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The Cubic Enigma: A Tale of Cubosomes

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ABSTRACT

Cubosomes are self-assembled, nanostructured, versatile, thermodynamically stable, square and dot-like particles with cubic lattices visible. Cubosomes have honeycomb-like structure which comprises of curved bicontinuous lipid bilayer and made up of amphiphilic surfactant, lipids, and polymers. Cubosomes can be used as drug delivery carriers and it has ability to incorporate amphiphilic, lipophilic and hydrophilic drugs. Cubosomes have capacity to incorporate large molecular weight compounds and thus, considered as effective, stable and safe method of drug delivery. This article gives an overview on structure, classification, properties, components, forms, preparation methods, evaluation. Cubosomes have applications and can be given by various routes of drug administration. Anticancer agents can be given by incorporating in Cubosomes, which is found to be a very effective application. Thus, Cubosomes can be considered as a promising method of drug delivery.

INTRODUCTION:

Cubosomes are discrete, sub-micron, nanostructured particles of the bicontinuous cubic liquid crystalline phase. The term "bicontinuous" refers to two distinct hydrophilic regions separated by the bilayer. Cubosomes are micro- and nanoparticles having self-assembled cubic liquid crystalline phases [1]. The fourth state of matter is liquid crystals as it intervenes between the properties of liquids and solids. They show medium fluidity like a liquid and possess regular orientation seen in the case of solids[2]. Cubosomes are nanoparticles but instead of the solid particles usually encountered, these are self-assembled liquid crystalline particles with a solid-like rheology that provides unique properties of practical interest [3,4]. Cubosomes appear like a Dots Square shaped, slightly spherical. Each dot corresponds to the presence of pore containing aqueous phase cubic phases in lipid water system[5]. The structural behaviour of cubic nanoparticles was earlier investigated by Luzzati and Husson in the 1960's; later geometric model was provided by Scriven[6]. The "cubosomes" term was first coined by Larsson, which is like liposomes[7]. Cubosomes have honeycomb-like structures due to self-assembled surfactants[8]. Cubosomes are made up of amphiphilic surfactants, lipids, and polymers. The polymer drug compound ratios are 1:1 or 2:1 complex depending on the substance[3]. When encountering a polar solvent, amphiphilic molecules are driven to identify and assemble into a nanometre-sized liquid crystal [9]. Cubosomes are drug carrier system that enhances drug stability and target specific delivery[10]. They have cubic crystallographic symmetry, are optically isotropic, and are viscous in nature, and because of their ability to fracture, the cubic phase can produce colloidal and thermodynamically stable particle dispersions[9]. Cubosomes may be utilized to transfer various proteins into biological systems, known as proteocubosomes. Peptides and nucleic acids can be delivered with expected loading and release[11]. Three structures of cubosomes have been proposed by Luz- zati et. al.9); (i) Pn3m (D-surface) (Diamond surface), (ii) Ia3d (G-surface) (Gyroid surface), and (iii) Im3m (P-surface) (Primitive surface) [12]. Cubosomes have honeycombed (cavernous) structures whose size ranges from **10–500 nm** in diameter. And due to less particle size, cubosomes can be considered as the most potent, stable, and effective drug vehicle that carries the drug to the targeted site and enhances its bioavailability[10].

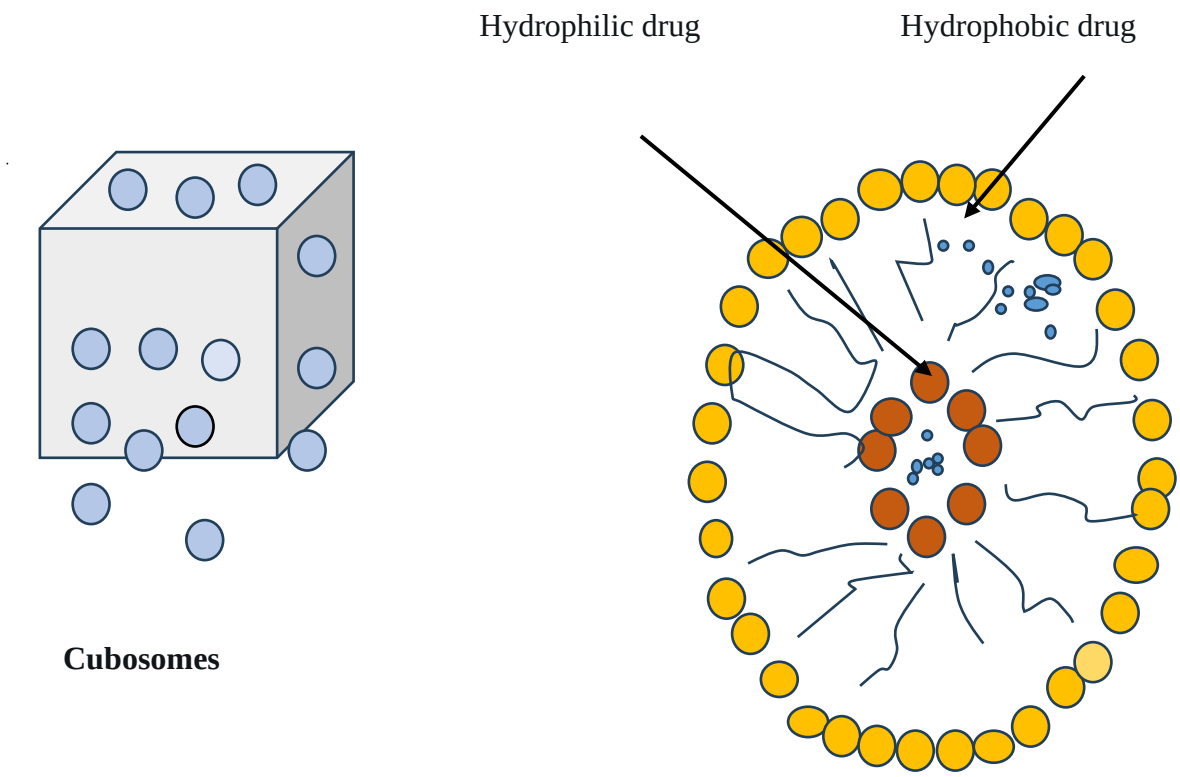


Figure 1: Diagrammatic representation of cubosomes

ADVANTAGES OF CUBOSOMES:

1. High drug loading capacity due to cubic crystalline formation.
2. It can be easily penetrated through the skin and is most widely used for topical formulation.
3. It can encapsulate hydrophilic, hydrophobic, and amphiphilic molecules.
4. The preparation process is easy as compared to other techniques.
5. The ability of the cubic phase to fracture enhances thermodynamically stable particle dispersions.
6.It is non-toxic and biocompatible.
7. Controlled and target specific drug delivery can be achieved.
8. It is economical[2,3,9].

DISADVANTAGES OF CUBOSOMES:

1. Hydrophilic drugs show minimum entrapment efficiency due to the presence of a large amount of water inside cubosomes.
2. Large-scale production on cubosomes is quite difficult due to high viscosity.

3. Drug leakage may occur during transportation [3,9].

TYPES OF CUBOSOMES:

Cubosomes mainly have two types namely liquid precursors and powdered precursors. The precursor form exists as a solid or liquid material and forms a cubic phase when encounters liquid.

1. Liquid cubosomes precursor: The hydrotrope dilution method which is used for cubosomes preparation gives stable and smaller cubosomes. In this method, monoolein which is an important component of cubosomes is dissolved in hydrotrope-like ethanol that prevents liquid crystalline formation. If this mixture is diluted, it crystallizes or precipitates to form cubosomes. This method is suitable for thermo sensitive molecules like proteins[10,13].

2. Powdered cubosomes precursors: This type of cubosomes is composed of dehydrated surfactants which are coated with polymers and which on hydration form cubosomes. The lipids used to make cubosomes are waxy, sticky solids. The water-soluble-cohesive starch coating on the waxy lipid prevents agglomeration and allows control of particle size. Spray drying is an excellent process for his purpose [10,13].

COMPONENTS OF CUBOSOMES:

Components of cubosomes include amphiphilic lipids, stabilizers, and water. Hydration of amphiphilic lipids produces cubic liquid crystalline phases. It is said that the cubic liquid crystalline phases are produced upon the hydration of amphiphilic lipids. Stabilizers prevent the conversion of reconstitution to bulk cubic phase. Depending on the composition, lipid molecular structure, electrostatic interactions, and pressure and temperature, amphiphilic lipids can self-assemble with distinct physicochemical properties and geometries. Lipids that are incorporated in cubosomes preparation usually include monoglycerides, glycol- and phospholipids, and alkyl glycerates[14].

The most common and widely used amphiphilic lipid for the formulation of cubosomes is glyceryl monooleate (GMO), which is also called monoolein and Phytantriol.

Monoolein: Monoolein is amphiphile having hydroxyl groups in the head portion and hydrocarbon chains in the tail portion. It is usually colourless and clear in nature. It occurs as a waxy yellow paste with a characteristic odour and swells in water. Monoolein is the most

widely used lipid in cubosomes preparation as its physicochemical properties provide favourable conditions in the process of cubosomes formation. It has a melting point of 35 to 37 ◦C, and can be stored at 20–30 ◦C. [2,14].

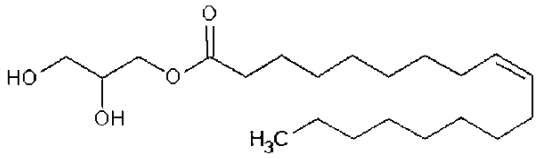


Figure 2: Chemical structure of Monoolein

Phytantriol: Cubosomes containing phytantriol as amphiphile are known to deliver the drug at a predetermined rate. Cubosomes formed by using phytantriol are found to be thermodynamically stable but are not kinetically stable due to their interaction with aqueous media. To avoid this instability, stabilizers can be included in the formulation[2,14].

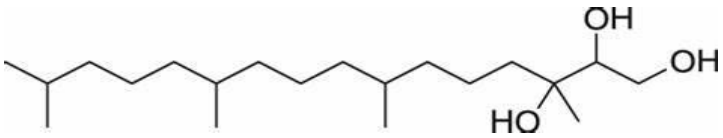


Figure 3: Chemical structure of Phytantriol

Stabilizers: Stabilizers prevent the conversion of reconstitution to bulk cubic phase. The most used materials for stabilizing cubosomes dispersion are PEO99-PPO67-PEO99 a tri-block copolymer and poloxamer 407. Cubic structured nanoparticulate dispersion is formed by adding an adequate amount of P407 [2].

Water content in cubosomes: Three different structural morphologies of cubosomes are studied namely D- surfaces, G- surfaces and P- surfaces. Among these three morphologies, D- -surfaces are formed by the monoolein water system when a high-water level is used. G-surfaces can be formed at low water levels while P- surfaces are formed only when a third component such as amphiphile block copolymer or casein is incorporated.

Table 1: Amphiphile

DRUG	AMPHIPHILE
Gambogenic acid	Monoolein
Doxorubicin	Monoolein
Rifampicin	Monoolein
Polymyxins	Phytantriol
Ketotifen fumarate	Phytantriol
Finasteride	Phytantriol

Mechanism of action: The transport of drug across the biological membrane is mainly influenced by nature of carrier's activity. Small molecules can be easily transported. Passive transportation is mainly influenced by pore size. Also, the drug is exposed to enzymatic environment when enteric absorption occurs through transcellular diffusion. Due to this exposure, the amount of drug entering systemic circulation is reduced[15].

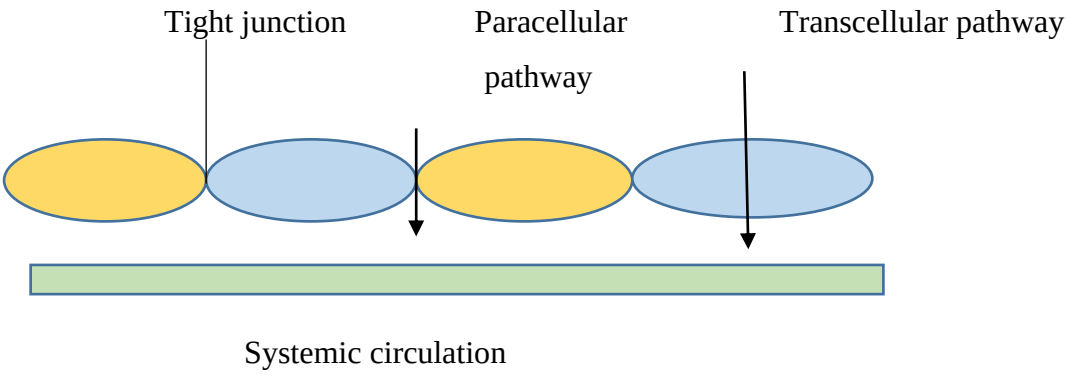
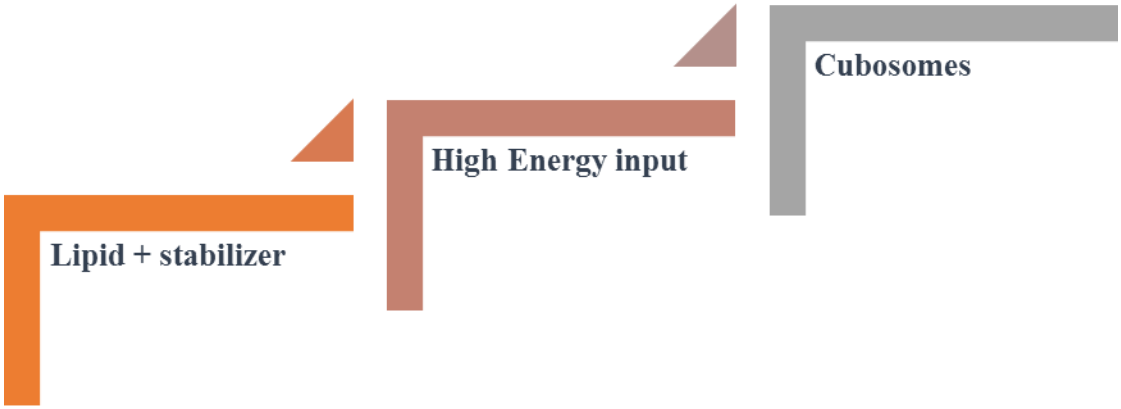


Figure 4: Mechanism of drug transport via skin

Methods of preparation: Two main approaches used to produce Cubosomes are Bottom-up technology and Top-down technology.



1] Bottom-up technology:

Bottom-up technology involves the formation of cubosomes from the process of crystallization. In this method, the cubosomes are produced from the precursors. Almgren et. al. discussed the formation of Cubosomes by dispersing micellar phase droplets in water at 80ºC, and allowing them to slowly cool, and gradually droplets get crystallize to Cubosomes. This technique is applicable for the robust preparation of cubosomes and requires less energy input[7,16,17,17].

2] Top-down technology:

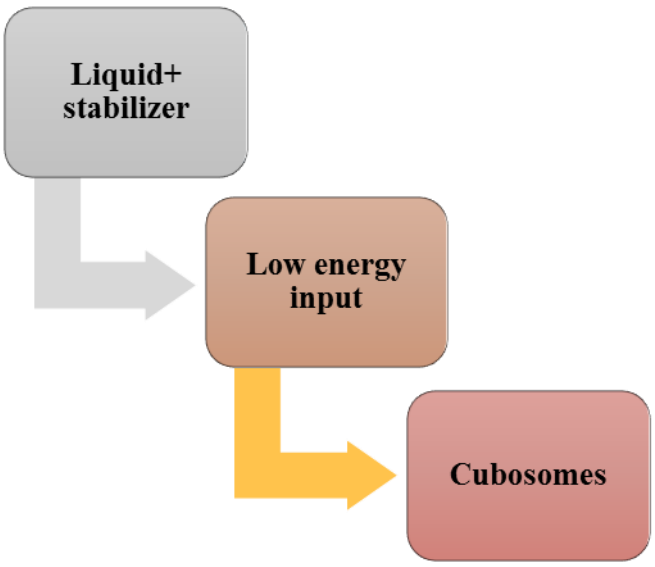


Figure 5: Top-down technology

This method is used for preparation of Cubosomes, when monoolein is used a lipid polymer. This technique requires high energy input such as process like homogenization. By adding stabilizer in lipid bulk cubic aggregates are formed and then high energy is applied to form dispersion. This method of Cubosomes preparation gives stable product and stability is for up to one year. One of the drawback of this method is that, it is not suitable for large scale batches having thermo sensitive materials like peptides and proteins [14].

Methods:

1. Automated cubosomes preparation
2. High pressure homogenization
3. Probe ultra-sonication

Automated Cubosomes preparation: This method produces large number of Cubosomes and it is similar to probe sonication method. In this process, with the help of stabilizer, gels are produced using 96 well plate having solvent capacity of 600 µl. Further sonication is carried out using probe sonicator and robotic system[7,18].

High pressure homogenization: This method is most frequently used method for cubosomes preparation. Cubosomes prepared by this method are relatively more stable. This process involves three steps namely gel preparation, shearing, High pressure homogenization.

a) Gel preparation: In this step, the breakdown of lipids and amphiphilic surfactant is carried out using organic phase. Homogenous mixture is formed and gel phase is produced[19].

b) Shearing: In this step, the gel which is produced is sheared and critical phase formation takes place just before homogenization[20].

c) High Pressure Homogenization: This step in only applicable for high volume sample. In this, the produced dispersion is homogenised in a higher pressure homogenizer[6].

Probe ultra-sonication: This method is use for production of Cubosomes have small volume (600 µl) in size. Gels are prepared using stabilizer and solvent equilibration takes place resulting in the formation of cubic phase. This cubic phase is then subjected for sonication. To avoid overheating of sample, the frequency and amplitude should be maintained[6,18].

CHARACTERIZATION OF CUBOSOMES:

Visual inspection: The cubosomes are visually observed for the optical appearance like colour, turbidity, homogeneity and presence of macroscopic particles[21].

Photon- correlation spectroscopy: Particle size distributions of cubosomes are mainly determined by dynamic laser light scattering using Zeta sizer (Photon correlation spectroscopy). The sample diluted with a suitable solvent is adjusted to light scattering intensity. The data can be collected and generally shown by using average volume weight size[3].

Transmission electron microscopy: The cubosomes can be studied by using cryogenic transmission electron microscopy (Cryo-TEM)[22]. In this technique, a beam of electrons is transmitted through an ultrathin specimen and due to this interaction image is formed Cryo-TEMs are capable of imaging at a significantly higher resolution than light microscopes, owing to the small wavelength of electrons[5].

Small Angle X-ray Scattering (SAXS): This technique is effectively use for determination of crystallographic structure of liquid crystalline phases**.** X-rays interact with the electrons in the particles and are elastically dispersed in a SAXS experiment which recognizes periodic spatial configurations of various groups in any given direction [22].

Polarized light microscopy: It is use to differentiate between the isotropic and anisotropic compounds and to determine the release of the optically birefringent surface coating of cubosomes[23].

X-ray diffraction method (XRD): This method is used to determine the crystalline structure. In this method, samples will be held in vacuum-tight cylindrical cells provided with Mylar windows. The Diffraction data are collected. The diffraction patterns are observed[23].

Stability studies: Stability assessment for particle size and drug content at different time intervals can be studied while visual inspection can be don periodically[24].

Zeta Potential: The zeta potential of cubosomes dispersions can be analysed by using zeta sizer at 25 °C. The samples can be kept in the polystyrene cuvette and a zeta dip cell was used to measure the zeta potential. If the zeta potential of the formulations is > or<30mv. It is assumed that the formulations are stable without any aggregation[6,25].

Entrapment Efficiency:

The entrapment efficiency of prepared cubosomes formulation can be observed by centrifugation method. A centrifugation can be carried out at 10000 rpm for 1 hour at controlled temperature. Supernatant containing unentrapped drug in cubosomes can be separated and measured by a UV spectrophotometer[25]. The remaining entrapped drug in the cubosomes can be measured after rupturing it by using Triton X 100.

$$\% \text{ Entrapment efficiency} = \frac{\text{Total drug content} - \text{Drug content in supernatant}}{\text{Total drug content}} \times 100$$

Viscosity: The viscosity is determined by the different angular velocities at 250 C using (Brookfield) Viscometer by keeping the rotation speed at 20 rpm. The averages three reading are taken for the calculation of viscosity**.**

Measurement of drug release: The amount of drug release from cubosomes is measured by using pressure ultrafiltration method [21].

APPLICATIONS:

Oral: Oral route of drug administration is always associated with poor absorption, low therapeutic windows, large molecular and all of these problems can be overcome by formulating Cubosomes. Larger molecules such as proteins can be encapsulated in Cubosomes and can be given by oral route[7]. **Clopidogrel bisulphate is** a first line antiplatelet drug for treatment of myocardial infarction and stroke. But it has poor solubility and efficacy and hence, cubosomes nanoparticles loaded with Clopidogrel bisulphate was found to be effective [26]. Oral administration of amphotericin B has boor bioavailability. AmB-loaded Cubosomes by using the SolEmuls was found to be effective approach for bioavailability enhancement [19].

Intravenous: The internal liquid crystal structure of the curved lipid membrane is used to solubilize and to deliver the loaded drug at specific site. Cubosomes increases payload of large molecules such as protein and peptides making them ideal carrier for injectable[27,23].

Ophthalmic drug delivery: In order to overcome the challenges faced due to conventional dosage form ophthalmic Cubosomes was developed with aim to enhance corneal permeability and bioavailability. Topical formulation of Beclomethasone dipropionate was

reported with poor solubility and limited pre-corneal residence time result in insufficient drug penetration. Hence to enhance the residence time and ocular bioavailability ophthalmic Cubosomes was formed [sherifA]. Acetazolamide is a drug of choice in treatment of glaucoma in case of emergency but it has poor aqueous solubility and low corneal permeability. Acetazolamide loaded Cubosomes was found to increase therapeutic efficacy[28].

Topical: Cubosomes was found to be very effective in topical application because Cubosomes contains ethanol which enhances skin permeability. Nature of Cubosomes is very bio adhesive and it also protects from skin sensitivity[7]. Clotrimazole is a broad-spectrum antimycotic that widely used to treat fungal infections topically and developing cubosomes preparation was most promising and effective drug delivery[29]. Topical hydrogel containing ketoconazole Cubosomes was prepared using 'Quality by Design' approach. Sustained drug release was observed in this formulation[30]. Methotrexate cubosomes is a novel medication delivery in rheumatoid arthritis treatment. The formulations were found to be promising in terms of its characterization parameters like particle size, zeta potential, entrapment efficiency, loading capacity, release kinetics, and stability, suitable for topical delivery[31].

Cubosomes as drug delivery vehicle: Some companies (L'Oreal& Nivea) are trying for the cosmetic formulation (O/W emulsion stabilizers, pollutant absorbents, etc.), which consists of the use of cubosomes[6,7].

Cancer therapy: Cubosomes are most commonly used in cancer therapy, because they possess greater entrapment efficiency for hydrophobic drugs compared to liposomes, while also exhibiting high stability due to their bicontinuous structure and steric polymer-based stabilization. In the past decade, there has been significant interest in cubosomes due to their ability to deliver therapeutic and contrast agents for cancer treatment and imaging with minimal side effects, establishing them as a safe and effective approach[32]. When drug is used alone it fails to detect cancer cell but when it is enclosed in cubosomes it differentiate cancer cell from normal cells. Anticancer agents enclosed in Cubosomes has less side effects and more therapeutic efficacy[33].

DRUG	POLYMER	STABILIZER	RESULT
Paclitaxel	GMO	Pluronic F127	Safety and efficacy
Doxorubicin	GMO	Pluronic F127	Therapeutic efficacy
Lumefantrin	GMO	Poloxamer	Greater anticancer action than drug alone
5- Fluorouracil	Phytantriol	Pluronic F127	Effective
Cisplatin	GMO	Pluronic F127	Decrease cytotoxicity

Current development: Cubosomes are considered as stable, most promising and biocompatible drug delivery system. Cubosomes have become topic of interest for pharmaceutical, cosmeceutical and personal care industries. Due to their cost effectiveness can be used as vehicle for drug delivery. Cubosomes can be used in effective treatment of brain targeted drug delivery and to achieve controlled release drug delivery in cancer therapy[34,35]. Cubosomes which are pH sensitive offers new opportunities for cancer therapy and can be given by oral as well as topical route. Cubosomes provide larger surface area as a carrier and thus, incorporation of larger molecules like proteins and peptides are possible. In coming years, high molecular weight proteins and peptides loaded in cubosomes will be able to generate antibodies have controlled release pattern.

CONCLUSION:

Bicontinuous cubic liquid crystalline phases offers interest in various applications. It is possible to form cubosomes during use, or during formulation or manufacturing process which gives flexibility during product development. As cubosomes have smaller particle size, offers greater pharmacological and therapeutic activity. Two methods such as top down and bottom-up approaches could be easily employed to produce cubosomes either by ultra-sonication techniques or high-pressure homogenization. Cubosomes are applicable to wide range of drug candidates, proteins, immune substances and also to cosmetics. Owing to their various advantages, they have application in various types of drug delivery. Anticancer treatment can be considered as the powerful treatment by using cubosomes as carrier because they differential normal cells from cancerous cells. Thus, cubosomes are versatile, stable and biocompatible drug delivery.

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