Review Article

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# CUBOSOMES: A NOVEL DRUG DELIVERY SYSTEM OVERVIEW

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**ABSTRACT**

Cubosomes are self-assembled, nanostructured, thermodynamically stable, square and rounded particles with cubic lattices visible. These are considered as versatile systems because of their properties and hence administrable in different ways such as orally, percutaneously, and parenterally. Cubosomes are organized in three dimensions as honey combed structures that are comprised of curved bicontinuous lipid bilayers which are divided into two internal aqueous channels that can be exploited by various bioactive ingredients, such as chemical drugs, peptides and proteins. Cubosomes can easily be incorporated into product formulations as they remain stable almost at any dilution level because of the relative insolubility of cubic phase forming lipid in water. This article gives an overview on structure, classification, properties, components, forms, preparation methods, evaluation and applications of cubosomes.

**Keywords:** Cubosomes, Honey combed structures, Bicontinuous cubic phases.

## INTRODUCTION

Cubosomes were introduced into the literature by Larsson and co-worker. These are discrete, sub-micron, nanostructured particles of the bicontinuous cubic liquid crystalline phase. These are self-assembled invert nanoparticles comprising of hydrophobic regions segregating two continuous but nonintersecting hydrophilic regions. Cubic nanoparticles are formed when fragmentation is achieved by high energy devices and these comprise isotropic, thermodynamically stable colloidal particles. Cubosomes have drawn significant attention due to their potential improvements in physicochemical stability, improved skin retention and hydrophobic drug loading.[1,2]

### Structure

Cubic nanoparticles look like honeycomb by exhibiting three dimensional hierarchically arranged lipid and water regions. Structural behaviour of cubic nanoparticles was earlier investigated by Luzzati and Husson in 1960's; later geometric model was provided by Scriven. Cubosomes internal and structural changes could be controlled by adjustment in lipid composition. These are discrete, sub-micron nanostructures in size range from 100-500 nm in diameter. Cubosomes were first identified by using X-Ray scattering technique.[3] These appear like square shaped or spherical dots corresponding to the presence of pore with aqueous cubic phases in lipid-water system. The cubic phases have high viscosity due to unique property of intriguing bicontinuous structures that enclose two distinct regions of water separated by a controlled bilayer of surfactant. The Cubosomes have high internal surface area along with cubic crystalline structures.The structure of cubosomes mainly consists of monoolein and water.[4]

### Monoolein

It is also called as the glycerolmonooleate (GMO). The acyl chain in it is attached to the glycerol backbone by an ester bond and the remaining two carbons of the glycerol have active hydroxyl groups which are responsible for giving polar characteristics to this portion of the molecule. In an aqueous environment the glycerol moiety may form hydrogen bonds with water and is referred to as head group and the hydrocarbon chain giving hydrophobic characteristics is referred to as tail. It occurs as a waxy yellow paste with a characteristic odour and swells in water. The phase behaviour shows several interesting points from pharmaceutical standpoint like some phases being in equilibrium with excess water solutions and occurrence of temperature-induced transitions between phases of different rheology. Also, monoolein is a nontoxic, biodegradable, and biocompatible material classified as generally recognized as safe; it is included in the FDA (Inactive Ingredients Guide) and nonparenteral medicines, licensed in the United Kingdom. The biodegradability of monoolein is due to lipolysis of diverse kinds of esterase activity in different tissues.[5,6]

### Water content (≤1%)

The Monoolein-water system possesses a unique phase region containing broad compositional and temperature range. The cubic phase structure can be described by using the concept of periodic minimal surfaces and differential geometry. Depending upon their curvatures, 3 types of minimal surfaces are studied as follows; D surfaces, G surfaces, P surfaces. D surfaces are formed by the monoolein water system at high water levels, G surfaces at low water levels and P surfaces are formed only when a third component such as casein or amphiphilic block copolymer is added.[7,8]

### Classification

Cubosomes are classified into two kinds based on principles of differential geometry: an 'open' structure and a 'closed' cubosome structure. In an open structure the two aqueous channels are in contact with the external environment where as one water channel open towards the external environment with

the other compartment closed in relation to the outside in the case of closed cubosome. It was proposed earlier that closed Cubosome was more stable. But recent studies support strongly that open model was more stable structure. Also cubosomes are classified into gyroid, primitive or diamond like that of bulk parent cubic phase.[9]

**Properties**

- Cubosomes have the ability to encapsulate hydrophilic, hydrophobic and amphiphilic drug molecules.
- These have bioadhesivity and biocompatibility properties.
- Cubosomes are bicontinuous cubic liquid crystalline phases that are stable in excess water.
- They have sustained drug delivery release characteristics.
- The bioavailability range of water- soluble peptides would increase 20-100 times with these cuboidal systems.
- Cubosomes serve as an excellent vehicle for protecting the sensitive drug from enzymatic degradation.
- For sparingly soluble drugs cubosomes show high drug carrier capacity.
- These are excellent solubilizers when compared to lipid or non-lipid carriers.[10]

**Components of Cubosomes**

**Amphiphilic lipids**

GMO and phytantriol are the most commonly used amphiphilic lipids in the preparation of cubosomes. GMO is a synthetic compound which is a mixture of glycerides of oleic acid and other fatty acids. These fatty acids mainly consist of monooleate which belongs to the class of amphiphilic lipids and it has the ability to form various lyotropic liquid crystals. Because of the presence of hydroxyl groups in the head region, which can form H- bonds with water in an aqueous medium and the hydrocarbon chains in the tail, GMO has both hydrophilic and hydrophobic characteristics at the same time. Basing on the Lutton'sresults, monoglycerides having hydrocarbon chain length between 12 and 22 have an extreme tendency to form cubic phases.[11,12] Upon increasing the water content PHYT which is having phytanyl chain also displaysthe phase behaviour. The commonly used ingredient in cosmetic products is PHYT, 3, 7, 11, 15-tetramethyl-1, 2, 3-hexadecanetriol. This is suggested as the brilliant alternative for GMO in the preparation of cubosomes because PHYT offers high structural stability. Although the two substances differ in their properties and molecular structure, with increased water content and temperature they show similar phase behaviour which was determined by X-Ray diffraction. Upon increasing the water concentration the phase sequence is as follows: reversed micellar, lamellar, Q230 and Q224 at room temperature. Cubic phase turns to a hexagonal structure at an elevated temperature of 44 ºC. PHYT Cubosomes exist in equilibrium with water which is a required condition for formation of Cubosomes. Also, PHYT-based liquid crystalline matrices suits as remarkable sustained drug delivery system.[13,14]

**Stabilizers**

Surfactant is important to provide colloidal stability for cubosomes. There are many ongoing projects to introduce and apply these in the preparation of cubosomes. Poloxamer 407 (P407), a $PEO_{99}$ -$PPO_{67}$ -$PEO_{99}$tri-block copolymer, is the most used surfactant in cubosomes preparation. The P407 consists of both PPO portions and PEO chains, where PPO portions located either at the surface of the cubosomes or within the bilayer structure and PEO chains are exposed to the surrounding water phase. Depending upon the dispersed phase, P407 is applied up to a concentration of 20% w/w and depending upon the weight of the dispersion monoglyceride-polymer mixture is usually in the concentration of 2.5 and 10% (w/w).[15,16] Worle *et al*. investigated the effect of different concentrations of P407 on the properties of Cubosomes. At higher P407 concentrations the success rate of creating smaller particles was high but resulted in the formation of vesicular particles rather than the preferred nanostructured particles with cubic matrix. Also, P407 is adsorbed onto the surface of PHYT cubic phase whereas in the case of GMO cubic phase it is integrated into the liquid crystalline structures.[17] Wadsten-Hindrichsen *et al*., studied the effect of propylene glycol (PG), polyethylene glycol 400 ($PEG_{400}$) and 2-methyl-2, 4-pentanediol(MPD) on a PHYT-based system which are three water-miscible solvents. It was showed that MPD produced sponge phase whereas the PG and $PEG_{400}$ showed cubic, lamellar, and non-ordered liquid phases.[18] The reason for this was identified as difference in phase behaviour that is more hydrophobic nature of PHYT than GMO and branched hydrocarbon chain of PHYT making it less flexible than GMO. The internal structure and morphology of GMO and PHYT-based cubosomes on β-casein with P407 as the stabilizer was also studied.[19]

**Forms of Cubosomes**

Three forms of macroscopic cubic phase are as follows: precursor, bulk gel, and particulate dispersions. The precursor form exists as a solid or liquid material and forms cubic phase when contacts with liquid, in response to a stimulus. The bulk phase is commonly a clear, viscous, semi-solid gel that is similar in appearance and rheology to cross-linked polymer hydrogels and its high viscosity limits its application. Also, when bulk phase comes in contact with the biological epithelia it may cause the irritation reaction. In the particulate dispersions bulk phase is dispersed into the water in the form of small particles; the dispersed cubic particles are denoted as cubosomes. These can exist stably in equilibrium.[20]

**Liquid Cubosome Precursors**

Due to the difficulty and expense of high shear dispersion of viscous bulk cubic phase to form into cubosomes, it is desirable to seek less aggressive process of manufacture. The hydrotrope dilution method is such method to give smaller, more stable cubosomes. This is achieved by dissolving the monoolein in a hydrotrope like ethanol that prevents liquid crystalline formation. Subsequent dilution of this mixture spontaneously crystallizes or precipitates the cubosomes. The particles here are formed by nucleation and growth, similar to that of crystallization and precipitation processes. The liquid precursor process allows for easier scale up of cubosome preparations and also useful for thermo-sensitive ingredients like proteins.[21]

**Powdered Cubosome Precursors**

Powdered Cubosome precursors offer advantages to liquid phase hydrotropic cubosome precursors as these are composed of dehydrated surfactants coated with polymer. Cubosomes formed by hydration of the precursor powders are with a particle size of 600 nm which is confirmed by light scattering and Cryo TEM. Spray drying is an excellent process to produce cubosomes by employing lipids that are waxy, sticky solids, rendering them unable to form small discrete particles. Spray drying produces encapsulated particles from a dispersion of solid particles or from an emulsion of liquid droplets in a concentrated aqueous polymer solution. For producing continuous and dispersed phases nozzle is used, which sprays throughout to create suspension droplets

that are contacted with a heated, dry air stream flowing in the opposite direction. Finally, dry powder particles are formed which are encapsulated by a shell of previously formed polymer. This process also aids in preloading the active drug prior to the drying of cubosomes. The important step here is the selection of polymer which is responsible for imparting surface properties to the hydrated cubosomes. The powder with 3:1 ratio of starch and monoolein exhibits good encapsulation of the Monoolein and small particle size. Hence these powders offer some process and performance advantages to cubosomes.[22,23]

**Advantages**

- Cubosomes can be relatively prepared by simple method.
- They have ability to encapsulate both hydrophilic, hydrophobic and amphiphilic substances.
- Cubosomes have biocompatibility and bioadhesivity properties.
- Cubosomes are excellent solubilizers, compared with conventional lipids or non-lipid carriers.
- Numerous promising compounds having poor aqueous solubility, poor absorption and large molecular size can be addressed with cubosomes.
- High drug payloads can be achieved due to high internal surface area and cubic crystalline structures.
- Cubosomes particles as oil-in- water emulsion stabilizers and pollutants absorbents used in cosmetics.
- Most of the liquid crystalline systems transform into micelles at higher levels of dilution but cubosomes remain stable at most at any dilution level because of the relative insolubility of cubic phase forming lipid in water. So, cubosomes can easily be incorporated into product formulations.
- The fractured and dispersed cubic phase of cubosomes leads to the formation of particulate dispersions that are colloidally and/or thermodynamically stable for longer time.
- Cubosomes serve as an excellent vehicle to protect the sensitive drugs such as proteins and peptides from enzymatic degradation and *in-vivo* degradation.
- Low cost of raw materials.
- Improves efficacy and decreases risk of drug misuse and misdirection.
- The cuboidal system enhances the bioavailability range 20-100 times for water soluble peptides.
- Cubosomes increases convenience and compliance.[24]

**Disadvantages**

- Cubosomes may lead to low drug loading efficiency and drug leakage during preparation, preservation, and transport *in vivo*, thus the major problem of their stability acts as a barrier and thus limiting their use.
- Because of their high viscosity large scale production is sometimes difficult.
- Some big drugs cannot penetrate inside the channels and drugs can ruin the lattice structure of bicontinuous liquid crystalline phase.[25]

**Methods of preparation of Cubosomes**

The crucial objective for many pharmaceutical applications is the liability to create nanostructured aqueous dispersions with a desirable uniform particle size. Cubosome nanoparticles can be produced mainly by two approaches:

**Top- Down Approach**

It is the most widely used method for the preparation of Cubosomes. It was reported in 1996 by Ljusberg-Wahren. It consists of two steps. The bulk cubic phase is produced in the first step by mixing lipid(s) with stabilizer(s). In the second step through the application of high energy such as high-pressure homogenization or sonication the resultant mixtures from the first step is dispersed into aqueous medium to form the cubosomes. Bulk cubic phase resembles a clear rigid gel formed by water-swollen cross-linked polymer chains. The bilayer breaks under applied shear stresses resulting in the rupture of cubic phases in a direction parallel to the shear direction, the energy required is directly proportional to the number of tubular network branches that rupture. Cubosomes produced through this top-down method are stable against aggregation for about a year and always and coexist with vesicles such as the dispersed nano particles of lamellar liquid crystalline phase or vesicle-likestructures. However a drawback in large scale production is limiting the incorporation of temperature sensitive ingredients like proteins and peptides due to the requirement of high amount of energy for dispersing the cubic phase into cubosomes.[26,27]

**Bottom- Up Approach**

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. 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.

When these two approaches are compared with one another it was found that bottom- up approach is more efficient in creating smaller cubosomes with higher encapsulation efficiency and slower release rates. Some other advantages of this method include producing cubosomes that show long term stability and allow working with temperature sensitive materials.[28]

**Drug Release from Cubic Phases**

Because of unique structure of cubosomes, Hyde *et al*., have studied the controlled release application of them and further investigation stated that their distinct structure provides a tortuous diffusion pathway for controlled release.[29] The general mechanism of drug release is diffusion as the drug concentration gradient is the driving force across the Cubosomes. Various factors influencing the drug release rate are as follows:

a) Drug solubility, partition coefficient, diffusion coefficient, etc.
b) Cubic liquid crystalline geometry, interface curvature, and the pore size and distribution.
c) Temperature, pH, and ionic strength of the release medium [30]

**Evaluation of Cubosomes**

**a) 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.

**b) 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.

**c) 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.[31]

**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 ($C_f$) which when reduced from the total drug concentration ($C_t$) gives the amount of drug entrapped in the cubosomes to get more accurately, each experiment was repeated 3 times.

$$\text{Entrapment efficiency \% of cubosomes} = \left[\frac{(C_t - C_f)}{C_t}\right] \text{x} 100$$

**e) Particle Size Distribution Measurements**
Characterization of both spray dried powders and the aqueous dispersions of cubosomes is carried out by using laser diffraction.[32]

**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.[33,34]

**g) Pressure Ultra-filtration Method**
By pressure ultra-filtration method drug release measurement from cubosomes is done. It is based on an Amicon pressure ultra-filtration cell fitted with a Millipore membrane at ambient temperature of (22 ± 2)°C.

**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.[35]

**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.[36]

**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.

**o) 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.[37]

**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 can be assessed, over the time.[38]

**Applications of Cubosomes**

**Brain targeting**

The delivery of drugs to brain for the treatment of CNS diseases is blocked by the BBB. This barrier poses a considerable challenge for the administration of both small and large drug molecules. One type of lipid-based nanoparticles, cubosomes has been investigated to increase drug loading into the brain. One of the examples is enhancing the delivery of resveratrol to brain through transnasal route by cubosomes. These were prepared by using glycerol monooleate lipid and Lutrol® F 127 by probe sonication process. After obtaining optimized cubosomal dispersion, it was dispersed into Poloxamer 407 polymer to form *in situ* gel for nasal use. It showed higher transnasal permeation and better distribution than drug solution.[39]

**Oral drug delivery**

Cubosomes aid in oral delivery of numerous compounds having poor aqueous solubility, poor absorption, and large molecular size. In an application, large proteins have been encapsulated for local activity in the GIT. One of the examples is improving the oral efficacy of amphotericin B (AmB) by formulating Cubosomes with Glycerol monooleate (GMO). Orally AmB cubosomes were investigated for antifungal efficacy *in vivo* in

rats and *in vitro* with Caco-2 cells and found that GMO cubosomes increase the oral delivery of AmB.[40]

**Increasing the corneal permeability**

Because of low corneal permeability and bioavailability, ocular drug delivery faces different challenges. For glaucoma treatment a cubosome drug delivery was constructed for Timolol Maleate (TM) in a study with the help of glycerol monooleate and Poloxamer 407. It was found that TM cubosomes penetration was higher than commercially available eye drops.[41]

**Sustained release behaviour**

Drugs with broad range of molecular weights and water solubility's have showed sustained release in cubic phase liquid crystals. Eventhough the GMO-based cubosomes achieve sustain release they are susceptible to degradation in GIT. This is now overcome with development of cross-linked Chitosan cubosomes which could prevent the digestion and also achieve sustain release behaviour. Examples include aspirin, vitamin E and others.[42,43]

**In cancer cell targeting**

Many cancer drugs have been successfully encapsulated in cubosomes. One of the examples includes resveratrol which suffers from low aqueous solubility, extensive first pass metabolism and isomerisation to the inactive cis-isomer during light exposure. The cellular uptake of this anticancer drug was increased by formulating into cubosomes.[44]

**Transdermal drug delivery systems**

As the cubic phase structure between cubosomes and *stratum corneum* are similar, the cubosomes have penetration enhancing effect on the skin as the lipid part of particles mix with the lipids of the *stratum corneum.* Also, cubosomes are known to be skin-adhesive hence these drug carriers are promisingly administrable by transdermal route.[45,46]

**Cosmetics**

Cubosomes have been formulated as cosmetic products like hair care, skin care, antiperspirants, and others. Alpha-lipoic acid (ALA) is a naturally occurring fatty acid of mitochondria with a potent antioxidant activity. This ALA in cubosome dispersions has excellent results in reducing facial lines with improvement in skin texture and colour.[47,48]

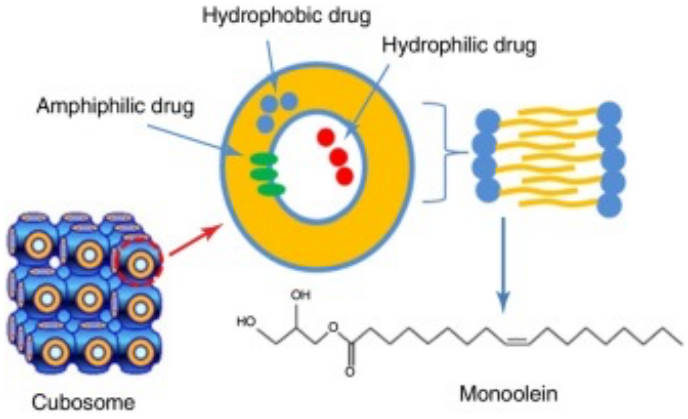
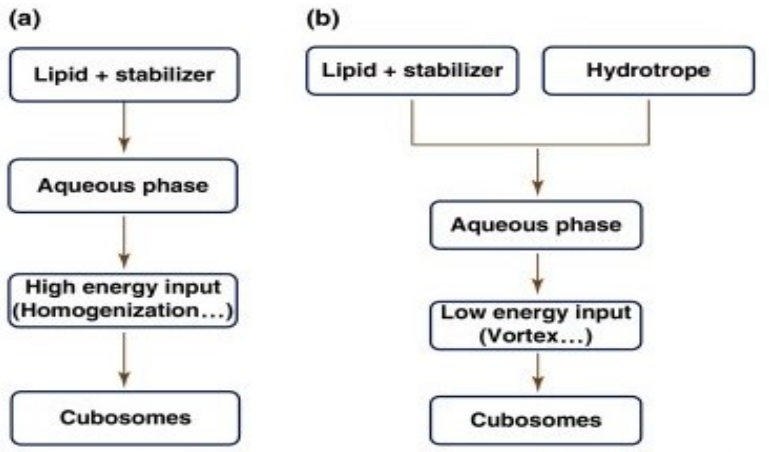



**Figure 1: Structure of Cubosome**




**(a) top-down approach** **(b) bottom-up approach**

**Figure 2: Methods of Preparation of Cubosomes**

## CONCLUSION

Cubicphase material can be formed by simple combination of biologically compatible lipids and water and are thus well suited for pharmaceutical and body tissue. The ability to form cubosomes either in use, during formulation, or during manufacture offers greatly enhanced flexibility for product development efforts. The precursor form enhances its further scope in technology field. Although there is much research on cubic phases in formulation studies, there is still more to explore this application for development of newer methods of production and also for applying this nanoparticulate carrier in various other fields of drug delivery.

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