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# Cubosomes: A Promising Vehicle for Drug Delivery

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**ABSTRACT**

Cubosomes are square and round-shaped particles that are individually separated nanoparticles of sub-microns size. They are in a bi-continuous phase in cubic crystalline form. Cubosomes are thermos-stable micro-particles(at 60ºC for 10 days) having structure like frame of hexagonal cells. They form colloidal particulate dispersions. Cubosomes are the most recent microstructures which is gaining attention in the field of drug delivery. Cubosomes are prominent for targeted drug delivery and thereby used for enhancing the pharmacokinetics of poorly soluble drugs. Being Amphiphilic in nature its use in the pharmaceutical industry is increasing in the present scenario. The present review work tries to correlate the pre-formulation parameters of cubosomes with that of its pharmaceutical utilization.

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## INTRODUCTION

Cubosomes were first proposed by Larsson, which reflects the cubic molecular crystallography and similar to liposomes Cubosomes is a three-dimensional micro cubic crystal which is interconnected by structural phase [1].Parent cubic phase surface area is larger and dispersion medium of cubosomes has lower viscosity compared to bulk cubic phase [2-3]. In cubosomes active chemical constituent molecules are coordinated through chemical bonds to the polar head of the phospholipids. The polymer and the individual drug compound form a 1:1 or 2:1 complex ratio depending on the substance [3].Cubosomes are formed by aqueous liquid and surfactants using Bottom and Top-down techniques. They have a somewhat non-Newtonian flow [4].It comprises of both hydrophilic and hydrophobic tail [5-8] or both polar and non-polar components which is referred as "Amphiphilic". They are thermo-stable components[4,9, 10] and consists of small hexagonal cell(honeycomb).

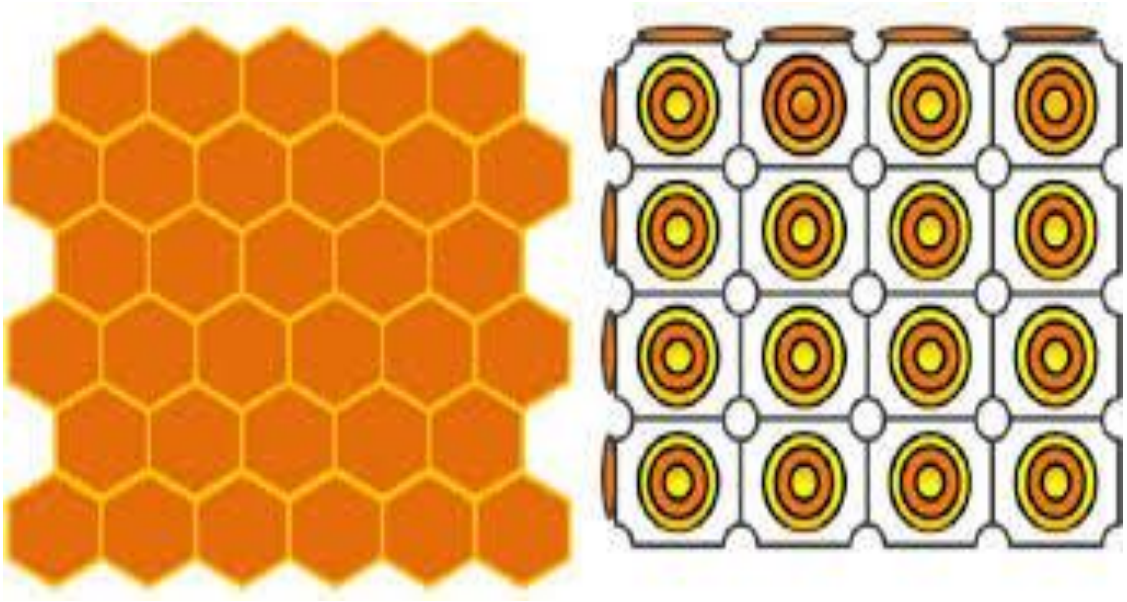

Figure: 1(a) Figure: 1(b)

**Figure 1: (a) Shows the Honeycomb structures(b) Shows the structure of Cubic Cubosomes similar to honey comb.**

**Characteristics of Cubosomes**

| S. No | Characteristics | References |
|---|---|---|
| 1. | Cubosomes are sub-Micron micro-shaped particles | 11, 12, 13, 14 |
| 2. | They are composed of polymers, lipids, surfactants with a hydrophilic and hydrophobic component called as "Amphiphilic" | 11, 12, 13, 14, 15 |
| 3. | Cubosomes have high grade impact in the formulation of nano drugs | 13, 14 |
| 4. | They are used for targeting and controlling release of drug, which is analysed by UV-spectroscopy and X-ray scattering | 15, 16 |
| 5. | It is derived from emulsion i.e., oil in water | 16 |
| 6. | They are in liquid cubic crystalline form which are bi-continuous | 11, 13, 14, 15, 17 |
| 7. | Viscous property of dispersion cubosomes is enough less | 16, 17 |
| 8. | Used as novel drug delivery system | 18 |

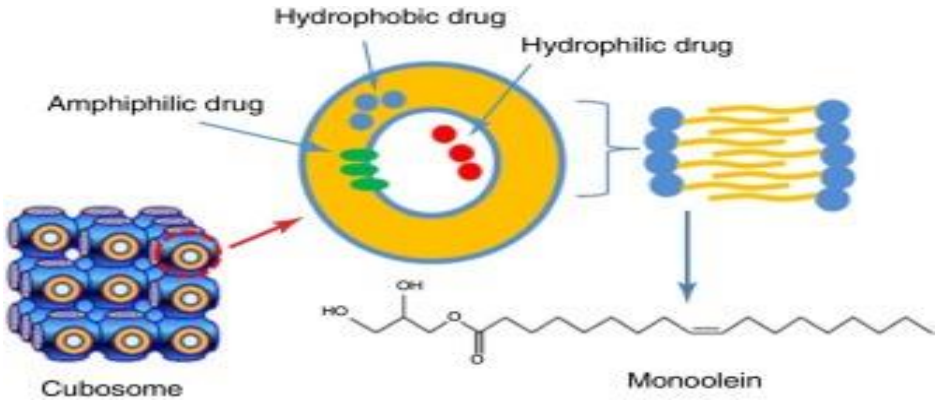


**Figure 2: Bi-Continuous Cubic Liquid Crystal [19].**

**Merits of cubosomal based delivery system**

1. Ability to encapsulate polar/non-polar or amphiphilic substances [20- 25].

2. High drug payloads because of large internal surface and shape of cubic crystal [13, 21,24,25, 26].

3. Production is elementary [13, 21, 24, 25, 26].

4. It is affordable, innocuous, bi-compatibly is good, high-grade bio-adhesiveness, and enhanced skin permeation [12, 23, 27].

5. Lipid bio-degradability[13, 21, 25, 26, 28].

6. Bioactive components have controlled and targeted release[13, 21, 23, 24, 25, 26, 28].

**Demerits of cubosomal-based delivery system**

1. Production on large scale is difficult as its viscous property is high [11,24,25]

2. Loading efficiency of the drug is low [23].

3. Due to the presence of large amount of water inside cubosomes there is low entrapment of water-soluble drugs [29, 30]

**Elevation of cubosomes can be interpreted by underneath strategy: [23, 24, 27, 28, 31, 32,33, 34, 35]**

**Bottom-up techniques**-Bottom-up techniques is also known as Solvent Dilution Method. Dispersion of mixture containing cubosomes forming lipids, the stabilizers and a Hydrotrope In an excess of water with the application of minimal energy input. Hydrotrope (urea, sodium alginate, sodium benzoate) used as Key factor in this approach. Add to dissolve water-insoluble lipid to form lipid precursors and prevent the formation of lipid crystals at increase concentration.

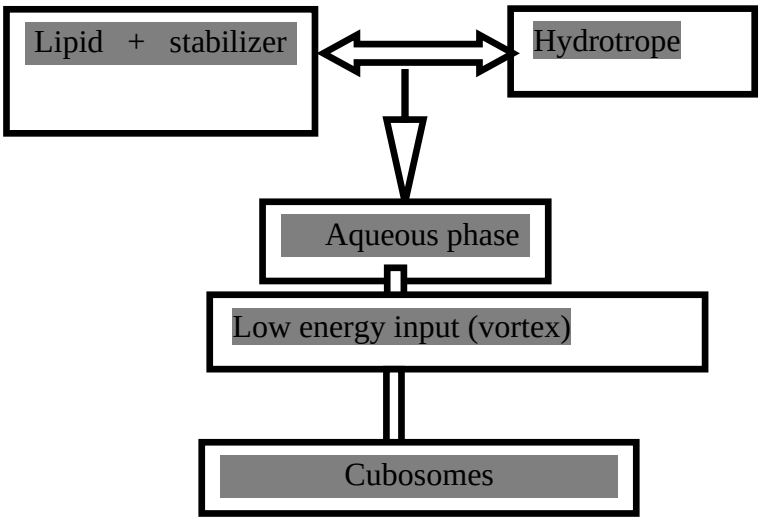


**Figure 3: Schematic representation of preparing cubosomes by Top-down approach**

**Top down Techniques**

It is most commonly Technique Used in preparation of Cubosomes. The process can be differentiated into two steps: Firstly, mix the lipids capable of making cubosomes with Stabilizers to form aggregates which are in bulk and cubic shape. In the Next step the dispersion of the produced viscous cubic aggregates in aqueous media by application of high energy as high pressure homogenizer or by sonication process it gives the formation of cube like structure known as Cubosomes.

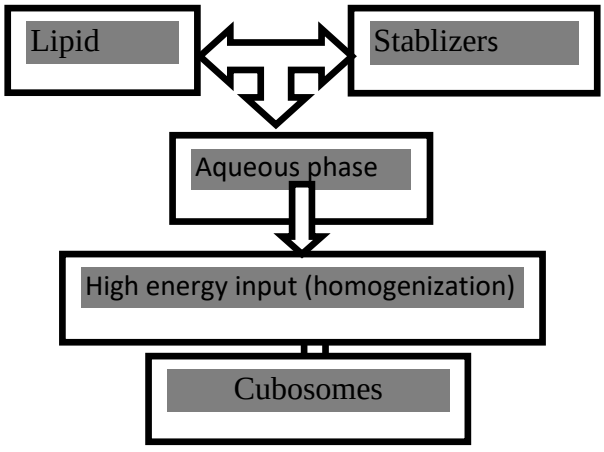


**Figure 4: Schematic representation of preparing cubosomes by bottom-up approach**

**CUBOSOMES BY DIFFERENT ROUTES**

| S.no. | Route | Drug/imaging Probe | Advantages/Purpose | References |
|---|---|---|---|---|
| 1. | Oral | Amphotericin B | Increased Bioavailability. | [36] |
| | | Cinnarizine | Drug release is sustained. | [36] |
| | | Ibuprofen | Increased absorption + increased half-life + appropriate oral bioavailability. | [37, 38] |
| | | Co-trimazole | Improved activity of oral route rather than | [37, 39] |
| | | Glibenclamide | suspension. | [37, 40] |
| | | 5-Fluorouracil | Increased duration of action and release of drug. Slow drug release + proper distribution. | [37,41] |
| 2. | Topical | Silver Sulfadiazine + cubosomal hydrogel | Burns treatment. | [42] |
| | | Herbal preparation:- i>Hinokitiol ii>Korean barberry (soluble extract ) iii>Tacrolimus | Increased skin pierce and better therapeutic effect. | [43 44 45 46] |
| | | Synthetic preparation :- i>Diclofenac Sodium ii> Fluconazole iii> Miconazole iv>Curcumin v>Indomethacin | Prepared for: Effective penetration. Skin probe. Improvement of stability. Increasedand better therapeutic action. | [47 48 49 50 51] |
| | | SiRNA | Increment skin probe without provoking the skin. | [36] |
| 3. | Intravenous | Nitroxide | For In-vivo MRI adjacent effective route. | [36] |
| | | Fluorescin/dansyl+ Querectin | Theranostic stability as nano-carrier. | [36] |
| | | Technetium | For SPECT/CT it is device used for visualization of | [36] |

| | | | | |
|---|---|---|---|---|
| | | | medical procedures. | |
| 4. | Intranasal | odorranalectin | In non-invasive system , increased therapeutic effect | [36] |
| 5. | Mucosal | 4-oleic acid | Better and increased absorption in mucosal layers. | [36] |
| 6. | Intraocular | Flurbiprofen (FB)<br><br>Dexamethasone (DEX) | Better and increased bioavailability and irritability is poor.<br>Increased pre-ocular retention and better ocular bioavailability. | [36, 52]<br><br>[53] |

**EVALUATION**

**Visual analysis**-Optical analysis of cubosomes are done by various parameters like colour of the preparation, sample turbidity, homogeneity of sample and detect the presence of macroscopic particles.

**Drug release**-This step is used to check the Safety, Efficacy and Quality of preparation. In this cubosomes type of preparation can be done by pressure ultrafiltration method. Most commonly used an Amicon Pressure Ultrafiltration cell fitted with Millipore membrane at Temp. (22±2) ℃ [54].

**Stability parameters**-Stability of any preparation can be studied by Physically or chemically. In Case of physical, Organoleptic and Morphological properties are important to study. Chemically we are assessed the different Time intervals to evaluate the drug content and Particle size Distribution. Evaluation of possible changes for time is studied [55].

**Microscopic inspection**-Microscopic evaluation can be done by Polarized light Microscopy with this we can easily determine and assessed. Cubosomes surface coatings, Anisotropic and Isotropic Differentiation and also provide information about the possible Co-Existence of layered (Hexagonal cross Straight) [55].

**Viscous property**-Cubosomes having low Viscosity than bulk Cubic phase as they shown better storing stability at Room Temperature and good Durability of heat treatment viscosity can easily accessed by use of viscometer Rotational Brookfield Viscometer with approx. speeds of 20rpm. [55]

**Transmission Electron Microscopy**- TEM is mostly used techniques now adays to identify the shapes ofcubosmes as well as Soft Matter dispersions. It gives microphotographs with high resolution images, helpful to determine shapes of particular particle [56].

**X-RAY**- Small angle X-ray Scattering could be applied to different group present in sample and also help to know about Pore Size, Shape of Particles, Structural information on molecules like Size i.e., 5 to25nm.Also applied to determine 3D arrangement of various groups present in formulation[57].

**Efficiency for entrapment**- The concentration of unentrapped drug is measured with the help of spectrophotometer. What we are doing is making a dilution first with water(deionised)then centrifuge after this go for the ultrafiltration process which consist of a certain amount of drug [57].

$$EE\% \text{ of cubosomes} = [(Ct-Cf)/Ct] \times 100$$

Cf =not encapsulated in cubosomes

Ct = Total drug concentration

**Particle Size Evaluation**- Instrument used for the determination is Laser Light Scattering (Zeta Sizer). Sample diluted with a suitable solvent is adjusted to light scattering intensity about 300 Hz & further measures at 25 C in Triplicate. The data can be collected and generally shown by using Average Volume weight Size[57].

**Zeta potential**- It is a potential difference, Degree of Repulsion. Which Predicts interactions with surfaces & optimize the formulation of films & coatings also help to determine the stability of formulation [57].

## APPLICATIONS

**Controlled or Sustained release action**- In Recent days, some anticancer drugs have been naturally packaged (encapsulated) in bulk& are characterized by physiochemical properties. The special structure of these promising nanocarriers indicates its application in this therapy. Various techniques have been investigated to specifically Target nano-drugs to tumour regions of the body with active and passive targeting of cancer cells in preclinical & clinical

studies to target nano-medicines to tumour regions in the body by active and passive targeting of cancer [58].

**Deals with viral infections**. Deals with viral infection lipids used in cubosomes, formulations such as monoglycerides, have bactericidal activity. they are therefore suitable for the treatment of STD Caused by both virus (HIV) and bacteria (Genorrticae) [58].

**Optical (ocular) delivery system**-Oral Drug delivery system presents many challenges such as Large Molecules, Water solubility, less absorption. Cubosomes type of preparation can overcome all these challenges. They also have another advantage, which is to release the drug at different sites and this is necessary in cases where the drug has a narrow absorption window of 80. Local Actionlike in the gastro intestinal tract. [59]

**Mucosal and topical depositions**-Cubic Phase is inherently more bio adhesive and convenient for topical & mucosal deposition and delivery of various drugs [60].

**Intravenous Drug delivery system**s compared to liposomescubosmes have promising properties of high drug loading. It is also the most suitable carrier for injection. Some of the insoluble small molecules are supplied by cubosomes .it also act as a precursor for the delivery of viscous substances. Therefore, upon subcutaneous injection the lamellar phase is initially fluid but later absorbs water for the environment and Transforms into the cubic phase. It is involved in forming a depot in situ [60].

**Topical Drug Delivery System**-Cubosomes are basically bio-Adhesive in Nature and High Permeability which help in increase liquid fluidity and enhance the skin permeability of the druyg.so we are used them in mucosal as well as topical drug delivery systems [61].

**Oral Drug Delivery**-Dosage form challenges, lowsolubility, lowabsorption, large molecular size. Cubosomes technology provides drug release at different absorption sites having narrow absorption window. This type of dosage form is important for dugs clopidogrel bisulphate myocardial infarction & stroke and increase release of drug. [62]

**Drug Delivery Vehicle**- latest evolution by L”oreal and Nivea in the field of cubosomes is they had prepared emulsion (oil in water type) for cosmetic purposes. [62]

**In malignant melanoma therapy and Transcutaneous drug delivery system**- used to increase the therapeutic effect of drug example: Insulin patches and Scopolamine patches used to cure motion sickness [63-64].

## CONCLUSION:

This review engrosses the characteristic features and implementation of cubosomes. Cubosomes are forms by binding biotic compatible liquid and water which is best suited and compatible with body tissues and used as drug delivery for targeted release of drug. Cubosomes has prominent capability to use as vehicle for delivery of drug for enhancing therapeutic effect. Precursor form of cubosomes has magnified the therapeutic effect and use of drug. The main utilization of cubosomes efficient drug delivery in particular system of body.

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