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REVIEW ARTICLE

Cubosomes as Advanced Nanocarriers for Drug Delivery

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Abstract: Cubosomes are nanostructured liquid crystalline particles that have emerged as promising drug delivery systems in pharmaceutical research. These self-assembled lipid-based systems possess a distinctive cubic crystalline structure with interconnected water channels, enabling the accommodation of both hydrophilic and hydrophobic therapeutic agents. The structural organization, preparation methodologies, and physicochemical properties of cubosomes determine their effectiveness as drug carriers. Top-down and bottom-up approaches represent the primary preparation techniques, each offering unique advantages and limitations in cubosome formation. The remarkable features of cubosomes include high internal surface area, biodegradability, and biocompatibility, establishing them as excellent candidates for pharmaceutical applications. Their ability to enhance drug solubility, improve bioavailability, and provide controlled release characteristics has been demonstrated across oral, parenteral, and topical delivery routes. Applications in cancer therapy, antimicrobial treatments, and disease management have shown promising outcomes. However, challenges persist in large-scale production and maintaining long-term stability. Recent technological advances and emerging applications indicate significant potential for cubosome-based systems to enhance therapeutic strategies in modern medicine, particularly in targeted drug delivery and personalized treatment approaches.

Keywords: Liquid crystalline nanoparticles; Drug delivery systems; Lipid-based carriers; Controlled release; Bioavailability enhancement.

1. Introduction

Nanocarrier-based drug delivery systems have revolutionized pharmaceutical research by offering enhanced therapeutic efficacy and improved drug targeting capabilities. Among these systems, cubosomes have emerged as a distinctive class of lipid-based nanocarriers characterized by their unique bicontinuous cubic liquid crystalline structure [1]. These self-assembled structures form spontaneously when specific amphiphilic molecules are dispersed in an aqueous environment under appropriate conditions [2].

The fundamental architecture of cubosomes consists of a complex three-dimensional network of continuous lipid bilayers arranged in a cubic lattice pattern. This distinctive arrangement creates two non-intersecting water channels, resulting in a structure that resembles a honeycomb [3]. The typical size range of cubosomes spans from 100 to 500 nanometers, making them suitable for various pharmaceutical applications [4].

The primary building blocks of cubosomes are amphiphilic lipids, predominantly glycerol monooleate (GMO) and phytantriol (PHYT). These lipids possess the inherent ability to self-assemble in aqueous media, forming stable cubic phase structures [5]. Unlike conventional drug delivery systems, cubosomes exhibit superior versatility in accommodating various types of therapeutic agents, regardless of their solubility characteristics [6]. A significant advantage of cubosome-based delivery systems lies in their ability to enhance the bioavailability of poorly water-soluble drugs. The internal structure of cubosomes provides distinct domains for both hydrophilic and hydrophobic molecules, facilitating the incorporation of diverse drug molecules [7]. Additionally, the biodegradable nature of the lipid components ensures biocompatibility and reduces the risk of adverse effects [8].

Cubosomes demonstrate several advantageous properties that distinguish them from other nanocarrier systems. Their high internal surface area enables substantial drug loading capacity, while their bioadhesive nature promotes enhanced interaction with biological membranes [9]. The structural stability of cubosomes in excess water conditions, coupled with their ability to protect sensitive drug molecules from degradation, makes them particularly attractive for pharmaceutical applications [10]. Despite these advantages, certain limitations need consideration. The high viscosity of the cubic phase presents challenges in large-scale manufacturing, and

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the water content in their structure can affect the entrapment efficiency of hydrophilic drugs [11]. This review explores the fundamental aspects of cubosomes, including their composition, preparation methods, characterization techniques, and diverse therapeutic applications.

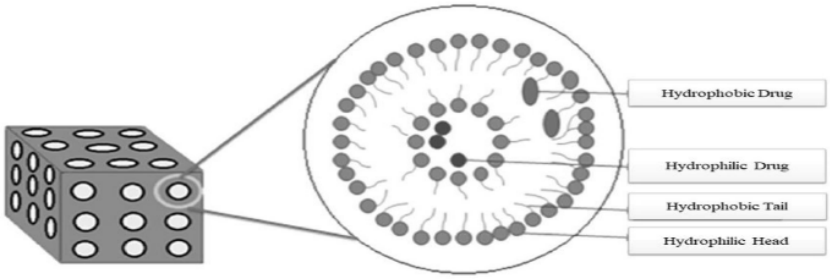

Figure 1. Cubosome structure

2. Structure and Composition of Cubosomes

The architectural framework of cubosomes exhibits a complex hierarchical organization that directly influences their functionality as drug delivery vehicles. The fundamental structure comprises continuous lipid bilayers arranged in a three-dimensional cubic lattice, creating two distinct water channel networks [12]. These channels, typically 5-10 nanometers in diameter, play a crucial role in determining the drug loading capacity and release characteristics of the system [13].

2.1. Lipid Components and Self-Assembly

The formation of cubosomes primarily depends on the self-assembly properties of amphiphilic lipids. The most commonly employed lipids include:

2.1.1. Glycerol Monooleate (GMO)

A biocompatible lipid that forms stable cubic phases at room temperature and demonstrates excellent drug solubilization properties [14].

2.1.2. Phytantriol (PHYT)

An alternative to GMO, offering enhanced stability and reduced susceptibility to enzymatic degradation [15].

The self-assembly process occurs spontaneously when these lipids encounter aqueous environments, driven by thermodynamic forces and hydrophobic interactions. The process results in the formation of two distinct regions:

1. A continuous lipid bilayer region
2. An interconnected aqueous channel network

2.2. Stabilization Mechanisms

The stability of cubosome dispersions is maintained through the incorporation of stabilizing agents, predominantly:

- Poloxamer 407: Acts as a steric stabilizer preventing particle aggregation
- Other polymeric stabilizers: Help maintain the cubic structure and control particle size distribution [16]

3. Methods of Preparation

The preparation of cubosomes can be achieved through several methodologies, each offering distinct advantages and challenges.

3.1. Top-Down Approach

This method involves the fragmentation of bulk cubic phase into smaller cubosome particles. The process typically includes:

1. Initial formation of bulk cubic phase
2. Addition of stabilizers
3. High-energy dispersion using i. High-pressure homogenization, ii. Ultrasonication and iii. Mechanical disruption

The top-down approach consistently produces stable cubosomes but requires significant energy input and specialized equipment [17].

3.2. Bottom-Up Approach

This alternative method relies on the spontaneous formation of cubosomes from precursor solutions. The process involves:

1. Dissolution of lipids in hydrotropic solutions
2. Controlled dilution leading to cubosome formation
3. Minimal energy input requirements

The bottom-up approach offers advantages in terms of energy efficiency and scalability, though particle size control may be more challenging [18].

3.3. Alternative Preparation Methods

Recent developments have introduced modified preparation techniques:

3.3.1. Spray Drying

Spray drying represents an advanced technological approach for producing dry cubosome precursor powders. This method involves the atomization of a liquid feed containing lipids and stabilizers into fine droplets, followed by rapid drying in a heated chamber. The process parameters, including inlet temperature, feed rate, and atomization pressure, significantly influence the characteristics of the final product. The typical temperature range for spray drying cubosome precursors lies between 120-160°C, with an atomization pressure of 2-4 bar. The resulting powder demonstrates excellent flow properties and can be readily reconstituted to form cubic phase dispersions upon hydration. This method offers several advantages, including enhanced storage stability, reduced transportation costs, and improved handling characteristics. The morphology of spray-dried particles typically exhibits a spherical shape with sizes ranging from 5-50 μm. The reconstitution process requires careful optimization of hydration conditions to ensure the formation of properly structured cubosomes

3.3.2. Solvent Evaporation

The solvent evaporation method provides precise control over particle size distribution and morphological characteristics of cubosomes. This technique involves dissolving lipids and stabilizers in an organic solvent system, followed by controlled evaporation under specific conditions. The choice of solvent system is crucial, with common options including chloroform, ethanol, or their mixtures. The evaporation process is typically conducted under reduced pressure (approximately 100-200 mbar) at temperatures between 40-60°C. The rate of solvent removal significantly influences the internal structure and particle size distribution of the resulting cubosomes. A slower evaporation rate generally yields more uniform particles with better-defined internal structures. The method allows for the incorporation of various bioactive compounds during the preparation process, with loading efficiencies ranging from 70-95% depending on the drug properties. The final particle size can be effectively controlled within the range of 100-300 nm through careful adjustment of process parameters

3.3.3. Heat Treatment

Heat treatment methodology encompasses a sophisticated approach to cubosome preparation that enhances stability characteristics and structural uniformity. This method involves carefully controlled thermal cycling of lipid-stabilizer mixtures to achieve optimal phase behavior and structural organization. The process typically begins with heating the mixture to temperatures between 70-90°C, followed by controlled cooling rates of 1-2°C per minute. Multiple heating-cooling cycles may be employed to improve structural organization and stability. The thermal history of the preparation significantly influences the final cubic phase structure and its stability. Critical parameters include the maximum temperature reached, duration of heat exposure, and cooling rate. This method particularly benefits from the thermotropic behavior of lipids, allowing for the formation of well-organized cubic phases. The resulting cubosomes show enhanced stability with storage periods extending beyond 12 months when maintained under appropriate conditions. The method also facilitates the incorporation of thermally stable bioactive compounds with minimal degradation risks. Particle size control is achieved through post-preparation homogenization, typically yielding distributions in the range of 150-400 nm

Table 1. Comparison of Different Preparation Methods for Cubosomes

Method	Advantages	Limitations	Particle Size Range (nm)	Scale-up Potential
Top-down approach	Consistent particle size distribution; Well-established process	High energy input; Expensive equipment needed	100-300	Moderate
Bottom-up approach	Low energy requirement; Simple process	Variable particle size; Less control over morphology	150-400	High
Spray drying	Produces stable dry powder; Long shelf life	Thermal stress on components; Complex process optimization	200-500	High
Solvent displacement	Good size control; Organic solvent-free possible	Limited drug loading; Process sensitivity	100-250	Low
Heat treatment	Simple process; Cost-effective	Temperature sensitivity; Limited to thermal-stable compounds	150-350	Moderate

4. Methods of characterization

The characterization of cubosomes involves multiple analytical techniques to evaluate their physical, chemical, and structural properties. Particle size analysis represents a fundamental characterization parameter, typically performed using dynamic light scattering techniques. The Zetasizer instrument, equipped with a helium-neon laser operating at 633 nm wavelength, provides accurate measurements under controlled temperature conditions of 25°C [19]. Morphological evaluation of cubosomes utilizes transmission electron microscopy (TEM), offering detailed insights into their structural organization. Sample preparation involves careful placement of cubosome dispersions on carbon-coated copper grids, followed by negative staining with sodium phosphotungstate solution. This technique enables visualization of the characteristic cubic structure and confirms the formation of discrete particles [20]. Surface charge characteristics, quantified through zeta potential measurements, provide crucial information about colloidal stability. The electrophoretic mobility of cubosomes, analyzed using the Smoluchowski equation, indicates the degree of electronic repulsion between particles and predicts long-term stability behavior [21].

Drug loading and entrapment efficiency constitute essential parameters for evaluating cubosome performance as drug carriers. Spectrophotometric analysis, combined with ultrafiltration techniques, enables accurate determination of drug incorporation levels. The pressure ultrafiltration cell method, utilizing specific molecular weight cut-off membranes, provides reliable data on drug entrapment [22]. Stability studies encompass various aspects of cubosome formulation performance over time. Physical stability evaluation includes monitoring morphological characteristics, particle size distribution, and zeta potential at predetermined time intervals. Chemical stability assessment focuses on drug content analysis and potential degradation products formation. Environmental factors such as temperature, light exposure, and humidity significantly influence cubosome stability, necessitating careful control during storage and handling [23]. The evaluation of drug release patterns from cubosome formulations typically employs membrane diffusion techniques. The release studies, conducted under controlled temperature conditions, provide insights into the mechanism and rate of drug liberation. Mathematical modeling of release data helps understand the underlying kinetics and aids in optimizing formulation parameters for desired therapeutic outcomes [24].

Table 2. Analytical Techniques for Cubosome Characterization

Analytical Technique	Parameters Measured	Resolution/Detection Limit	Sample Preparation Requirements	Analysis Time
Small-angle X-ray scattering	Internal structure; Lattice parameter	1-100 nm	Minimal	30-60 min
Cryo-TEM	Morphology; Structure	0.1-1 nm	Complex, cryo-fixation	1-2 hours
Dynamic light scattering	Particle size distribution	1-1000 nm	Simple dilution	10-15 min
Zeta potential analyzer	Surface charge	±0.1 mV	Dilution required	15-20 min
Differential scanning calorimetry	Phase transitions; Thermal behavior	0.1°C	Minimal	1-3 hours
Rheological analysis	Viscosity; Flow properties	0.01 Pa·s	None	30-45 min

5. Therapeutic Applications

Recent advances in cubosome technology have expanded their applications across various therapeutic areas. In cancer therapy, cubosomes demonstrate remarkable potential as carriers for anticancer agents, offering enhanced tumor targeting and reduced

systemic toxicity. The incorporation of chemotherapeutic agents within the cubosome matrix provides protection against degradation while maintaining therapeutic efficacy [25]

5.1. Cancer Therapy Applications

Cubosomes demonstrate exceptional potential in cancer treatment through enhanced drug delivery mechanisms. The nanostructured framework enables efficient encapsulation of anticancer agents while protecting them from degradation. Integration of targeting ligands on the cubosome surface facilitates specific binding to cancer cells, improving therapeutic efficacy. The sustained release characteristics of cubosomes maintain therapeutic drug concentrations at tumor sites, reducing systemic exposure and associated side effects [26].

5.2. Oral Drug Delivery Systems

The application of cubosomes in oral drug delivery addresses several challenges associated with conventional formulations. Their ability to enhance the solubility and permeability of poorly water-soluble drugs significantly improves oral bioavailability. The protective environment within the cubosome structure shields sensitive molecules from harsh gastrointestinal conditions. Additionally, the bioadhesive properties of cubosomes promote increased residence time in the gastrointestinal tract, enabling sustained drug release and improved therapeutic outcomes [27].

5.3. Transdermal Drug Delivery

Cubosomes excel in transdermal applications due to their unique interaction with skin barriers. The lipid-based structure facilitates enhanced skin penetration, while the sustained release properties maintain consistent drug levels. Advanced formulations incorporating penetration enhancers further optimize drug delivery across the stratum corneum. This delivery route proves particularly beneficial for drugs requiring sustained plasma levels or those subject to significant first-pass metabolism [28].

5.4. Ophthalmic Applications

The development of cubosome-based ophthalmic formulations addresses the challenges of conventional eye drops. Their mucoadhesive properties increase corneal residence time, improving drug bioavailability. The ability to incorporate both hydrophilic and hydrophobic drugs makes them versatile carriers for various ocular medications. Studies demonstrate enhanced penetration through ocular barriers and improved therapeutic efficacy in treating various eye conditions [29].

5.5. Antimicrobial Applications

Cubosomes show promising results in antimicrobial therapy, particularly against resistant strains. The incorporation of antimicrobial agents within cubosomes enhances their efficacy through improved delivery to infection sites. Their ability to interact with bacterial cell membranes potentially offers additional antimicrobial mechanisms. Recent studies indicate successful applications in treating both bacterial and viral infections [30].

Table 3. Selected Drug Molecules Successfully Incorporated in Cubosomes

Drug	Therapeutic Category	Log P	Loading Efficiency (%)	Route of Administration	Clinical Status
Docetaxel	Anticancer	2.4	85-92	Intravenous	Phase II
Insulin	Antidiabetic	-0.7	76-82	Oral	Preclinical
Rifampicin	Antimicrobial	3.7	88-94	Oral	Phase I
Diclofenac	Anti-inflammatory	4.5	78-85	Transdermal	Marketed
Fluconazole	Antifungal	0.4	70-75	Topical	Preclinical
Dexamethasone	Corticosteroid	1.8	82-89	Ophthalmic	Phase III
Acyclovir	Antiviral	-1.6	65-72	Topical	Preclinical

6. Challenges in cubosomes formulation

6.1. Manufacturing Considerations

Large-scale production of cubosomes presents significant challenges requiring innovative solutions. The development of standardized manufacturing processes ensuring batch-to-batch consistency remains crucial. Advanced technologies focusing on continuous production methods show promise in addressing scaling issues. Implementation of quality control measures throughout the manufacturing process ensures product reliability and safety [31].

6.2. Regulatory Aspects

The regulatory landscape for cubosome-based formulations continues to evolve. Establishment of standardized protocols for characterization and quality assessment is essential for regulatory compliance. Safety evaluations and toxicological studies provide necessary data for regulatory submissions. Understanding and addressing these regulatory requirements facilitates successful commercialization of cubosome-based products [32].

6.3. Emerging Applications

Novel applications of cubosomes in gene delivery and vaccination show promising preliminary results. Their potential in diagnostic imaging and theranostic applications opens new therapeutic possibilities. Integration with other advanced technologies, such as stimuli-responsive systems, enhances their therapeutic versatility. Ongoing research explores additional applications in regenerative medicine and tissue engineering [33].

7. Conclusion

Cubosomes represent a significant advancement in drug delivery technology, offering unique advantages over conventional systems. Their versatile nature accommodates diverse therapeutic agents while providing controlled release characteristics. The demonstrated success across various therapeutic applications highlights their potential in advancing medical treatments. Continued research and technological developments will further expand their applications and overcome existing limitations. The future of cubosome-based drug delivery systems appears promising, with potential impacts across multiple therapeutic areas.

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