Cubosomes as smart nanocarriers for antimicrobial agents: A review of emerging applications

Bazigha K. Abdul Rasool*, Raneem Zakaria, Nour Hijazi, and Aliasgar Shahiwala

ABSTRACT

Cubosomes, a distinctive class of lipid-based nanocarriers, have gained increasing attention as an advanced platform for drug delivery due to their bicontinuous cubic phase structure, high drug-loading capacity, and ability to provide sustained and controlled release. These nanoparticles are self-assembled from amphiphilic lipids and stabilizers, forming a highly ordered internal architecture that enables efficient encapsulation of hydrophilic, lipophilic, and amphiphilic molecules. This review summarizes recent advancements in the design and application of cubosome-based delivery systems, with emphasis on their structural composition, preparation techniques, and the advantages that they offer over conventional nanocarriers. Focus is also placed on their emerging role in antimicrobial therapy, where cubosomes have demonstrated significant potential as carriers for antibacterial, antiviral, and antifungal agents. Current research highlights the proficiency of cubosomes in enhancing solubility, improving bioavailability, and increasing the therapeutic effectiveness of various antimicrobial drugs. Their ability to overcome limitations such as rapid degradation, poor permeability, and drug resistance positions them as promising tools in combating persistent and emerging infectious diseases. Moreover, cubosomes have shown potential in disrupting biofilms and improving targeted delivery, further expanding their therapeutic relevance. Despite their promising attributes, challenges remain regarding large-scale manufacturing, stability during storage, and optimization of formulation parameters. Addressing these limitations will be essential to facilitate the clinical translation of cubosome-based nanomedicines. Future studies should focus on scalable production methods, enhanced stability strategies, and comprehensive *in vivo* evaluations to fully harness the potential of cubosomes in modern antimicrobial therapy.

Keywords:
Cubosomes; Nanocarriers; Antimicrobial therapy; Drug delivery; Sustained release; Bioavailability

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1. Introduction

Cubosomes are innovative nanostructured colloidal carriers that exhibit a unique liquid-crystal cubic phase. These particles are isotropic and transparent, typically ranging in size from 10 to 300 nm. Cubosomes exhibit physical stability in aqueous environments. Their bicontinuous cubic structure allows for the encapsulation of various compounds, including lipophilic, hydrophilic, and amphiphilic molecules, enhancing drug bioavailability and loading capacity.[1]

Cubosomes are also biodegradable, non-toxic, and exhibit thermodynamic stability, enabling them to remain stable over long periods. Unlike other vesicular systems, such as liposomes, cubosomes offer lower viscosity and maintain their structure across various dilutions.[2] The key differences between cubosomes and liposomes are depicted in **Table 1**. Consequently, their unique properties make them suitable for a range of drug delivery applications, including oral, transdermal, ocular, and chemotherapy therapy.[3,4] **Figure 1** presents a schematic illustrating the applications of cubosomes in antimicrobial therapy.

2. Methodology

A comprehensive literature search was conducted to collect relevant studies on cubosomes as

nanocarriers for antimicrobial agents. The search spanned the period from 2010 to 2024, utilizing databases such as PubMed, ScienceDirect, Embase, SpringerLink, and Google Scholar. Keywords such as "cubosomes," "nanocarriers," "antimicrobial," "antibacterial," "antiviral," "antifungal," "biofilm," and "drug delivery" were used in various combinations. Only peer-reviewed articles published in English were included. Studies focusing on cubosome-based antimicrobial delivery were selected, while non-English papers, conference abstracts, and unrelated reports were excluded. Relevant information on formulation methods, components, and antimicrobial outcomes was extracted and synthesized to provide a comprehensive overview of recent advances in cubosome-based antimicrobial therapies.

Table 1. Comparison between cubosomes and liposomes[1,5-10]

Feature	Liposomes	Cubosomes
Structure	Spherical vesicles composed of phospholipid bilayers encapsulating an aqueous core	Nanostructured particles with a cubic phase characterized by interconnected water channels
Size range	Sizes typically range from 50 nm to several micrometers	Generally, 10–500 nm in size
Preparation methods	Methods include thin film hydration, ethanol injection, and sonication	Prepared through emulsification and high-energy dispersion methods
Stability	Prone to fusion, leakage, and oxidation; however, cholesterol can enhance their stability	High stability is attributed to their cubic phase structure
Drug loading capacity	Encapsulate hydrophilic drugs in the core and lipophilic drugs in the bilayer	Effective for hydrophilic, lipophilic, and amphiphilic drugs due to their unique internal structures
Release profile	Can exhibit rapid drug release; requires modifications for sustained release.	Offer sustained and controlled release due to tortuous diffusion pathways
Biocompatibility	Biocompatible and biodegradable; mimic cell membranes	Biocompatible and bioresorbable; derived from naturally occurring lipids

3. Nanotechnology-based strategies for treating bacterial infections

Nanotechnology offers innovative approaches for treating microbial infections, particularly in addressing challenges such as drug resistance and poor drug bioavailability. Nanoparticles (NPs), such as metal-based (silver and gold), lipid-based (cubosomes and liposomes), and polymeric systems, possess unique properties that enhance drug delivery, target specificity, and antimicrobial activity.[2,11]

Metal NPs, particularly silver NPs (AgNPs), exert antimicrobial effects by disrupting membranes, inducing oxidative stress, or inhibiting enzymes. Silver ions released from AgNPs interact with bacterial membranes, causing permeability and leakage, disruption of critical enzymes, and generation of reactive oxygen species, resulting in microbial cell death.[12,13] Gold NPs (AuNPs), functionalized with antibacterial agents, demonstrate efficacy through similar mechanisms, with promising antibacterial properties.[14,15]

Lipid-based NPs, including cubosomes and liposomes, encapsulate therapeutic agents, significantly enhancing their stability, bioavailability, and targeting capabilities. Liposomal amphotericin B is an example of a successful clinical application, effectively treating fungal infections with improved safety and efficacy profiles.[16]

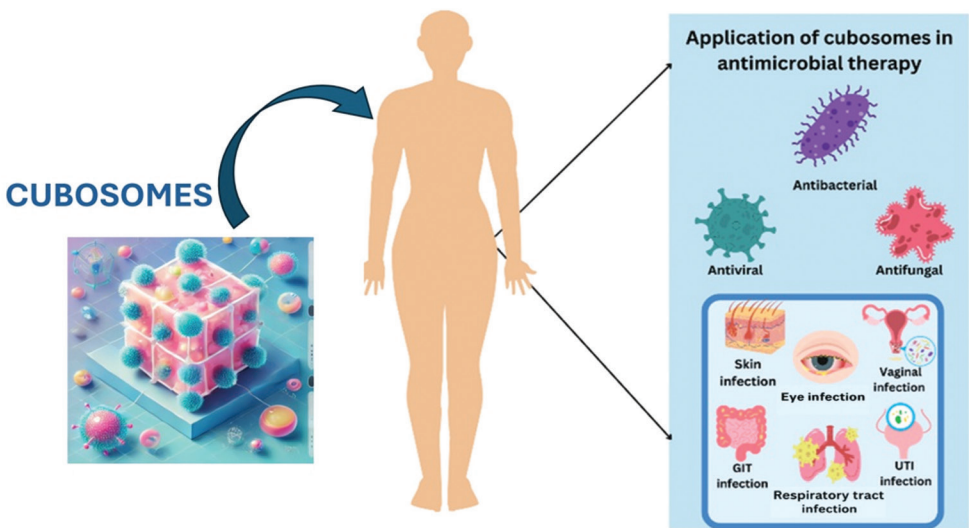

Figure 1. Schematic illustration of the application of cubosomes in antimicrobial therapy. This figure was created with the assistance of an AI-based image generation tool (OpenAI) and subsequently edited and verified by the authors for scientific accuracy.
Abbreviations: AI: Artificial intelligence; GIT: Gastrointestinal tract; UTI: Urinary tract infection.

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On the other hand, polymeric NPs such as poly(lactic-co-glycolic acid), dendrimers, and chitosan NPs offer versatile solutions in antimicrobial therapy. They encapsulate various drugs, enable targeted and sustained delivery, and reduce adverse effects. Dendrimers, for instance, demonstrate antiviral capabilities by effectively blocking viral entry and infection, notably in human immunodeficiency virus (HIV) and herpes simplex virus infections.[17]

4. Advantages and limitations of cubosomes as antimicrobial carriers

Cubosomes are biocompatible and biodegradable, and they can load hydrophilic, lipophilic, and amphiphilic drugs with high efficiency, thanks to their large internal surface area.[4] Other advantages of cubosomes include the ease of their preparation, enhanced bioavailability, and minimal dosing, which is associated with lower healthcare costs.[4] However, challenges include less effective entrapment of water-soluble drugs, production difficulties due to high viscosity, potential leakage, size growth over time, and sensitivity to environmental changes. **Table 2** lists the advantages and disadvantages of cubosomes.[1]

Table 2. Advantages and disadvantages of cubosomes

Advantages	Disadvantages
• Bio-adhesive, non-irritant, non-allergic, biocompatible, and biodegradable • Hydrophilic, lipophilic, and amphiphilic drugs can be loaded into cubosomes • Extensive internal surface area enables high drug loading • The preparation process is straightforward • Superior solubilizing properties compared to other lipid-based carriers • Enhance bioavailability of small and macromolecular drugs. • Sustained drug release, minimizing the need for frequent administration	• Water-soluble drugs are less effectively entrapped due to the high-water content within the system • The large-scale production of cubosomes presents challenges, primarily due to their inherently high viscosity • Potential to leakage during storage or *in vivo* transmission • The size of cubosomes may grow over time • May undergo phase transitions in response to changes in the external environment

5. Cubosome structure and components

Cubosomes display a sophisticated bicontinuous cubic liquid crystalline structure (**Figure 2**). Two hydrophilic regions are separated by lipid bilayers, enabling the encapsulation of hydrophilic, hydrophobic, and amphiphilic molecules.[18] Cubosomes are primarily composed of amphiphilic lipids and stabilizers. Glyceryl monooleate (GMO) is the most used lipid due to its amphiphilic properties, biocompatibility, and ability to form bicontinuous cubic structures. GMOs' unique structure allows hydrogen bonding with water molecules, facilitating their use in pharmaceutical and food applications.[1,7] Phytantriol (PHYT), another lipid, has garnered interest due to its superior chemical stability, moisture retention, and sustained drug release, particularly for hydrophilic drugs.

In addition, stabilizers such as Poloxamer 407 (P407) are added to prevent particle agglomeration and maintain colloidal dispersion. P407 interacts with the cubic phase, enhancing stability and structural integrity.[19,20] While P407 is widely used, alternatives such as Myrj59 and polyvinyl alcohol have shown promise in stabilizing cubosomes, especially those formulated with phytantriol.[4,7] Commonly used stabilizing agents and lipids in cubosome preparation are given in **Table 3**.

6. Cubosome preparation techniques

Cubosomes are typically prepared using either the top-down or bottom-up methods, as illustrated in **Figure 3**.

In the top-down methods, a lipid-stabilizer mixture is first melted and combined with water, followed by vortex-mixing to

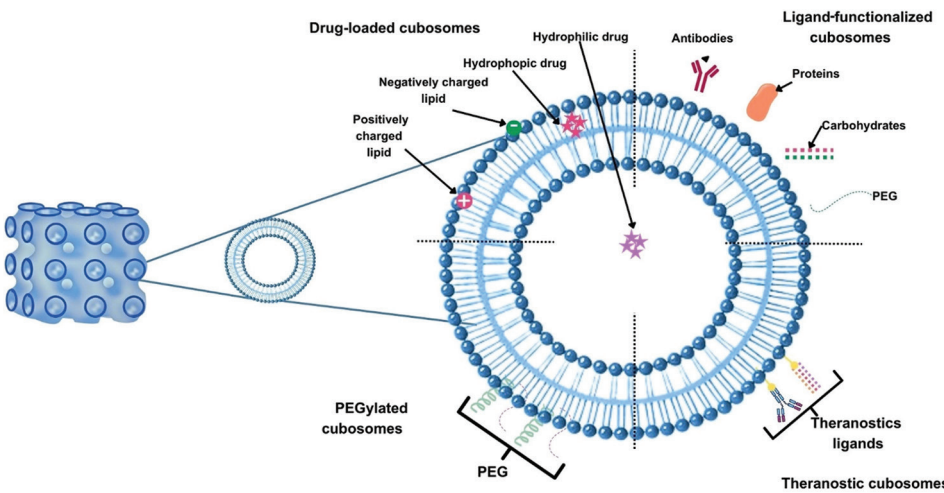

Figure 2. Illustration of the structural organization and multifunctional properties of cubosome nanoparticles. (A) The outer surface can be functionalized using ligand-gated modifications such as antibodies, proteins, carbohydrates, PEG, and disease-specific targeting ligands for enhanced selectivity and receptor-mediated cell uptake. (B) The internal bicontinuous cubic structure enables versatile drug-loading strategies, allowing for the simultaneous encapsulation of both hydrophilic and hydrophobic therapeutic agents. (C) PEGylation improves systemic circulation time, colloidal stability, and resistance to opsonization and premature clearance. (D) Cubosomes can be utilized as targeted delivery systems in cancer therapy to enhance intracellular delivery, reduce systemic toxicity, and improve therapeutic outcomes.
Abbreviation: PEG: Polyethene glycol.

create a uniform bulk cubic phase. This phase is then carefully broken down into nanosized cubosomes using sonication or high-pressure homogenization.[30] While this technique is highly effective for producing stable cubosome dispersions, it requires a significant amount of energy, which can introduce variability in particle size. In addition, scaling up this process can be challenging, especially when working with temperature-sensitive compounds such as peptides and proteins.[31]

In one study, cubosomes were prepared using the emulsification method.[32] A crude emulsion was formed by gradually adding the oil phase to the liquid phase using a high-shear dispersing emulsifier, followed by homogenization of the crude emulsion at a high-speed homogenizer. This process was then followed by adjustments to the osmotic pressure and pH, ultimately leading to the formation of cubosomes.[32]

The bottom-up method involves combining a lipid, stabilizer, and hydrotrope, followed by mixing and controlled stirring.[33] This approach is efficient, requiring minimal energy, and produces stable nanosized cubosomes suitable for encapsulating sensitive agents.[18] However, the use of hydrotrope may result in limited stability and potential risks of allergic reactions.[34]

To increase the stability of cubosomes, spray drying and freeze-drying methods were employed. Spray-drying is a method used to create dry powders from liquid mixtures. It involves spraying the mixture into hot airflow, causing the water to evaporate and leaving behind the desired particles.[35] The aqueous phase is combined with the lipid phase, then sprayed through a nozzle, generating a suspension droplet to clash with a dry, hot airflow (**Figure 3**). As the water evaporates, it leaves dry powder particles composed of dispersed phase enclosed by a shell of the dissolved polymer.[36] Similarly, freeze-drying, also known as lyophilization, is a technique used to convert liquid formulations into stable dry powders by removing water through sublimation. The process involves freezing the sample and then reducing the pressure to allow the direct ice transition into vapor, preserving the structural integrity of the cubosomes.

Table 3. Commonly used stabilizing agents and lipids in cubosome preparation

Lipids	Stabilizer	References
Monoolein	Pluronic F127	21
Phytantriol	Pluronic F127	22
Monoelaidin	Pluronic F127	23
B-XP (1-*O*-phytanyl-β-d-xyloside)	Pluronic F127	24
Monoolein or phytantriol	Pluronic F108	25
Phytantriol	Myrj 59	26
Monoolein	Modified starch	27
Sodium octyl sulfate (SCS)	Arginine-based cationic surfactant	28
Monoolein	Laponite XLG	29

7. Applications of cubosomes

Cubosomes have demonstrated significant potential across various antimicrobial applications due to their ability to enhance drug solubility, bioavailability, and sustained release. Their applications can be broadly categorized by route of administration and therapeutic area.

7.1. Antibiotics-loaded cubosomes

The development of cubosome formulations for fluoroquinolone and macrolide antibiotics has garnered significant attention in recent years, due to their benefits in enhanced therapeutic efficacy, improved patient compliance, and amelioration of challenges associated with conventional

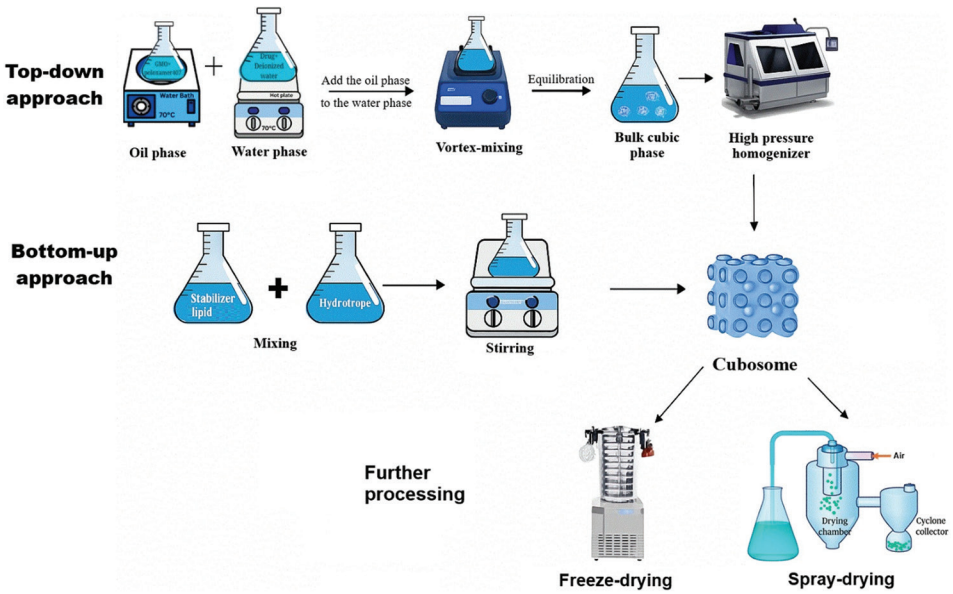

Figure 3. The two major pathways for cubosome preparation. Top-down methods involve the fragmentation of bulk cubic phase precursors into nanoscale particles, whereas bottom-up methods rely on the spontaneous self-assembly of molecular precursors in aqueous environments. After formation, cubosomes can be further processed and stabilized using freeze-drying (lyophilization) or spray-drying to obtain dry, storage-stable formulations suitable for reconstitution and large-scale pharmaceutical applications.

drug delivery systems.[37,38] Cubosomes, as nanostructured lipid carriers, offer unique advantages, including high drug encapsulation efficiency, controlled release profiles, and the ability to encapsulate both hydrophilic and hydrophobic drugs.[39,40] These properties make them promising candidates for delivering antibiotics in a more effective and patient-friendly manner. The detailed characteristics and key findings of these cubosome formulations are summarized in **Table 4**.

Fluoroquinolones such as ciprofloxacin,[41] gatifloxacin,[42] and moxifloxacin[43] have been formulated into cubosomal systems to overcome limitations of traditional eye drops, such as poor bioavailability and frequent dosing requirements. For example, a ciprofloxacin-loaded cubosome formulation demonstrated a significant increase in antimicrobial effectiveness compared to commercial eye drops, allowing for reduced dosing frequency while maintaining therapeutic efficacy. Similarly, gatifloxacin-loaded cubosomes exhibited enhanced corneal permeation and required a lower minimum inhibitory concentration to achieve effectiveness, indicating their potential in treating ocular bacterial infections and reducing the risk of resistance.[42] Moxifloxacin-loaded cubosomal gels also provided prolonged antibacterial activity without causing corneal irritation, suggesting their suitability as safe and effective alternatives for prolonged conjunctivitis treatment.[43]

A comparative analysis of these formulations reveals that particle size, zeta potential, and lipid composition have a critical influence on ocular performance. Smaller particles (<150 nm), such as those in ciprofloxacin cubosomes, enabled a rapid onset but shorter duration of action, whereas larger moxifloxacin cubogels (>300 nm) prolonged drug retention on the corneal surface. Similarly, negatively charged cubosomes demonstrated superior mucoadhesion and reduced precorneal clearance, corroborating findings from recent studies on pH-sensitive cubosomal gels.[43] These outcomes highlight that optimization of physicochemical parameters is essential to balance penetration with sustained release.

Beyond fluoroquinolones, macrolide antibiotics such as erythromycin,[44] azithromycin,[45] and rapamycin[46] have been incorporated into cubosomal formulations to address challenges such as poor solubility, rapid degradation, and an unpalatable taste. Erythromycin-loaded cubosomal gels achieved sustained drug release for up to 36 h, offering an alternative to frequent topical dosing for acne therapy.[44] Azithromycin-loaded cubosomes improved palatability while maintaining antimicrobial potency, addressing a key challenge in oral administration.[45] Rapamycin-loaded cubosomes, which were delivered through dissolving microneedles, achieved high encapsulation (>95%), and sustained transdermal release over 2 weeks, significantly reducing dosing frequency and improving delivery to immune-rich skin layers.[46]

In summary, antibiotic-loaded cubosomes represent a versatile and effective nanocarrier system, demonstrating improvements in solubility, bioavailability, and sustained release. However, the relationship between formulation parameters and pharmacological performance remains complex, requiring systematic optimization. Future research should prioritize comparative studies across antibiotic classes, a mechanistic understanding of lipid–drug interactions, and the clinical validation of cubosome formulations for treating multidrug-resistant infections.

7.2. Antiviral-loaded cubosomes

Cubosomes have demonstrated considerable promise in overcoming the pharmacokinetic and physicochemical limitations of antiretroviral drugs, including protease inhibitors (PIs), reverse transcriptase inhibitors (RTIs), and non-nucleoside RTIs (NNRTIs). Their bicontinuous cubic nanostructure enables simultaneous encapsulation of hydrophilic and lipophilic compounds, promoting sustained release, enhanced solubility, and improved tissue permeability.[47-50] Since 2024, intranasal and hydrogel-embedded cubosomes have been highlighted for mucoadhesive delivery and prolonged mucosal residence, features that directly

Table 4. Characterization and results of cubosome formulations containing antibiotics

Drugs	Type of study	Particle size (nm)	Zeta potential (mV)	EE%	PDI	Results	References
Ciprofloxacin	*In vivo* and *in vitro*	121	-	75%	-	• 2.54 times more effective than commercial eye drops • Similar effectiveness of once daily dosing compared to 3–4 doses/day for commercial eye drops	41
Gatifloxacin	*In vivo* and *in vitro*	197.46	−21.90±2.03	52.8%	1.3±0.05	• 1.3 times higher corneal permeation compared to a simple GTX solution • Required only one-fourth the minimum inhibitory concentration (MIC) compared to the GTX solution • Significantly reduced corneal opacity and showed no adverse tissue effects	42
Moxifloxacin	*In vivo* and *in vitro*	306.5–714.2	−39.8	85	0.753	Prolonged antibacterial activity with a larger inhibition zone, and no corneal irritation	43
Erythromycin	*In vivo*	264.5	-	95	-	Sustained drug release up to 36 h	44
Azithromycin	*In vivo* and *in vitro*	166–272	-	89	0.33	Preserves drug potency while significantly improving its palatability	45
Rapamycin	*In vivo* and *in vitro*	221±14	-	>95	0.4	Sustained transdermal release over 2 weeks	46

Abbreviations: EE%: Entrapment efficiency percentage; mV: Millivolt; nm: Nanometer; PDI: Polydispersity index.

address the adherence challenges emphasized in the latest HIV guidance and the push toward non-IV remdesivir options.[51,52] **Table 5** summarizes representative studies on antiviral-loaded cubosome formulations.

PIs such as atazanavir[47,53] and saquinavir mesylate[54] have been widely investigated in cubosomal systems. Atazanavir-loaded cubosomal gels demonstrated a 4.6-fold higher transdermal bioavailability compared to oral solutions, primarily due to their optimized nanoscale dimensions and negative zeta potential, which facilitated dermal diffusion. In contrast, saquinavir mesylate cubosomes designed for intranasal delivery showed a 12-fold and 2.5-fold increase in relative bioavailability over oral and nasal suspensions, respectively, underscoring the potential of cubosomes for nose-to-brain targeting. These distinct improvements demonstrate how route-specific formulation strategies can significantly impact pharmacokinetics and drug distribution.

For nucleoside RTIs such as lamivudine and zidovudine,[48] cubosome formulations prepared through green chemistry achieved nanoscale uniformity with low polydispersity indices. However, their entrapment efficiencies remained moderate, reflecting the inherent challenge of loading hydrophilic antivirals into lipid matrices. Conversely, NNRTIs like efavirenz[55] displayed exceptional solubility enhancement (≈ 2200-fold), confirming that highly lipophilic agents benefit most from the lipid-rich cubic architecture. These contrasts emphasize the necessity of matching drug physicochemical properties with cubosome composition, a critical factor often overlooked in current formulation design.

Across antiviral classes, performance is tightly linked to particle size, interfacial charge, and internal lipid composition: smaller particles and modest negative zeta potentials favor mucosal and dermal transport, while phytantriol matrices often support chemically robust, slow-diffusion systems suitable for sustained delivery. At the same time, hydrophilic agents (*e.g.*, nucleoside RTIs) routinely underperform in passive loading relative to lipophilic antivirals, such as efavirenz, which motivates the use of active/gradient-based loading to increase entrapment efficiency and reduce burst release.

Despite these advances, critical challenges remain. Many reports rely on *in vitro* antiviral assays that may overestimate *in vivo* efficacy, and comparative pharmacokinetic data are still scarce. In addition, the scalability and reproducibility of cubosomal formulations remain unresolved due to high-energy homogenization requirements and batch-to-batch variability in lipid organization.[56] The limited stability of hydrotrope-based systems and the potential for mucosal irritation from surfactants also warrant attention. Regulatory evaluation will require standardized analytical methods for morphology, drug release, and immunogenicity.

7.3. Antifungal-loaded cubosomes

Cubosome-based nanocarriers have gained substantial attention for the delivery of antifungal agents, particularly those belonging to the azole and polyene classes. Their unique bicontinuous cubic phase structure enhances drug solubility, stabilizes thermostable agents, and provides sustained release while improving tissue penetration. These features are particularly advantageous in treating cutaneous, ocular, and mucosal fungal infections, where achieving effective local concentrations is often challenging.[39,57] Representative studies of antifungal-loaded cubosomes are summarized in **Table 6**.

Azole antifungals such as fluconazole,[58] voriconazole,[59] and itraconazole[60] have been successfully encapsulated in cubosomal systems to overcome solubility and permeability limitations associated with conventional formulations. Fluconazole-loaded cubosomes exhibited improved skin penetration and enhanced efficacy against *Candida albicans* infections compared with commercial creams. Voriconazole-loaded cubosomes demonstrated superior ocular bioavailability and deeper tissue penetration than suspension formulations, while itraconazole cubosomal gels provided sustained dermal release for up to 24 h. These findings collectively suggest that cubosomes are highly effective in maintaining prolonged local antifungal activity and reducing the frequency of application. Comparable results were reported for inhalable cubosome NPs of nystatin for effective management of invasive pulmonary aspergillosis.[61]

Imidazole derivatives, such as clotrimazole[63] and miconazole,[62] have also been successfully incorporated into cubosomal systems. Clotrimazole-loaded cubosomes have demonstrated significantly enhanced skin retention and controlled drug release, resulting in improved antifungal efficacy and accelerated healing of *Candida albicans* infections.[63] Miconazole nitrate-based cubosome hydrogels have been developed for topical applications, offering controlled drug release and superior antifungal activity.[62] Recently, Purohit *et al.*[64] developed a novel luliconazole cubosomal emulgel exhibiting

Table 5. Studies on cubosome formulations containing antivirals

Drug	Type of study	Particle size (nm)	Zeta potential (mV)	EE%	PDI	Key findings	References
Atazanavir	*In vivo* and *in vitro*	100±7.9	−32.45	93±0.8	0.54±0.02	Cubosomal gel enhances transdermal drug absorption and exhibits 4.6 times higher bioavailability compared to an oral solution	47,53
Saquinavir mesylate	*In vivo* and *in vitro*	120±2.3	-	72±1		12-fold and 2.5-fold higher bioavailability than the oral and nasal suspensions	54
Lamivudine+ Zidovudine	*In vivo*	82±12	−4.0	-	0.09±0.004	• Prepared using a green chemistry process • Narrow size distribution	48
Efavirenz	*In vivo* and *in vitro*	104.19±0.21	−23.14	>91.40±0.10		2216 times increase in drug solubility	55

Abbreviations: EE%: Entrapment efficiency percentage; PDI: Polydispersity index.

enhanced topical antifungal activity and sustained release properties compared with conventional creams. In a most recent study, Nath *et al.*[65] developed a dual-drug–loaded topical cubosomal gel that showed potent *in vitro* and *in vivo* activity against *Candida albicans*, confirming the synergistic antifungal potential of cubosome-based combination therapies.

The encapsulation of these antifungal agents within cubosomes not only enhances their bioavailability but also provides a controlled release mechanism, reducing the frequency of administration and potentially minimizing side effects. The physicochemical properties of these formulations, such as particle size, zeta potential, encapsulation efficiency, and polydispersity index, play a crucial role in determining their stability and efficacy. Optimizing these parameters is essential for developing effective cubosome-based drug delivery systems. Voriconazole-loaded cubosomes,[59] coated with chitosan, have enhanced bioadhesion and prolonged ocular residence, thereby addressing challenges such as poor precorneal retention.

8. Mechanisms of antimicrobial loading into cubosomes

Cubosomes can encapsulate antimicrobials through three distinct mechanisms.

8.1. Passive loading

Antimicrobials are typically mixed with lipids before cubosome formation, usually by dissolving the drug in the lipid melt or lipid solution before dispersion. This allows drugs, especially hydrophobic ones, to integrate spontaneously within the cubic lipid bilayers, resulting in high encapsulation efficiency due to the strong affinity between lipids and drugs. Hydrophilic drugs can also be loaded passively, localizing within the aqueous nanochannels formed on hydration. However, achieving high encapsulation efficiencies for highly hydrophilic agents can be challenging due to potential leakage.[1,66]

8.2. Active loading

Gradient-based active loading utilizes concentration or ion gradients (*e.g.*, pH gradient) to actively drive antimicrobials into preformed cubosomes. By establishing gradients across the cubosomal membranes, antimicrobials—especially those with suitable charge and permeability—can be efficiently "trapped" inside the cubosome. This method significantly improves encapsulation, even for hydrophilic drugs that otherwise exhibit poor loading through passive methods.[66]

8.3. Post loading

This method involves incubating pre-formed, drug-free cubosomes with antimicrobial agents, allowing drug molecules to diffuse passively into cubosomes driven by concentration gradients. This approach often results in lower encapsulation efficiency, especially for hydrophilic drugs, as their diffusion into the internal cubic structure is limited. Thus, this method generally results in increased surface adsorption and a potential initial burst release on application.[67,68]

9. Factors affecting antimicrobial loading and entrapment efficiency

The choice and concentration of lipids are crucial in determining the internal structure and drug-loading capacity of cubosomes. Research has shown that the composition of the lipid matrix directly impacts the encapsulation, efficiency, and release profile of the drug.[4] Monoolein or phytantriol, as cubic-phase lipids, and poloxamer stabilizers influence phase behavior and biocompatibility. Maintaining an optimal drug-to-lipid ratio is essential for achieving high loading efficiency without compromising the structural integrity of cubosomes. Studies have demonstrated that appropriate ratios prevent saturation of the lipid matrix, ensuring formulation stability.

The method of preparation has a significant impact on the encapsulation efficiency of cubosomes. A study developed amphotericin B-loaded cubosomes using SolEmuls technology, which resulted in high encapsulation efficiency and improved oral bioavailability of the drug.[69] The concentration of stabilizers, such as Poloxamer 407, plays a key role in maintaining the stability and encapsulation efficiency of cubosomes. The optimal stabilizer levels enhance stability, but excessive amounts can lead to drug leakage and reduced loading efficiency.[70]

Table 6: Studies on Cubosomal Antifungal Formulations

Drug	Type of study	Particle size (nm)	Zeta potential (mV)	EE%	PDI	Key outcomes	References
Fluconazole	*In vivo* and *in vitro*	258.4±4.64	-	67.6±4.66	0.32	Enhanced skin penetration and improved efficacy against cutaneous candidiasis	58
Voriconazole	In vitro	160	-27.70±1.20	59.30%	0.40±0.06	Superior pharmacokinetics and deeper ocular tissue penetration, with higher drug levels in the vitreous humor than in the drug suspension	59
Itraconazole	*In vitro*	86.69±0.258	-	37%	0.258	Sustained and enhanced *in vitro* drug release through skin	60
Miconazole	*In vitro* and *ex vivo*	170	26.64	80.45%	-	Controlled drug release, superior antifungal activity, and safe use confirmed through histopathological studies	62
Clotrimazole	*In vitro* and *ex vivo*	180.70±2.40	22.90±0.14	97.00±0.01	0.30±0.04	5.87-fold higher skin retention than commercial cream, controlled drug release (42.87% over 8 h), and complete healing of *Candida albicans* infections in 7 days	63

Environmental factors, including pH, ionic strength, temperature, and osmolarity, can influence the structural stability of cubosomes, thereby affecting drug entrapment and release profiles. For instance, the composition of the dispersion medium can affect the size, shape, entrapment efficiency, and release of drugs from alginate-based beads.[71] The solubility, permeability, and stability of the drug can indirectly influence its loading efficiency and encapsulation stability within cubosomes, thereby impacting its pharmacokinetic performance. For example, amphotericin B-loaded cubosomes exhibited enhanced oral bioavailability compared to traditional formulations, attributed to improved drug encapsulation and release characteristics.[69]

10. Prospects

Table 7 lists several cubosome-based products that have been granted patents. This highlights the growing interest in using this technology in different areas of medicine. However, none of these products is currently developed for antimicrobial use. This indicates that, while cubosomes have great potential, their application in antimicrobial therapy remains underexplored. With their ability to carry both hydrophilic and hydrophobic drugs, protect active ingredients, and offer targeted delivery, cubosomes could play a critical role in future anti-infection treatment. Their unique features make them a promising option for addressing challenges such as antibiotic resistance and enhancing the effectiveness of antimicrobial therapies.

Several nanocarrier-based drug delivery systems have successfully reached the market for antimicrobial applications, demonstrating the clinical value of nanotechnology in treating infections.[72] For example, AmBisome®,[73] a liposomal formulation of amphotericin B, is widely used for systemic fungal infections due to its enhanced safety and targeted delivery. Similarly, Arikayce®,[74] a liposomal amikacin formulation, has been approved for the treatment of lung infections caused by *Mycobacterium avium* complex, offering improved localization and reduced toxicity. Acticoat®[75] wound dressings utilize silver NPs to provide broad-spectrum antimicrobial protection, particularly in burns and chronic wounds. In addition, products like VitaZinc®,[76] which incorporate zinc oxide NPs, are employed in topical formulations for their antimicrobial properties.

While these examples highlight the successful use of liposomes and metallic NPs in antimicrobial therapy, no cubosome-based products have yet been approved or marketed for such applications. This underscores a significant opportunity for further research and development.[11] Given their unique internal structure, high surface area, ability to encapsulate diverse drug types, and potential for targeted delivery, cubosomes hold great promise as next-generation nanocarriers in the fight against microbial infections. Microfluidics and controlled bottom-up are being developed to improve batch uniformity and scalability.[53] In addition, pH-responsive and ionizable lipids are showing clear antifungal targeting potential.[77]

11. Cubosomes in combating biofilms

Biofilms, complex communities of microorganisms embedded within a protective extracellular matrix, represent a major

Table 7. Patented cubosome-based products and their potential applications

Patent no.	Year of filing	Filing country	Description of the patent	Status
KR1020180032842	2018	South Korea	Cosmetic composition containing phytosphingosine- and ceramide-loaded cubosome improves the solubility of phytosphingosine and ceramide, rate of penetration, and persistence.	Granted
KR1020050011153	2003	South Korea	Cubosomes containing the active ingredient (*Trifolium repens* L. extract) possessing anti-aging activity result in enhanced elasticity and a moisturizing effect on the skin, leading to minimal moisture loss of keratin.	Granted
IN202321011171	2023	India	Topiramate-loaded cubosomes for nasal spray offer the potential to increase the drug's bioavailability, as well as its residence time, and reduce the frequency of drug dosage.	Pending
IN202141018014	2021	India	A transdermal cubosomal gel containing resveratrol and piperine shows potential anticancer activity in managing melanoma. The composition of the cubosomal gel includes monoolein (3–5% w/v), Pluronic F-127 (1–1.5% w/v), resveratrol and piperine (0.1% w/v each), and Carbopol 934 (1% w/v).	Pending
WO2005077336A1	2005	South Korea	The formulation and composition of sterically stabilized emulsions and cubosomes were described. The sterically stabilized cubosomes contain phytantriol (0.1–30% by weight), drug (0.1–10% by weight), oils (0.1–6% by weight), biocompatible hydrophilic polymer (0.01–5% by weight), and water or an aqueous solution.	Pending
KR102458630	2021	South Korea	A cosmetic composition featuring retinal-loaded cubosomes combined with covalently bonded organic frameworks for effective transdermal delivery.	Granted
KR102307587B1	2019	South Korea	pH-responsive monoolein cubosomes contains *Bambusae caulis* (BCT) as the active ingredient. Albumin and pectin were modified to control drug release based on pH or temperature.	Granted
KR102310044B1	2019	South Korea	Lutein-encapsulated cubosomes, which are designed for skin applications, enhance penetration, offer antioxidant and anti-aging benefits, and cause no skin irritation.	Granted
KR102105256B1	2018	South Korea	Cubosomes encapsulating *Phyllostachys caulis* extract to enhance skin moisturization and antioxidant effects. They are suitable for products such as face masks, creams, and eyeliners.	Granted
CN106619573A	2016	China	Cubosomes prepared using glyceryl monooleate and poloxamer for eye drops enhance corneal absorption, reduce intraocular pressure, and extend retention time.	Granted

Note: Currently, none of these products have demonstrated antimicrobial uses.

barrier to effective antimicrobial therapy. These structures drastically reduce drug penetration, promote resistance gene exchange, and shield pathogens from host immune responses, rendering infections persistent and difficult to eradicate.[78] Traditional antibiotics often fail to achieve sufficient concentrations within biofilms, necessitating the development of innovative strategies to enhance drug delivery and therapeutic outcomes.

Cubosome-based nanocarriers offer several distinct advantages for targeting and disrupting biofilms. The bicontinuous cubic architecture of cubosomes provides a high internal surface area and interconnected aqueous channels, enabling the co-encapsulation of both hydrophilic and hydrophobic agents. This allows for the simultaneous delivery of antibiotics with biofilm-disrupting adjuvants such as enzymes (*e.g.*, DNase and proteases) or quorum-sensing inhibitors, enhancing the ability to both dismantle the biofilm matrix and kill resident microorganisms.[79]

Furthermore, surface engineering of cubosomes, such as the incorporation of targeting ligands (*e.g.*, lectins and antibodies) or charge modifications, can promote preferential adhesion to negatively charged biofilm surfaces, increasing local drug concentrations at the infection site.[80] The ability to functionalize cubosome surfaces with molecules that recognize biofilm-specific markers offers exciting opportunities for selective targeting and reduced systemic toxicity.

Cubosomes also exhibit sustained drug release profiles, which are particularly beneficial for treating biofilm-associated infections where prolonged drug exposure is needed to penetrate the dense extracellular polymeric matrix and maintain therapeutic levels over time.[81] This sustained release can help prevent regrowth of persisted cells, a subpopulation within biofilms that exhibits transient antibiotic tolerance.

Emerging studies demonstrate that cubosome formulations can significantly enhance antimicrobial activity against established biofilms. For instance, peptide-loaded cubosomes have shown potent disruption of *Staphylococcus aureus* and *Pseudomonas aeruginosa* biofilms *in vitro*, outperforming free drug solutions by improving penetration and retention within the biofilm matrix.[82]

Despite these promising findings, several challenges remain. The optimization of cubosome formulations for various biofilm types (*e.g.*, fungal, bacterial, and mixed species) warrants further exploration, as biofilm architecture and composition can exhibit substantial variations. Moreover, *in vivo* models that accurately mimic human biofilm infections are needed to validate the translational potential of cubosome-based therapies.

12. Clinical translation challenges of cubosome-based antimicrobial therapies

Despite the promising potential of cubosomes in antimicrobial drug delivery, their successful clinical translation faces several challenges. Regulatory agencies such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have established rigorous standards for nanomedicine products, necessitating a comprehensive evaluation of cubosome formulations in terms of quality, safety, and efficacy before market approval.[83,84]

A major challenge is the complexity of cubosome characterization. Due to their internal bicontinuous cubic structures, traditional analytical methods such as dynamic light scattering (DLS) and zeta potential analysis are often insufficient to fully describe their morphology, stability, and drug release behavior. Advanced techniques such as cryogenic transmission electron microscopy (cryo-TEM), small-angle X-ray scattering (SAXS), and synchrotron-based methods are essential but require specialized facilities and expertise.[85,86]

Scale-up manufacturing represents another critical hurdle. While laboratory-scale preparation methods, such as high-pressure homogenization and probe sonication, are well-established, achieving consistency in particle size, drug loading, and batch-to-batch reproducibility at industrial scales remains challenging. Furthermore, sterilization processes, whether by filtration, autoclaving, or gamma irradiation, must be optimized carefully to preserve cubosome structure and functionality.[87]

Safety considerations also play a pivotal role. Although cubosomes are generally composed of biocompatible and GRAS (Generally Recognized as Safe) ingredients, their nanoscale size and high surface area could potentially trigger immunological reactions, unintended biodistribution, or cumulative toxicity after repeated dosing.[88,89] Therefore, extensive preclinical studies focusing on biodistribution, toxicokinetics, immunogenicity, and long-term stability are required to ensure regulatory acceptance.

13. Conclusion

Cubosome NPs are revolutionizing drug delivery, providing innovative solutions to longstanding therapeutic challenges.[90] Their unique reverse, bicontinuous cubic-phase structure enables high drug-loading capacity and sustained release, allowing for the efficient encapsulation and delivery of hydrophilic, lipophilic, and amphiphilic drugs. These features overcome critical limitations of traditional delivery systems, such as poor solubility and rapid degradation. In addition, their biocompatibility, low immunogenicity, and potential for functionalization enhance their clinical applicability.

While cubosomes show great promise in antimicrobial therapy[40,79] further research and development are crucial to unlocking their full potential. Key areas to focus on include optimizing formulations for various administration routes, particularly intravenous delivery, where issues such as blood compatibility, stability in biological fluids, and potential infusion-related adverse reactions must be addressed. Addressing these challenges could position cubosomes as a key player in the fight against antimicrobial resistance and multidrug-resistant pathogens, further making them as a versatile platform for advanced drug delivery systems in modern medicine.

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