Available online on 15.05.2026 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Full Text Article Check for updates Review Article

Bicontinuous Cubic Phase Lipid Nanoparticles Cubosomes: Formulation, Characterization, and Therapeutic Applications

M. Ranjith [1*], Shruti A. Khandke [2], R. Niha [3], Sahil Ansari [4], S. Tamilnila [5]

[1,3] *Department of Pharmaceutics, Dr Kalam College of Pharmacy, Thanjavur, Tamil Nadu, India*

[2] *Department of Pharmacy Practice, KLE College of Pharmacy, Hubballi, Karnataka, India*

[4] *Department of Pharmacy, SRM Modinagar College of Pharmacy, Faculty of Medicine and Health Sciences, SRM Institute of Science and Technology, Delhi-NCR Campus, Delhi-Meerut Road, Modinagar, Ghaziabad, UP, India*

[5] *Department of Pharmaceutical Analysis, , Dr Kalam College of Pharmacy, Thanjavur, Tamil Nadu, India*

Article Info:

Article History:

Received 19 Feb 2026
Reviewed 06 April 2026
Accepted 29 April 2026
Published 15 May 2026

Cite this article as:

Ranjith M, Khandke SA, Niha R, Ansari S, Tamilnila S, Bicontinuous Cubic Phase Lipid Nanoparticles Cubosomes: Formulation, Characterization, and Therapeutic Applications, Journal of Drug Delivery and Therapeutics. 2026; 16(5):173-181 *DOI: https://dx.doi.org/10.22270/jddt.v16i5.7733*

For Correspondence:

Ranjith M., Department of Pharmaceutics, Dr Kalam College of Pharmacy, Thanjavur, Tamil Nadu, India;

Abstract

Cubosomes, also known as bicontinuous cubic phase lipid nanoparticles, have attracted significant attention as advanced drug delivery systems due to their unique structural and functional properties. Conventional drug delivery systems often face challenges such as poor solubility, low bioavailability, instability, and non-specific distribution, which limit therapeutic efficacy. Cubosomes overcome these limitations through their distinctive bicontinuous cubic architecture composed of lipid bilayers and interconnected aqueous channels, enabling the encapsulation of hydrophilic, lipophilic, and amphiphilic drugs within a single carrier system.

This review provides a comprehensive overview of cubosomes, including their structure, composition, preparation techniques, characterization methods, and drug loading and release mechanisms. Preparation approaches such as top-down and bottom-up methods are discussed, along with key characterization parameters like particle size, zeta potential, morphology, and internal structure analysis. The controlled and sustained drug release from cubosomes, governed by diffusion and partition mechanisms, enhances therapeutic outcomes and reduces dosing frequency.

Additionally, cubosomes demonstrate broad applications across various routes of administration, including oral, topical, ocular, transdermal, and parenteral delivery. Their emerging roles in gene delivery, vaccine delivery, and combination therapies further highlight their versatility. Despite certain challenges related to stability, scale-up, and production costs, ongoing advancements in formulation strategies and manufacturing technologies are expected to address these limitations. Overall, cubosomes represent a promising platform for next-generation drug delivery systems and personalized medicine.

Keywords: Cubosomes, bicontinuous cubic phase, lipid nanoparticles, drug delivery systems, controlled release, bioavailability.

1. Introduction

The development of novel drug delivery systems has become a central focus in modern pharmaceutics due to the limitations associated with conventional dosage forms. Many therapeutic agents suffer from poor aqueous solubility, low bioavailability, instability in biological environments, and non-specific distribution, which significantly reduces their clinical effectiveness. To overcome these challenges, lipid-based nanocarriers have emerged as promising platforms for improving drug performance and therapeutic outcomes[1].

Among various lipid-based systems, such as vesicular and particulate carriers, Liposomes have been widely investigated; however, they often face stability issues, leakage of encapsulated drugs, and limited loading capacity. Similarly, solid lipid-based systems such as Solid Lipid Nanoparticles provide improved stability but are restricted by drug expulsion during storage and limited incorporation of hydrophilic drugs.

In this context, bicontinuous cubic phase lipid nanoparticles, commonly known as cubosomes, have gained significant attention[2]. Cubosomes are nanostructured systems formed by the self-assembly of amphiphilic lipids in aqueous media, stabilized by suitable surfactants[3]. These systems exhibit a unique internal architecture that enables high drug loading, sustained release, and improved stability.

Cubosomes are particularly attractive due to their ability to encapsulate hydrophilic, lipophilic, and amphiphilic drugs within a single carrier system. Their biocompatibility, versatility, and structural robustness make them a promising platform for advanced drug delivery applications across various routes of administration[4].

2. Structure of Cubosomes

Cubosomes possess a highly ordered bicontinuous cubic liquid crystalline structure, which is one of their most defining characteristics. This structure consists of a continuous lipid bilayer arranged in a periodic minimal surface, separating two interpenetrating but non-connected aqueous channels[5]. This unique architecture allows simultaneous incorporation of both water-soluble and lipid-soluble drugs.

The internal structure belongs to the class of Liquid crystalline phase systems, which exhibit properties intermediate between solid crystals and liquid phases. The cubic phase is thermodynamically stable and highly organized, providing structural integrity and controlled diffusion pathways for drug release[6].

The large internal surface area and tortuous water channel network significantly enhance drug loading capacity and sustain release behavior. These structural features make cubosomes highly efficient nanocarriers for controlled and targeted drug delivery applications.

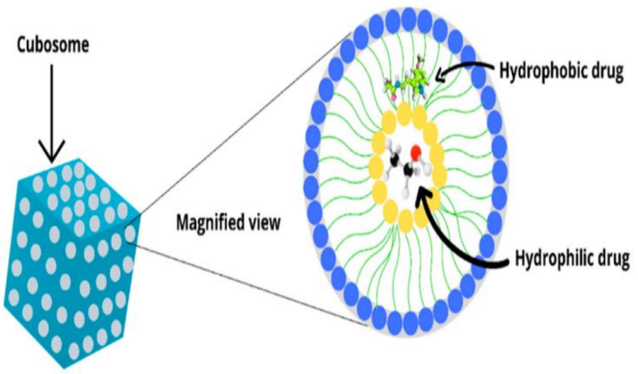

Figure 1: Structure of cubosomes

3. Composition of Cubosomes

The composition of Cubosomes plays a crucial role in determining their structural organization, physical stability, and drug delivery performance. They are mainly composed of a lipid phase, stabilizers, and an aqueous phase, each contributing to the formation of the bicontinuous cubic structure and influencing drug encapsulation behavior[7].

3.1 Lipid Phase

The lipid phase forms the fundamental structural framework of cubosomes. It consists of amphiphilic lipids that spontaneously self-assemble in the presence of water to form a highly ordered bicontinuous cubic phase. Commonly used lipids include Glyceryl monooleate and Phytantriol, which are well known for their ability to generate stable and thermodynamically favorable cubic mesophases upon hydration[8].

3.2 Stabilizers

Stabilizers are essential to prevent aggregation and maintain the colloidal stability of cubosomal dispersions. Due to the high surface energy of cubosomes, surfactants such as Poloxamer 407, Poloxamer 188, and other Pluronic-based polymers are commonly used[9]. These stabilizers adsorb onto the particle surface and provide steric repulsion, ensuring uniform dispersion and long-term stability.

3.3 Aqueous Phase

The aqueous phase is responsible for the formation of the internal bicontinuous structure. Water molecules penetrate the lipid matrix, resulting in the development of interconnected aqueous channels separated by lipid bilayers. This unique architecture is a defining feature of cubosomes and enables efficient drug encapsulation and controlled release[10].

3.4 Drug Incorporation

Cubosomes allow versatile drug incorporation based on physicochemical properties. Hydrophilic drugs are localized within the aqueous channels, lipophilic drugs are embedded within the lipid bilayer, and amphiphilic drugs are positioned at the lipid-water interface. This unique distribution capability makes cubosomes highly efficient carriers for a wide range of therapeutic agents[11].

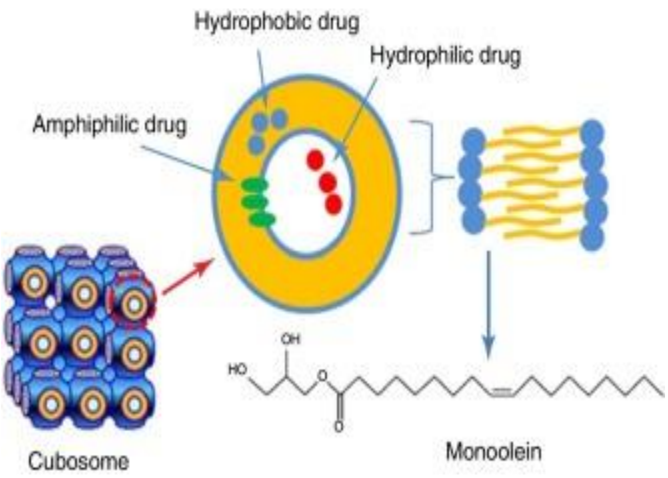

Figure 2: Composition of cubosomes

Table 1: Composition of Cubosomes and Functional Roles

Component	Examples	Physicochemical Properties	Functional Role
Lipid Phase	Glyceryl monooleate	Amphiphilic, forms cubic mesophase	Core structure formation, drug encapsulation
	Phytantriol	Chemically stable, non-hydrolysable	Provides structural stability
Stabilizers	Poloxamer 407	Non-ionic surfactant	Prevents aggregation, steric stabilization
	Poloxamer 188	Amphiphilic polymer	Improves dispersion stability
Aqueous Phase	Purified water, buffers	Hydration medium	Forms internal water channels
Additives	Charged lipids, PEG	Surface modifiers	Enhances targeting and stability

4. Preparation Methods of Cubosomes

The preparation of Cubosomes is generally carried out using two major approaches: the top-down and bottom-up methods, both of which aim to generate stable nanosized dispersions from lipid-based cubic phases[12].

4.1 Top-Down Approach

In the top-down approach, a preformed bulk cubic phase is mechanically fragmented into nanosized cubosomal particles using high-energy processes. Common techniques include high-pressure homogenization, probe sonication, and high-shear mixing. In this method, mechanical energy is applied to break down the bulk cubic gel into colloidal nanoparticles while preserving the internal bicontinuous cubic structure. The main advantages of this approach include ease of scale-up and reproducible control over particle size distribution. However, it requires high energy input and may lead to potential thermal degradation of temperature-sensitive drug molecules[1]

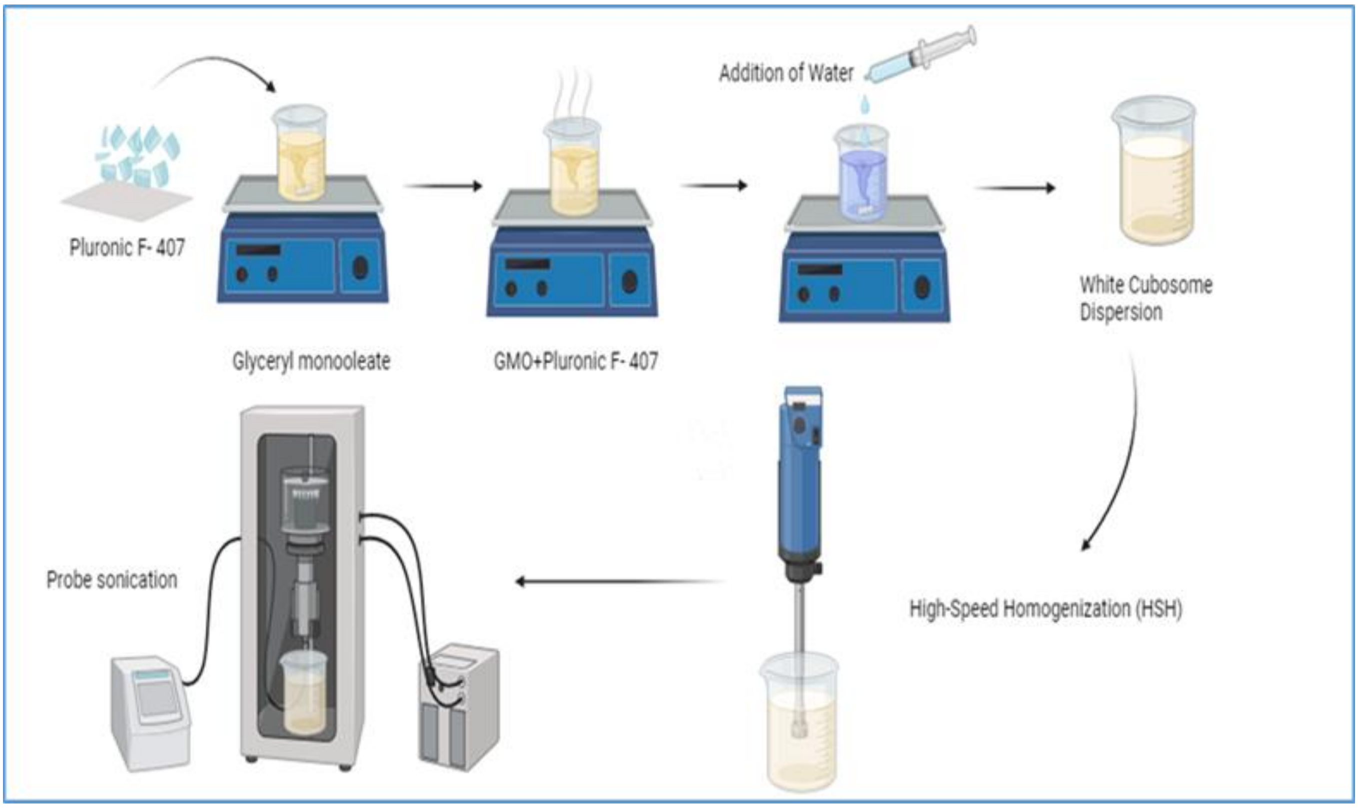

Figure 3: Preparation of cubosomes by the include high-pressure homogenization

4.2 Bottom-Up Approach

In the bottom-up approach, cubosomes are formed through the spontaneous self-assembly of lipid molecules in aqueous media. Techniques such as solvent dilution, emulsification-diffusion, and controlled precipitation are commonly employed. The underlying principle involves the spontaneous organization of amphiphilic lipids into a cubic phase structure upon contact with water, which is subsequently stabilized using surfactants. This method offers advantages such as lower energy requirements and better control over nanostructure formation. However, it may involve challenges related to solvent removal and is generally less suitable for large-scale industrial production without further optimization[14].

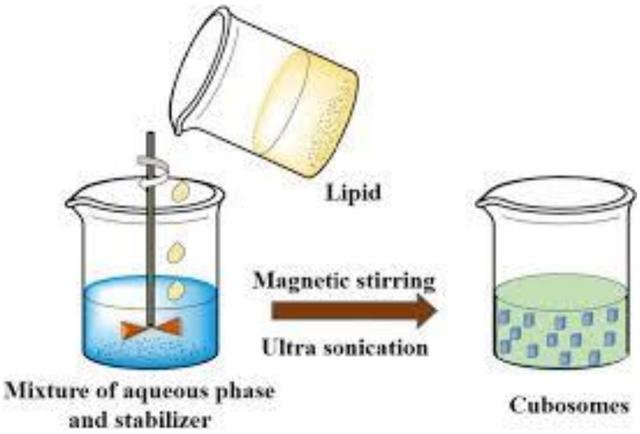

Figure 4: Preparation of cubosomes by the solvent evaporation method

Table 2: Detailed Preparation Methods of Cubosomes

Method	Technique	Process Description	Advantages	Limitations
Top-Down	High-pressure homogenization	Bulk cubic phase broken under pressure	Scalable, uniform size	High energy, thermal stress
	Probe sonication	Ultrasonic waves reduce particle size	Simple, fast	Heat generation
	High-shear mixing	Mechanical shear reduces size	Easy process	Less precise control
Bottom-Up	Solvent dilution	Lipids dissolve → precipitate into cubic phase	Low energy, controlled assembly	Solvent removal required
	Emulsification-diffusion	Emulsion formation followed by diffusion	Good size control	Complex process
	Controlled precipitation	Lipid crystallization in aqueous medium	Efficient formation	Limited industrial use

5. Characterization of Cubosomes

The physicochemical characterization of Cubosomes is essential to confirm their structural integrity, colloidal stability, and suitability for drug delivery applications. A range of analytical techniques is employed to evaluate particle size, surface charge, morphology, internal structure, drug loading efficiency, release behavior, and stability profile[15].

5.1 Particle Size and Polydispersity Index (PDI)

Particle size is a critical parameter that influences biodistribution, cellular uptake, and drug release behavior. It is commonly determined using Dynamic Light Scattering (DLS). An ideal cubosomal formulation typically exhibits a particle size in the range of 100-300 nm, which is suitable for enhanced drug delivery applications. A low polydispersity index (PDI < 0.3) indicates a uniform particle size distribution, which is essential for formulation stability and reproducibility. Smaller particle sizes generally enhance bioavailability and tissue penetration[16].

5.2 Zeta Potential

Zeta potential is used to assess the surface charge of cubosomal particles and predict their colloidal stability. High positive or negative zeta potential values indicate strong electrostatic repulsion between particles, thereby reducing aggregation. The magnitude of zeta potential is influenced by the type of lipid and surfactant used in the formulation and plays a key role in maintaining long-term stability[16].

5.3 Morphological Analysis

The morphological characteristics of cubosomes, including shape and surface features, are typically examined using electron microscopy techniques. Transmission Electron Microscopy is widely employed to confirm the nanosized structure and to visualize the characteristic cuboidal or spherical morphology depending on the formulation conditions. This technique also helps in verifying the integrity of the nanostructure[17].

5.4 Entrapment Efficiency

Entrapment efficiency determines the percentage of drug successfully incorporated into the cubosomal system. High entrapment is typically achieved due to the presence of both aqueous channels and lipid bilayers within the structure. It depends on factors such as drug solubility, lipid composition, and preparation method. Entrapment efficiency is calculated using separation techniques followed by quantitative drug analysis[18].

5.5 In Vitro Drug Release Studies

In vitro drug release studies are performed using dialysis membrane diffusion or similar methods to evaluate the release profile of the drug from cubosomes. These systems generally exhibit a sustained and controlled release pattern due to the tortuous diffusion pathways within the cubic structure. The release behavior is strongly influenced by lipid composition and internal nanostructure, and it provides an indication of in vivo performance[19].

5.6 Stability Studies

Stability studies are conducted under different environmental conditions such as temperature variations, pH changes, and long-term storage. The major challenges associated with cubosomal systems include aggregation, phase transitions, and structural rearrangements over time. The incorporation of appropriate stabilizers significantly improves the physical stability and shelf-life of the formulation[20].

Table 3: Advanced Characterization Techniques

Parameter	Technique	Principle	Information Obtained
Particle Size	Dynamic Light Scattering (DLS)	Light scattering by particles	Size distribution, PDI
Surface Charge	Zeta Potential	Electrophoretic mobility	Stability prediction
Morphology	Transmission Electron Microscopy	Electron beam imaging	Shape, size confirmation
Thermal Behavior	DSC	Heat flow measurement	Phase transition
Chemical Interaction	FTIR	Infrared absorption	Drug-lipid interaction

6. Drug Loading and Release Mechanism

The drug loading and release behavior of Cubosomes is primarily governed by their unique bicontinuous cubic nanostructure, which consists of interconnected aqueous channels separated by lipid bilayers. This dual-domain architecture enables efficient encapsulation of a wide range of therapeutic agents and provides sustained and controlled drug release characteristics.

6.1 Drug Loading Mechanism

Cubosomes exhibit high drug loading capacity due to their internal nanostructure, which accommodates drug molecules based on their physicochemical properties and affinity toward lipid or aqueous domains[21].

6.1.1 Hydrophilic Drugs

Hydrophilic drugs are primarily localized within the continuous aqueous channels of the cubic structure. They are entrapped through diffusion into the water-filled domains and are particularly suitable for polar and water-soluble therapeutic agents[22].

6.1.2 Lipophilic Drugs

Lipophilic drugs are incorporated into the lipid bilayer matrix of cubosomes, where they are stabilized through hydrophobic interactions. This makes cubosomes suitable for the delivery of poorly water-soluble drugs[22].

6.1.3 Amphiphilic Drugs

Amphiphilic drugs are distributed at the lipid-water interface, where they interact with both hydrophilic and lipophilic regions. This dual interaction enhances drug stability and loading efficiency[22].

This structural versatility allows cubosomes to simultaneously encapsulate multiple drugs with different solubility profiles, making them highly adaptable drug delivery systems[23].

6.2 Drug Release Mechanism

Drug release from cubosomes occurs in a controlled and sustained manner due to the complex and tortuous diffusion pathways within the cubic structure[24].

6.2.1 Diffusion-Controlled Release

In this mechanism, drug molecules gradually diffuse through the aqueous channels or lipid bilayer depending on their localization within the cubosomal structure[25].

6.2.2 Partition-Controlled Release

Drug release is also governed by partitioning between lipid and aqueous phases, where redistribution occurs based on the drug's partition coefficient[26].

6.2.3 Matrix Erosion

In certain formulations, gradual degradation or restructuring of the lipid matrix contributes to the overall drug release process[27].

6.3 Factors Affecting Drug Release

Several formulation and environmental parameters influence the release behavior of cubosomal systems, including:

- Lipid composition and internal phase behavior
- Type and concentration of stabilizers
- Drug-lipid interaction strength
- Particle size and surface area
- External conditions such as pH and temperature

6.4 Release Kinetics

Cubosomal drug delivery systems typically demonstrate sustained release profiles with reduced initial burst release compared to conventional dosage forms. Depending on the formulation, drug release may follow zero-order kinetics or Higuchi diffusion-controlled models, indicating predictable and controlled release behavior[28].

6.5 Advantages in Drug Delivery

The controlled loading and release characteristics of cubosomes provide several pharmaceutical benefits, including:

- Improved bioavailability of poorly soluble drugs
- Reduced dosing frequency
- Enhanced therapeutic efficacy
- Protection of drug molecules from degradation

Table 4: Drug Loading and Release Characteristics

Drug Type	Localization in Cubosome	Interaction Mechanism	Release Behavior
Hydrophilic	Aqueous channels	Hydrogen bonding	Diffusion-controlled
Lipophilic	Lipid bilayer	Hydrophobic interaction	Partition-controlled
Amphiphilic	Lipid-water interface	Dual interaction	Mixed release mechanism
Macromolecules	Internal matrix	Physical entrapment	Sustained release

7. Therapeutic Applications

The unique bicontinuous nanostructure of Cubosomes enables their application across multiple routes of administration and diverse therapeutic areas. Their ability to encapsulate hydrophilic, lipophilic, and amphiphilic drugs makes them highly versatile carriers in modern pharmaceutics[29].

7.1 Oral Drug Delivery

Cubosomes are extensively investigated for oral delivery due to their ability to enhance the solubility and absorption of poorly water-soluble drugs. They improve dissolution rate, protect drugs from enzymatic degradation in the gastrointestinal tract, enhance intestinal permeability, and provide sustained release. These properties make cubosomes particularly useful for Biopharmaceutics Classification System (BCS) Class II and IV drugs, where bioavailability is a major limitation[30].

7.2 Topical and Dermal Delivery

Cubosomes have significant potential in topical and dermal drug delivery owing to their bioadhesive nature and controlled release properties. They enhance skin penetration, increase drug retention within skin layers, and reduce systemic exposure. As a result, they are useful in the treatment of dermatological conditions such as inflammation, infections, and other skin disorders[31].

7.3 Ocular Drug Delivery

Ocular drug delivery presents challenges due to rapid tear turnover and limited precorneal residence time. Cubosomes improve ocular drug retention by increasing corneal contact time, reducing dosing frequency, and enhancing drug absorption in the anterior segment of the eye, thereby improving therapeutic outcomes[32].

7.4 Parenteral and Targeted Delivery

Cubosomes can also be utilized for parenteral administration to achieve systemic and targeted drug delivery. They are being explored for controlled systemic release, tumor targeting, and reduction of toxicity to healthy tissues. In oncology, cubosomal systems are under investigation for improved delivery of anticancer agents for the treatment of Cancer[33].

7.5 Vaccine and Biotherapeutic Delivery

Cubosomes are emerging as promising carriers for proteins, peptides, and vaccine antigens due to their protective lipid environment. They enhance the stability of biological molecules, promote sustained antigen release, and improve immune response, making them suitable for advanced vaccine delivery systems[34].

7.6 Transdermal Delivery

Cubosomes enhance drug permeation through the skin by interacting with stratum corneum lipids and facilitating diffusion across deeper skin layers. This improves systemic absorption of drugs administered via the transdermal route[35].

7.7 Emerging Applications Recent advancements have expanded cubosome applications to:

- Gene delivery systems
- Co-delivery of multiple therapeutic agents
- Combination therapy platforms
- Nanotheranostic applications

Table 5: Therapeutic Applications Across Routes

Route	Application Area	Examples of Use	Advantages
Oral	Poorly soluble drugs	Antifungals, antivirals	Enhanced bioavailability
Topical	Skin disorders	Anti-inflammatory drugs	Improved penetration
Ocular	Eye diseases	Antibiotics	Increased retention
Parenteral	Cancer therapy	Anticancer drugs	Targeted delivery
Transdermal	Systemic therapy	Hormones	Controlled release

8. Advantages and Limitations

The development of Cubosomes as drug delivery systems offers several pharmaceutical advantages due to their unique bicontinuous cubic nanostructure. However, despite their promising potential, certain limitations still restrict their large-scale clinical and industrial translation[36].

8.1 Advantages

Cubosomes provide several important benefits in drug delivery, including high drug loading capacity due to their dual aqueous-lipid architecture, controlled and sustained release behavior, and improved bioavailability of poorly soluble drugs. Their biocompatible lipid composition ensures safety and reduced toxicity, while their structural versatility allows delivery through multiple routes such as oral, topical, ocular, and parenteral administration. Additionally, cubosomes offer protection to labile drugs against chemical and enzymatic degradation, thereby enhancing therapeutic efficacy[37].

8.2 Limitations

Despite their advantages, cubosomes face several challenges. These include physical instability during long-term storage, potential aggregation or phase transitions, and difficulties in large-scale manufacturing. The requirement of specialized preparation techniques and relatively high production costs further limits their commercial feasibility. In addition, formulation optimization is often complex due to sensitivity to lipid composition, surfactant concentration, and processing conditions[38].

Table 6: Advantages vs Limitations of Cubosomes

Aspect	Advantages	Limitations
Drug Loading	High (dual structure)	Leakage possible
Release	Sustained, controlled	Initial burst (rare)
Stability	Biocompatible	Aggregation risk
Manufacturing	Scalable (top-down)	Complex process
Cost	High therapeutic value	Expensive raw materials
Applications	Multi-route delivery	Limited commercialization

9. Future Perspectives

The future development of Cubosomes is highly promising, particularly in advancing novel drug delivery strategies. However, several aspects require further investigation to enable successful clinical and industrial translation. Future studies should focus on bridging the gap between laboratory research and clinical application by conducting extensive in vivo evaluations and well-designed clinical trials to establish safety, efficacy, and therapeutic relevance in humans[39].

Industrial-scale production of cubosomes remains a significant challenge. Therefore, future research should emphasize the development of cost-effective and scalable manufacturing techniques, along with improving reproducibility of cubic phase formation and ensuring process standardization for consistent product quality. In addition, the emergence of smart and stimuli-responsive cubosomal systems offers exciting opportunities for targeted drug delivery. These systems, including pH-responsive, temperature-sensitive, and enzyme-triggered formulations, can enhance site-specific drug release and improve therapeutic efficiency.

Cubosomes also demonstrate strong potential in the delivery of biotherapeutics, including proteins, peptides, nucleic acids, and mRNA-based therapeutics, owing to their protective lipid environment and ability to facilitate intracellular delivery. Furthermore, future applications may involve combination therapy and personalized medicine approaches, where cubosomes can be used for the co-delivery of multiple drugs and tailored treatments for complex diseases[40].

From a regulatory and commercial perspective, there is a need to establish clear guidelines for lipid-based nanocarriers, improve quality control standards, and develop robust frameworks to support industrial commercialization. Overall, continued research and technological advancements are expected to overcome current limitations and expand the role of cubosomes in next-generation pharmaceutical formulations[41].

Results

This review highlights that Cubosomes exhibit a highly organized bicontinuous cubic structure that significantly enhances drug loading and controlled release behavior. The dual aqueous-lipid architecture enables efficient encapsulation of hydrophilic, lipophilic, and amphiphilic drugs, making cubosomes versatile drug delivery carriers.

Studies reviewed indicate that cubosomes improve the bioavailability of poorly water-soluble drugs, particularly those belonging to BCS Class II and IV, by enhancing solubilization and intestinal permeability. Characterization results demonstrate that optimized cubosomal formulations typically show nanoscale particle size (100-300 nm), low polydispersity index, and adequate zeta potential, ensuring stability and uniformity.

Drug release studies consistently reveal sustained and controlled release profiles, governed primarily by diffusion and partition mechanisms within the cubic structure. Furthermore, cubosomes show promising performance across multiple delivery routes, including oral, topical, ocular, and parenteral systems.

Despite these advantages, limitations such as physical instability, scale-up challenges, and higher production costs remain significant barriers to commercialization. However, recent advancements in formulation strategies and manufacturing techniques are addressing these challenges.

Overall, the findings confirm that cubosomes are highly promising nanocarriers with potential to improve therapeutic efficacy, reduce dosing frequency, and support future developments in targeted and personalized drug delivery systems.

CONCLUSION

Cubosomes represent a versatile and promising class of lipid-based nanocarriers characterized by a bicontinuous cubic internal architecture. Their ability to encapsulate hydrophilic, lipophilic, and amphiphilic therapeutic agents, combined with controlled and sustained release behavior, high surface area, and inherent biocompatibility, makes them attractive candidates for Advanced drug delivery applications across multiple routes of administration.

Although challenges related to physical stability, large-scale manufacturing, and production cost remain, ongoing advances in formulation design, stabilization strategies, and process optimization continue to address these limitations. With sustained research and technological innovation, cubosomes are expected to play an increasingly important role in next-generation drug delivery systems, including targeted therapies and personalized medicine.

Conflicts of Interest: The authors declare no conflicts of interest.

Funding sources: This paper did not receive any grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical Approval: Not applicable

Reference

1. Choudhari MP, Rathi MT. A Review on Transdermal Drug Delivery Systems.
2. Uppar AL, Patil CC, Namannavar S, Deshmane PA. Formulation and Evaluation of Caffeine-Loaded Cubosomes Hydrogel for Topical Delivery. Journal of Drug Delivery and Therapeutics. 2026 Apr 15;16(4):39-47. DOI: https://doi.org/10.22270/jddt.v16i4.7666
3. Liu L, Barber E, Kellow NJ, Williamson G. Improving quercetin bioavailability: A systematic review and meta-analysis of human intervention studies. Food chemistry. 2025 Jun 15;477:143630. DOI: https://doi.org/10.1016/j.foodchem.2025.143630 PMid:40037045
4. Suvac A, Ashton J, Bristow RG. Tumour hypoxia in driving genomic instability and tumour evolution. Nature Reviews Cancer. 2025 Mar;25(3):167-88. DOI: https://doi.org/10.1038/s41568-024-00781-9 PMid:39875616
5. Creswell C, Taylor L, Giles S, Howitt S, Radley L, Whitaker E, Brooks E, Knight F, Raymont V, Hill C, van Santen J. Digitally augmented, parent-led CBT versus treatment as usual for child anxiety problems in child mental health services in England and Northern Ireland: a pragmatic, non-inferiority, clinical effectiveness and cost-effectiveness randomised controlled trial. The Lancet Psychiatry. 2024 Mar 1;11(3):193-209. DOI: https://doi.org/10.1016/S2215-0366(23)00429-7 PMid:38335987
6. Li Y, Du K, Peng D, Zhang X, Piao Y, Peng M, He W, Wang Y, Wu H, Liu Y, Xiao J. Local delivery of siRNA using lipid-based nanocarriers with ROS-scavenging ability for accelerated chronic wound healing in diabetes. Biomaterials. 2025 Nov 1;322:123411. https://doi.org/10.1016/j.biomaterials.2025.123411 PMid:40381523
7. Hegazy D, Fayed NM, Nour El-Din HT, Habib BA, Abdelrehim RT. Optimized tazarotene transfersomes versus previously optimized tazarotene cubosomes: exploring their in vivo anti-acne activity in a cutibacterium acnes inflammatory murine model. BioNanoScience. 2025 Sep;15(3):410. https://doi.org/10.1007/s12668-025-02009-y
8. Freire RV, Salentinig S. Amphiphilic lipids for food functionality. Current Opinion in Colloid & Interface Science. 2024 Aug 1;72:101817. DOI: https://doi.org/10.1016/j.cocis.2024.101817
9. Uppar AL, Patil CC. Poloxamers in the pharmaceutical industry: Multifunctional excipients for modern drug delivery. In: Pharma-Chemical Interface: Innovations, Sustainability and Challenges. Pune (India): Nature Light Publication; 2025. p. 1-10. DOI: https://doi.org/10.5281/zenodo.15680470
10. Hou X, Zaks T, Langer R, Dong Y. Lipid nanoparticles for mRNA delivery. Nature Reviews Materials. 2021 Dec;6(12):1078-94. DOI: https://doi.org/10.1038/s41578-021-00358-0 PMid:34394960 PMCid:PMC8353930
11. Nixon-Abell J, Ruggeri FS, Qamar S, Herling TW, Czekalska MA, Shen Y, Wang G, King C, Fernandopulle MS, Sneideris T, Watson JL. ANXA11 biomolecular condensates facilitate protein-lipid phase coupling on lysosomal membranes. Nature communications. 2025 Mar 21;16(1):2814. DOI: https://doi.org/10.1101/2023.03.22.533832
12. Zhang Y, Fu P, Ni W, Zhang S, Li S, Deng W, Hu W, Li J, Pei F, Du L, Wang Y. A review of solid wastes-based stabilizers for remediating heavy metals co-contaminated soil: Applications and challenges. Science of the Total Environment. 2024 Apr 10;920:170667. https://doi.org/10.1016/j.scitotenv.2024.170667 PMid:38331289
13. Li W, Ito A, Wang G, Zhi M, Xu L, Yuan Q, Zhang J, Liu L, Wu F, Laskin A, Zhang D. Aqueous-phase secondary organic aerosol formation on mineral dust. National science review. 2025 Jul;12(7):nwaf221. DOI: https://doi.org/10.1093/nsr/nwaf221 PMid:40661120 PMCid:PMC12258144
14. Lindner S, Ricci F, Sandmeier M, Holm R, Michalowski CB, Washburn N, Sun D, Di Pretoro G, Bernkop-Schnürch A. Optimizing hydrophilic drug incorporation into SEDDS using dry reverse micelles: a comparative study of preparation methods. Drug Delivery and Translational Research. 2025 Aug;15(8):2904-23. https://doi.org/10.1007/s13346-024-01787-4 PMid:39821869
15. Pedersen KB, Ingólfsson HI, Ramirez-Echemendia DP, Borges-Araújo L, Andreasen MD, Empereur-Mot C, Melcr J, Ozturk TN, Bennett WD, Kjølbye LR, Brasnett C. The Martini 3 lipidome: expanded and refined parameters improve lipid phase behavior. ACS central science. 2025 Jul 31;11(9):1598-610. https://doi.org/10.1021/acscentsci.5c00755 PMid:41019112 PMCid:PMC12464760

16. Mishra S, Pattnaik S, Mohanty C. Berberine loaded glyceryl monooleate nanoparticles exhibited potent intrinsic anticancer activity against pancreatic cancer therapy: in vitro and in silico studies. Nano Trends. 2025 Mar 1;9:100092. https://doi.org/10.1016/j.nwnano.2025.100092

17. Thakur S, Godela R, Mandava K, Kolure R. Advances in nanocarrier technology for drug encapsulation: A comprehensive overview. Discover Materials. 2025 Jul 8;5(1):124. https://doi.org/10.1007/s43939-025-00271-1

18. Mathews PD, Mertins O, Angelov B, Angelova A. Cubosomal lipid nanoassemblies with pH-sensitive shells created by biopolymer complexes: A synchrotron SAXS study. Journal of Colloid and Interface Science. 2022 Feb 1;607:440-50. https://doi.org/10.1016/j.jcis.2021.08.187 PMid:34509118

19. Algharib SA, Dawood A, Zhou K, Chen D, Li C, Meng K, Zhang A, Luo W, Ahmed S, Huang L, Xie S. Preparation of chitosan nanoparticles by ionotropic gelation technique: Effects of formulation parameters and in vitro characterization. Journal of Molecular Structure. 2022 Mar 15;1252:132129. https://doi.org/10.1016/j.molstruc.2021.132129

20. Radulović S, Sunkara S, Rachel R, Leitinger G. Three-dimensional SEM, TEM, and STEM for analysis of large-scale biological systems. Histochemistry and Cell Biology. 2022 Sep;158(3):203-11. https://doi.org/10.1007/s00418-022-02117-w PMid:35829815 PMCid:PMC9399040

21. El-Dakroury WA, Asaad GF, Shabana ME, Sallam AA, AbdelRazek MM, El-Tokhy FS, Elbokhomy AS, El-Moghawry SA, Abdel-Malek SM, Abdelhay RW, Ahmed FA. Famotidine-loaded chitosan hybridized fibroin nanoparticles exhibit outstanding efficacy in ameliorating peptic ulcer. International Journal of Biological Macromolecules. 2025 Sep 4:147321. DOI: https://doi.org/10.1016/j.ijbiomac.2025.147321 PMid:40914367

22. Joiner JB, Prasher A, Young IC, Kim J, Shrivastava R, Maturavongsadit P, Benhabbour SR. Effects of drug physicochemical properties on in-situ forming implant polymer degradation and drug release kinetics. Pharmaceutics. 2022 Jun 1;14(6):1188. DOI: https://doi.org/10.3390/pharmaceutics14061188 PMid:35745761 PMCid:PMC9228340

23. Németh Z, Csóka I, Semnani Jazani R, Sipos B, Haspel H, Kozma G, Kónya Z, Dobó DG. Quality by design-driven zeta potential optimisation study of liposomes with charge imparting membrane additives. Pharmaceutics. 2022 Aug 26;14(9):1798. DOI: https://doi.org/10.3390/pharmaceutics14091798 PMid:36145546 PMCid:PMC9503861

24. Kırımlıoğlu GY. Drug loading methods and drug release mechanisms of PLGA nanoparticles. InPoly (lactic-co-glycolic acid)(PLGA) Nanoparticles for Drug Delivery 2023 Jan 1 (pp. 55-86). Elsevier. DOI: https://doi.org/10.1016/B978-0-323-91215-0.00005-4

25. Sonawane G, Pansare K, Patil C, Mahajan S, Sonawane D, Gilhotra R, Sharma S. A Comprehensive Review on Development of Nanomicellar-Based Topical Drug Delivery System for The Treatment of Uveitis. Research Journal of Pharmaceutical Dosage Forms and Technology. 2026 Jan;18(1):65-72. DOI: https://doi.org/10.52711/0975-4377.2026.00011

26. Talevi A, Ruiz ME. Drug release. InThe ADME Encyclopedia: A Comprehensive Guide on Biopharmacy and Pharmacokinetics 2022 Jun 15 (pp. 413-418). Cham: Springer International Publishing. https://doi.org/10.1007/978-3-030-84860-6_32

27. Steinbach M. Development and Characterization of 3D Printable Diffusion Controlled Drug Formulations With UV-Curable Photopolymer Resins (Doctoral dissertation, Universität Koblenz).

28. Murphy DJ, Lim D, Armstrong R, McCoy CF, Bashi YH, Boyd P, Derrick T, Spence P, Devlin B, Malcolm RK. Refining the in vitro release test method for a dapivirine-releasing vaginal ring to match in vivo performance. Drug Delivery and Translational Research. 2023 Aug;13(8):2072-82. https://doi.org/10.1007/s13346-021-01081-7 PMid:34674162 PMCid:PMC10315348

29. Jayakumar R, Murali VP, editors. Natural biopolymers in drug delivery and tissue engineering. Elsevier; 2023 Aug 14.

30. Pande S. Factors affecting response variables with emphasis on drug release and loading for optimization of liposomes. Artificial Cells, Nanomedicine, and Biotechnology. 2024 Dec 31;52(1):334-44. https://doi.org/10.1080/21691401.2024.2360634 PMid:38833335

31. Yi F, Chen X, Hou F, Song L, Zhan S, Wang X, Zhang R, Yang Q, Wang X, Liu Z. Chitosan/zein-based sustained-release composite films: Fabrication, physicochemical properties and release kinetics of tea polyphenols from polymer matrix. International Journal of Biological Macromolecules. 2024 Jun 1;269:131970. DOI: https://doi.org/10.1016/j.ijbiomac.2024.131970 PMid:38697413

32. Li Z, Xu K, Qin L, Zhao D, Yang N, Wang D, Yang Y. Hollow nanomaterials in advanced drug delivery systems: from single-to multiple shells. Advanced Materials. 2023 Mar;35(12):2203890. https://doi.org/10.1002/adma.202203890 PMid:35998336

33. Lou J, Duan H, Qin Q, Teng Z, Gan F, Zhou X, Zhou X. Advances in oral drug delivery systems: challenges and opportunities. Pharmaceutics. 2023 Feb 1;15(2):484. DOI: https://doi.org/10.3390/pharmaceutics15020484 PMid:36839807 PMCid:PMC9960885

34. Akombaetwa N, Ilangala AB, Thom L, Memvanga PB, Witika BA, Buya AB. Current advances in lipid nanosystems intended for topical and transdermal drug delivery applications. Pharmaceutics. 2023 Feb 15;15(2):656. DOI: https://doi.org/10.3390/pharmaceutics15020656 PMid:36839978 PMCid:PMC9967415

35. Dosmar E, Walsh J, Doyel M, Bussett K, Oladipupo A, Amer S, Goebel K. Targeting ocular drug delivery: an examination of local anatomy and current approaches. Bioengineering. 2022 Jan 17;9(1):41. DOI: https://doi.org/10.3390/bioengineering9010041 PMid:35049750 PMCid:PMC8772869

36. Alam MI, Yadav AK. Parenteral Drug Delivery. InNovel Carrier Systems for Targeted and Controlled Drug Delivery 2024 Dec 24 (pp. 87-114). Singapore: Springer Nature Singapore. https://doi.org/10.1007/978-981-97-4970-6_4

37. Singh N. Chapter-3 Mechanistic Insight of Bacterial Ghost as a Delivery Carrier in Cancer Therapy: Enemies to Allies (Doctoral dissertation, Institute of Pharmacy, Amity University, Noida).

38. Aly NS, Matsumori H, Dinh TQ, Sato A, Miyoshi SI, Chang KS, Yu HS, Kim HS. Formulation and evaluation of the antimalarial N-89 as a transdermal drug candidate. Parasitology International. 2023 Apr 1;93:102720. https://doi.org/10.1016/j.parint.2022.102720 PMid:36516945

39. Singhal K, Kaushik N, Kumar A. Cubosomes: versatile nanosized formulation for efficient delivery of therapeutics. Current Drug Delivery. 2022 Jul 1;19(6):644-57. https://doi.org/10.2174/1567201818666210708123855 PMid:34238187

40. Rehman U, Ali SP, Hani U, Gupta G, Goh KW, Kesharwani P. Cubosome-Based Nanocarriers in Cancer Therapy: Design Optimization, Analytical Characterization, and Translational Perspectives. Annals of Biomedical Engineering. 2026 Apr 13:1-23. https://doi.org/10.1007/s10439-026-04124-7 PMid:41973189

41. Cai, X., Refaat, A., Gan, P., Fan, B.-A., Yu, H., Thang, S. H., Drummond, C., Voelcker, N., Tran, N., & Zhai, J. (2024). Angiopep-2-Functionalized Lipid Cubosomes for Blood-Brain Barrier Crossing and Glioblastoma Treatment. ACS applied materials & interfaces. DOI: https://doi.org/10.1021/acsami.3c14709 PMid:38416873