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CUBOSOMES: A POTENTIAL NANOCARRIER FOR DRUG DELIVERY

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ABSTRACT
Cubosomes, also known as bicontinuous cubic phase liquid crystals, are nanoparticles with a specific ratio of amphiphilic lipids as their major constituents. Cubosomes are typically created by hydrating a surfactant or polar lipid that produces a cubic phase and then dispersing it into smaller particles. They exhibit unusual features of practical interest and solid-like rheology. They have carvenous (honeycomb) structures that are tightly packed and twisted into three-dimensional bilayers, and they are thermodynamically stable. They are extensively employed in a variety of drug delivery applications, including transdermal, oral, and chemotherapeutic drug administration. The pertinent literature on cubosomes, with a focus on theories of self-assembling, cubosome composition, preparation techniques, and drug delivery applications, will be critically addressed in this study.

KEYWORDS: Cubosomes, Nanoparticles, Bicontinous, Honeycomb, Amphiphilic.

INTRODUCTION
Lipid-based nanoparticles are dispersions with bulk lipid phases and polymers such as block co-polymer or PEG moieties that stabilise the outer surface. These stabilisers make it possible to target specific cells without relying on the majority of the lipid membrane assembly. The outcome is highly stable nanoparticles made of biocompatible lipids that can be generated under biological circumstances. Cubosomes are nanoparticles with a lipid bicontinuous cubic phase that have been generated for over 25 years.[1]

Cubosomes are bicontinuous cubic liquid crystalline phase discrete, sub-micron nanostructured particles. 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 specific surfactants with the correct water-microstructure ratio. In contrast to most liquid crystalline systems, which change into micelles at greater levels of dilution, the relative insolubility of cubic phase forming lipid in water permits cubosomes to exist at practically any dilution level. The cubic phase has a unique property: it possesses a very high solid-like viscosity. Such cubic phases are distinguished by their bicontinuous nature from miceller or discontinuous cubic phases having micelles packed in cubic symmetry. The ability of some kinds of amphiphiles to disseminate their cubic phase into cubosomes is a unique feature of this phase. Cubosomes are nanoparticles that range in size from 10 to 50 nanometers in diameter and look like square, slightly round dots.[2]

Cubosomes have the same microstructure as the parent cubic phase, but they have a greater specific surface area and lower viscosity in their dispersions than the bulk cubic phase. Amphiphilic compounds include polar and non-polar components in lipids, surfactants, and polymer molecules. Amphiphilic molecules in polar liquids spontaneously self-assemble into an array of thermodynamically stable liquid crystalline phases with lengths on the nanometer scale due to the hydrophobic effect.[3]

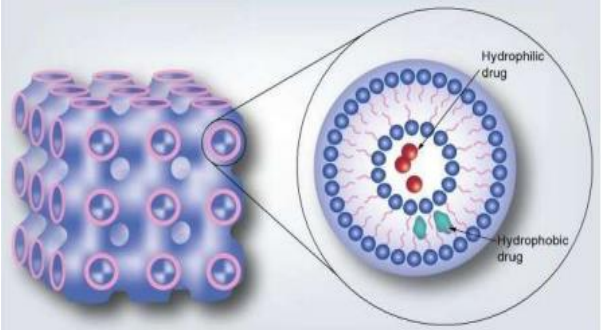

FIG 1: Cubosomes with a cavernous internal and cubic structure, as well as a variety of membrane compositions and drug loading modalities.[4]

Structure of Cubosomes[5]
The honeycombed (cavernous) structures seen in cubosomes have a diameter that ranges from 10 to 500

nm. They have the appearance of little, somewhat round spots. Each dot denotes the presence of an aqueous cubic phase-containing pore in the lipid water system. Using an X-ray scattering technique, Luzzati and Husson were the ones to initially identify it.

Advantages[6,7]

- Due to the high internal surface area and cubic crystalline structures, high drug payloads are possible.
- Preparation is relatively simple.
- Lipid biodegradability
- Encapsulation of hydrophilic, hydrophobic, and amphiphilic substances.
- Controlled and targeted release of bioactive agents

Disadvantages[8,9]

- Cubosome production on a large scale was difficult due to their viscosity.
- High-intensity processes
- Dangerous to temperature-sensitive active ingredients
- Expensive
- It is difficult to scale up.

COMPOSITION OF CUBOSOMES

These are the main components of cubosomes:

A) Glyceryl monooleate (GMO)[10,11,12]

Glyceryl monooleate (GMO) is the most commonly used amphiphilic lipids in preparation of cubosomes and it is generally referred to as monoolein. It is a synthetic mixture of glycerides ester of oleic acid and other fatty acids, primarily monooleate, which can self-assemble in water to form bicontinuous cubic structures. GMO is a polar unsaturated monoglyceride, with a melting point: 35-37 °c, storage temperature −20°c, having HLB value 3 and it is clear and colourless in appearance.

B) Stabilizers[13,14]

Although the bulk cubic aggregates are thermodynamically stable, using stabilising agents becomes an important step in the preparation of cubosomes to prevent re-coalescence of the dispersed particles into the parent bulk cubic structure when dispensed. This is because the hydrophobic portions of the dispersed particles are prone to aggregate as a result of exposure to the external hydrophilic aqueous media. Pluronics are the stabilising agents that are most frequently utilised, particularly F127 (Poloxamer 407), which is regarded as the "gold standard."

PREPARATION OF CUBOSOMES

Cubosomes can be manufactured by four distinct methods:

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

1. Top-down approach[15,16]

It is the most often utilised method, as Ljusberg- Wahren first noted in 1996. Cubosomes nanoparticles are created by processing bulk cubic phase with high energy methods such high pressure homogenization. Cross-linked polymer chains that are water-swollen resemble a transparent, hard gel when they form the bulk cubic phase. The cubic phases are distinct because they have a periodic liquid crystalline structure and are one thermodynamic phase. The energy used is inversely correlated with the number of rupturing branches in the tubular network during cubic phases, which rupture in a direction parallel to the shear direction.

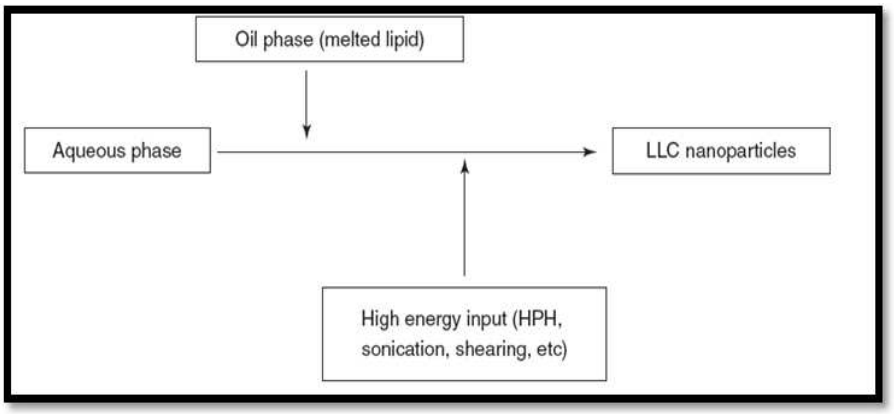

FIG. 2: Top Down approach method.[17]

2. Bottom-up approach[18]

Cubosomes are allowed to develop or crystallise from their predecessors in this process. The bottom-up method initially creates the basic components of the nanostructure before putting them together to create the finished product. It is a more contemporary method of cubosome production that enables cubosomes to form and crystallise from molecular-scale progenitors. The hydrotrope, which can turn water-insoluble lipids into liquid precursors, is the main component of this method. Compared to the top down method, this dilution-based method uses less energy to manufacture cubosomes.

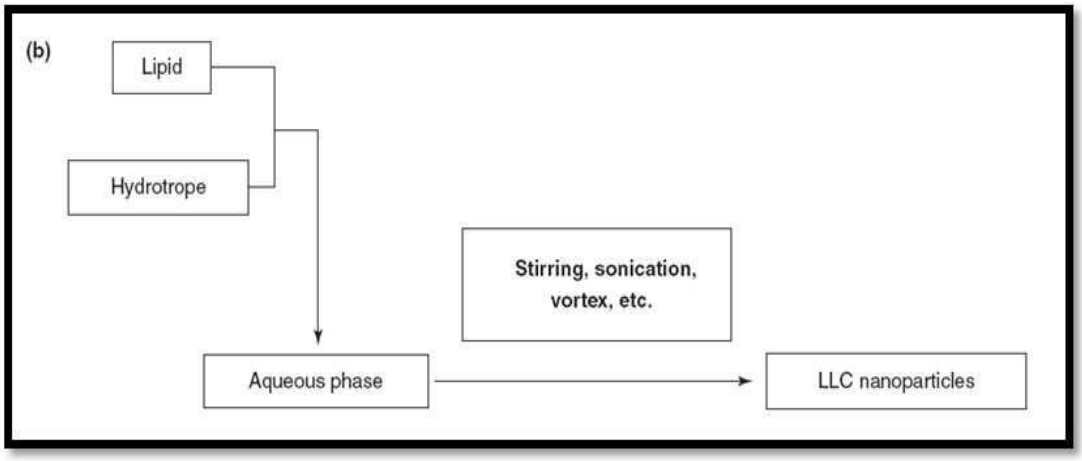

Fig. 3: Bottom - up Approach.[19]

3. Heat Transfer[20]

Heat therapy is a viable option in this situation. Because heat treatment merely facilitates the conversion of non-cubic vesicles to well-ordered cubic particles, it should be noted that in the simplest form, it is not an integrated process for the production of cubosomes. Therefore, a straightforward processing approach that includes a homogenization and heat-treatment step can be used to create the dispersed particles. According to the research that have been published, heat treatment could lead to a reduction in the small particle size fraction that corresponds to vesicles and the formation of more cubic phases with a narrow particle distribution and strong colloidal stability.

It is clear that the changeover occurs throughout the heat treatment process when the entire preparation process is taken into account. One theory for the cause of the transition is that a rise in temperature caused a decrease in solubility and stability. Because the surfactant had a high solubility at temperatures below cloud point, the particles could live steadily and the fusion occurrence was virtually ever noticed. As soon as the surfactant reached cloud point, its solubility significantly dropped and vesicles began to fuse quickly.

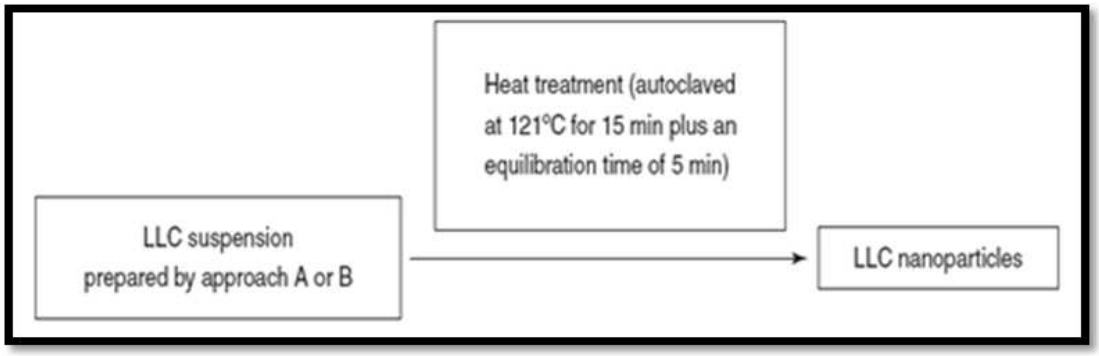

FIG. 4: Heat transfer.[21]

The cubosome dispersion carried out by two methods

a) Fabrication method[22]

P407 cubic gel with GM In a hot water bath at 60°C, GMO 5% and P407 1 percent were melted. The needed amount of medication was added, and the mixture was continually stirred until it was dissolved. Drops of deionized water are added while a vortex is set to homogenise the mixture.

The optically isotropic cubic gel was created and stirred mechanically for up to 48 hours at ambient temperature before being broken up by a sonicater probe with 200 W of power while at 20°C in a water bath for 20 minutes.

b) Emulsification method[22]

In this procedure, GMO and P407 are added to the water, and after ultrasonication, 5 percent GMO, 1 percent P407, and 5 percent ethanol are removed from the 89 percent water. At 60 °C, GMO and P407 are melted and combined. Ethanolic solution is added to the melting process. The resulting combination is added dropwise to deionized water that has been prepared to 70°C. It is then ultrasonically processed for 50 minutes at the same temperature using a maximum power of 130kW. The dispersion solution is then maintained at room temperature and shielded from light.

CHARACTERIZATION OF CUBOSOMES

1. Visual inspection[23]

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

2. X-ray scattering[24,25]

Various groups in the sample can be distinguished by their spatial configurations using small angle X-ray scattering (SAXS). Plots of intensity versus q value are created using the obtained diffraction patterns, which allow for the recognition of peak positions and the conversion of such values to Miller indices. The Miller Indices might then be used to identify liquid crystalline structures and space groups by correlating them with values for those structures and groups.

3. Particle size distribution[26]

Using photon correlation spectroscopy, the dispersions' particle size distribution was identified. At intervals of 100 s, measurements were made at 25^0C utilising the refractive index (RI) of cubosomes. Water was added to samples to dilute them and change the signal level. The poly dispersity index and average particle size (z-average) were calculated.

4. Zeta potential[27]

The size and zeta potential represents the strength of the electrical attraction between two similarly charged particles. Zeta potential is a crucial indicator of the formulation's stability.

5. Entrapment efficiency[28]

Ultra filtering techniques can be used to assess the cubosomes' entrapment effectiveness. The unentrapped drug concentration is calculated in the later method and deducted from the overall amount of drug added. A spectrophotometer is used to measure the drug's quantity.

6. Stability studies[29]

By examining organoleptic and morphological features as a function of time, the physical stability can be investigated. Additionally, the potential alterations by time can be examined using the drug content and particle size distribution at various time intervals.

Some of The Evaluation Parameters of Various Articles and The Results Are Shown In Table 1.

S.no	Article name	Evaluation parameters	Results	References
1.	Formulation and evaluation of Dexamethasone loaded cubosomes	Particle size	119.4 nm	[30]
		Zeta potential	-22.1 mV	
		Entrapment efficiency	85%	
		Drug release	90%	
		PDI	4.05	
2.	Preparation and evaluation of Diclofenac sodium cubosomes for percutaneous administration	Particle size	200.5 nm	[31]
		Zeta potential	-26.8mV	
		Entrapment efficiency	88%	
3.	Formulation and evaluation of ketoprofen loaded cubogel for topical sustained delivery	Particle size	61.1 nm	[32]
		Zeta potential	-46.7mV	
		Entrapment efficiency	70%	
		Drug release	85%	
4.	Design, Formulation , In-vitro and Ex-vivo evaluation of Atazanavir loaded cubosomal gel	Particle size	306.5 nm	[33]
		Zeta potential	-30.7mV	
		Entrapment efficiency	81%	
5.	Development of methotrexate-loaded cubosomes with improved skin permeation for the topical treatment of rheumatoid arthritis	Particle size	626.1 nm	[34]
		Zeta potential	-6.29 mV	

APPLICATIONS

1. In cancer therapy[35,36]

Lately, various anti-cancer medications were successfully encapsulated in cubosomes and their physicochemical features were identified. This intriguing nano carrier's distinctive shape points to a potential use in the treatment of cancer. Different strategies have been considered to specifically target nanomedicines to tumours; passive and active targeting of cancer cells have both been demonstrated to be effective strategies in preclinical and clinical research.

2. Ocular applications[37]

Cubosome use in ocular medication delivery has been the subject of numerous recent investigations. Utilizing their advantages of biodegradability, the ability to encapsulate all three types of therapeutic molecules as hydrophilic, hydrophobic, and amphiphilic, and their ability to produce bioactive agents with controlled and targeted release. They are discovered to have lengthy residence times at the corneal surface, are characterised by mucoadhesive qualities because of the presence of GMO, which improves corneal permeability and, as a result, improves ocular bioavailability of the loaded

medications. (Table 2) lists a few instances of cubosomes loaded with drugs for ocular application. All results demonstrated the great benefits of cubosomes for ocular drug delivery in extending precorneal residence time and enhancing ocular bioavailability of loaded drug. Histopathology studies also demonstrated that cubosome preparations are secure and non-irritating for ocular uses.

Examples of cubosome applications in ocular medication administration are shown in Table 2.

Loaded drug	Oil used	Stabilizer used	Pharmacological uses	References
Pilocarpine Nitrate	GMO	Pol. 407	open-angle treatment and acute angle-closure glaucoma	[38]
Timolol	GMO	Pol. 407	a non-selective beta-blocker medication used to treat glaucoma.	[39]
Flurbiprofen	GMO	Pol. 407	NSAIDs are prescribed to alleviate eye irritation.	[40]
Cyclosporine A	GMO	Pol. 407	Agents that inhibit the immune system are used to treat inflammatory and immunological-related eye disorders.	[41]
Ketorolac	GMO	Pol. 407	An NSAID is used to treat itchy eyes brought on by seasonal allergies	[42]
Dexamethasone	GMO	Pol. 407	treatment for inflammation of the anterior eye.	[43]

3. Controlled release of drugs[44]

The most common use of cubosomes is for the controlled release of solubilized material. Because of its tiny pore size (5–10 nm), capacity to solubilize hydrophilic, hydrophobic, and amphiphilic compounds, and biodegradability by straightforward enzymes, cubic phase is better suitable for control release.

4. As injectable vehicles[45]

Due to their mechanical rigidity and high viscosity, cubosomes are awkward to handle and challenging to inject. Some comparable strategies, such as the usage of LLC nanoparticles and the application of flowable precursor forms, have been suggested to address this flaw. The shift from lamellar to cubic phases can be finished by heating from room temperature to body temperature or swelling with water, according to the phase diagram of structure-forming lipid. As a result, lamellar phases with fluid properties by nature can serve as a prelude to viscous cubic phases. Flowable lamellar phases that have been subcutaneously or muscularly injected into the body will progressively take up water from bodily fluids or surrounding tissues and change into cubic phases, which can create the sustained release depot in situ.

5. Dermatological Applications[46]

The stratum corneum, the skin's highly structured outermost layer, acts as a formidable barrier to the skin-penetrating effects of topically applied medicines in transdermal drug delivery. Cubosomes, on the other hand, offer a potential vehicle for transdermal medication delivery due to their distinct structure and characteristics. Due to cubosomes' bioadhesive qualities to the stratum corneum as a result of GMO, they can be used to deliver drugs to the skin and mucous membranes in these ways. Examples of cubosome uses for topical medication administration in dermatology are listed in (Table 3).

Examples of cubosome usage in dermatology are shown in Table 3.

Loaded drug	Oil used	Stabilizer used	Pharmacological Use	References
Dapsone	GMO	POL. 407	an antibiotic and anti-inflammatory drug used to treat systemic lupus erythematosus, leprosy, and acne	[47]
Palmitoyl peptides	PYT	POL. 407	Pal-GHK and pal-GQPR, when administered topically to the skin, have anti-wrinkle characteristics (Skincare product).	[48]
Capsaicin	GMO	POL. 407	used to treat contact allergies, pruritus, and psoriasis.	[49]
Antimicrobial peptides	GMO	POL. 407	used as a therapy for staphylococcus aureus skin infections.	[50]
Silver sulfadiazine	GMO	POL. 407	Used for the treatment of infected burns.	[51]
Erythromycin	GMO	POL. 407	Due to its bacteriostatic activity against	[52]

			Propionibacterium acnes, it can be used for both the treatment and prevention of various forms of acne.	
Hydroxypropyl β cyclodextin	GMO	POL. 407	Hair growth is promoted by minoxidil.	[53]

6. Intravenous drug delivery[54]

To solubilize, encapsulate, and distribute drugs to patients, curved lipid membranes with internal liquid crystal structures are employed in lipid nanoparticles. parts of the body that are diseased. Although emulsions and utilizing liposomes as intravenous carriers in pharmaceuticals, structures of liquid crystal nanoparticles enhanced peptide, protein, and other payloads tiny compounds that are difficult to dissolve and make excellent many actives through injection or infusion.

7. Current application[55]

The use of cubosome particles as oil-in-water emulsion stabilisers and pollutant absorbents in cosmetics is a current application field being developed by L'Oreal.

8. In treatment of viral diseases[56]

Because monoglycerieds have microbic characteristics, they can be used to create intravaginal treatments for sexually transmitted diseases brought on by bacteria and viruses including Chlamydia trachomatis and Neisseria gonorrhoeae.

9. Oral drug delivery[57]

The multiple difficulties in oral distribution of several substances, such as low water solubility, poor absorption, and huge molecular size, are controlled by cubosomes. Large proteins have been encapsulated for local action in the digestive tract in one application. For medications with a limited absorption window, cubosome technology offers drug release at various absorption sites, such as in the upper or lower gut. Additionally, cubosomes offer a promising method for oral administration of insoluble in water substances. Due to the mucoadhesive qualities of GMO, they also enhance intestinal adsorption by incorporating the poorly water soluble medicine in the solubilized form within the lipid bilayer section of their structure, preventing drug precipitation in the GIT tract.

Examples of cubosome applications in oral medication delivery are shown in (Table 4).

Examples of oral medication administration using cubosome formulations are shown in Table 4.

Loaded drug	Oil used	Stabilizer used	Pharmacological Uses	References
Amphotericin B	PYT	POL. 407	an antifungal medication used to treat many fungal infections, including leishmaniasis and histoplasmosis.	[58]
Simvastatin	GMO	POL. 407	used to increase good cholesterol and lower bad cholesterol and lipids in the blood.	[59]
Insulin	GMO	POL. 407	used to treat mice with type 1 diabetes that has been created (insulin-dependent diabetes)	[60]
Piperine	GMO	POL. 407 TWEEN 80	It is a natural alkaloid with promise to improve memory that is used to treat Alzheimer's disease (AD)	[61]
Ibuprofen	PYT	POL. 407	Analgesic non-steroidal anti-inflammatory medication	[62]

CONCLUSION

Bicontinuous cubic liquid crystals can be found in bulk or as cubosomes, depending on the application. Cubosome formation is either used to increase flexibility in product development efforts or as a template for complex solid materials by material science researchers. Cubosomes prepared through the dispersion process have a structure at the nanometer scale that is identical to that of bulk cubic phases. Although cubosomes are too small and have a large surface area for such performance, they still demonstrate burst release even though bulk cubic phase has a suitable length scale to provide regulated release of solutes. Researchers in material science are likewise interested in the twisted but regular structure of the cubic phase as a model for complicated solid materials.

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