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A REVIEW ON CUBOSOMES: AS A NOVEL DRUG DELIVERY SYSTEM

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Abstract: Cubosomes are nanoparticles in structure which is mainly made of certain amphiphilic lipids in definite proportion, known as BI continuous cubic phase liquid crystals. Hydrating a surfactant or polar lipid that forms cubic phase and then dispersing a solid like phase into smaller particles usually forms a cubosomes. They perform solid like rheology with unique properties of practical interest. They are thermodynamically stable and they have carvenous (honeycomb) structures which are tightly packed twisted into three-dimensional bilayers. This type of complex structure allows them to have greater drug loading ability. Cubosomes have ability to encapsulate the hydrophobic, hydrophilic, amphiphilic substances. Cubosomes can increase the solubility of poorly soluble drug. Cubosome dispersions are bioadhesive and biocompatible. Because of their properties, cubosome are versatile systems, administrable by different ways such as orally, percutaneously and parenterally. Cubosome structure by means of electron microscopy, light scattering, x-ray and NMR, nevertheless few researchers has been studying the potential of cubosome as delivery systems.

Keywords: Cubosomes, Nanoparticles, Novel Drug Delivery System, BI continuous, Controlled Drug Release

INTRODUCTION

Cubosomes are nanostructured lipid-based drug delivery systems formed from bicontinuous cubic liquid crystalline phases. They are composed mainly of amphiphilic lipids such as glyceryl monooleate (GMO) or phytantriol, stabilized by surfactants like Poloxamer 407. When these lipids are dispersed in water under controlled conditions, they self-assemble into a three-dimensional cubic structure containing two continuous but non-intersecting aqueous channels separated by a lipid bilayer.1This unique internal structure provides cubosomes with a large internal surface area and the ability to encapsulate hydrophilic, lipophilic, and amphiphilic drugs simultaneously. Due to their nanoscale size and bio adhesive nature, cubosomes enhance drug solubilization, stability, and bioavailability. Cubosomes are considered promising carriers in Novel Drug Delivery Systems (NDDS) because they can provide controlled and sustained drug release. They have been widely investigated for oral, topical, transdermal, and parenteral drug delivery applications. Their structural similarity to biological membranes also contributes to improved drug absorption and reduced toxicity.2 Controlled drug delivery systems are designed to release therapeutic agents at a predetermined rate for a specified period of time in order to maintain optimal drug concentration within the therapeutic window. Conventional dosage forms often produce fluctuations in plasma drug levels, leading to reduced efficacy and increased side effects. Therefore, there is a growing need for advanced delivery systems that can provide sustained and controlled release while improving bioavailability and patient compliance.3 Cubosomes have emerged as a promising nanostructured lipid carrier for controlled drug delivery. They are discrete nanoparticles formed from the fragmentation of bulk cubic liquid crystalline phases composed of amphiphilic lipids such as glyceryl monooleate or phytantriol, stabilized by surfactants like Poloxamer 407. Cubosomes possess a unique bicontinuous cubic structure consisting of two non-intersecting aqueous channels separated by a lipid bilayer arranged in a three-dimensional periodic pattern.4 This internal structure provides

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a large surface area and enables encapsulation of hydrophilic, lipophilic, and amphiphilic drugs. The structural architecture of cubosomes plays a critical role in achieving controlled drug release. The interconnected aqueous channels allow diffusion-controlled release of drug molecules, resulting in sustained therapeutic action over an extended period. Additionally, the lipid matrix provides protection to the encapsulated drug from enzymatic degradation and environmental instability. Due to their nanoscale size and bioadhesive properties, cubosomes enhance drug absorption and prolong residence time at the site of administration. Cubosomes are versatile carriers suitable for various routes of administration, including oral, topical, ocular, and parenteral delivery. Their biocompatibility, biodegradability, and ability to improve solubility make them especially useful for poorly water-soluble drugs. Furthermore, the release rate can be modified by adjusting formulation variables such as lipid concentration, type of stabilizer, and particle size.5

Advantages of Cubosomes [6,7]

1. Controlled and Sustained Drug Release The cubic structure allows gradual diffusion of drug molecules, providing prolonged therapeutic effect.
2. High Drug Loading Capacity Can encapsulate hydrophilic, lipophilic, and amphiphilic drugs due to their bicontinuous structure.
3. Improved Bioavailability Enhances solubility and absorption of poorly water-soluble drugs.
4. Biocompatibility and Biodegradability Prepared from lipids that are generally recognized as safe (GRAS).
5. Protection of Drug Protects sensitive drugs from enzymatic degradation and environmental conditions.

Disadvantages of Cubosomes8,9

1. High Viscosity of Cubic Phase Bulk cubic phase is highly viscous, making handling and processing difficult.
2. Complex Manufacturing Process Requires specialized equipment such as high-pressure homogenizers or sonicators.
3. Cost of Materials Certain lipids and stabilizers can be expensive.
4. Stability Issues During Storage Risk of aggregation or phase transition under improper storage conditions.
5. Limited Large-Scale Commercial Production Industrial scalability remains challenging.
6. Possible Drug Leakage Improper stabilization may lead to drug leakage during storage.

Preparation Methods of Cubosomes

Cubosomes can be prepared mainly by two approaches:

1. Top-Down Approach
2. Bottom-Up Approach

Both methods aim to disperse bulk cubic phase gel into nanosized cubosomal particles stabilized by surfactants.

1. Top-Down Approach

The top-down approach is the most widely used method for cubosome preparation. In this method, a bulk cubic phase is first prepared and then broken down into nanoparticles using high-energy mechanical processes.10

Procedure:

- The lipid (e.g., Glyceryl Monooleate or Phytantriol) is melted.
- The required amount of stabilizer (e.g., Poloxamer 407) is added.
- Water is slowly added with continuous stirring to form a viscous cubic gel phase.
- The bulk cubic phase is then subjected to high-pressure homogenization or probe sonication.
- The high mechanical energy breaks the gel into nanosized cubosomal particles.
- The dispersion is cooled and stored for further characterization.

Advantages:

- Produces uniform particle size.
- Well-established and reproducible method.

Limitations:

- Requires high energy input.
- Time-consuming.
- Possible heat generation may affect heat-sensitive drugs.

2. Bottom-Up Approach (Solvent Dilution Method)

The bottom-up approach involves spontaneous formation of cubosomes from molecular building blocks without applying high mechanical energy.11

Procedure:

- Lipid and stabilizer are dissolved in a suitable organic solvent (e.g., ethanol).
- The solution is slowly injected into an aqueous phase under stirring.
- Upon dilution with water, the lipid self-assembles into cubosomal nanoparticles.
- The organic solvent is removed by evaporation.

Advantages:

- Low energy requirement.
- Suitable for heat-sensitive drugs.
- Simple and less equipment-intensive.

Limitations:

- Requires solvent removal.
- Residual solvent may affect safety if not properly eliminated.

3. Spray Drying Method12

- Cubosomes are first prepared as a dispersion.
- The dispersion is spray-dried to obtain a dry powder precursor.
- Upon rehydration, cubosomes are re-formed.

Advantages:

- Improves stability.
- Suitable for large-scale production.

Limitations:

- Requires specialized spray drying equipment.

4. Emulsification Method13

- Lipid is melted and emulsified in an aqueous phase containing stabilizer.
- High-speed stirring or homogenization is applied.
- Upon cooling, cubosomes are formed.

EVALUATION PARAMETERS [14,15,16]

Visual Inspection

First, observe the prepared cubosome dispersion for color, homogeneity, phase separation, and aggregation. The formulation should appear milky or slightly opalescent without visible lumps.

Particle Size

1. Dilute a small quantity of cubosome dispersion with distilled water.
2. Transfer the sample into a cuvette.
3. Measure particle size and
4. Record the average particle size and PDI value.

Zeta Potential Measurement

1. Dilute the formulation appropriately.
2. Fill the zeta cell with the sample.
3. Measure surface charge using a zeta potential analyzer.
4. Record the zeta potential value to assess stability.

Determination of Drug Content

1. Take a known volume of cubosome dispersion.
2. Break the cubosomal structure using a suitable solvent (e.g., methanol).
3. Dilute appropriately.
4. Analyze using UV-Visible spectrophotometer .
5. Calculate percentage drug content.

Determination of Entrapment Efficiency

1. Centrifuge the cubosome dispersion at high speed.
2. Separate the supernatant containing free drug.
3. Analyze the free drug concentration.
4. Calculate entrapment efficiency using:

$$EE\% = \text{Total Drug} - \text{Free Drug} / \text{Total Drug} \times 100$$

In-Vitro Drug Release Study

1. Place the cubosome formulation in a dialysis bag.
2. Immerse it in dissolution medium (e.g., phosphate buffer).
3. Maintain constant temperature (37°C) and stirring.
4. Withdraw samples at regular time intervals.
5. Replace with fresh medium after each withdrawal.
6. Analyze samples using UV or HPLC.
7. Calculate cumulative percentage drug release.

Morphological Study (SEM)

1. Place a drop of diluted formulation on a carbon-coated grid.
2. Allow it to dry.
3. Observe under SEM.
4. Record particle shape and structural characteristics.

pH Measurement

1. Calibrate the digital pH meter.
2. Dip the electrode into the formulation.
3. Record the pH value

Viscosity Measurement

1. Transfer formulation to a viscometer sample container.

2. Use Brookfield viscometer.
3. Record viscosity at specified rpm

Stability Studies

1. Store samples at different temperature and humidity conditions (as per ICH guidelines).
2. Evaluate at specific time intervals (0, 1, 3 months).
3. Recheck particle size, entrapment efficiency, and drug content.

APPLICATIONS OF CUBOSOMES

Controlled release of drugs

Control release of solubilised substance is the most popular application of cubosomes. Cubic phase is more applicable for control release because of its small pore size (5-10nm), ability to solubilise hydrophilic, hydrophobic, amphiphilic molecules and its biodegradability by simple enzymes.17

Melanoma (cancer) therapy

Recently few anticancer drugs have been successfully encapsulated in cubosomes and characterized physiochemically. The unique structure of this promising nanocarrier suggests its application in melanoma therapy.18

Oral drug delivery

Cubosomes address the varied challenges in oral delivery of numerous promising compounds including poor aqueous solubility, poor absorption, and large molecular size. These are both liquid and powder in capsule products comprising our self-emulsifying liquid crystalline nanoparticles technology (LCNP). In an alternative application large proteins have been encapsulated for local activity in the gastrointestinal tract. Liquid crystalline nanoparticles technology carriers can be combined with controlled release and targeting functionalities. The particles are designed to form in situ in a controlled rate, which enables an effective in vivo distribution of the drug. Liquid crystalline nanoparticles technology carriers can also be released at different absorption sites, for example in the upper or lower intestine, which is important for the drugs that have narrow regional absorption window.19

Intravenous drug delivery systems

Lipid nanoparticles comprising interior liquid crystal structures of curved lipid membranes are used to solubilize encapsulate and deliver medications to disease areas within the body. While emulsions and liposomes have found use as intravenous carriers in drug products, liquid crystal nanoparticle structures increased payloads of peptides, proteins and many insoluble small molecules, and are ideal carriers for injection or infusion of many actives.20

Topical drug delivery systems

Cubic phases are more bioadhesive in nature, so that they can conveniently use in topical and mucosal depositions and delivery of different drugs. Topical delivery systems are based on the exploitation of unique properties of liquid crystal (LC) and liquid crystal nanoparticle (LCNP) technologies. Topical drug delivery systems are unique in situ forming bioadhesive LC systems facilitate controlled and effective drug delivery to mucosal surfaces (buccal, ophthalmic, vaginal and others). This fascinating system forms a thin surface film at mucosal surfaces consisting of a liquid crystal matrix which nanostructure can be controlled for achieving an optimal delivery profile and provides good temporary protection of sore and sensitive skin .21

CONCLUSION

Cubosomes have emerged as a promising nanostructured lipid-based drug delivery system owing to their unique bicontinuous cubic liquid crystalline structure, high drug-loading capacity, biocompatibility, and ability to encapsulate hydrophilic, lipophilic, and amphiphilic drugs. Their large internal surface area and interconnected aqueous channels enable controlled and sustained drug release while enhancing the solubility, stability, and bioavailability of poorly water-soluble drugs. Cubosomes can be administered through various routes, including oral, topical, transdermal, ocular, and parenteral delivery, making them versatile carriers for a wide range of therapeutic agents. In addition, their bioadhesive nature, biodegradability, and structural similarity to biological membranes contribute to improved drug absorption and reduced systemic side effects. Although challenges such as complex manufacturing processes, high production costs, and stability during large-scale production still exist, continuous advancements in formulation techniques and characterization methods are expected to overcome these limitations. Overall, cubosomes represent a highly promising platform in novel drug delivery systems, with significant potential for targeted, controlled, and effective drug delivery. Further research and clinical investigations will facilitate their successful translation from laboratory research to commercial pharmaceutical

products, thereby expanding their applications in modern therapeutics.

REFERENCES

[1]. Rao SV, Sravya BN, Padmalatha K. A review on cubosome: The novel drug delivery system. GSC Biol Pharm Sci. 2018;5(1):1-5.

[2]. Sinko PJ. Martin's Physical Pharmacy and Pharmaceutical Sciences. 6th ed. Lippincott Williams & Wilkins; 2011.

[3]. Higuchi T. Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J Pharm Sci. 1963;52:1145–1149.

[4]. Korsmeyer RW, Gurny R, Doelker E, Buri P, Peppas NA. Mechanisms of solute release from porous hydrophilic polymers. Int J Pharm. 1983;15:25–35.

[5]. Singhal K, Kaushik N, Kumar A. Cubosomes: Versatile nanosized formulation for efficient delivery of therapeutics. Current Drug Metabolism. 2022;19(6):644-657. doi:10.2174/1567201818666210708123855.

[6]. Patil SM, Mulla JA. Cubosomes uncovered: Insights into their types, preparation techniques, evaluation methods and emerging applications. Indian Journal of Novel Drug Delivery. 2024;16(2):104-112.

[7]. Mukherjee S, Dutta A, Ash D, Karati D. An insight into cubosomal drug delivery approaches: An explicative review. Current Drug Delivery. 2025;13(4):794-803. doi:10.2174/0122117385306495240529052911.

[8]. Waghmode RR, Wal P, Nalla S, et al. Detailed comprehensive review on advancement of cubosomes and their currently available applications. Current Pharmaceutical Biotechnology. 2025. Doi : 10 . 2174 / 0113892010347758250122173337.

[9]. Bhatt AH, Patel HP, Patel PR, et al. Cubosomes in non-oral drug delivery: Advancing precision therapeutics from bench to bedside. International Journal of Pharmaceutics. 2025 ; 684 : 126108. Doi : 10 . 1016 / j . ijpharm . 2025 . 126108.

[10]. Larsson K. Cubic lipid–water phases: structures and biomembrane aspects. J Phys Chem. 1989 ; 93 : 7304–7314.

[11]. Spicer PT. Cubosome processing industrial nanoparticles for advanced delivery. Curr Opin Colloid Interface Sci. 2005;10:274–279.

[12]. Shah MH, Paradkar A. Cubic liquid crystalline glyceryl monooleate matrices for oral delivery of enzyme. Int J Pharm. 2005;294:161–171.

[13]. Esposito E, Cortesi R, Drechsler M, et al. Cubosome dispersions as delivery systems for percutaneous administration of indomethacin. Pharm Res. 2005;22:2163–2173.

[14]. Boyd BJ, Whittaker DV, Khoo SM, Davey G. Lyotropic liquid crystalline phases formed from glycerate surfactants as sustained release drug delivery systems. Int J Pharm. 2006;309:218–226.

[15]. International Council for Harmonisation (ICH). ICH Q1A (R2): Stability Testing of New Drug Substances and Products. Geneva; 2003.

[16]. United States Pharmacopeia (USP). USP–NF. Rockville, MD: United States Pharmacopeial Convention.

[17]. British Pharmacopoeia Commission. British Pharmacopoeia. London: The Stationery Office.

[18]. Rang HP, Dale MM, Ritter JM, Flower RJ. Rang and Dale's Pharmacology. 9th ed. Elsevier; 2020.

[19]. Hanan M, et al. Cubosome nanoparticles for enhancement of intestinal drug release. Drug Dev Ind Pharm. 2018.

[20]. Pandya BD, Rana HK. Cubosomes: A review on their design, function and applications in drug delivery systems. European Journal of Pharmaceutical and Medical Research. 2025;12(3):460-476.

[21]. Fatima AF, Gandla K. Cubosomes in drug delivery: A comprehensive overview of mechanisms, applications, and future direction. Saudi Journal of Medical and Pharmaceutical Sciences. 2025;11(6):444-451.