

CUBOSOMES: A REVIEW

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ABSTRACT

Cubosomes are self-assembled, lipid-based nanoparticles featuring a unique bicontinuous cubic liquid crystalline structure—a continuous lipid bilayer intertwined with interconnected water channels. This internal architecture allows them to simultaneously encapsulate hydrophobic, hydrophilic, and amphiphilic therapeutic agents with high loading capacity, biocompatibility, and controlled release properties. Structural & Functional Superiority offers distinct advantages in solubility, stability, and bioavailability compared to traditional nanocarriers like liposomes, niosomes, and lipid nanoparticles. Versatile Delivery Routes can be applicable across oral, topical, transdermal, ocular, pulmonary, intranasal, and parenteral administration. Targeted & Advanced Applications are utilized in cancer therapy, brain targeting, gene delivery, vaccines & antimicrobial treatments. Cubosomes are formulated through specific preparation techniques and evaluated using specialized analytical methods for structural integrity and release kinetics. Preclinical success about cubosome is strong, but widespread clinical adoption requires overcoming scale-up manufacturing, long-term stability, and regulatory hurdles. Integration with AI, Quality-by-Design (QbD), and precision medicine is key to their future clinical viability.

KEYWORDS: Cubosomes, Lipid-Based Nanocarriers, Controlled Drug Delivery, Targeted Drug Delivery, Liquid Crystalline, Nanoparticles.

INTRODUCTION^[1-5]

Larsson first used the word "cubosomes," which is comparable to liposomes. The discrete, sub-micron-sized particles of the bicontinuous cubic liquid crystalline phase are known as cubosomes. One particular advantage of the bicontinuous cubic phases is their capacity to adjust the curvature of the membrane. Cubosomes are liquid crystalline particles that self-assemble and have a solid-like rheology. One possible quarter state of matter is liquid crystals.

By providing increased therapeutic effectiveness and better medication targeting capabilities, nanocarrier-based drug delivery technologies have transformed pharmaceutical research. Cubosomes are a unique kind of lipid-based nanocarriers among these systems, distinguished by their bicontinuous cubic liquid crystalline structure.

When certain amphiphilic molecules are distributed in an aqueous environment under the right circumstances, these self-assembling structures spontaneously arise.

Lipids, polymers, and surfactants—which are often amphiphilic—make up these cubosomes. In this context, "bicontinuous" refers to the division of two distinct water enclosures by surfactant bilayers.

Cubosomes have a number of beneficial characteristics that set them apart from other nanocarrier systems. Their bioadhesive nature encourages improved contact with biological membranes, and their large interior surface area allows for significant drug loading capacity. Cubosomes are particularly appealing for pharmaceutical applications due to their structural stability under excess water circumstances and their capacity to shield delicate medicinal molecules from destruction. Despite these benefits, there are certain drawbacks that should be taken into account.

Large-scale production is hampered by the cubic phase's high viscosity, and the water content of their structure may have an impact on how well hydrophilic medications are entrapped. The basic characteristics of cubosomes are examined in this paper, along with their composition, production processes, characterisation methods, and several therapeutic uses.

ADVANTAGES^[6-9]

- Cubosomes are biocompatible, biodegradable, non-irritating, non-allergic, and bio-adhesive.
- Its preparation process is straightforward. Their large interior surface area gives them a great drug-loading capacity.
- For an extended duration, they exhibit thermodynamic stability.
- It is physicochemically stable, even when there is too much water.
- They can encapsulate hydrophilic (like cyclosporine), hydrophobic/lipophilic (like cinnarizine), and amphiphilic compounds.
- A specific polymer can be used to provide both targeted and controlled release of bioactives. Its size contributes to its superior bioavailability.
- The overall cost of health care is reduced since there are fewer recurrent administrations.
- They lessen adverse effects associated with injection-related burst release.
- The ratio of particle volume to bilayer area is higher than that of liposomes.
- Cubosomes are superior solubilizers when compared to other traditional carriers (based on lipids).
- They demonstrated the ability to encapsulate medications that are just weakly soluble in water.
- They serve as a carrier for the delicate drug moiety that is being broken down by enzymes (proteins, peptides).
- They increase water-soluble peptides' bioavailability by around 20–100%.
- Organic solvents are not needed for producing cubosomes using shear and homogenization processes.

DISADVANTAGES^[10-12]

- Because cubosomes contain a lot of water, there is less trapping of water-soluble medicines.
- The high viscosity of cubosomes makes their large-scale manufacture challenging.

- Without the use of a particular polymer, regulated medication delivery is not feasible.
- They might cause leaks during in-vivo transfers or storage. Particle growth is possible after prolonged exposure.
- If the external environment changes, cubosomes can induce a phase shift (their dynamics).

TYPES^[13-18]

Liquid Cubosome Precursor: This involves the production of particles by nucleation, followed by growth through saturation. It has been noted that the hydrotrope dilution process results in smaller and very stable cubosomes. Monoolein is dissolved in any hydrotrope to produce this. The mixture then spontaneously precipitates or crystallizes after being diluted. It bulks solid handling and prevents high-energy operations. It makes it simple to scale up the synthesis of cubosomes 47, 48. These are typically found in mouthwashes and hand washes.

Powdered Cubosome Precursors: They are made up of a polymer-coated, dehydrated surfactant. The precursor powders hydrate to generate the cubosomes. Here, the lipids are waxy, sticky solids. Spray drying procedure 48, which is appropriate for large-scale manufacturing, is the process that works well for this.

STRUCTURE^[19-22]

Cubic nanoparticles have three-dimensional hierarchically structured lipid and water regions, giving them a honeycomb-like appearance. Changes in the lipid content of cubosomes might regulate their internal and structural alterations. These are distinct, sub-micron nanostructures with diameters ranging from 100 to 500 nm. The X-ray scattering method was initially used to identify cubosomes. These resemble round or square-shaped specks that indicate the existence of pores with aqueous cubic phases in the lipid-water system. The fascinating bicontinuous structures that contain two distinct areas of water separated by a regulated bilayer of surfactant give the cubic phases their high viscosity. Cubosomes contain cubic crystalline structures and a large interior surface area. Water and monoolein make up the majority of cubosome structure.

Cubosomes' intricate hierarchical structure has a direct impact on how well they operate as drug delivery vehicles. The basic structure consists of two different networks of water channels made up of continuous lipid bilayers organized in a three-dimensional cubic lattice. These channels, which are usually between five and ten nanometers in diameter, are essential in establishing the system's drug loading capacity and release properties.

COMPONENTS^[23-28]

The primary ingredients of cubosome formulation include polymers, amphiphilic surfactants, and natural lipids with bicontinuous cubic phases. In the presence of water, lipids such as monoglycerides, glycolipids, phospholipids, and urea-based lipids can self-assemble. GMOs are typically referred to as phytantriol and monoolein. The primary antecedent to cubosome formation is monoolein, which comes in two different forms. These come in two forms: distilled monoolein and mixed glyceride. Because distilled monoolein is pure, it may be used in medications.

It is said to as "generally recognized as safe" (GRAS).

Poloxamer (concentration range 0%-20%w/w) is the most often utilized surfactant in cubosome formulation. An alternative to poloxamer as a stabilizing agent is polyvinyl alcohol. GMO is a biodegradable lipid since it has an ester moiety. There are structural similarities between GMO (which forms a bicontinuous cubic phase) and oleylglycerate (OG), which produces a reverse hexagonal phase.

GMO-induced hemolysis was emphasized in certain publications about the parenteral usage of GMOs. When creating the oral dose form, the OG is safe. When compared to GMOs, phytantriol has advantages including improved penetration, time-controlled and sustained release, structural stability, and high purity. A good substitute for a genetically modified organism is phytantriol. Although phytantriol has a longer branched hydrocarbon chain than GMO, it is more hydrophobic. GMO is hence more adaptable. The drug-polymer compatibility is the physicochemical element that should be taken into account when choosing excipients. Polymers are given preference in order to reduce the stability problem, and the carrier molecule's melting point should be higher than 45 °C.

Mechanisms of Drug Transport^[29-34]

The movement of drug molecules across biological membranes is significantly influenced by the material composition and physiology of the cell membrane. The two primary mechanisms of drug transfer are transcellular and paracellular transporters. Intra- and intercellular transports (trans and para) are common components of skin membrane transport systems. By modifying the carriers, drugs can be included into the core or as an intrinsic part of the vesicles.

Paracellular diffusion is the process by which a material crosses a membrane by moving between two cells rather than through them. By definition, this process is completely passive and depends not only on the pore size but also on the size and form of the xenobiotic. Transcellular diffusion is the process by which a drug moves through a cell.

The drug interacts with the cell's enzymes and any efflux pumps on the membrane's apical region when intestinal absorption occurs via transcellular diffusion. The amount of medicine that reaches the systemic circulation may decrease as a result. There are three types of cell diffusion: passive, aided, and active. The most common approach is drug transport by transcellular mobility, or drug transit across cells. Nevertheless, certain drugs are too polar to pass through the lipoidal cell membrane; in these situations, the paracellular pathway, which joins the cells, is typically the sole available pathway.

FORMULATION TECHNIQUE/ METHOD OF PREPARATION^[35-41]

Cubosome formation methods include solvent evaporation, spray-drying, top-down, and bottom-up. Nonetheless, the top-down and bottom-up approaches are the primary methods for preparation. As previously mentioned, both methods need an appropriate stabilizer, such F127, to stop cubosome dispersion aggregation. The goal of choosing the best approach is to guarantee stability, biocompatibility, and the best possible drug release via the cubosomes' cubic matrix.

- 1. Top-Down Approach:** This is the most popular technique for creating cubosomes, particularly when using glyceryl monooleate (GMO) as a lipid polymer. To create the fine dispersion of cubosomes using this method, significant energy levels must be used. The procedures are as follows: first, an appropriate stabilizer is added to a lipid to produce bulk cubic aggregates; next, high energy is applied through a homogenizer to generate the dispersion. Cubosomes made using this method are fortunately stable for up to a year. However, the primary disadvantage of this approach is that the incorporation of temperature-sensitive bioactive molecules, particularly peptides and proteins, makes the application of high amounts of energy impractical for manufacturing large-scale batches.
- 2. Bottom-Up Approach:** The other method for cubosome preparation is the bottom-up approach, which is widely used when preparing cubosomes containing phytantriol as the lipid. This approach is also known as the solvent dilution method. This method requires a low energy input compared with the top-down approach. This approach focused on forming cubosomes with a hydrotrope and stabilizer in an excess of water by applying minimal energy.

In this technique, the hydrotrope is the key factor, as it controls the solubilization process to dissolve the water-insoluble lipids. It also prevents the formation of liquid crystals at high concentrations. The hydrotrope acts as a surface-active agent and is a molecule able to solubilize poorly soluble agents in aqueous media by hydrotropic solubilization. The bottom-up technique has advantages over the top-down approach because it requires low energy; thus, it can be safely used for the preparation of cubosomes incorporated with temperature-sensitive agents. Due to the uniform dispersion of stabilizers on the surface of the produced nanoparticles, this technique shows long-term formulation stability.

3. **Spray-Drying Method:** The spray-drying method is used in order to formulate powder precursors of cubosomes, and involves the use of organic solvents that evaporate upon the application of air. The lipid-surfactant solvent mixture is atomized with a wave of hot air, resulting in rapid solvent evaporation and the formation of the dry powder form of the cubosome precursor. It starts with mixing the lipid with the stabilizer and then dissolving them into ethanol (binary solutions can also be used). A separate mixture of aqueous phase, consisting of a hydrophilic solid carrier, i.e., sorbitol or dextran, is prepared, which is then combined with the previously prepared lipid mixture. Both mixtures are combined with continuous stirring, which leads to the formulation of a low viscosity emulsion. This technique is simple, cost effective, and normally easy to scale-up.
4. **Solvent Evaporation Method:** Solvent evaporation is another method of producing powder cubosomes by using a homogenizer or ultra-sonicator. The process is quite similar to the spray-drying method, except for the use of a high-energy sonicator. In this method, first, an organic solvent such as ethanol or chloroform is used to dissolve the lipids, which are then added dropwise to the other mixture containing a stabilizer, such as Pluronics in aqueous phase. The mixture is maintained at an elevated temperature under magnetic stirring. The drug can be dispersed in the lipid or the aqueous surfactant solution. Stirring under elevated temperatures removes the volatile organic solvent, and the mixture is homogenized by ultra-sonication or homogenizer, resulting in the formation of cubosomes.

CHARACTERIZATION^[42-46]

- ❖ **Visual Inspection Studies:** In this, the cubosomes are inspected for their external appearance, such as morphology, turbidity, color, uniformity, and presence of particles.
- ❖ **Viscosity:** Viscosity could be assessed by use of viscometer, i.e., Rotational Brookfield Viscometer.
- ❖ **Polarized Light Microscopy:** The possibly surface coating of the cubosomes can be revealed by using polarized light microscopical method. This can also be used to distinguish between isotropic and anisotropic substances.
- ❖ **Particle Size Analysis:** In this, the samples are diluted with compatible solvent and are exposed to 300 Hz, which is the scattering intensity of light at 25 °C. It is measured by dynamic laser light scattering by the use of a Zeta sizer. In this, the PDI and zeta potential can also be measured. It gives data that contains the average weight, volume, size. For the determination of particle size by Malvern zeta sizer, there is a need; that is, the samples could be diluted to 100 folds with water.
- ❖ **Entrapment Efficiency:** For knowing the entrapment efficiency, 1 ml from each of the dispersions was taken and diluted with 4 ml of deionised water. Again 1 ml of the diluted dispersion is taken and further diluted with another 4 ml of deionised water. This formed dispersion is passed through a syringe filter with pore size of 0.1 µm and the filtrate was analysed spectrophotometrically at 250 nm. Considering the dilution factor, this obtained concentration was multiplied by the total volume of the dispersion produced. This gives the free concentration of

drug (C_f) which when reduced from the total drug concentration (C_t) gives the amount of drug entrapped in the cubosomes to get more accurately, each experiment was repeated 3 times.

$$\text{Entrapment efficiency \% of cubosomes} = \left[\frac{(C_t - C_f)}{C_t} \right] \times 100$$

- ❖ **Particle Size Distribution:** Measurements Characterization of both spray dried powders and the aqueous dispersions of cubosomes is carried out by using laser diffraction.
- ❖ **Differential Scanning Calorimetry:** DSC could give information about whether the phase transition occurs or not, as the liquid crystals are thermodynamic equilibrium systems, as the endothermic and exothermic processes are responsible for phase transitions.
- ❖ **Stability Studies:** In this, the stability could be assessed on the basis of organoleptic as well as morphological characteristics with respect to the time period. Also, the drug content and particle size distribution determination with the time. In this, evaluations of possible changes with respect to time are studied.

APPLICATIONS^[47-50]

- ❖ **For the Controlled and Sustained-release Behavior:** This is achievable because of the unique behavior of cubosomal particles, i.e., the leftovers. It is the most popular application of cubosomes achieved by researchers. The cubic phase is the one that is very favorable for controlled release, as it has a small (5-10 nm) pore size. A variety of ingredients or API's having different physicochemical characteristics could be encapsulated in cubosomes. Because of the advantage of biodegradability of cubosomal material by enzymes, controlled and sustained release of drug is achievable, and they are not accumulating inside the body.
- ❖ **As a Drug Delivery Vehicle:** Some companies (L'Oréal & Nivea) are trying for the cosmetic formulation (O/W emulsion stabilizers, pollutant absorbents, etc.), which consists of the use of cubosomes. This is a very common use of cubosomes and is a universal application of cubosomes.
- ❖ **For Topical Drug Delivery Systems:** As the nature of cubosomes is very bio-adhesive, therefore they are used in mucosal as well as topical drug delivery systems. They are useful for providing protection for skin sensitivity. Cubosomes possess high permeability as they consist of ethanol, and ethanol is responsible for the disruption of the skin. Because of this, there is an enhancement of lipid fluidity, and they enhance the skin permeability of the drug.
- ❖ **For the Treatment of Viral Diseases:** The lipids which are used in the formulation of cubosomes, such as monoglycerides, possess microbicidal activities. Therefore, they are applicable for the treatment of sexually transmitted diseases, which are caused by viruses (HIV) as well as by bacteria (genorrthicae).
- ❖ **For Cancer Therapy:** There are many anticancer drugs whose encapsulation within cubosomes has been successfully done. Cubosomes acts as a very favorable carrier for anticancer agents. The delivery system, which is having a small size, is the important parameter for the anticancer agents so as to get increased effects as well as retention.
- ❖ **For Intravenous Drug Delivery:** The cubosomes have the promising characteristic of high drug payload as compared to the liposomes. Also, it is a carrier, which acts as an ideal carrier for injections. Some of the small molecules, which are insoluble, are given by cubosomes. They also act as a precursor for the delivery of viscous substances. Because of, when the lamellar phases are injected via subcutaneous route, initially it is flowable, but

later it absorbs water from surrounding, and therefore, it converts into cubic phase. This is responsible for the formation of in situ depot.

- ❖ **For Oral Drug Delivery:** The oral drug delivery system consists of many challenges. Cubosomes are able to overcome all these challenges. They also have another advantage, which is the release of drugs at various sites and this is required in the case of drugs whose absorption window is narrow. The local effect i.e., in the gastrointestinal tract, is also possible.

CONCLUSION

As an advanced drug delivery platform, cubosomes offer key advantages over conventional formulations due to their ability to encapsulate diverse therapeutics and regulate drug release. Their demonstrated success across various clinical applications underscores their transformative potential. Continued innovation will help address existing challenges, further expanding their utility in modern medicine. Cubosomes are shaping the next generation of drug delivery. Superior to standard delivery systems, they can transport a wide range of therapeutic agents while precisely controlling release rates.

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