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Original Article

Cubosomes : Novel Emerging Drug Delivery System

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ABSTRACT

C*ubosomes 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. Conventional anticancer agents often fail because of their inability to distinguish cancer cells from normal cells resulting in severe toxic side effects. Cubosomes have the potential to improve the biodistribution of anticancer drugs by protecting them from degradation, delivering them directly to the tumor site. Cubosomes have potential in drug nano formulations for cancer therapy because of their advantages which include high drug loading capacity as they provide large internal surface area structures, simple preparation method, ability of encapsulation of hydrophobic, hydrophilic and amphiphilic drug, targeted and controlled release of many drugs.*

Keywords: *Cubosomes, Nanoparticle, Cubic phase, Precursor, Liquid crystals, Melanoma*

1. INTRODUCTION:

Cubosomes are discrete, sub-micron, nano-structured particles of bicontinuous cubic liquid crystalline phase. Cubosomes have 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]. The ability of cubic phases to exist as discrete dispersed colloidal particles, or cubosomes is perhaps the most intriguing [2]. Whereas most concentrated surfactants that form cubic liquid crystals lose these phases to micelle formation at high dilutions, a few surfactants have optimal water insolubility. Their cubic phases exist in equilibrium with excess water and can be dispersed to form cubosomes. Cubosomes are produced by high-energy dispersion of bulk cubic phase, followed by colloidal stabilization using polymeric surfactants. After formation of the cubosomes, the dispersion is formulated into a product [3].

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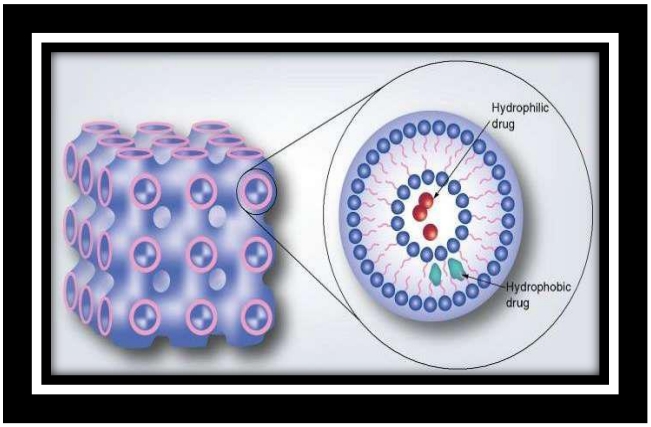

Fig. 1: Structure of Cubosomes

Cubosomes provides large surface area, low viscosity. They have high heat stability and are capable of carrying hydrophilic and hydrophobic molecules[[4]. Bulk cubic phase is formed by hydration of monoolein at levels between 20-40% w/w. Cubic phase is unique and desirable as a result of its mesoscale structure: a contorted lipid bilayer separating two continuous but nonintersecting water regions [5,6]. The tortuous structure of bulk cubic phase offer controlled release of solubilized active ingredients [7] Cubosomes may show burst release because of their sub-micron length scales [8]

1.1. Advantages of Cubosomes Equipment and Reagent:

1. High drug loading due to high internal surface area and cubic crystalline structures.

2. Simple method of preparation.

3. Biodegradable lipids.

4. Capable of encapsulating hydrophilic, hydrophobic and amphiphilic substances.

5. Targeted and controlled release of bioactive agents.

6. The cubic phases of cubosomes can be fractured and dispersed to form particulate dispersions that are colloidally and/or thermodynamically stable for longer time.

1.2. Disadvantages of Cubosomes.

Because of high viscosity large scale production is sometimes difficult.

1.3. STRUCTURE

Cubosomes are nanoparticles of a liquid crystalline phase with cubic crystallographic symmetry formed by the self assembly of amphiphilic or surfactant like molecules. The cubosomes having high internal surface area along with cubic crystalline structures. The cubic phases have high solid like viscosity because of their intriguing bicontinuous structures which enclose two distinct regions of water separated by a controlled bilayer of surfactant. Amphiphilic molecules form bicontinuous water and oil channels, where "bicontinuous" refers to two distinct hydrophilic regions separated by the bilayer. The interconnectedness of the structure results in a clear viscous gel similar in appearance and rheology to cross-linked polymer hydrogels.

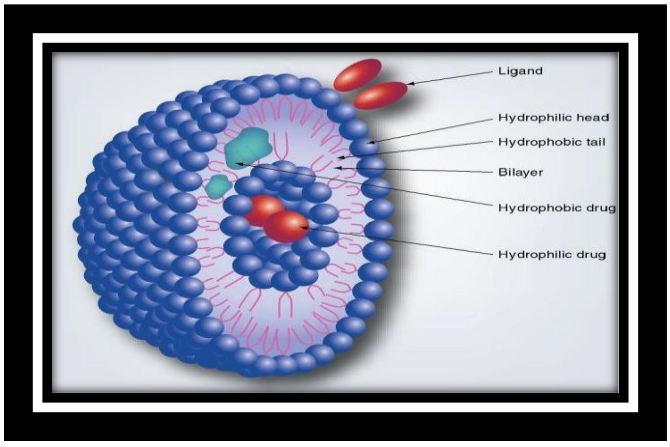

Fig. 2: Honeycombed structure of cubosomes

2. PRECURSOR OF CUBOSOME:

2.1. Liquid Cubosome Precursors:

The hydrotrope dilution process forms smaller, more stable cubosomes. Particles are formed by nucleation and growth, as employed in crystallization and precipitation processes. This is achieved by dissolving the mono-olein in a hydrotrope, such as ethanol, that prevents liquid crystalline formation. Subsequent dilution of this mixture spontaneously crystallizes or precipitates the cubosomes. Liquid precursor process offers easy scale up of cubosome preparations and avoids bulk solids handling [11, 12].

2.2. Powdered Cubosome Precursors:

Powdered cubosome precursors consist of dehydrated surfactant coated with polymer. Such powders provide benefits to liquid phase hydrotropic cubosome precursors. Hydration of the precursor powders forms cubosomes with a mean particle size of 600 nm [13]. The lipids used to make cubosomes are waxy, sticky solids. Water-soluble non-cohesive starch coating on the waxy lipid prevents agglomeration and allows control of particle size. Spray drying is an excellent process for this purpose [12].

3. METHOD OF PREPARATION OF CUBOSOMES

Cubosomes can be manufactured by following two methods:

3.1. Top down Technique

Bulk cubic phase is first produced by high pressure homogenization and then it is processed into cubosomes. Bulk phase is similar to a clear rigid gel formed by water-swollen cross-linked polymer chains. The cubic phases differ than the bulk phase as they are a single thermodynamic phase and have periodic liquid crystalline structure. Cubic phases ruptures in a direction parallel to the shear direction[14].

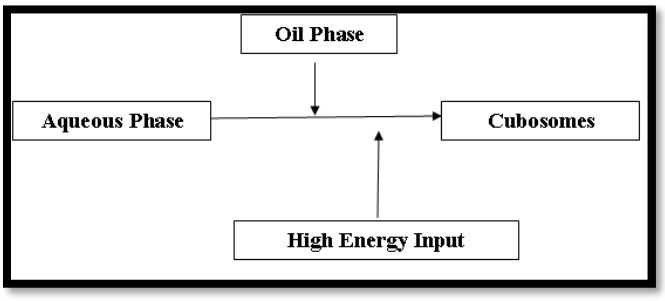

Fig 3: Top down technique

3.2. Bottom up Technique

In this technique cubosomes are allowed to crystallize from precursors. There is first formation of nanostructure building blocks and then assembles them into the final material. It is more recently developed technique allowing cubosomes to form and crystallize from precursors. The main factor of this technique is hydrotrope that can dissolve water insoluble lipids into liquid precursors. [15].

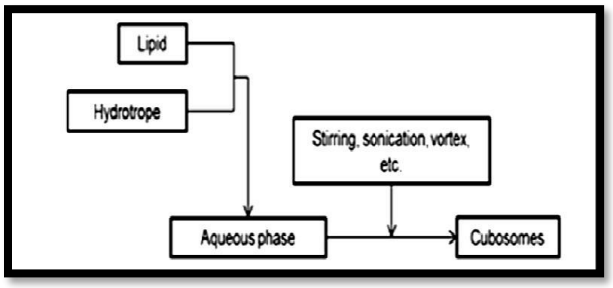

Fig 4: Bottom up technique

4. METHODS FOR CHARACTERIZATION AND EVALUATION OF CUBOSOMES

4.1. 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 [17,18].

4.2. 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 [18].

4.3. 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 [19,20].

4.4. 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 [21].

4.5. 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 [22]. 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.

4.6. 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 [23].

4.7. 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 [24].

5. APPLICATIONS OF CUBOSOMES [25-27]

5.1. Oral drug delivery

Cubosomes have the varied challenges in oral delivery of many promising compounds such as poor aqueous solubility, poor absorption, and large molecular size. Proteins have been encapsulated for local activity in the gastrointestinal tract. The particles are designed to form in situ in a controlled rate, which enables an effective in vivo distribution of the drug. Cubosomes can also be targeted in the upper or lower intestine, which is important for the drugs that have narrow regional absorption window.

5.2. Cancer therapy

Recently some anticancer drugs have been encapsulated in cubosomes. In order to target nanomedicines to tumours passive and active targeting of cancer cells having been shown to be valid approaches in preclinical and clinical studies. Passive targeting is largely dependent on the ability of a drug nanocarrier to exhibit an increased circulation lifetime

resulting in enhanced accumulation at the target site. The most common modification used to evade macrophage capture and increase circulation time is accomplished by making the nanoparticle surface hydrophilic through the addition of a polyethylene glycol(PEG) coating on the surface. Active targeting uses specific ligands such as peptides or antibodies that bind to molecules specifically expressed or over expressed on target cells. Thus, active targeting does not actually improve overall accumulation at the tumour site.Transferrin and folate ligands are two examples of commonly used active targeting moieties in nanomedicine formulations targeting tumours.

5.3. Intravenous drug delivery

Lipid nanoparticles consisting of interior liquid crystal structures of curved lipid membranes are used to solubilize encapsulate and deliver drugs to disease areas within the body. Liquid crystal nanoparticle structures increased loading capacity of many insoluble small drug molecules, peptides, proteins and are ideal carriers for injection or infusion of many actives.

5.4. Topical drug delivery

Cubic phases are bioadhesive in nature therefore they can be used in topical and mucosal delivery of many drugs. Topical delivery systems exploits unique properties of liquid crystal (LC) and liquid crystal nanoparticle (LCNP) technologies. Topical drug delivery systems are in situ forming bioadhesive LC systems which enable controlled and effective drug delivery to mucosal surfaces This system forms a thin surface film at mucosal surfaces for achieving an optimal delivery.

5.5. Drug delivery vehicle

Drug delivery vehicle is a common application for such new materials. Self-assembled surfactant phases have been tested for compatibility with many active ingredients.The number of research in association with cosmetic companies are trying for the use of cubosome particles as oil-in-water emulsion stabilizers and pollutant absorbents in cosmetics.

5.6. As sustained release behavior

The cubic phase provides a vehicle for several in vivo delivery routes namely depot, transdermal, mucoadhesion and ophthalmic. Because of fusogenic property of monoolein it increases the penetration of macro molecules. A variety of drugs with different physicochemical properties have been incorporated in cubosomes and their sustained release behavior was also studied. Monoglyceride based cubosome dispersion can be used for topical use, such as for percutaneous or mucosal applications.

5.7. In treatment of viral diseases

Monoglycerieds because of their microbicidal properties could be used to design intravaginal treatment of sexually transmitted diseases caused by viruses Because of similarity between the cubic phase structure and the structure of the stratum corneum, there may be formation of mixture of cubosomal monolein with stratum corneum lipids. This interaction might lead to the formation of a cubosome depot from which drug can be released in a controlled fashion. The cubosome technology is used to develop a synthetic vernix– the cheesy white substance that coats infants in late gestation – to help premature infants who are born without it. The vernix is a complex mixture of lipid (fats), proteins and water. It is formed late in gestation and has an integral role in normal skin development.

5.8. Controlled-Release Drug Delivery

Cubic phase can provide controlled release because of its small pore size and its ability to solubilize hydrophobic, hydrophilic and amphiphilic molecules. Cubic phase is bioadhesive and can be used as skin penetration enhancer therefore may have excellent compatibility with topical and mucosal deposition and delivery of active drug molecules. Despite the potential of bulk cubic phase as a delivery vehicle, some applications are not compatible with the extremely high viscosity of the bulk cubic phase and require the use of cubosomes.

6. CURRENT APPLICATION

1. 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.

2. In melanoma therapy

7. CONCLUSION

Cubosomes are nanoparticles which provide large surface area and also they have capability of encapsulating hydrophilic and hydrophobic drugs they can be used as a effective nanocarrier drug delivery system in treatment of cancer. Cubic phase materials can be formed by simple combination of biologically compatible lipids and water and are thus well suited for pharmaceutical and body tissue. As cubosomes offer targeted and controlled drug delivery they can be potentially used for drugs with short half-life .Because of their strong bioadhesive property they have wide applicability in mucosal and topical drug delivery. The ability to form cubosomes either in use, during formulation, or during manufacture offers greatly enhanced flexibility for product development efforts. The precursor forms enhance its further scope in technological field. Moreover, the literature reviews also specifics cubosomal utility as a controlled release drug carrier.

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