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A Review on Cubosome: The Novel Drug Delivery System

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Abstract-

Because of the extraordinary advancements in biomedical nanotechnology over the last few decades, traditional drug delivery systems have been transformed into smart drug delivery systems that respond to stimuli. These well-defined nanoplatforms can boost therapeutic targeting efficiency while reducing the side effects/toxicities of payloads, which are vital variables for enhancing patient compliance by responding to specific internal or external triggers. Cubosomes are lipid-based nano systems that are analogous to familiar vesicular systems, such as lipo- and niosomes. They could be used as part of a exceptional drug delivery system that includes hydro-, lipophilic, and amphiphilic drug molecules. In this review, we critically analyze the relevant literature on cubosomes regarding theories of cubosome self-assembly, composition, and manufacturing methods, with an emphasis on tumor-targeted drug delivery applications. Due to the bioadhesive and compatible nature of cubosome dispersion, this review also focuses on a variety of drug delivery applications, including oral, ophthalmic and transdermal.

Keywords- Cubosome, Monoglycerides, Monoolein, Controlled release

Introduction [1-6]

The Father of word “Cubosome” was Larsson since the structure resembles cubic molecular crystals, its internal structure was confirmed in 1967.Cubosomes having particle size ranging between 10-500 nm in diameter and square-shaped structure. Cubosomes are distinct, sub-micron, nanostructured specks of the bicontinuous cubic liquid crystalline phase. Cubosomes are nanoparticles which are self-assembled liquid crystalline particles of certain surfactants with proper ratio of water with microstructure Cubosomes refer as “bicontinuous” because it is having two distinct large interfacial area (continuous, but non-intersecting) consisting hydrophilic regions separated by the bilayer. Cubosomes are composed of polymers, lipids and surfactants with polar and nonpolar constituents hence said as amphiphilic.

Structure [7-10]

It consists of honeycombed (cavernous) structures splitting two internal aqueous channels and a large interfacial area. They contain indistinguishable microstructure as that of its parent with high surface area and their dispersions are less viscid than the parent cubic phase. Cubosomes were first recognized by using X-Ray scattering technique. These appear like square shaped or spherical dots consistent to the presence of pore with aqueous cubic phases in lipid-water system. Cubosomes are merely the liquid crystalline nanoparticles or nanostructure particles.

Advantage [3, 5, 7, 8]

1 .It is economic, biocompatible and non-toxic.

3. The preparation process is easy.

4. It has outstanding bio adhesive qualities.

5 They are thermodynamically stable for a longer period of time.

6. The ability to encapsulate compounds that are amphiphilic, hydrophobic, and hydrophilic.

7. Controlled and targeted release of bioactive substances.

8. High drug loading is caused by increased internal surface area and cubic crystalline formations.

9. These are excellent solubilizes when compared to lipid or non-lipid carriers.

10. The bioavailability range of water- soluble peptides would increase 20-100 times with these cuboidal systems.

11. Cubosomes serve as an excellent vehicle for protecting the sensitive drug from enzymatic degradation.

12. For sparingly soluble drugs cubosomes show high drug carrier capacity.

13. Increased convenience and compliance (orally, topically and intravenously).

14. Improved bioavailability due to size

15. Improved efficacy

Disadvantage [5, 7, 10]

1. Entrapment of water-soluble drugs is less due to of the presence of a large amount of water exclusive cubosomes.

2. Due to high viscosity, large-scale production of cubosome is difficult.

3. Without a specific polymer, controlled drug delivery is not possible. They may lead to leakage during storage.

Material used in cubosomes [8, 13]

Bicontinuous cubic phases are found in -

1) Natural lipids

2) Cationic and nonionic surfactants

3) Polymer system

1) Natural lipids

Though the lipid most commonly used to construct bicontinuous cubic phases are Monoglyceride and Monoolein.

2) Monoglycerides

Monoglycerides are freely form bicontinuous cubic phases upon the addition of water, are relatively insoluble are impervious to changes in temperature.

3) Monoolein

The main precursor of cubosome conformation is monoolein. Monoolein or glyceryl monooleate is a combination of the glycerides of oleic acid and other fatty acids, containing mainly of the monooleate. Commercially available monoolein may be obtained in two forms, a mixed glyceride form or as distilled monoolein the distilled monoolein is preferred for medical operations latterly of its high chastity. It swells in water, giving rise to several lyotropic liquid crystalline structures Monoolein is a nontoxic, ecological and biocompatible material classified as GRAS (generally recognized as safe) and it is included in the FDA inactive constituents companion and is Non - parenteral drugs licensed in the United Kingdom. Monoolein show the mesomorphic phase, important in making further accessible the implicit medicinal operation of the lipid.

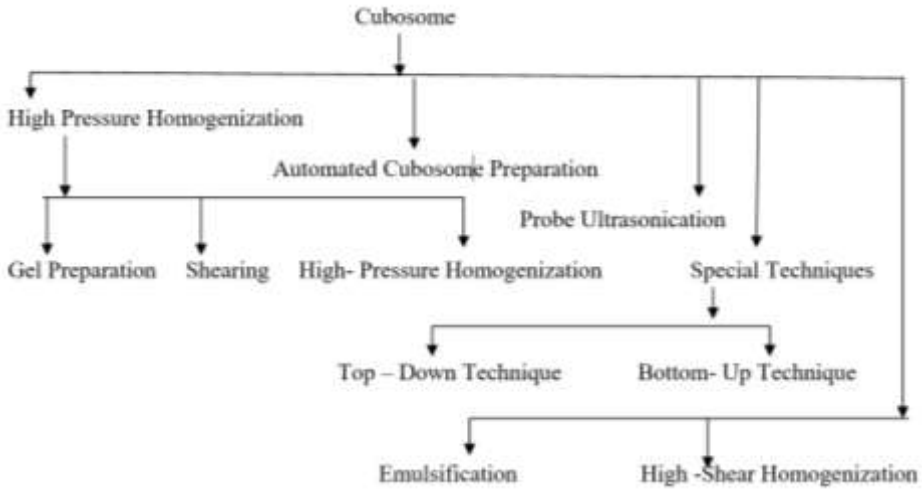
4) Surfactant

Surfactants which are used in the timber of cubosomes are poloxamer 407 in attention range between 0% and 20% w/w with respect to the disperse phase. The attention of the surfactant admixture typically takes between 2.5% and 10% w/w w.r.t. the total weight of the dissipation.

5) Polymer system

Polyvinyl alcohol (PVA) used in addition to poloxamer as a stabilizing agent of the dissipation.

Method of Preparation [5]



Evaluation [7, 8, 9, 10]

1. Visual examination:-

The cubosomes are visually assessed for optical appearance colour, turbidity, unity, presence of macroscopic patches.

2. Shape of the cubosome:-

Transmission electron microscopy can be used to view the shape of the cubosomes.

3. Flyspeck size distribution:-

Flyspeck size distributions of cubosomes are mainly determined by dynamic light scattering using Zeta seizer (Photon correlation spectroscopy). The sample adulterated with a suitable detergent is acclimated to light scattering intensity of about 300 Hz and measured at 25°C in triplet. The data can be collected and generally shown by using average volume weight size. The zeta eventuality and polydispersity indicator can also be recorded.

4. Zeta implicit:-

The magnitude of zeta eventuality indicates the degree of electronic aversion between acclimate, also charge flyspeck. Zeta eventuality is crucial index of the stability of formulation.

5. Entrapment efficiency:-

The ruse effectiveness of cubosomes can be determined using ultra filtration ways. In the later fashion, unentrapped medicine attention is determined, which is abated from the total drug added. The quantum of medicine is anatomized by using spectrophotometer.

6. Dimension of drug release:-

Medicine release from cubosomes can be done by pressure ultrafiltration method. It's grounded on that proposed by Magenheim et al. using an Amicon pressure ultrafiltration cell fitted with a Millipore membrane at ambient temperature (22±2) °C.

7. Stability studies:-

The physical stability can be studied by disquisition of organoleptic and morphological aspects as a function of time. Flyspeck size distribution and drug content can be assessed at different time intervals can also be used to estimate the possible variations by time.

Applications

1. Cubosomes as tumor targeted drug delivery
2. Skin cancer therapy
3. Glioblastoma Multiforme therapy
4. Lung cancer treatment

5. Colorectal cancer therapy
6. Liver cancer treatment
7. Ovarian cancer treatment
8. Cervical carcinoma
9. Hepatocellular carcinoma therapy
10. Brain tumor therapy

Drug embedded in cubosomes

Drugs	Objectives of study	Outcome of study	Ref.no.
Docetaxel	Synthesis and evaluation of controlled release of cubosomes incorporated with docetaxel as thermo-sensitive depot.	The depot offered gradual drug release , preparation was free flowing at room temperature and changed to the depot at body temperature	16
Antimicrobial Peptide	The antimicrobial potential of cubosomal LL-37 was evaluated using in vitro adenovirus	The formulation provides superior protection to LL-37 against enzymatic degradation and significant bacterial effects and ensures a controlled release.	15
Ketorolac	Monoolein and poloxmer cubic nanoparticles for ocular delivery of ketorolac	Optimized cubosomes loaded with ketorolac provided transcorneal permeation and retension	17
Indomethacin	Evaluation of Indomethacin fabricated cubosome for anti-inflammatory activity	Homogenized monoolein and poloxamer containing cubosomes prolonged the delivery of lipophilic drug through the skin.	14
Flurbiprofen	NSAID used for treatment of ocular inflammation.	The formulation expressed less ocular irritation and enhanced trans-corneal permeation of FB	17
Erythromycin	Treatment and prevention of several types of acne as a result of its bacteriostatic activity against propionibacterium acnes.	The formulation prevents the acne due to the topical application of erythromycin impregnated with cobosomes	18
Insulin	Tested against the C-Type -1-diabetic induced rat	Cubosomes provide shield to insulin against proteolysis. It is found to be stable at normal temperature and controlled the hyperglycemia in a reproducible manner.	19

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5AN OVERVIEW ON THE STUDY OF CUBOSOMES –NANOPARTICLES

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