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Cubic liquid crystalline nanoparticles (cubosomes) to improve solubility and bioavailability of poorly water soluble drugs: A review

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ABSTRACT

The advances in lipid-based drug carriers have gained a greater significance in the field of drug delivery systems. There are several kinds of lipidic carriers, including emulsions, Liposomes, solid lipid nanoparticles, cubosomes, and micelles. Recently the use of monoolein based cubosomes for the delivery of drug have attracted much of the scientists due to their bioadhesion, sustained release of incorporated drugs, protecting drugs from physical and enzymatic degradation, nontoxic nature of structure-forming materials of cubosomes and solubilization of hydrophilic, amphiphilic and lipophilic drugs. Cubosomes are liquid crystalline nanostructures formed from the cubic phase of lipids, such as monooleate, or any other amphiphilic macromolecules with the unique property to be dispersed into particles. The present review gives an overview of cubosomes that includes structure, materials, and methods of preparation and their characterization.

Keywords: Cubosomes, Liposomes, Nanoparticles, Emulsion, Lipidic Carriers, Monooleate.

INTRODUCTION

The use of lipids in drug delivery has proven to be the most promising concept. Lipid-based drug delivery systems(LBDDS) are one of the most widely used and well-known technologies designed to overcome challenges like the solubility and bioavailability of drugs that are insoluble in water[1,2].Lipid formulations are flexible enough to be formulated as per the route of administration, disease condition with good stability and efficacy. Due to their efficacy and safety lipid-based carriers have become the most appealing carriers for the formulation of a wide range of products including pharmaceuticals, diagnostics, as well as vaccines and nutraceuticals [3].

Nowadays implementation of lipid-based carriers has been increasing predominantly in drug delivery systems. LBDDS have resulted in the development of various types of carriers such as nanoparticles, liposomes, ethosomes, phytosomes,

cubosomes, transfersomes, etc; each of them possess remarkable abilities that help to enhance the delivery of drugs to blood, brain, cancerous cells, lymphatic organs and across the skin. [4,5,6]

In recent times, the application of cubosomes has been increasing owing to its specific shape, stability, and biocompatibility. Cubosomes are isotropic liquid crystalline square or round shaped lipidic nanoparticles stabilized by poloxamer with internal cubic lattices [6,7]. These are the lipid carriers with inverse bicontinuous cubic phases of lipids that are colloidally and thermodynamically stable [8]. Cubosomes have the high internal surface area and have both hydrophilic and hydrophobic domains within their three-dimensional structure that enable them to encapsulate hydrophilic, lipophilic and amphiphilic substances effectively [9,10].

A Cubosomal preparation offers some of the advantages like

- It provides the drug in Nano size of 10-500nm.
- Simple preparation method.
- Improves solubility of water-insoluble drugs.
- It provides the controlled release of drugs.
- Able to encapsulate a high amount of drugs within its cubic lattice structure.
- It is mostly used in melanoma therapy.

Limitations of cubosomes include

- Large scale manufacturing is difficult sometimes as they become highly viscous.
- Problematic in preparation of water-soluble drugs
- When compared with polymer-based drug delivery systems cubosomes offer less controlled drug delivery.

STRUCTURE OF CUBOSOMES

A lyotropic liquid crystal consisting of two or more components exhibits liquid crystalline behavior at particular concentrations. Depending on the balance between hydrophilic part and hydrophobic part many amphiphilic molecules exhibit lyotropic liquid crystalline phases.

Cubosomes are termed as liquid crystalline nanostructures formed from the cubic phase of lipids, such as monooleate, or any other amphiphilic macromolecules with the unique property to be dispersed into particles. Cubosomes are square and round-shaped particles with internally visible cubic lattices [8] (see Fig.1).

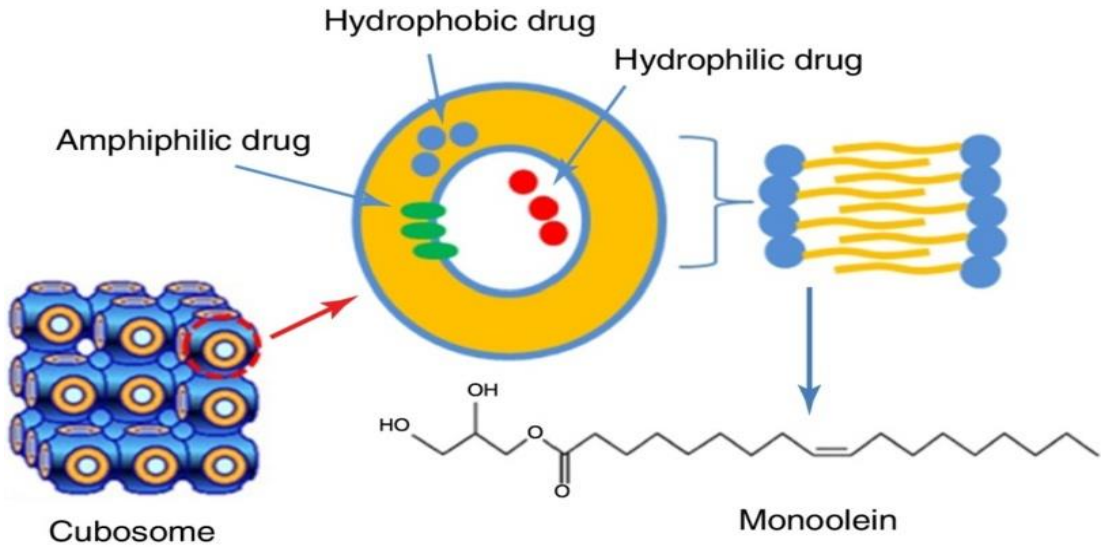

Fig.1: Structure of Cubosome

The structure of liquid crystals is influenced by the content of water and other solvent molecules and by the varying concentrations of amphiphile. At a very low concentration of amphiphile random dispersion of molecules takes place. At slightly high concentrations, a spontaneous arrangement of

molecules into micelles or vesicles occurs due to which the hydrophobic tail is inwards of micelle core and the hydrophobic surface is towards the aqueous solution, these micelles do not arrange themselves. At higher concentrations, the amphiphile molecules are assembled orderly.

The hexagonal columnar phase is a typical phase, in which the amphiphiles arrange themselves into a rough hexagonal lattice with a hydrophobic surface (middle soap phase). At still higher concentrations, a lamellar phase (neat soap phase) may form, wherein extended sheets of amphiphiles are separated by thin layers of water. The cubic phase (also called viscous lyotropic) exists between the hexagonal and lamellar phases (see Fig.2), wherein spheres are formed that create a dense cubic lattice. The spheres may also be connected to form a bicontinuous cubic phase [11].

A generic progression of phases, going from low to high amphiphilic concentration, is

- Discontinuous cubic phase (micellar cubic phase)
- Hexagonal phase (hexagonal columnar phase) (middle phase)
- Lamellar phase
- Bicontinuous cubic phase
- Reverse hexagonal columnar phase
- Inverse cubic phase (Inverse micellar phase)

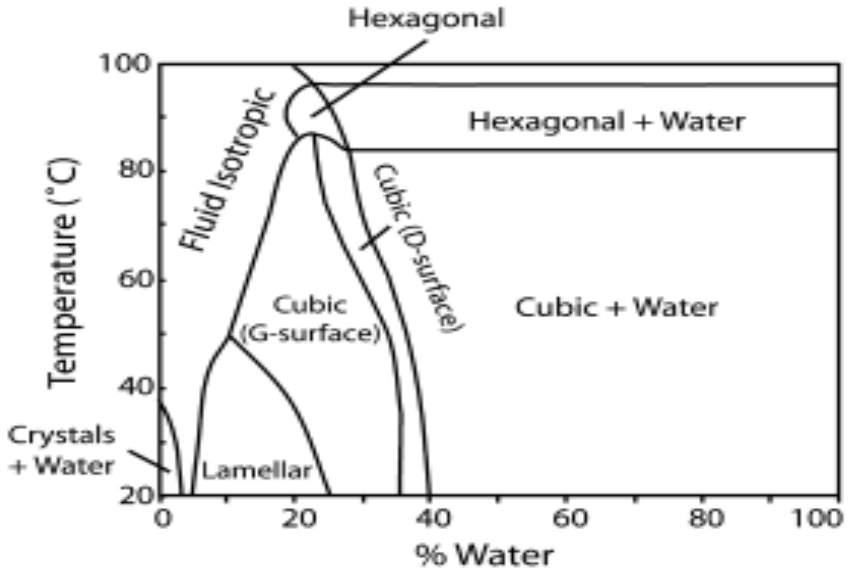

Fig. 2 Binary phase diagram of GMO-water system depicting the lamellar, cubic phases and hexagonal phases

The most popular lipid used in the preparation of lyotropic liquid crystals (LLC) is glyceryl monooleate (GMO) [12]. The lamellar phase consists of planar lipid bilayers separated by water channels, whereas the reversed hexagonal shows extended micellar column structures, with the long-range order in two dimensions with no direct contact between the water within and out of the LLC. Meanwhile, the cubic phase made of bicontinuous lipid bilayers develops a 3D network separating two distinct, continuous but nonintersecting, hydrophilic sections. The main characters of the cubic phase including interfacial area, the thickness of the bilayers and the diameter of pores in the fully hydrated condition are 400sq.m/g, 3.5 nm and 5 nm, respectively [13, 14]. By adjusting the temperature or water content, the conversion between the phases is achievable.

Cubosomes are formed at controlled temperatures into a lipid bi-layered system with three-dimensional structures having minimal surface, forming a tightly packed structure with bicontinuous domains of water and lipid. The 3 types of minimal surfaces studied in cubic phases were discovered mathematically by Schwarz. The monoolein water system forms the D-surfaces at high water levels and the G-surface at lower levels. The P-surface is formed in the monoolein water system see Fig.3 [15]. In the GMO-water system, at higher levels of water, the G-surface is transformed

into the D-surface. Upon the addition of a third component such as caseins or amphiphilic block copolymers, the P-surface is formed [16].

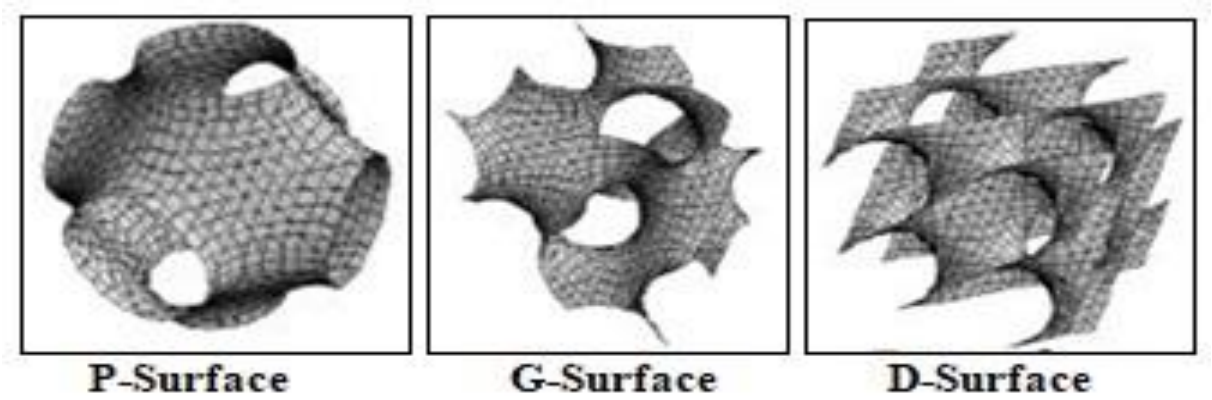

Fig.3: Representation of P-surface, G-surface, D-surface cubic structures

METHODS OF PREPARATION

The most popular methods used for the preparation of cubosomes are of two types namely,

- ❖ Powder cubosomes precursor (Top-down technique)
- ❖ Cubosome dispersion formed by dilution of an isotropic solution (Bottom-up technique)

To prevent cubosome dispersion aggregation, both techniques require a colloidal stabilizer such as P407.

Top-down approach

This method involves the mixing of lipid with stabilizer to form a homogenized solution. The resultant solution is then dispersed into the aqueous medium under high-pressure homogenization or sonication eventually to form cubosomes [17] [see Fig.4 (a)]. Cubic phases may behave as lamellar phases during dispersion with increasing shear, dispersed liquid crystalline particles form at intermediate shear rates, whereas a defect-free bulk phase re-forms at higher shear rates. At high oscillatory frequencies, cubic phases become highly elastic [18].

Bottom-up approach

The bottom-up approach first forms the nanostructure building blocks and then assembles them into the final material. It is a more recently developed technique of cubosome formation, allowing cubosomes to form and crystallize from precursors on the molecular length scale. The formation of cubosomes is done by the dispersion of inverse micellar phase droplets in the water at 80°C, then slow cooling allows the droplets to gradually crystallize into cubosomes [19] see Fig.4(b).

Dispersion of the nanoparticles in the cubosomes formation is carried out by several techniques

i. Sonication
ii. High-pressure homogenization
iii. Spontaneous emulsification
iv. Spray drying
v. Sonication and high-pressure.

Homogenization suggests the formation of complex dispersions containing vesicles and cubosomes with time-dependent ratios of each particle type [20, 21].A process was also developed to allow cubosome production from a powdered precursor. Spray-dried powders comprising monoolein coated with starch or dextran form cubosomes on simple hydration. The polymers immediately provide colloidal stabilization of the cubosomes.

(a) Top-down approach:

(b) Bottom-up approach:

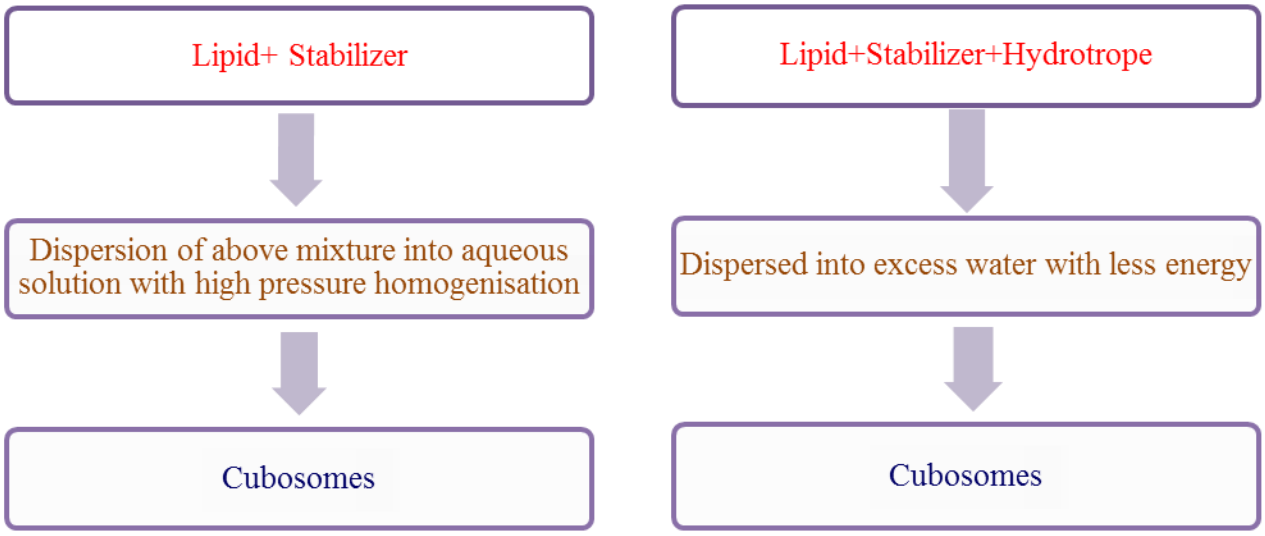

Fig.4: Schematic representation of preparation methods of cubosomes using (A) Top-down approach, (B) Bottom-up approach

MATERIALS USED FOR CUBOSOMAL FORMULATION

As discussed earlier the preparation/formulation of cubosomes is as simple as they are composed of only three components namely amphiphilic lipids, stabilizer, and water.

Lipids

Bicontinuous cubic phases are found in natural lipids, cationic and non ionic surfactants and also in polymer systems, although the lipid most widely used to construct bicontinuous cubic phases is the monoglyceride monoolein. Monoglycerides spontaneously forms bicontinuous cubic phases upon the addition of water; they are insoluble in water and resistant to changes in temperature. The main precursor of cubosome formation is monoolein. Monoolein or glyceryl monooleate (GMO) is a mixture of the glycerides of oleic acid and other fatty acids, consisting mainly of the monooleate [22-24]. GMO has a hydrophilic head and a hydrophobic tail (see Fig. 5). GMO is biodegradable, biocompatible and is recognized as safe by GRAS to be used in the food industry as an emulsifier. The glycerol moiety may form hydrogen bonds with water in an aqueous environment and is commonly referred to as the head group [25, 26].

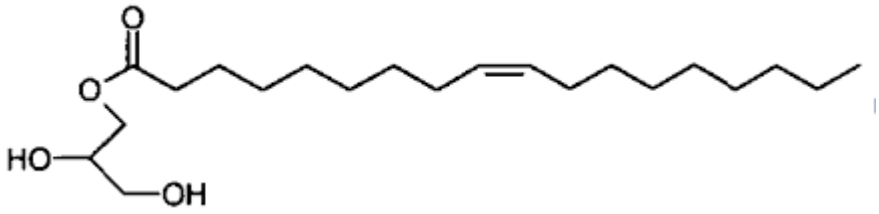

Fig. 5: Structure of Glyceryl Monooleate

Other than GMO's phytantriol (PHYT) is known as a good alternative to be used in the preparation of cubosomes. Phytantriol 3, 7, 11, 15-tetramethyl-1, 2, 3-hexadecane thiol ($C_{20}H_{42}O_3$) is

usually and mostly used in cosmetic industry as a key component, it consists of a molecule that has phytanyl chain (see Fig.6) [27]. PHYT is a fatty acid based substance susceptible to esterase-catalyzed hydrolysis and offers higher structural stability [28].

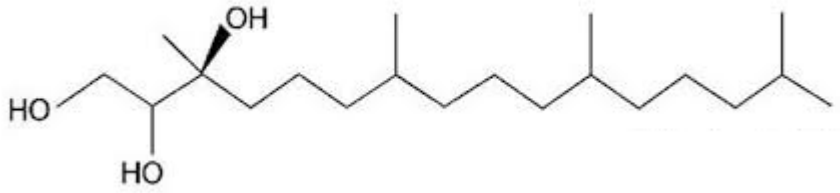

Fig. 6: Structure of Phytantriol

Although the two substances differ in their molecular structure and properties, they show similar phase behavior with increased water content and temperature.

Stabilizers

When a lipid molecule is heated, instead of melting, it directly converts into an isotropic liquid. Surfactants provide colloidal stability to prepared cubosomes. Cubosomes by nature re-coalesce to the bulk cubic phase. Ideal stabilizer for cubosomes prevents unwanted interactions between hydrophobic domains but encounters between particles, without causing any disruption to the cubic structure. This occurs due to the electrostatic-repulsive barrier between the approaching particles. Hence, these stabilizers were considered to be the essential components of the cubosome formation [29].

Of all, the most widely used stabilizer in cubosome formation is poloxamer 407 (BASF trade name Pluronic® F127). It stabilizes by participating within the structure of dispersed particles and manipulates the phase behavior [16]. Usually, poloxamer 407 are used at concentrations upto 20%w/w with reference to dispersed phase, while the concentration of monoglyceride-polymer mixture is usually between 2.5 and 10% w/w.

Worle *et al.*, [30] investigated the effect of different concentrations of P407 on the properties of cubosomes. Higher concentrations of P407 promotes the formation of smaller particles but at this state vesicular particle are formed than nanostructure cubic phases. An adequate amount of P407 yields cubic structured nanoparticulate dispersions.

CHARACTERISATION OF PREPARED CUBOSOMES

The prepared cubosomes are characterized by surface morphology, particle size analysis, entrapment efficiency, *in-vitro* drug release studies, and *in-vivo* studies.

Morphological Studies

The prepared cubosomes are examined for surface morphology to observe the cubic structures of formed cubosomes. These studies are carried out using scanning electron microscopy (SEM) or transmission electron microscopy (TEM). One drop of cubosomal suspension was mounted on a clear glass stub. It was air-dried and coated with sodium aurothiomaleate to visualize under SEM.

Particle Size Analysis

Particle size distribution and polydispersity index of cubosomes are determined by dynamic light scattering using zeta nano sizer. The magnitude of the zeta potential indicates the degree of electrostatic repulsion between adjacent, similarly charged particles in the dispersion.

Dialysis Bag Method

The entrapment efficiency of cubosomes is estimated by the dialysis bag method, in which the adequate amount of cubosomal suspension sample to be analyzed is placed inside the dialysis tube and is then placed in a beaker containing suitable buffer solution, the whole set up is kept aside for 24 hours. After 24 hours, the resultant solution inside the dialysis tube is analyzed for the entrapped drug-using UV spectrophotometer.

In-Vitro Drug Release Studies

In-vitro drug release studies were performed using the Franz Diffusion cell i.e. Bi-chambered

donor receiver compartment model and this was placed on a magnetic stirrer and temperature was adjusted to 37±0.5˚C. One end of the compartment was covered with the Gelatin sheet, which was previously soaked in warm water. Phosphate buffer saline (PBS) was placed in the receptor compartment. Cubosomal formulation was placed on the membrane, which was in contact with the receptor medium. Samples were withdrawn from the receptor compartment at a specified time interval. Replace the receptor medium with the equal amounts of fresh phosphate buffer solution after each withdrawal. The samples were analyzed for drug content using a UV Spectrophotometer.

CONCLUSION

With growing interest in lipid-based drug delivery systems, cubosomes can serve as a promising vehicle for the delivery of various therapeutic agents. With cubosomes, enhanced solubility and bioavailability of a wide variety of poorly water-soluble drugs can be attained. As cubosomes are made up of simple mixtures with less/no toxic effects they can be used effectively for the delivery of drugs through the oral route, topical route, and parenteral route. The formulation of cubosomes is economical with less consumption of time.

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CONFLICT OF INTEREST

The author declares no conflict of interest.

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