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CUBOSOMES: A COMPREHENSIVE REVIEW

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ABSTRACT
Cubosomes can be considered as a novel lipid-based nanosystems similar to well-known vesicular systems such as liposomes and niosomes. Cubosomes have been widely formulated using certain amphiphilic lipids (e.g. glyceryl monooleate and phytantriol) in the presence of a suitable stabilizer. They can represent a novel drug delivery system which could be loaded with hydrophilic, lipophilic and amphiphilic drug molecules. They are widely used for various drug delivery applications such as oral, ocular, transdermal and chemotherapy drug delivery. In this review, the pertinent literature of cubosomes with emphasis on theories of self-assembling, the composition of cubosomes, methods of preparation and drug delivery applications will be critically reviewed.

KEYWORDS: Cubosomes can be considered as a novel lipid-based nanosystems similar to well-known vesicular systems such as liposomes and niosomes.

INTRODUCTION

Larsson was the first to develop the word "cubosomes," which is akin to liposomes. The discrete, sub-micron sized particles of the bicontinuous cubic liquid crystalline phase are known as cubosomes, or nanostructured particles. One particular advantage of the bicontinuous cubic phases is their capacity to adjust membrane curvature.[1] Cubosomes are self-assembling crystalline liquid particles with a solid-like rheology. One possible quarter state of matter is liquid crystals. Lipids, polymers, and surfactants- which are often amphiphilic- make up these cubosomes. The term "bicontinuous" in this context refers to the division of two distinct water areas' enclosures by surfactant bilayers. Cubosomes resemble liquid crystalline substances in that they possess cubic crystallographic symmetry, are viscous, and are both optically isotropic and solid.[2]

Cubosomes, which range in size from 50 to 1000 nm, are self-assembling liquid crystalline particles with a microstructure that offers special characteristics. Bicontinuous cubic liquid crystalline phases disperse to produce them. An optically transparent, very viscous substance with a distinct structure at the nanoscale scale is known as the bicontinuous cubic liquid crystalline phase.[3] The term "bicontinuous" describes how a lipid bilayer that has been twisted into a space-filling structure divides the two continuous but non-intersecting aqueous zones. Cubosomes are typically formed by hydrating a polar lipid or surfactant that produces a cubic phase, and then dispersing the solid-like phase into smaller particles. Cubosomes are liquid-crystalline cubic nanoparticles that combine characteristics of crystalline and liquid materials.[4] They are sometimes referred to as "mesophases" because of their intermediate condition. Cubic liquid crystals are stable in excess of water and provide a novel mechanism for the synthesis of medicinal dosage forms. They are physically transparent and isotropic phases.[5] Selected water- and oil-soluble compounds are released under control using liquid crystals in the cubic phase.[6] They have cubic crystallographic symmetry, are isotropic, viscous, and solid like liquid crystalline materials. A liquid crystal is a type of material with characteristics halfway between solid crystal and regular liquid. A lipid bilayer divides the two distinct, continuous, but non-intersecting hydrophilic areas that make up the thermodynamically stable structure of cubic phases. This makes it possible to add amphiphiles and materials that dissolve in both oil and water to the system. Lipid-based cubic systems are bioadhesive and biocompatible. These cubic phases are distinguished from micellar or discontinuous cubic systems with micelles arranged in cubic symmetry by their bicontinuous character.[7] Cubosomes play a major role in medication delivery systems based on nanotechnology. The focus on pharmaceuticals has recently expanded to include particles that range in size from a few hundred nm to 500 nm.[8] The proportion of medication to polymer is approximately 1:2 or 1:1, depending on the specific chemical. Cubosome-derived anticancer medications have been developed with success. The viscosity and phase behavior of cubosomes made their large-scale manufacture challenging. A spontaneous cubic phase development occurs when certain surfactants are combined with water. The microstructure of the cubosomes and the parent cubic phase are identical, and the viscosity of the cubosome

dispersions is significantly less than that of the bulk cubic phase.[9] Compared to the parent cubic phase, the cubosomes' surface area is greater. Amphiphilic molecules or molecules that resemble surfactants self-assemble to produce cubosomes. In general, the structure protects the potency and stability of active components like vitamins and proteins. In terms of thermodynamic stability, cubosomes are perpetually stable. Polymers can be added to cubosome colloidal dispersions to increase their stability. They may also be used to administer actives in a controlled manner since diffusion is controlled by the active's meandering path through the "regular" channel form of the cubic phase.[10] Cubosomes may be distinguished by structural symmetry due to their average degree of molecular orientation order, which enables them to form in aqueous surfactant systems at relatively high amphiphile concentrations. The cubic phase exhibits greater suitability for regulated drug release due to its tiny pore size and capacity to solubilize molecules that are hydrophilic, hydrophobic, and amphiphilic.[11] The medicine falls under BCS classification II, and cubosomes are chosen for it because to its high permeability and low water solubility. The drug's water solubility will be increased by cubosomes, increasing its bioavailability. Due to its greatest features—large internal surface area and cubic crystal formations, which allow for a high drug payload—cubicosomes offer considerable potential in drug nano formulations for oral drug administration.[12]

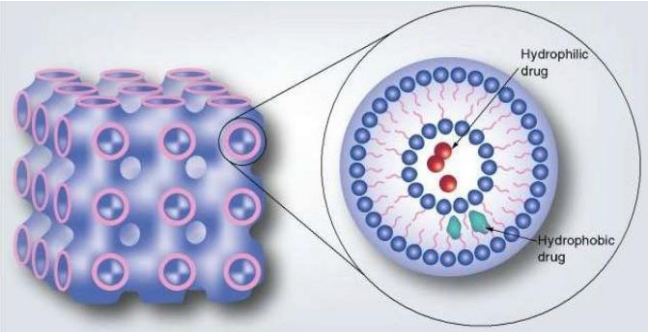

Figure 1: Cubosomes.

Cubosome structural components

Water, stabilizers, and amphiphilic lipids make up the majority of cubosomes.

- **Ampiphilic lipids**

Phytantriol and glyceryl monooleate/monoolein (GMO) are the two amphiphilic lipids that are often used in the cubosome production process (PHYT). GMOs are very biocompatible and bioadhesive, but in the gastrointestinal tract, they are broken down by lipase enzymes. Although at the expense of decreased biocompatibility, the phytanyl chain's backbone gives the PHYT structural stability, which in turn gives liquid crystalline phases more stability than glyceryl monooleate.[13] The composition of PHYT and GMO. Phytantriol and GMOs have distinct structures, but as the temperature and water content rise, they both show comparable phase changes. According to toxicity tests conducted on PHYT and GMO-based cubosomes, PHYT-based cubosomes are more hazardous than GMO-based cubosomes, which causes a sustained-release inflammatory response that is absent from GMO cubosomes. These results led to the conclusion that GMO-based cubosomes might be useful for effectively targeting a lower pH environment, which is similar to the environment prevalent in cancer cells.[14]

- **Surfactants/ Stabilizers**

To be used effectively in biological applications, cubosomes must have their internal structure preserved. The main job of the stabilizer is to provide an electrical barrier that keeps the scattered particles in a stable condition by preventing near-particle interactions. Pluronics®, self-assembling water soluble triblock copolymers comprising polyethylene oxide (PEO) and polypropylene oxide (PPO) arranged in PEO-PPO-PEO conformation, which imparts hydrophobic and hydrophilic properties by the PPO and PEO portions, respectively, are the most widely used cubosome stabilizers. The balance between the hydrophobic domain's (PEO) size and the hydrophilic domain's (PPO) steric repulsion intensity determines the overall stability of the cubosomes.[15]

Cubosome properties

1. The viscosity of cubosome dispersions is substantially lower.
2. Discrete, sub-micron-sized, bicontinuous cubic liquid crystalline phase particles are known as cubosomes.
3. In excess of water, transparent, isotropic phases known as cubic liquid crystals remain physically stable.
4. Cubosomes are appealing for controlled release because of their tiny pore size.[16]

Advantages of cubosomes

1. It is inexpensive, non-toxic, biocompatible, and made using a relatively straightforward process.
2. Its bioadhesive qualities are exceptional.
3. Its larger surface area and cubic crystalline phase allow for a large drug loading area.

4. They have improved skin penetrating capabilities and long-lasting thermodynamic stability.
5. It can load pharmacological molecules that are hydrophilic, hydrophobic, or amphiphilic, as was previously indicated.
6. The cubosome has added greater control and targeted medication distribution.[17]

Disadvantages of cubosomes

1. Medication that is soluble in water is not as likely to get trapped inside Cubosomes due to their high water content.
2. The high viscosity of cubosomes makes large-scale production difficult.
3. Medication distribution cannot be controlled if a certain polymer is not used.
4. They might result in leakage while being transferred or stored in vivo.
5. There's a chance that the particle count will rise with time.
6. The dynamics of cubosomes can cause a phase shift if the external environment changes.[18]

Self-Assembling of ampiphilic lipids

Aqueous environments cause amphiphilic lipids to self-assemble into aggregates, such as micelles, inverted micelles, open lipid bilayers, and closed lipid bilayers. Two hypotheses that are based on the idea of opposing forces and packing parameters can explain this. The first one states that amphiphilic molecules are arranged in a polar solvent to minimise free energy. The hydrophilic portion of the molecules is exposed to the polar solvent, while the hydrophobic portion is shielded. This causes an opposite force to be aroused between the hydrophilic head and the hydrophobic tails of the molecules, a phenomenon known as the hydrophobic effect. Conversely, Eq. 1 illustrates the packing parameter idea put out by H. Abdelkader.[19]

$$P = \frac{v}{al} \quad \ldots(1)$$

Where an is the polar head group's ideal surface area and v, l, and an are the hydrophobic chain's volume and length, respectively. P, the packing parameter, displayed the architecture and form of the generated mesophases. For typical micelles, packing parameters such as (P) > 1/2, 1/2 > (P) > 1, for closed lipid bilayers, (P) = 1, open lipid bilayers with zero curvature, and (P) > 1, for inverted micelles, are used.[20]

Phase formation

Cubic phase development results from the interaction of the bicontinuous lipid bilayer with the aqueous environment to generate a three-dimensional network that divides two continuous hydrophilic portions. The development and thermodynamic stability of the cubic structure are primarily attributed to two free energies: the stretching energy of the lipid chain and the curvature energy of the monolayer. The thickness of the bilayers, the interfacial tensions, and the pore diameter in hydrated conditions—roughly 3 and 5 nm—were the key features of the cubic phase. Lipids are classified into two groups: first, lamellar (Lα) lipids that create planner bilayers; second, non-lamellar lipids that influence the development of bicontinuous phase (QII) and hexagonal (HII) phases. The cubic phase, which forms between the hexagonal and lamellar phases, has a lower frustration energy.[21]

These are all referred to as lyotropic liquid crystals (LLC) together. These lipids' structure and stability are influenced by temperature, pressure, hydration, and lipid makeup. Three forms of lipid bicontinuous cubic phases have been described in lipid membrane systems generally: the gyroid (Ia3d/Q11G, G-surface), the double diamond (Pn3m/Q11D, D-surface), and the primitive (Im3m/Q11P, P-surface). It has been found that the majority of cubosomes feature simple or double diamond shapes. The G-surface in the GMO-water system was more prone to changing into a D-surface due to higher water levels, rather than a P-surface, which could only be attained by adding a third component that altered the system's surface energy.[22]

Mechanisms of drug transport

The biological membrane's ability to transport drugs depends on the carrier's makeup and activity, as well as the skin's physiology and structure. Without a lot of complicated process, tiny ions are carried via the pores in epidermal membranes, hair follicles, and tight junctions. Skin membrane transport mechanisms typically involve intra- and intercellular transports (Trans and Para). Drugs can be included into the vesicles as an integral component or in the core by adjusting the carriers.[23]

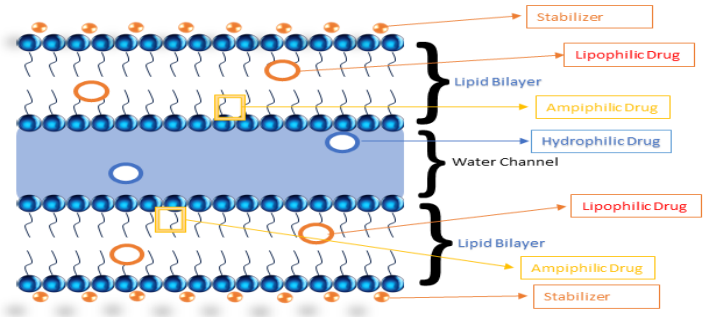

Figure 2: Mechanism of drug transport.

Approaches for preparation of cubosomes

Generally speaking, there are two basic methods for manufacturing cubosomes: the top-down and bottom-up methods. As previously mentioned, both of these methods call for the use of an appropriate stabilizer, such as F127, to avoid cubosome dispersion aggregation. Stability, biocompatibility, and ideal drug release, however, continue to be the primary considerations for selecting the best preparation technique.[24]

Top-down approach

There are two primary processes involved in this approach, which is the most often utilized methodology for manufacturing cubosomes. To create the bulk viscous cubic aggregates, first combine the lipid that forms the cubosomes with an appropriate stabilizer. Second, high energy is used as a high-pressure homogenizer or sonication to disperse the generated viscous cubic aggregates in aqueous medium, which ultimately leads to the creation of cubosomes. Thankfully, it has been discovered that cubosomes made via the top-down approach are stable against aggregation for up to a year. Nevertheless, this process has limitations when it comes to large-scale production because it takes a lot of energy to form viscous cubic aggregates that are then dispersed into cubosomes. This can be problematic when temperature-sensitive bioactive agents, like peptides and proteins, need to be incorporated.[25]

Bottom-up approach

This method, which is also known as the solvent dilution method, entails dispersing a mixture that contains a hydrotrope, a stabilizer, and cubosome-forming lipid in excess of water while requiring the least amount of energy. As hydrotrope is used to breakdown water-insoluble lipids to generate lipid precursors and prevent the development of liquid crystals at high concentrations, it is essential to the bottom-up strategy. A hydrotrope is a molecule that may boost the solubility of one solute by adding another solute, a process known as hydrotropic solubilization, which can be used to solubilize weakly soluble compounds in aqueous conditions.[26] The most often utilized hydrotropes are sodium benzoate, sodium alginate, and urea. The hydrotrope and the hydrophobic agent create a complex as part of the hydrotrope solubilization procedure. When preparing cubosomes containing temperature-sensitive agents, the bottom-up technique offers greater advantages than the top-down approach because it requires less energy input. Additionally, the cubosomes produced exhibit long-term stability because stabilizers are evenly distributed across the surface of the generated nanovesicles.[27]

Evaluation and Characterization of cubosomes

Visual inspection studies

This means analyzing the exterior characteristics of the cubosomes, including their shape, turbidity, color, homogeneity, and particle presence.[28]

Transmission electron microscopy

Cubosome morphology may be assessed by TEM. It may offer forms of cubosomal particles. It generates a high-resolution image as well as electron microphotographs for viewing. Visualization is therefore feasible. It can provide a resolution that is significantly higher than that of light microscopes. It may be possible to overcome every issue with conventional electron microscopy, including the vacuum setting, poor picture quality, the induction of structural changes in cubic phase, etc.[29]

Zeta potential

The stability of a preparation may be determined using its zeta potential. It has a really disgusting quality about it.[30]

Viscosity

A rotational Brookfield viscometer, or viscometer, can be used to measure viscosity.[31]

Particle size analysis

In order to perform this analysis, the samples must be diluted with an appropriate solvent and exposed to 300 Hz, or the light scattering intensity at 25 °C. It is measured using a Zeta sizer via dynamic scattering of laser light. This allows for the assessment of both the PDI and zeta potential. It gives statistics about average size, volume, and weight.[32]

Polarized light microscopy

Cubosomal surface coatings that are optically short ringent or vesicular can be assessed using polarized light microscopy. Additionally, anisotropic and isotropic differentiation may be obtained using this approach. It could monitor the evolution of cubic phases. It provides information on how layered liquid crystals and hexagonal liquid crystals could coexist.[33]

Differential Scanning Calorimetry (DSC)

Since phase shifts are caused by endothermic and exothermic processes and liquid crystals are thermodynamic equilibrium processes, DSC may be able to identify whether and when a phase transition takes place.[34]

Entrapment efficiency

Ultrafiltration techniques may be used to assess the efficiency of cubosomal entrapment. This method calculates the concentration of an unentrapped drug using a spectrophotometer and extrapolates that value to the concentration of an entrapped medication. This involves diluting the sample with deionized water and centrifugation. Subsequently, a spectrophotometrically determined amount of medication is used in an ultrafiltration procedure.[35]

Drug loading determination

The determination can be made by ultrafiltration or gel permeation chromatography. After that, HPLC might be used to assess it.[36]

Measuring drug release

In this case, the stability may be assessed in relation to the time period based on morphological and organoleptic characteristics. furthermore, the evaluation of the drug's concentration and the distribution of particle sizes over time. This examines evaluations of prospective changes across time.[37]

Applications of cubosomes in drug delivery

Ocular applications

A number of recent researches have focused on the use of cubosomes for medication delivery to the eyes. They make use of their biodegradable nature, capacity to encapsulate hydrophilic, hydrophobic, and amphiphilic medicinal molecules, and ability to produce bioactive agents with controlled and targeted release. Because they have a long residence time at the corneal surface and are mucoadhesive due to the presence of GMOs, which improve corneal permeability and, in turn, improve ocular bioavailability of the incorporated drugs, it is discovered that they improve the ocular bioavailability of the loaded drugs. Interesting results were seen when cubosomes were studied as a topical ocular drug delivery technique. An in vitro permeation test of cubosomes loaded with dexamethasone through excised rabbit corneas shown that the cubosome formulation increased the apparent permeability coefficient. Moreover, cubosome formulations result in a notable increase in preocular retention time when compared to Dex-Na phosphate eye drop, which raises the concentration of dexamethasone in the aqueous humor as a whole. These results came from the pharmacokinetic analysis of aqueous humor samples and the precorneal residence time test.[38]

Dermatological applications

The stratum corneum, the skin's highly structured outermost layer, serves as a powerful barrier to prevent topically administered medications from penetrating the skin during transdermal drug administration. Nonetheless, cubosomes provide a viable method of transdermal medication administration because of their distinct structure and characteristics. Due to cubosomes' ability to bind to the stratum corneum as a result of genetic modification, topical and mucosal medication administration can be accomplished with success. Cubosomes have been applied to dermatology in a number of ways recently. Transcutaneous (TCI) immunization is a significant use in dermatology. Nonetheless, the administration of vaccinations via the skin has successfully employed a synergistic strategy including microneedles (MNs) and cubosomes. The use of MNs improved the aqueous peptide mixture's penetration into the skin layers, and the peptide in the cubosome-formulated peptide exhibited prolonged skin retention, according to the results. As a result, it was discovered that using MNs and cubosomes in combination was an effective method for local antigen delivery to the skin's intended cells.[39]

For the treatment of viral diseases

One kind of lipid that is used to make cubosomes and has microbicidal qualities is monoglycerides. Consequently, they can be used to treat STDs, including those caused by viruses and bacteria (HIV).[40]

Regarding cancer therapy

Cubosomes have shown to be an excellent way to encapsulate a variety of anticancer drugs. Cubosomes are a great delivery system for anticancer medications. The small size of the delivery method is an essential component for achieving better retention and effects for anticancer medications.[41]

Regarding intravenous drug delivery

Cubosomes have the possibility of a larger pharmacological payload compared to liposomes. It is the ideal carrier for injections since it is also a carrier. Numerous small, insoluble substances originate from cubosomes.[42]

CONCLUSION

The cubosomes are one of lipid-based nanovesicles that composed liquid crystalline nanostructure, synthesized from amphiphilic lipids which selfassembled in water and stabilizer particles generates the structure responsible for its morphological appearance. In recent past plenty of research publications have shown their possibilities as new drug delivery systems. Recently, Cubosomes have been identified as a promising approach for effective ocular drug delivery with prolonged corneal residence time and bioavailability without any irritation effect on the eye. *In vivo* oral application demonstrated that cubosomes are effective as carriers for improving the solubilization of poorly water-soluble drugs, protecting liable drug from enzymatic degradation and leading to a site targeting effect. They also serve as an auspicious system providing improved skin permeation, and irritancy ability for the transdermal delivery of drugs. Moreover, cubosomes were used for anticancer drug delivery.

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