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A Review on: The Bicontinuous Cubic Phase Nanoparticulate

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Review Article

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ABSTRACT

Cubosomes have a very interesting structureal property. Cubosomes are the square shaped particles with internal visible cubic lattices. Compared to other novel drug delivery system cubosomes have advantages including ease of preparation, special liquid crystalline properties and better physlnical stability cubosomes consist of honeycombed structures separating two internal aqueous channels and a large interfacial area. Cubic nanoparticles are self-assembled liquid crystalline particles of surfactants with natural lipid. It has high internal surface area which allows loading drug in cubic crystalline structures. Cubosomes are relatively simple to prepare and it has ability of encapsulating hydrophobic, hydrophilic and amphiphilic drug substances. This review article provide an overview of cubosome, types, structure, composition, recent formulations of cubosomes, methods of preparation, characterization and applications of cubosomes in the formulations with various categories drugs.

INTRODUCTION

Cubosomes are bicontinuous lipid containing nanoparticles which are discrete, sub-micron, cubic liquid crystalline phase. They are self-arrange liquid crystalline particles with high surface area. Mostly cubosomes are amphiphilic because of polymers, lipids and surfactants with polar and non-polar constituents. In amphiphilic molecules due to the hydrophobic effect molecules are move into polar solvent. Bicontinuous cubic liquid crystals are emerging discovery. The initial observations of crystalline phase cubic liquid came in the course of the study of polar lipids, such as monoolein that are used as food emulsifiers. The term “Cubosomes” were originate by Larsson that reflects the cubic molecular crystallography and resemblance to liposomes [1]. Descovry of their honeycombstructure was lugged out by Luzzati and Husson, Luzzati et al., during 1960 to 1985 by using X-ray scattering technique [2].

Even with the early remembrance (1980) large scale manufacture of cubosomes was difficult due to their composite phase behavior and viscous properties. The cubic liquid crystalline phase is unique as have a high solid structure like because of their intriguing bicontinuous structures. Few surfactants voluntarily form cubic structure when mixed with water above a certain concentration [3]. Cubosome have very unique features which include high drug payloads capacity, high internal surface area, biodegradability of lipid, encapsulating amphiphilic substance, Controlled and Targeted release bioactive agent and easy to prepare [4,5].

- Cubosome have certain advantages reported as the following
- Properties of drug enhanced by encapsulate drug molecules into hydrophilic, hydrophobic and amphiphilic wall [6].
- Bioavailability of poorly water soluble drugs enhanced [7,8].
- It required simple techniques to for production [9].
- Biodegradable lipids are used [10].
- Drug molecules are protected from physical and chemical degradation [1].
- Glycerol monooleate (GMO) lipid used as a nanovesicles which enhance the permeation of Cubosomes during penetration through corneal and skin layers [11].
- High internal surface provide high drug loading properties [12].
- They can be used for targeted and controlled release [9-14].

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Apart from those interesting advantages of cubosomes exist few drawbacks

- Due to the high viscosity of cubic phase large scale production are Challenging [15].
- Low entrapment efficiency for water-soluble drug molecules due to their high water content inside their structure [1,16].

Mechanisms of Drug Transport

Transportation of drug molecules across the biological membrane is mainly dependent on the nature of composition of materials and physiology of the membrane. There are two mechanisms involved in drug transport generally they are Trans cellular and Para cellular transports [16] (Figure 1).

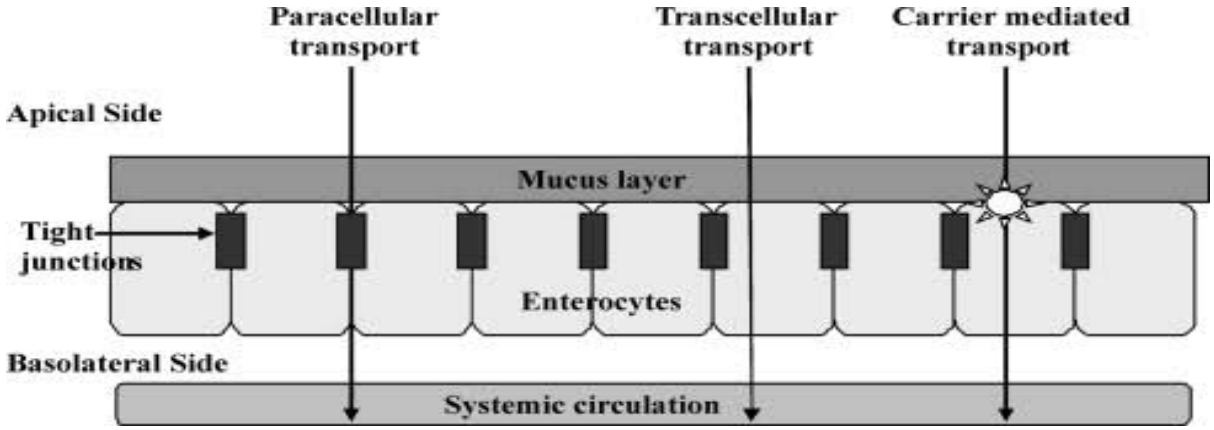

Figure 1. Mechanisms of Drug Transport.

Structure of cubosomes: Cubosomes are discrete, sub-micron, nanoparticles, more accurately nanostructure particles containing lipid with cubic crystal symmetry formed by the self-arrangement of amphiphilic. It has honeycombed structures with size range from 10–500 nm in diameter [17] (Figure 2).

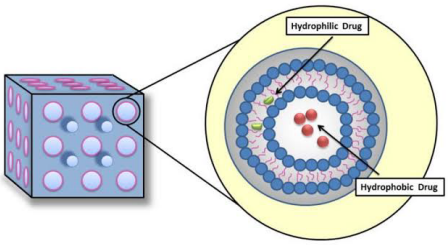

Figure 2. Drug Loaded Cubosome.

Material used in cubosomes: The cubosomes are prepared by using natural lipid, surfactant and polymer system [18-20] (Tables 1 and 2).

Table 1. Materials used in formulation of cubosomes.

S.No.	Material Used	Examples
1	Natural lipids	Monoglycerides, Monoolein
2	Surfactant	Poloxamer 407
3	Polymer	Polyvinyl alcohol

Table 2. Recent research on applications of cubosomes as a drug delivery system.

Drug delivery system	Drug	Oil used	Stabilizer used	Pharmacological uses	References
Ocular drug delivery system	Pilocarpine nitrate	GMO	Pol.407	Treatment of open-angle glaucoma and acute angle-closure glaucoma	21
Ocular drug delivery system	Timolol	GMO	Pol.407	Non-selective beta-blocker drug used for treatment of glaucoma	22
Ocular drug delivery system	Cyclosporine A	GMO	Pol.407	Immunosuppressive agent used in the treatment of inflammatory and immune related ocular diseases	23
Ocular drug delivery system	Ketorolac	GMO	Pol.407	NSAID used to relieveitchingeyescaused byseasonal allergies	24

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Topical drug delivery system	Silver sulfadiazine	GMO	Pol.407	Used for the treatment of infected burns	25
Topical drug delivery system	Indomethacin	GMO	Pol.407	Anti-inflammatory drug	26
Topical drug delivery system	Erythromycin	GMO	Pol.407	Treatment and prevention of several types of acne as a result of its bacteriostatic activity against Propionibacterium acnes	27
Oral drug delivery system	Insulin	GMO	Pol.407	Used in the treatment of type 1 diabetic induced rats	28
Oral drug delivery system	Simvastatin	GMO	Pol.407	Used to lower bad cholesterol and fats and raise good cholesterol in the blood	29
Anticancer drug delivery	5-fluorouracil	GMO	Pol.407	Antineoplastic agent widely used in the treatment of advanced gastrointestinal cancers including hepatocellular carcinoma	30
Anticancer drug delivery	Dacarbazine	GMO	Pol.407	First-line chemotherapy medication against melanoma	31

Manufacture of cubosomes

- Top down technique.
- Bottom up technique.

Top down technique: Top down method is the most extensively used procedure and initially reported by Ljusberg- Wahren in 1996. It has two steps process. In first step, cubic phase is prepared by mixing the lipid with a suitable stabilizer to form the bulk viscous cubic aggregates and in secondly, by use of high energy (high pressure homogenization) dispersion of the viscous cubic aggregates in aqueous media and finally resulting in the formation of cubosomes [32] (Figure 3).

Bottom up technique: Bottom up method is known as solvent dilution method, in which Cubosomes are allowed to form or crystallize from precursors. It implies dispersion of mixture containing lipid, the stabilizer and a hydrotropic agent in surplus of water with the application of minimal energy input [32] (Figures 3 and 4, Table 3).

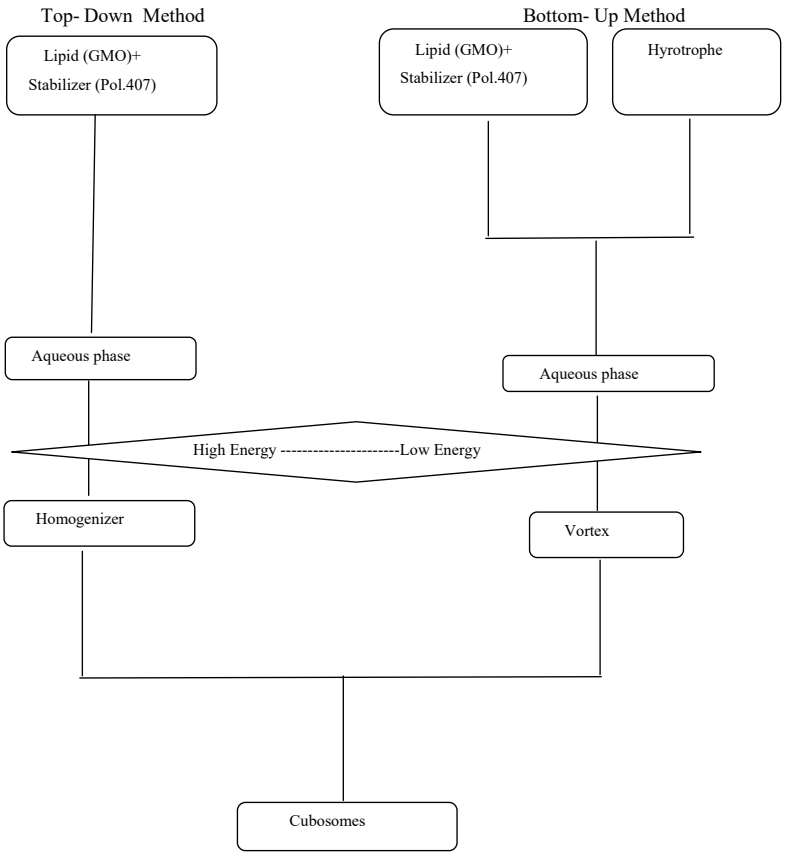

Figure 3. Top down method and bottom up method.

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Table 3. Characterization and evaluation of cubosome.

Evaluation parameters	Description
Zeta potential	The magnitude of zeta potential indicates the degree of electronic repulsion between adjust, similarly charge particle. Zeta potential is key indicator of the stability of formulation [33].
Polarizing light microscopy	Polarized light microscopy used to descover and distinguish isotropic substances and anisotropic substance. the surface coating of the cubosomes can also be examine by Polarizing Light Microscopy [34].
(X-ray scattering)	X-ray scattering can be used to spot the structural arrangements of different groups in the sample. The diffraction patterns obtained by scattering are converted to plots of intensity versus q value, which enable the identification of peak positions [35,36].
Drug release	Drug release from cubosomes can be done by pressure ultrafiltration method [10]. It is based on that proposed by Magenheim et al. using an Amicon pressure ultrafiltration cell fitted with a Millipore membrane at ambient temperature (22±2) °C [37].
Entrapment efficiency	The entrapment efficiency of cubosomes can be determined using ultrafiltration 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 spectrophotometer [38].
Stability studies	The stability studied can investigate by Particle size distribution and drug content. The organoleptic and morphological parameters also examine during stability studies [39].
Viscosity	The viscosity of the formulation will be determined by Brookfield viscometer at different angular velocities The rotation speed was 20 rpm, with spin # 18. The average of three readings was used to calculate the viscosity of the sample [40].

Cubosome Applications

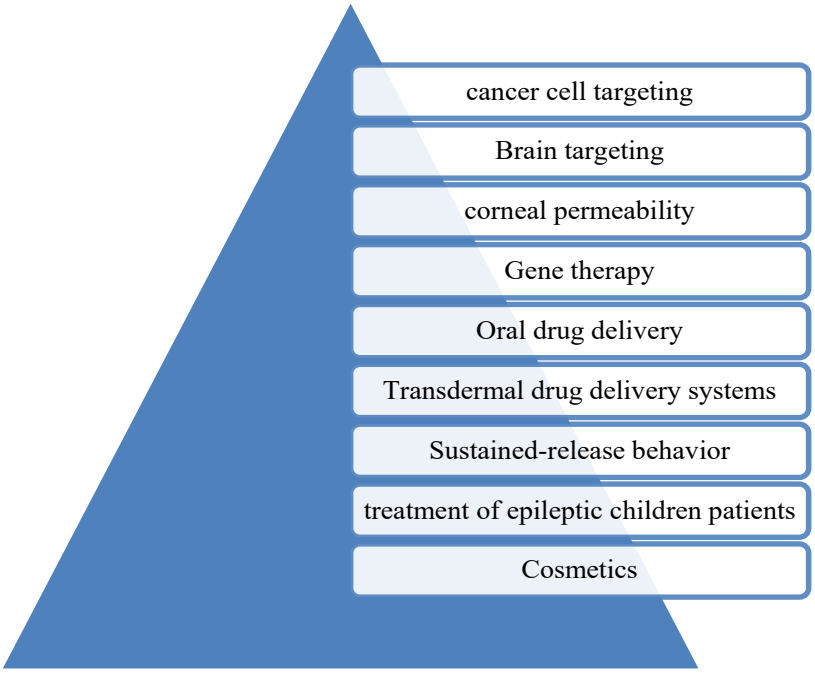

Figure 4. Application of cubosome drug delivery system.

Melanoma (Cancer) Therapy

Recent researches showed that anti-cancer drug have been encapsulated in cubosome and show positive responses towards oncological treatment. The nanocarrier structure of cubosome provides a wide scope for many drugs and it minimizes the side effects, which is vital need for this therapy [41].

Elesclomol (ELC) is an anticancer drug inducing mitochondria cytotoxicity through reactive oxygen species. Here, for the first time, encapsulate the poorly water soluble ELC in monoolein-based cubosomes stabilized with Pluronic F127. Cellular uptake and nanocarrier accumulation close to the mitochondria with sub-micrometer distance is identified via three-dimensional (3D) confocal microscopy and edge-to-edge compartment analysis [42].

lumefantrine with calcium phosphate nanoparticles loaded lipidic cubosomes for the effective treatment of lung cancer [43].

Hydrophilic anticancer drug 5-fluorouracil (5-FU) was used for liver targeting. Cubosomal dispersions were prepared by disrupting a cubic gel phase of monoolein and water in the presence of Poloxamer 407 as a stabilizer. These results demonstrate the successful development of cubosomal nanoparticles containing 5-FU for liver targeting [44].

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Oral drug delivery

Oral drug delivery of drugs has many challenges including molecular size, poor aqueous solubility and poor absorption. This trouble shooting can be address by cubosome formulations. The larger biomolecules also encapsulated for localized activity. The cubic phase nanoparticles can be combined with controlled release and receptor targeting functionalities [45].

Intravenous drug delivery systems

Lipid comprising cubic liquid crystal structure of curved membranes is used to encapsulate and deliver medicaments for their respective site. Liposome and emulsion have use as intravenous carriers. Cubosome also possess these characteristics. Liquid cubic nanoparticles increase payloads of drug, peptides, protines and many small insoluble molecules [46].

Topical drug delivery systems

Cubic phase is bioadhesive in nature and can conveniently use in topical and mucosal deposition with varieties of drugs. Topical drug delivery of cubosomes provides unique properties by forming *In Situ* bioadhesive system for controlled and effective drug delivery. This system form a thin surface film at mucosal surface containing a liquid crystal matrix that can controlled optimal delivery of drug and provide protection to skin [47].

In treatment of viral diseases

Due to microbicidal properties of monoglyceried, cubosome could use treatment of diseases caused by viruses or bacteria. Due to similarity between cubic phase structure and stratum corneum, it is easy to form cubosome by mixture of monolein with stratum corneum lipid. This kind of interaction may led to form cubosome depot from which drug can be released [48].

Current application

L"Oreal use cubosome in their formulation and absorbents in cosmetics [49].

CONCLUSION

Cubosomes are relatively simple to prepare and it has ability of encapsulating hydrophobic, hydrophilic and amphiphilic drug substances. This review article provide an overview of cubosome, types, structure, composition, recent formulations of cubosomes, methods of preparation, characterization and applications of cubosomes in the formulations with various categories drugs.

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