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A REVIEW ON CUBOSOMES AND IT'S APPLICATIONS

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Abstract:
Cubosomes are nanoparticles in structure which is mainly made of certain amphiphilic lipids in definite proportion, known as bicontinuous cubic phase liquid crystals. Hydrated a surfactant or polar lipid that forms cubic phase and then dispersing a solid like phase into smaller particles usually forms a cubosomes. They perform solid like rheology with unique properties of practical interest. They are thermodynamically stable and they have carvenous (honeycomb)structures which are tightly packed twisted into three dimensional bilayers. This type of complex structure allows them to have greater drug loading ability. Cubosomes have ability to encapsulate the hydrophobic, hydrophilic, amphiphilic substances. Cubosomes can increase the solubility of poorly soluble drug. Cubosomes dispersions are bio adhesive and biocompatible. Because of their properties, cubosomes are versatile systems, administrable by different ways such as orally, percutaneously and parenterally. Cubosomes structure by means of electron microscopy, light scattering-ray and NMR, nevertheless few researchers has been studying the potential of cubosomes as delivery systems.

Keywords: *Cubosomes; Nanoparticles; Bicontinuous; Honeycomb, Surfactant.*

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INTRODUCTION:

Definition:

Cubosomes are discrete, sub-micron, nanostructured particles of the bicontinuous cubic liquid crystalline phase [1]. Cubosomes are nanoparticles which are self-assembled liquid crystalline particles of certain surfactants with proper ratio of water with microstructure. Cubosomes are nanoparticles but instead of the solid particles usually encountered, cubosomes are self-assembled liquid crystalline particles with a solid like rheology that provides unique properties of practical interest.

HISTORY

Despite the early recognition [in 1980] large scale manufacture of cubosomes was difficult due to their complex phase behaviour and viscous properties. The cubic phases are unique as possess very high solid like viscosities because of their intriguing bicontinuous structures. Cubic phases can be fractured and dispersed to form particulate dispersions which are colloidally and/or thermodynamically stable for longer period of time. Certain surfactants spontaneously form cubic phases when mixed with water above a certain concentration. Determination of their honeycomb structure was carried out by Luzzati and Hussan, Luzzatiet al., Larsson and Hyde et al between 1960 and 1985. The term "Cubosomes" were coined by Larsson, that reflects the cubic molecular crystallography and similarity to liposomes. Effort to develop scalable processes to produce cubosomes in large scale is under development. A few anticancer drugs have been successfully encapsulated in cubosomes and characterized [1].

ADVANTAGES:

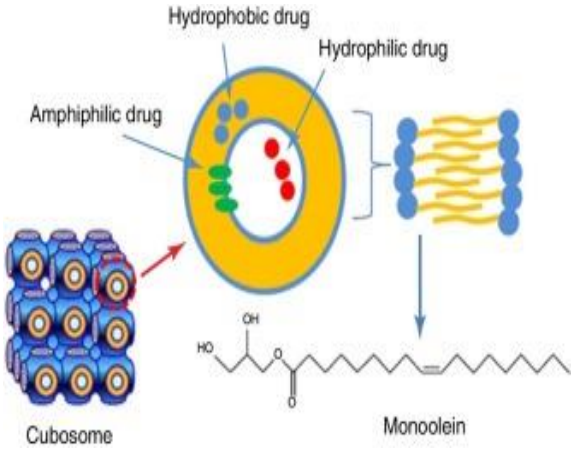
- It is economic.
- It is non -toxic and biocompatible.
- Method of preparation is simple.
- It has excellent bio adhesive properties.
- It has skin permeation enhancement.
- For longer time they are thermodynamically stable.
- High drug payloads due to high internal surface area an cubic crystalline shapes.
- Biodegradability of lipids.
- Capability of encapsulating hydrophilic, hydrophobic, and amphiphilic substances.
- Targeted release and controlled release of bioactive agents.
- Due to high internal surface area & cubic crystalline structures there is high drug loading.

DISADVANTAGES:

- Due to presence of large amounts of water inside cubosomes there is low entrapment of water-soluble drugs [2].
- Because of the high viscosity the large-scale production is sometimes difficult [3].

STRUCTURE OF CUBOSOME:

The basic structure of cubosomes includes honeycombed structures separating the two internal aqueous channels along with large interfacial area whose size range from 10-500mm in diameter. They appear like dots, which are slightly spherical in shape. Each dot corresponds to the presence of pore contains aqueous cubic phase in lipid water system. It was first identified by Luzzati and Hussan using x-ray scattering technique.



These are nanoparticles, more accurately nanostructure particles of liquid crystalline phases with cubic crystallographic symmetry formed by the self-aseembly pf amphiphilic or surfactant like molecules. 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 application[6]. Amphiphilic molecules form bicontinuous water and oil channels, where bicontinuous refers to two distinct [continuous, but not 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.

MANUFACTURE OF CUBOSOMES:

There are two methods for the manufacture of cubosomes they are:

I. Top down technique
II. Bottom up technique

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1. Top down technique
2. Bottom up technique

TOP DOWN TECHNIQUE:
It is the most widely used technique initially reported in 1996 by Ljusberg - Wahren. Bulk cubic phase is first manufacture and by use of high energy such as high-pressure homogenization it is processed into cubosomes nanoparticles. Bulk cubic phase mimic a clear rigid gel formed by water-swollen crosslinked polymer chains. The cubic phases differ in that they are a single thermodynamic phase and have periodic liquid crystalline structure. Cubic phases break in a direction parallel to the shear direction, the energy required is equivalent to the number of tubular network branches that breaks. It is the most broadly used in research area, where the bulk cubic phase is first manufacture and then separates by high energy processing in to cubosomes Nano particles. Bulk cubic phase is mimic a clear rigid gel formed by wate

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BOTTOM UP TECHNIQUE:
Cubosomes are allowed to form or crystalline from precursors. The formation of cubosomes by dispersing L2 or inverse micellar phase droplets in water at 80^0c, and allow them to cool slowly, gradually droplets get crystallizes into cubosomes. This is more vigorous 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 automatically formed by emulsification. Another procedure is also developed to produce the cubosomes from powdered precursors by spray drying method. Spray dried powders including monoolein coated with starch or dextran form cubosomes on simple hydration. Colloidal stabilization of cubosomes is spontaneously provided by the polymers. The bottom-up approach first forms the nanostructure building blocks and then gather them into the final material. It is more recently developed method of cubosomes formation, allowing cubosomes to form and crystallize from precursors on the molecular length scale. The key factor of this method 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 down technique [(5)].

IV.MATERIALS USED IN CUBOSOME FORMATION:
Bicontinuous cubic phases are found in natural lipids, cationic and non-ionic surfactants and polymer systems [6]. The lipid most widely used to construct bicontinuous cubic phases is the monoglyceride monoolein, monoglycerides spontaneously form continuous cubic phases upon the addition of water, are relatively insoluble and are resistant to changes in temperature. The main precursor of cubosomes formation is monoolein. Monoolein or glyceryl monooleate is a mixture of the glycerides of oleic acid and other fatty acids, consisting mainly the monooleate [7]. 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 odour. It swells in water, giving rise to several lyotropic liquid crystalline structures. 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 nonparental medicines licensed in the United Kingdom. Monoolein show the mesomorphic phase, important in making more comprehensible the potential pharmaceutical application of the lipid.

In general, monoglycerides exhibit different phase behaviors when they exposed to water. 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. Polyvinyl alcohol used in alternative to polyxamer as stabilizing agent in the dispersion.

METHODS OF CHARACTERIZATION AND EVALUATION OF CUBOSOMES:

Gel permeation chromatography or ultra-filtration techniques & UV spectrophotometer or HPLC analysis [1]

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.

Photon correlation spectroscopy [1]

Particle size distributions of cubosomes are mainly determined by dynamic laser light scattering using Zeta sizer (Photon correlation spectroscopy).

Polarized light microscopy [1]

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.

X-ray scattering [1]

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.

Transmission electron microscopy [1]

It 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 (200mesh) , air dried at room temperature .The electron microphotographs were taken on an EM , SEM analysis may not be lost during the procedure while exposing to electron array.

Pressure ultrafiltration method [1]

Drug release measurement of cubosomes can done by pressure ultrafiltration method. It is based closely on that proposed by Magenhein et al. using an Amicon pressure ultrafiltration cell fitted with a Millipore membrane at ambient temperature (22+/-2)^{0}C.

Stability studies [1]

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.

Visual inspection [8]

About 1 week after preparation, the dispersions were visually assessed for optical appearance (e.g; colour, turbidity, homogeneity, presence of macroscopic particles).

Light microscopy [8]

Samples of the prepared cubosomes were suitably diluted with deionized water and examined using an optical microscope (Lecia DMRXP) calibrated with a micrometer slide at magnification of x 400 and x 1000.

Viscosity [8]

The viscosity of the prepared formulations was determined at different angular velocities at 25^{0}c using a rotary viscometer [Brookfield] . The rotation speed was 20 rpm , with spin # 18. The average of three readings was used to calculate the viscosity.

Entrapment efficiency

The entrapment efficiency of cubosomes can be determined using ultrafiltration tehniques[9].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 spectrophotometer.

EE% OF cubosomes = [(Ct-Cf)/Ct]

In-vitro drug release [8]

Samples of ALA cubosomes dispersions for release studies were prepared containing 50 mg ALA using both approaches. Each sample was placed in a disc and covered by a membrane then placed at the bottom of the dissolution vessel using using dissolution tester type II . The membrane was used to retain the formula inside the disc. The dissolution medium used was 700 ml of hydroalcoholic solution [1:1]. The apparatus was equilibrated to 32+/- 0.5 ^{0}c and the stirrer paddle speed was set at 50 rpm. Aliquots were withdrawn at appropriate time intervals [0.5,1,2,3,4,5, and 6 hrs] and filtered through a syringe filter having a pore size of 0.1 um then analysed spectrophotometrically at wavelength of 250 nm {according to the method of drug assay}.The amount of drug released was calculated from the standard curve. This procedure was performed in triplicates for each formulation.

Q=[DmCd(2A-Cd) t/2

Where "Q " is the mass of ALA released at time"t" and is proportional to the apparent diffusion coefficient of the drug in the matrix,"Dm" . "A" is the initial amount of ALA in the matrix, and "Cd" is the solubility of the drug in the matrix.

APPLICATIONS

IN CANCER THERAPY

Recently some anticancer drugs have been successfully encapsulated in cubosomes and characterized physiochemical properties [10]. The unique structure of this promising nano carrier suggests its application in melanoma therapy. In order to specifically target nano medicines to tumors, different approaches have been envisaged, with passive and active targeting of cancer cells having been shown to be valid approaches in preclinical and clinical studies.

ORAL DRUG DELIVERY

Cubosomes direct the varied challenges in oral delivery of numerous compounds including poor aqueous solubility, poor aqueous solubility, poor absorption, and large molecular size. In an application large protein have been encapsulated for local activity in the gastrointestinal tract [11]. Cubosomes technology provides drug release at different absorption sites, for example in the upper or lower intestine, which is important for the drugs that have narrow absorption window.

INTRAVENOUS DRUG DELIVERY SYSTEMS

Lipid nanoparticles comprising interior liquid crystal structures of curved lipid membranes are used to solubilize encapsulate and deliver medications to disease areas within the body [12]. Compare to emulsions and liposomes the cubosome nanoparticle shows increased payloads of peptides, proteins and many insoluble small molecules, and are ideal carriers for injection.

TOPICAL DRUG DELIVERY SYSTEMS

Cubosomes are more bio adhesive in nature, so that they can conveniently use in topical and mucosal delivery of different drugs. Topical delivery systems are based on the exploitation of unique properties of liquid crystal and liquid crystal nanoparticle technologies. Topical drug delivery systems are unique in situ forming bio adhesive liquid crystal systems facilitate controlled and effective drug delivery to mucosal surfaces like buccal, ophthalmic and vagina.

DRUG DELIVERY VEHICLE

Drug delivery vehicle is a common application for such new materials. The research in association with cosmetic companies like L'Oreal and Nivea are trying for the use of cubosome particles as oil-in-water emulsion stabilizers and pollutant absorbents in cosmetics [13].

CONTROLLED OR SUSTAINED RELEASE BEHAVIOUR

Number of drugs with different physiochemical properties has been incorporated in cubosomes and their sustained drug release behavior was also studied. Sustained behavior of cubosomes was because of cubosomes remnant particles. Monoglyceride based cubosomes can be proposed for topical use, such as for percutaneous or mucosal application.

IN TREATMENT OF VIRAL DISEASES

Because of the microbicidal properties of monoglycerides, could be used to design intravaginal treatment of sexually transmitted diseases caused by viruses [eg. HSV, HIV] or by bacteria like Chlamydia trachomatis and Neisseria genorrticae[14].

Table 1: Composition of ALA cubosome dispersion

Dispersion	GMO [%W/W]	P407 [%W/W]	ETHANOL [%W/W]	WATER [%W/W]
Less	5.0	1.0	_	94.0
D2[b]	5.0	1.0	5.0	89.0
D3[b]	10.0	1.0	5.0	84.0
D4[b]	15.0	1.0	5.0	79.0
D5[b]	15.0	2.5	5.0	77.5
D6[b]	15.0	5.0	5.0	75.0

Table 2: Comparison of drugs with and without cubosomes

Drug alone	Drug enclosed in cubosomes
Fail to distinguish normal cells from cancer cells.	Distinguishes normal cells from cancer cells.
low efficacy.	More efficacy.
Low biodistribution.	More biodistribution.
Severe toxic side- effects.	Reduced side –effects.
Affect healthy tissues.	Prevent affecting healthy tissues.
Eg : Cisplatin.	Eg : Doxorubicin.
Tamoxifen .	

Table 3: List of drugs incorporated in cubosomes for sustained drug delivery

SNO	Researcher	Drug	category	Associated Disease
1	Engstrom et al.	2-amino-1-phenylpropanol HCL	Antidepressant	Mania , depression
2	Sadhale et al.	Cefazolin	Antibiotics	Genito-urinary , respiratory tract infection.
3	Damani	Clindamycin phosphate	Antibiotics	Peritonitis, staphylococcal bone and joint infection
4	Neilson et al.	Indomethacin	$NSAID_S$	Gout, rheumatoid arthritis
5	Boyd	Diazepam	Sedative-hypnotic	Anxiety, insomnia, seizures.

CONCLUSION:

Cubosomes are nanoparticles but instead of the solid particles, cubosomes are self-assembled liquid crystalline particles, they have ability to incorporate many hydrophilic and lipophilic drugs and shows sustained and targeted drug delivery. Two methods such as top down and bottom up approaches could be easily employed to produce cubosomes either by ultrasonication techniques or high-pressure homogenization. Cubosomes are applicable to wide range of drug candidates, proteins, immune substances and also to cosmetics. Due to the potential site specificity, the cubosomal preparations may be widely employed as targeted drug delivery systems for ophthalmic, diabetic and also for anticancer therapy. The cubosome technology is relatively new with high output and would have wide scope of research in developing new formulations with commercial and industrial viability.

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