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A Review on Cubosomes

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ABSTRACT
Cubosomes are the submicron, nanostructure nanoparticles that consist of the "Bicontinuous' ' liquid crystalline phase. It is of greater importance in nanoformulation and the Cubosomes can encapsulate the Hydrophobic, Hydrophilic, and Amphiphilic drug molecules. They are biocompatible and bioadhesive in nature. As they are nanoparticles the size varies from 10-500nm in diameter and it appears like a point with a round shape. The basic components required for the formulation of cubosomes are lipids and stabilizers. The most commonly used lipid is glyceryl monooleate (GMO), phytantriol (PHYT) and the most commonly used stabilizer is Pluronics (F127 or P-407). This overview focuses on the method of preparation, evaluation, and application of cubosomes.

Keywords: Amphiphilic, Bicontinuous, Phytantriol, Pluronics, nanocarrier, nanostructure.

I. INTRODUCTION:

[1].The word cubosomes was coined by "Larson". Cubosomes are submicron nanostructure nanoparticles of the bicontinuous liquid crystalline phase. Bicontinuous means two different hydrophilic regions are separated by two-layer. Cubosomes have more importance in nanoformulations and they can encapsulate the hydrophilic, hydrophobic, and amphiphilic compounds and the solubility of poorly soluble drugs can be increased. The prepared formulation can be given by different routes such as Transdermal, Parenterally, orally (mostly for delayed-release).

[2].Cubosomes are liquid crystalline nanoparticles made from the cubic phase of lipid such as monooleate and surfactants, which can be polar or nonpolar, so they are known as amphiphilic molecules and has different properties of being dispersed in particles. Cubosomes have a similar microstructure as that of the cubic mother phase and have a greater surface area and the dispersion has less viscosity than the bulk cubic phase the dispersions are bioadhesive and biocompatible. Cubosomes can be prepared through elevated energy dispersion of bulk cubic phase which can be followed by using polymeric surfactants.

[3].The cubic phase can be split and becomes thermodynamically to a stable state for particle dispersions. They are self-assembled in nature and have a different internal cubic structure and composition from that of a variety of active ingredients.

Merits and Demerits

[4,6] **.Merits:**

- ✓ Easy method for formulation.
- ✓ Drug payload is high due to more internal surface area and cubic shapes.
- ✓ Lipids are biodegradable and biocompatible such that hydrophilic, hydrophobic, and amphiphilic compounds can be encapsulated.
- ✓ The controlled and targeted release of active ingredients can be achieved.
- ✓ It is non-toxic.
- ✓ It can protect the active ingredient by the means of physical and chemical degradations.
- ✓ Cubosomes are excellent solubilizers.

[4,6].**Demerits:**

- ✓ Large-scale production is not possible because of the high viscosity of the cubic phase.
- ✓ As the water content is high so it possesses less entrapment efficiency for the water-soluble drugs.

Structure of Cubosomes

[5] .Cubosomes are nanoparticles size varies from 10-500nm in diameter and looks like point which is mostly to be round in shape each dots contain lipid and water it was first reported by "LUZZATI and HUSSON " by using X-ray scattering method. By Fontell and Drew whereas the ternary system of amphiphiles water and oil with some monoglycerides such that it forms the

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cubic phase. The structure of the cubosomes consists of cavernous (honeycomb-shaped). The structure is divided into two internal aqueous channels with a greater interfacial area. As the Cubosomes are "Amphiphilic" carrier systems so the hydrophilic and lipophilic drugs can be encapsulated easily.

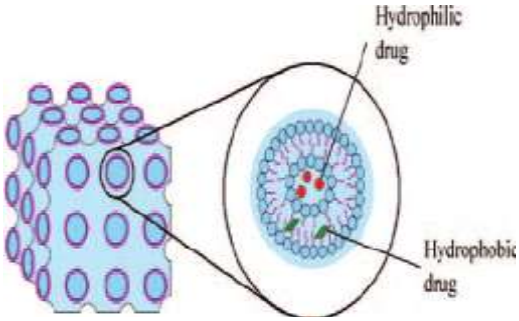

Figure 1: Structure of cubosomes.

Basic Components used in the Preparation of Cubosomes

Amphiphilic lipids:

[2].The most common lipid used in the preparation of Cubosomes is GMO (Glyceryl MonoOleate). The GMO is consists of the glycerides of oleic acid with other fatty acids, mostly it contains monooleate, which is suitable for the group of amphiphilic lipids, which can form different Lyotropic liquid crystals. the GMO hydrocarbon chain ranges from 12-22 and it has a stronger tendency for the formation of the cubic phase. GMO is inherently biocompatible and biodegradable and it is used as an Emulsifier in most of the food industry.

Phytantriol (PHYT)

[4]. Phytantriol is commonly used in cosmetics preparation products it is the alternative to GMO in cubosomes formulation the IUPAC Name of phytantriol is **(**3,7,11,15-tetramethyl-1,2,3-hexadecane thiol) phytantriol can form the bicontinuous cubic phase in an aqueous medium under physiological conditions and temperature. It possesses more chemical stability than GMOs because of the absence of ester groups. PHYT based "liquid crystalline matrices" was known and it was able to sustain the release of various active molecules mostly for the substances having hydrophilic properties and can be used in the formulation of the Sustained drug delivery systems. PHYT can help in moisture retention and also enhance skin penetration.

Stabilizers

[4]. The function of stabilizers is to give the electrostatic barrier between the particles such that to prevent the close contact between them and to maintain them in a stable state. The effect produced by the stabilizer in lipid water assembly without disturbing the cubic phase so the appropriate choice needed to be done for the selection of the required stabilizers. The most widely used stabilizer in cubosomes preparation is "Pluronics' ' mostly F127 or P-407 it has been considered the Gold standard. The pluronic are water-soluble and self-assembled tri-block copolymers which are mainly composed of Polyethylene Oxide (PEO), Polypropylene (PPO) they align as PEO-PPO-PEO configuration the PEO and PPO are liable for the hydrophilic and hydrophobic properties. The stabilizing action of P-407 or F127 is adsorption of a hydrophobic (PPO) region on the surface of particles whereas a hydrophilic (PPO) region extends out in an aqueous medium which acts as a shield. The stabilizers are used depending upon the dispersed particles they can be used in the concentration of 20% whereas GMO can be used in a concentration of 2.5%.

The method used for the Formulation of Cubosomes:

The mostly two methods are used in the preparation of the cubosomes are:

1) **Top-down method**
2) **Bottom-up method**

Top-down method

[4].This method was introduced by Ljusber-Wahren in 1996. It is one of the most widely used methods for the formulation of cubosomes. The two main steps involved in this method are. In the First step the mixing of the Lipids such as (GMO or PHYT) with an appropriate stabilizer like Pluronics (P-407) so that they can form as the bulk viscous cubic aggregates. In the second step, the process of dispersion

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involves the form of cubic aggregates that are needed to be dispersed in an aqueous medium by the means of "high-pressure homogenization or sonication process" finally the Cubosomes can be formed. The cubosomes produced by this method are stable against the aggregation for the year. The disadvantage of this method is large-scale production cannot be done by using this method.

Bottom up- method

[4]. This method is known as the solvent dilution method in this method the dispersion of a mixture of cubosomes containing the lipids, stabilizer and the other mixture known as hydrotrope such as (ethanol, sodium benzoate, Urea, etc.) can be used as hydrotrope it is the important step in this method as it is done to dissolve the water-insoluble lipids so that it can act as the lipid precursors which can prevent the formation of the liquid crystals at the high concentration the hydrotrope is a molecule which can solubilize the poorly soluble substances in an aqueous medium the solubilizing mechanism of hydrotrope leads to the formation of the complex in-between hydrotrope and hydrophobic substances. In this method, the three mixtures are prepared separately the first mixture is lipid and stabilizer mixture such as(GMO +P-407) the Second mixture is known as hydrotrope it may some of the hydrotrope like (Ethanol, Urea, Sodium benzoate) and the third mixture will be the aqueous medium. The above two mixtures first and second are dispersed into the aqueous medium in the form of droplets and the less energy input is required such as (Vortex) the energy needed to be supplied for the required period and the formed droplets are needed to be cool finally which led to the formation of Cubosomes. This method has more merits than comparing with the top-down method such as the energy input involve is less and this method is suitable for the preparation of cubosomes for those substances which are sensitive it has long-term stability because of the homogenous dispersion of stabilizer to form nanovesicles.

[7] .The various dispersion methods for the formulation of Cubosomes are

- ✓ Sonication
- ✓ High-pressure homogenization
- ✓ Spray drying
- ✓ Spontaneous emulsification

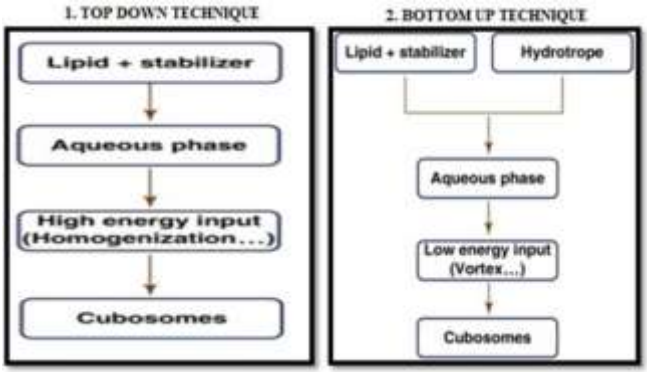

Figure 2: Diagrammatic representation of Top-down method and Bottom-up method.

Evaluation and Characterization method of Cubosomes:

The various methods that can be used for the cubosomes evaluation and characterization are:

1. Visual inspection
2. Particle size distribution
3. Shape of cubosomes
4. Zeta potential
5. Efficiency of entrapment
6. Drug release measurement
7. Stability studies
8. Gel permeation chromatography or HPLC analysis
9. Polarized light microscopy
10. X-ray diffraction
11. Light microscopy
12. Viscosity

1. Visual inspection

[1,3].With this method, the Cubosomes are visualized for their optical appearance such as color, turbidity, Homogeneity, etc. This can be determined after the one-week preparation of the sample

2.Particle size distribution

[1,3].The distribution of the particle size can be measured by using dynamic laser light scattering via zeta sizer (photon correlation

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spectroscopy). In this method, the sample is diluted with an appropriate solvent, and then it is adjusted to the light scattering intensity of 300Hz and determined at 25^0C in triplicate, and the data needed to be collected of overall average weight size and volume. Such that the zeta potential and polydispersity index can be determined.

3.Shape of Cubosomes

[1,3] .Transmission electron microscopy can be used for determining the shape of Cubosomes. In this method, the suspension of the cubic phase is negatively stained by using 2% phosphotungstic acid solution with pH 6.8 and it is transferred to a carbon-coated grid and then air-dried at room temperature and then the electronic microphotograph is taken. Whereas SEM analysis cannot be done for the cubosomes formulation because the integrity and robustness of compounds can be lost due to the electron array.

4.Zeta potential

[23]. Zeta potential is an important indicator of the stability of the formulation. The magnitude of zeta potential determines the degree of electron repulsion between the same particle charges. It is important for knowing the long-term stability of the colloidal dispersion; the high value of zeta potential gives sufficient electric repulsion.

5.Efficiency of entrapment

[1,23].A Cubosomes entrapment efficiency can be measure by using the Ultrafiltration method. In this method, the cubosomal dispersion will be first separated employing centrifugation. The untrapped drug concentration is determined which is subtracted from the total drug which has been added then the amount of drug is analyzed utilizing a Spectrophotometer.

6.Drug release measurement

[1,24]. The amount of drug release can be determined by using the pressure ultrafiltration method. This method was proposed by Magenheim et al by using a micron pressure ultrafiltration cell which will be attached to the Millipore membrane at ambient temperature (22 ± 2^0C).

7.Stability studies

[3,23].Physical stability study can be done by investigation of organoleptic and morphological properties with an aspect of time and stability studies must be carried as per ICH guidelines such that the drug content and pH must be determined periodically.

8.Gel permeation chromatography

[3].The drug loading of cubosomes can be determined by using this method or by using ultrafiltration methods. In this, the untrapped drug concentration will be determined and it is subtracted from the total amount of drug added and then the amount of the drug can be analyzed by using a UV spectrophotometer or HPLC analysis.

9.Polarized light microscopy

[3,24].It is used for the release of the optically birefringent surface coating of cubosomes and it can determine the difference between the isotropic and anisotropic compounds the samples can be viewed between the crossed polarizers.

10.X-ray diffraction method (XRD)

[24].This method is used to determine the spatial arrangement of different groups in the sample. In this method, samples will be held in vacuum-tight cylindrical cells provided with mylar windows. The Diffraction data are collected. The diffraction patterns obtained are plotted as intensity vs q value which helps in the identification of peaks and converted into miller indices. The miller indices can be correlated with the known values of various liquid crystalline structures and space groups to know the internal nanostructure of the sample.

11.Light microscopy

[3].The cubosomes prepared sample will be diluted with deionized water and it can be measured by using an optical microscope and it is calibrated with the help of a micrometer slide by using the magnification lens of x400 and x1000.

12. Viscosity

[3,23].The viscosity of the sample can be determined at various angular velocities by using Brookfield viscometer. The rotation speed needed to be maintained at 20rpm with 18 spin and the average three readings will be used for the viscosity determination of the sample and the viscosity will be noted in cps.

Application of Cubosomes:

The cubosomes formulation has enormous applications as they act as carriers so it can be used in different drug delivery systems and it also uses in preparation of the cosmetics products the various drug delivery system such as

- Ocular drug delivery system
- Intravenous drug delivery system
- Transdermal drug delivery system
- Oral drug delivery system
- Controlled release drug delivery system
- In Chemotherapy (cancer)

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Ocular drug delivery system

[4].As the cubosomes can encapsulate the drugs which are amphiphilic, hydrophobic, and hydrophilic and they can release the drug at the targeted site in a controlled manner. The recent studies are concerned with the application of cubosomes in an Ocular drug delivery system. The cubosomes formulation contains the GMO as lipid in the formulation it shows the mucoadhesive properties which affects the loaded drug and the drug shows the long residence time at the surface of the cornea. To overcome this effect corneal permeability and bioavailability of the incorporated drug needed to be improved.

Example of drug-loaded as cubosomal formulation for ocular drug delivery system

[8].**Drug-**Dexamethasone, **Lipid used**-GMO, **Stabilizer used**-pluronic, **Uses-**use for anterior ocular inflammation.

[9].**Drug-**Flubiprofen, **Lipid used**-GMO, **Stabilizer used**-Pluronics, **Uses-**Used as NSAID for ocular inflammation.

[10].**Drug-**Pilocarpine nitrate, **Lipid used-**GMO, **Stabilizer used**-Pluronics, **Uses-**Use to treat glaucoma.

Intravenous drug delivery system

[2,24].The lipid nanoparticles compress the internal liquid crystal structure of the curved lipid membrane which is used to solubilize the encapsulated or loaded drug and then to deliver the drug to the targeted sites. The lipid nanoparticle increases the payloads of proteins, peptides and the substance which are insoluble. These are carriers for the injection of many activities.

Transdermal/ Topical drug delivery system

[2].Cubosomes are more adhesive so they can be used easily for topical or transdermal routes and the mucosal deposition and delivery of various drugs. The topical drug delivery is based on the unique property of liquid crystal (LC) and liquid crystal nanoparticles technologies (LCNT) this drug delivery has a unique in situ forming bioadhesive LC system which controls and affects the drug delivery to the mucosal surface such as vaginal, buccal, ophthalmic and others. The LC system forms a thin film surface at mucosal lining which consists of a liquid crystal matrix by which the nanostructure can be controlled for achieving the optimum drug delivery profile and can provide good temporary protection for sore and sensitive skin.

Examples of drug-loaded cubosomal formulation for Transdermal drug delivery

[11].**Drug-**Dapsone, **Lipid used**-GMO(Glyceryl monooleate), **Stabilizer used**-Pluronics, **Uses-**Used to treat acne, leprosy, systemic lupus erythematosus.

[12].**Drug-**Silver sulfadiazine, **Lipid used**- GMO, **Stabilizer used**-Pluronics, **Uses-**Used to treat infected burns.

[13].**Drug-**Palmitoyl peptides(pal-GHK, pal-GQPR), **Lipid used-**GMO, **Stabilizer used-**Pluronics, **Uses-**Can be used to treat wrinkles acts as anti-wrinkle agents.

Oral drug delivery system

[2,24] .The cubosomes can be used in oral drug delivery for various drug substances such as for the drug which is poorly soluble in water, the drug which is poorly absorbed, and for the drug with high molecular weight. The liquid and powder in capsule form compress self-emulsifying liquid crystalline nanoparticle technology. The large proteins can also be encapsulated. The liquid crystalline nanoparticle technology carriers can release at various absorption sites such as the upper and lower intestine which is important for the narrow absorption window.

Example of drug-loaded cubosomal formulation for oral drug delivery

[14].Drug-Simvastatin, Lipid used-GMO (Glyceryl monooleate), Stabilizer used-Pluronics, Uses-Used to lower the bad cholesterol and fats and increases good cholesterol in the blood.

[15].**Drug-**Amphotericin B, **Lipid used-**Phytantriol, **Stabilizer used**-Pluronics, **Uses-**Used to treat fungal infections.

[16].**Drug-**Ibuprofen, **Lipid used-**phytantriol, **Stabilizer used**-Pluronics**, Uses-**Use as NSAID with analgesic effect.

In chemotherapy (cancer therapy)

[4].As the cubosomes are the novel drug delivery system that can be used effectively for targeted drug delivery for the various anti-cancer drugs as it provides improved bioavailability, pharmacokinetics, and the safety profiles of the drug-loaded and it improves the oral bioavailability of the given drugs. The anticancer drugs which have low oral absorption properties can be encapsulated as cubosomes because of their bioadhesive properties

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Example of cubosomal formulation of anticancer drugs.

[17].**Drug**-5-Fluorouracil, Lipid used-GMO(Glyceryl monooleate), **Stabilizer used**-Pluronics, **Uses**-Used to treat GI cancer and also used for Hepatocellular carcinoma.

[18].**Drug**-Dacarbizine, Lipid used-GMO, **Stabilizer used**-Pluronics, Uses-Used to treat melanoma.

[19].**Drug**-20(S)-Proptopanaxadiol(PPD), Lipid used-GMO, **Stabilizer used**-Pluronics, **Uses**-Use to treat cancer(Anticancer drug).

Controlled release drug delivery

[2,24].The controlled release of the solubilized compound is an important application of cubosomes. As the cubic phase is more applicable for the sustained release of drugs because of the small pore size 5-10nm and also it can solubilize the hydrophilic, hydrophobic, and amphiphilic compounds and can be biodegradable by mean of enzymes. The liquid nanoparticles carriers can be released at different absorption sites.

Example of drug-loaded cubosomes for controlled release drug delivery system

[20].**Drug**-Diazepam, **Category**-Sedative hypnotic, **Uses**-Anxiety, Insomnia.

[21].**Drug**-Rifampicin, **Category**-Antibiotic, **Uses**-Tuberculosis.

[22].**Drug**-Clotrimazole, **Category**-Anti fungal**, Uses**-Used for fungal infection treatment.

[22].**Drug**-Cefazoline, **Category**-Antibiotic,**Uses**-used to treat respiratory tract infection, urinary tract infections.

II. CONCLUSION:

Cubosomes are nano-carriers based on lipids. They are considered the important nano-formulation such that they can be used to encapsulate the drug molecules which are amphiphilic, hydrophilic, and hydrophobic. They commonly use constituents in the formulation of cubosomes are lipids and stabilizers the commonly used lipid is glyceryl monooleate (GMO) it is biocompatible and biodegradable the commonly use stabilizer is Pluronics (F127 or P-407). The two different methods are used for formulation Top-down method and the bottom-up method. The most widely used method is the top-down method. The various evaluation parameters involved are Gel permeation chromatography, zeta potential, Ultrafiltration, Light microscopy, Zeta sizer for the determination of the particle size, Transmission electron microscopy (TEM). Cubosomes has a wide range of applications it can be used for the targeted drug delivery system, Controlled release drug delivery system, Ocular drug delivery system, and Anti-cancer drugs. Cubosomes can act as a vehicle for the various drug delivery systems.

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