Cubosomes A New Versatile Drug Delivery System

Sushma await

Assistant professor

Pharmaceutics, BVVS Hanagal Shri Kumareshwar College of Pharmacy,

Bagalkot,

sushmawati@gmail.com

Metre Anil Suresh

Assistant professor

Pharmaceutical Chemistry BLDEAS college of pharmacy

basavan bagewadi, 58203

metreanil1@gmail.com

Sachinkumar wali

Assistant professor

HKE'S matoshree Taradevi Rampure institute of pharmaceutical science,

kalaburagi

Vinod Babaleshwar

Assistant Professor

Department of Pharmaceutics

Shri Sharanabasaveshwar College of Pharmacy

Vijayapura-586101

vinodbabaleshwar25@gmail.com

ABSTRACT

Cubosomes are self-assembled liquid crystalline particles. They are formed by dispersion of discontinuous cubic liquid crystalline phases.Cubosome are honey comb like structure. Cubic liquid crystals are physically transparent and isotropic phases that are stable in excess water and show a unique system for the production of pharmaceutical dosage forms. The liquid crystals of cubic phase are used in the controlled release of selected water and oil soluble molecules. Cubic phases have a thermodynamically stable structure consisting of two separate, continuous but non intersecting hydrophilic regions divided by a lipid bilayer. This allows the incorporation of hydrophilic and hydrophobic materials and also amphiphilic materials into the system. Lipid based cubic system is biocompatible, and bio adhesive. Mainly two methods are employed for the preparation of cubosome, they are top- down technique and bottom -up technique. Cubosome structure is investigated through electron microscopy, light scattering, X-rays, and NMR, although some researchers are studying the potential of cubosomes as a delivery system.

Key words: Cubosome, Honeycomb, Hydrophilic, Hydrophobic, Drug delivery systems

# INTRODUCTION

Cubosomes get their name from their structure, which is 'phases' suffixed as'some' and they have a cubic crystal lattice. These are nanoparticles which are self-assembled liquid crystalline particles of certain surfactants with proper ratio of water with microstructure. Larsson coined the term Cubosomes to reflect the cubic molecular crystallography and similarity to liposomes. Certain lipids, detergents, and polymer molecules, or amphiphilic molecules, contain both polar and non-polar components. Physically transparent and isotropic phases known as 8 liquid crystals exhibit a novel method for the synthesis of pharmaceutical dosage forms. They are stable in excess water. In the bicontinuous cubic liquid crystalline phase, cubosomes are distinct, sub-micron-sized nanostructured particles. The square and rounded particles with discernible interior cubic lattices are called cubosomes. Because of the complexity of their structure, they can load more drugs. Cubosomes can encapsulate hydrophobic, hydrophilic, and amphiphilic substances. They are thermodynamically stable and have carvenous (honeycomb) structures with sizes ranging from 100 to 500 nm that are tightly packed and twisted into three-dimensional bilayers. Cubosomes are nanoparticles, but instead of the usual solid particles, they are self-assembled liquid crystalline particles with a solid-like rheology that provides unique practical properties. Figure: Cubosomes with various drug loading modalities. Depending on the content substance, the medication-to-polymer ratio is roughly 1:2 or 1:1. 3Cubosomes and the parent cubic phase share the same microstructure; however, cubosome dispersions have a significantly lower viscosity than the cubic in bulk phase. 13 Because 'phases' is prefixed with'some' and contains a cubic crystal lattice, the term cubosomes was coined.9 Cubosomes form at a specific temperature. They exist in three distinct phases: - P-surface, G-surface, and D-surface are used for primitive, gyroid, and diamond structures. [14,15] Temperature, stability, bicontinuous structure, high internal surface area, solid-like viscosity, and low coast raw material make them appealing for consumer and pharmaceutical industrial applications. Despite widespread interest in cubosome applications, no studies have been conducted to investigate the practical aspects of large-scale cubosome processing and production.

**ADVANATGES OF CUBOSOMES1**

1. It is economic.
2. It is non-toxic and biocompatible.
3. Method of preparation is simple.
4. They have ability to encapsulate both hydrophilic& hydrophobic & also amphiphilic drugs
5. They have a sustained- release drug delivery characteristics
6. Cubosomes have biocompatibility and bioadhesivity properties.
7. Bicontinuous cubic liquid crystalline phase of cubosomes even stable in excess water
8. Cubic phase materials can be formed by simple combination of biologically compatible lipids and water and are thus well suited for use in treatments of skin, hair, and other body tissue.
9. With respect to liposomes, cubosomes possesses a larger ratio between the bilayer area and the particle volume and a larger breaking resistance
10. Because of their high internal surface area and crystalline cubic structures they have high drug payloads.
11. They can be prepared by simple method and possess lipid biodegradability
12. Targeted release and controlled release of bioactive agents
13. Cubosomes are excellent solubilizers, compared with conventional lipid or non-lipid carriers.
14. They show high drug carrier capacity for a range of sparingly water-soluble drugs.
15. These are an excellent vehicle to protect the sensitive drug from enzymatic degradation and in-vivo degradation, such as peptides and proteins.
16. The cuboidal system enhances the bioavailability range twenty to more than one hundred times of water-soluble peptides.
17. The cubic phases of cubosomes can be fractured and dispersed to form particulate dispersions that are colloidally and/or thermodynamically stable for longer time.

 **DISADVANTAGES: 1,4,10**

1. Manufacture of Cubosomes on a large scale embodied
2. difficulty because of their viscosity
3. High energy processes
4. Harmful to fragile temperature-sensitive active ingredients
5. Expensive
6. Difficult to scale up

**Preparation methods of cubosomes**

The cubic lipid phases of cubosomes consists of three macroscopic forms that are typically encountered precursors, bulk phase gel and particulate dispersion. Bulk phase cubic gels that are rigid, strong, optically isotropic, and solid like particles which are in equilibrium with water and are dispersed into cubosome nanoparticles that has been made easier than their dispersions [26]. The nanoparticle dispersions prepared in the cubosomes can be done by several techniques such as spray drying, sonication, high pressure homogenization and spontaneous emulsification, whereas sonication and high-pressure homogenization and then forms the complex dispersions that contains vesicle like structures and cubosomes with time dependent ratios of each type of particle.

1. Top-down approach

2. Bottom-up approach

3. Heat treatment

4. Spray drying

The cubosomes dispersion carried out by

#### Fabrication method

1. Emulsification method.

**Top-down approach**

It is the most frequently performed operation, as first noted by Ljusberg-Wahren in 1996. There are two stages involved in using this technology. Aggregation occurs because the thick bulk cubic phase is first created by combining the lipids with stabilisers. The second stage involves applying high power processing, such as excessive-strain homogenization, sonication, or excessive electricity dispersions, to the bulk cubic segment in order to create Lyotropic Liquid Crystal (LLC) nanoparticles (cubosome dispersions).1

Nanoparticles. The most popular technique for creating LLC nanoparticles is HPH. Cubosomes created using this top-down technique coexist with vesicles like dispersed nanoparticles of lamellar liquid crystalline phase or vesicle-like structures and are stable against aggregation for about a year. However, since it takes a lot of energy to disperse the cubic phase into cubosomes in large-scale manufacturing, it is difficult to incorporate ingredients like proteins and peptides that are sensitive to temperature.5,19

The cubic phases are distinguished by the fact that they are a single thermodynamic phase with a periodic liquid crystalline structure. The energy required to rupture a cubic phase in a direction parallel to the shear direction is proportional to the number of tubular networks. 2 The yield stress in the cubic phase increases with increasing temperature.

The amount of bilayer-forming surfactant and oils. According to Warr and Chen, cubic phases may behave as lamellar phases during dispersion as shear increases, dispersed liquid crystalline particles form at intermediate shear rates, and defect free bulk phase reforms at higher shear rates.

Oil phase (melted lipid)

Liquid + stabilizer

Aqueous phase

LLC nanoparticles

 Aqueous phase

High energy input (homoginization..)

High energy input (HPH,Sonication .shearing etc.)

**2. Bottom-up approach**

The bottom-up approach first forms the nanostructure building blocks and then assembles them into the final material. In this method cubosomes are allowed to form or crystallize from precursors. The cubosomes are formed by dispersing inverse micellar phase droplets in water at 80°C and are allowed to slowly cool.5,11Gradually these droplets crystallize to cubosomes. The cubosomes at room temperature is produced by diluting monoolein-ethanol solution with aqueous poloxamer 407 solution. The cubosomes are spontaneously formed by emulsification. Another process is also developed to produce the cubosomes from powdered precursors by spray drying technique. Spray dried powders comprising monoolein coated with starch or dextran form cubosomes on simple hydration.5

This is more useful in large scale production of cubosomes.1 It is also called as liquid precursor or solvent dilution method. The bottom - up approach first forms the nano structure building blocks and then assembles them into the final material. These nano structures are formed by the dispersion of a mixture comprising the liquid crystal forming lipid, the polymer and a hydrotrope in excess water. Hydrotrope helps in dissolving water insoluble lipids in liquid precursors.41,45 Thus, cubosomes are produced from precursors through crystallization. This method is useful for producing cubosomes in large scale and requires less energy than top-down approach.7 Scale up of this approach is found to be very difficult by the high process energy requirements to form the cubosome particle dispersions from the viscous bulk cubic phase. To avoid these problems Patric T. Spicer studied the formation of cubic phase in the presence of a hydrotrope.8 Hydrotrope here is a molecule that is either hydrophilic or hydrophobic but is incapable of exhibiting surfactant behaviour (Micelle formation).45 Hydrotropes do not produce LLC, but they increase the lipid solubility and then exhibit a phenomenon called “salting out” precursor may be either of a liquid or a solid. The liquid precursor is made by adding ethanol to the lipid (monoolein) ethanol. Cubosomes are produced, when the precursor is diluted. Powdered precursors comprise of a dehydrated substance that is coated with a polymer, forms cubosomes upon the hydration substance that is coated with a polymer, forms cubosomes upon the hydration.12

 Hydrotrope

 Liquid + stabilizer

 Aqueous solution

Low energy input (vortex....)

 cubosomes

***Heat treatment approach***

This technique does not constitute an integrated cubosome manufacturing process because it only promotes the transformation of non-cubic vesicles to well-ordered cubic particles through a homogenization and heat-treatment step, resulting in a decrease in the small particle size fraction that corresponds to vesicles and the formation of more cubic phases with narrow particle distribution and good colloidal stability.

**Spray drying** Using a spray drying method Due to the limited flexibility of liquid precursors for cubosome production (Spicer et al), a dry powder precursor for cubosome preparation was devised. For the manufacture of starch encapsulated monoolein precursor and dextran encapsulated monoolein precursor, they used a spray drying process. Encapsulation with a high proportion of polymer (75 percent w/w for starch and 60 percent w/w for dextran) reduced the amount of active material loading, hence the method was limited for powerful medicaments, vitamins, flavours, or smells. Cuboidal preparation method in general Monoolein and water are frequently combined around 40° C to make cubosomes. Mechanical or ultrasonic energy is used to disperse the resulting cubic liquid crystalline gel into particles. To make cubosomes, high-pressure homogenizers are frequently used. The cubosomes are finally secured against flocculation. Phase aqueous Input of a lot of energy 3,24

 Or converted Using a spray drying technique Because liquid precursors for cubosome production have limited flexibility (Spicer et al), a dry powder precursor for cubosome preparation was developed. They used a spray drying process to make starch encapsulated monoolein precursor and dextran encapsulated monoolein precursor. Encapsulation with a high polymer proportion (75 percent w/w for starch and 60 percent w/w for dextran) reduced the amount of active material loading, so the method was limited for powerful medicaments, vitamins, flavours, or odours. In general, the cuboidal preparation method Cubosomes are frequently formed by combining monoolein and water at temperatures around 40° C. The resulting cubic liquid crystalline gel is dispersed into particles using mechanical or ultrasonic energy. High-pressure homogenizers are frequently used to create cubosomes. Finally, the cubosomes are protected from flocculation. Phase aqueous Input of a lot of energy 3,24

 **Fabrication method**

GMO/p407 cubic gel GMO 5% and P407 1.0% were melted in a hot water bath at 60°C, then the required amount of drug was added and stirred continuously until dissolved. Drop by drop, deionized water is added, and the vortex is set to homogenise. It was kept at room temperature for up to 48 hours before the optically isotropic cubic gel was formed and disturbed by mechanical stirring crude dispersion was subsequently fragmented by sonicater probe with the energy 200W under cool temperature at 20°C in water bath for 20 minutes (16,17,6)

 **Emulsification method**

In this process, GMO and P407 are added to water and then followed by the ultrasonication method; the 1% P407, 5% GMO and 5% ethanol in 89% water are taken. GMO and P407 are melting at 60° and then mixed with the ethanolic solution that was added to the melting. The resultant mixture is added dropwise to deionized water preheated at the 70 °C, it ultrasonicated at the maximum power of 130kW for about 50 min at the same temperature as the disperse mixture kept at the ambient temperature and protected from direct sunlight.17,18,6

 **Evaluation of Cubosomes:**

**Visual inspection**

The Cubosomes were visually assessed for optical appearance like colour, turbidity, homogeneity, presence of macroscopic particles for about 6-10 days after preparation.20,54

**Photon Correlation Spectroscopy**

By using zeta-sizer (photon correlation spectroscopy) particle size distributions in cubosomes are determined with dynamic laser light scattering. The sample is diluted with suitable solvent and adjusted to light scattering intensity of about 300 Hz and measured at 25°C in triplicate. By using average volume weight size, the collected data can be generally shown. The zeta potential and polydispersity index can also be recorded.

**Polarized Light Microscopy**

The possibly surface coating of the cubosomes can be revealed by using polarized light microscopical method. This can also be used to distinguish between isotropic and anisotropic substances.

**HPLC Procedure**

A validated HPLC densitometry method was used for analysing the samples. Developed plates were stained with a mobile phase which is cupric sulphate (penta hydrate): phosphoric acid: water and quantified using a UV light source set at respected wave length.21,20

**d) Entrapment Efficiency**

For knowing the entrapment efficiency, 1 ml from each of the dispersions was taken and diluted with 4 ml of deionised water. Again 1 ml of the diluted dispersion is taken and further diluted with another 4 ml of deionised water. This formed dispersion is passed through a syringe filter with pore size of 0.1 μm and the filtrate was analysed spectrophotometrically at 250 nm. Considering the dilution factor, this obtained concentration was multiplied by the total volume of the dispersion produced. This gives the free concentration of drug (Cf) which when reduced from the total drug concentration (Ct) gives the amount of drug entrapped in the cubosomes to get more accurately, each experiment was repeated 3 times. **Entrapment efficiency % of cubosomes**

**e) Particle Size Distribution Measurements**

Characterization of both spray dried powders and the aqueous dispersions of cubosomes is carried out by using laser diffraction.22

**f) Cryo-Transmission Electron Microscopy**

A small amount of prepared sample is placed on a pure thin bar 600-mesh transmission electron microscopy grid at ambient condition. The solution was blotted with filter paper to form a thin film for spanning the holes of transmission electron microscopy grid. Now verifications of sample are done by immersing into liquid ethane near its freezing point. This is transferred to TEM for imaging at a temperature of -180°C by using a cryo holder.

Images are digitally recorded.23,51

**g) Pressure Ultra-filtration Method**

By pressure ultra-filtration method drug release measurement from cubosomes is done. It is based on an Amicon pressure ultrafiltration cell fitted with a Millipore membrane at ambient

temperature **of (22 }2)°**

**h) Thermal Analysis**

To evaluate the physical status of drug within the Cubosome, DSC was used at temperature of around 37°C to 56°C where ingredients of cubosomes seem to melt together, which may result in plasticizing of glycerol monooleate. The thermal events between 200°C-300°C may be related to glycerol monooleate degradation because no sharp melting peak of drug is observed around 200°C.

**i) Light Microscopy**

Cubosomes that are prepared are diluted with deionised water and examined using an optical microscope which was calibrated with a micrometer slide at magnification of 400x and 1000x.

**j) Drug content of dispersions**

It is evaluated by diluting the filtered dispersion sample in methanol (1:9 v/v) and analysed by HPLC.52

**k) Transmission Electron Microscopy**

It can be used to view the shape and internal structure of the cubosomes. The suspension of cubic phase nanoparticles (Cubosomes) were negatively stained with 2% phosphotungstic

acid solution of pH 6.8 and transformed on to a carbon coated grid of 200 mesh and air dried at room temperature. By using electron microscope, electron micrographs were conducted.

**l) X-Ray Diffraction Measurements**

XRD is used to identify the spatial arrangements of different groups in the sample and this is carried out by using Philips PW 1830 X-Ray generator.53

**m) Gel permeation chromatography**

With the help of gel permeation chromatography we can know the entrapment efficiency and drug loading in cubosomes. By using ultra-filtration technique the unentraped drug concentration is determined, which is subtracted from the total amount of drug added.

**n) Viscosity**

By using Brookfield rotary viscometer the viscosity of prepared formulation of cubosomes was determined at different angular velocities at 25°C. The rotation speed of viscometer was with spindle #18 and 20 rpm. To calculate the viscosity of formulation; average of three readings was taken.

**p) Stability Studies**

By investigating the organoleptic and morphological characteristics with respect to time, the physical stability studies can be performed. Drug content and particle size distribution canbe assessed, over the time.55

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