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CUBOSOMAL TECHNIQUE: A REVIEW
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Abstract

“CUBOSOMES” are nanoparticles but instead of solid particles usually encounter cubosomes are self assemble liquid crystalline particles with a solid like rheology and provide unique properties of practical intrest. It is nothing but a honey comb (cavernous) structure separating two internal aqueous channel and large interfacial area. In cubosomes exhibit different internal cubic structure and composition with different drug loading modalities with simple mixing of surfactant and drug homogenization in suitable 8000-10000 rpm. The over all cubosomes have great potential in drug nano-formulation for melanoma theraphy owing to their potential advantages including high drug load due to high internal surface area and encapsulation of hydrophobic, hydrophilic, ampiphilic substance.

Key Words: Cubosomes, Surfectant, Hydrophobic, Hydrophilic, Ampiphilic.

I. Introduction

Cubosomes are nano particle more accurate nano structured particles of biocontinous cubic liquid crystalline phase. cubosomes possess the same microstructure as the parent cubic phase but have much larger specific surface area and their dispersions have much lower viscosity then the bulk cubic phase ¹. The relative insolubility of cubic phase forming lipid in water allows cubosomes to exist at almost any dilution level as opposed to most liquid crystalline system that transform in to micelles at higher level of dilution. The cubic phase posses a very high solid like viscosity, which is unique property. The bicontinuous nature of such cubic phase differentiate them from the miceller or discontinuous cubic containing micelles packed in cubic symmetry ⁵. A special property of cubic phase formed by certain classes of amphiphiles is their ability to be dispersed in to particles, termed as cubosomes. One of the best characterized system

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glycerylmonooleate water. eg two main forms of the bicontinuous cubic phase. The bicontinuous arrangement minimizes stress and free energy and produced bicontinuous water and oil domains with an extremely high surface area and the order of 400m$^2$/g of cubic phase. The monoglyceride base cubic gels posses significantly more long range order then hydrogel and because of their composition excellent biocompatibility. The particular properties of mono glyceride base cubic phase. Temperature, stability, bicontinuous structure, high internal surface area, solid like viscosity, low cost raw material, make them desirable for consumer product and pharmaceutical industrial application. Despite intense interest in cubosomes application it is found no work examine the practical aspect of large scale processing and production of cubosomes.

**Cubic phase structure and its mechanism:**

Cubosomes are nano particles whose size range 10-500nm in diameter they appear like dots square shape, slightly spherical. Each dot corresponds to the presence of polar containing aqueous phase cubic phases in lipid water system in X-ray scattering technique was first indentified. 

**Monoolein**

![Structure of monoolein](image)

**Properties:**

- Melting point: 35-37%
- FEMA: 2526
- Flash point: 180
- Storage temperature: 20
- Solubility: Chloroform 50mg/ml clear colorless.
The cubic phases are found to be sandwiched between lamellar and hexagonal liquid crystalline phase, especially in non ionic surfactant system. The monoolein-water system uniquely possesses a cubic phase region containing broad composition and temperature range. But surfactant packaging concept are more approaching normally monoolein has continuous hydrophilic headed and hydrophobic tail. Produced reversed or inversed cubic phase indicating phases towards the polar medium so that cubic phases are determine in different geometry in that P-shape, G-surface, D-surface. 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. The tortuous structure of bulk cubic phase provides controlled release of solubilized active ingredients, while cubosomes exhibit burst release because of their sub-micron length scales. Cubosomes have been patented for use as active delivery vehicles, emulsion stabilizers, and pollutant scavengers in various pharmaceutical and personal care products. 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 and inter cellular transports. By manipulating carriers, drugs can be incorporated either in the core or as an integral part of the vesicles. 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 trans cellular 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. The polar lipids used in formation of glycercylmonooleate. It has polar headed compound of the glycercyl moiety and lipophillic tail represented by the C18 chain containing single double bonded C9. GMO is non irritant and non toxic material. It is lipophillic with very low solubility and HLB range between 3 and 4. Inside the body, it could be degraded by lipase enzyme. It not suitable for IV injection due to its hemolytic effect.
Types:

**Liquid Cubosome Precursors:** There is difficulty and expense of high shear dispersion of viscous bulk cubic phase to form cubosomes because it aggressive process of manufacturing high energy process and expensive difficult to scale up and harm ful to the fragile temperature sensitive active ingredient like protin. In cubosomes a strong driving force are exist for development of liquid phase to cubosomes to avoid the high energy processing and produced them insitu. hense the hydrotrophy dilution process are found to be consistently whichproduced smaller more stable cubosomes the paricles and growth are employed by nucleation crystallization and precipitation method. 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.

**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. 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 his purpose the encapsulation of particles are done. The process provide easy rout to preload active drug in to cubosomes prior to driving. Spray-drying experiments are required a PulvisBasic Unit. That is a cylindrical chamber having a cyclone collector and airexisted. The nozzle having liquid orifice size of 0.1 cm that is used to encorporateliquid to spray-dried into the top of the spray-dryerbody. The air pressure having the 300 kPa is pump by which orifice size is 0.25-cm. Drying of liquid feed done by the heated, drying air at 200°C that flows down and passes to the nozzle. That prevent any oxidation of themonoolein at the elevated temperatures and liquid crystalline material are form that provide the high shear to disperse the high-viscosity.

**Cubosomal Application.**

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

Relatively simple method of preparation.
Control released of solublized substance is the most popular application of cubosomes.

It provides the drug nano size 5 to 10 nm.

It is mostly used in melanoma therapy.

Enhances the solubility of the poorly water soluble drug.

Biodegradability of lipids.

Capability of encapsulating hydrophilic, hydrophobic and amphiphilic substances.

Targeted release and controlled release of bioactive agents.

It produces high levels of dilution and shows higher levels of dilution.

By the cubosomal techniques, substrates are incorporated into skin and mucosal surface.

Manufacture of Cubosomes:

Cubosomes can be manufactured by two distinct methods:

- Top down technique.
- Bottom up technique.

**Top down technique.**

Bulk cubic phase is first produced by the 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 are different in that they are a single thermodynamic phase and have periodic liquid crystalline structure. Cubic phases rupture in a direction parallel to the shear direction, the energy required is proportional to the number of tubular network. The cubic phase’s exhibits yield stress that increases with increasing amount of bilayer forming surfactant and oils. Warr & Chen gave the cubic phases may behave as lamellar phases during dispersion with increasing shear, dispersed liquid crystalline particles are forming at intermediate shear rates, whereas defect-free bulk phase reforms at higher shear rate.

**Top down approach:**

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Oily phase
↓
Aqueous phase
□ □
Cubosomes
↑
High shear
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1. Manufacture of Cubosomes:
2. Top down technique.
3. Cubosomes can be manufactured by two distinct methods:
4. Top down technique.
5. Bottom up technique.
6. Bulk cubic phase is first produced by the 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 are different in that they are a single thermodynamic phase and have periodic liquid crystalline structure. Cubic phases rupture in a direction parallel to the shear direction, the energy required is proportional to the number of tubular network. The cubic phase’s exhibits yield stress that increases with increasing amount of bilayer forming surfactant and oils. Warr & Chen gave the cubic phases may behave as lamellar phases during dispersion with increasing shear, dispersed liquid crystalline particles are forming at intermediate shear rates, whereas defect-free bulk phase reforms at higher shear rate.

**Top down approach:**

1. Oily phase
2. Aqueous phase
3. High shear
4. Cubosomes
5. **Diagram**: Oily phase → Aqueous phase → Cubosomes → High shear
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 themolecular 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 top down approach.²

This method is more robust in large scale production of cubosomes. The cubosomes at room temperature is by diluting monoolein-ethanol solution with aqueous poloxamer 407 solution. The cubosomes are spontaneously formed by emulsification. Another process is also developed to produce the cubosomes from powdered precursors by spray drying technique. Spray dried powders comprising monoolein coated with starch or dextran form cubosomes on simple hydration. Colloidal stabilization of cubosomes is immediately provided by the polymers.¹²

Lipid.

Hydrotrope.

Aqueous phase. Cubosomes

Preparation method of cubosomes:

The cubosomes dispersion carried out by the fabrication method and emulsification method.

Fabrication method:

GMO/P407 cubic gel GMO 5% and P407 1.0% were firstly melted at the 60⁰C in hot water bath the X amount of drug is kept in to the melted mass and stirred continuously to dissolve . deionized water are added drop by drop and vortex mixer are set to the homogenization. It kept in to 48 hrs.at the room temperature the optically isotropic cubic gel are form and it disturbed by mechanical stirring the crude dispersion was subsequently fragmented by sonicater probe having the energy 200W under the cool temperature at the 20⁰C in water bath for the 20 min.¹⁴,¹³.
Emulsification method:

In this method the GMO and P407 are put in to the water and it followed the ultra sonication the 5% GMO and 1% P407 and 5% ethanol in 89% water are taken GMO and P407 are melted at the 60°C and mixed the ehanolic solution was added to the melting. the resultant mixture are added drop wise to deionized water preheated at the 70°C it ultrasonicated at maximum power 130kW for 50min at the same temperature the disperse solution are kept bin to the ambient temperature and protected from light.14,15

Characterization of cubosomes:


It carried out by the transmission electron microscope. The droplet of cubosomes are placed on 200 mesh carbon coated copper gride, and excess fluid are remove by the absorbent filter paper. The sample was stain with the 1% sodium phosphor tungstste solution view under the magnification up to 1,000,000X.

2. Paticle size analysis:14

Z average and polydispersion index were determine by the dynamic light scattering source. The sample were diluted by the 100 fold with the deionized water and measured at the 25°C in triplicate.

3. Entrapment efficiency:14,15

The dispersion sample is obtain by the top down and bottom up technique the 0.05 gm of the sample are taken the amount of the drug in the dispersion was analyzed spectrophotometrically at the $\lambda_{max}$ 250 nm by this way the subtract the
total amount of drug. The volume of the 1ml from each of the dispersion was diluted with 4 ml of deionized water. The solution is passed through the syringe filter and examined under the spectrophotometer.

4. Viscosity: \(^7,14,15\)

The viscosity is determined by the different angular velocities at 25\(^0\)C using (Brookfield) Viscometer. The rotation speed was 20 rpm, with the speed of 18. The average of three readings is taken for the calculation of viscosity.

5. Differential scanning calorimetry: \(^14\)

To detect any physical changes of drug, the DSC is performed. The GMO and Poloxomer are used for the thermal analysis with the drug sample. The sample 5 mg is heated at the constant rate of 10\(^0\)C/min in an aluminum pan under the nitrogen atmosphere. A similar empty pan is used as the reference.

6. X-RAY Diffraction calorimetry: \(^15\)

The prepared cubic gel is obtained by the drug, Poloxomer, and GMO. The diffractometer having a tube of the “Cu” that has a voltage 45Kv, the current 30mA, at 0.02\(^0\) and the counting rate 0.5s/step at room temperature. Data were collected using the scattering angle 2(\(\phi\)) at the range 4-50\(^0\)

7. Stability study:

The stability study can be carried out by investigating organoleptic and morphological aspects as a function of time. Particle size distribution and drug content can be assessed at different time intervals and can also be used in possible variation by time. \(^10\) The cubic gel was stored in amber color glass vials sealed with aluminum foil at refrigeration temperature 4-8\(^0\)C for a period of 3 months. The sample was withdrawn at the end of the study period and were dispersed in deionized water by vortex for 3 min. The prepared cubosomal dispersion was subject for mean particle size and EE(%) measurement. \(^15,14\)

Conclusion:

Bicontinuous cubic liquid crystals are either bulk or cubosomes. They are used in particular application. The ability to form the cubosomes either used during enhanced flexibility for product development efforts. Cubosomes prepared in dispersion process a nanometer scale structure identical to bulk cubic phases but dispersion itself have lower water like viscosity. It also have material science researchers as template for complex solid material.
Were the cubosomes prepared by the fragmentation method and emulsification method both in the method the fragmentation method show the higher drug released then cubosomes prepared by emulsification method. In the study increase the GMO concentration increase the entrapment efficiency and were increase the poloxomer concentration that reduced the entrapment efficiency.

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