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# CUBOSOMES IN OPHTHALMIC DRUG DELIVERY- A REVIEW

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**ABSTRACT**

Cubosomes, also known as bicontinuous cubic phase liquid crystals, are nanoparticles with a structure mostly composed of certain amphiphilic lipids in a specific proportion. Cubosomes are formed by hydrating a surfactant or polar lipid that generates a cubic phase and then dispersing a solid-like phase into smaller particles. They have honeycomb structures that are tightly packed twisted form three-dimensional bilayers and are thermodynamically stable. They are able to load more drugs because of their complex structure. Cubosomes can encapsulate hydrophobic, hydrophilic, and amphiphilic molecules. Ultrasonication techniques or high-pressure homogenization could be used to generate cubosomes using top-down and bottom-up procedures, respectively. Due to poor water solubility and limited corneal permeability, topical treatments currently on the market have low ocular bioavailability and insufficient medicine reaching the ciliary body. Several studies have shown that cubosomal ophthalmic drug delivery improves medicine bioavailability by enhancing trans corneal/transconjunctival penetration and improve medication bioavailability. Cubosomes also use full in in cancer therapy, oral drug delivery, Intravenous drug delivery, Topical drug delivery, sustained and targeted drug delivery applications.

**KEYWORDS:** Cubosomes, Structure of Cubosomes, Methods of preparation, Ophthalmic delivery.

## INTRODUCTION

Cubosomes are discrete, sub-micron, nanostructured particles of the bicontinuous cubic liquid crystalline phase. Larsson coined the word Cubosomes to represent the cubic molecular crystallography and similarities to liposomes. These are nanoparticles, which are self-assembled liquid crystalline particles of certain surfactants with an appropriate water-to-microstructure ratio. Cubosomes are nanoparticles, however they are self-assembled liquid crystalline particles with a solid-like rheology that provide unique features of practical significance.[1] Cubosomes are most likely made up of polymers, lipids, and surfactants that contain both polar and non-polar components, making them amphiphilic. The hydrophobic effect drives amphiphilic molecules into polar solvent, causing them to spontaneously identify and assemble into a nanometre-scale liquid crystal. Cubosomes are thus bicontinuous cubic liquid phases that include two distinct water regions separated by surfactant-controlled bilayers. These are also optically isotropic, viscous, and solid, similar to liquid crystalline substances with cubic crystallographic symmetry. The cubic phase has the ability to fracture, resulting in colloidally and thermodynamically stable particle dispersions. Cubosomes are formed by hydrating a mixture of monoolein and poloxamer 407 into a bicontinuous cubic liquid crystalline phase, which is important in nanodrug formulations.[2] Dots Square shaped, slightly spherical of 10-500 nm in diameter. Chemical bonds bind active chemical constituent molecules to the polar head of the phospholipids in cubosomes. Depending on the material, the polymer and the specific medicinal ingredient produce a 1:1 or 2:1 combination. Despite its early recognition (in 1980), cubosomes were challenging to manufacture on a wide scale due to their complex phase behaviour and viscous qualities. When some surfactants are combined with water at specific concentrations, they spontaneously create cubic phases[3] Efforts are being made to develop scalable procedures for producing cubosomes on a large scale.

### Advantages

- It is economic.
- It is non-toxic and biocompatible.
- Method of preparation is simple.
- It has excellent bio adhesive properties.
- It has skin permeation enhancement.
- Targeted release and controlled release of bioactive agents.
- For longer time they are thermodynamically stable.

- Capability of encapsulating hydrophilic, hydrophobic and amphiphilic substances.
- Due to high internal surface area & cubic crystalline structures there is high drug loading.

**Disadvantages**[4]

- Due to presence of large amounts of water inside cubosomes there is low entrapment of water-soluble drugs
- Because of the high viscosity the large-scale production is sometimes difficult.
- Large scale production is difficult for sometimes because of high viscosity

**Structure of cubosomes**

Cubosomes have a honeycombed structure that separates the two internal aqueous channels, as well as a significant interfacial surface. Cubosomes are nanoparticles, or more precisely nanostructure particles, generated by the self-assembly of amphiphilic or surfactant-like molecules in liquid crystalline phases with cubic crystallographic symmetry. Because of their interesting bicontinuous architectures, which encompass two distinct areas of water separated by a controlled bilayer of surfactant application, the cubic phases have a very high solid like viscosity, which is a unique feature[5]. Bicontinuous water and oil channels are formed by amphiphilic molecules, with bicontinuous referring to two distinct (but non-intersecting) hydrophilic regions separated by the bilayer. The structure's interconnectivity produces a clear viscous gel with a rheology and look similar to cross-linked polymer hydrogels.

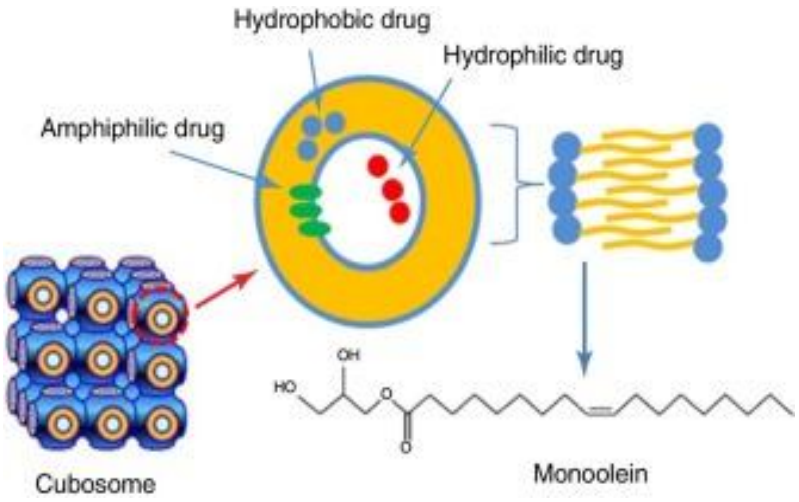


**Figure 1: Structure of cubosome separating two internal aqueous channels along with large interfacial area.**

**Components used in formulation of cubosomes**

**Glyceryl Mono-Oleate (GMO)**

GMO is the main component of an amphiphilic lipid class that can be made from glycerides of oleic acid and other fatty acids. It has a hydrophilic head and a hydrophobic tail. GMOs are also utilised in the food business to manufacture cubic lipid phases and as a food emulsifier. According to Lutton's findings, monoglycerides with a chain length of 12-22 have a higher tendency to form cubic phases.[6]

**Phytantriol (PHTY)**

Phytantriol is a chemical with phytanyl chains that is a good substitute for GMO since they have comparable phase behaviour. Both have physical and chemical properties, as well as a different structure. Phytantriol is a major component in the cosmetics business. 3, 7, 11, 15-tetra-methyl-1, 2, 3-hexadecane thiol is its chemical name.[7] Because it is vulnerable to esterase-catalysed hydrolysis, PHYT has a better structural stability. The reverse micelles, lamellar, Q230, and Q224 structures are generated by raising the concentration at room temperature, according to the PHTY-water phase diagram.

**Stabilizers**

Colloidal stability, which can be given by surfactants, is critical for cubosome synthesis. Cubosomes are clumping together to form the bulk cubic phase. An ideal stabiliser prevents unfavourable interactions between hydrophobic domains of cubosomes as it encounters particles, without causing any damage to the cubic structure, due to the electrostatic-repulsive barrier that the stabiliser can build between the approaching particles. As a result, the stabiliser is a critical component for cubosome development. Because of their large interior surface area, cubosomes sequester stabilizers.[8] PEO99-PPO67-PEO99, a tri-block copolymer, and poloxamer 407 are the most often utilised materials for stabilising cubosomal dispersion. The phase activity inside the framework of scattered particles is engaged and controlled by the stabiliser. P407 at its highest concentration resulted in the formation of smaller particles, but vesicular particles rather than cubic nanostructure phases. When a sufficient amount of P407 is added, a cubic structured nanoparticulate dispersion is generated. The internal crystalline structure and composition play a role in the development of distinct forms of cubic crystals. The P407 is absorbed on the

surface of the bulk PHYT cubic phase. The monoolein cubic phase P407 was incorporated into the liquid crystalline structure.[9]

**Method of preparation of cubosomes**

1. Top-down approach
2. Bottom-up approach
3. Heat treatment

**Top-down approach**

It is the most extensively utilised in research, in which bulk cubic phase is first created and then dispersed into Cubosomes nanoparticles by high energy processing. Cubic phases resemble a clear stiff gel created by water-swollen crossed linked polymer chains, whereas bulk cubic phases resemble a liquid crystalline structure.[10] The yield stress in the cubic phases increases as the amount of bilayer producing surfactant and oils increases.

The creation of complex dispersions incorporating vesicles and Cubosomes with time dependent ratios of each particle type is suggested by most available studies comparing dispersion produced by sonication and high-pressure homogenization. On a micron scale, coarse Cubosomes have the same D-surface structure as their original bulk cubic phase, but due to additional polymers, the P-surface dominates following homogenization. The structure-forming lipids are mixed with stabilisers to generate the extreme viscous bulk phase, which is subsequently dispersed into aqueous solution using high energy (such as high-pressure homogenization [HPH], sonication, or shearing) to form LLC nanoparticles.[11]

**Bottom-up approach**

Cubosomes are permitted to develop or crystallise from precursors in this method. Development of Cubosomes by scattering L2 or inverse micellar phase droplets in water at $80^0$ C and allowing them to cool slowly, eventually forming Cubosomes. This is more durable in Cubosome manufacture on a wide scale. Cubosomes were created at room temperature by diluting monoolein-ethanol solution with aqueous poloxamer 407 solution. Cubosomes arise spontaneously as a result of emulsification.[10]

**Hydro trope:** which can breakdown water-insoluble lipids to make liquid precursors and inhibit the formation of liquid crystals at high concentrations, is a fundamental component of the bottom-up strategy. This dilution-based strategy, as opposed to the top-down approach, can manufacture Cubosomes without the need for time-consuming fragmentation. To put it another way, it requires less energy input. Furthermore, this method is significantly more effective in producing small particles. The cause for this could be related to Cubosomes' formation mechanism. The top-down technique is more equivalent to attrition of giant particles, but the dilution-based approach is more analogous to small particles generating big particles by aggregation, which is analogous to the employment of precipitation processes to make nanoparticles. Furthermore, Cubosomes formed via dilution have long-term stability, which may be due to the homodisperse stabilisers deposited on the surface of Cubosomes. Indeed, the usage of hydrotrope can speed up the preparation process and result in Cubosomes with similar or superior qualities than those created via the top-down method.

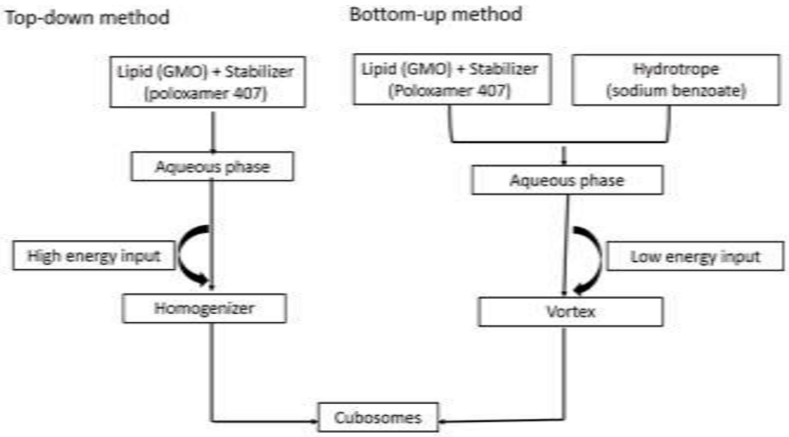


**Figure 2: Preparation of cubosomes.[10]**

**Heat treatment**

Heat therapy can be considered a useful option in this instance. Heat treatment is not an integrated procedure for the production of Cubosomes in the strictest sense because it merely supports the transformation from non-cubic vesicles to well-ordered cubic particles. As a result, dispersed particles can be made using a basic processing technique that includes a homogenization and heat-treatment step. According to the investigations, heat treatment reduces the small particle size fraction that corresponds to vesicles and causes the formation of larger cubic phases with narrow particle distribution and strong colloidal stability. When considering the entire preparation process, it is clear that the transition occurs during the heat treatment operation.

An increase in temperature could cause a decrease in solubility and stability, which could be the cause of the

transition. When the temperature was below cloud point, the surfactant exhibited a high solubility, allowing the particles to exist in a stable state with little fusion. When the surfactant solubility dropped below a certain threshold, a noticeable quick fusion among vesicles occurred.

**Ophthalmic delivery of cubosomes**

The human eye is a complicated organ with many anatomical and physiological barriers to overcome.

The cornea, conjunctiva, aqueous fluid, iris, ciliary body, and lens make up the anterior section of the eye. The vitreous humour, retina, choroid, and optic nerve make up the majority of the posterior segment.[12] The traditional dosage forms used to deliver drugs to the anterior portion of the eye via the topical route include solutions (62.4 percent), suspensions (8.7%), and ointments (17.4%), which make up an estimated 90% of marketed ophthalmic formulations. However, due to lacrimal secretions that cause poor retention time and limited permeability across the corneal epithelium, topical medication delivery has a low ocular bioavailability (5%). The majority of medication loss is caused by tear turnover from lacrimal secretions. A healthy eye with a tear volume of ~7–9 µL has a turnover rate of 0.5–2.2 µL/min.[13] The average volume of major formulations during topical administration is 35–56 L, with surplus liquid draining into systemic circulation via the nasolacrimal duct. Furthermore, topical medication absorption is influenced by conjunctival blood circulation. When all of the hurdles are taken into account, topical administration results in a drug loss of 95%. The remainder of the medication comes into contact with the corneal epithelial barrier. The cornea's important role as a barrier is addressed in detail in the following sections.

**Anterior segment drug delivery barriers**

**Epithelial tight junction**

The corneal epithelium is the principal barrier to medication absorption when drugs are applied topically.

A base layer of columnar cells, two to three layers of wing cells, and one or two outer layers of squamous cells make up the stratified corneal epithelium.[14] The cells on the surface are surrounded by tight connections between cells (zonula occludens). The tight connections act as permeation barriers. The paracellular pathway is used to transport medicinal compounds. Anastomotic strands make up tight connections that offer drug absorption resistance in the paracellular environment.[15]

**Reflex blinking**

A normal eyedropper delivers 25–56 µL of the topical formulation with an average volume of 39 µL. However, an eye can transiently hold up to 30 µL, and the rest is lost either by nasolacrimal drainage or reflex blinking (5–7 blinks/min), significantly decreasing the overall drug available for therapeutic action.[16]

**Metabolism in ocular tissues**

Drugs containing aromatic hydrocarbons are converted to their corresponding epoxides and phenols in the pigmented epithelium and ciliary body, or further processed by other enzymes in the eye.[17]

**Tear turnover**

Tear turnover is a substantial barrier to topical ocular administration. Following topical administration, the volume of the cul-de-sac increases, causing reflex blinking and increased tear secretion, ultimately leading to fast drug loss from the precorneal area.[18] Tear turnover and nasolacrimal drainage cause the solution to be lost until the tear volume in the conjunctiva cul-de-sac returns to normal (7–9 µL).[19] The initial first order drainage rate of eye drops from the ocular surface is 1.2 µL/min in humans.

**Nasolacrimal drainage**

As mentioned above, a majority of the instilled drug is lost due to tear turnover or nasolacrimal drainage. About 95% of the dose administered is eliminated systemically via the conjunctiva and nasolacrimal duct.[20] In adults, the lacrimal drainage system acts as a conduit for tears to flow from the eye to the nasal cavity. The puncta, canaliculi, lacrimal sac, and nasolacrimal duct make up the route. The lacrimal sac and nasolacrimal duct walls are vascularized histologically, making them possible locations for systemic medication absorption. The eye drop solution initially combines with lacrimal fluid after topical administration. Due to the continual creation of lacrimal fluid, the medication has a 1–2 minute contact period with ocular tissues. Approximately half of the medication flows into the upper canaliculus of the lacrimal sac and the remainder into the lower canaliculus. The blood continues into the nasolacrimal duct before draining into the nose. The amount of the instilled medication solution, the patient's reflex blinking, and the patient's age are all factors that influence the topically applied drug concentration. The nasolacrimal sac quickly passes larger injected contents into the nose, while the lacrimal sac easily eliminates smaller amounts. Because of direct exposure to systemic circulation, medication loss through the nasolacrimal duct via transconjunctival or trans nasal absorption is undesirable.[21-23]

**Efflux pumps**

The efflux proteins are found on the apical and basolateral cell membranes, respectively. Depending on their cellular location, these proteins either hinder or facilitate drug absorption. ABC proteins are a subfamily of ATP-binding cassette proteins that are expressed by the MDR1 gene and are responsible for the efflux of different substrates through the plasma membrane and extracellular fluid, as well as cytoplasm. Drug resistance is generally caused by two efflux pumps: (a) P-glycoprotein, which prevents amphipathic substances from entering normal and malignant tissue, and (b) multidrug resistant protein (MRP) (ABCC1), which is

known to export organic anions and conjugated molecules.[24-25]

**Cubosomes for ophthalmic delivery**

The topical preparations currently on the market have poor water solubility and restricted corneal permeability, resulting in low ocular bioavailability and insufficient medication reaching the ciliary body. Several studies have attempted to increase ocular absorption in order to generate a useful topical formulation. The majority of ocular disorders are treated with topical medication solutions (eye drops). However, medication ocular bioavailability is limited because too quick and significant pre-corneal losses induced by drainage and high tear fluid turnover. Meanwhile, the cornea is the primary route of anterior drug absorption for medicines entering the ocular tissue. The corneal epithelium is the principal limiting barrier in ocular medication absorption due to its lipophilicity and tight coupling. Several ophthalmic drug delivery techniques, such as emulsions, nanoparticles, and liposomes, have been proposed to improve ocular bioavailability. By enhancing trans corneal/transconjunctival penetration, these devices may be able to improve medication bioavailability. Nonetheless, quick clearance from the precorneal region limits their potential in ocular medication delivery, as the same rapid drainage has been observed as with aqueous eye drops. The dispersion of these vesicular systems into mucoadhesive gels has been proposed to improve adhesion to the corneal/conjunctival surface.[26-28] The mesomorphic phase of Monoolein (MO), a nontoxic, biodegradable, and biocompatible substance categorised as GRAS (generally regarded as safe), is significant in understanding the lipid's potential therapeutic application. The ability to incorporate compounds independently of their solubility, protect them from physical and enzymatic degradation, and sustain their delivery are all appealing properties for a topical delivery system, as they (i) are bio adhesive, (ii) present a permeation enhancer as the structure forming lipid (MO), and (iii) afford the ability to incorporate compounds regardless of their solubility, protecting them from physical and enzymatic degradation and sustaining their delivery.[29]

**CONCLUSION**

Cubosomes are nanoparticles, but instead of solid particles, they are self-assembled liquid crystalline particles that can include a wide range of hydrophilic and lipophilic medicines and distribute them in a targeted and sustained manner. Two methods such as top down and bottom-up approaches could be easily employed to produce cubosomes either by ultrasonication techniques or high-pressure homogenization. In case of ophthalmic delivery conventional formulations gives minimum drug concentration on ocular region due to many anatomical and physiological barriers and it reduce the overall bioavailability. Several studies are done to Increase the ocular absorption and find out that ophthalmic delivery of cubosomes is one of the best drug delivery systems. Mainly, their application as delivery carriers has two major benefits including solubilization of poorly water-soluble drugs and controlled or sustained release of loaded actives. Cubosomes can be used in a variety of medication candidates, proteins, immunological compounds, and cosmetics. Cubosomal preparations may be widely used as targeted drug delivery methods for ophthalmic, diabetic, and anticancer therapy due to their potential site specificity. The cubosome technology is relatively new with high output and would have wide scope of research in developing new formulations with commercial and industrial viability.

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