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REVIEW: CUBOSOMES AS A LIPID CUBIC PHASE NANO DRUG DELIVERY SYSTEM

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ABSTRACT

Cubosomes are extremely strong nanoparticles formed from the lipid cubic phase which is stabilized by polumer based outer layer. Bicomtinuous lipid cubic phases involve single lipid bilayer that forms continuous periodic membrane lattice structure consisted of pores which is formed from two interwoven water channels. There is a lot of enthusiasm ebout cubic phases because its unique microstructure is biologically compatible and capable of controlled release of solubilized active ingrdients such as drugs and protiens. Cubosome structure is observed by electron microscopy, light scattering, x-ray and NMR, still some of the researchers has been studying the potential of cubosome as a drug delivery systems

INTRODUCTION

Amphiphilic molecules in aqueous solutions can associate into a variety of structures that undergoes transformation depends upon types of ionic content, change in ionic strength, pH, or temperature.When dispersed in water, amphiphilic molecules have the property of self-assembly into liposome. These molecules owing to their self-assembly properties leads to highly organized structures capable of being used in drug delivery systems[1].Amphiphilic molecules owing to advantageous properties of protecting drug molecules against physical, chemical and physiological degradation, improvement in bioavailability, and reduction in side effects plays a key role as nanocarrier drug delivery[2]. Amphiphilic lipids self-assemble into lyotropic Liquid crystalline phases in the presence of excess water.The liquid crystalline structures may exhibit various mesophases including lamellar crystalline phase and inverse hexagonal phase [3].Lipid-based nanoparticles are in the form of dispersion of bulk lipid phases. Block co-polymer or PEG moieties are acts stabilizers which enables cell targeting approach independent from lipid membrane assembly. Thus highly stable nanoparticle can be formed under biological conditions and composed of biocompatible lipids. Such nanoparticles contains the lipid bicontinuous cubic phase, known as' CUBOSOMES"[4].

Lipids are divided in to two Types i.e. 1) Lamellar lipids 2) Non lamellar lipids

Lamellar lipids helps in the formation of lipid by layer and non-lamellar lipids helps in formation of phases like hexagonal, bicontinuous cubic phase. Structure and stability of these phases are depending upon experimental conditions like, lipid composition, temperature, hydration and pressure. The primitive (also referred to as Im3m / QII P), the double diamond (Pn3m / QII D), the gyroid (Ia3d / QII G).[20] and the primitive (also referred to as Im3m / QII P these three types of lipid phases are observer in lipid membrane system, while in cubosomes structures primitive and double diamond morphology is present[5]. Cubic phase consists of a curved bi continuous lipid bilayer in three dimensions enclosing hydrophilic, amphiphilic, and hydrophobic substances. Three forms of cubic phase have been used as drug delivery systems such as, cubic phase gel, cubic phase precursor, and cubosomes. Thesecuicphases are used In mucosal, vaginal, periodontal, and transdermal drug delivery. The stiffness and viscous nature of cubic phase gels can resist their potential application as delivery system. The cubic phase precursor is successfully used for arterial transcatheter chemoembolization on hepatocellular carcinoma also[6]. Cubosomes are discrete, sub-micron or nanostructured particles formed from fragmentation and steric stabilization of inverse bi-continuous cubic phases of lipids. Because of this, cubosomes are much larger specific surface area and still remain the inner structures with sustained release property and mechanism of cubic phase as delivery system[7]. Liquid-crystalline particles are prepared from the dispersion of glycerylmonooleate (GMO) and a mixture of GMO with other lipids in the presence of a stabilizing polymer such as Pluronic F127, although some other amphiphilic lipids such as phytantriol receiving increasing attention. The numbers of different methods are used for preparation of the particles, such as high-temperature mechanical dispersion, room temperature fragmentation, dilution of hydrotropic solvent solutions of the amphiphile in water, and the dilution of mixed micelles of the amphiphilic lipids and surfactants [8]. The formation of cubosomes relies on the concept that the lipid mixture, in combination with the stabilizer and loaded protein or molecule of interest, self-assembles to form a lipid bicontinuous cubic phase. Other lipid mixtures can be used to create dispersed mesophases spanning a range of phase morphologies including the hexagonal phase micellar cubic phases and sponge phases Monoolein and phytantriol are the most common lipids used for cubosome formation. Cubosomes has major importance in nanodrug formulations and formetions if bicontinuous cubic liquid crystalline phase from the hydrating mixer of monoolein and poloxamer 407

Advantages

1. It is economic.
2. It is non-toxic and biocompatible.
3. Method of preparation is simple.
4. It has excellent bio adhesive properties.
5. It has skin permeation enhancement.
6. For longer time they are thermodynamically stable.
7. Capability of encapsulating hydrophilic, hydrophobic and amphiphilic substances.
8. Targeted release and controlled release of bioactive agents.
9. Due to high internal surface area & cubic crystalline structures there is high drug loading.

Disadvantages

1. There is low entrapment of water soluble drug beause of these is presence of larg amount of water inside cubosomes.
2. Because of the high viscosity the large scale production is sometimes difficult.
3. Large scale production is difficult for sometimes because of high viscosity

MANUFACTURE OF CUBOSOMES:

Mainly following two methods are used to manufacturing of cubosomes.

1. Top down technique
2. Bottom up technique

TOP DOWN TECHNIQUE: In this technique of cubosome formulation the process starts with suitable starting material and then creates the functionality from the material. Most of the researches frim last twenty years are focused

on this technique. In this technique first bulk cubic phase is prepared and then it is dispersed by high energy processing into final cubosome nanoparticles.

Bulk cubic phase contains rigid gel formed by water-swollen cross linked polymer chains.
Rupture of these cubic phases is parallel in direction to the shear direction and required energy is proportional to ruptured number of tubular network branches[9].

BOTTOM-UP TECHNIQUE: In the Bottom-up technique first forms the nanostructure building blocks and then assembles into final material. This is recently developed technique of cubosome formation[10].Cubosomes are formed by dispersion of L2 or inverse micellar phase droplets in water at 80 °C, then by slow cooling to allow the droplets to gradually crystallize into cubosomes[7].

METHODS FOR CHARACTERIZATION AND EVALUATION OF CUBOSOMES

Gel permeation chromatography or ultrafiltration techniques & UV spectrophotometer

1. **HPLCanalysis:** Entrapment planning and drug loading of cubosomes can be determined by using gel permeation chromatography or ultrafiltration methods. In the later technique, unentrapped drug concentration was determined, which is subtracted from the total amount of drug added. The amount of drug is analyzed by using UV spectrophotometer or HPLC analysis.
2. **Photon correlation spectroscopy:** Dynamic laser light scatteringtechnique using Zeta Sizer (Photon correlation spectroscopy) is majorly used to determine the particle size of the cubosomes . The sample was diluted with a suitable solvent and adjusted to light scattering intensity of about 300 Hz and measured at 25°C in triplicate. By using average volume weight size, data is collected. The zeta potential and polydispersity index can also be recorded.
3. **X-ray scattering:** Small angle X-ray scattering can be used to determine the cubic arrangements of different groups in the sample, small angle X-ray scattering can be used. The diffraction patterns obtained are change into plots of intensity versus q value, this enable the identification of peak positions, and their conversion to Miller Indices. The Miller Indices can be correlated with known values for different liquid crystalline structures and space groups to identify the internal nanostructure of the sample.
4. **Transmission electron microscopy:** Transmission electron microscopy can be used to check the shape of the cubosomes, reports that the suspensions of cubic phase nanoparticles are stained negatively with freshly preparedphosphortungstic acid solution (2%, pH 6.8) and was shifted into a carbon coated grid (200 mesh) and air drying is done at room temperature. The electron microphotographs were taken on an electron microscope. SEM analysis not be performed on cubosomes or some vesicular systems because the integrity and robustness of the formulation may be lost by exposing to electron array.
5. **Pressure Ultrafiltration Method:** Pressure ultrafiltration technique is used to messure drug release from cubosomes. It isbased closely on that proposed by Magenheim, using an Amicon pressure ultrafiltration cell fittedwith a Millipore membrane at ambient temperature (22±2) °C.
6. **Stability studies:** The physical stability of cubosomal formulation can be studied by the investigation of organoleptic and morphological aspects as a function of time. Particle size distribution and drug content can be evaluated at different time intervals can also be used to evaluate the possible variations by time
7. **Visual inspection:** After 1 week of preparation, the dispersions were visually evaluated for its optical appearance which includes examination of colour, turbidity, homogeneity, presence of macroscopic particles.

8. **Lightmicroscopy:** Samples of the prepared cubosomes was diluted with deionized water and examined under the optical microscope and calibrated with a micrometerslide at magnification of x 400 and x1000.
9. **Viscosity:** The viscosity of the prepared formulations was determined at different angular velocities at 250C using a rotary viscometer (Brookfield). With Spin # 18, the rotation speed was 20 rpm. The average of three readings was used to calculate the viscosity of the samples [11].

APPLICATION OF CUBOSOME:

Applications of cubosomes are as follows:

a. Formulations of control release drug delivery system of solubilize substances**.**
b. Cubic phase is more applicable for control release because of its small pore size.
c. Ability to solubilize hydrophilic, hydrophobic and amphiphilic molecules.
d. Its biodegradability by simple enzyme.
e. Widely used in cancer therapy.
f. Used in topical, mucosal deposition and delivery of different drugs.
g. The properties of bioadhesion and penetration enhancement of cubosomes suggest their potential utility in skin cancer (e.g., melanoma) treatment, there is currently no formulation addressing this need. Moreover, there is emerging interest in using statistical methods to optimize pharmaceutical formulations[12].

A short list of applications includes the delivery of actives for periodontal disease and implants *via in vivo* and topical delivery, and as bioadhesives[13],[14],[15].

CONCLUSION

Cubosomes are solid nanoparticles, these are self-assembled liquid crystalline particles, which is having ability to incorporate many hydrophilic and lipophilic drugs and gives sustained and targeted drug delivery. Top down and bottom up are two easy method of preparation of cubosomes used to produce cubosomes either by ultrasonication techniques orby high pressure homogenization.Moreover, the literature reviews also specifics cubosomal utility as a controlled release drug carrier.

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