ejbps, 2025, Volume 12, Issue 12, 298-302. Review Article Impact Factor 7.482

EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES

http://www.ejbps.com

ISSN 2349-8870
Coden USA: EJBPBO
Volume: 12
Issue: 12
Year: 2025

SUSTAINABLE NANOTECHNOLOGY THROUGH GREEN-SYNTHESIZED CUBOSOMES: A NEW HORIZON IN DRUG DELIVERY

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How to cite this Article: Gadhave Ankita*1, Sameer Shafi1, Swami Shivlila1, Waghmare Pranita1, Damane Madhuri1. (2025). Sustainable Nanotechnology Through Green-Synthesized Cubosomes: A New Horizon In Drug Delivery. European Journal of Biomedical and Pharmaceutical Sciences, 12(12), 298–302.

Article Received on 08/11/2025 **Article Revised on 28/11/2025** **Article Accepted on 01/12/2025**

ABSTRACT

Cubosomes, also referred to as lyotropic cubic liquid crystalline nanoparticles (NPs), are innovative nanocarriers that have attracted considerable attention for their efficiency in targeted and controlled drug delivery. These nanosystems are typically composed of amphiphilic lipids such as glyceryl monooleate and phytantriol, which spontaneously self-assemble in aqueous environments to form a bicontinuous cubic nanostructure capable of encapsulating both hydrophilic and lipophilic therapeutic agents. Incorporation of biocompatible stabilizers and natural polymers, including Pluronic F127, chitosan, and alginate, enhances their stability, safety, and loading efficiency. In recent years, green synthesis strategies utilizing plant extracts and natural surfactants have gained prominence for producing cubosomes through sustainable, non-toxic, and environmentally friendly methods. Preparation techniques such as top-down and bottom-up approaches enable control over particle characteristics and formulation performance. Due to their biodegradability, bio adhesive nature, and prolonged drug-release potential, green-synthesized cubosomes represent a promising platform for advanced pharmaceutical applications, including transdermal, ocular, oral, and anticancer drug delivery.

KEYWORDS: Cubosomes, Green synthesis, Pluronic F127, Nanocarriers, Sustainable formulation etc.

INTRODUCTION

Improved therapeutic efficiency and bioavailability, Cubosomes, or lyotropic cubic liquid crystalline nanoparticles (NPs), have gained appeal as useful carriers for solubilization of a range of pharmaceuticals Cubosomes have recently gained significant attention among research investigators due to their numerous advantages over conventional NPs. A defined proportion of amphiphilic liquids, known as bicontinuous lipid-phase liquid crystals, assemble to form discrete nanostructured particles called cubosomes, typically ranging in size from 10 to 500 nm. Their intricate three-dimensional honeycomb-like structure and inherent thermodynamic stability confer superior drug-loading capacity.[1]

In the mid-1980s, Kåre Larsson first introduced the concept of cubosomes in his review on cubic phases in water systems, wherein he utilized X-ray diffraction and NMR diffusion studies to analyse structures formed in the monoolein water framework.[2] Building on these findings, Larsson was the first to establish foundational work on cubosomes.[3]

The formation of these highly organized and stable submicron particles is based on the principle that amphiphilic molecules can self-assemble into ordered structures upon dispersion in aqueous media, thereby protecting the encapsulated drug from degradation. In essence, the self-assembling nature of lipid mixtures combined with an appropriate stabilizer and a therapeutic agent results in the formation of lipid bicontinuous cubic-phase structures known as cubosomes. Such nanoparticles represent an effective and versatile drug delivery platform.[4]

Cubosomes exhibit outstanding characteristics, including excellent bio adhesiveness, the ability to encapsulate hydrophilic, hydrophobic, and amphiphilic compounds, controlled and sustained release of bioactive agents at target sites, biocompatibility, protection of drugs from physical and chemical degradation, non-toxicity, and high drug-loading efficiency.[4,5] The self-assembling behaviour of amphiphilic lipids such as GMO and phytantriol (PHYT) in aqueous media makes them ideal components for cubosome formulation. Owing to these attributes, cubosomes have drawn remarkable interest in therapeutic research, particularly as nanocarriers for drug delivery in cancer, ocular, oral, and dermatological therapies.[5]

Lipids are broadly classified as lamellar and non-lamellar, which drive the formation of planar lipid bilayers and bicontinuous or hexagonal cubic phases, respectively. Dispersion of non-lamellar lipids in water leads to the formation of three types of lipid bicontinuous cubic phases differing in structural organization and stability Pn3m, Im3m, and Ia3d commonly referred to as the double diamond (QIID), primitive (QIIP), and gyroid (QIIG) phases, respectively.[6,7]

Cubic aggregates derived from lipid cubic phases, when dispersed in aqueous media, are inherently kinetically unstable and may exhibit a degree of cytotoxicity toward erythrocytes. Hence, stabilizing these cubic dispersions with polymer-based agents, particularly Pluronic's, aids in producing thermodynamically stable and biocompatible formulations with improved bio accessibility of the encapsulated drug.[8]

A triblock Pluronic compound is formed by the conglomeration of polyethylene oxide (PEO) and polypropylene oxide (PPO) arranged in a PEO–PPO–PEO configuration. The temperature and hydrophobicity of Pluronic compounds are key factors influencing their interaction and binding affinity with cell membranes. Pluronic's are considered the gold-standard stabilizing agents due to their ability to reduce membrane viscosity and facilitate the transmembrane transport of low-molecular-weight drugs.[9] Among them, the most commonly used stabilizer is a non-ionic surfactant, poloxamer 407, also known as Pluronic F127.[10] Although Pluronic F127 is the most widely utilized copolymer in cubosome drug carrier formulations, a study by Uyama et al. (2009) reported that hydroxypropyl methylcellulose acetate succinate (HPMCAS), a modified cellulose polymer, also shows promising potential as an emulsifier for cubosomes without inducing structural modification.[11]

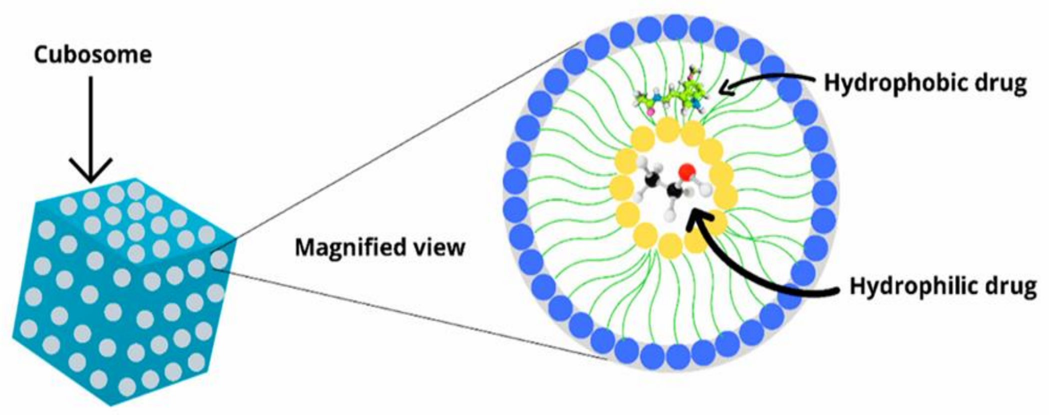

Figure 1: Structure of Cubosomes.

Advantages

1. High drug-loading capacity due to the large internal surface area and cubic crystalline structure.
2. Simple and reproducible methods of preparation.
3. Composed of biodegradable and biocompatible lipids.
4. Capable of encapsulating hydrophilic, hydrophobic, and amphiphilic substances.
5. Enables targeted and controlled release of bioactive agents.
6. Enhances skin permeation and drug absorption.
7. Cost-effective in formulation and large-scale production.[12]
8. Improves bioavailability of poorly water-soluble drugs and protects them from physical and chemical degradation.
9. Lipid nanovesicles containing GMO act as penetration enhancers, aiding cubosome diffusion through corneal and skin layers.[13]

Disadvantages

1. Cubosomes contain a high proportion of water, which reduces the entrapment efficiency of water-soluble drugs.
2. Their high viscosity poses challenges for large-scale manufacturing and processing.
3. Controlled drug release is often difficult to achieve without incorporating suitable polymers or stabilizers.
4. Cubosome dispersions may exhibit physical instability during storage or in vivo administration, leading to leakage or particle growth over time.
5. Changes in environmental conditions, such as temperature or pH, can induce phase transitions that affect formulation stability.
6. The overall scalability of cubosome production remains limited due to formulation complexity and rheological properties.[12,13]

GREEN SYSNTHESIS OF CUBOSOMES

Green synthesis of NPs aims to minimize waste generation and promote sustainable processes. This approach utilizes mild reaction conditions and non-toxic precursors, eliminating the need for expensive or harmful chemicals. Various metallic NPs can be synthesized through this eco-friendly method in a single step using biological sources such as bacteria, algae, yeast, Molds, and plants or their derivatives. Biomolecules like phenolic compounds, amines, proteins, and alkaloids from these organisms act as natural reducing and stabilizing agents. Being free from toxic substances, this method allows the use of different plant parts for nanoparticle synthesis. In particular, the green synthesis of cubosomes using plant extracts has recently gained significant attention for its environmental safety and efficiency.

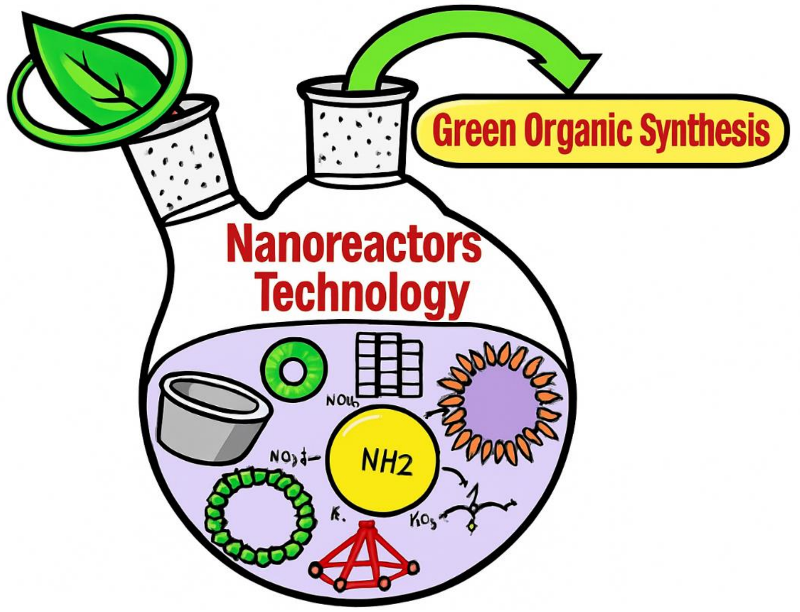

Figure 2: Nanotechnology in Green Synthesis.

Reducing and stabilizing agents can also be extracted from plants to synthesize metallic nanoparticles. Several plant-derived components have been effectively used in the synthesis of cubosomes, including Curcuma longa, Capsicum, Azadirachta indica (neem), Ocimum tenuiflorum (Tulasi), red onion, Moringa oleifera, Lippia citriodora, Allium cepa, Eucalyptus, and Tridax procumbens, among others.[14]

Figure 3: Principles of Green Synthesis.

PREPARATION METHODS OF CUBOSOMES

The basic method of preparation includes either top-down approach or bottom-up approach.

Bottom-up method

This method, commonly known as the solvent dilution technique, involves dispersing a mixture containing cubosome-forming lipids, a stabilizer, and a hydrotrope into an excess of water with minimal energy input. The hydrotrope plays a crucial role in this bottom-up approach, as it helps dissolve water-insoluble lipids to form lipid precursors and prevents liquid crystal formation at high concentrations. A hydrotrope is a molecule that enhances the solubility of poorly soluble substances in aqueous media through hydrotropic solubilization an effect where the solubility of one solute increases due to the addition of another. Common hydrotropes include urea, sodium alginate, and sodium benzoate. The solubilization mechanism involves the formation of complexes between the hydrotrope and hydrophobic molecules. Compared to the top-down approach, the bottom-up technique offers distinct advantages such as lower energy requirements, making it suitable for preparing cubosomes loaded with temperature-sensitive agents. Additionally, the resulting cubosomes exhibit enhanced long-term stability due to the uniform dispersion of stabilizers on the surface of the nanovesicles.[15]

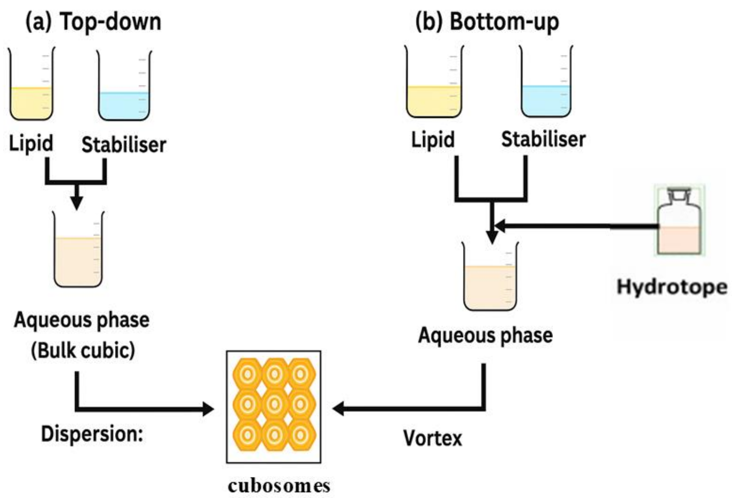

Figure 4: preparation method of cubosomes.

Top-down method

The production of the viscous bulk cubic phase begins with the combination of lipids and stabilizers. This mixture is then dispersed into an aqueous solution using high energy methods such as high-pressure homogenization (HPH), sonication, or shearing to form lyotropic liquid crystal (LLC) NPs. Among these methods, HPH is the most widely employed technique for preparing LLC NPs. In the top-down approach, vesicles dispersed nanoparticles of the lamellar liquid crystalline phase or vesicle-like structures are often observed coexisting with the cubosomes produced.[16]

APPLICATIONS

1. Formulations for controlled-release drug delivery systems are designed to solubilize therapeutic substances efficiently.
2. The cubic phase is particularly suitable for controlled-release applications because of:
   - Its small pore size.
   - Its ability to solubilize hydrophilic, hydrophobic, and amphiphilic molecules.
   - Its biodegradability by simple enzymes.
   - Its wide application in cancer therapy.
   - Its use in topical, mucosal deposition, and delivery of various drugs.
3. Although the bio adhesive and penetration-enhancing properties of cubosomes indicate strong potential for skin cancer treatments (such as melanoma), no specific formulation currently addresses this application. Furthermore, there is growing interest in employing statistical methods to optimize pharmaceutical formulations.[17]

CONCLUSION

Cubosomes are an advanced and adaptable nanocarrier system with remarkable potential in contemporary pharmaceutical applications. Their distinctive bicontinuous cubic structure, high drug-loading efficiency, and capacity to encapsulate hydrophilic, hydrophobic, and amphiphilic molecules make them highly effective for targeted and controlled drug delivery. The adoption of green synthesis methods using plant extracts and natural stabilizers further improves their safety, sustainability, and environmental friendliness compared to traditional chemical approaches. Both top-down and bottom-up preparation techniques offer flexibility in formulation design to meet diverse therapeutic requirements. Although certain challenges such as viscosity, scalability, and storage stability remain, ongoing research continues to optimize cubosome formulations. In summary, green-synthesized cubosomes stand out as eco-friendly, biocompatible nanoplatforms with great potential for next-generation drug delivery systems.

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