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# A REVIEW ON NOVEL CUBOSOMAL DRUG DELIVERY SYSTEM

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## ABSTRACT

Cubosomes are spherical or square particles with visible internal cubic lattices. The intriguing story of the discovery of the cubosome incorporates concepts from biological membranes, differential geometry, food science, and digestive processes. Cubosomes are thermodynamically stable and feature a "honey combed" structure. Cubosome production composed of lipids that are amphiphilic and are joined by a polymer. Cubosomes can be applied parenterally, orally, mucosally, transdermally, or elsewhere to treat skin, hair, and other biological tissues. Polymers can be used to target the outer circle, and cubosome formation can be adjusted to incorporate bioactive lipids or to design the pore size. Drugs that are hydrophilic, lipophilic, or amphiphilic can all be loaded into cubosomes. Either a top-down or bottom-up method can be used to prepare this. Monoolein is the primary precursor for the creation of cubosomes, while poloxamer 407 is used as a surfactant in the disperse phase at concentrations ranging from 0% to 20% w/w.

**Keywords:** Cubosomes, amphiphilic, encapsulated, bioreactors, biosensors.

## INTRODUCTION

Larsson and colleagues introduced cubosomes into the literature. These nanostructured particles are sub-micron, discrete, bicontinuous cubic liquid crystalline phase. These nanostructured particles are sub-micron, discrete, bicontinuous cubic liquid crystalline phase. These are inversion nanoparticles that self-assemble, with hydrophobic areas dividing two consecutive but non- intersecting.

Cubosomes are discrete, sub-micron, nanostructured, bicontinuous cubic liquid crystalline phase particles. Cubosomes are self-assembled, liquid-crystalline nanoparticles of certain surfactants with the ideal water-to-microstructure ratio. Cubosomes are nanoparticles, however they're self-assembling liquid crystalline particles with a solid-like rheology that have special features of practical interest, as opposed to the solid particles typically seen.

## STRUCTURE & COMPONENTS

Cubosomes have two internal water channels divided by features resembling honeycombs, and the enormous region between surfaces. Cubosomes are nanoparticles, or more precisely, nanostructure particles of a liquid crystal phase that are created when molecules that resemble surfactants or amphiphilic compounds self-assemble. The cubosomes have cubic crystalline structures and a large internal surface area. Because of their fascinating Bicontinuous architectures, which encompass two distinct areas of water separated by a regulated bilayer of surfactant, the cubic phases have a very high viscosity that is unique to them. Bicontinuous water and oil channels are created by amphiphilic molecules; the term "Bicontinuous" describes two discrete, non-intersecting, continuous hydrophilic zones that are kept apart by the bilayer [1-3].

As a generic drug delivery method, cubosomes, also known as bi-continuous cubic phases liquid crystal, exhibit several intriguing properties. Inside the surfactant, it forms bilayers and is wrapped into a three-dimensional, periodic, minimal surface, creating a structure that is tightly packed.

## PROPERTIES

The higher surface area, cubic crystalline structures, biodegradability of lipids, precise and regulated release of bioactive compounds, hydrophilic, amphiphilic, and hydrophobic substance encapsulation, and sufficiently straightforward fabrication technique are all present. Because of its special qualities, which has thermodynamic stability, bio-adhesion, the capacity to encapsulate hydrophilic, hydrophobic, amphiphilic substance, the possibility of controlled release through functionalization, cubosomes are possible delivery systems for several medication delivery pathways [4].

Cubosomes can be characterized by a variety of assessment factors and are used in various fields. Therefore, the pharmaceutical development sector is paying more favourable attention to cubosomes. Cubosomes are created by dispersing a solid-like phase into smaller particles after wetting a surfactant or polar lipid to produce a cubic phase. Their rheology is like that of solids. Hydrophobic, hydrophilic, and amphiphilic compounds can all be encapsulated in cubosomes [5-6].

- **Bicontinuous Structure**

Two different lipid bilayers are arranged in a three-dimensional network to form the cubic structure bi-continuous that is characteristic of cubosomes. Their bi-continuous nature offers them a high degree of stability and a vast surface area [7].

## DRUG LOADING IN CUBOSOMES

The produced cubosomes can hold a suitable quantity of peptides, biologics, small-molecule medications, or bioactive. Loading the cargo across the lipid bilayer, binding to the lipid membrane, or localizing the medication within the cubic phase's water channels are the three primary methods. One possible method to load the drug moieties into the lipid is to either co- lyophilize with the lipid film prior to dispersion or add the therapeutic agent to the molten lipid. As an alternative, drug moieties could be added by incubating them after being dispersed onto cubosomes that have already been created. Most proteins, peptides, and small-molecule medications are loaded into the lipid bilayer. Moreover, single, or binary lipid compositions, primarily consisting of phytantriol and monoolein, used in cubosomes formation [8-10].

There are many ways to quantify drug loading, small-angle X-ray scattering (SAXS) is still the most used technique. Consequently, these investigations demonstrated the promise of cubosomes as a drug delivery method, particularly for the administration of anticancer drugs. The main benefit of cubosomes over other particles, such as liposomes, is their bigger hydrophobic region, which increases many hydrophobic medications which are loaded while allowing hydrophilic pharmaceuticals to be loaded as well. According to the study, curcumin in phytantriol cubosomes can load more efficiently than curcumin liposomes [11-15].

- **Solvent Displacement procedure.**

In this procedure, the lipids needed to produce cubosomes are dissolved in an organic solvent together with the medication. After that, the organic solvent is eliminated by evaporation or another method, which causes cubosomes to form and encapsulate the medication inside of them.

- **pH-Driven Loading**

pH-driven techniques can be used to load some medications into cubosomes. Drugs can be encapsulated or released in reaction to pH changes by using pH-sensitive lipids, for instance, to create cubosomes that alter structurally in response to pH fluctuations.

## MECHANISMS OF DRUG RELEASE OF CUBOSOMES

Depending on several variables, including the lipid composition, the type of medication contained, and the surrounding environment, there can be variations in the methods of drug release from cubosomes. Drug release from cubosomes has been explained by several processes, including:

- **Controlled Diffusion Release**

Drug molecules flow out of the cubosome structure via water channels or lipid bilayers in diffusion-controlled release. The lipid content of the cubosomes, the concentration gradient between the inside to the cubosome and its surrounding medium, and the size of its drug molecules all have an impact on this mechanism. medications that are hydrophobic usually diffuse through lipid bilayers, whereas medications that are hydrophilic may diffuse through aqueous channels.

- **Erosion and Swelling**

Drug release may potentially result from enzymatic breakdown or interactions with physiological fluids that cause the cubosome structure to erode. Cubosomes made with biodegradable lipids or additions that change structurally in response to external stimuli frequently include these processes.

## TYPES OF CUBOSOMES

Cubosomes are a class of liquid crystalline nanoparticles distinguished by their cubic phase structure, which is Bicontinuous. Cubosomes can be further divided into many varieties based on how the lipid bilayers are arranged within their cubic phase. The primary cubosome types are as follows:

- **Cubosomes of Type I**

Primitive cubic (P) phase structure characterizes type I cubosomes. The lipid bilayers in this structure create interconnected aqueous channels by forming a three-dimensional network with a

cubic symmetry. High degrees of curvature and a comparatively low ratio of surface area and volume that define type I cubosomes.

- **Cubosomes of Type II**

The phase structure of type II cubosomes is body-centered cubic (Ia3d). Compared to Type I cubosomes, the lipid bilayers of this structure assemble more orderly, producing larger.

## METHODS OF PREPARATION OF CUBOSOMES

- **Top-Down Technique**

  The Up-Down Methodology The most popular method was first described by Ljusberg-Wahren in 1996. After generating bulk cubic phase, cubosome nanoparticles are created by applying high energy, such as high-pressure homogenization. Bulk cubic phase is a transparent, hard gel made of cross-linked polymer chains swelled by water. The cubic phases are different from each other because they possess a structure like periodic liquid crystallin. The number of network branches that form in a cubic phase is proportional to energy necessary for the rupture, which occurs parallelly with shear direction. It is most employed in research areas where phase is created initially, and then high energy processing is used to disperse it into cubosome nanoparticles.

- **Bottom-Up Technique**

  The Bottom-Up is permitted to develop in this way. Cubosomes are created by spreading L2 or inverse micellar phase droplets in 80°C water and letting them cool down gradually. This causes the droplets to crystallize into cubosomes. When producing cubosomes on a large scale, this is more reliable. Aqueous poloxamer 407 solution is used to dilute the monoolein-ethanol solution to create cubosomes at room temperature. Emulsification leads to the spontaneous formation of cubosomes. Another method is also being explored to use spray drying to create cubosomes from powdered precursors. Upon simple hydration, spray-dried powders made of monoolein coated in starch or dextran produce cubosomes. The polymers give cubosomes instantaneous colloidal stability. This permits the formation or crystallization of cubosomes from progenitors.

**COMPARISON OF TECHNIQUES.**

- **Top-Down Approach**

  Formulation has stability against aggregation for up to one year. It requires high energy input to disperse the aggregates into cubosomes.

- **Bottom-Up Approach.**

  It requires low energy input; thus, it can be safely used with temperature-sensitive agents. Preferable for only thermo-sensitive reactants, and preparations are stable for less time.

- **Spray-Drying Method**

  The technique is a highly versatile, cheap, and scalable method. It is well-suited for drying labile products, such as vaccines and proteins. The mixture was difficult to spray-dry as a cubic phase is immediately formed upon hydration of monoolein.

- **Solvent Evaporation Method**

  Cubosomes formed using solvent evaporation approach are smaller, with higher physical stability. High polydispersity of particle sizes is reported due to large-scale mixing of ethanol and water.

**IMPORTANCE OF CUBOSOMES**

Because of their special qualities and possible uses, cubosomes are important in a lot of sectors. Cubosomes are essential for several reasons, some of which are as follows:

- **Versatile Drug-Delivery System**

  The hydrophobic and hydrophilic medicines within their bicontinuous cubic phase structure, cubosomes present a viable platform for drug delivery. This adaptability makes it possible to administer a variety of therapeutic substances, including as nucleic acids, proteins, peptides, and tiny compounds.

- **Increased Bioavailability**

The enormous surface area and great stability of cubosomes' bicontinuous cubic phase structure aid in the solubilization and distribution of medication which weakly soluble in water. Cubosomes have the potential for growing the therapeutic efficacy of medications, decrease adverse effects, and improve their bioavailability[16].

## ADVANTAGE OF CUBOSOMES [17]

- **Targeted Administration of Medicines**

Targeting ligands added to the surface of cubosomes allow for site-specific medication delivery to sick tissues or cells. With targeted medication administration, systemic toxicity is decreased, and patient outcomes are improved while off-target effects are minimized.

- **Both biodegradability and biocompatibility**

The body may metabolize or discard the biocompatible lipids that make up cubosomes without experiencing any harmful effects. These lipids are generally well-tolerated by the body. Cubosome-based drug delivery systems are safe because of their biodegradability, which also lowers the possibility of negative side effects.

## DISADVANTAGES OF CUBOSOMES

- **Possible Instability**

Changes in temperature, pH, or ionic strength can cause cubosomes to become unstable, which can have an impact on the kinetics of drug release and the structural integrity of the vesicles. During storage, lipid hydrolysis and oxidation may also take place, which could result in cubosome degradation and diminished medication efficacy.

- **Limited Scalability**

The difficulty of scaling up cubosome production for commercial manufacture is attributed to the intricacy for formation process.

- **Restricted Loading Potential for Big Molecules**

Although a great variety of medicinal substances can be encapsulated in cubosomes, the loading capacity of cubosomes for big molecules like proteins or nucleic acids may be restricted. The stability and drug release profile of cubosomes may be impacted by large molecules that break the cubic lattice or have trouble diffusing into the cubic phase structure.

## METHOD OF CHARACTERIZATION AND EVALUATION OF CUBOSOMES [18-20]

To comprehend cubosomes' structure, stability, and efficacy as drug delivery vehicles, it is imperative to characterize them. Several analytical methods are frequently employed to describe cubosomes. Here are a few of the crucial techniques:

- **Electron microscopy with cryotransmission (Cryo-TEM):**

A potent method for seeing cubosome interior structure at the nanoscale level is cryo-tem. To maintain their original structure, samples are quickly frozen in liquid ethane and then photographed using a transmission electron microscope. The internal structure, size distribution, and appearance of cubosomes are all thoroughly described by cryo-TEM.

- **SAXS, or small-angle X-ray scattering:**

Cubosome structural characteristics, including as periodicity, lattice parameters, and phase behaviour, are examined using SAXS. Cubosome samples are subjected to X-ray exposure, and the scattering pattern that results from the X-rays' interaction with the sample.

## APPLICATION OF CUBOSOMAL

Cubosomes are very versatile drug delivery vehicles with unique features that make them useful in various applications across multiple industries. Among the principal uses for cubosomes are:

- **Drug Delivery**

Small chemicals, proteins, peptides, nucleic acids, and imaging agents are among the many therapeutic agents that are delivered by cubosomes. Targeted Drug Delivery: By adding targeting ligands to the surface of cubosomes, it is possible to deliver drugs to diseased tissues or cells at

specific sites, increasing therapeutic efficacy and reducing off-target effects. Controlled Release: Cubosomes provide exact control over the kinetics of drug release, enabling the sustained and regulated release of medications over an extended period. This improves patient compliance and therapeutic outcomes.

## USES OF CUBOSOMES

The use of cubosomes to transport agrochemicals and pesticides in agriculture is being researched to increase their stability, efficacy, and environmental safety. By coating seeds with bioactive substances, they can improve crop output, plant growth, and germination.

- **Remediation of the Environment**

  Environmental uses of cubosomes, like pollutant removal and water purification, are being investigated. To help with environmental remediation operations, they can encapsulate catalytic agents and adsorbent materials for the removal of pollutants and toxins from soil and water. Cubosomes are useful in a variety of disciplines because of their special qualities and adaptability.

- **Medication Administration**

  A variety of medicinal substances, such as tiny compounds, proteins, peptides, nucleic acids, and imaging agents, can be efficiently delivered using cubosomes. They increase the bioavailability, stability, and solubility of drugs, maximizing their therapeutic benefit and reducing their adverse effects. Drug delivery kinetics can be precisely modulated using cubosomes, which allow for regulated and prolonged drug release.

## CHALLENGES AND FUTURE PERSPECTIVES

Obstacles and Prospects for the future these advantages and current developments, there are a few problems and areas of concern that still need to be addressed. The biggest challenge is overcoming the high viscosity, which can make large-scale production challenging, and the enormous amounts of water present inside cubosomes, which reduce the amount of water-soluble medication that is trapped. The surface modification of cubosomes with specific polymers (such as poly-lysine) can limit the burst release of hydrophilic drugs, such as cisplatin, in this regard. Regretfully, no compelling studies on formulations containing cubosomes oxaliplatin and carboplatin have been

conducted yet. Therefore, more investigation is required to ascertain these formulations' anticancer effects.

## CONCLUSION

Numerous recent investigations have exhibited their potential as an innovative method of delivering medication. Since they have a longer ocular residence time, are more bioavailable, and cause less irritation to the eyes, cubosomes have been approved as an efficient ocular drug delivery method. It is mentioned that the use of cubosomes can improve the absorption of poorly soluble pharmaceuticals, shield the substance from enzymatic degradation, and deliver specific therapeutics orally. They present a viable technique for more effective transdermal drug delivery that causes less irritation and better skin penetration.

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