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Review Article

Cubosomes: The Inimitable Nanoparticulate Drug Carriers

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Abstract: Cubosomes consist of honeycombed (cavernous) structures separating two internal aqueous channels and a large interfacial area. Cubosomes are nanoparticles which are self assembled liquid crystalline particles of certain surfactants with proper ratio of water with microstructure that provides unique properties of practical interest. Bicontinuous cubic liquid crystalline phase is optically clear and very viscous material has the unique structure at nanometer scale. The word bicontinuous refers to the division of the two continuous but non-intersecting aqueous regions by lipid bilayer that is twisted into space filling structure. Hydrating a surfactant or polar lipid that forms cubic phase and then dispersing a solid like phase into smaller particles usually forms a cubosomes. Self-assembled cubosomes as active drug delivery systems are receiving more and more attention and interest after the first discovery and nomination. They exhibit different internal cubic structure and composition with different drug-loading modalities. It has high internal surface area and cubic crystalline structures, relatively simple preparation method, biodegradability of lipids, the ability of encapsulating hydrophobic, hydrophilic and amphiphilic substances, targeting and controlled release of bioactive agents. Cubosomes are having wide range of applications in various fields and they can be characterized by various evaluation parameters. So, Cubosomes are gaining more attention by pharmaceutical development sector.
Keywords: Cubosomes; Monoleins; Cubic phase; Liquid crystals

INTRODUCTION

Cubosomes are discrete, sub-micron, nano-structured particles of bicontinuous cubic liquid crystalline phase. Cubosomes possess the same microstructure as the parent cubic phase but have larger specific surface area and their dispersions have much lower viscosity in comparison to the bulk cubic phase [1]. Lipids, surfactants and polymer molecules have both polar and non polar components, termed as amphiphilic. The hydrophobic effect drives amphiphilic molecules in polar solvents to spontaneously self assembling in to an array of thermodynamically stable liquid crystalline phases with lengths on nanometer scale. An example is the bicontinous cubic liquid crystalline phase. Bicontinous cubic phases are optically isotropic, very viscous and solid like liquid crystalline substance having cubic crystallographic symmetry [2].

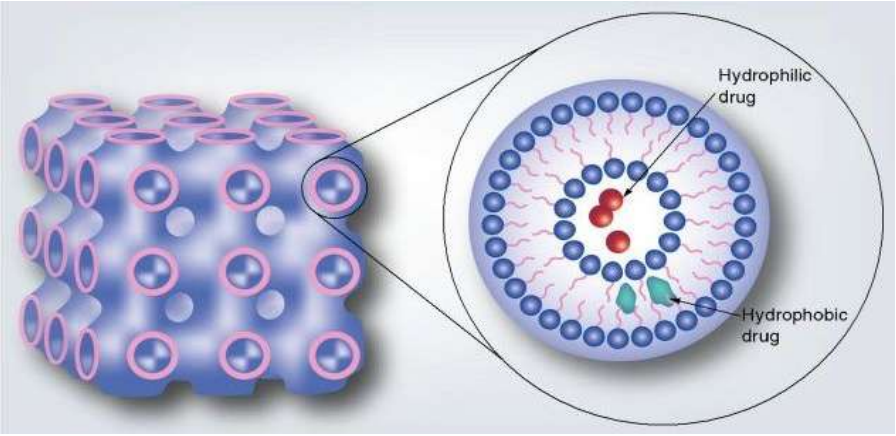

Fig. 1: Cubosomes exhibiting its cavernous internal and cubic structure and its membrane composition with different drug loading modalities

Cubosomes are nanoparticles, more accurately nanostructure particles of a liquid crystalline phase with cubic crystallographic symmetry formed by the self assembly of amphiphilic or surfactant like molecules [3]. However, the cubic phases possess a very high solid like viscosity, which is a unique property because of their intriguing bicontinuous structures which enclose two distinct regions of water separated by a controlled bilayer of surfactant [4]. As a result, the cubic phases can be fractured and dispersed to form particulate dispersions that are colloidally and/or thermodynamically stable for longer time [3]. Cubosomes have a great potential in drug nano-formulations.

Advantages of Cubosomes [5, 6]

- High drug payloads due to high internal surface area and cubic crystalline structures.
- Relatively simple method of preparation.
- Biodegradability of lipids.
- Capability of encapsulating hydrophilic, hydrophobic and amphiphilic substances.
- Targeted release and controlled release of bioactive agents.

While most liquid crystalline systems transform into micelles at higher levels of dilution, cubosomes remain stable almost 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. Cubosomes are typically produced by high energy dispersion of bulk cubic phase [7], followed by colloidal stabilization using polymeric surfactants [9]. After formation, the dispersion is formulated into a product and is then applied to a substrate, usually skin or mucosal surface. After that materials are either absorbed or released via diffusion [1].

HISTORY

Despite the early recognization (in 1980) large scale manufacture of cubosomes was difficult due to their complex phase behavior and viscous properties. The cubic phases are unique as possess very high solid like viscosities because of their intriguing bicontinuous structures [10]. Cubic phases can be fractured and dispersed to form particulate dispersions which are colloidally and/or thermodynamically stable for longer period of time. Certain surfactants spontaneously form cubic phases when mixed with water above a certain concentration. Determination of their 'honeycomb' structure was carried out by Luzzati and Husson [11], Luzzati *et al*. [12] , Larsson [13] and Hyde et al. [14] between 1960 and 1985.

The term 'Cubosomes' were coined by Larsson, that reflects the cubic molecular crystallography and similarity to liposomes [15].

Effort to develop scalable processes to produce cubosomes in large scale is under development. A few anticancer drugs have been successfully encapsulated in cubosomes and characterized [15].

MECHANISMS OF DRUG TRANSPORT

Drug transportation across the biological membrane is dependent on the nature of the activity and composition of the carrier, the anatomy and physiology of the skin. Small ions are transported through the hair follicles, pores of skin membranes, the tight junctions without much complex mechanism. Mechanisms involved in skin membrane transport generally involve in intra (*trans*) and inter (*para*) cellular transports. By manipulating carriers, drugs can be incorporated either in the core or as an integral part of the vesicles [15].

Paracellular diffusion is the movement of drug across a membrane by going between, rather than through, two cells. By definition, this process is solely passive and is dependent upon pore size, as well as the size and shape of the xenobiotic. Transcellular diffusion is the movement of a drug across the cell. When intestinal absorption occurs by transcellular diffusion, the drug is exposed to the enzymes within the cell, as well as any efflux pumps that are present on the apical region of the membrane. These may result in a reduction in the amount of drug that reaches the systemic circulation. Transcellular diffusion may be passive, facilitated, or active [16].

Transcellular movement, which involves the passage of drug through cells, is the most common route of drug transport. Some drugs, however, are too polar to pass across the lipoidal cell membrane and for them only the paracellular pathway, between the cells, is generally available [17].

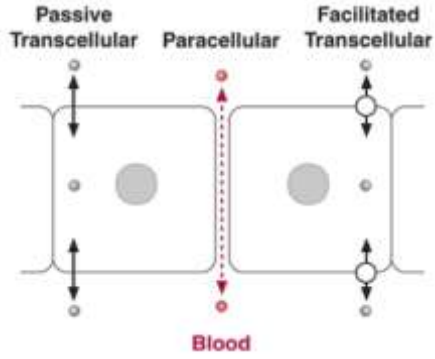

Fig. 2: Paracellular and Transcellular Transports

Structure of Cubosomes

Cubosomes have honeycombed (cavernous) structures whose size range from 10–500 nm in diameter. They appear like dots, which are slightly spherical in structure. Each dot corresponds to the presence of pore containing aqueous cubic phase in lipid water system. It was first identified by Luzzati and Husson using X-ray scattering technique [15].

Liquid Cubosome Precursors

The hydrotrope dilution process is found to produce smaller, more stable cubosomes. Particles are formed by nucleation and growth, as employed in crystallization and precipitation processes. This is achieved by dissolving the monoolein in a hydrotrope, such as ethanol, that prevents liquid crystalline formation. Subsequent dilution of this mixture spontaneously "crystallizes" or precipitates the cubosomes. quid precursor process allows for easier scale up of cubosome preparations and avoids bulk solids handling and potentially damaging high energy processes [18, 19].

Powdered Cubosome Precursors

Powdered cubosome precursors are composed of dehydrated surfactant coated with polymer. Such powders offer advantages to liquid phase hydrotropic cubosome precursors. Hydration of the precursor powders forms cubosomes
with a mean particle size of 600 nm, as confirmed by light scattering and cryo-TEM [20]. The lipids used to make cubosomes are waxy, sticky solids. Water-soluble non-cohesive starch coating onthe waxy lipid prevents agglomeration and allows control of particle size. Spray drying is an excellent process for his purpose [19].
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MANUFACTURING OF CUBOSOMES

Cubosomes can be manufactured by two distinct methods:

Top down Technique

It is the most widely used procedure initially reported in 1996 by Ljusberg- Wahren [15]. Bulk cubic phase is first produced and by application of high energy such as high pressure homogenization it is processed into cubosomes nanoparticles. Bulk cubic phase resembles a clear rigid gel formed by water-swollen cross-linked polymer chains. The cubic phases differ in that they are a single thermodynamic phase and have periodic liquid crystalline structure. Cubic phases ruptures in a direction parallel to the shear direction, the energy required is proportional to the number of tubular network branches that rupture [22].

Bottom up Technique

In this cubosomes are allowed to form or crystallize from precursors. The bottom-up approach first forms the nanostructure building blocks and then assembles them into the final material. It is more recently developed technique of cubosome formation, allowing cubosomes to form and crystallize from precursors on the molecular length scale.

The key factor of this technique is hydrotrope that can dissolve water insoluble lipids into liquid precursors. This is a dilution based approach that produces cubosomes with less energy input when compared to op down approach [15].

METHODS FOR CHARACTERIZATION AND EVALUATION OF CUBOSOMES

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 of about 300 Hz and measured at 25 °C in triplicate. The data can be collected and generally shown by using average volume weight size. The zeta potential and polydispersity index can also be recorded [23, 24].

Polarized light microscopy

Polarized light microscopy can be used reveal the optically birefringent (possibly vesicular) surface coating of the cubosomes and also can distinguish between anisotropic and isotropic substances [25].

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

Entrapment efficiency and drug loading of cubosomes can be determined using gel permeation chromatography or ultra filtration techniques. In the later technique, unentrapped drug concentration is determined, which is subtracted from the total drug added. The amount of drug is analyzed by using UV spectrophotometer or HPLC analysis [23].

X-ray scattering

Small angle X-ray scattering (SAXS) can be used to identify the spatial arrangements of different groups in the sample. The diffraction patterns obtained are converted to plots of intensity versus q value, which enable the identification of peak positions, and their conversion to Miller Indices. The Miller Indices could then be correlated with known values for different liquid crystalline structures and space groups to identify the dominant internal nanostructure of the sample [26, 27].

Transmission electron microscopy

Transmission electron microscopy can be used to view the shape of the cubosomes. Kim et al. described that the suspensions of cubic phase nanoparticles were negatively stained with freshly prepared phosphotungstic acid solution (2%, pH 6.8) and were transferred onto a formvar/carbon coated grid (200 mesh), air dried at room temperature. The electron microphotographs were taken on an electron microscope [28]. SEM analysis may not be performed on cubosomes or some vesicular systems since the integrity and robustness of the formulation may be lost during the procedure while exposing to electron array.

Pressure Ultrafiltration Method

Drug release measurement of cubosomes can be done by pressure ultrafiltration method. It is based closely on

that proposed by Magenheim et al. using an Amicon pressure ultrafiltration cell fitted with a Millipore membrane at ambient temperature (22±2) °C [29].

Stability studies

The physical stability can be studied 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 to evaluate the possible variations by time [30].

APPLICATIONS OF CUBOSOMES

Controlled release of drugs

Control release of solubilised substance is the most popular application of cubosomes. Cubic phase is more applicable for control release because of its small pore size (5-10nm), ability to solubilise hydrophilic, hydrophobic, amphiphilic molecules and its biodegradability by simple enzymes [31].

Melanoma (cancer) therapy

Recently few anticancer drugs have been successfully encapsulated in cubosomes and characterized physicochemically. The unique structure of this promising nanocarrier suggests its application in melanoma therapy [32].

Oral drug delivery

Cubosomes address the varied challenges in oral delivery of numerous promising compounds including poor aqueous solubility, poor absorption, and large molecular size. These are both liquid and powder in capsule products comprising our self emulsifying liquid crystalline nanoparticles technology (LCNP). In an alternative application large proteins have been encapsulated for local activity in the gastrointestinal tract. Liquid crystalline nanoparticles technology carriers can be combined with controlled release and targeting functionalities. The particles are designed to form in situ in a controlled rate, which enables an effective *in vivo* distribution of the drug. Liquid crystalline nanoparticles technology carriers can also be released at different absorption sites, for example in the upper or lower intestine, which is important for the drugs that have narrow regional absorption window [33].

Intravenous drug delivery systems

Lipid nanoparticles comprising interior liquid crystal structures of curved lipid membranes are used to solubilize encapsulate and deliver medications to disease areas within the body. While emulsions and liposomes have found use as intravenous carriers in drug products, liquid crystal nanoparticle structures increased payloads of peptides, proteins and many insoluble small molecules, and are ideal carriers for injection or infusion of many actives [34].

Topical drug delivery systems

Cubic phases are more bioadhesive in nature, so that they can conveniently use in topical and mucosal depositions and delivery of different drugs. Topical delivery systems are based on the exploitation of unique properties of liquid crystal (LC) and liquid crystal nanoparticle (LCNP) technologies. Topical drug delivery systems are unique in situ forming bioadhesive LC systems facilitate controlled and effective drug delivery to mucosal surfaces (buccal, ophthalmic, vaginal and others). This fascinating system forms a thin surface film at mucosal surfaces consisting of a liquid crystal matrix which nanostructure can be controlled for achieving an optimal delivery profile and provides good temporary protection of sore and sensitive skin [35].

Current application

An application area under current development by L'Oreal is the use of cubosome particles as oil-in-water emulsion stabilizers and pollutant absorbents in cosmetics [19].

CONCLUSION

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

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