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A REVIEW ON CUBOSOME: A NOVEL APPROACH FOR DRUG DELIVERY

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ABSTRACT: Cubosomes are very stable nanoparticles, which consist of cavernous or honeycombed structures. Cubosomes are formed from some amphiphilic lipids and stabilized by a polymer. They are known as bicontinuous cubic phase liquid crystals. The bicontinuous word refers to the two continuous but non-intersecting aqueous regions by a lipid bilayer. Cubosomes are self-assembled liquid crystalline particles of a specific ratio of water and surfactant. Self-assembled cubosomes act like an active drug delivery system. They are having rheology like a solid. Cubosomes are thermodynamically stable, and their dispersions are biocompatible as well as bio-adhesive. Cubosomes are administrable in various ways, like parenteral, oral, mucosal, transdermal, *etc*., for the treatment of skin, hair, or any other body tissues. Cubosomes could encapsulate the amphiphilic, hydrophilic, and also hydrophobic substances. Nevertheless, some researchers have been identifying the scope of cubosomes as delivery systems. They have different drug loading modalities and having high internal surface areas. Controlled release and targeting of bioactive agents are other abilities of cubosomes. They are also applicable as membrane bioreactors, biosensors, artificial cells, etc. They are prepared by a simple method. As compared to the liposome, cubosomes possess larger breaking resistance. The present article reviews and discusses the advanced methods of preparation of cubosomes.

INTRODUCTION: The "cubosomes" term was firstly coined by Larsson, which is similar to liposomes [1]. Cubosomes are the nanostructured particles and these are the discrete and sub-micron size particles of the bicontinuous cubic liquid crystalline phase. The bicontinuous cubic phases are having a specific benefit, that is, their ability to tune membrane curvature. Cubosomesare self-assembled liquid crystalline particles, which have rheology like a solid [2]. Liquid crystals could be a quarter state of matter.

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These cubosomes are made up of lipids, polymers, and surfactants, which are usually amphiphilic. Here, the meaning of bicontinuous is that the enclosures of two different regions of water are divided by surfactant bilayers.

Cubosomes are similar to liquid crystalline substance, viscous, optically isotropic as well as solid and having cubic crystallographic symmetry [3]. Cubosomes are highly important in nano-technology based drug delivery system [4]. Recently, the interest in pharma has increased into a particle with a few hundred nm in diameter that is 10-500 nm in diameter [5]. The ratio of drug to the polymer is around 1:2 or 1:1, which may vary substance to substance. Some anticancer drugs have been successfully formulated in the form of cubosomes. The large-scale production of cubosomes was

difficult because of their viscosity and behavior of phase. When water is mixed with some specific surfactants, then there is a spontaneous formation of cubic phase [6]. The cubosomes and the parent cubic phase possess the same microstructure; also the cubosome dispersions have much lower viscosity as compared to the bulk cubic phase [7]. The cubosomes have a larger surface area in comparison to the parent cubic phase [8]. Cubosomes are formed by the self-assembly of surfactant-like molecules or amphiphilic molecules [9].

Cubosomes are generally prepared by high energy dispersion of the bulk cubic phase [10]. There is a colloidal stabilization by polymeric surfactants [11]. The cubosomal formulations are either released via diffusion or absorbed [12]. At higher levels of dilutions, most of the liquid crystalline systems are converted into micelles. But, at any dilution levels, the cubosomes remain stable. This is because of the relative insolubility of the cubic phase, which is formed by lipids in water. The controlled drug release is nothing but a release of a drug in a pre-designed manner. A drug delivery system is like a device that carries a drug moiety to the specific site of the body (or towards a specific tissue) to achieve an effective concentration at the site of action.

There are some benefits of controlled drug release, such as – enhances the therapeutic benefits, minimizes untoward side effects, reduce the need of multiple dosing, increases patient compliance, reduces cost, *etc.* [13-15] In the cubosomal vesicles, when drugs are incorporated into it, then it will transport drugs to the site of action (even a high molecular weight drugs). It acts as a penetration enhancer, and it will increase drug transport across skin [16]. Cubosomes are a part of vesicular drug delivery system, which were discovered in 1980 [17] and had great importance in a nanotechnology [18]. Cubic gel phase, cubosomes, and cubic phase precursor are the three forms of cubic phase. Cubosomes acts as a promising delivery system for various substances, such as proteins, amino acids, peptides, low molecular weight substances, nucleic acid, *etc.* [19, 20]. The mechanism of a cubic phase is as a delivery vehicle. They showed better stability than the liposomes [21-23]. Cubic liquid crystals are transparent and stable even in excess of water. Cubosomes are the form of binary systems [24]. Cubosomes have many applications such as antibiotics delivery, analgesics, enzymes, anti-muscarinic drugs and peptides delivery [25]. Cubosomes consist of highly twisted lipid bilayers, and they possess a high surface area, which is about 400 m^2/g [26]. The cubosomes size ranges from 10-50 nm in diameter. The cubosomal systems are superior to other novel delivery systems because there is an improvement in the stability of the drug in formulation, maximizing drug loading capacity, controlled drug release, and also optimum particle size. The drug in a cubosome will diffuse through a channel present on cubic phase [27].

Polymers used in cubosomes preparation are responsible for both stability as well as controlled release behavior [28]. These polymers also include block copolymers as well as PEG moieties. This is modifiable with protein molecules. There are few companies (Nivea, L'Oréal, Procter & Gamble) who are engaged in a researching activity for cosmetical (cosmeceutical) applications of cubosomes. Recently, researchers are investigated the cubosomes for the therapy of cancer, cosmetic production, topical applicability as well as other drug delivery systems. In practice, the anticancer drugs which are being formulated are very less [29].

1.1. Advantages: Cubosomes are bio-adhesive, non-irritant, non-allergic, biocompatible, and biodegradable [30]. It has a simple method of preparation [31]. They have a high drug-loading capacity because of their high internal surface area. They are thermodynamically stable for a longer time period [32]. It has physicochemical stability (even in excess of water) [33]. They have an ability to encapsulate amphiphilic, hydrophobic/lipophilic (cinnarizine), as well as hydrophilic (like cyclosporine) substances [34, 35]. The controlled release and targeted release of bio-actives are achievable with the use of a certain polymer. Bioavailability is good because of its size. Since less repeated administration is there, it minimizes overall health care cost. They reduce side effects, which are related to the burst release in case of injections. Particle volume and a bilayer area possess a larger ratio as compared to liposome [36]. In comparison with the other conventional carriers (lipid-based), cubosomes possess the property of excellent solubilizers. They showed a capacity to encapsulate the drugs which are sparingly water-soluble. They act as a vehicle that carries the

sensitive drug moiety from the enzymatic degradation (proteins, peptides). They enhance the bioavailability of water-soluble peptides in the range of about 20-100% [37]. The methods for the preparation of cubosomes (*i.e.,* shear and homogenization techniques) do not require the use of organic solvents [38, 39].

1.2. Disadvantages: There is less entrapment of water-soluble drugs because of the presence of a large amount of water inside cubosomes [40]. The large-scale production of cubosome is difficult, due to high viscosity [41]. The controlled drug delivery cannot be possible without the use of a specific polymer. They may lead to leakage during storage or during *in-vivo* transfer [42]. There are chances of growth of particles upon long-standing. Cubosomes have the capability to cause a phase change (their dynamics), if there is a change in external environment [43].

2. Structure of Cubosome: The honeycombed structure is the basic structure of cubosome. They possess a solid-like viscosity [44]. They look like a dot, and every dot is related to the presence of pore [45]. There are two internal aqueous channels, and in between them, there is a large interfacial area. Simply, cubosomes are the nanoparticles or nano-structure particles of liquid crystalline phases.

They possess crystallographic symmetry. They are self-assembled with amphiphilic substances. They are bicontinuous (distinct, but continuous and non-intersecting) regions of water which is separated by surfactant. This interconnected property makes cubosomes a viscous gel which is very similar to hydrogels. The composition of cubosomes, *i.e.,* water and lipid, make them biocompatible [46].

2.1. Types of Cubosome Precursors: They are able to protect the thermosensitive drug moieties.

2.1.1. Liquid Cubosome Precursor: In this, the particles are produced by nucleation, and then there is a growth by saturation. It is observed that the process of hydrotrope dilution produces comparatively stable as well as smaller cubosomes. This is obtained by dissolving monoolein in any of the hydrotrope. Then the subsequent dilution of the mixture spontaneously precipitates or crystallizes. It avoids the high energy processes and also bulks solid handling. It permits the easy scale-up of cubosomes preparation [47, 48]. These are generally used in hand washes and mouthwashes.

2.1.2. Powdered Cubosome Precursors: They consist of surfactant, which is dehydrated and coated with a polymer. The cubosomes are formed by the hydration of the precursor powders.

The lipids used here are sticky and waxy solids. The suitable process which is applicable to this is a spray drying process [48], which is suitable for large-scale production.

3. Components of Cubosomes: Natural lipids which possess bicontinuous cubic phase, amphiphilic surfactants as well as polymers are the main components of cubosome formulation [49]. Lipids like monoglycerides, glycolipids, phospholipids, and urea-based lipids have the ability to self-assemble spontaneously in the presence of water [50]. Usually, GMO addressed as monoolein and phytantriol [51, 52]. Monoolein is the main precursor of cubosome formulation, and it is present in two forms. These are – as a mixed glyceride form and as a distilled monoolein. Distilled monoolein is applicable in pharmaceuticals because of its purity.

It is known as ‘a generally recognized as safe’ (GRAS).The most commonly used surfactant in cubosome formulation is the Poloxamer (concentration range 0%-20%w/w). Polyvinyl alcohol is an alternative for poloxamer as a stabilizing agent. The presence of ester moiety makes GMO a biodegradable lipid [53]. Oleyl-glycerate (OG) (forms reverse hexagonal phase) and GMO (forms bicontinuous cubic phase) are structurally similar.

For parenteral use of GMO, some literature were highlighted GMO-induced hemolysis. The OG is safe for the formulation of the oral dosage form. Phytantriol possesses benefits such as penetration enhancer [54], time-controlled release as well as sustained release, then structural stability and high purity as compared to GMO [55, 56]. Phytantriol is a good alternative for a GMO. Phytantriol is more hydrophobic than GMO, but Phytantriol has a more branched hydrocarbon chain than GMO. Therefore, GMO is more flexible. The physicochemical factor to be considered while selecting excipients is that, the compatibility of drug and polymer [57]. So as to

minimize the stability issue, there goes a selection priority towards the polymers, and the melting point of that carrier molecule should be more than 45 ºC [58].

4. Methods of Preparation of Cubosomes:

1) High-Pressure Homogenization

2) Automated Cubosome Preparation

3) Probe Ultrasonication

4) Other Methods:

4.1) Emulsification

4.2) High Shear Homogenization Technique

4.3) Spray-Drying Technique

5) Special Techniques:

5.1) Top-Down Technique

5.2) Bottom-Up Technique

4.1. High-Pressure Homogenization: It is the most suitable method [59, 60] for the cubosome preparations, which are highly stable during high-pressure homogenization process and also retains a long shelf life [61, 62]. It consists of three steps:

4.1.1. Gel Preparation: In this step, the lipid and amphiphilic surfactants are dissolved in solvent (organic) followed by mixing properly, so as to appear as a uniform mixture. Here, the rotary evaporator is used to evaporate the organic solvent to form the gel phase of a formulation.

4.1.2. Shearing: In this step, the prepared gel is going for shear. The aqueous solvents are used to produce a micro-dispersion. It is the determining step before homogenization in the process of cubosome formation.

4.1.3. High-Pressure Homogenization: This method is applicable to the large volume sample systems (30 ml), and it is not acceptable for the small volume sample systems.

In this step, the temperature is selected as per the properties of lipid since this method is temperature-sensitive. In this, the prepared dispersion is undergoing the high-pressure homogenizer for homogenization. Only a single sample could be processed by this method.

2. Automated Cubosome Preparation: It is similar to the probe sonication method with few changes. A large number of cubosomes could be prepared by this method. The probe sonicator and robotic systems are used in this method of cubosome preparation. In this method, the gels are prepared by using a 96 well plate which has a solvent capacity of 600 µl. Then the sonication is performed by a robot. Here, in this method, the physicochemical properties can be easily assessed [63].

3. Probe Ultra Sonication: This process is fast and is used for the preparation of small volume samples. It is capable of dispersing samples, even if it is 600 µl in quantity. It depends on probe size. In this process, the gels are prepared by the addition of stabilizers. Then there is a solvent equilibration which forms a cubic phase. After this, the cubic phase is transferred for the ultra sonication64. So as to control the pulsing frequency and to avoid overheating of samples, there is a need for careful maintaining of variables, *i.e.,* frequency and amplitude.

3.1. Advantages: The equipment's which are applicable in this method is very common. This method is easy and is widely used.

3.2. Disadvantages: There are chances of contamination due to metal. During the storage phase, particle growth could happen.

4. Other Methods:

4.1. Emulsification: In this method, the cubosomes are produced by poloxamer 407, which dilutes the monoolein-ethanol solution [65].

4.2. High Shear Homogenization Technique: In this method, stabilizers are added so as to avoid the aggregation of particles in the shelf-life period. (It is a good method, but it has some limitations also, which is because there is a high shear application [66]).

4.3. Spray-Dried Technique: This technique is also applicable for the production of cubosomes. In this method, the monoolein is covered by polysaccharides (dextran/starch) after hydration.

Then the polymers are added into this so as to maintain stabilization [67].

4.3.1. Advantages: This method is applicable for powder formulations. By using this method, microencapsulation is possible. In this method, organic solvents are also applicable.

4.3.2. Disadvantages: This method is complicated (as compared to other methods). A very low amount of yield is obtained by this method (5 to 30%).

5. Special Techniques:

5.1. Top-Down Technique: This technique is applicable for the cubic phases in bulk and it needs a high energy input. It is prepared by the addition of amphiphilic surfactants with lipid. Then the above mixture is dispersed in an aqueous phase by the use of high-pressure homogenization, which is followed by sonication. This produces liquid crystal nanoparticles.

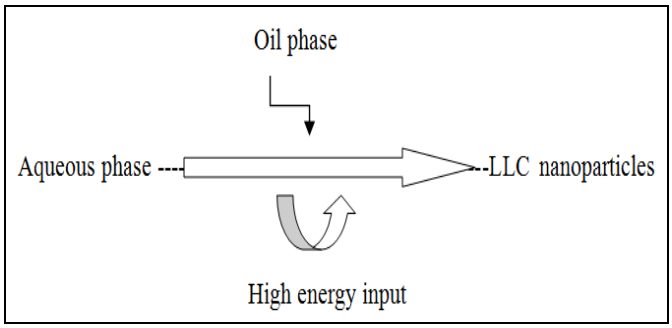

FIG. 1: TOP-DOWN TECHNIQUE OF CUBOSOME PREPARATION

It is a widely used technique. It is invented by Ljusberg-Wahren, in 1996. It requires high energy input. The cubosomesco-exist with vesicles like structure 68. In this method, firstly, the cubic phases are formed in bulk, and then it gets dispersed by high energy. There is a rupturing of the cubic phases; therefore, there is a requirement of high energy input [69].

5.1.1. Advantages: Prepared formulations are clear and visible. The use of organic solvents is not required in this method. This method is comparatively simple.

5.1.2. Disadvantages: It is a time-consuming process. This is a method, which needs high energy input.

5.2. Bottom-Up Technique: This technique is applicable for the robust preparation of cubosomes. It is very effective in the preparation of small particles. A very less energy input is required.

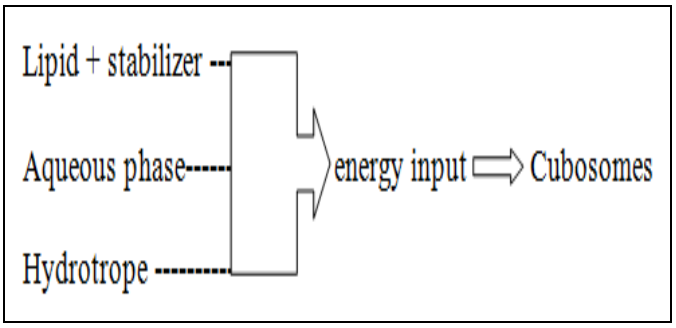

FIG. 2: BOTTOM-UP APPROACH FOR CUBOSOME PREPARATION.

In this method, the cubosomes are produced from the precursors. In this, there is a spontaneous formation of cubosomes by the process of emulsification [70]. In this method, hydrotrope is the important element. It is a process in which the large particles are formed from the aggregation of particles (approach=dilution-based). Therefore, they exhibit stability for a longer-term.

5.2.1. Advantages: It is not time consuming process. The use of any organic solvent is not required. Here, very low energy is needed.

5.2.2. Disadvantages: It may produce allergic reactions if taken orally because of hydrotropes. It produces milky white preparations.

6. Evaluation and Characterization of Cubosomes:

6.1. Visual Inspection Studies: In this, the cubosomes are inspected for their external appearance, such as morphology, turbidity, color, uniformity, and presence of particles.

6.2. Transmission Electron Microscopy (TEM): The morphology of cubosomes could be assessed by using TEM. It could provide shapes of cubosomal particles. It could give electron microphotographs' for observation and gives a high-resolution image. Therefore, visualization is possible. It is capable of giving much high resolution as compared to light microscopes. It acts as an excellent tool for character determination of soft matter dispersions. It could overcome all the demerits (vacuum environment, poor images,

inducing structural changes in cubic phase, *etc*.) of regular electron microscopy.

6.3. Zeta Potential: The stability of preparation could be assessed by a magnitude of zeta potential. It shows a high degree of repulsion.

6.4. Viscosity: Viscosity could be assessed by use of viscometer, *i.e.,* Rotational Brookfield Viscometer.

6.5. Particle Size Analysis: In this, the samples are diluted with compatible solvent and are exposed to 300 Hz, which is the scattering intensity of light at 25 ºC [71]. It is measured by dynamic laser light scattering by the use of a Zeta sizer. In this, the PDI and zeta potential can also be measured. It gives data that contains the average weight, volume, size. For the determination of particle size by Malvern zeta sizer, there is a need; that is, the samples could be diluted to 100 folds with water.

6.6. Polarized Light Microscopy: The determination of the cubosomal surface coatings, which are optically brief ringent or vesicular, could be possibly assessed by polarized light microscopy. The anisotropic and isotropic differentiation could also be provided by this method [72]. It could observe the alteration of cubic phases. It provides information about the possible co-existence of layered (cross or striated pattern) and hexagonal liquid crystals [73].

6.7. Differential Scanning Calorimetry: DSC could give information about whether the phase transition occurs or not, as the liquid crystals are thermodynamic equilibrium systems, as the endothermic and exothermic processes are responsible for phase transitions.

6.8. Small Angle X-ray Scattering: To determine different groups in a sample and their spatial arrangement, the small-angle X-ray scattering could be applied. It also provides information about pore sizes, distances of partially ordered substances, and the shape of particles. It can measure structural information on molecules, which is in very small size, *i.e.,* 5 to 25 nm. It is applicable for determining the 3-D arrangement of various groups present in the formulation.

6.9. Entrapment Efficiency: The ultrafiltration techniques could be used for the assessment of cubosomal entrapment efficiency [74]. In this method, the concentration of an unentrapped drug is measured and from this, the concentration of entrapped drug could be found, and this is achieved by the use of a spectrophotometer. In this, the dilution of the sample is made with deionized water, and then there is centrifugation. After this, there is a process of ultrafiltration, which consists of a certain amount of drug, measured spectrophotometrically.

6.10. Drug-loading Determination: It could be determined by the use of ultrafiltration methods or gel permeation chromatography. Then it could be analyzed by HPLC [75].

6.11. Drug Release Measurement: It could also be measured by pressure ultrafiltration method [76]. It consists of an Amicon pressure ultrafiltration cell. This is joined with the Millipore membrane.

6.12. Stability Studies: In this, the stability could be assessed on the basis of organoleptic as well as morphological characteristics with respect to the time period. Also, the drug content and particle size distribution determination with the time [77]. In this, evaluations of possible changes with respect to time are studied.

7. Applications:

7.1. For the Controlled and Sustained-release Behavior: This is achievable because of the unique behavior of cubosomal particles, *i.e.,* the leftovers. It is the most popular application of cubosomes achieved by researchers. The cubic phase is the one that is very favorable for controlled release, as it has a small (5-10 nm) pore size. A variety of ingredients or API's having different physicochemical characteristics could be encapsulated in cubosomes. Because of the advantage of biodegradability of cubosomal material by enzymes, controlled and sustained release of drug is achievable, and they are not accumulating inside the body.

7.2. As a Drug Delivery Vehicle: Some companies (L'Oréal& Nivea) are trying for the cosmetic formulation (O/W emulsion stabilizers, pollutant absorbents, *etc*.), which consists of the use of cubosomes [78]. This is a very common use of cubosomes and is a universal application of cubosomes.

7.3. For Topical Drug Delivery Systems: As the nature of cubosomes is very bio-adhesive, therefore they are used in mucosal as well as topical drug delivery systems. They are useful for providing protection for skin sensitivity.

Cubosomes possess high permeability as they consist of ethanol, and ethanol is responsible for the disruption of the skin. Because of this, there is an enhancement of lipid fluidity, and they enhance the skin permeability of the drug.

7.4. For the Treatment of Viral Diseases: The lipids which are used in the formulation of cubosomes, such as monoglycerides, possess microbicidal activities. Therefore, they are applicable for the treatment of sexually transmitted diseases, which are caused by viruses (HIV) as well as by bacteria (genorrticae) [79].

7.5. For Cancer Therapy: There are many anticancer drugs whose encapsulation within cubosomes has been successfully done. Cubosomes acts as a very favorable carrier for anticancer agents. The delivery system, which is having a small size, is the important parameter for the anticancer agents so as to get increased effects as well as retention.

7.6. For Intravenous Drug Delivery: The cubosomes have the promising characteristic of high drug payload as compared to the liposomes.

Also, it is a carrier, which acts as an ideal carrier for injections. Some of the small molecules, which are insoluble, are given by cubosomes.

They also act as a precursor for the delivery of viscous substances. Because of, when the lamellar phases are injected *via* subcutaneous route, initially it is flowable, but later it absorbs water from surrounding, and therefore, it converts into cubic phase. This is responsible for the formation of in situ depot.

7.7. For Oral Drug Delivery: The oral drug delivery system consists of many challenges. Such as

a) Large size molecules

b) Aqueous solubility

c) Absorption (poor)

Cubosomes are able to overcome all these challenges. They also have another advantage, which is the release of drugs at various sites and this is required in the case of drugs whose absorption window is narrow 80. The local effect *i.e.*, in the gastrointestinal tract, is also possible.

8. Future Prospects: The cubosomes grip a great capability in the application of drug delivery as well as sustained drug delivery. The previous studies on cubosomes are needed to be broadened because these are still at the very basic level, and further investigation is needed. The exact studies are required for the drug loading capacities as well as their release behavior. In the future, there is a requirement for further optimization and development so as to understand the suitability of cubosomes with body tissues and blood. Then another thing, which is a must in the development, is that the stability requirements of cubosomes in the biological fluids. Also, studies are required so as to get knowledge about the factors, which affect drug release from cubosomes.

CONCLUSION: Cubosomes possess the capability to encapsulate many drugs, *i.e.*, both hydrophilic as well as hydrophobic; also, they are able to reach the targeted sites, like the brain or central nervous system. Cubosomes are usable for the various types of drug moieties, immunogenic substances, proteins, and cosmetic preparations.

They are very small in size but possess a wide drug loading area. The cubosomes have been widely applicable for ophthalmic, oral, intravenous, topical, melanoma therapy, and also for diabetes. It also has a unique property in personal care products. There is a similarity between the internal structure of body tissues and cubosomes. They are suitable for the skin and various tissues of the body for treatments.

This is because of their ability to target specificity. This cubosome technology is comparatively novel, and it has a lot of scope in the research area for the formulation and development of new products with high output.

This leads to industrial and commercial progress in the field of the pharmaceutical sector. Cubosome formulations are prepared by only a simple combination of lipids with water and they offer

flexibility in the development procedure of the product. They are suitable for body tissues because of the compatibility of lipids. In conclusion, there is a need for further study on cubosomes, so as to better understand the safety testing and the role of vesicles of cubosomes in the drug delivery systems.

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