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Cubosomes: A Distinctively Potential Novel Vesicular Nano-Carrier for Efficient Drug Delivery

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ABSTRACT

Internally Self-assembling particles (ISAsomes), such as cubosomes and hexosomes, have distinctive structural characteristics that make them desirable as drug-deliverynano-carriers. In the past few decades, numerous lyotropic non-lamellar liquid-crystalline-nano-particle-mediated formulations have been formulated, exhibiting a promise for drug delivery. Cubosomes are liquid-crystalline, nano-structured particles composed of certain concentrations of amphiphilic lipids and stabilizers. They can accommodate lipophilic, hydrophilic, and amphiphilic molecules within their cubic structure which makes them a special kind among other vesicular carriers. They are versatile as they are biocompatible and can deliver drugs through various routes. This review based on the relevant cubosome literature has emphasized on cubosome composition, preparation techniques, and characterization and drug delivery applications. It further discusses on the phase behavior of cubosomes coupled with guest molecules; the impact of various lipophilic materials on phase behavior and the changes in the local orientation order of lipids and the structural transitions in the bicontinuous cubic phase. The most common method of preparation is the direct emulsification of a Monoglyceride with a polymer, which is then homogenized and sonicated. There are two distinct types of preparation techniques: top-down and bottom-up. The cubosomes are evaluated for their particle size, Morphology, entrapment efficacy, Zeta potential, *in vitro* and *in vivo* characteristics. This article discusses various instances of cubosomes formulations being successfully applied to administer medications via a variety of administration methods. It concludes with some of the more recent and novel developments in this field of study.

INTRODUCTION

Cubosomes are single nanostructure particles of submicron size that exist in a crystalline form of two continuous cubic liquids. Larsson invented the name Cubosomes to describe the crystallization of cubic molecules and its similarity to liposomes. Nanoparticles are self-assembling liquid crystal crystals with surfactants that have the appropriate water-microstructure ratio. Cubosomes are nanoparticles that self-assemble into liquid crystal particles with solid-like rheology and unique practical properties. Cubosomes are usually composed of amphiphilic polymers, lipids and surfactants, which contain both polar and non-polar components. Amphiphile molecules are drawn into polar liquids by hydrophobic force, resulting in a spontaneous identification and organization of nanometer-sized liquid crystals[1]. Cubosomes are two-cycle cubic liquid phases that include two different water regions separated by membranes controlled by solvents [Fig 1]. All of them are optically isotropic, viscous, and hard, similar to liquid crystal solids with cube crystallographic symmetry. Colloidal and thermodynamically stable particle dispersion is formed by the cubic approach because it can fragment. When monoolein and poloxamer 407 are hydrated together, they form cubosomes, which are the crystalline phases of two continuous cubic liquids. They are crucial in nondrug formulations. The dot has a diameter of 10 to 500 nm and is square in shape and slightly round[2].

They are used in drug formulations due to their ability to encapsulate hydrophobic, hydrophilic, and amphiphilic chemicals and release bioactive substances in a regulated manner. Cubosomes have a wide range of applications, including oncotherapy, oral, intravenous, and topical drug delivery, acting as a drug delivery vehicle, and exhibiting controlled or sustained release behavior[3].

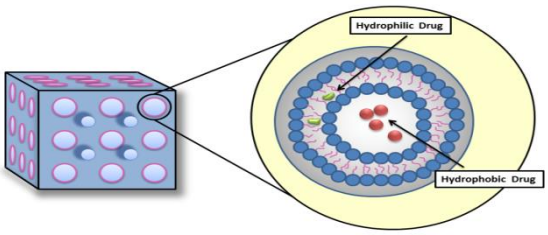

Figure 1: The basic structure of Cubosomes[8].

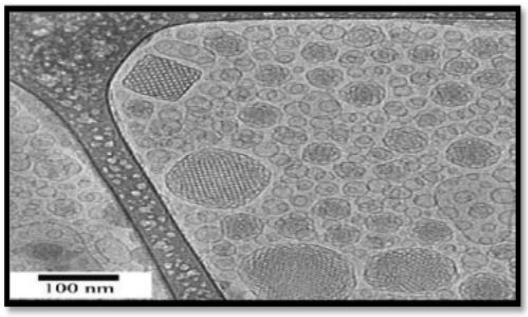

Figure 2: Square or spherical shaped Cubosomes[6].

Cubosomes are the liquid crystals of the bicontinuous cube phase that possess several inherent characteristics that make them a potential universal medium for the transport of various active drugs. Similar to conventional drug delivery systems, these nanoparticles also use supra-assemblies and polymer systems that are widely used as active transport vesicles. These surfactants assemble in bilayer, forming the three dimensions of the minimum surface, with periodic, densely packed structures, with bi-continuous lipid and water zones, which further resemble the honey comb structure[4]. Cubosomes are generally produced through time-consuming and cumbersome processes, which usually involve high-energy inputs. First, they are prepared from the breakdown of the cubic lipid-water phase in a region of three phases, which includes liposomal dispersion. To distinguish these particles from liposomes, however, they have been called cubosomes due to structural differences and the ability to adapt amphiphilic, lipid-soluble and water-soluble active substances.

ADVANTAGES OF CUBOSOMES[4, 5, 21, 26, 30]

They can contain amphiphilic medicines that are both hydrophilic and hydrophobic.

They have features related to long-term release medication delivery.

Biocompatibility and bioadhesion are characteristics of cubosomes.

Even with an excess of water, the bicontinuous phase of the cube liquid crystal phase of cubes remains stable.

Cubic phase materials can be used to treat skin, hair, and other body tissues.

Cubic phase materials can be formed by simple combination of biologically compatible lipids and water and are thus well suited for use in treatments of skin, hair, and other body tissue.

Cubosomes have a stronger fracture resistance and a larger ratio between the volume of particles and the bilayer surface than liposomes do.

Their crystalline cubic structure and large surface area allow them to hold a large amount of medicines.

They are lipid biodegradable and have an easy preparation process.

Regulated and targeted release of bioactive substances.

When compared to non-lipid or typical lipid carriers, cubosomes are superior oligomeric carriers.

High transport capacity is demonstrated for a class of less water-soluble medicines.

These are great instruments to prevent peptides and proteins, which are sensitive medications, from degrading in vitro and by enzymes.

LIMITATIONS OF CUBOSOMES [6, 7]

The elevated viscosity can make large-scale production challenging.

Low entrapment of hydrophilic medicines is a result of the high water content inside the cubic structure.

COMPONENTS OF CUBOSOMES[12, 15]

In the 1980s, Kare Larsson introduced the concept of cubosomes in his review of cubic lipid/water phases. Patton and Carey then reported on their findings in fat digestion studies, where they observed that the combination of lipase and bile salts with simulated stomach contents resulted in the formation of dispersed particles of bicontinuous cubic structures. But Larsson initiated the work on cubic structures; he found that when the bulk cubic structure is distributed in water, cubosomes can grow from it into submicron particles that share the parent cubic structure's interior structure.

AMPHIPHILIC LIPIDS

Monoglyceride[16, 17, 18]

When water is added to Monoglyceride, they spontaneously form bicontinuous cubic phases and are comparatively insoluble, which permits the production of colloidal dispersions of cubosomes, and they can withstand temperature fluctuations. Glyceryl monooleate (GMO), phytantriol (PT, 3,7,11,15- tetramethyl-1,2,3-hexadecane-triol) and other lipids such as monolinolein, monoelaidin phosphatidyl ethanolamine, oleoyl ethanolamide, phospholipids PEGylated phospholipids, alkyl glycerates, and glycolipids have been reported to form cubic phase. But the most commonly studied to form cubic phase liquid crystals as drug delivery systems are GMO and PT.

Monoolein

Glyceryl monooleate, another name for monoolein, is a combination of oleic acid glyceride and other fatty acids, with the monooleate making up the majority of the mixture. Monoolein is a yellow, waxy material with a peculiar smell. There are two commercial types of monoolein: distilled monoolein and mixed glyceride. Because of its high purity, distilled monoolein is preferred for use in pharmaceutical applications. They have a Pn3m cubic-phase structure and, in response to excess water and temperatures between room temperature and 80 ◦C, go through inverted micellar and lamellar phases [12].On the outside, they are clear, colorless, and polar unsaturated Monoglyceride with a melting point of 27–35 ◦C[23].It has been stated that GMO with hydrocarbon chain lengths in the range of 12-22 have a higher propensity to produce cubic phases. Monoolein is a nontoxic, biodegradable, and biocompatible substance. GMO is amphiphilic molecule that can self-assemble in water to form bicontinuous cubic structures[12].In the food industry, it is frequently utilized as an emulsifier.

Phytantriol (PHYT)[13, 14, 15, 19]

Phytantriol is an alternative to GMO; it has better structural stability due to the presence of a saturated phytanyl backbone compared to GMO because GMO is more prone to esterase-catalyzed hydrolysis due to the presence of ester linkage. It is important to remember that the Phytantriol/water system in PHYT produces QII and HII stable phases at a temperature of 40 ◦C as opposed to 80 ◦C for monoolein.

STABILIZERS[44, 39, 36]

Although cubic aggregates are thermodynamically stable, the dispersed particles in aqueous fluids are not kinetically stable because they tend to aggregate as a result of exposure to the external hydrophilic aqueous media. Therefore, using stabilizing agents becomes an essential step in cubosome preparation to prevent the re-coalescence of the dispersed particles into the parent bulk cubic structure. The stabilizer's primary job is to provide an electrical barrier between particles to stop them from coming into close contact with one another and therefore preserve the stable form of dispersed particles. When it comes to cubosomes, the stabilizing effect of F127 is assumed to be caused by the hydrophobic (PPO) portion adhering to the particle surface; in contrast, the hydrophilic (PPO) section provides steric shielding by extending into the aqueous media. This result is occurred without disrupting the crystallinity

of the cubic liquid phase.Pluronics are the most widely used stabilizing agents; F127 (Poloxamer 407) is regarded as the "gold standard".

Polyethylene oxide (PEO) and polypropylene (PPO) are combined to form pluronics, which are water-soluble self-assembled triblock copolymers with PPO and PEO parts organized in a PEO-PPO-PEO configuration.Stabilizer is typically used at concentrations up to 20% w/w,depending on the dispersed particles, while GMO-polymer combination is typically utilized in concentrations ranging from 2.5% (w/w) to 10%, depending on the dispersion's overall weight.

The types of Poloxamer include Poloxamer™407 (Pluronic ® F127), Poloxamer™338 (Pluronic ® F108), and other Poloxamers™/Pluronics ® such as F87, F68, P123, P105, P104, and P84. Poloxamer™407 is widely used to stabilize cubosome dispersions in various lipid systems, while Poloxamer™338 has longer hydrophilic arms and has been successfully used to sterically stabilize cubosomes. Other Poloxamers™/Pluronics ® with lower molecular weights than Pluronic ® F127 have also been employed as steric stabilizers for cubosomes, with specific PEG chain lengths being essential for effective steric stabilization[51, 52, 53, 54].

Concentration of Poloxamer[51, 52]

The ideal concentration of Poloxamer 407 (Pluronic F127) for stabilizing cubosomes varies depending on the lipid system. For example, at low stabilizer concentrations (<4%, w/w, vs. GMO), Pluronic ® F127 stabilized GMO dispersions form Q 224 cubosomes, while at higher stabilizer concentrations (i.e., 7.4 or 10%, w/w, vs. GMO), Q 229 cubosomes are formed. Similarly, the use of high concentration of Pluronic F127 with either glycerol monooleate or phytantriol as the main lipid results in retention of the Pn3m diamond bicontinuous cubic phase within their dispersions. The concentration of Poloxamer 338 (Pluronic F108) and other Poloxamers /Pluronics are also crucial for the effective steric stabilization of cubosomes.

The future aspect of Poloxamer™ involves the exploration of more customized steric stabilizers, improvements in stealth behavior and colloidal stability, and the investigation of charged stabilizers for the advancement of stabilization of lyotropic liquid crystalline nanostructure particles. Additionally, future developments may focus on the stimuli responsiveness of these particles, maintaining stable dispersions in the absence of a stabilizer, and the exploration of charged polymers for stabilization[55].

CUBIC PHASE STRUCTURE[33]

In cubic phases, three different kinds of minimum surfaces are examined depending on their curvature based on the mathematical discovery by Schwartz.

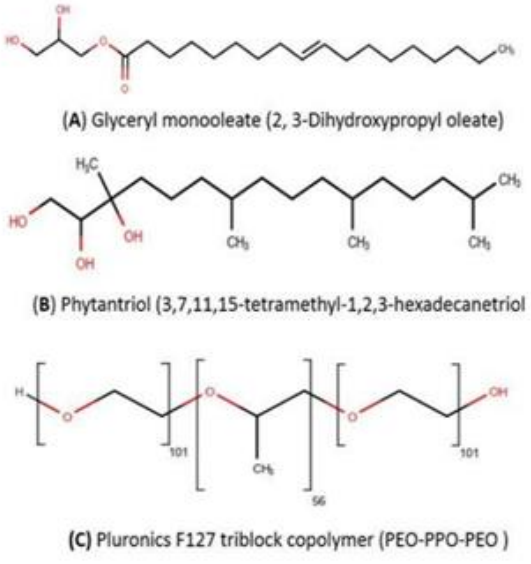

Figure 3: Molecular structure of cubosomes forming lipid (A) glyceryl monooleate, (B) phytantriol, and (C) stabilizer (poloxamer 407)[12].

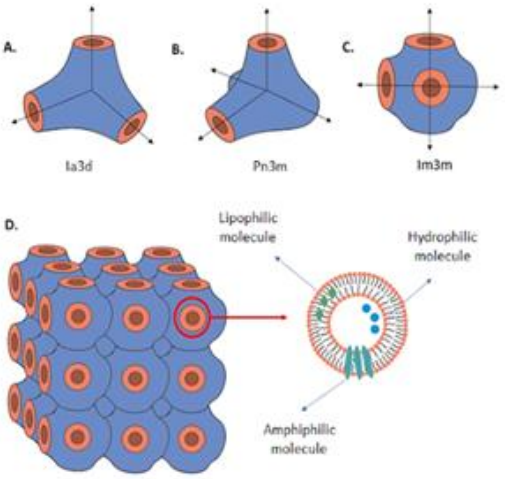

Figure 4: Schematic representations of the inverse bicontinuous cubic phases[24].

ADDITION OF GUEST MOLECULES CAUSES CHANGES IN THE CUBIC PHASE

Many significant characteristics, including medication release, rely heavily on the phase behavior of cubosomes in reaction to the loaded guest molecules, making it imperative to understand how they behave. We have concentrated on the phase behavior of the cubic phase coupled with guest molecules in this section[33]. The study examined the thermal phase behavior of two systems: the binary PHYT–water system and the ternary PHYT–vitamin E acetate (VitEA)–water system.

The temperature of the QII to HII to L2 transitions was decreased by the presence of lipophilic VitEA in the PHYT system, suggesting that lipophilic materials—even in relatively small amounts—may have a substantial effect on phase behavior[34]. Nakano et al. looked into the changes in the local orientation order of lipids in a lamellar-bicontinuous cubic phase as well as the phase behavior of a binary system made up of GMO and egg yolk

Phosphatidylcholine[35]. The GMO molar percentage at which the lamellar-to-cubic transition takes place is between 0.6 and 0.7. The impact of DL-α-tocopheryl acetate on the phase behavior of the GMO system was additionally compared with that of other lipids, including triolein, limonene, and tetradecane[36].

According to Efrat et al. type I compounds such as cholesterol and Carbamazepine most likely localize in the hydrophobic portions of the lipid and alter the mesophase packing by affecting the polar head group interactions and lipid acyl chain order.

Thus, it was discovered that adding oleic acid to GMO-based cubosomes raised the system's crucial packing parameter. With an increase in oleic acid concentration, bicontinuous cubosomes undergo structural transitions from hexosomes and micellarcubosomes (Fd3m symmetry) to emulsified microemulsions[33].

According to findings from another study, the internal nanostructure changes from the biphasic phase, which includes a bicontinuous cubic phase (Pn3m) and an inverted-type hexagonal (H2), when plasma is present, resulting in a reduction of the average nanoparticle size[35].

Liquid Cubosome Precursors[1,22, 25]

The hydrotrope dilution method results in more compact and smaller cubosomes. Particles are produced during the nucleation and growth processes used in crystallization and precipitation. This is achieved by dissolving the monoolein in a hydrotrope—such as ethanol—that prevents the formation of liquid crystals. After this combination is further diluted, the cubosomes naturally "crystallize," or precipitate. Cubosome preparations can easily scale up since the liquid precursor phase removes the need for bulk solids processing and potentially harmful high-energy procedures.

Powdered Cubosome Precursors[28, 31]

In powdered cubosomes precursors, dehydrated surfactant is covered with polymer. These powders offer advantages over liquid-phase hydrotropic cubosomes precursors. The hydration of the precursor powders resulted in cubosomes with a mean particle size of 600 nm, as demonstrated by light scattering and Cryo-TEM. Lipids are the waxy, sticky substances that make up cubosomes. To control particle size and avoid agglomeration, a non-

cohesive water-soluble starch is placed over the waxy lipid. Spray drying is a great solution for these needs.

PREPARATION METHODS

A lot of techniques have been proposed to investigate the preparation of cubosomes. This provides details on the optimal conditions required for the preparation. In this article, two main methods of preparation have been discussed.

Top-Down (TD) method

The most widely used method for creating liquid crystal colloidal nanoparticles during the past few decades has been the TD approach. Ljusberg-Wahren et al. initially described this strategy in 1996[26].To obtain the bulk liquid crystal phase of interest in the TD method, the lipid of interest is first combined with a stabilizer that contains water, which is the bulk phase. While bulk cubic phases are similar to a clear, stiff gel made of cross-linked polymer chains swelled by water, cubic phases are different in that they have a periodic liquid crystalline structure and are in a single thermodynamic state[27]. The highly viscous liquid crystal phase is dispersed into an aqueous solution in the second stage utilizing high-energy processes means like high pressure homogenization, shearing, and ultrasonication; among these ultrasonication is the most commonly used technique[28]. The so-formed cubosomes nanoparticles are equilibrated at a specified temperature and time[29].

Limitations of this Method[30]

Only practical for small-scale production.

High energy throughput requirements may prevent it from being used in situations where the inclusion of labile chemicals is necessary.

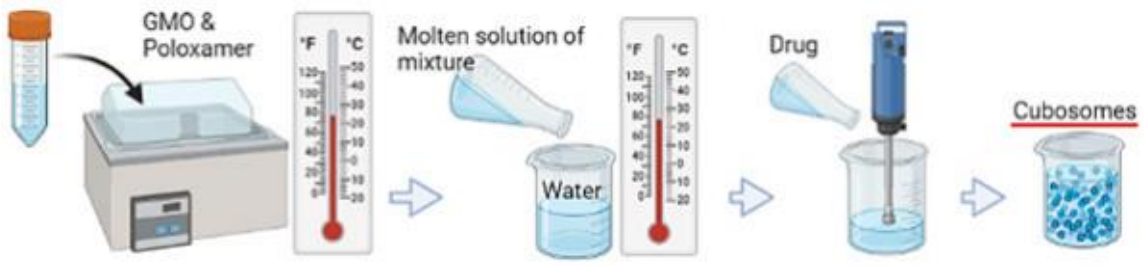

Figure 5: Pictorial illustration of cubosomes preparation[59].

Bottom-Up (BU) method

The BU method, also known as the solvent dilution method or hydrotrope method, is a recently invented cubosomes production process that was initially published by Spicer et al[31].The bottom-up method builds the building pieces of the nanostructure first and then puts them together to create the finished product.A hydrotrope is a non-aqueous solvent (ethanol being the most common type) that dissolves lipid molecules that are insoluble in water at high concentrations, creating a precursor solution without causing liquid crystal phases to form. A rotary evaporator is used to remove the hydrotrope. In this method aggregation process occurs through which small particles combine to form big ones, whereas in TD method breaking up of large particles occur. But BU method is more considered as it requires less energy for the production of liquid crystal nanoparticles[30].

Limitations of this method

Different concentration of hydrotrope is used, which can cause change in the physiochemical properties of the liquid crtystals[30].

Severe irritation and allergy reactions can occur due to the presence of hydrotrope in liquid crystals[30].

Uni-lamellar and bi-lamellar vesicles are also present in certain amounts along with cubosomes[30].

Bottom-up techniques result in the simultaneous synthesis of liposomes as it frequently relyon organic solvents like ethanol as diluents. To prevent this heat treatment of the medium is done which results in the conversion of non-cubic particles to well-defined cubosomes. But this technique is not applicable for labile substances[32].

PHYSIOLOGICAL PROPERTIES AND DRUG DELIVERY OF CUBOSOME

Cubosomes have many advantages among which the most important is that it can accommodate hydrophilic, hydrophobic, and amphiphilic drug molecules. They are widely used in Pharmaceutical formulation for their sustained release property, biocompatibility, bio-adhesion, drug molecules' defense against processes such as oxidation, hydrolysis, and deamidation; protein molecules' defense against denaturation, precipitation, aggregation, and adhesion at the surface[37]. Cubosomes are used in various routes like oral, Topical, Transdermal, Intranasal, Intravenous, and many more.

Cubosomes as a Potential Oral Drug Delivery System

Particularly Cubosomes are perfect for oral medication administration because of their morphological characteristics. Cubosomes provide a high level of protection against the precipitation of oral drugs because of their lyotropic shape, which traps water-soluble substances in the lipid bilayer absorption membrane. Cubosomes have the ability to enhance molecular absorption through the gastrointestinal tract's production of surfactants and their bio-adhesive qualities, which makes them even more suitable for oral delivery[38]. Mohsen et al., conducted a study on Coenzyme Q10, which is an antioxidant used in the treatment of liver disorders, formulated it as cubosomes for oral delivery and showed that it increased the bioavailability of Coenzyme Q10[39].

Cubosomes as a Potential Topical Drug Delivery System

In case of topical delivery of drugs, the major problem of concern is to facilitate the permeation of drugs through the skin. Even with the existence of permeation enhancers, this issue is still a matter of concern. This problem is been resolved by the use of cubosomes. Nadia M. Morsi et al. study evaluated the preparation and characterization of silver sulfadiazine (SSD) cubosomes and cubogels for topical treatment of burns. The cubosomal advantages mentioned in the article include the ability to solubilize water-soluble, oil-soluble, and amphiphilic substances, controlled release of substances, mucoadhesive properties, and potential for drug delivery. The cubosomes also showed potential for burn healing, with the chitosan/carbopol mixture cubogel exhibiting the best results in an in vivo study compared to other test groups and the commercial product group[40].Additionally, it has been shown that the transdermal preparation of colchicine in the form of a cubosome enhances the absorption of topical treatment as compared to oral administration[41].

Cubosomes as a Potential Intravenous Drug Delivery System

Cubosomes have the potential to facilitate the passage of colloidal materials without blocking capillaries. They might alsoreduce the interactions between drugs and plasma proteins, hence improving the stability and bioavailability of drug molecules[37].

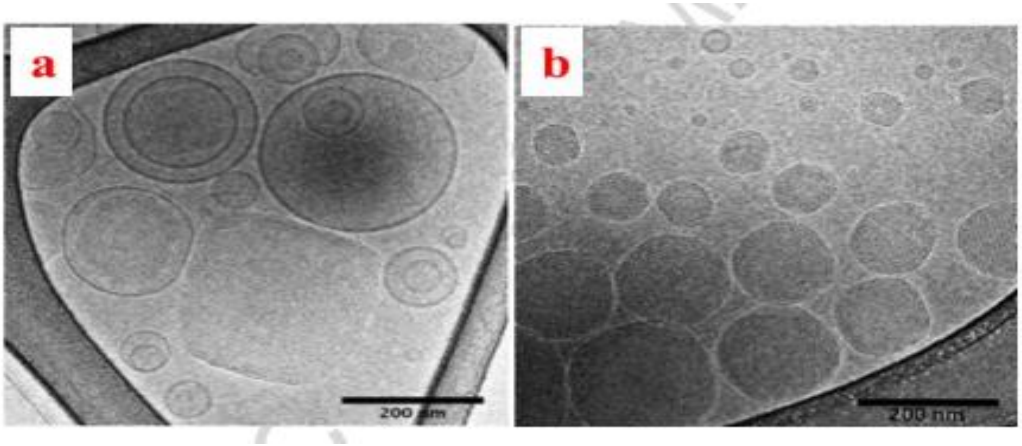

Figure 6: Cryo-TEM images of samples prepared using (a) BU method displaying cubosomes and multi- and single- layer liposomes and (b) one uni-lamellar liposome in TD sample. Adapted and modified with permission from Akhlaghi et al[12].

Cubosomes as a Potential Intranasal Drug Delivery System

Cubosomes may pass through the blood-brain barrier to deliver medications straight to the central nervous system (CNS). Essam M. Eissa et al. formulated and optimized glyceryl monooleate-based cubosomes (GS-CBS) for brain targeting. The entrapment efficiency (EE) of the developed cubosomal formulations varied from 35.4 to 68.5%, with P 407 and T 80 positively affecting EE. The optimized GS-CBS formulation exhibited distinct cubic structures with no evidence of large aggregates, attributed to steric stability and electrostatic repulsion; and showed higher percentage of drug reaching the brain[42].

TOXICITY PROFILES OF PLURONIC AND STABILIZERS (POLOXAMER

Cubosomes have been used in numerous experiments to demonstrate their potential for delivery as nanoparticles using a variety of disease scenarios. On the other hand, not much researchers has been done to assess the toxicity profiles of components and stabilizers[37]. Jiali Zhai et al. conducted a study to examine the ability of PEGylated phospholipids to engineer and stabilize phytantriol-based lyotropic liquid crystalline dispersions.

The toxicity addressed in the document is the cytotoxicity of phytantriol cubosomes stabilized by different PEGylated phospholipids, such as DSPE-PEG 2000, DSPE-PEG 3400, and DSPE-PEG 5000, as well as Pluronic F127. The study shows that increasing the PEG chain length promotes greater interfacial curvature of the dispersions, resulting in different

nanoarchitectures. DSPE-PEG 5000-stabilized cubosomes exhibited reduced cytotoxicity compared to DSPE-PEG 3400 or Pluronic F127-stabilized dispersions. The study also highlights the importance of stability and cytotoxicity of the nanoparticles in vitro, emphasizing the need for further investigations into the link between in vitro and in vivo toxicity of the lipid lyotropic liquid crystalline nanoparticles[43].

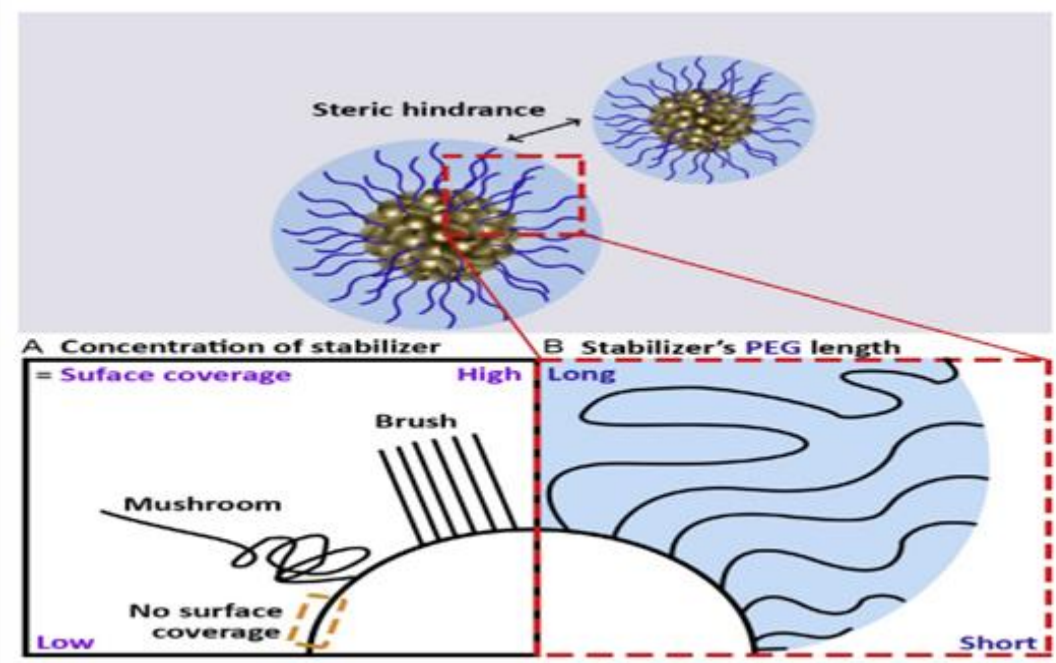

Figure 7: (A) the concentration of steric stabilizer used and (B) PEG length in steric stabilizer.

PEG (polyethylene glycol) plays a crucial role as a steric stabilizer for nanostructure particles. Studies have shown that increasing the PEG length and concentration enhances the stability of particles, providing stealth and hindering aggregation under physiological conditions. PEG is an ideal hydrophilic domain for steric stabilizers, with longer PEG chains being more effective at providing stabilization to hydrophobic particles. The ideal PEG chain length for maximum steric stabilization effectiveness onto cubosomes is not yet fully understood. PEGylated lipids and customized lipid-copolymer series have been reported as effective steric stabilizers for cubosomes, with specific PEG lengths and hydrophilic-lipophilic balance (HLB) being essential for effective steric stabilization. The concentration of PEG chains and the balance between the anchoring unit and extending unit in copolymer structures are also crucial for achieving optimum stability performance[44, 45].

PEG has been used to stabilize cubosomes in various examples. For instance, 1, 3-didodecyloxy-propane-2-ol (DDP)-PEG was reported to stabilize cubosomes with Im3m space group symmetry[46, 47], while 1, 3-didodecyloxy-2-glycidyl-glycerol (DDGG)-PEG stabilized cubosomes with Ia3d space group[48]. Additionally, PEG-stearates with 40 or greater PEG units were effective in stabilizing phytantriol dispersions in water, while PEG-100-stearate and PEG-150-stearate retained the Pn3m space group of phytantriol[50]. Furthermore, PEGylated lipid copolymers like DMPE-PEG 550 and MO-PEG 660 have been used to stabilize cubosomes with specific space group symmetries[49]. These examples demonstrate the effectiveness of PEG in stabilizing cubosomes with different lipid matrices and space group symmetries.

CHARACTERISATION OF CUBOSOMES

Visual inspection [56]

The cubosomes are visually evaluated for optical appearance (e.g colour, turbidity, homogeneity, presence of macroscopic particles).

Determination of particle size, shape, and morphology[64]

The size distribution of cubosomes is measured using a Zetasizer Nano ZS90 (Malvern Instruments, Malvern, UK). The samples are diluted 50-fold with water to 2% before measurement. Cubosomal size was analyzed by the Dispersion Technology Software provided by Malvern Instruments.

Transmission electron microscopy

The cubosomes were observed under TEM to determine the surface morphology and size of the formulation. The formulation was diluted 50 times with double distilled water and stained negatively by Phosphotungstic acid and then dried on the carbon-coated grid. Excess of Phosphotungstic was removed using filter paper. Finally, it was observed using Morgagni 268D (magnification x 2 50 000, Fei Electron Optics, Netherlands) transmission electron microscope.

Small-angle X-ray scattering

Small-angle X-ray scattering (SAXS) measurements were carried out on a high-flux SAXS instrument (Anton Paar GmbH, Graz, Austria) operating in the line of collimation and

equipped with an imaging plate (IP) as a detector. The IP with a pixel size of 42.3×42.3 μm2 was extended into a wide angle range (the q range covered by the IP was up to 28 nm-1, $q=[4\pi\sin\theta]/\lambda$, where λ is the wavelength of 0.1542 nm and 2θ is the scattering angle). The liquid samples were carefully loaded into a quartz capillary with a diameter of 1 mm and exposed for 60 minutes.

Particle Size Distribution (PSD)[56, 57]

Particle size distributions of cubosomes are mainly determined by dynamic laser light scattering using a Zetasizer (Photon correlation spectroscopy). The sample diluted with a suitable solvent is adjusted to a light scattering intensity of about 300 Hz and measured at 25°C in triplicate. The data can be collected and generally shown by using average volume weight size. The zeta potential and Polydispersity index can also be recorded.

Zeta potential[56]

The magnitude of zeta potential indicates the degree of electronic repulsion between adjusted, similarly charge particle. Zeta potential is key indicator of the stability of formulation.

Entrapment efficiency and drug loading[56, 59]

The entrapment efficiency of cubosomes can be determined using ultra filtration techniques. In the later technique, the unentrapped drug concentration is determined, which is subtracted from the total drug added. The amount of drug is analyzed by using a spectrophotometer.

$$\text{Entrapment Efficiency (\%w/w)} = \frac{\text{Amount of Encapsulated Drug}}{\text{Total amount of the drug}} \text{ X } 100$$

$$\text{Drug Loading (\%w/w)} = \frac{\text{Amount of Encapsulated Drug}}{\text{Total amount of cubosomes}} \text{ X } 100$$

Stability study [58]

The physical stability can be studied by investigation of organoleptic and morphological aspects as a function of time. Particle size distribution and drug content can be assessed at different time intervals can also be used to evaluate the possible variations over time.

Rheological behavior[62, 63]

The rheological conduct of drug-loaded cubosomes was discovered utilizing a cone and plate rheometer (Brookfield DV3THB cone/plate rheometer).

In vitro release and evaluation of the release mechanism [60]

The release of drug from cubosomes in water at 37°C was evaluated by the dialysis method. The cubosomal sample (5 mL) was transferred into a dialysis bag, which was placed into a flask and filled with 250 mL of water. The flask was then put into a rotary incubator shaker at 50 rpm and 37°C. An aliquot of 5 mL was taken periodically and replaced with the same volume of water. The concentration of the released capsaicin was determined by HPLC or spectrophotometer based on the standard curve. Different mathematical models of Higuchi, first-order, zero-order, and Weibull, Hixson–Crowell, and Ritger–Peppas equations were used to explain the mechanism of drug release from the cubosomes.

APPICATIONS OF CUBOSOMES IN PHARMACEUTICAL FORMULATIONS

Oral drug delivery formulation fabricated as cubosomes.

Drug loaded	Oil used	Stabilizer used	Outcomes	Reference
Coenzyme Q10	GMO	Poloxamer 407	CoQ10 loaded cubosomes revealed a sustained release up to 48hrs.cubosomal nanoparticles had a superior effect in retaining liver functions and oxidative stress markers to their normal levels, after TAA-induced hepatotoxicity in rats.	65
Tamoxifen citrate	GMO	Poloxamer 407	A Sorbitol-based powder precursor of cubosomes loaded with a poorly water soluble Tamoxifen citrate improves the bioavailability of drug in terms of rate and extent of absorption compared to plain powder drugs.	66
Amphotericin B	GMO	Poloxamer 407	The proposed regimen for oral GMO cubosomes was successful in reducing the	67

			fungal burden in the kidney, which indicated an effective approach for enhancing the oral bioavailability of Amphotericin B.	
5-Fluorouracil	GMO	Poloxamer and Tween 80	The study concludes that the 5-Fluorouracil (5-FU) cubosomal formulations show potential for effective therapy in the clinical management of superficial cancers, with stable formulations and suitable drug release and permeation profiles. Further optimization may enhance the formulation's effectiveness in treating superficial tumors.	68
Gefitinib	GMO	Poloxamer 407	GFT-CNPs provide a sustained GFT release rate. This study firmly suggests the possible usage of GFT-CNPs as an oral vesicular system for the treatment of colon cancer.	69
Telmisartan	GMO	Poloxamer 407	The dry free-flowing cubosomes formulae which overcome the physicochemical issues connected to liquid cubosome have been effectively prepared for oral intake. TEL-loaded cubosome processed a noteworthy change in the bioavailability compared for TEL commercial tablets.	70
Glimepiride	GMO	Poloxamer 407	The above research specifies cubosomal utility as a controlled-release drug carrier. Prolonged released is achieved when they are formulated as granules maintaining the cubosome structure.	71

Topical and Dermatological drug delivery formulation fabricated as cubosomes.

Drug loaded	Oil used	Stabilizer used	Outcomes	Reference
Erythromycin	GMO	Poloxamer 407	Sustained release and improved skin retention as compared to plain gel of erythromycin for the treatment of acne. Cubosomes easily penetrate the skin and improve drug retention for a long period.	72
Methotrexate	GMO	Poloxamer 407	Methotrexate cubosomes is a fruitful treatment of rheumatoids as it gives controlled conveyance of the medication in human by means of the noninvasive skin course with additionally continuing, less successive dosing.	73
Minoxidil	GMO	Poloxamer 407	Hair re-growth study revealed greater hair growth boosting effect of the prepared Cubosomes compared to Minoxidil solution. Proved superior penetration and retention. A safe and effective dosage form for Minoxidil that overcome the drawbacks of the commercial formulations.	74
Capsaicin	GMO Phytantriol	Poloxamer 407	Cubosomes allowed for the steady release of capsaicin, extended skin retention without causing skin irritation, and capsaicin was stable under high temperatures and light.	75
Silver sulfadiazine (SSD)	GMO	Poloxamer 407	Second-degree burn patients responded well to the introduction of cubosomes in gel formulations, with improved patient compliance and superior therapeutic outcomes and with fewer adverse effects as compared conventional ones.	76
Palmitoyl peptides (palmitoyl- GHK and palmitoyl-GQPR).	Phytantriol	Poloxamer 407	Pal-GHK and pal-GQPR are efficiently incorporated into phytotantriol cubosomes, which are released gradually over several days. Rise in stability at room temperature to a considerable degree.	77

Intranasal drug delivery formulation fabricated as cubosomes.

Drug loaded	Oil used	Stabilizer used	Outcomes	Reference
Donepezil HCL	GMO	Poloxamer 407	Showed a significant improvement in the drug permeation through the nasal membrane and enhanced distribution was achieved compared to drug solution.	78
Granisetron	GMO Tween 80	Poloxamer 407	Significantly improved drug penetration across the nasal membrane, greater bioavailability and better brain distribution following intranasal delivery. Suitable nano-carrier for intranasal brain targeting.	79
Lamotrigine(LTG)	GMO	Poloxamer 407	*In vivo* experiments on rats showed that LTG cubosomes had greater antiepileptic efficacy than free medication. Results show that the cubosomal thermosensitive in situ gel can improve LTG's antiepileptic effectiveness when administered via intranasal route. .	83

Ocular drug delivery formulation fabricated as cubosomes.

Drug loaded	Oil used	Stabilizer used	Outcomes	Reference
Ketorolac	GMO	Poloxamer 407	In addition to extending the precorneal retention period and enhancing transcorneal penetration of ketorolac, histopathology investigations demonstrated the safety of using cubosomes loaded with ketorolac for ocular applications.	80
Pilocarpine nitrate(PN)	GMO Tween 80	Poloxamer 407	When compared to conventional eye drops, cubosomes increased the apparent permeability coefficient while having a greater effect on lowering rabbits' intraocular pressure and reducing their ocular discomfort.	81
Timolol (TM)	GMO	Poloxamer 407	Compared to commercially available eye drops, timolol-loaded cubosomes demonstrated superior intraocular pressure-lowering effects, longer precorneal retention times, and higher corneal penetration.	82

CONCLUSION

Cubosomes are special nanostructures composed of unsaturated Monoglyceride, specifically GMO and PHYT, that self-assemble in the form of a bicontinuous cubic liquid crystalline phase. The overall context of the documents revolves around the behavior and applications of cubosomes, focusing on factors like the impact of guest molecules on phase behavior, structural transitions, preparation methods, characterization and potential applications in drug delivery systems. Studies discuss the influence of different compounds on cubosome behavior, the role of stabilizers like PEG, and the characterization of cubosomes in terms of particle size and morphology. Because of their unique characteristics, cubosomes can be administered by intravenous, intranasal, topical, ocular, and oral routes. When used orally, cubosomes have demonstrated their efficacy in protecting drugs from enzymatic destruction, boosting absorption of poorly water-soluble ones, and facilitating targeted drug administration. They serve as a tool for the delivery of anticancer medications with fewer severe side effects as than that of chemotherapy medicines. They offer a potentially effective transdermal medication delivery carrier with less irritation potential and improved skin penetration. They have been recognized as a successful method of delivering drugs into the eyes that have improved bioavailability and ocular residence time without causing ocular irritation. Additionally, cubosomes have a crystalline cubic structure making them suitable for sustained release formulations and targeted delivery of drugs. Even though cubosomes have been the subject of numerous studies, there are still many obstacles that may need to be understood before such medication may be used in clinical setting. But with the knowledge of even better understanding of Cubosomes, it will be a versatile and potential drug delivery platform in the near future.

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