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A Review on Cubosomes

Upadhye SS*, Kothali BK, Apte AK, Kulkarni AA., Khot VS
1. Dr. J J. Magdum Pharmacy College, Jaysingpur

ABSTRACT

The discovery of the cubosomes is the unique story & spans the fields of the food science, biological membranes, differential geometry & digestive processes. The cubosomes are the square & rounded particles with the internal cubic lattices visible. The cubosomes are self-assembled nanostructured particles formed by the aqueous lipid & surfactant systems. The cubosomes are the thermodynamically stable, they have the structure like "honeycombed" with the bicontinuous domains of the water & lipid in which the surfactant assembles into the bilayers & twisted into the 3 dimension, periodic & the minimal surface forming the structure which are tightly packed. They exhibit the different internal cubic structure & composition with different drug-loading modalities. In drug nano formulations the cubosome have great potential for the melanoma therapy owing to their potential advantages which includes high drug payloads due to the high internal surface area & cubic crystalline structures relatively biodegradability of lipids, the simple preparation method, targeting & controlled release of the bioactive agents, the ability of encapsulating the hydrophilic, hydrophobic & amphiphilic substances, The cubosome dispersions are biocompatible & bioadhesive. Due to their properties the cubosome are versatile systems administrable by different routes such as parenterally, orally& percutaneously. Hydrating the surfactant or the polar lipid that forms the cubic phase & then dispersing the solid like phase into the smaller particles usually forms the cubosomes. To encapsulate guest molecules such novel particles are utilized which are either amphiphilic, lipophilic or hydrophilic due to its structure compartmentalization.

Keywords: Cubosomes, nanostructured, Surfactants, Melanoma therapy

*Corresponding Author Email: ssupadhye7@gmail.com
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INTRODUCTION

The cubosomes are the discrete, sub-micron, nano-structured particles of the bicontinuous cubic liquid crystalline phase. The cubosomes possess the same microstructure as the parent cubic phase but have the larger specific surface area & their dispersions have much lower viscosity in comparison to that of bulk cubic phase. The surfactants, Lipids & the polymer molecules have both polar & non polar components which is termed as the amphiphilic. The hydrophobic effect drives the amphiphilic molecules in the polar solvents to spontaneously self assembling in to an array of the thermodynamically stable liquid crystalline phases with lengths on the nanometer scale. The example is the bicontinuous cubic liquid crystalline phase. The bicontinuous cubic phases are the optically isotropic, very viscous & solid like liquid crystalline substance having the cubic crystallographic symmetry. The cubosomes are nanoparticles more accurately nanostructure particles of the liquid crystalline phase with the cubic crystallographic symmetry formed by a self assembly of the amphiphilic or the surfactant like molecules. The cubic phases possess the very high solid like viscosity which is the unique property because of their intriguing bicontinuous structures which enclose 2 distinct regions of the water separated by the controlled bilayer of the surfactant. As the result, the cubic phases can be fractured & dispersed to form the particulate dispersions that are colloidally or/& thermodynamically stable for the longer time. The cubosomes have the great potential in the drug nanoformulations. [1-4]

History of Cubosomes

Due to their complex phase behavior & viscous properties the large scale manufacture of the cubosomes was difficult, despite their early recognization [in 1980]. The cubic phases are unique as they possess very high solid like viscosities because of their intriguing bicontinuous structures. To form particulate dispersions which are colloidally and/or thermodynamically stable for longer period of time the cubic phases can be fractured & dispersed. There are certain surfactants that spontaneously form the cubic phases when mixed with the water above the certain concentration. The determination of their honeycomb structure was carried out by the Luzzati & Husson, Luzzati *et al.*, Larsson & Hyde *et al in* between 1960 & 1985. Larsson coined the term “Cubosomes” that reflects a cubic molecular crystallography & similarity to the liposomes. The effort to develop the scalable processes to produce the cubosomes in the large scale is under development. Few anticancer drugs have been successfully encapsulated in cubosomes & characterized.

Structure

A basic structure of the cubosomes includes the honeycombed structures that separate the 2 internal aqueous channels along with the large interfacial area. The cubosomes are the nanoparticles more accurately the nanostructure particles of the liquid crystalline phase with the cubic crystallographic symmetry formed by a self assembly of the amphiphilic or the molecules that are like surfactant. The cubosomes having a high internal surface area along with the cubic crystalline structures. A cubic phase possess a very high solid like viscosity which is the unique property because of their intriguing bicontinuous structures which enclose the two distinct regions of the water separated by the controlled bilayer of the surfactant. The amphiphilic molecules form the bicontinuous water & oil channels, where "bicontinuous" refers to the 2 distinct [continuous, but non-intersecting] hydrophilic regions separated by a bilayer. An interconnectedness of the structure results in the clear viscous gel similar in the appearance & the rheology to the cross-linked polymer hydrogels. The monoglyceride-based cubic gels possess the significantly more long-range order than the hydrogels & because of their composition [i.e., lipid & water] & excellent biocompatibility.[5]

Merits/ Advantages of the cubosomes

- Due to high internal surface area & cubic crystalline structures there is high drug loading
- These are excellent solubilizers
- For longer time they are thermodynamically stable
- It is economic
- It has sustained & targeted release profiles for drugs
- It can entrap both lipophilic & hydrophilic drugs
- It is non- toxic & biocompatible
- Method of preparation is simple
- It has excellent bioadhesive properties
- It has skin permeation enhancement
- It can be easily incorporated into product formulations

Demerits/ Disadvantages of the cubosomes

- Due to presence of large amounts of water inside cubosomes there is low entrapment of water soluble drugs
- Because of the high viscosity the large scale production is sometimes difficult. [5-7, 10]

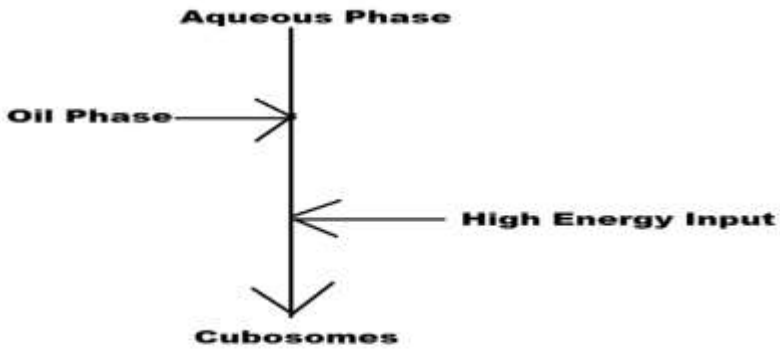
MANUFACTURE OF CUBOSOMES

Cubosomes are mainly prepared by 2 methods:

1. Top down technique
2. Bottom up technique

The Top down technique

In research area It is the most widely used method. It was reported By Ljusberg-Wahren in 1996. Here first the bulk cubic phase is produced. Then by the application of the high energy such as the high pressure homogenization it is processed into the cubosome nanoparticles. The bulk cubic phase resembles the clear rigid gel formed by a water-swollen cross-linked polymer chains. The rupture of a cubic phase occurs as a bilayer breaks under the applied shear stresses & flows along the slip planes. In the direction parallel to the shear direction they rupture, the energy required is proportional to the number of the tubular network branches that rupture. A cubic phase exhibits the yield stress that increases with the increasing amount of the bilayer forming the surfactant & the oils. Based on the most recent studies the comparison of the dispersion produced by the sonication & the high pressure homogenization suggests that the formation of the complex dispersions containing the vesicles & the cubosomes with time dependent ratios of each type of the particle.

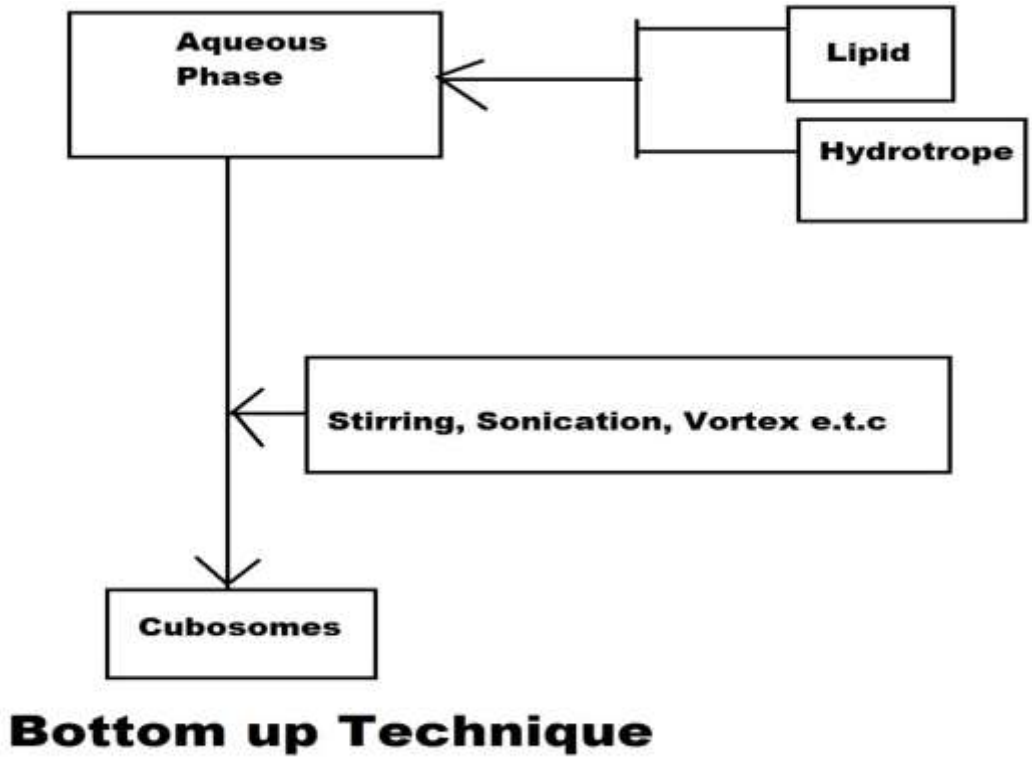


Top down Technique

The Bottom up technique

This technique first forms the nanostructure building blocks & then assembles them into the final material. The cubosomes are allowed to form or crystallize from precursors, in this method. By dispersing inverse micellar phase droplets in water at 80°C & are allowed to slowly cool, the cubosomes are formed. Gradually these droplets crystallize to the cubosomes. This is more useful in the large scale production of the cubosomes. The cubosomes at the room temperature is produced by diluting the monoolein-ethanol solution with the aqueous poloxamer 407 solution. The cubosomes are spontaneously formed by the emulsification. To produce the cubosomes from powdered precursors by spray drying technique, other process is also developed. Spray dried powders comprising the monoolein coated with the starch or the dextran forms the cubosomes on

simple hydration. This bottom-up approach first forms the nanostructure building blocks & then assembles them into a final material. It is the recently developed technique of the cubosome formation by allowing the cubosomes to form & crystallize from the precursors on the molecular length scale. The key factor of this technique is the hydrotrope that can dissolve the water insoluble lipids into the liquid precursors. When compared top down approach this is the dilution based approach that produces the cubosomes with the less energy input. [9-11]



CUBOSOMAL PRECURSOR FORMS

The development of the cubosomal precursors results in a production of the *in-situ* cubosomes, which not only avoids the high energy procedure which is an difficult & expensive to scale-up but also to protect the thermosensitive moieties like the proteins.

The Liquid Precursors

To produce the cubosomes from liquid phase precursors, the strong driving force is required. More stable cubosomes of desired size can be produced, upon the dilution of the liquid precursors. The cubosomal particles are produced by the nucleation & the growth mechanism in the hydrotrope dilution method, which is similar to the crystallization & precipitation procedure. The liquid phase precursors are widely used in the hand washes, mouth washes where the cubosomes can be formed during washing, rinsing respectively. As the high shear is not required in this method & thereby the degradation of the active moiety can be minimized in the cubic crystals. Thus, for the

production of the cubosomes the liquid precursors offer an easy scale-up technique by reducing the handling of the bulk solids & the avoidance of the high energy process techniques that degrade a drug.

The Powdered Precursors

The powdered cubosomal precursors are made up of the dehydrated surfactants coated with the suitable polymer. The cubosomes with an average particle size of 600 nm are formed upon reconstitution of the powdered precursors with water, as conformed by the characterization studies such as the light scattering technique & cryo- transmission electron microscopy [cryo-TEM]. To formulate the cubosomal powdered precursors, the spray drying is an excellent technique It involves the production of the encapsulated particles from the liquid droplets in the emulsion as well as from the dispersed solid particles in the concentrated aqueous polymer solution. The spray drying technique is a well suitable to scale-up the production of the consumer goods like the detergents & foods. To provide the easy way to preload the potent drug in cubosomes before drying, this process also helpful. As compared to the liquid phase cubosomal precursors these powdered precursors propose process & the performance oriented advantages. [12-14]

METHODS FOR CHARACTERIZATION AND EVALUATION OF CUBOSOMES

The Gel permeation chromatography or ultra filtration techniques & UV spectrophotometer or HPLC analysis

The entrapment efficiency & the drug loading of the cubosomes can be determined by using the gel permeation chromatography or the ultra filtration techniques. The unentrapped drug concentration is determined, which is subtracted from the total drug added, in the later technique. By using UV spectrophotometer or HPLC analysis, the amount of drug is analyzed.

The X-ray scattering

To identify the spatial arrangements of different groups in the sample the small angle X-ray scattering [SAXS] can be used. The diffraction patterns obtained are converted to the plots of intensity versus the q value, which enable the identification of the peak positions & their conversion to the Miller Indices. To identify the dominant internal nanostructure of the sample, the Miller Indices could then be correlated with the known values for the different liquid crystalline structures & the space groups.

The Transmission electron microscopy [TEM]

To view the shape of the cubosomes, the Transmission electron microscopy can be used. The Kim et al. described that, with the freshly prepared phosphotungstic acid solution [2%, pH 6.8] the suspensions of the cubic phase nanoparticles were negatively stained & were transferred onto the

formvar/carbon coated grid [mesh200], air dried at the room temperature. On an electron microscope the electron microphotographs were taken. Since while exposing to the electron array, the robustness & integrity of the formulation may be lost during the procedure, the SEM [Scanning Electron Microscopy] analysis may not be performed on the cubosomes or some vesicular systems.

The Photon correlation spectroscopy

By using zeta sizer [photon correlation spectroscopy] the particle size distributions of the cubosomes are mainly determined. Dilute the sample with the suitable solvent, adjusted to the light scattering intensity of about 300 Hz & measured at the 25 °C in the triplicate as an average volume weight size. The polydispersity index & zeta potential can also be recorded.

The Polarized light microscopy

To identify the morphology of liquid crystalline the polarized light microscopy is used depending on the optical birefringence phenomena. To differentiate between anisotropic & isotropic material it is also useful.

The In vitro drug release studies

By using the dynamic dialysis method the In vitro release of drug from the cubosomes is evaluated. The samples of the various formulations were placed in the dialysis bags [cellulose membrane], then immersed in the release medium at 37±1 °C under the specific paddle rotation speed. At the predetermined time intervals, the 5 ml sample was withdrawn & immediately replaced with the equal volume of the release medium & then the concentration of the released drug is measured.

The Light microscopy

By using deionized water the samples of the prepared cubosomes were suitably diluted & examined by using an optical microscope [Lecia DMRXP] calibrated with the micrometer slide at the magnification of 400X & 1000X.

The Visual inspection

The dispersions were visually assessed for optical appearance [e.g., colour, turbidity, homogeneity, presence of macroscopic particles], about one week after preparation,

The Viscosity

Viscosity is determined by the different anguler velocities atb 250 C using [Brookfield Viscometer].The rotation speed was 20 rpm, with thevspeen #18. For the calculation of the viscosity the averages 3 reading are taken.

The Entrapment efficiency

By the top down and bottom up technique the dispersion sample is obtained. The 0.05 gm of the sample are taken. The amount of a drug in the dispersion was then analyzed spectrophotometrically at the λmax 250 nm. By this way subtract the total amount of drug. The volume of the 1ml from each of the dispersion was diluted with the 4 ml of the deionized water. The solution nis passes to the syringe filter is examine under the spectrophotometer.

The Stability study

By investigation of organoleptic and morphological aspects as a function of time particle size distribution and drug content can be assessed at different time intervals can also be used in possible variation by time the stability study can carried out. In amber color glass viales sealed with aluminum foil at refrigeration temperature 4-80C for period of 3 month, the cubic gel were stored. At the end of the study period the sample were withdrawn & were dispersed in deionized water by vortex for 3 min. For the mean particle size & EE [%] measurement the prepared cubosomal dispersion was subject. [5, 12, 15-24]

APPLICATIONS OF CUBOSOMES

The Melanoma [cancer] therapy

Few anticancer drugs have been successfully encapsulated in the cubosomes & characterized physicochemically. Recently a unique structure of this promising nanocarrier suggests its application in the melanoma therapy. [25]

The Intravenous drug delivery systems

The lipid nanoparticles comprising the interior liquid crystal structures of the curved lipid membranes that are used to solubilize the encapsulate & deliver the medications to the disease areas within the body. While the emulsions & liposomes have found the use as the intravenous carriers in the drug products the liquid crystal nanoparticle structures increased the payloads of the peptides, proteins & the many insoluble small molecules & are ideal carriers for the injection or the infusion of many actives. [26]

The Topical drug delivery systems

The cubic phases are more bioadhesive in the nature so that they can conveniently use in the topical & mucosal depositions & delivery of the different drugs. On the exploitation of unique properties of liquid crystal [LC] & liquid crystal nanoparticle [LCNP] technologies the topical delivery systems are based. The topical drug delivery systems are unique in situ forming the bioadhesive LC systems facilitate the controlled & effective drug delivery to the mucosal surfaces [ophthalmic, buccal, vaginal & others]. This fascinating system forms the thin surface film at the mucosal surfaces consisting of the liquid crystal matrix which the nanostructure can be controlled

for the achieving of an optimal delivery profile & provides the good temporary protection of the sensitive & sore skin. [27]

The Oral drug delivery

In oral delivery of numerous promising compounds the cubosomes address the varied challenges including the poor absorption, poor aqueous solubility & large molecular size. These are both powder & liquid in capsule products comprising our self emulsifying liquid crystalline nanoparticles technology [LCNP]. The large proteins have been encapsulated for local activity in the gastrointestinal tract in an alternative application. With the controlled release & targeting functionalities the liquid crystalline nanoparticles technology [LCNP] carriers can be combined. The particles are designed to form the in situ in the controlled rate which enables an effective *in vivo* distribution of the drug. At different absorption sites, the liquid crystalline nanoparticles technology carriers can also be released. For example in the upper or lower intestine which is important for the drugs that have the narrow regional absorption window. [28]

In the topical & mucosal depositions

As the Cubic phases are more bioadhesive in nature, so that they can be conveniently used in the topical & mucosal depositions & delivery of the different drugs.

As sustained release behavior

Also the more recent patent activity by points to the cubosome used in the personal care product areas as varied as cosmetics, skin care, antiperspirants & hair care. There remains the lack of the practical elements like material customization & manufacturing scalability that is necessary to lead formulators to consider using cubosomes in commercial products, despite the recent activity. The cubic phase has been shown to provide the vehicle for the several *in vivo* delivery routes, including mucoadhesion, ophthalmic depot & transdermal. Due to the fusogenic property of the monoolein it increases the penetration of the macro molecules. The wide variety of the drugs with different physicochemical properties has been incorporated in the cubosomes & their sustained release behavior was also studied. The Sustained behavior of the cubosomes was due to cubosome remnant particles. The monoglyceride based cubosome dispersion can be proposed for the topical use, such as for mucosal applications or perctuneous applications.

The Drug delivery vehicle

For such new materials the drug delivery vehicle is the common application. A rapid expansion of the life-sciences industry is expected to drive the previously “exotic” delivery vehicles & ingredients into the broader marketplaces, such as consumer & personal care products. For compatibility with numerous medical active ingredients and their applications, self-assembled

surfactant phases have been extensively examined consequently. The number of research in association with the cosmetic companies like Nivea & L'Oreal are trying for the use of the cubosome particles as the pollutant absorbents & oil-in-water emulsion stabilizers in cosmetics. Also these researches have also discovered that the second amphiphile, phytantriol has an aqueous phase behavior which is sufficiently close to that of the monoolein to form the cubosomes under the similar conditions.

In the treatment of viral diseases

The cubosomes could be used to design intravaginal treatment of sexually transmitted diseases caused by viruses [For e.g. HIV, HSV] or by bacteria [e.g. Chlamydia trachomatis and Neisseria genorrticae] because of the microbicidal properties of monoglycerides. Due to the similarity between the cubic phase structure & the structure of the stratum corneum it is reasonable to suppose the formation of the mixture of the cubosomalmonolein with the stratum corneum lipids. This kind of a interaction might lead to the formation of the cubosome depot in this layer from which a drug can be released in the controlled fashion. To develop the synthetic vernix– the cheesy white substance that coats infants in the late gestation – to help the premature infants who are born without it the cubosome technology is used. The vernix is the complex mixture of water, proteins & lipid [fats].It has an integral role in the development of normal skin & it is formed late in the gestation. [6]

As the biologically active substances

At 25°C in water monoolein-alcohol mixtures, the cubic phases were produced. The ethanol was found to be more efficient than the butanol & propanol. We identified the new transparent, low viscosity [flowing] phase that we called OL, in the composition range of the 49 to 56 wt% water, 31 to 40 wt% monooleine & 10 to 13 wt% ethanol. By bright field light microscopy and polarized light microscopy no structures were found by indicating that OL is an isotropic phase. Large domains of this ordered phase is shown by Cryo- TEM which by the Fast Fourier Transformation was identified as the cubic phase. By SAXS the symmetry was also confirmed. The bioactive compounds were incorporated into the OL phase & the phase was then dispersed into the cubosomes of 100 – 250 nm in diameter by homogenization, in the presence of Pluronics 127 as the stabilizing agent. Several guest molecules were solubilized including the drugs [carbamazepin & diclofenac] & nutraceuticals [Lycopene & coenzyme Q10, phytosterols]. Before the ordered phase was broken and vesicles formed, typically only the trace amounts of the given bioactive compound could be solubilized in the cubosomes. When two guest molecules of different character

were solubilized together however it is the synergistic effects that significantly increased the loading & the order of the nanovehicles where found.[2]

The Materials Synthesis

The creation of ordered structures with nanoscale pore geometries is of great interest to numerous fields from the materials science perspective which includes photonics, medicine, electronics & catalysis. The creation of the solid structures by using the cubic phases as the template usually entails either the polymerization or the reaction to form solids from the precursors that are solubilized in or comprises the cubic phase matrix. Aluminosilicate zeolite MCM-48 is one of the earliest & most successful materials formed in the cubic phase template, which is used for the catalytic processing of the petroleum. The Yang et al successfully carried out the polymerization inside the cubosomes by yielding the solid nanostructured particle with the cubic symmetry. For use in photonic and semiconductor applications such particles hold promise. The Lu et al, have developed the novel aerosol processes that create the particles with the nanometerscale structure by the evaporation of the solvent from the isotropic phase liquid droplets simultaneously driving them into the cubic phase structures & solidifying the particles. The optimization of the structures will be a leading interest area as the sophistication in the cubic phase template area builds. Alongwith these lines, Larson suggests the possibility of the aligning the cubic phases by steady or the large-amplitude oscillatory shearing prior to the templating, forming materials with the unique & highly anisotropic properties. Using careful growth of faceted cubosomes in the C12E2–water system, beautiful structures have been formed by offering future promise of the multiple-decade length scale control over a morphology of the particles which are formed from such templates.[29-34]

PHARMACEUTICAL PREPARATIONS ENCLOSING CUBOSOMES [35]

SR. No.	Researcher	Drug	Category	Associated Disease
1	Sadhale et al.	Cefazolin	Antibiotics	Genito-urinary, respiratory tract infection
		Cefuroxime	Antibiotics	Meningitis, bone and soft tissue infection
		Prilocaine	Local anesthetic	In Dentistry
2	Engstrom et al.	Clomethiazole	Psychotropic	Insomnia
3	Engstrom et al.	2-amino-1-phenylpropanol HCl	Antidepressant	Mania, depression
		Nitroglycerin	Anti-anginal	Angina pectoris
		Oestriol	Hormonal therapy	Atrophic vaginitis, pruritus
4	Damani	Clindamycin	Antibiotics	Peritonitis, staphylococcal

		phosphate		bone and joint infection
5	Engstrom et al.	Gramicidin	Topical steroid	Corticosteroid sensitive dermatoses
		Insulin	Hypo/Hyper glycaemics	Diabetes mellitus
6	Boyd	Diazepam	Sedative-hypnotic	Anxiety, insomnia, seizures
		Rifampicin	Bactericidal antibiotic	Tuberculosis
		Griseofulvin	Antifungal	Fungal infection of skin
		Propofol	Hypnotic	Procedural sedation, to induce and maintain General Anesthesia
7	Engstrom et al.	Clotrimazole	Antifungal	vagina, mouth, & skin infection
8	Nielsen et al.	Indomethacin	NSAIDs	Gout, rheumatoid arthritis
		Isosorbide mononitrate	Anti-anginal	Angina pectoris
		Lidocaine hydrochloride	Oral prepration	Fungal infection of external ear

CONCLUSION

Either in bulk or cubosomes forms the bicontinuous cubic liquid crystalline phases offers unique properties of the particular interest for the various applications. The ability to form cubosomes either in use, during manufacture or during formulation offers greatly enhanced flexibility for the efforts of product development. The cubosomes prepared in the dispersion possess the nanometer scale structure identical to the bulk cubic phase but the dispersion itself has much lower water like viscosity. Although the bulk cubic phase has sufficient length scale to allow the controlled release of the solutes the cubosomes are too small & have the high surface area for such performance exhibiting instead burst release. As the template for the complex solid materials the contorted but regular structure of the cubic phase is also of interest to the material science researchers.

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