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CUBOSOMES: A NANOPARTICULATEDRUG DELIVERY SYSTEM

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ABSTRACT

Cubosomes are nanostructured liquid crystalline particles, made of certain amphiphilic lipids in definite proportions, known as biocompatible carriers in drug delivery.Owing to unique properties such as thermodynamic stability, bioadhesion, the ability of encapsulating hydrophilic, hydrophobic and amphiphilic substances, and the potential for controlled release through functionalization, cubosomes are regarded as promising vehicles for different routes of administration. Based on the most recent reports, this review introduces cubosomes focusing on their structure, preparation methods, mechanism of release and potential routes of administration.

INTRODUCTION

Cubosomes are discrete, sub-micron, nanostructured particles of the bicontinuous cubic liquid crystalline phases. They consist of honeycombed structures separating two internal aqueous channels along with a large interfacial area. They contain similar microstructure as that of the parent with high surface area and their dispersions are less viscous than the parent cubic phases [3]. Almost all cubosomes are composed of polymers, lipids and a surfactant with polar and non-polar components (amphiphilic). Due to the hydrophobic effect, amphiphilic molecules are driven into the polar solvent to impulsively identify and assemble into a liquid crystalline dispersion of nanometer scale. Thus cubosomes are bicontinuous cubic liquid phase enclosing two distinct regions of water, divided by surfactant controlled bilayers[4].It is used to form the bilayers of the membrane. Cubic liquid crystalline phases were physically transparent, isotropic and stable in excess water also shows unique system for the production of pharmaceutical products[6]. The liquid crystalline cubic phases are used in the controlled release of water and oil soluble molecules. They are viscous, isotropic, and solid like liquid crystalline substances having cubic crystallographic symmetry[5]. In cubosomes, the cubic phases composed of two separate thermodynamically stable structure consisting of, continuous but non intersecting hydrophilic regions which are separated by a lipid bilayer. This provides the

incorporation of amphiphiles and oil and water soluble materials into the system[6].

The structure of cubosome generally retains the stability and efficacy of actives like proteins and vitamins. Cubosomes are thermodynamically stable, long lasting. By the addition of polymers the colloidal dispersions of cubosomes can be stabilized. They also shows the potential for controlled delivery of drugs, in which diffusion is governed by the passage of the drug through the "regular" channel present in structure of the cubic phase[7]. Cubosomes are liquid crystalline nanostructured particles with the same unique properties of the bulk cubic phase, although cubosome dispersions have much lower viscosity. Fundamental research has been focused sharply on bulk cubic phases, it is commercial applications that drive much of the existing and still very active research into cubosomes[8].

Structure of cubosomes

The structure of cubosome includes honey-combed structures separating two internal aqueous channels along with large interfacial areas. Cubosomes are nanosized, more accurately nanostructure particles of a liquid crystalline phase having cubic crystallographic symmetry which is formed by the self assembly of surfactant like molecules.

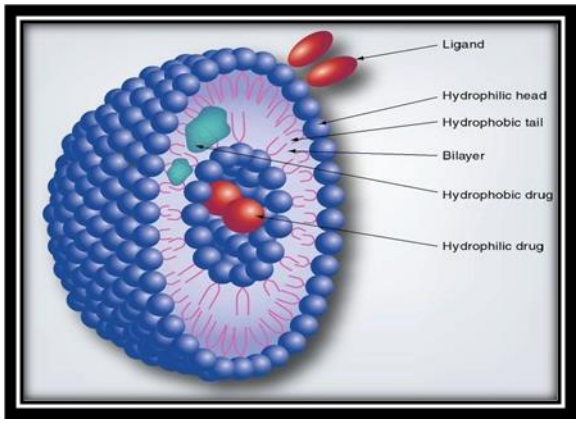

Fig. 2: Honeycombed structure separating two internal aqueous channels

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. Amphiphilic molecules form bicontinuous water and oil channels, where "bicontinuous" refers to two distinct (continuous, but non-intersecting) 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. However, monoglyceride-based cubic gels possess significantly more long range order than hydrogels and, because of their composition (i.e., lipid and water), excellent biocompatibility [9].

Structural characteristics of cubosomes

• Cubosomal personal care products are prepared by mixing biocompatible lipids and aqueous phase which promotes their use in the production of skin care, hair care and other body care products [10].

• Cubosomal skin care products are gaining importance because of the possible interaction of stratum corneum and lipids used in cubosomal formulation promoting the permeation of drugs [4].

•Cubosomes being self-assembled cubic crystals are biocompatible and bioadhesive, thereby well suitable for oral administration which was proved with the oral administration of insulin loaded cubosomes for hypoglycemic effect [11].

• Phase Transition Amphiphilic lipids in aqueous environments are characteristic to establish self-assembled nanostructures and facilitate cosmetic application, drug delivery and diagnostics [12].

•The phase transition and self-assembly of ionic surfactant- phytantriol cubosomal dispersion in aqueous medium depends not only on the concentration of surfactant lipid mixture but also on the ionic strength [6]

Components of cubosomes: Cubosomes composed of ;-

- Natural lipids
- Cationic and nonionic surfactants
- Polymer systems

❖ **Natural lipids**

Although the lipid most widely used to construct bicontinuous cubic phases are

- **Monoglyceride**
- **monoolein**

Monoglycerides: Monoglycerides are spontaneously form bicontinuous cubic phases upon the addition of water, are relatively insoluble (allowing the formation of colloidal dispersions of cubosomes), and are resistant to changes in temperature[10].

Monoolien: The main precursor of cubosome formation is monoolein. Monoolein or glyceryl monooleate is a mixture of the glycerides of oleic acid and other fatty acids, consisting mainly of the monooleate[3]. Commercially available monoolein may be obtained in two forms, a mixed glyceride form or as distilled monoolein; the distilled monoolein is preferred for pharmaceutical applications because of its high purity. Monoolein occurs as a waxy yellow paste with a characteristic odor. Monoolein is a nontoxic, biodegradable and biocompatible material classified as GRAS (generally recognized as safe) and it is included in the FDA inactive ingredients guide and in non-parenteral medicines licensed in the United Kingdom. Monoolein show the mesomorphic phase, important in making more comprehensible the potential pharmaceutical application of the lipid[13].

❖ **Surfactant**

Surfactants, which are used in the production of cubosomes, are poloxamer 407 in a concentration range between 0% and 20% w/w with respect to the disperse phase. The concentration of the monoglyceride/surfactant mixture generally takes between 2.5% and 10% w/w with respect to the total weight of the dispersion[14].

❖ **Polymer system;-**

Polyvinyl alcohol (PVA) used in addition to poloxamer as a stabilizing agent of the dispersion[13].

Advantages of cubosomes[15]

1. High drug payloads due to high internal surface area and cubic crystalline structures.
2. Relatively simple method of preparation.
3. Biodegradability of lipids.
4. Capability of encapsulating hydrophilic, hydrophobic and amphiphilic substances.
5. Targeted release 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.

Disadvantages of cubosomes[15]

Large scale production is sometimes difficult because of high viscosity.

Drug release from cubosome

Cubosomes have been proposed as a controlled release, intravenous drug delivery system. The pressure ultra-filtration method and equilibrium dialysis were used to elucidate the in vitro drug release mechanisms. On dilution of cubosomes, lipophilic compounds were released rapidly when studied by the pressure ultra-filtration method. In contrast, equilibrium dialysis incorrectly indicated sustained drug release from cubosomes[16]. Research shows that cubosomes should be burst release delivery systems where drug is released by diffusion from the cubic phase matrix, and that pressure ultrafiltration may have benefits over dialysis methods for measurement of drug release from colloidal particle-based drug delivery systems[17].

Methods for preparation of cubosomes

1. High-Pressure Homogenization: The most suitable method for processing of cubosomes with low polydispersity index that are highly stable and retain a long shelf-life is high pressure homogenization. It involves 3 main steps;

1.1. Gel Preparation: Lipids and surfactants are dissolved in the suitable organic solvent and mixed well until all the content appears uniform followed by evaporation of the organic solvent by using rotary evaporator. This will form the gel phase of the preparation.

1.2. Shearing: The formed gel is sheared with aqueous solvent to form the micro dispersion.

1.3. High-Pressure Homogenization: The dispersion is processed under high pressure homogenizer. This step is temperature sensitive and the temperature is set according to the thermal properties of selected lipid in the formulation. This method is best suitable for large volume sample systems having retention of cubic structure with good confidence (specified storage environment and amphiphile used). The methods assess the quality of the cubosome prior to use, but this is not a suitable preparative approach for low volumes sample systems.

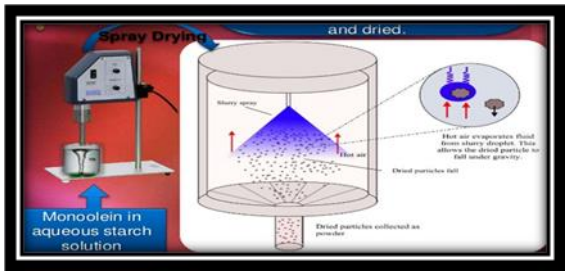

Fig 3: High-Pressure Homogenization process

2. Probe Ultrasonication: This method is mainly used for small volume samples. It can disperse the mixture into particles even with sample volume of 600 µl depending on probe size. This method is quick and time dependent process and involves the following steps. The process involves:

a) Preparation of gel involves addition of a stabilizer
b) Generation of cubic phase with equilibration of solvent
c) Ultrasonication

Amplitude and frequency are the main variables that are needed to be maintained so that to avoid the sample from overheat and phase transition due to pulsing frequency.

3. Automated Cubosome Preparation;

In this process robotic systems and probe sonicator are used to produce large number of cubosomes that are similar to probe sonication with small changes as.

1) 96 well plate is used for the preparation of gels

2) Each well has a capacity of 600 µl of solvent

3) Automated sonication is performed by the robot. The main advantage of this technique is that the cubosomes are produced in large amounts. So their physicochemical properties can be easily assessed. The partitioning of the cubic phases tend to host the lipophilic, hydrophilic or amphiphilic molecules. Polar head of the surfactant molecules will localize the hydrophilic moieties whereas the lipophilic moieties will localize in the lipid bilayer and amphiphilic drugs at the interface [14].

4. Special Techniques for the Preparation of Cubosomes

4.1 Top down Technique: It is the most widely used procedure initially reported in 1996 by Ljusberg- Wahren. 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 phase's ruptures in a direction parallel to the shear direction, the energy required is proportional to the number of tubular network branches that rupture

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 [10].

SUMMARY:

On the whole, cubosome render high importance in nano drug preparations for melanoma treatment outstanding to their advantages, including heavy payloads of drug because of increased surface area and cuboidal structures. They have very simple method of preparation; whereas biodegradability of lipids have the capability of encapsulating hydrophobic, hydrophilic and amphiphilic substances meanwhile targeted and controlled release of bioactive agents. The capability to shape cubosomes both in use, throughout formulation or throughout manufacture offer great extent of flexibility for product development.

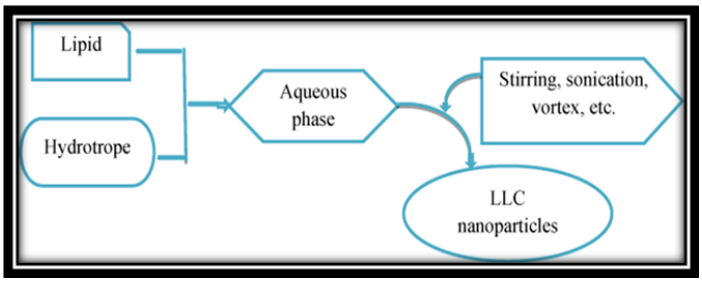

Fig 4: Top down technique

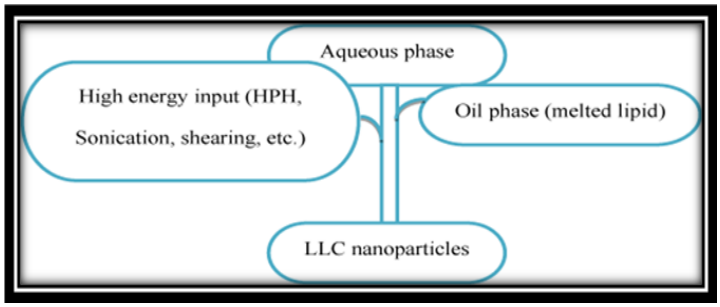

Fig 5: Bottom up technique

REFERENCES:

1. Varde N. M., Mehta N. K., Thakor N. M., Shah V. A and Upadhyay U. M. Phytosomes:A potential phospholipid nanoparticulate carrier for the bioavailability enhancement of herbal extracts. Pharmacie Globale (IJCP) 2012; 10 (02):1-7.
2. Dr.Vijaya.K. et al. Development and Characterization of Curcumin Nano Cubosomal Formulation by Factorial Design. Indo American Journal of Pharm Research.2014:4(02).
3. Prashar D and Sharma D. Cubosomes A Sustained Drug Delivery Carrier, Department of Pharmaceutical Sciences, ManavBharti University, Solan (H.P.), India.
4. Bhosale RR, Osmani RA, Harkare BR and Ghodake PP. Cubosomes. The Inimitable Nanoparticulate Drug Carriers. Scholars Academic Journal of Pharmacy. 2013; 2(6):481-486.
5. Sagnella S and Drummond C. Drug Delivery ANanomedicine Approach, Australian Biochemist. 2012; (43):5-7.
6. SpicerPT. Cubosomes,Bicontinuous Cubic Liquid Crystalline Nanostructured Particles, The Procter & Gamble Company, West Chester, Ohio, U.S.A.
7. Shah JC, Sadhale Y, Chilukuri DM. Cubic phase gels as drug delivery systems. Adv Drug Deliv Rev, 2001; 47: 229-250.
8. Worle G, Transformation of vesicular into cubic nanoparticles by autoclaving of aqueous monoolein/ poloxamer dispersion. Eur J Pharm Sci., 2006; 27: 44-53.
9. Komel Tilekar, Prashant khade, Sujitkakade.Cubosomes-A Drug deliverysystem. International journal of pharmaceutical, chemical and biological sciences.2014;4(4); 812-824.
10. Bhosale RR, Osmani RA, Harkare BR andGhodake PP. Cubosomes. The Inimitable Nanoparticulate Drug Carriers. SchAcad J Pharm. 2013;2(6):481-486.
11. Urvi S, Dhiren D, Patel G, Bhavin B, Patel U and Shah R. Overview Of Cubosomes. A Nano Particle International Journal of Pharmacy and Integrated Life Sciences. ISSN: 2320 - 0782(I5):36-47
12. Saly S, Ehab RB and Sabry B. The Design and Evaluation of Novel Encapsulation Technique for Topical Application of Alpha Lipoic Acid. Journal of Advanced Pharmaceutical Research. 2013; 4(1):13-22.
13. Anbarasan.B, Fatima Grace Shanmuganathn. An overview of Cubosomes: Smart drug delivery system. Sri Ramachandra journal of medicine. 2015; 8(1);215-220.
14. Dr.Kala D, Aiswarya C S. Cubosomes; A Novel drug delivery system and its functionalization. World journal of Pharmacy and Pharmaceutical Sciences. 2017; 6(3); 286-300.
15. Prashar and Sharma. Cubosomes A Sustained Drug Delivery Carrier,Department of Pharmaceutical Sciences, ManavBharti University, Solan (H.P.), India.
16. Hyde S, Andersson A, Larsson K, Blum Z, Landh T, LidinS,et al. The Language of Shape. Elsevier, New York, 1997.
17. Mohanachandran PS. Phytosomes: A novel dosage form for enhancement of bioavailability of botanicals and nutraceuticals. International Journal of Pharmacy and Pharmaceutical Sciences, 2010; 2: 10-14.