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Cubosomes: A Unique Nanostructured Lipid Carrier for Drug Delivery -A Review

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A B S T R A C T :

Cubosomes are spherical or square particles with internal cubic lattices that are visible. The narrative of cubosome discovery is an intriguing one that focuses on biological membranes, differential geometry, food science, and digestive processes. Cubosomes are thermodynamically stable and contain a "honey combed" structure. A polymer holds the amphiphilic lipids that make up cubosomes together. Cubosomes can be administered parenterally, orally, mucosally, or transdermally . To target the outer circle, polymers can be used, and cubosome formation can be adjusted to incorporate bioactive lipids or to design pore size. Additionally, they are safe in physiological conditions. Because of their network structure, they have a greater potential for drug entrapment. Cubosomes are self-assembling nanostructured liquid crystalline particles with a distinct interior cubic structure and composition. Cubosomes are created by dispersing a solid-like phase into smaller particles after hydrating a polar lipid or surfactant that produces a cubic phase. Hydrophobic, hydrophilic, and amphiphilic compounds can all be encapsulated in cubosomes. Drugs that aren't highly soluble can become more soluble with the help of cubosomes.

Keywords: Cubosomes, nanostructured liquid crystals, amphiphilic lipids, drug delivery.

INTRODUCTION

The word "Cubosomes" which resemble liposomes, was initially used by Larsson. The distinct, sub-micron-sized particles of the bicontinuous cubic liquid crystalline phase are known as cubosomes, and they are nanostructured particles[1].

The lipids, polymers, and surfactants that make up these cubosomes are often amphiphilic. When two distinct water zones are enclosed by surfactant bilayers, this is referred to as being bicontinuous. Cubosomes share characteristics with liquid crystalline substances, including viscosity, optical isotropy, solidity, and cubic crystallographic symmetry [2,3].

In drug delivery systems based on nanotechnology, cubosomes are crucial. Pharma has recently gained more attention due to particles that range in size from 10 to 500 nm. The drug-to-polymer ratio is approximately 1:2 or 1:1, though this can differ from substance to substance. Cubosomes have been successfully used in the formulation of various anticancer medications. Cubosomes' viscosity and phase behavior made their large-scale manufacture challenging. The creation of a cubic phase occurs spontaneously when certain surfactants are combined with water. In addition to having the same microstructure as the parent cubic phase, cubosome dispersions are significantly less viscous than the bulk cubic phase. Compared to the parent cubic phase, the cubosomes have a greater surface area. Cubosomes are created when amphiphilic or surfactant-like molecules self-assemble[4, 5].

When medications, including those with a high molecular weight, are integrated into cubosomal vesicles, they are transported to the site of action. It increases drug transport via the skin and functions as a penetration enhancer. The vesicular drug delivery system, which was developed in 1980 and played a significant role in nanotechnology[6]. There are numerous uses for cubosomes, including the delivery of peptides, enzymes, anti-muscarinic medications, analgesics, and antibiotics. Cubosomes have a large surface area of over 400 m^2/g and are made up of severely twisted lipid bilayers[7]. Because of their improved formulation stability, maximum drug loading capacity, regulated drug release, and ideal particle size, cubosomal systems outperform other innovative delivery methods. A channel on cubic phase will allow the medicine in a cubosome to disseminate. Both stability and controlled release behavior are attributed to the polymers (contain PEG moieties and block copolymers) utilized in the cubosome preparation process. Researchers have recently looked into cubosomes for topical application, cosmetic manufacturing, cancer treatment, and other drug delivery methods. In reality, there are hardly any anticancer medications being developed[8].

1.1 Properties of Cubosomes[9]

- The viscosity is significantly lower in cubosome dispersions.
- Cubosomes are discrete bicontinuous cubic liquid crystalline particles with a sub-micron nanostructure.
- Probably the most fascinating are cubosomes.
- Cubic liquid crystals are physically stable in excess of water due to their transparency and isotropy.
- Cubosomes' narrow pore size makes them attractive for controlled release.

- It is biodegradable and capable of solubilizing hydrophilic, hydrophobic, and amphiphilic compounds.

1.2 Advantages [10]

- It's cost-effective, non-toxic, and biocompatible.
- The preparation process is straightforward.
- Its bioadhesive properties are excellent.
- It has the ability to improve skin penetration.
- They are thermodynamically stable for a longer period of time.
- Hydrophilic, hydrophobic, and amphiphilic compounds can be encapsulated.
- Bioactive agents can be released with controlled and targeted release.
- There is a substantial drug loading because of the cubic crystalline structures and large interior surface area.
- Because the lipid that forms the cubic phase is relatively insoluble in water, cubosomes stay stable at almost any dilution level. Cubosomes are very simple to incorporate in product formulations.
- Better oral, topical, and intravenous compliance and convenience.
- Reduced medical expenses as a result of less frequent administration and easier managing.

1.3 Disadvantages [11]

- Due to cubosomes' high viscosity, large-scale manufacture might occasionally be challenging.
- The high water content of cubosomes results in a low entrapment of water-soluble medications.
- When a polymer-based drug form is present, cubosomes do not provide controlled drug delivery.

2. STRUCTURE[12]

A high interfacial area and honeycombed structures dividing the two internal aqueous channels are features of the basic cubosome structure. When amphiphilic or surfactant-like molecules self-assemble, they create cubosomes, which are nanoparticles—more precisely, nanostructure particles of a liquid crystalline phase with cubic crystallographic symmetry. Cubosomes have cubic crystalline structures and a large interior surface area. Because of their intriguing bicontinuous structures, which encompass two independent areas of water separated by a regulated bilayer of surfactant, the cubic phases have a very high solid-like viscosity, which is a unique feature. Amphiphilic molecules create bicontinuous oil and water channels, where "bicontinuous" means that the bilayer separates two discrete (continuous, but non-intersecting) hydrophilic zones. A transparent, viscous gel that resembles cross-linked polymer hydrogels in both appearance and rheology is produced by the structure's interconnection. However, due to their composition (lipid and water), monoglyceride-based cubic gels have good biocompatibility and a substantially higher long-range order than hydrogels.

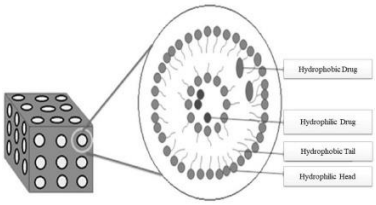

Fig 1: Structure of Cubosome

3. COMPONENTS OF CUBOSOMES[13,14,15]

The cubosomes are easy to prepare and just require three basic ingredients: water, stabilizer, and amphiphilic lipids. It is claimed that when amphiphilic lipids are hydrated, cubic liquid crystalline phases are created. The compounds that stop reconstitution from converting to the bulk cubic phase are known as stabilizers. The following experimental compounds are utilized to create lyotropic liquid crystals: ethylene oxide amphiphiles, urea, phosphatidyl ethanolamine, different glycolipids, monoglycerides and phytotriol.

3.1. Amphiphilic lipids

Glyceryl mono-oleate and phytotriol are both amphiphilic lipids that are used to make cubosomes.

3.2. Glyceryl Mono-Oleate (GMO)

GMO is the main constituent of an amphiphilic lipid class that can be produced from oleic acid glycerides and other fatty acids. Its head is hydrophilic and its tail is hydrophobic. In the food industry, GMOs are also utilized to create cubic lipid phases, which are used as food emulsifiers. According to Lutton's findings, monoglycerides with a chain length of 12–22 are more likely to form cubic phases.

3.3. Phytantriol (PHTY)

A good substitute for GMOs, phytotriol is a chemical with phytanyl chains that exhibits comparable phase behavior. Both have different chemical and physical properties and structures. Phytantriol is a crucial component in the cosmetics industry. 3, 7, 11, 15-tetra-methyl-1, 2, 3-hexadecane thiol ($C_{20}H_{42}O_3$) is its chemical name. Because PHYT is prone to hydrolysis by esterase, it provides more structural stability. By raising the concentration at room temperature, the reverse micelles, lamellar, Q230, and Q224 structures are created based on the PHTY-water phase diagram. At a higher temperature of 44 ^{o}C, the cubic phase transforms into the hexagonal structure. Existence in equilibrium with water is a prerequisite for cubosome development. The PHTY-made dispersion is stable, permits the incorporation of hydrophilic excipients, and preserves the internal nanostructure of Pn3m as demonstrated by Rizwan et al. The compound's purity may have an impact on the phase transition.

3.4.Stabilizer

Colloidal stability, which the surfactants may offer, is crucial for cubosome preparations. The bulk cubic phase is being formed by the coalescence of cubosomes. Because stabilizers can create an electrostatic-repellent barrier between the approaching particles, they can prevent unfavorable interactions between the hydrophobic domains of cubosomes as they encounter between particles without disrupting the cubic structure. Therefore, the stabilizer is the essential element needed for the creation of cubosomes. Cubosomes' large interior surface area causes stabilizer sequestration. The most often utilized materials for cubosomal dispersion stabilization are poloxamer 407. and the tri-block copolymer PEO99-PPO67-PEO99. Phase action within the framework of scattered particles is engaged and controlled by the stabilizer. Worle et al. investigated how the characteristics of cubosomes were affected by varying P407 concentrations. In contrast to cubic phases of the nanostructure, vesicular particles are generated at the maximal concentration of P407, although smaller particles do emerge at this stage. When enough P407 is added, a cubic-structured nanoparticulate dispersion is created. The intrinsic crystalline structure and composition determine the development of various cubic crystal forms. The P407 is absorbed on the bulk PHYT cubic phase surface. There was integration of the monoolein cubic phase P407 in the liquid crystalline structure.

3.5.Cubosome precursor:

The drug's thermosensitive components can be shielded by them. Types are :

- Liquid cubosomes Precursor: In this, nucleation creates the particles, which subsequently increase through saturation. It has been noted that the hydrotrope dilution process results in smaller and more stable cubosomes. Monoolein is dissolved in any hydrotrope to produce this. The mixture then spontaneously precipitates or crystallizes after being diluted. It also avoids handling solids in bulk and high-energy procedures. It makes it simple to scale up the synthesis of cubosomes .
- Powdered cubosome precursors: They are made up of dehydrated surfactant that has been coated with a polymer. The precursor powders are hydrated to generate the cubosomes. Here, lipids used here are solids that are waxy and sticky.

4. METHODS OF PREPARATION OF CUBOSOMES[16]

1) High-Pressure Homogenization

2) Automated Cubosome Preparation

3) Probe Ultrasonication

Other methods

1) Emulsification

2) High Shear Homogenization Technique

3) Spray-Drying Technique

Special techniques

1) Top-Down Technique
2) Bottom-Up Technique

4.1. High-Pressure homogenization: This method works well for cubosome preparations because they are very stable during the process and have a long shelf life. Three steps make up this process:

- Gel preparation: Involves dissolving the lipid and amphiphilic surfactants in an organic solvent and then thoroughly mixing the mixture to create a homogenous appearance. Here, the gel phase of a formulation is created by evaporating the organic solvent using a rotary evaporator.
- Shearing: This stage involves shearing the created gel. In order to create a micro-dispersion, aqueous solvents are utilized. In the process of Cubosomes development, it is the decisive phase prior to homogenization.
- High-pressure homogenization: This technique works well with sample systems with a large capacity (30 ml), but it is not suitable for systems with smaller volumes.
  Since this approach is temperature-sensitive, the temperature is chosen in this step based on the lipid's characteristics. This involves homogenizing the produced dispersion using a high-pressure homogenizer. This approach was limited to processing a single sample.

4.2. Automated cubosome preparation: With a few modifications, this method is comparable to the probe sonication approach. This technique could be used to prepare a huge number of Cubosomes. This cubosome preparation technique makes use of robotic equipment and a probe sonicator. This approach uses a 96-well plate with a 600 µl solvent capacity to prepare the gels. After that, a robot does the sonication. The physicochemical properties can be readily evaluated using this method.

4.3. Probe ultra-sonication: This quick method is used to prepare samples with a tiny volume. Even samples as small as 600 µl can be dispersed using it. The size of the probe determines this. Stabilizers are added in this step to prepare the gels. A cubic phase is formed after a solvent equilibration. The cubic phase is then transferred in preparation for the ultra-sonication. Variables, such as frequency and amplitude, must be carefully maintained in order to regulate the pulsing frequency and prevent sample overheating.

Advantage: The tools used in this technique are widely available. This approach is popular and simple.

Disadvantage: Metal contamination is a possibility, and particle growth may occur over the storage period.

4.4. Other methods

Emulsification: In this process, poloxamer 407 dilutes the monoolein-ethanol solution to create the cubosomes.

High shear homogenization technique: Stabilizers are introduced in this technique to prevent particle aggregation during the shelf life. It is a good approach, but due of its high shear application, it also has certain limits.

Spray-drying technique: This method can also be used to produce cubosomes. This process involves hydrating the monoolein and then covering it with polysaccharides (starch or dextran). In order to keep this stable, the polymers are then added.

Advantages: This technique works with powder formulations. This technique makes microencapsulation feasible. Organic solvents can also be used with this technique. Disadvantages: Compared to other approaches, this one is more complex. This approach yields a relatively modest quantity of yield (5 to 30%).

4.5. Special Techniques

Top-Down technique

It is the most widely used method for cubosome manufacturing. The hexasome was invented in the 1990s. High energy techniques like shearing or ultra-sonication are used to stir the polymeric stabilizing agent, drug solution, and amphiphiles for a long enough period of time to create a homogeneous dispersion. Pluronic F127 is frequently employed in a variety of preparation techniques as a steric stabilizing agent. Although it is dependent on the temperature and quantity of pluronic polymer employed in its production, this procedure is also implemented through the use of a high-pressure homogenization technique.

Advantage: Formulations that have been prepared are visible and transparent. This method does not involve the use of organic solvents. This method is relatively easy.

Disadvantage: it takes a lot of time. It requires a significant amount of energy.

Bottom-Up technique

It is a newly developed method for creating cubosomes that involves first forming nanostructure building blocks and then assembling them to create the finished product. When the hydrotrope dissolves in water-insoluble lipids, liquid precursors are created. Less energy is needed at high concentrations to prevent the formation of liquid crystals. Cubosomes are formed in water at 80°C after the inverse micellar phase droplets are dispersed into it and then gradually cooled. The emulsification method is utilized to prepare cubosomes because the monoolein-ethanol solution is diluted at room temperature by

the aqueous poloxamer 407 solutions that the cubosomes produce. This technique cannot avoid vesicle production by cryo-TEM. In other vesicles, liquid crystal development is seen.

5.0 EVALUATION AND CHARACTERIZATION OF CUBOSOMES17

5.1 Visual Inspection Studies:

This include analysing the exterior characteristics of the cubosomes, including their shape, turbidity, color, homogeneity, and particle presence.

5.2 Transmission Electron Microscopy:

Cubosome morphology can be assessed by TEM. It could provide cubosomal particle shapes. It creates a high-resolution image and may offer electron microphotographs for examination. Visualization is therefore feasible. In comparison to light microscopes, it can provide a much higher resolution. It is a great tool for researching how soft matter dispersions behave. It may be possible to overcome every issue with conventional electron microscopy, including the vacuum setting, poor image quality, the induction of structural changes in the cubic phase, etc.

5.3 Zeta Potential:

One could measure the stability of a preparation by analyzing its zeta potential. It radiates a powerful repulsiveness.

5.4 Viscosity:

Viscosity can be measured with a viscometer, also known as a rotational Brookfield viscometer.

5.5 Particle Size Analysis:

In order to do this, the samples must be diluted with an appropriate solvent and exposed to 300 Hz, or the intensity of light scattering at 25 ℃. It is measured using dynamic laser light scattering with a Zeta sizer. This allows for the evaluation of both zeta potential and the PDI. It gives details on the typical size, weight, and volume. The samples could be diluted 100 times with water because the Malvern Zeta Sizer is required to measure particle size.

5.6 Polarized Light Microscopy:

The cubosomal surface coatings that are optically short ringent or vesicular can be assessed using polarized light microscopy. Anisotropic and isotropic differentiation may also be provided using this method. It may monitor changes in cubic phases. It provides information about the possible coexistence of layered liquid crystals and hexagonal liquid crystals.

5.7 Differential Scanning Calorimetry:

Since liquid crystals are thermodynamic equilibrium processes and phase transitions are caused by endothermic and exothermic processes, DSC may be used to identify whether and when a phase transition takes place.

5.8 Entrapment Efficiency:

Ultrafiltration techniques may be used to assess the effectiveness of cubosomal entrapment. This method calculates the concentration of an unentrapped drug using a spectrophotometer, then extrapolates that value to the concentration of an entrapped drug. This involves centrifugation after the material has been diluted with deionized water. Subsequently, an ultrafiltration technique employs a specific amount of medication that is measured using spectrophotometry.

5.9 Drug Loading Determination:

The determination may be made using ultrafiltration or gel permeation chromatography techniques. It can then be evaluated by HPLC.

5.10 Drug Release Measurement:

In this case, morphological and organoleptic characteristics regard to the time period may be used to assess the stability. Furthermore, the evaluation of the drug concentration and particle size distribution over time. In this, assessments of possible changes throughout time are examined.

6.0 APPLICATION OF CUBOSOMES

6.1 For the Controlled and Sustained-release behaviour:

The peculiar behaviour of cubosomal particles, or the leftovers, makes this possible. It is the most often used cubosome application that researchers have discovered. Because of its tiny (5–10 nm) pore size, the cubic phase is the most advantageous for controlled release. Cubosomes could encapsulate a range of substances or APIs with distinct physicochemical properties. The benefit of cubosomal material's biodegradability by enzymes is that it allows for regulated and prolonged medication release without building up inside the body[28].

6.2 As a Drug Delivery Vehicle:

Several companies including L'Oréal and Nivea, are attempting to incorporate cubosomes in their cosmetic formulations (O/W emulsion stabilizers, pollutant absorbents, etc.). This is a general use of cubosomes and one of their most frequent uses.[29]

6.3 For Topical Drug Delivery Systems:

For topical and transdermal administration, cubosomes work effectively, especially for medications that must cross the epidermal barrier. Drug penetration can be improved by interactions between the stratum corneum and the lipid bilayer of cubosomes. This makes cubosomes useful for dispensing medications like silver sulfadiazine for burn injuries or antifungal agents like clotrimazole, as well as for treating skin disorders. Cubosomes can also be used in conjunction with microneedles to enhance drug delivery and skin penetration. These are some major benefits of topical administration: Increased drug penetration through the skin Delivering medications continuous drug release over time[30]

6.4 In cancer therapy

Only a few anticancer drugs have lately undergone successful cubosome encapsulation and physicochemical analysis. The unique structure of this fascinating nanocarrier suggests a possible application in the treatment of cancer. Numerous approaches have been put forth to target nanomedicines specifically to tumors; preclinical and clinical studies have shown that both passive and active targeting of cancer cells are feasible.[31]

6.5 Oral Drug Delivery Systems

Several issues with traditional formulations are solved by the use of cubosomes in oral medication administration. Oral bioavailability is greatly increased by their capacity to boost the permeability and solubility of medications that are poorly soluble in water. Sensitive molecules are protected from harsh gastrointestinal circumstances by the protective environment found within the cubosome structure. Furthermore, cubosomes' bioadhesive qualities encourage longer residence times in the gastrointestinal tract, allowing for longer-lasting drug release and better therapeutic results [32].

6.6 Increasing the corneal permeability

Drug distribution in the eyes is complicated by limited corneal permeability and bioavailability. In a single study, glycerol monooleate and Poloxamer 407 were used to create a cubosome drug delivery system for Timolol Maleate (TM) for the treatment of glaucoma. The penetration of TM cubosomes was shown to be higher than that of commercially available eye drops.

6.7 Brain targeting

The BBB prevents medications used to treat CNS disorders from reaching the brain. The administration of both tiny and large drug molecules significantly hampered by this barrier. Cubosomes are a type of lipid-based nanoparticle that has been studied to improve drug loading into the brain. Enhancing the transnasal pathway of resveratrol administration to the brain via cubosomes is one example. These were made utilizing the probe sonication method using Lutrol® F 127 and glycerol monooleate lipid. To create an in situ gel for nasal application, the optimized cubosomal dispersion was incorporated with Poloxamer 407 polymer. Compared to drug solution, it demonstrated superior distribution and increased transnasal penetration. [33]

FUTURE PROSPECTS

When it comes to assisted drug delivery and pharmaceutical delivery, the cubosomes have unusual capabilities. The previous cubosome-focused studies must have been broadened because they are currently at a very basic level and more research is needed. It is anticipated that particular investigations will be conducted about the delivery behavior and medication stacking restrictions. Later on, more development and improvement will be necessary to understand the rationality of cubosomes with bodily tissues and blood.

The security requirements of cubosomes in natural liquids are then another factor that is unquestionably necessary in the course of events. Similarly, research is needed to learn more about the factors influencing drug release from cubosomes[34].

CONCLUSION

Cubosomes are liquid crystalline nanoparticles that self-assemble. Because of their advantages over other types of nanoparticles, such as their larger surface area, easy preparation, bioadhesiveness, biocompatibility, and adaptability to incorporate hydrophobic, amphiphilic, or hydrophilic drugs in drug delivery as carrier systems, their interest in the pharmaceutical industry is steadily growing. Cubosomes can be made using both top-down and bottom-up techniques, such as high-pressure homogenization or ultra sonication processes. Proteins, immunogenic compounds, different kinds of pharmacological moieties, and cosmetic preparations can all be used with cubosomes. Cubosomal preparations may be frequently used as selective drug delivery techniques for the treatment of diseases because of their potential site specificity. Since cubosome technology is new and has a high yield, there is a lot of potential for research into novel formulations that are both economically and industrially viable.

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