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Cubosomes Are Versatile Nano Platform for Controlled and Targeted Drug Delivery

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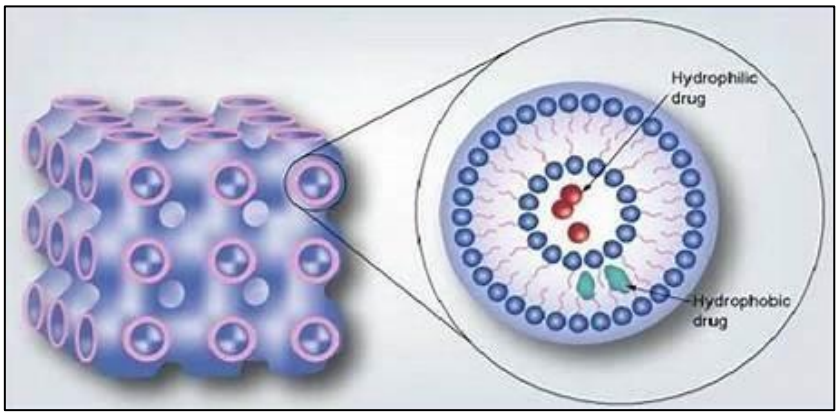
ABSTRACT

Cubosomes are lipid-based nanoparticles with a unique bicontinuous cubic structure that makes them a promising system for controlled and targeted drug delivery. They are commonly formed from amphiphilic lipids such as glycerol monooleate and phytantriol, which self-assemble in water to produce nanoparticles with a large internal surface area and interconnected aqueous channels. This structure allows cubosomes to encapsulate different types of drugs, including hydrophilic, hydrophobic, and amphiphilic molecules. They can be prepared using either top-down or bottom-up methods, and their properties can be adjusted by modifying the bilayer composition, membrane curvature, and channel size to control drug loading and release. Because of their biodegradability, bioadhesive nature, and high drug-loading capacity, cubosomes have gained significant attention for biomedical applications, particularly in ocular, dermatological, and oral drug delivery, where they help improve drug permeability, stability, and bioavailability compared with conventional formulations.

Keywords: Cubosomes, Versatile Nano Platform, Controlled and Targeted Drug Delivery

INTRODUCTION

Cubosomes are special types of nanovesicles that have a complex bicontinuous cubic structure. They are formed when liquid-crystalline cubic phases are dispersed in water. Cubosomes stand out because they have a very large surface area and maintain the same internal microstructure as the original cubic phase from which they are created.(1) Cubosomes are formed using certain amphiphilic lipids, such as glycerol monooleate (GMO) and phytantriol (PHYT). When these lipids come into contact with water, they naturally organize themselves into structured particles known as cubosomes. These particles have a honeycomb-like internal structure with many tiny cavities, and their size usually ranges from about 100 to 500 nanometers.(2) Cubosomes are gaining increasing attention as an innovative drug-delivery system. In recent years, they have been used in various medical applications, including treatments for eye disorders, skin conditions, oral drug delivery, and cancer therapy.(3) Cubosomes are capable of carrying a wide variety of drug molecules, including water-soluble (hydrophilic), fat-soluble (hydrophobic), and amphiphilic compounds, making them highly versatile for drug delivery.(4)



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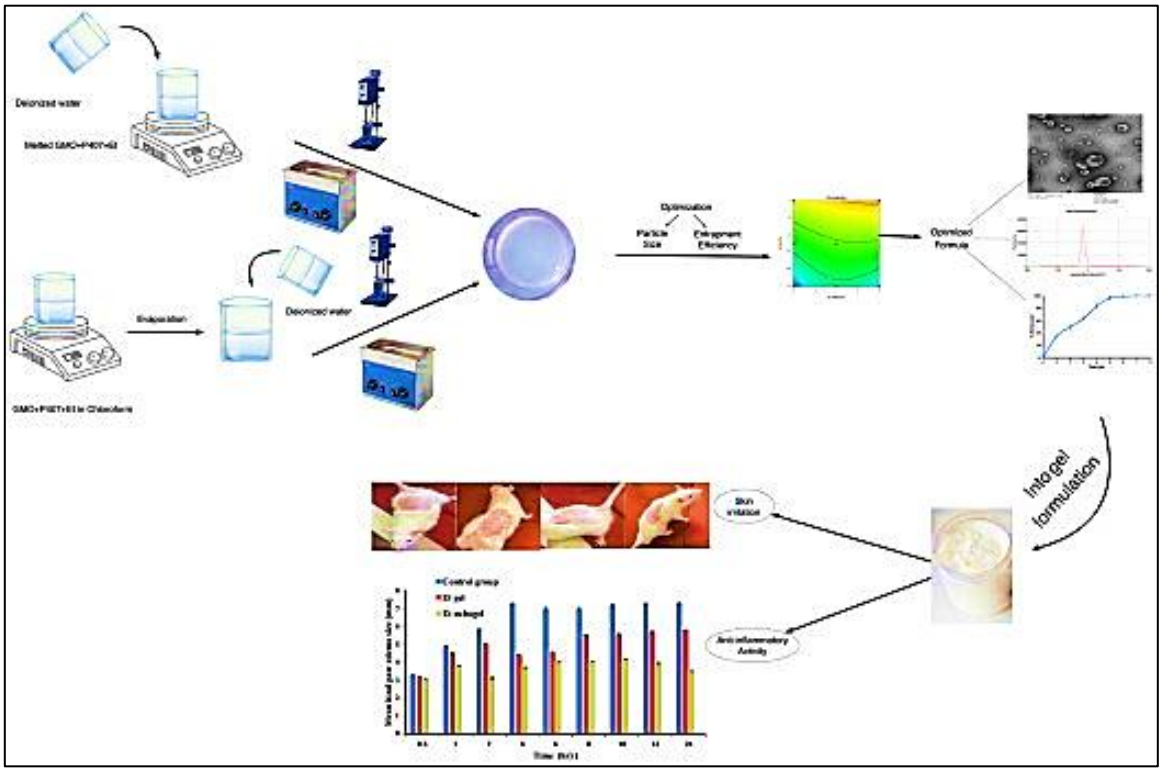
Preparation of method

It is imperative to have facilities to produce uniform-sized nanostructured dispersions for any pharmaceutical applica tions. The preparation method of cubosomes will significantly affect the overall formulation characteristics. Two common approaches to preparing cubosomal preparations are top down and bottom up method.



Top- down method

This is a commonly used method for preparing cubosomes and involves two main steps. First, a thick and highly viscous cubic bulk phase is formed by mixing lipids with stabilizers. The stabilizers help prevent the lipids from assembling too early. In the second step, this bulk phase is dispersed in water using high-energy techniques such as high-pressure homogenization or ultrasonication. This process breaks the bulk material into tiny cubosome particles. The cubosomes produced through this method are generally stable and can resist aggregation for up to a year.(5)

However, this technique has some limitations. Producing the highly viscous cubic phase can be difficult when scaling up for large-scale manufacturing. In addition, the large amount of energy required to break the bulk phase into nanosized cubosomes makes it unsuitable for heat-sensitive molecules such as proteins and peptides. Another drawback is that other types of vesicular particles, such as lamellar liquid-crystalline nanoparticles or vesicle-based systems, are often formed along with cubosomes during the top-down process.(6)

Studies have also shown that stable colloidal dispersions of cubic nanoparticles can typically be formed only within a temperature range of 40–60 °C. When the mixing temperature is increased to around 80 °C, interactions between hexagonal and inverse micellar phases begin to occur. This phase coexistence can reduce the overall performance of the formulation, negatively affecting properties such as particle size distribution, polydispersity index, drug-loading capacity, and other important characteristics.(7)

Bottom-up method

In this method, cubosome dispersions are produced by crystallizing a precursor solution, a process commonly known as the liquid-precursor or solvent-dilution technique. It involves preparing two separate solutions:

1. a lipid solution dissolved in a suitable hydrotrope, and

2. an aqueous solution that contains stabilizing agents.

Hydrotropes are added to the lipid solution to prevent the formation of a highly viscous liquid phase at high concentrations. Commonly used hydrotropes for cubosome preparation include ethanol, polyethylene glycol (PEG), and propylene glycol, with ethanol being the most frequently used. (8,9)

However, the use of hydrotropes has some drawbacks. They can sometimes cause allergic reactions or inflammation, and vesicular structures may still form during the preparation process. To address these limitations of the bottom-up method, researchers have developed modified approaches. One such method uses phosphate-buffered saline (PBS) within a bilayer lipid matrix made of phytantriol and dodecyl dimethyl ammonium bromide (DDAB) as the cationic lipophilic component.(10,11)

In this system, the addition of PBS helps restore the bicontinuous cubic bulk phase by forming a charged layer around DDAB, which alters the structure of the lipid bilayer. A similar effect can also be observed when the negatively charged fatty acid 1,2-dipalmitoyl phosphatidylserine (DPPS) is combined with phytantriol.(12)

Drug loading capacity

One of the main applications of cubosome systems is the delivery of drugs and peptides for treating diseases. Traditionally, lipid-based carriers—especially drug-loaded vesicles—have been widely used for this purpose. However, vesicles and cubosomes differ significantly in terms of their internal water-holding capacity and surface structure.(13)

For instance, a cubosome made from monoolein with a diameter of about 100 nm is estimated to have a hydrophobic volume more than three times larger than that of a single-bilayer vesicle of a similar size. This unique structure allows cubosomes to accommodate a greater amount of hydrophobic compounds, making them highly effective carriers for drug delivery.(14)

The composition and structure of the bilayer membrane can be modified by adding lipids with different acyl chains. These changes can adjust the charge within the aqueous channels and influence how the membrane interacts with the molecules incorporated into it.(15)

In addition, the transport efficiency of molecules can be controlled by altering the size of the water channels within the cubic phase. Further regulation can be achieved by adjusting the strength of the electrostatic interactions between the loaded molecules and the surfaces of these channels.(16)

Factors affecting structure of cubosomes

Only a limited number of studies have focused on modifying cubosome membranes for specialized applications such as drug delivery, imaging contrast agents, and biosensing. Researchers have explored changes to the bulk lipid phase, especially in efforts to support membrane protein crystallization. However, incorporating larger proteins into cubosomes remains difficult because their size can exceed the structural limits of the system.

Another approach is to modify the membrane curvature in lipid-based systems. This can be done by adding lipids or other components with different structural properties. These additions help influence the flexibility of the membrane curvature and can improve or alter how the lipid molecules pack together within the bilayer structure.(17)

Changing the curvature of the lipid bicontinuous cubic phase can influence the size of the water-filled channels within the structure. In some cases, these changes can also lead to a shift from one structural phase to another.(18)

Several methods have been used to modify the curvature of cubic phases. One common approach involves adding substances such as cholesterol or phospholipids to the lipid system. In many cases, up to about 25 mol% of these components can be incorporated into monoolein to influence the structure and curvature of the cubic phase.(19)

As the hydrostatic pressure increased, the cubic phases expanded in both bulk materials and nanoparticle systems, although the changes were more noticeable in the nanoparticle formulations. This method provides a way to control particle encapsulation using pressure instead of temperature. It is particularly useful for peptide-based applications because it reduces the risk of biomolecule denaturation, which can occur at higher temperatures.(20)

Miscellaneous drug delivery system

Ocular application

Recent studies have widely investigated the use of cubosomes for ocular drug delivery. These systems offer several advantages, including biodegradability, the ability to carry hydrophilic, hydrophobic, and amphiphilic drugs, and the capacity to provide targeted and controlled release of therapeutic agents. Because cubosomes can remain on the corneal surface for a longer time, they help improve the ocular bioavailability of the drugs they deliver.(21)

Cubosomes made with glycerol monooleate (GMO) also show mucoadhesive properties, which enhance their interaction with the eye surface. This improves corneal permeability and further increases drug bioavailability. Studies on topical ocular formulations based on cubosomes have reported promising results. For example, dexamethasone-loaded cubosomes have been extensively studied for their ability to permeate excised rabbit corneas in vitro. The findings showed a higher apparent permeability coefficient, longer residence time on the eye surface, and greater dexamethasone levels in the aqueous humor compared with dexamethasone sodium phosphate eye drops. These results indicate improved drug retention and absorption with cubosome-based formulations.(22,23)

Dermatological application

Dermatological drugs are commonly used to treat various skin conditions, but the stratum corneum acts as a strong barrier to transdermal drug delivery. Its highly organized structure makes it difficult for many topically applied drugs to penetrate the skin effectively.

Cubosomes offer a promising approach to overcome this challenge because of their unique structure and properties. In particular, cubosomes containing glycerol monooleate (GMO) are well suited for mucosal and topical drug delivery. This is mainly due to the bioadhesive nature of GMO, which allows the cubosomes to interact with the stratum corneum and improve drug penetration.(24)

Another important topical application of cubosomes is in transcutaneous immunization (TCI) for vaccination. In this strategy, microneedles (MNs) are used together with cubosomes to enhance vaccine delivery through the skin. Microneedles help peptides dissolved in water pass through the skin layers more easily, while cubosomes carrying the peptides ensure prolonged retention within the skin. Together, this combination provides an effective method for delivering antigens directly to targeted skin cells. (25)

Although oral administration is the most common and convenient way to deliver drugs, it often presents difficulties when dealing with poorly water-soluble compounds. Such drugs usually have low absorption in the gastrointestinal tract and may also have large molecular sizes, which further limits their bioavailability.

Cubosomes can help improve the absorption of orally administered drugs. This is mainly due to their ability to interact with intestinal cell membranes, stimulate natural physiological secretions during lipid digestion in the gastrointestinal tract, and their bioadhesive properties, which allow them to remain in contact with the intestinal surface for longer periods.

For example, in one study, insulin-loaded cubosomes were given orally to fasted streptozotocin-induced diabetic rats. In the preparation process, water, an emulsifier, and glycerol monooleate (GMO) were mixed using microfluidization at 80 °C and then cooled to room temperature. To protect the stability of insulin, the formulation was later prepared at room temperature and larger aggregates were collected. Because of the mucoadhesive nature of GMO and the good biocompatibility of cubosomes, the formulation produced consistent hypoglycemic effects and improved insulin uptake across the intestinal epithelium.

In addition, cubosomes are particularly useful for delivering poorly water-soluble drugs orally. They can encapsulate these drugs in a solubilized form within the lipid bilayer, preventing drug precipitation in the gastrointestinal tract. This, combined with the mucoadhesive properties of GMO, helps enhance drug absorption in the intestine.(25)

Conclusion

In conclusion, cubosomes are a promising and versatile nanoparticle system for controlled and targeted drug delivery. Their unique cubic structure, large internal surface area, and ability to carry different types of drugs—including hydrophilic, hydrophobic, and amphiphilic compounds—make them highly useful in pharmaceutical applications. Cubosomes can be prepared using various methods, and their structural properties can be adjusted to control how drugs are loaded and released. Because of their biodegradability, bioadhesive nature, and ability to improve drug stability and bioavailability, they have shown great potential in ocular, dermatological, and oral drug delivery. Although challenges such as large-scale production and formulation stability still

exist, ongoing research is expected to further enhance the development and application of cubosomes in advanced drug delivery systems.

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