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CUBOSOMES: A FIRST GLANCE AT A NOVEL DRUG DELIVERY SYSTEM

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ABSTRACT

Cubosomes are square and rounded particles that self-assemble, are nanostructured, thermodynamically stable, and have visible cubic lattices. These versatile systems can be administered orally, percutaneously, or parenterally due to their unique properties. Cubosomes are three-dimensional honeycomb structures made of curved bicontinuous lipid bilayers divided into two parts. Various bioactive ingredients, such as chemical drugs, peptides, and proteins, can use the internal aqueous channels. Cubosomes are stable at any dilution level due to the insolubility of the cubic phase forming lipid in water, making them easily incorporated into product formulations. This article provides an overview of cubosomes, including their structure, classification, properties, components, forms, preparation methods, and applications.

KEYWORDS: Cubosomes, Components, Methods of preparation applications.

INTRODUCTION

The “cubosomes” term was firstly coined by Larsson, which is similar to liposomes 1. Cubosomes are the nanostructured particles and these are the discrete and sub-micron size particles of the bicontinuous cubic liquid crystalline phase. The bicontinuous cubic phases are having a specific benefit, that is, their ability to tune membrane curvature. Cubosomesare self-assembled liquid crystalline particles, which have rheology like a solid 2. Liquid crystals could be a quarter state of matter.

These cubosomes are made up of lipids, polymers, and surfactants, which are usually amphiphilic. Here, the meaning of bicontinuous is that the enclosures of two different regions of water are divided by surfactant bilayers.

Cubosomes are similar to liquid crystalline substance, viscous, optically isotropic as well as solid and having cubic crystallographic symmetry. Cubosomes are highly important in nano-technology based drug delivery system. Recently, the interest in pharma has increased into a particle with a few hundred nm in diameter that is 10-500 nm in diameter. The ratio of drug to the polymer is around 1:2 or 1:1, which may vary substance to substance. Some anticancer drugs have been successfully formulated in the form of cubosomes. The large-scale production of cubosomes wasdifficult because of their viscosity and behavior of phase. When water is mixed with some specific surfactants, then there is a spontaneous formation of cubic phase. The cubosomes and the parent cubic phase possess the same microstructure; also the cubosome dispersions have much lower viscosity as compared to the bulk cubic phase. The cubosomes have a larger surface area in comparison to the parent cubic phase. Cubosomes are formed by the self-assembly of surfactant-like molecules or amphiphilic molecules.

Advantages

1. Economic as compared to other nano-formulation.
2. Bio-compatible due to biodegradable in nature.
3. The preparation of cubosomes is simple.
4. It has good skin permeability hence can be formulated as a transdermal skin patch.
5. Amphiphilic, hydrophobic, and hydrophilic substances can be encapsulated into it.[35]
6. Cubosomes stable in excess water because of the relative insolubility of the cubic phase.[36]
7. High drug loading capacity.

Disadvantages

1. Minimum entrapment of water-soluble drugs in cubosomes because of the presence of a large amount of water inside the cubosomes.[38]
2. Cubosomes having a high viscosity, because of this difficult to production.[30]
3. It has limited use because of drug leakage from preparation during transportation, preservation, and minimum drug loading efficacy.

Structure

The basic structure of cubosomes includes honeycombed structures separating the two internal aqueous channels along with largeinterfacial area. Cubosomes are nanoparticles, more accurately nanostructure particles of aliquid crystalline phase with cubic crystallographic symmetry formed by the selfassembly of amphiphilic or surfactant likemolecules. The cubosomes having high internalsurface area along with cubiccrystalline structures. The cubic phases possessa very high solid like viscosity, which is a uniqueproperty because of their intriguingbicontinuous structures which enclose twodistinct regions of water separated by a controlled bilayer of surfactant. Amphiphilicmolecules form bicontinuous water and oil channels, where "bicontinuous" refers to twodistinct (continuous, but non-intersecting) hydrophilic regions separated by the bilayer. Theinterconnectedness of the structure results in aclear viscous gel similar in appearance andrheology to cross-linked polymer hydrogels. However, monoglyceride-based cubic gelspossess significantly more long-range order than hydrogels and, because of theircomposition (i.e., lipid and water), excellentbiocompatibility.

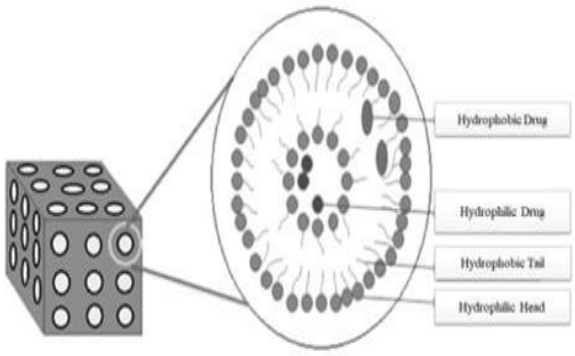


Figure 1: Structure of cubosome.

Components of cubosomes

The preparation of the cubosomes are simple and are consists of three essential components such as amphiphilic lipids, stabilizer, and water. It is said that the cubic liquid crystalline phases are produced upon the hydration of amphiphilic lipids. Stabilizers are those substances that prevent the conversion of reconstitution to bulk cubic phase. Some of the investigational molecules are used to form lyotropic liquid crystals are ethylene oxide amphiphiles, Monoglycerides,[40,41] various glycolipids,[42,43] urea, phosphatidyl ethanolamine,[44] phytantriol.[45,46]

Amphiphilic lipids

Phytantriol and glyceryl mono-oleate both are amphiphilic lipids used for Cubosomes preparation.

Glyceryl Mono-Oleate (GMO)

From an amphiphilic lipid class, GMO is the principal component that can be synthesized from glyceride of oleic acid and other fatty acids. It has hydrophobic tail and hydrophilic head.[47] GMO are also used to produce cubic lipid phases in the food industry where it isused as a food emulsifier.[48,49] Based on Lutton's results, the monoglycerides have a greater tendency to form cubic phases with a 12-22 chain length.

Phytantriol (PHTY)

Phytantriol is a molecule that contains phytanyl chains and a good alternative for GMO, and both possess similar phase behavior. Both are differs in their physical as well as chemical properties and structure. In cosmetic industry, it phytantriol is key components. It is chemically 3, 7, 11, 15-tetra-methyl-1, 2, 3-hexadecane thiol (C20H42O3).[50] PHYT offers higher structure stability as it is susceptible to esterase-catalyzed hydrolysis.[51] On the basis of PHTY-water phase diagram, the reverse micelles, lamellar, Q230, and Q224 structures are produced by increasing the concentration at room temperature. The cubic phase turns to the hexagonal structure at an elevated temperature of 44 ºC. A required condition for cubosome formation is that it should exist in equilibrium with water.[38] Dispersion made by using PHTY is stable and allow to incorporating the hydrophilic excipients and protecting the Pn3m internal nanostructure shown by Rizwan *et al*.[52] Phase transition can be affected by the purity of the compound.

Stabilizer

For the preparations of cubosomes, colloidal stability is important that can be provided by the surfactants. Cubosomes are coalescing to the bulk cubic phase. Unfavorable interactions between hydrophobic domains of cubosomes are prevented by an ideal stabilizer as it encounters between particles, without causing any disruption to the cubic structure because of electrostatic- repulsive barrier that can be formed by stabilizer between the approaching particles. Thus, the stabilizer is the vital component required for the cubosome formation. Stabilizer sequestration occurs in cubosomes due to the high internal surface area.[54] Most commonly used material for stabilizing cubosomal dispersion are PEO99-PPO67-PEO99 a tri-block copolymer and poloxamer 407.[55] Stabilizer works by engaging and controlling the

phase action within the framework of dispersed particles. Worle *et al*. studied the impact of different P407 concentration on the cubosomes properties.[56] At maximum concentration of P407 results in development of smaller particles but vesicular particles are formed at this state compared to cubic phases of nanostructure. Cubic structured nanoparticulate dispersion is formed by adding an adequate amount of P407. Development of different types of cubic crystal depends upon the internal crystalline structure and its composition. On the surface ofthe bulk PHYT cubic phase, the P407 is absorbed. In the liquid crystalline structure, the monoolein cubic phase P407 was integrated.

Types of cubosome precursors: They are able to protect the thermosensitive drug moieties.

Liquid cubosome precursor: In this, the particles are produced by nucleation, and then there is a growth by saturation. It is observed that the process of hydrotrope dilution produces comparatively stable as well as smaller cubosomes. This is obtained by dissolving monoolein in any of the hydrotrope. Then the subsequent dilution of the mixture spontaneously precipitates or crystallizes. It avoids the high energy processes and also bulks solid handling. It permits the easy scale-up ofcubosomes preparation 47, 48. These are generally used in hand washes and mouthwashes.

Powdered cubosome precursors: They consist of surfactant, which is dehydrated and coated with a polymer. The cubosomes are formed by the hydration of the precursor powders. The lipids used here are sticky and waxy solids. The suitable process which is applicable to this is a spray drying process 48, which is suitable for large-scale production.

Methods of preparation of cubosomes

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

Top-Down Technique

Bottom-Up Technique

High-Pressure homogenization: It is the most suitable method 59, 60 for the cubosome preparations, which are highly stable during high-pressure homogenization process and also retains a long shelf life 61, 62. It consists of three steps:

Gel preparation: In this step, the lipid and amphiphilic surfactants are dissolved in solvent (organic) followed by mixing properly, so as to appear as a uniform mixture. Here, the rotary evaporator is used to evaporate the organic solvent to form the gel phase of a formulation.

Shearing: In this step, the prepared gel is going for shear. The aqueous solvents are used to produce a micro-dispersion. It is the determining step before homogenization in the process of cubosome formation.

High-Pressure homogenization: This method is applicable to the large volume sample systems (30 ml), and it is not acceptable for the small volume sample systems.

In this step, the temperature is selected as per the properties of lipid since this method is temperature-sensitive. In this, the prepared dispersion is undergoing the high-pressure homogenizer forhomogenization. Only a single sample could be processed by this method.

Automated cubosome preparation: It is similar to the probe sonication method with few changes. A large number of cubosomes could be prepared by this method. The probe sonicator and robotic systems are used in this method of cubosome preparation. In this method, the gels are prepared by using a 96 well plate which has a solvent capacity of 600 µl. Then the sonication is performed by a robot. Here, in this method, the physicochemical properties can be easily assessed.

Probe ultra sonication: This process is fast and is used for the preparation of small volume samples. It is capable of dispersing samples, even if it is 600 µl in quantity. It depends on probe size. In this process, the gels are prepared by the addition of stabilizers. Then there is a solvent equilibration which forms a cubic phase. After this, the cubic phase is transferred for the ultra sonication64. So as to control the pulsing frequency and to avoid overheating of samples, there is a need for careful maintaining of variables, *i.e.*, frequency and amplitude.

Advantages: The equipment's which are applicable in this method is very common. This method is easy and is widely used.

Disadvantages: There are chances of contamination due to metal. During the storage phase, particle growth could happen.

Other methods

Emulsification: In this method, the cubosomes are produced by poloxamer 407, which dilutes the monoolein-ethanol solution.

High shear homogenization technique: In this method, stabilizers are added so as to avoid the aggregation of particles in the shelf-life period. (It is a good method, but it has some limitations also, which is because there is a high shear application.

Spray-Dried technique: This technique is also applicable for the production of cubosomes. In this method, the monoolein is covered by polysaccharides (dextran/starch) after hydration. Then the polymers are added into this so as to maintain stabilization.

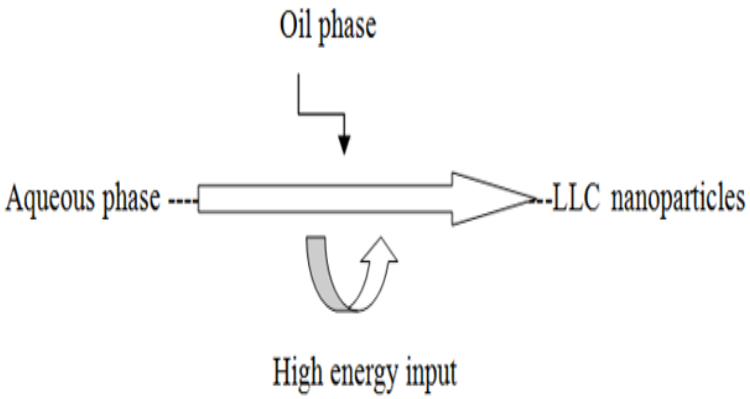
Advantages: This method is applicable for powder formulations. By using this method, microencapsulation is possible. In this method, organic solvents are also applicable.

Disadvantages: This method is complicated (as compared to other methods). A very low amount of yield is obtained by this method (5 to 30%).

Special techniques

Top-Down technique

It is most popular technique for the production of cubosomes. In 1990s, hexasome was pioneered.[72,73] To form a homogenous dispersion, the polymeric stabilizing agent, drug solution, and amphiphiles are agitated by high energy techniques such as shearing or ultrasonication for a sufficient time. Pluronic F127 is used many times as a steric stabilizing agent in a multiple preparation methods.[74-76] By using a high-pressure homogenization technique, this method is also carried out, but it depends on the temperature and the amount of the pluronic polymer used during its preparation.



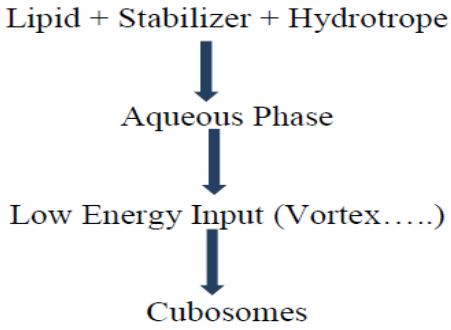
Top-down technique of cubosome preparation

Advantages: Prepared formulations are clear and visible. The use of organic solvents is not required in this method. This method is comparatively simple.

Disadvantages: It is a time-consuming process. This is a method, which needs high energy input.

Bottom-Up technique

It is a recently developed technique for the preparation of a cubosomes in which nanostructure building blocks are formed firstly followed by assembling it into the final material.[19] In water-insoluble lipids, the hydrotrope is dissolved results in formation of liquid precursors. At high concentrations, less energy input is required to avoid liquid crystals formation. In water at 80℃, dispersing the inverse micellar phase droplets into it, followed bya gradual cooling that leads to the formation of cubosomes. At room temperature, aqueous poloxamer 407 solutions produced by cubosomes is used to dilute the monoolein-ethanol solution, thus the emulsification method is used for the preparation of cubosomes. The formation of vesicles by Cryo-TEM cannot be avoided from this method. The formation of liquid crystal can be seen in other vesicles.



Bottom-up approach for cubosome preparation

Advantages: It is not time consuming process. The use of any organic solvent is not required. Here, very low energy is needed.

Disadvantages: It may produce allergic reactions if taken orally because of hydrotropes. It produces milky white preparations.

Evaluation and Characterization of cubosomes

Visual inspection studies

This entails examining the cubosomes' external features, such as their form, turbid, colour, uniformity, and existence of particles.

Shape of cubosomes[35]

The shape of cubosomes can be seen by using TEM (Transmission electron microscopy)

Transmission electron microscopy

Using TEM, cubosome morphology may be evaluated. Cubosomal particle forms might be provided by it. For observation, it could provide electron microphotographs, and it also produces a high-resolution picture. Therefore, visualisation is possible. It can offer a significantly greater resolution than light microscopes. It is an excellent instrument for studying the behaviour of soft matter dispersions. All the problems with traditional electron microscopy, such as the vacuum setting, poor image quality, the induction of structural changes in cubic phase, etc., may be resolved.

Zeta potential: The stability of preparation could be assessed by a magnitude of zeta potential. It shows a high degree of repulsion.

Viscosity: Viscosity could be assessed by use of viscometer, *i.e.*, Rotational Brookfield Viscometer.

Particle size analysis: In this, the samples are diluted with compatible solvent and are exposed to 300 Hz, which is the scattering intensity of light at 25 ºC 71. It is measured by dynamic laser light scattering by the use of a Zeta sizer. In this, the PDI and zeta potential can also be measured. It gives data that contains the average weight, volume, size. For the determination of particle size by Malvern zeta sizer, there is a need; that is, the samples could be diluted to 100 folds with water.

Polarized light microscopy

Polarized light microscopy may be used to evaluate the cubosomal surface coatings, that are optically short ringent or vesicular. This technique might also give the anisotropic and isotropic differentiation.35 It could track how cubic phases changed. It offers details on the potential coexistence of hexagonal liquid crystals and layered liquid crystals.36

Differential scanning calorimetry

DSC may be able to determine if and when a phase transition occurs since liquid crystals are thermodynamic equilibrium processes and phase changes are brought on by endothermic and exothermic processes.

Entrapment efficiency

The evaluation of cubosomal entrapment effectiveness might be done using ultrafiltration methods.37 This approach uses a spectrophotometer to determine the concentration of anunentrapped drug and extrapolate that value to the concentration of an entrapped medication. In this, the sample is diluted with deionized water, and then centrifugation is performed. Following this, there is an ultrafiltration method that uses a certain quantity of medication that is quantified spectrophotometrically.

Drug loading determination

Gel permeation chromatography or ultrafiltration techniques may be used to make the determination.38 HPLC may then be used to evaluate it.

Drug release measurement

In this, the stability may be evaluated based on morphological and organoleptic traits with regard to the time period.39 additionally, the assessment of the drug concentration and particle size distribution at time.40 this looks at assessments of potential alterations over time.

Stability studies: In this, the stability could be assessed on the basis of organoleptic as well as morphological characteristics with respect to the time period. Also, the drug content and particle size distribution determination with the time 77. In this, evaluations of possible changes with respect to time are studied.

Application of cubosomes

For the Controlled and Sustained-release behavior: This is achievable because of the unique behavior of cubosomal particles, *i.e.*, the leftovers. It is the most popular application of cubosomes achieved by researchers. The cubic phase is the one that is very favorable for controlled release, as it has a small (5-10 nm) pore size. A variety of ingredients or API‟s having different physicochemical characteristics could be encapsulated in cubosomes. Because of the advantage of biodegradability of cubosomal material by enzymes, controlled and sustained release of drug is achievable, and they are not accumulating inside the body.

As a drug delivery vehicle: Some companies (L‟Oréal& Nivea) are trying for the cosmetic formulation (O/W emulsion stabilizers, pollutant absorbents, *etc.*), which consists of the use of cubosomes 78. This is a very common use of cubosomes and is a universal application of cubosomes.

For topical drug delivery system

Cubosomes are employed in mucosal as well as topical medication delivery systems because of their strong bio-adhesion. They are helpful in protecting skin that is sensitive.

Due to the presence of ethanol, which is responsible for the rupture of the skin, cubosomes have a high level of permeability. The outcome is an improvement in fat fluidity that also raises the medication's skin penetration.

For treatment of viral diseases

Monoglycerides are one type of lipid that is utilised to create cubosomes and has microbicidal properties. They can thus be used to treat sexually transmitted illnesses, including those brought on by bacteria and viruses (HIV).

For cancer therapy

Numerous anticancer medications have been effectively encapsulated inside cubosomes. Cubosomes serve as an excellent vehicle for anticancer drugs. In order to get greater effects and retention for anticancer medicines, the delivery system's tiny size is a crucial factor.

For intravenous drug delivery

In contrast to liposomes, the cubosomes offer the potential property of having a higher pharmacological payload. It also functions as a carrier, making it the perfect carrier for injections. Cubosomes are the source of several insoluble tiny compounds.

For oral drug delivery

The oral drug delivery system consists of many challenges. Such as

a) Large size molecules
b) Aqueous solubility
c) Absorption (Poor)

Cubosomes are able to overcome all these challenges. They also have another advantage, which is the release of drugs at various sites and this is required in the case of drugs whose absorption window is narrow 80. The local effect *i.e.*, in the gastrointestinal tract, is also possible.

Current application

An application area under currentdevelopment by L"Oreal is the use of cubosome particles as oil-in-wateremulsion stabilizers and pollutantabsorbents in cosmetics in melanoma therapy.

Future prospects: The cubosomes grip a great capability in the application of drug delivery as well as sustained drug delivery. The previous studies on cubosomes are needed to be broadened because these are still at the very basic level, and further investigation is needed. The exact studies are required for the drug loading capacities as well as their release behavior. In the future, there is a requirement for further optimization and development so as to understand the suitability of cubosomes with body tissues and blood. Then another thing, which is a must in the development, is that the stability requirements of cubosomes in the biological fluids. Also, studies are required so as to get knowledge about the factors, which affect drug release from cubosomes.

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