominantly composed of natural fats and non-harmful stabilizers.

• **Uniform Optical Properties**:

Their radial configuration makes them even in action with light, irrespective of the direction. [9,10]

Advantages

•Improved drug loading for hydrophilic, hydrophobic, and amphiphilic drugs

•Controlled and sustained drug release

•Biocompatible and biodegradable

•Thermodynamically stable even when diluted

•easy to produce with scalable procedures

•Potential for targeted delivery by surface modification

•Improved bioavailability of drugs having low solubility

•Applicable for diverse administration routes (oral, topical, ocular, intravenous).[1,4]

4. Methods of Cubosome Preparation

Cubosomes are predominantly prepared using two primary methods: top-down and bottom-up. Spray-drying and solvent evaporation methods have also been utilized, but to a lesser extent.

1. Top-Down Method

•One of the most commonly used methods, especially with lipids such as glyceryl monooleate (GMO).

•Process:

The bulk cubic phase is first generated by mixing the lipid and stabilizer (typically Poloxamer 407).

A high-energy input (such as sonication, high-pressure homogenization, or ultrasonication) is used to break down the bulk cubic phase into nanosized cubosomes.

Advantages:

Produces stable cubosome dispersions for up to one year.

Limitations:

1. Temperature-sensitive drugs, such as proteins or peptides, can be destroyed by high energy input.
2. Scaling can be challenging because of energy requirements.

2. Bottom-Up Approach (Solvent Dilution or Hydrotrope Method)

Low energy is used in this method, and it can be applied to temperature-sensitive compounds.

Process:

- Lipids are dissolved in a hydrotropic solvent (e.g., ethanol) and diluted with an excess amount of water containing a stabilizer.
- Cubosomes formed spontaneously as the solvent concentration decreased, with controlled particle nucleation and growth.

• Advantages:

Less energy is required to preserve sensitive bioactive agents.

It is easier to scale up and control the particle size.

• Key Factor:

Hydrotropes control lipid solubilization and prevent premature liquid crystal formation.

3. Spray-Drying Method

• Transfers liquid cubosome dispersions to dry powders for convenient storage and handling.

• Facilitates the preparation of powdered cubosome precursors that rehydrate to yield cubosomes.

• Prevents aggregation and increases stability during storage.

4. Solvent Evaporation

• Organic solvents are evaporated to prepare lipid and stabilizer films, which are then hydrated and dispersed by sonication or homogenization.

5.Other Methods

• Microfluidization and other high-energy mechanical processes are also used to reduce the particle size. [1,11]

Summary Table

Method	**Energy Input**	**Suitable For**	**Advantages**	**Limitations**
Top-Down	High	Thermostable drugs	Stable, well-dispersed cubosomes	Not ideal for heat-sensitive drugs; scale-up issues
Bottom-Up	Low	Temperature-sensitive drugs	Low energy, easy scale-up	Requires careful solvent control
Spray-Drying	Moderate	Powdered	Improved storage and stability	Additional processing step
Solvent Evaporation	Moderate	Various	Simple film hydration method	Use of organic solvents

In summary, the **top-down method** is the most common for producing stable cubosomes but involves high energy, whereas the **bottom-up method** offers a gentler alternative suitable for sensitive molecules. Spray drying and solvent evaporation provide additional options for formulation and storage. The choice depends on the drug properties and intended application.

Characterization Techniques for Cubosomes

There are several methods to examine their size, shape, structure, and drug-carrying ability. The main techniques are as follows:

1. Small Angle X-ray Scattering (SAXS)

1. This helps to observe the special internal 3D pattern (cubic structure) inside cubosomes.
2. This confirms that the cubosomes have the correct repeating lattice inside.

2. Transmission Electron Microscopy (TEM) and Cryo-TEM

- Takes close-up pictures of cubosomes to show their shape and size.
- Cryo-TEM keeps cubosomes in their natural watery state so we can see their inner structure clearly.

3. Dynamic Light Scattering (DLS)

- The size of the cubosome particles and the uniformity of their size are measured.

4. Zeta Potential Measurement

1) The surface charge of cubosomes was checked to determine their stability in a solution (whether they clump together or remain apart).

5. Differential Scanning Calorimetry (DSC) and Nuclear Magnetic Resonance (NMR)

i. DSC studies the behavior of cubosomes when heated or cooled (important for stability).

ii. NMR examines the movement and organization of lipid molecules inside cubosomes move and organize.

6. UV-Visible Spectroscopy

- The amount of drug inside the cubosomes was measured by checking the amount of light absorbed by the drug.

7. Rheological Studies

1) The thickness or runniness of the cubosome mixture affects its ease of use.

8. X-ray Diffraction (XRD)

- It Confirms the crystalline structure of the cubosome materials.[11,12]

Summary Table

Technique	**What It Shows**
SAXS	Internal 3D cubic structure
TEM / Cryo-TEM	Shape and size of cubosomes
DLS	Particle size and uniformity
Zeta Potential	Stability in solution
DSC	How cubosomes react to heat
NMR	Movement of lipid molecules
UV-Vis Spectroscopy	Amount of drug inside
Rheological Studies	Rheological Studies
XRD	Crystalline structure

5. Drug Delivery Applications of Cubosomes

Cubosomes are multifunctional nanocarriers used in different drug delivery applications because of their cubic structure and biocompatibility.

•Cancer therapy: Anticancer drugs can be delivered with high loading, controlled release, and targeted delivery to tumors.

•Oral delivery: Increased solubility and bioavailability of poorly water-soluble drugs with sustained release.

• Transdermal/topical delivery: Enhances skin penetration and delivers sustained release for skin diseases.

•Ocular delivery: Enhances drug retention and absorption on the eye surface to provide improved treatment.

•Intravenous and brain targeting: Enables delivery through biological barriers for systemic and brain treatments.

•Cosmeceuticals: Employed in cosmetics for controlled release of active components enhancing skin well-being.[4,13]

Limitations

•Risk of particle agglomeration in the absence of appropriate stabilization

•Optimization complexity involving size, loading, and release

•Scale-up issues, particularly with high-energy procedures

•Drug leakage risk during storage or dilution

•Few clinical applications due to regulatory and safety barriers

•Susceptible to environmental conditions such as pH and temperature

Cubosomes have huge potential as drug carriers but need careful formulation and development before they can be applied broadly in the clinic.[2]

5.1 Recent Advances

1) Improved drug loading and controlled release for diverse drugs
2) Surface modification enables targeted and smart delivery
3) Advanced imaging techniques enhance understanding of structure and drug interactions
4) Effective topical and ocular delivery due to
5) bioadhesion and membrane-like structureEnhanced formulation methods improve stability and scalability. [1]

S.NO	DRUG	METHOD	PURPOSE
1	Beclomethasone	Top-Down technique	Treat Uveitis and enhance
2	Flurbiprofen	Hot and High-Pressure Homogenization	Ophthalmic delivery enhances Bioavailabilityand low irritancy
3	Brimonidine tartrate	Emulsification Technique	Treat Glaucoma with sustained release manner
4	Amphotericin B	High Pressure Homogenization	Enhances Oral Bioavailability
5	Norfloxacin	Emulsification Technique	Treat Otitis externa

5.2. Future Prospects

1. More clinical trials needed for regulatory approval and widespread use
2. Potential for personalized and precision medicine applications
3. Integration with gene therapy, immunotherapy, and biologics for multifunctional delivery
4. Research focused on overcoming scale-up, stability, and sterilization challenges
5. Expansion into vaccines, anti-inflammatory, and chronic disease treatments

Cubosomes show great promise as advanced drug carriers with ongoing developments aimed at clinical translation and broader therapeutic use.[14]

6. CONCLUSION

Cubosomes hold a pivotal position in the realms of nanotechnology and drug delivery, primarily because they bring together several advantageous characteristics. Their versatility arises from their unique bicontinuous cubic structure, which allows them to encapsulate a wide array of hydrophilic, hydrophobic, and amphiphilic substances. This makes them suitable for a variety of therapeutic applications. The stability of cubosomes, even upon dilution, ensures that they maintain their structural integrity, which is crucial for reliable drug delivery.

Moreover, their high loading capacity means they can carry a significant amount of drug, enhancing their efficiency. The ability to provide controlled and targeted delivery further enhances their appeal, as drugs can be released at a specific rate and location, maximizing therapeutic effects while minimizing side effects. Because of these combined benefits, cubosomes represent a promising platform for a broad spectrum of therapeutic and biomedical applications, ranging from cancer therapy to vaccine delivery, and hold significant potential for future advancements in nanomedicine.

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Conflict of interest:

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