



CUBOSOMES AS VERSATILE LIPID NANOCARRIER: STRUCTURAL BASIS, PREPARATION STRATEGIES, BIOMEDICAL APPLICATIONS, AND EMERGING TRENDS

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Article Information

Received: 31st January 2026

Revised: 4th May 2026

Accepted: 7th June 2026

Published: 30th June 2026

Keywords

Cubosomes, Self-Assembly, Smart Nanocarrier, Liquid Crystalline Structures

ABSTRACT

Background: Cubosomes are lipid-based nanocarriers with a bicontinuous self-assembled structure and significant potential for advanced drug delivery applications. Their unique cubic internal configuration, extensive surface area, and potential to encapsulate a wide variety of agents, comprising hydrophilic, lipophilic, and amphiphilic compounds, render them advantageous for improving drug properties such as solubility, stability, loading efficiency, and controlled release. **Methodology:** These innovative nanocarriers have garnered considerable attention across various biomedical domains, including cancer treatment, antimicrobial and antiviral therapy, transdermal formulations, oral bioavailability enhancement, vaccine delivery, and responsive systems. **Results and Discussion:** This review outlines the structural features, compositions, stabilization methods, self-assembly theories, drug-encapsulation dynamics, release profiles, preparation techniques, and essential characterization methods of cubosomes. **Conclusion:** It examines recent advances in biomedical applications targeting different diseases, along with emerging technologies that help clarify the future directions of these nanocarriers.

1. INTRODUCTION

The pharmaceutical sciences increasingly demand novel drug delivery systems (DDS) that overcome the limitations of traditional routes of administration, such as oral, intravenous, and topical approaches, especially in managing chronic illnesses, cancer, and infectious diseases [1]. By introducing innovative techniques that improve treatment efficacy while reducing adverse reactions, nanotechnology has fundamentally

changed pharmaceutical administration. Low-solubility active pharmaceutical ingredients face challenges such as limited oral bioavailability, reduced cellular membrane permeability, higher intravenous dosage requirements, and unwanted side effects associated with traditional formulation techniques. One approach to overcome these limitations is incorporating nanotechnology into drug delivery systems. A promising example of a self-organizing nanomaterial is a lyotropic liquid

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crystalline nanoparticle (LLCNP). Among nanostructured carriers, cubosomes are an expanding class of nanosystems that can accommodate different types of active pharmaceutical ingredients, including hydrophobic and hydrophilic drugs, as well as biotherapeutics such as peptides, proteins, and nucleic acids [2].

Cubosomes represent self-assembled colloidal dispersions comprising bicontinuous crystalline structures in a cubic phase. They feature a lipid bilayer configuration with a continuous, cubic-symmetrical surface and interconnected aqueous channels. Cubosomes are a type of Solid lipid particle (SLP) made of amphiphilic lipids and are thermodynamically more stable than other SLPs, such as liposomes [3].

In recent years, cubosomes, a novel drug delivery carrier, have attained considerable attention for their distinctive self-assembled configurations and increased drug entrapment capabilities. They can be utilized for various administration routes, such as oral, ophthalmic, and transdermal, as well as for chemotherapeutic agents. Their potential advantages include a cubic architecture that facilitates extensive drug dispersion, a large surface area, a relatively simple production method, biocompatibility, the ability to encapsulate lipophilic, lipophobic, and amphiphilic agents, and targeted, controlled drug release. Given the biodegradable properties of the lipid components, cubosomes show substantial promise in nanoscale drug formulations [3].

Cubosomes and polymeric micelles are structurally similar and have widespread utility in diverse drug delivery systems. Polymeric micelles comprise amphiphilic polymers that spontaneously assemble into core-shell configurations in aqueous environments once they surpass the critical micelle concentration threshold. In contrast, cubosomes are bicontinuous cubic structures dispersed in water. Liposomes, niosomes, and cubosomes are all closed bilayer systems, but cubosomes have cubic crystallographic structures, which distinguishes them from the others [4]. These cubic structures can also encapsulate hydrophobic, hydrophilic, and amphiphilic drugs, setting them apart from other nanoparticles. Thus, Cubosomes have shown promise as effective transport vehicles for delicate pharmaceutical compounds like proteins and peptides, shielding them from enzymatic degradation within living organisms [5], [6]. Despite these advantages, cubosomes

face challenges due to their high viscosity, the complexity of scaling up from laboratory to industrial production, and variability in properties. Additionally, residual water trapped within cubosomes can reduce the effectiveness of delivering water-soluble drugs.

In the following sections, we introduce cubosomes and their potential as a drug-delivery carrier. Specifically, we discuss the structure, composition, preparation methods, theories of lipid self-assembly, drug-encapsulation and release mechanisms, and the current use of cubosomes as a favorable platform for drug delivery via various routes, supported by recent research.

2. STRUCTURAL INSIGHTS

In the literature, cubic phases are categorized as 'V' or 'Q'. Researchers have distinguished eight unique subcategories of cubic crystal space-group symmetries: (Q229), (Q225), (Q223), (P432), (3P63Immc), (Q227), (Q224), and (Q230). While Q229, Q225, Q224, Q230, and the other bicontinuous cubic phases are arranged around triply [7] periodic minimal surfaces (TPMS), Q223 and Q227 are discontinuous micellar phases. Triply periodic minimal surfaces (TPMS) are three-dimensionally repeating surfaces of zero mean curvature that form the structural basis of bicontinuous cubic phases. They explain the internal structure of P-, D-, and G-type cubic phases by forming two interpenetrating aqueous networks that are divided by a continuous lipid bilayer.

The Im3m, Pn3m, and Ia3d cubic phases are represented by the P, D, and G minimum surfaces, respectively. This structural distinction accounts for the change from micellar to bicontinuous arrangements [7]. The bilayer lipid membrane forms a conventional 3-dimensional structure within the bicontinuous cubic crystalline phase. Within these systems, three specific types of inverse cubic crystalline phases have been recognized: the Q229 cubic phase, which presents the Schwartz primitive (P) minimal surface and showcases Im3m crystallographic space group symmetry; and the Q230 cubic phase, reliant on the Schoen gyroid [G] minimal surface and exhibiting Ia3d crystallographic space group symmetry; and the Q224 cubic phase, distinguished by the Schwartz diamond [D] minimal surface and featuring Pn3m crystallographic space group symmetry. These space groups play a crucial role in accommodating hydrophilic molecules within their intertwining water channels. Furthermore, water-accommodation capacity decreases from the P to the D and from the D to the G phases

[5]. Coarse cubosomes exhibit a morphology characterized by the Pn3m/QIID structure, analogous to their bulk cubic phase. Conversely, after homogenization, the prevalence of the Im3m/QIIP morphology, also known as Primitive, is notable and may be attributed to supplementary polymers or other contributing factors [1].

Amphiphilic Bicontinuous Cubic Phases [BCPs] exhibit diverse morphologies when they self-assemble in specific solvents, like ribbons, spheres, vesicles, films, fibers, tubules, cylinders, and multi-geometry nanoparticles. These morphologies result from minimizing unfavorable interactions between segments and solvents. BCPs encompass bicontinuous mesostructures, defined by a 3D interconnected phase arrangement. Although bicontinuous phases are recognized, their stability is limited. Cubosomes, which contain liquid-crystalline cubic nanostructures, are commonly formed with low-molecular-weight surfactants [1].

Cubosomes are self-assembled liquid-crystalline entities characterized by solid-like rheology and bicontinuous cubic-

phase liquid-crystal properties. The intricate bicontinuous topologies of cubic phases result in notably elevated viscosity levels. The bicontinuous cubic liquid-crystalline phase, which is optically transparent, is a highly viscous material structured at the nanoscale [8]. The lipids used in cubosome formulation are adhesive, preventing the formation of small discrete particles. Adding polymers to cubosome colloidal suspensions enhances their stability.

Nevertheless, applying a non-adhesive, water-soluble starch coating to these sticky, waxy lipids has been shown to prevent agglomeration and enable precise particle-size control [1]. Figure 1 shows the distinction between Niosomes, Liposomes, and Cubosomes. A theoretical model delineating drug dispersion patterns within this phase has been formulated, fabricated, and assessed. The surfactant components organize into bilayers contorted into a 3-dimensional, periodically recurring minimal-surface configuration, yielding a compact arrangement reminiscent of a honeycomb, with distinct water and lipid compartments [8].

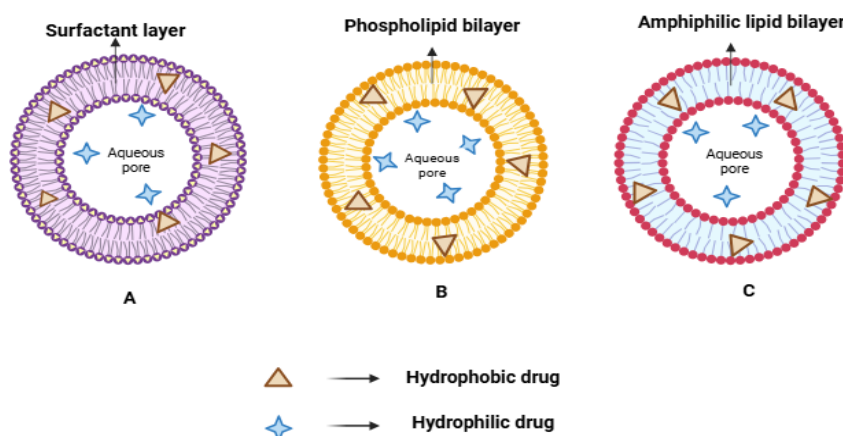


Figure 1: Distinction between A) Niosomes, B) Liposomes and C) Cubosomes

3. COMPOSITION

During the preparation of cubosomes, lipids like monoolein or phytantriol can naturally self-assemble in water, which are in turn stabilized by poloxamers like F127 or F108. They are thermodynamically stable & they have cavernous (honeycomb) structures that are tightly packed and twisted into three-dimensional bilayers.

Amphiphilic lipids

Glyceryl monooleate is a monoglyceride with a melting point between 35–37°C, displaying an HLB value of 3. It consists

mainly of oleic acid glycerides and other fatty acids, notably monooleate, an amphiphilic lipid that can form lyotropic liquid crystals in diverse configurations [4]. GMOs exhibit amphiphilic properties due to hydroxyl groups in the head region, which facilitate hydrogen bonding with water, and the hydrocarbon chain in the tail. Additionally, GMOs are biodegradable, biocompatible, non-toxic, recognized as safe, and commonly used as emulsifiers [1]. Phytantriol (3,7, 11, 15-tetramethyl-1, 2, 3-hexadecantriol), a prevalent ingredient in cosmetics, serves as a substitute for Glyceryl monooleate in cubosomal formulations.

It can form a cubic arrangement in aqueous environments at biological temperatures. Its robust chemical stability, enhanced dermal permeation, and superior hydration preservation have increased its significance in biomedicine. Furthermore, it can sustain the release of diverse pharmaceutical compounds, particularly hydrophilic ones (1,4). Hammad et al. developed a chitosan-PVP block copolymer for the effective co-administration of Linagliptin and Empagliflozin, two complementary hypoglycaemic medications. They encapsulated these drugs in cubosomes to enhance their physicochemical properties. The cubosomes were fabricated using a top-down methodology, with different proportions of GMO or Isopropyl myristate: phosphatidylcholine (60:40) as the principal constituent lipid to enhance drug entrapment efficiency [9].

Surfactants

When cubosomes are dispersed in an aqueous environment, they tend to lose stability because lipophilic segments are exposed to the hydrophilic surroundings, leading to particle aggregation. To prevent cubosomes recoalescence, using a surfactant is imperative to maintain colloidal stability. This surfactant stabilizes the system by creating an electrostatic barrier between particles, inhibiting close contact and maintaining colloidal stability. Among commonly used stabilizing agents, Pluronics are frequently employed. Specifically, Poloxamer 407 (F127), a triblock copolymer composed of PEO99–PPO67–PEO99, is used as a surfactant to stabilize cubosomes. F127 stabilizes cubosomes through a mechanism that differs from that of conventional dispersions such as emulsions. F127's stabilization efficacy is attributed to the adsorption of its lipophilic segment PPO onto the particle surface, with the lipophobic portion PEO extending outward into the aqueous medium to provide steric protection. Through its interaction with the structural configuration of dispersed particles, the stabilizer influences phase behavior within cubosomes [5,10].

This interfacial configuration can alter bilayer hydration, chain arrangement, and membrane curvature, thereby affecting the internal lattice and phase characteristics of the cubic structure. Nevertheless, caution is advised when using high levels of artificial surfactants, as an overabundance may raise concerns about formulation acceptability, membrane perturbation, and regulatory compliance, especially for parenteral or long-term applications [11,12]. One study suggested Kolliphor RH40 as a viable substitute stabilizer because of its structural resemblance

to Pluronic F127 (Poloxamer 407). Comprising glycerol polyethylene glycol oxystearate along with fatty acid glycerol polyglycol esters, Kolliphor RH40's hydrophobic portion contributes to its stabilizing properties. The lyophobic segment comprises polyethylene glycols and glycerol ethoxylate.

By integrating the hydrophobic component into the lipid bilayer, the elongated hydrophilic chain facilitates interaction with the aqueous milieu. Furthermore, Kolliphor RH40 employs a steric stabilization mechanism that hampers vesicle aggregation, thereby enhancing its stabilizing capabilities [13]. The unique hydrophilic-lipophilic balance and membrane-insertion characteristics of Kolliphor RH40 may result in different modifications to the internal lattice parameter compared with Poloxamer 407. Therefore, it is crucial to employ small-angle X-ray scattering (SAXS) for ascertaining whether this stabilizer maintains or extends the cubic repeat distance [12,14]

4. THEORIES ON CUBOSOMES

Cubosomes form bilayers encapsulated within the surfactant, adopting a three-dimensional, periodic, minimal-surface configuration that results in a densely compacted arrangement. This material appears as a transparent, highly viscous liquid-crystalline bicontinuous cubic phase with a distinctive nanoscale structure. During cubosome formation, three distinct macroscopic phases commonly emerge within the cubic structure: the precursor, bulk gel, and particle dispersion phases. The precursor phase refers to a solid or semi-solid substance that, when triggered by various stimuli such as interaction with a liquid, transitions into the cubic phase. In contrast, the bulk gel cubic phase is rigid, isotropic, and can transform into cubosomes [1,4]. The packing parameter (P) predicts lipid self-assembly because it relates molecular shape to interfacial curvature and, therefore, to the type of aggregate formed. While hydration, temperature, and stabilizer conditions ultimately determine which cubic space group forms, lipids with smaller head-group areas & proportionally larger hydrophobic volumes tend to favor inverse curvature and bicontinuous cubic phases [15]. The System Forming Theory also highlights how lipid composition, solvent conditions, and stabilizers collectively determine the final phase identity; it should be introduced as a supplementary explanation of the packing parameter rather than as a stand-alone idea [7]. The different theories that explain the self-assembly of lipids that leads to the formation of cubic structures are given in (Table 1).

Table 1: Different theories on self-assembly of lipids

Name of Theory	Description	Ref.
Principle of Opposing Forces	Explains self-assembly as a balance between hydrophobic interactions (driving association of molecules to hide from water) and hydrophilic head-group interactions (competing at the interfacial energy).	[16] [4]
Principle of Packing Parameter (P)	Predicts the topology of lipid aggregates based on the molecular shape of the lipid. It is defined as the Packing Parameter (P) = $v / (al)$, where (v) is the volume of the hydrophobic chain, (a) is the polar head group area, and (l) is the chain length. (Table 2) shows the different (P) values and the type of curvature formed.	[4]
Fontell & Drew Theory	Identified that cubic phases exist in ternary systems involving amphiphiles, oil, and water, particularly noting that monoglycerides with C-12 and C-22 chains contain large cubic areas.	[17]
Gustafson et al. Theory	Describes cubosomes as single-crystal formations that may coexist with distributed lamellar liquid-crystalline particles; notes that membrane fusion over time transforms metastable vesicles into cubosomes.	[18]
Schwarz, Jacob & Anderson Theory	Represents cubic phase structures using differential geometry and periodic minimum surfaces (D-surface, G-surface, and P-surface) based on curvature and water levels.	[18]
System Forming Theory	States that cubosomes form either in binary or ternary systems when there is a significant solubility difference between the cubic phase and the solvent, often requiring stabilizers like Poloxamer 407	[18]

Table 2: Different (P) values and type of curvature formed

Curvature Type	Packaging Parameter (P) value	Description
Micelle (oil in water)	$(P) > 1/2$	Curvature occurs toward the lipophilic region; amphiphiles adopt a cone shape, and this conical geometry leads to sphere formation.
Lipid bilayer (closed)	$1/2 > (P) > 1$	The lipid molecules assemble to form a closed lipid bilayer structure
Lipid bilayer (open)	$(P) = 1$	Zero curvature is formed with identical cross-sections of the polar heads and the non-polar tails.
Inverted micelles (water in oil)	$(P) > 1$	The curvature occurs toward the aqueous region, leading to inverted spheres.

5. MECHANISM OF DRUG RELEASE

Drug release from a cubosome relies on drug diffusion; therefore, the driving force directing drug diffusion away from a cubosome is the drug concentration gradient inside the cubosome. As such, drug release from cubosomes typically follows either a Higuchi or Fickian diffusion model. Studies have evaluated the drug-release mechanisms of lipophobic drugs from inverted hexagonal liquid crystalline and cubic systems; these studies have shown that diffusion primarily controls drug release from both inverted hexagonal liquid crystalline and cubic systems, with cubosomes showing a higher drug-release rate than inverted hexagonal liquid crystalline systems.

Additionally, in vitro drug-release patterns and the in vivo drug-release behavior of ^{14}C -glucose from cubosomes and hexagonal phases matched, indicating that the nanoarchitecture of cubosomes and GMO characteristics may control the extrication rate of lipophobic medicines. Conversely, extricating hydrophobic drugs from cubosomes in vitro poses challenges because of the drugs' affinity for the lipophilic domain. In the

gastrointestinal system, the liberation of lipophilic drugs from GMO-derived cubosomes is not controlled solely by passive diffusion.

Enzymatic breakdown of the lipid structure also plays a pivotal role. Gastric and intestinal lipases can break down GMO, producing monoacylglycerols and unbound fatty acids that gradually disrupt the cubic structure, increase membrane permeability, and accelerate drug release. Consequently, in vivo drug release can be significantly faster and more dynamic than in vitro assessments in buffer solutions, which often underestimate the impact of lipid digestion and neglect the interconnected dynamics of enzymatic degradation, bile-salt interactions, and phase restructuring [19–21].

Consequently, investigations into the release data of lipophilic compound-loaded cubosomes in a digestive environment (0.1 M Hydrochloric acid) and distilled water media demonstrated a marked enhancement in drug release rate within the digestive environment [18].

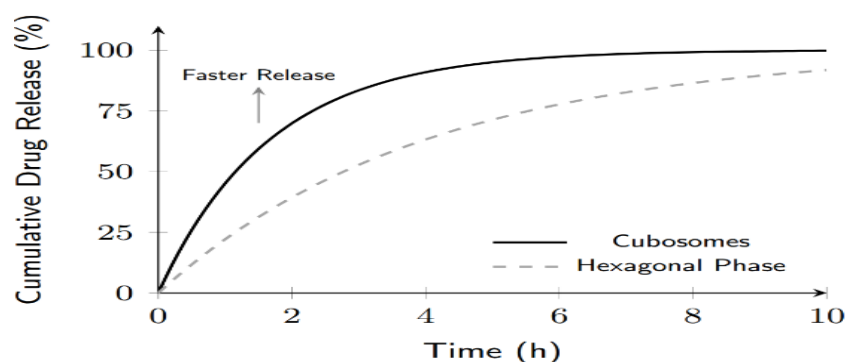


Figure 2: Drug release kinetics comparison between hexagonal liquid crystalline and cubic structures

Cubosomal systems can include ionizable lipids or thermosensitive polymeric coatings, introducing pH-responsive and temperature-sensitive release functionalities [22]. These responsive mechanisms facilitate drug liberation in response to acidic tumor or inflamed tissue environments, thereby limiting drug exposure to non-target cells. Moreover, the enzymatic breakdown of peptide linkers within these systems offers further control over drug release at specific sites. These sophisticated release approaches notably improve therapeutic precision and reduce the general toxicity linked to traditional drug delivery systems.

6. MECHANISM OF DRUG ENCAPSULATION

Because of their bicontinuous structure, cubosomes can encapsulate different kinds of molecules, including large amounts of drugs. Amphiphilic molecules can interact with the interfacial regions, lipophilic chemicals can reside in the lipid bilayer, and hydrophilic substances can be contained inside the aqueous channels. Compared with traditional spherical liposomes, this multi-compartmental structure often produces higher encapsulation rates [1, 23–25]. Drugs can be loaded into cubosomes either post-formation by exposing pre-formed cubosomes to dissolved drug compounds or during creation by incorporating the cargo molecules into the self-assembly process [5].

Loading efficacy is strongly influenced by the physicochemical characteristics of the enclosed substance, such as lipophilicity, ionization status, and molecular dimensions [26]. In GMO-derived cubosomes, highly hydrophobic substances show high encapsulation rates because of their strong affinity for lipid-rich regions, whereas hydrophilic compounds are effectively encapsulated within the aqueous channels. Adding permeation

enhancers and additives can increase drug solubility and stability within the cubic framework. Profound comprehension of the interactions between drugs and carriers at a molecular scale facilitates the systematic development of cubosomal compositions customized for particular therapeutic compounds. Drug loading can be accomplished through the addition of the drug into the melted GMO or by lyophilizing it with the lipid film before dispersing. Another approach involves loading drug moieties onto pre-formed cubosomes post-dispersion using an incubation method. [18]

7. METHODS OF PREPARATION

The top-down method, which uses high-pressure homogenization or ultrasonication to break bulk cubic phases into nanoscale cubosomes, is the most energy-intensive preparation technique. The significant mechanical stresses and localized heat generated during processing may disrupt the structural and functional integrity of labile biotherapeutics, especially proteins and peptides, even though this technique is frequently used to create physically stable dispersions [24].

The bottom-up approach is less energy-demanding and involves the spontaneous self-assembly of lipid components upon dilution or solvent exchange. However, depending on temperature, hydration level, stabilizer concentration, and lipid composition, the vesicle-to-cubosome transition is kinetically controlled and may go through temporary vesicular intermediates. Therefore, although bottom-up processing reduces mechanical stress, the dynamics of membrane fusion, rearrangement, and cubic-phase maturation control the final phase behavior [27,28]. The different methods of preparation, apart from the two most common – top-down and bottom-up approaches, are listed in Table 3.

Table 3: Different Approaches for Cubosome formation

Method	Principle / Approach	Short Description of Method	Key Features	Ref.
Top-down approach	High-energy fragmentation of bulk cubic phase	First, mix lipid and stabilizer to form a bulk cubic gel. Then disperse it into nanoparticles using high-pressure homogenization or ultrasonication.	Most widely used; produces stable cubosomes (up to 1 year); high energy required; vesicles may coexist	[29, 30]
Bottom-up approach	Self-assembly from molecular building blocks	Lipid + hydrotrope + stabilizer are mixed and then diluted with water, leading to spontaneous formation of cubosomes without high energy input.	Low-energy method; suitable for thermosensitive drugs; produces smaller particles with better entrapment efficiency	[29, 30]
Heat treatment method	Phase transition induced by temperature	Preformed vesicles are converted into cubic phase particles by controlled heating.	Not a standalone method; improves uniformity and stability; reduces vesicle fraction	[31]
Spray drying method	Conversion of dispersion into dry powder	Cubosomal dispersions are spray-dried with polymers like starch to form dry powder precursors; upon hydration, cubosomes form.	Scalable; useful for industrial production; suitable for protein/drug loading	[18]
Microfluidics Approach	Controlled microfluidic mixing between lipid (in ethanol) and aqueous phase leads to self-assembly into cubosomes	Lipid in ethanol and aqueous phases are injected into a SHM microdevice, creating chaotic mixing that leads to nanoemulsion formation. The resulting mixture is collected, and ethanol is removed using rotary evaporation, yielding a dispersion of cubosomes.	Precise size control, narrow size distribution; reproducible and low-energy process	[32, 33]

8. CHARACTERIZATION

Various evaluation parameters are involved in the characterization of cubosomes. Each characterization has a

significant role in determining the nanocarrier's properties. Table 4 summarizes the different characterization techniques used to evaluate cubosomes.

Table 4: Different characterization techniques for Cubosomes

Characterization Parameters	Instruments used	Inference	Ref.
Particle size, PDI, and zeta potential	Dynamic light scattering (DLS)/ Zeta sizer	To ascertain the effect of size and surface charge on dissolution, skin permeation, and adhesiveness.	[34]
Thermograms	Differential scanning calorimetry (DSC)	To ascertain the phase transition of materials	[35, 36]
Shape	Scanning electron Microscopy (SEM)	To ascertain the surface morphologies	[37]
Shape	Cryo-Transmission electron microscopy (TEM)	To ascertain the internal morphologies	[38]
Crystallinity	X-ray diffraction (XRD) and DSC	To characterize the phase identification of crystalline materials	[39]
Identification of phases	Small-angle X-ray scattering (SAXS) (Gold standard)	To determine the cubosomal internal symmetry by Bragg peak ratios and indexing cubis phases such as Im3m, Pn3m and Ia3d	[39]

9. BIOMEDICAL APPLICATIONS

Cubosomes in Cancer

Cubosomes show significant potential in oncology by improving the delivery of lipophobic chemotherapeutic agents, resulting in notably diminished systemic toxicity compared with unbound medications [40]. Cubosomes have notable drug-loading capacity and extended-release profiles, reducing peak plasma levels of cytotoxic agents while maintaining adequate intracellular concentrations at tumor sites for therapeutic

efficacy [41,42]. Preclinical investigations have shown the enhanced antineoplastic effectiveness of paclitaxel-incorporated cubosomes compared with Taxol preparations, with diminished cardiotoxicity and neurotoxicity associated with traditional taxane delivery. [43]. Utilization of doxorubicin-loaded cubosomes has demonstrated escalated therapeutic efficacy in diverse cancer models while markedly reducing cardiotoxic side effects. The versatility of cubosomes enables the co-encapsulation of chemotherapeutic agents with

immunomodulatory substances or photosensitizers, yielding synergistic compositions that enhance therapeutic efficacy through multiple pathways [44]. Recent advances in cubosomal theranostics combine therapeutic agents with fluorescent markers or radiotracers, enabling co-administration and real-time visualization of tumor distribution [43,45,46].

Antimicrobial and Antiviral Applications

Cubosomes are excellent for delivering antimicrobial peptides and conventional antibiotics to infection sites because of their bioadhesive properties and high loading capacity [47]. Using cubosomes as carriers for antimicrobial peptides (AMPs) has demonstrated long-lasting antibacterial activity that outperforms unbound peptides, thereby addressing the problem of peptide breakdown. [48]. The lipid-based composition of cubosomes contributes to their intrinsic antimicrobial activity through membrane disruption mechanisms that synergize with the encapsulated therapeutic agents [49]. Additionally, the ability to transport multiple antimicrobial agents in a single carrier enables combination therapy approaches to address resistance mechanisms effectively [50]. Antiviral-containing cubosomes have shown enhanced penetration through mucosal surfaces and epithelial barriers, indicating strong potential for intranasal and respiratory medication delivery [38,39,40].

Dermatological and Transdermal Delivery

The unique bicontinuous structure and substantial internal surface area of cubosomes offer strong potential to accommodate both hydrophilic and lipophilic bioactive compounds commonly used in pharmaceutical skincare and dermatological preparations [51]. Cubosome-based delivery systems are crucial for boosting medication bioavailability at specific dermal sites through mechanisms such as enhanced cutaneous penetration enabled by increased stratum corneum hydration and selective accumulation within sebaceous glands and hair follicles [52]. Key determinants of transdermal drug delivery effectiveness include cubosome size, surface polarity, lipid composition, and the integration of permeation enhancers, all of which can be systematically refined for specific therapeutic contexts [53].

Clinical observations using cubosomal formulations in dermatological treatment have significantly improved the therapeutic efficacy of topically applied medicines, including anti-inflammatory drugs, antibacterial compounds, and cosmeceuticals [54–57].

Oral Drug Delivery and Bioavailability Enhancement

Cubosomes offer a promising strategy to address the bioavailability obstacles linked to poorly soluble drugs, particularly BCS Class II and IV compounds. [58]. Their bicontinuous aqueous channels provide ideal microenvironments for increasing the solubility of aqueous-insoluble drugs, and the lipid component facilitates their transit through the intestinal epithelium [59]. Oral administration of CoQ10-loaded cubosomes has been shown to significantly boost hepatoprotective efficacy in animal models compared with free CoQ10. This enhanced bioavailability is evidenced by increased plasma levels and tissue distribution [26]. Additionally, the adhesive characteristics of cubosomes promote interactions with intestinal epithelial cells, facilitating cellular uptake through mucin interactions and direct adhesion to enterocyte surfaces [60]. These interactions can improve uptake by specialized epithelial cells, including M cells above Peyer's patches & facilitate transcytosis across the intestinal epithelium. For the oral administration of peptide-based medications and vaccinations, this characteristic is beneficial (61–63).

Vaccine Delivery and Immunomodulation

Because of their remarkable stability and compatibility with biological systems, cubosomes are considered optimal vehicles for vaccine delivery [64]. Their bicontinuous structure ensures antigens are presented to immune cells for an extended period by preventing their breakdown [65,66]. Additionally, their lipidic composition offers inherent adjuvant properties, enhancing immune responses through mechanisms such as dendritic cell maturation and activation of pattern recognition receptors [67,68]. Research on cubosomal vaccines has shown stronger immune reactions than traditional formulations, with higher antibody levels and enhanced T-cell immunity [68,69].

Preclinical research shows that cubosome-based vaccine platforms can dramatically boost immune responses compared with free antigen or non-cubosomal controls. The average size of PS-loaded cubosomes (Cub-PS) in one investigation was 324.4 ± 2.05 nm, the zeta potential was -16.13 ± 0.42 mV, and the PS encapsulation efficiency was $89.5 \pm 3.51\%$. Cub-PS-Ag boosted the frequency of mature dendritic-cell markers following vaccination; CD11c ++ MHC II ++ and CD11c ++ CD86 ++ populations reached 61.0% and 54.8% at 24 hours, respectively, and 24.8% and 31.5% at 48 hours. With TEM and TCM values of 8.90% and 3.19%, respectively, the formulation

additionally boosted memory T-helper subsets in draining lymph nodes, indicating a larger adjuvant effect than PS-Ag or Cub-Ag alone [70].

10. EMERGING TECHNOLOGIES AND FUTURE DIRECTIONS

Stimuli-Responsive and Smart Cubosomal Systems

Recent developments in formulation techniques have enabled cubosomes to respond to a variety of environmental stimuli, including pH, temperature, enzyme activity, and magnetic fields [35]. Different stimuli can trigger a transition from the cubic phase to the hexagonal phase. The lipid bilayer forms a highly ordered 3D network with interconnected aqueous channels. The stimulus-induced change in the packing parameter can reorganize the system into the hexagonal phase, where curvature changes and the internal structure is less favorable for retaining the drug, leading to faster release [71,72]. In temperature-sensitive formulations, elevated temperatures can alter polymer-shell conformation, chain mobility, and lipid hydration, weakening the structural constraints that preserve the cubic phase. Drug diffusion from the rearranged matrix is enhanced by the dehydration of polymer coatings and the breakdown of hydrogen bonds, which further improve membrane permeability. In pH-responsive methods, protonation of pH-sensitive head groups or ionizable lipids under acidic conditions modifies the effective packing parameter and reduces electrostatic repulsion, destabilizing the cubic organization and encouraging the transition to hexagonal, lamellar, or disordered phases [65,68,69]. Enzymatically degradable coatings and peptide crosslinks enable targeted drug release within tissues with relevant proteases, enhancing specificity in drug delivery.[2] Superparamagnetic iron oxide nanoparticles in magnetically responsive cubosomes for regulated medication release in the presence of alternating magnetic fields. This method promises tailored photodynamic therapy with photosensitizer-loaded cubosomes by combining the targeting advantages of cubosomes with the guidance and heating capabilities of magnetic nanoparticles [73].

Integration with Emerging Delivery Technologies

Recent advances in microfluidic manufacturing have enabled precise production of monodisperse cubosomes with exceptional size control and reproducibility [74]. Cubosomal manufacturing combined with real-time synchrotron scattering analysis provides rapid insight into internal cubic-phase development,

enabling modification of production parameters. Researchers create complex hybrid systems with complementary functionalities by combining cubosomes with hydrogel matrices, polymer micelles, and exosomes. Encasing carbon dots in cubosomes improves photoluminescence and increases cellular uptake compared with loose nanoparticles, providing dual-purpose platforms for drug delivery and imaging. For tissue regeneration applications, cubosomal matrices incorporated into hyaluronic acid hydrogels offer both scaffold support and prolonged drug release [75]. These hybrid systems exemplify the emerging trend of amalgamating diverse nanotechnologies to achieve enhanced therapeutic outcomes.

Structural Engineering and Phase Design

Recent advances in synthetic chemistry enable the deliberate synthesis of new amphiphilic lipids that form cubic phases, reducing reliance on natural or semi-synthetic lipid sources. Computational techniques such as modeling and simulations accelerate formulation improvement by predicting self-assembly tendencies. Beyond the common Pn3m and Im3m phases, investigating other cubic phase symmetries offers new ways to control particle properties [76].

11. CHALLENGES

Beyond the emerging technologies discussed above, the further progress of cubosomes toward clinical translation will depend on solving long-term storage and regulatory challenges. Despite their inherent structural benefits, cubosomes' use in clinical applications is limited by long-term storage stability issues, including phase transitions, particle enlargement, aggregation, and settling. The metastable internal cubic lattice is susceptible to environmental factors such as temperature variations, ionic strength changes, and steric stabilization effects. Consequently, meticulous optimization of formulation approaches is imperative to uphold the mesophase integrity during refrigerated or room-temperature storage. Key considerations include judicious stabilizer selection, lyophilization, cryoprotectant incorporation, and precise control of lattice parameters. These strategies are indispensable for averting the transformation into vesicular or hexagonal structures and ensuring consistent performance and durability over an extended period (77–79). Regulatory adaptation of lipid-based nanocarriers remains challenging because approval criteria vary across international markets, especially for product characterization, excipient safety assessment, sterility assurance, batch-to-batch consistency, and

demonstration of in vivo biological relevance. For cubosomes, regulatory bodies commonly require conclusive proof of the internal phase identity, stability in colloidal form, justification for surfactant levels based on toxicological assessments, and efficient scalability that adheres to quality-by-design principles. More consistent global regulatory standards would streamline development; however, approval for lipid-based nanocarriers remains more complex than for traditional lipid formulations [80–82].

12. CONCLUSION

Because of their exceptional structural flexibility, high drug-carrying capacity, superior biocompatibility, and sustained-release characteristics that set them apart from conventional liposomal platforms, cubosomes represent a major advancement in nanoparticle-based drug delivery systems [83]. Their bicontinuous cubic structure allows encapsulation of hydrophilic, lipophilic, and amphiphilic drugs, making cubosomes versatile nanocarriers applicable in various medical fields such as oncology, infectious diseases, dermatology, and vaccine delivery [1,84].

The considerable preclinical data supporting the efficacy of cubosomes in disease models, coupled with their demonstrated safety in initial clinical assessments, suggest promising prospects for clinical adoption and commercialization [85]. However, a smooth transfer from research prototypes to clinical products requires ongoing improvements in manufacturing processes, regulatory clarity, and comprehensive safety evaluations across diverse patient populations. Cubosomes can be combined with new technologies such as magnetic particles, smart polymers, and microfluidic manufacturing techniques to create innovative treatment and diagnostic platforms with increased precision and efficacy [2,83].

Future advancements in cubosomal technologies should prioritize sustainable manufacturing techniques to enable large-scale production. Additionally, efforts should focus on establishing clear structure-function correlations to predict formulation performance and clinically validate safety and efficacy across diverse medical contexts [60]. Cubosomes' unique structural features and biological behavior make them an essential tool in modern nanomedicine, with the potential to greatly improve treatment outcomes across a variety of disease categories by increasing drug bioavailability, reducing systemic

toxicity, and improving patient compliance through streamlined dosing protocols.

FINANCIAL ASSISTANCE

NIL

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

Khyati Mishra, Shreyansh Saha, Monideepa Dey, Garima Kumari, Sumeet Kumar Das, Amit Kumar Das, and Apurba Talukdar contributed to conceptualization, methodology, investigation, data curation, formal analysis, and manuscript preparation. Khyati Mishra contributed substantially to the investigation, data analysis, and writing of the original draft. Manoj Kumar Deka contributed to the conceptualization, supervision, project administration, critical review and editing of the manuscript, and overall coordination of the research work, and served as the Corresponding Author. All authors contributed to interpreting the results, critically reviewed and approved the final version of the manuscript, and agreed to be accountable for all aspects of the work.

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