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Review Article

A review on cubosomes: As a novel carrier for drug delivery

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ABSTRACT

Cubosomes are the novel drug delivery system which is nano structured particles. Cubosomes are bicontinues cubic liquid crystalline systems formed by the self-assembly of surfactant-like or amphiphilic molecules which are optically clear. Their intriguing bicontinuous structures possess very high solid like viscosities unique from other delivery system. Bicontinuous relates to the separation of the two continuous but non-intersecting lipid bilayer by aqueous region which is twisted into space filling structure. Cubosomes are three dimensional honeycombed (cavernous) structures with large interfacial area and separating two internal aqueous channels can be exploited by various bioactive ingredients, such as proteins, peptides and drugs. They possess unique properties such as the ability of encapsulating hydrophilic, hydrophobic and amphiphilic substances, bioadhesion, thermodynamically stable and controlled release through functionalization, as promising vehicles for different route of administration such as orally, percutaneously and parenterally. They are characterized by various evaluation parameters and have wide range of applications. The present study outlines advances about cubosomes as a drug carrier, the various techniques used in preparation of them lead to reach the edges in drug delivery, their characterization, evaluation and different applications.

Key words: Cubosomes, Bicontinues, Liquid crystal, Honey comb

INTRODUCTION

Cubosomes is the term coined by Larsson, which indicates the cubic molecular crystallography and similarity to liposomes [1]. Cubosomes are self-assembled liquid crystalline particles with size of 10-500 nm. Cubosomes are cubic nanoparticles which have features of both liquids and crystalline substances due to their intermediate state cubosomes are called as mesophases [3]. They are composed of lipids, polymers, surfactants with polar and non-polar components hence called as amphiphilic [1]. Cubosomes are basically lipid vesicles formed by amphiphilic molecules which

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acts as vesicular structure or biomembrane that act as carrier for lipophilic, hydrophilic and amphiphilic drugs as compare to free drug directly to the target site and allow drug targeting which results in sustained or controlled release of conventional medicines [4]. These are bicontinuous cubic phases consists of curved lipid bilayers formed into a three-dimensional honeycomb (cavernous) like structures separated as two internal aqueous channels and large interfacial area [5]. They are thermodynamically stable and have properties like optically isotropic, viscous, biocompatibility, bio adhesivity and solid too [6]. They have compartmentalized internal structures, highly ordered, high lipid content and large surface area which are prepared by using biocompatible, biodegradable and nontoxic ingredients which are used to encapsulate lipophilic drugs [7]. They look like dots, which are slightly spherical in shape first identified by Luzzati and Husson using X-ray scattering technique. Each dot represents to the presence of pore contains aqueous cubic phase in lipid water system [8]. In cubosomes active chemical moieties are attached to the polar head region of the phospholipids by chemical bonds which has great importance in nano formulations which can be administrated in different routes like Oral, Percutaneous, Intravenous route [1]. Cubosome structure can be determined by the means of electron microscopy, "light scattering", X-RAY and NMR [9]. Cubosomes has wide applications as a drug carrier. Structure of the cubosomes is as in fig 1.

ADVANTAGES OF CUBOSOMES

- Simple method of preparation
- Capability of encapsulating hydrophilic, hydrophobic and amphiphilic substance
- Excellent bio adhesive properties
- Skin permeation enhancement
- Controlled release and targeted release of bioactive agent.
- High drug loading efficiency due to their cubic crystalline structures and high internal surface area
- Thermodynamically stable
- Economic, non-toxic and biocompatible
- Composed of biodegradable lipid
- Protect the incorporated drug from physical and chemical degradation

DISADVANTAGES OF CUBOSOMES

- Low entrapment of water-soluble drugs due to presences of large amount of water inside the cubosomes
- Due to their high viscous nature large scale production is difficult

METHOD OF PREPARATION

Different approaches are been used for the preparation of cubosomes.

1. Top Down Technique
2. Bottom Up Technique
3. Heat Treatment
4. Spray Drying

Top down technique: It is widely used method firstly reported by Ljusberg-Wahren in 1996 which involves two steps for the preparation of cubosomes [4]. Initially by mixing the lipid with stabilizer results in the formation of viscous bulk cubic phase by aggregation process where the second step is dispersion of bulk cubic phase to aqueous medium through sonication or high-pressure homogenization or shearing to form cubosomes. Cubosomes obtained through this technique are vesicle-like structures of dispersed nanoparticles of the lamellar liquid crystalline phase or always coexist with vesicles [5]. Parameters like the concentration of stabilizers and temperature are very important. Highly stable nanoparticles are obtained from shearing process when compared to ultrasonication [8].

Bottom up technique: This technique is used to prepare cubosomes at room temperature by crystallization from the precursor by emulsification process [4]. In top down technique high energy is required to prepare cubosomes from bulk cubic phase which is very difficult to overcome it Patric T. Spicer et al studied formation of cubic phase in presences of hydrotrope. It is the molecule that has hydrophilic and hydrophobic nature but does not exhibit surfactant properties which plays important role by dissolving the lipid and prevent the formation of viscous liquid crystal by a process called salting out [5]. In this technique hydrotrope is dissolved in water insoluble lipid results in the formation of liquid precursor which is dispersed as droplets at 80 c upon cooling undergo crystallization and results in formation of cubosomes.

Heat treatment: This approach is not exact process for preparation of cubosomes because it is used for transformation of non-cubic vesicles to cubic vesicles upon heat treatment or homogenization size reduction of the particles occurs which increases the colloidal stability and particle distribution [8].

Spray drying: Liquid precursor for formation of cubosomes has less flexibility results in development of dry powder precursor for cubosomes preparation. They utilized spray drying technique for preparation of cubosomes [5].

CHARACTERIZATION OF CUBOSOMES

Optical Microscopy: Prepared formulation of cubosomes was taken on a glass slide and spreaded evenly then observed under optical microscope. Cubosomes structure was examined at different magnification power 10x,30x, 40x using digital cameras photomicrographs were taken [1].

Entrapment efficiency: Centrifugation method is been used to determine the entrapment efficiency. 5ml of the cubosomal solution was taken into the centrifugation tubes and then centrifuged to separate the un entrapped drug from the cubosomes. Supernant liquid was taken and by using UV spectroscopy the absorbance was determined at 428nm [3]. Percentage of the drug entrapped into the cubosomes can be determined by using formula

Entrapment efficiency = Drug entrapped / Total drug *100

Size and zeta potential analysis: Particle size and zeta potential can be determined by zeta sizer were the diluted Cubosomal formulation was taken and temperature was set at 25°c. Zeta potential and electrophoretic mobility values are directly obtained from the measurement [5].

EVALUATION OF CUBOSOMES

Visual inspection: Visual inspection of cubosomes is done for optical appearance such as turbidity, colour, presences of microscopic particles, homogeneity [1] etc.

Shape of cubosomes: It can be determined by using transmission electron microscopy [2].

Drug release: Pressure ultrafiltration technique was be used to determine the drug release from the cubosomes. It is based on theory which is proposed by Magenheim, by using an Amicon pressure ultrafiltration cell that is fitted at ambient temperature (22±2) °C to a Millipore membrane [1].

Viscosity: Rotary viscometer (Brookfield) was used to determine the viscosity of the prepared formulation at different angular velocities at 250°c. 20 rpm was the rotation speed and #18 is spin. To calculate viscosity of the samples average of three readings was taken [10].

X-ray scattering: Cubic arrangements of different groups in sample can be determined by X-ray scattering where diffraction patterns are converted to plots of intensity versus q value which helps in determination of peak positions and conversion to Miller Indices. It can correlate the known values of different space groups and liquid crystalline structures to identify sample internal nanostructure [10].

Stability studies: The physical stability 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 [11].

APPLICATIONS OF CUBOSOMES

- Cubosomes are used in cancer therapy [1].
- Cubosomal dispersion that containing monoglyceride used topically for mucosal or percutaneous application [4].
- Cubosomal technology is used in development of synthetic vernix which is a white substance that coats infants in late gestation for premature infants who born without it [4].
- Cubosomes are also been used in the treatment of fungal infections [8].
- Cubosomes are been used as a agent for delivery of vaccines [8].
- Controlled release of solubilized actives is the most popular application of cubosomes [9].
- Biodegradable by simple enzymes [11].
- Monoglycerides has microbiocidal properties therefore used in the treatment of sexually transmitted diseases by both bacteria and viruses [12].
- Cubosomes are recently used in cosmetics, skin care, antiperspirant and hair care.

CONCULSION

Cubosomes are self-assembled crystalline nanoparticles usually size range from 10-500 nm which can be prepared by different methods [1]. These cubosomes are appropriate for transdermal, parenteral, oral drug delivery and also as biosensor, gene transfection agent [2]. Cubosomes has ability to incorporate lipophilic, hydrophilic and amphiphilic drugs and posses targeted and sustained drug release which increases the interest of the researches to used it as a carrier [5]. The ability to form cubosomes during formulation, manufacturing or in use increases the flexibility of product development efforts. Due to their high potential ability cubosomes are been used as a carriers of drug delivery.

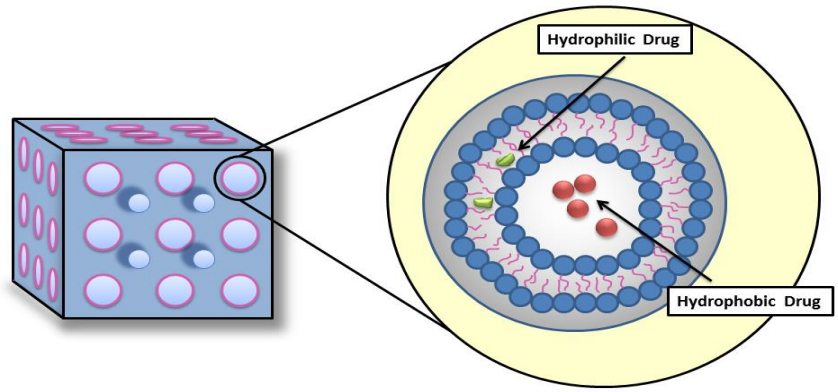

Figure.1: Cubosomes and its membrane composition

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