ejpmr, 2025, 12(2), 156-163

SJIF Impact Factor 7.065

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

CUBOSOMAL DRUG DELIVERY SYSTEM -A REVIEW ON ITS EXCIPIENTS, METHODS OF PREPARATION AND EVALUATION

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Article Received on 17/12/2024 **Article Revised on 07/01/2025** **Article Accepted on 27/01/2025**

ABSTRACT

The review article covers the details of cubosomes. This novel drug delivery system, which are emerging as promising drug delivery system for the delivery of both hydroplilic and lipophlilic drugs. Cubosomes are lipid vesicles and it's compared to vesicular system like liposomes. Cubosomes nanoparticles are look like dot square and slightly spherical in shape. Cubosomes are bicontinuous cubic liquid crystalline system formed by self-assembly of surfactants molecules. The present study of cubosomes as a drug carriers, excipients profile, mechanism of action, various techniques used in preparation of cubosomes, their evaluation and different application.

KEYWORD:- Cubosomes, Liquid crystal, Honeycomb, glyceryl mono oleate[GMO], poloxamer 407.

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.[1,2] 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.[3] The structure of cubosome retains the stability and efficacy of activities like vitamins and proteins.

Cubosomes are thermodynamically stable, long lasting. By the addition of polymers, the colloidal dispersions of cubosomes can be stabilized. It 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. Cubosomes are liquid crystalline nanostructured particles with the same unique properties of the bulk cubic phase, although cubosome dispersions have much lower viscosity.[4] Cubosome is a honey-combed structure separating two internal aqueous channels along with large interfacial areas. Cubosomes are Nano sized, more accurately nanostructure particles of a liquid crystalline phase having cubic crystallographic symmetry which is formed by the self assembly of surfactant like molecules.[5] Methods for preparation of cubosomes are high-pressure homogenization, Probe Ultra sonication, Automated Cubosome Preparation; Some Special techniques for The Preparation of Cubosomes are Top-down Technique, Bottom-up Technique.[6,7]

Structure of cubosomes

Cubosomes have honeycomb structures whose size range from 10-500 mm in diameter. They appear like dots, which are slightly spherical in structure. Each dot corresponding to the presence of pore containing aquous cubic phase in lipid water system.

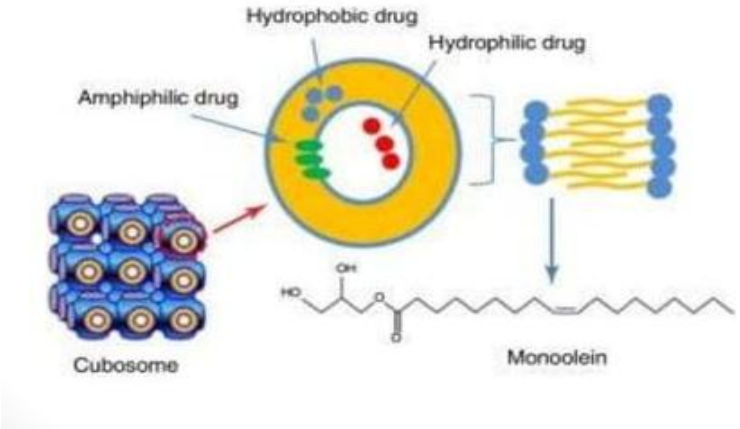

Figure 1: Structure of cubosomes.

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.

Theories on cubic phase structure

Cubosomes or bicontinuous cubic phase liquid crystals have several features that are intriguing as a generic medication delivery system. It is formed into bilayers inside the surfactant and wrapped into a three-dimensional, periodic, and minimum surface, generating a densely packed structure. The material is an optically transparent, very viscous bicontinuous cubic liquid-crystalline phase with a unique structure in the nanometer range. They are relatively easy to make, and the improved penetration power and emulsification properties of lipids allow them to encapsulate hydrophobic, hydrophilic, and amphiphilic compounds while ensuring the targeted and controlled release of bioactive compounds.[8] The three macroscopic phases of the cubic structure that are often seen during cubosome synthesis are the precursor, bulk gel, and particle dispersion phases. A solid or semisolid material that produces the cubic phase in reaction to stimuli, including contacting a liquid, is designated the precursor state. The bulk gel-cubic phase, on the other hand, is rigid, isotropic, and can be expanded into cubosomes. Finally, the dispersion of the solid-like phase into smaller particles forms cubosomes.[9]

a) Fontell & Drew theory

Cubic phases can be found in ternary systems of amphiphiles, oil and water, and various monoglycerides. Monoglycerides are polar lipids with low water solubility and aqueous phase behaviour that is structurally similar to non-ionic surfactants. Lutton's results show that monoglycerides with hydrocarbon chain lengths between C-12 and C-22, particularly monoolein, have a bigger cubic phase area. Monoolein, also known as C-18 Monoglycerides, is an unsaturated fatty acid.[10,11]

b) Gustafson et al. theory

Cubosomes are single-crystal formations with unilamellar vesicles visible and distributed lamellar liquid-crystalline phase particles. The formation of larger vesicles is aided by increasing the polymer-to-monoolein ratio.[11] Slow transport processes that form highly viscous crystalline structures and the high energy required for fragmentation result in mostly vesicles through ultrasonication of bulk cubic phases that are trace formed into cubosomes via membrane fusion over time. This metastability is one of the many characteristics of cubosomes systems (bulk cubic phase). Cubosomes are also colloidally stabilised by vesicles.[12]

c) Schwarz, Jacob & Anderson theory

In non-ionic surfactant systems, cubic phases are frequently encountered wedged between lamellar and hexagonal liquid-crystalline phases. The monoolein-water system is remarkable in that it has a cubic phase area with a wide range of composition and temperature. Surfactant packing concepts, on the other hand, are getting closer. Normally, monoolein has a hydrophilic head and a hydrophobic tail, resulting in reversed or inversed cubic phases, indicating polar medium phases. As a result, cubic phase structures can be represented using differential geometry and periodic minimum surfaces. The ideal way to characterise minimal surfaces is to compare them to soap films. Three types of minimum surfaces are investigated in cubic phases based

on their curvatures. At high water levels, the monoolein-water system creates the D-surface, and at lower water levels, the G surface. The p-surface forms in the monoolein-water system, but only when a third component, such as caseins or amphiphilic molecules, is present. The block copolymer is incorporated. The existence of cubic phases can be determined using the X-ray scattering technique. Cubosomes are visualised using transmission electron microscopy (TEM) and freeze-fracture electron microscopy.[12]

d) System forming theory

Cubosomes can form in binary and ternary systems if the cubic phase and the solvent have a significant miscibility gap. When poloxamer 407 is employed to prevent cubosome aggregation and flocculation, the cubosomes have good colloidal stability. They can be encased in lamellar bilayer caps, which seal the cubic bilayer opening created by fragmentation and offer colloidal stability by preventing hydrocarbon chains from coming into contact with water. The colloidal stability of cubosomes coated with a solid crystalline bilayer is better, whereas lamellar liquid-crystalline coatings are rigid. In addition, sponge phase coatings as a cubosome stabilising coating have been proposed. Another molecule with a high potential for cubosome development is phytonadione.[12]

Mechanism of drug release from cubosomes

The drug release mechanism from cubosomes is based on the principle of drug diffusion, where the concentration gradient of the drug across the cubosomes is the driving force of the diffusion. Therefore, the drug release rate from cubosomes is generally coincidental with the Higuchi or Fick diffusion equation. There are many factors influencing the drug release rate, such as drug solubility, diffusion coefficient, partition coefficient, cubic liquid-crystalline geometry, pore size and distribution, interface curvature, temperature, pH, and ionic strength of the release medium. The release mechanism of several hydrophilic model drugs from the cubic and reversed hexagonal liquid crystalline was investigated. These studies indicated that diffusion is the predominant mechanism of drug release, and the drug release rate from cubic ones is faster than the hexagonal liquid crystalline. Furthermore, the in vivo drug release profiles of[14] C-glucose from cubosomes and hexagonal phase were consistent with the in vitro release profiles, which indicated the nanostructure of cubosomes and the nature of lipid could be utilised to control the release rate of hydrophilic drugs.[13] But it is difficult for the hydrophobic drug to escape from the cubosomes in vitro due to the affinity of the drug with the hydrophobic domain in the cubic phase. Hence, the release profiles of hydrophobic drug-loading cubosomes in distilled water media (pH 6.5) and digestion media (0.1 M Hydrochloric acid) were investigated and found that the drug release rate in the digestion media was drastically improved. Also, it is reported that the plasma concentration of Silymarin in vivo showed an increased drug release rate from cubosome formulation as compared to Legalon®, a commercial capsule formulation.

Excipient profile

Glycerol Monooleate (GMO)

GMO is a polar, unsaturated monoglyceride with a melting point of 35–37°C, having a hydrophilic-lipophilic balance (HLB) value of 3, and is clear and colourless in appearance. It is composed of oleic acid glycerides and other fatty acids, the most notable being monooleate. Monooleate is an amphiphilic lipid which may form lyotropic liquid crystals in a variety of shapes.[15] GMO has both hydrophilic and hydrophobic qualities owing to the existence of hydroxyl groups within the head region, which can form H-bonds with water in an aqueous solution and hydrocarbon chains in the tail.[8] Furthermore, GMO is a biodegradable, biocompatible and non-toxic substance classified as GRAS (generally recognized as safe) and included in FDA inactive ingredients guide, widely used as an emulsifier.

Phytantriol (PHYT)

It is a common constituent in cosmetic products, used as an alternative to GMO in cubosome preparations. It has the ability to form a bicontinuous cubic structure in aqueous media under physiological conditions and temperature. Due to its high chemical stability, enhanced skin penetration properties, and improved moisture retention PHYT has gained more interest in the biomedical field. Also, it has the ability to sustain the release of various drug molecules, especially drugs having hydrophilic properties.[16]

Stabilizers

When cubosomes are dispersed in aqueous media, the dispersed particles become kinetically unstable, as they tend to aggregate due to the exposure of hydrophobic portions to the external hydrophilic aqueous media. A surfactant is required to keep cubosomes colloidally stable and prevent them from re-coalescing into the bulk cubic phase. The stabiliser provides an electrostatic barrier between particles to prevent close contact of particles hence keeping the dispersed particles in a highly stable form. The most commonly used stabilising agents are Pluronics. Poloxamer 407 (F127), a PEO_{99}–PPO_{67}–PEO_{99} tri-block copolymer, is a widely utilised surfactant for the production of cubosomes, with the PPO parts arranged at the surface or within the bilayer structure, and the PEO chains exposed to the surrounding water phase. In the case of cubosomes, the stabilising technique of F127 appears to be different from that in the case of simple dispersions like emulsions. The stabilising effect of F127 is due to the result of the adsorption of a hydrophobic portion (PPO) onto the surface of the particles, while the hydrophilic portion (PEO) extends out into the aqueous media, providing steric shielding. The stabiliser interacts with the scattered particles' structure and manipulates the phase behaviour in

cubosomes.[17] Stabilisers are used with a concentration of up to 20% *w*/*w* depending on the dispersed particles.

Carbopol

It is a pH sensitive polymer. It is also called as carbomer, acrylic acid polymer.[18]

Properties of carbopol

1) Carbopol is a high molecular weight, cross linked polyacrylic acid derivative and has strongest mucoadhesive property.
2) It is a water soluble vinyl polymer.
3) It shows sol to gel transition, in aqueous solution, when the pH is raised above its pKa value of about 5.5.
4) As the concentration of carbopol increases, its acidic nature may cause irritation to eye. Addition of cellulose will reduce polymer concentration and will also improve gelling property.

Sodium alginate

It is an ion-sensitive polymer. It is also known as algin, Alginic acid, sodium salt, E401, Kelcosol, Keltone, Protanal, sodium polymannuronate.

Properties of sodium alginate

1) Sodium alginate is a gum extracted from brown algae.
2) It is a salt of alginic acid.
3) It is a linear block polysaccharide consisting of two types of monomers-β-D-Mannuronic acid and α-L-glucouronic acid residues joined by 1,4-glycosidic linkages.
4) It exhibits good mucoadhesive property due to presence of carboxylic group.

Uses of sodium alginate

a) Thickening Agent.
b) Suspending Agent

Mechanism

The monomers of alginate (β-D-mannuronic acid (M) and α-L- glucuronic acid (G) are arranged as M-M block or G-G block with alternating sequence (M-G) block. Upon interaction of G block of polymer with calcium moieties, formation of homogenous gel takes place. Mechanical strength and porosity of hydrogel depends on G: M ratio, type of cross linker used and concentration of alginate solution.[19]

Hydroxy Propyl Methyl Cellulose (HPMC)

It is a temperature sensitive polymer. It is also known as Hypromellose, Methocel etc.[18]

Properties of HPMC

1) It is water soluble cellulose ether.
2) Widespread acceptance of HPMC due to.

a) Solubility characteristics of the polymer in organic and aqueous solvent system.
b) Non-interference with drug availability.
c) Flexibility and absence of taste and odour

3) It is composed of glucan chain with repeating β-(1,4)-D-glucopyranose unit.
4) It increases its viscosity when temperature increases.
5) At low concentrations (1-10 wt.%) aqueous solutions of HPMC are liquid at low temperature but gel upon heating.

Mechanism

Gelation of HPMC solutions is primarily caused by the hydrophobic interaction between molecules containing methoxy substitution. At low temperatures, the macromolecules are hydrated, and there is little polymer-polymer interaction other than simple entanglement. As the temperature is raised, the polymers gradually lose their water of hydration, which is reflected by a decline in relative viscosity. Eventually, when sufficient but not complete dehydration of the polymer occurs, polymer–polymer associations take place, and the system approaches an infinite network structure, as reflected experimentally by a sharp rise in relative viscosity. This sol–gel transformation has been exploited to design in situ gelling systems. These systems exhibited low viscosity at 23 °C and formed soft gels at 37ºC.

Uses of HPMC

a) Thickening Agent.
b) Stabilizing Agent.

Method of prepration

1. Top-down approach
2. Bottom-up approach
3. Heat treatment
4. Spray drying

1. Top-down approach

It is the most widely used in research area, where by bulk cubic phase is first produced and then dispersed by high energy processing in to Cubosomes nanoparticles. Bulk cubic phase is resembling a clear rigid gel formed by water swollen crossed linked polymer chains, whereas cubic phases are like liquid crystalline structure.[21] The cubic phases exhibits a yield stress that increases with increasing amount of bilayer forming surfactant and oils.

Based on most existing studies comparison of dispersion produced by sonication and high pressure homogenization suggests the formation of complex dispersions containing vesicles and Cubosomes with time dependent ratios of each particle type.[22]

Coarse Cubosomes on micron scale possess the same D-surface structure as their originating bulk cubic phase, but after homogenization, the P-surface dominates because of added polymers. The extreme viscous bulk phase is prepared by mixing structure-forming lipids with stabilizers, then the resultant is dispersed into aqueous solution through the input of high energy (such as high-pressure homogenization [HPH], sonication or shearing) to form LLC nanoparticles. At present, HPH is

the most extensively used technique in the preparation of LLC nanoparticles (cubosomes).[23]

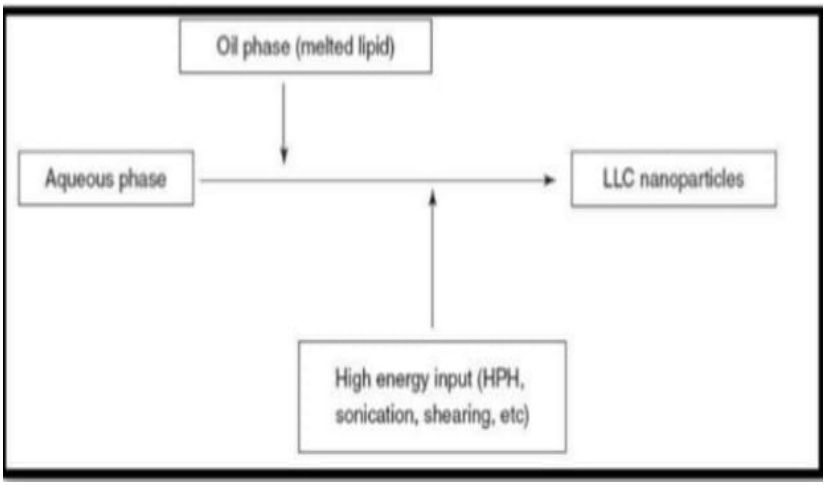

Figure 2: Top down technique.

2. Bottom-up approach

In this Cubosomes are allowed to form or crystallize from precursors. Almgren et., al. discuss the formation of Cubosomes by dispersing L2 or inverse micellar phase droplets in water at 80ºC,and allow them to slowly cool, gradually droplets get crystallizes to Cubosomes. This is more robust in large scale production of Cubosomes. Spicer et.al developed Cubosomes at room temperature is by diluting monoolein-ethanol solution with aqueous poloxamer 407 solution. The Cubosomes are spontaneously formed by emulsification.[21]

The key factor in the bottom-up approach is hydrotrope, which can dissolve water-insoluble lipids to create liquid precursors and prevent the formation of liquid crystals at high concentration. Compared with the top-down approach, this dilution-based approach can produce Cubosomes without laborious fragmentation. In other words, it needs less energy input. Moreover, this approach is far more efficient at generating small particles. The reason for this might relate to the forming mechanism of Cubosomes. The dilution-based approach can be regarded as a process of small particles forming big particles through aggregation, which is analogous to the use of precipitation processes to produce nanoparticles, whereas the top-down approach is more analogous to the attrition of big particles. In addition, Cubosomes prepared through dilution show long-term stability, which might be attributed to the homodisperse stabilizers onto the surface of Cubosomes. Indeed, the use of hydrotrope can simplify the preparation process and produce Cubosomes possessing similar or even better properties than those fabricated by the top-down approach.

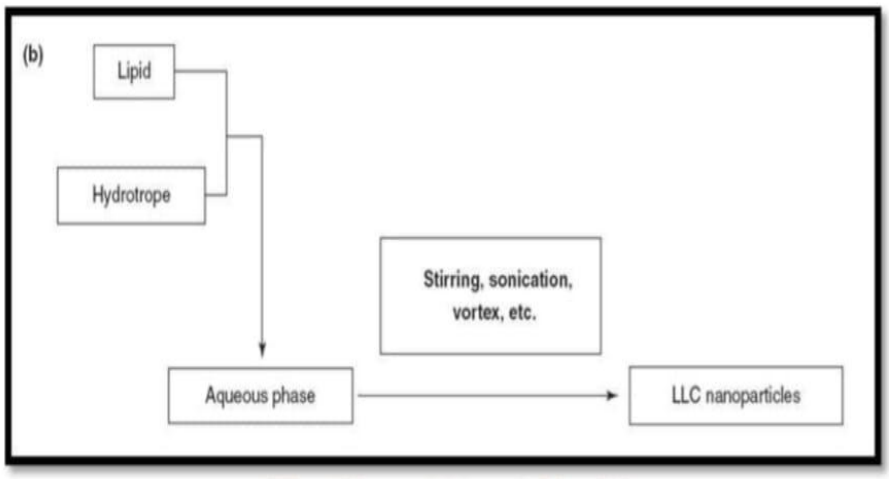

Figure 3: Bottom up technique.

3. Heat treatment

In this case, heat treatment can be regarded as a good approach. Note that in the strictest sense, heat treatment is not an integrated process for the manufacture of Cubosomes because it only promotes the transformation from non-cubic vesicles to well-ordered cubic particles. The dispersed particles, therefore, can be produced by a simple processing scheme comprising a homogenization and heat-treatment step. From the reported studies, heat treatment could cause a decrease in the small particle

size fraction that corresponded to vesicles and form more cubic phases with narrow particle distribution and good colloidal stability. Taking the whole process of preparation into account, it is obvious that the transition takes place during the procedure of heat treatment. The reason for transition could be speculated as an elevated temperature giving rise to a reduction in solubility and stability. When the temperature was below cloud point, the surfactant had a high solubility and thus the particles could exist stably and the phenomenon of fusion was hardly observed. Once reaching cloud point, the solubility of surfactant decreased notably and a notable fast fusion among vesicles would occur.

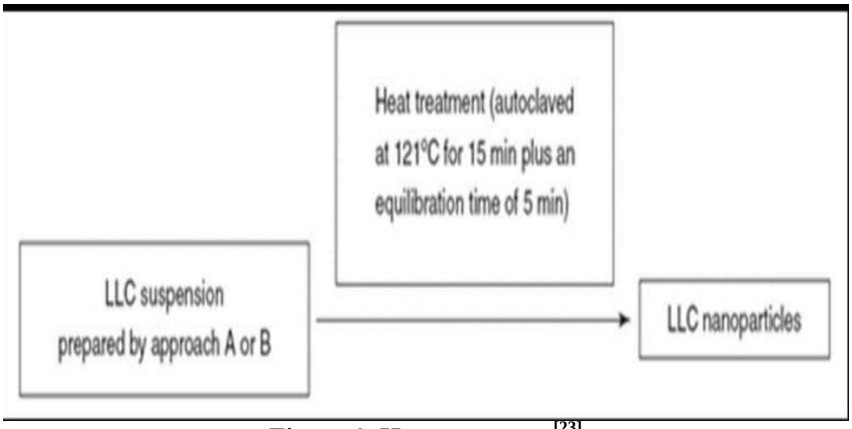

Figure 4: Heat treatment[23]

4. Spray drying

Another method of cubosome preparation is the spray-drying process. Spray-dried encapsulated particles are made from an emulsion of liquid droplets or dispersions of solid particles in concentrated water-polymer solutions.[24] Both phases are sprayed through a curated nozzle, creating suspension droplets to collide with a dry, hot airflow. Excess water quickly evaporates, leaving dry powder particles made composed of the dispersed phase surrounded by an encasing of the previously dissolved polymer. The spray-drying process is easy to scale up and is now frequently utilised in consumer goods such as detergents and meals. Furthermore, the method makes it simple to preload actives into cubosomes before drying.[25] Finally, the polymer coating on the powder gives the hydrated cubosomes surface properties, which can be changed by identifying the perfect encapsulating polymer. The liquid feed can be changed to alter the resulting powder's properties. For the production of starch-coated cubosomes powder precursors, high shear treatment of monoolein in aqueous starch solution produces a coarse cubosomes dispersion that is then pushed through a nozzle and dried. According to gravimetric measurements, drying removes approximately all of the water in the powder, resulting in a final composition of around 72% starch, 4% w/w water, and 24% monoolein in the finished powders.[26]

Evaluation of cubosomal dispersion

1. Analytical Method Used in the Determination of API

a) Determination of λmax of API

Absorption maximum of pure API was determined by dissolving drug in phosphate buffer saline pH 7.4. A sample of 10µg/ml was prepared and scanned for maximum absorbance using UV Visible spectrophotometer in the range from 200 - 400nm using phosphate buffer saline pH 7.4 as blank.[27]

b) Preparation of calibration curve of API drug

10mg of drug was accurately weighed and transferred into 100ml volumetric flask. The drug was dissolved and made up to the volume with phosphate buffer saline pH 7.4. It was further diluted with same buffer to get concentration of 2, 4, 6, 8 and 10µg/ml. The absorbance of solution was measured spectrophotometrically at 259 nm using buffer as blank. The absorbance values were plotted against concentration to obtain the standard graph.

c) Compatibility studies

Compatibility studies were done using FTIR and DSC.[28,29]

2. Optical microscopy

The cubosomal dispersions prepared were observed under binocular compound microscope at 10X and 40X magnification for studying the shape and surface morphology.[27]

3. Particle Size and Polydispersity index

The mean particle size and particle size distribution was determined by Malvern nano Zeta sizer instrument. The vesicles after diluted with distilled water were considered for the measurement of size.[28]

4. SEM

The prepared samples of cubosomes are coated with a gold film under vaccum for 2min. The specimens are transferred to an ISI ABT SX-40A scanning electron microscope and digital images captured.

5. Determination of percentage drug content

1ml of dispersion was pipetted from the dispersion and was further diluted with pH 7.4 phosphate buffer saline and the samples were analyzed spectrophotometrically at 259nm.

6. Determination of percentage entrapment efficiency

The %EE of the vesicles was determined using centrifugation technique. The vesicular dispersion was centrifuged for 20 min. Supernatant containing unentrapped drug was withdrawn and measured UV spectrophotometricaly at 259nm against phosphate buffer saline pH 7.4. The amount of drug entrapped in liposomes was determined by:[29]

$$\% EE = \frac{T-C}{C} \times 100$$

Where,

T = Total amount of drug calculated in both supernatant and sediment.

C = Drug in supernatant.

7. In vitro drug release

In vitro drug release was measured using Franz diffusion cell. Cubosomal dispersion was placed on one side of egg membrane in a vertical franz diffusion cell. Other side of membrane was in contact with the dissolution medium phosphate buffer saline of pH 7.4. Entire dissolution assembly was placed on a magnetic stirrer at temperature of 37°C. Aliquots of dissolution medium was withdrawn at different time intervals for 8hr. Drug concentration in the dissolution medium were determined by UV spectrophotometry at 259nm.[30]

Applications of cubosomes

- Cubosomes are used in cancer therapy.
- Cubosomal dispersion that containing monoglyceride used topically for mucosal or percutaneous application.[31]
- 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.
- Cubosomes are also been used in the treatment of fungal infections.
- Cubosomes are been used as a agent for delivery of vaccines.
- Controlled release of solubilized actives is the most popular application of cubosomes.[32]
- Biodegradable by simple enzymes.
- Monoglycerides has microbiocidal properties therefore used in the treatment of sexually transmitted diseases by both bacteria and viruses.[33]
- Cubosomes are recently used in cosmetics, skin care, antiperspirant and hair care.

CONCLUSION

Cubosomes are self-assembled liquid crystalline nanoparticle, which are more bioavailability and compatibility. Cubosomes are delivered into different route of administration like transdermal, parental, oral drug deliverey, biosensor and also gene transfection agent. Cubosomes are enchancing promising drug efficiency and flexibility for product development. Cubosomes is carried out the high load of drug molecule which should be delivered through the targeted site of action. There are many cubosomal dosage form like tablets, capsules are available in market. But still there is a need for new dosage form like gell, patches. It should be support both sustained release and controlled release of drug.

Funding

Nil.

Authors contributions

All the authors have contributed equally.

Conflict of interests

Declared none.

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