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Cubosomes As A Next Generation Innovative Nanocarriers: From Structural Engineering To Therapeutic Frontiers

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Abstract

Cubosomes are innovative lipid based nanocarriers distinguished by their unique cubic crystalline structure, composed of bicontinuous lipid bilayers that form a three-dimensional network separating hydrophilic and hydrophobic domains. This architecture enables them to encapsulate a wide variety of bioactive compounds, including hydrophilic, hydrophobic, and amphiphilic molecules, making them highly versatile in controlled and targeted drug delivery. Their structural adaptability, biocompatibility, and thermodynamic stability give them a clear advantage over traditional carriers such as liposomes.

Cubosomes can be synthesized using two main approaches: the top-down method, which involves mechanical dispersion of bulk cubic phases, and the bottom-up method, based on molecular self-assembly aided by hydrotropes. Glyceryl monooleate (GMO) and phytantriol (PHTY) are commonly used lipid matrices, while Pluronic F127 serves as a stabilizer to prevent aggregation. The drug release mechanism typically follows Higuchi's diffusion-controlled model, influenced by lipid composition, particle size, and drug characteristics. Theoretical models such as those by Fontell & Drew, Gustafson, and Schwarz Jacob Anderson explain cubic phase formation through molecular geometry and packing parameters.

Due to their strong bio adhesion and high skin permeability, cubosomes are effective in topical and transdermal drug delivery, improving drug absorption and bypassing first-pass metabolism. Surface modification with polymers like chitosan further enhances their stability, targeting precision, and sustained release behaviour. Despite challenges such as high viscosity, limited hydrophilic drug loading, and scale-up difficulties, cubosomes hold significant promise as next-generation nanocarriers for cancer therapy, transdermal systems, and other biomedical applications.

Keywords: Cubosomes, Nanostructured lipid carriers, Drug delivery, Controlled release, Transdermal delivery, Biocompatibility, Phytantriol, Glyceryl monooleate

Introduction

The term "cubosomes" comes from their cubic crystalline structure. They are bicontinuous liquid crystalline nanoparticles with hydrophilic regions separated by a twisted hydrophobic bilayer, forming a periodic minimal surface with zero curvature, hence called viscous isotropic phases (1). Larsson's X ray and NMR studies showed that cubosomes have continuous hydrophilic and hydrophobic domains, explained through differential geometry (2). These self-assembled nanostructured particles exhibit solid like rheology (3). In cancer, uncontrolled cell growth, loss of differentiation, and metastasis are key features. Treatments such as surgery, chemotherapy, radiotherapy, and immunotherapy often cause severe side effects. Therefore, cubosomes are gaining attention as targeted, biocompatible drug carriers capable of improving therapeutic efficiency while reducing systemic toxicity.

One of the most active areas in cancer research focuses on developing targeted drug delivery systems that can selectively transport therapeutic molecules to diseased sites while sparing healthy tissues (4). In modern nanomedicine, the emphasis is on enhancing treatment specificity to improve efficacy and minimize side effects. Nanoparticles play a key role in this approach, as they can accumulate in tumour tissues either passively through the enhanced permeation and retention (EPR) effect (5) or actively by attaching targeting ligands to their surface (6).

Cubosomes are structurally distinct from hexosomes, which have a hexagonal arrangement resulting from an inverse hexagonal phase. Cubosomes offer additional advantages due to their ability to transform among various liquid crystalline structures such as Pn3m, Im3m, and Ia3d depending on environmental factors like temperature, pH, or ionic strength (7,8). This tunable nature allows them to adapt to different biological conditions, making them suitable for precise and controlled drug delivery.

Moreover, the cubic architecture of cubosomes enables efficient encapsulation and release of drug molecules with varying molecular weights and polarities. Their drug release mechanism typically follows Higuchi's diffusion-controlled kinetics, allowing for sustained and predictable release profiles (9,10).

$$Q = [DmCd\ (2A-Cd)\ t]\ ½$$

According to the Higuchi diffusion equation, the release of drug molecules from the matrix is proportional to the square root of time. Here, Q represents the amount of drug released per unit area, Dm is the diffusion coefficient of the drug within the cubic matrix, Cd is the solubility of the drug in the matrix, A is the initial drug concentration per unit volume, and t denotes time. Using this relationship, both the rate and extent of drug release can be predicted.

Cubosomes possess a minimal surface structure, forming a tightly packed, honeycomb-like arrangement with bicontinuous domains of water and lipid. They are typically prepared by mechanical fragmentation of the cubic lipid water phase in a three-phase region that includes a liposomal dispersion. To distinguish them from liposomes, these nanoparticles are termed cubosomes. Unlike liposomes, cubosomes feature a three-dimensional cubic architecture capable of simultaneously encapsulating hydrophilic, lipophilic, and amphiphilic molecules, making them highly versatile and efficient carriers for controlled and targeted drug delivery. (11)

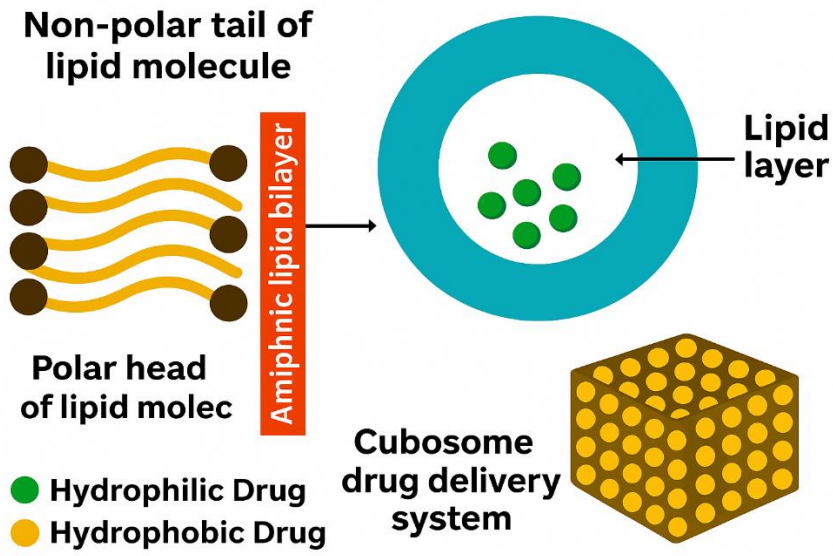

Figure 1. Structure of Cubosomes

Advantages

1. **Cost-effective:** Cubosomes are economical to produce.
2. **Simple preparation:** Their formulation process is relatively straightforward.
3. **Safe and biocompatible:** They are non-irritating, biodegradable, and biocompatible, making them suitable for biomedical use.
4. **High drug-loading capacity:** Due to their large internal surface area, they can carry significant amounts of drug and remain thermodynamically stable for long periods.
5. **Versatile encapsulation:** Cubosomes can simultaneously encapsulate hydrophilic, hydrophobic, and amphiphilic molecules.
6. **Controlled and targeted release:** The use of specific polymers allows for sustained and site-specific release of bioactive compounds.
7. **Reduced dosing frequency:** Prolonged release reduces the need for frequent administration, lowering overall medical costs.
8. **Fewer injection-related side effects:** They minimize adverse effects caused by sudden ("burst") drug release.
9. **Improved structure-to-surface ratio:** Compared to liposomes, cubosomes offer a higher particle volume-to-bilayer area ratio.
10. **Excellent solubilizing ability:** As lipid-based carriers, cubosomes can encapsulate poorly water-soluble drugs and protect sensitive molecules (e.g., proteins, peptides) from enzymatic degradation, improving peptide bioavailability by 20–100%.
11. **Enhanced skin permeability:** They exhibit strong bio adhesive properties and improved transdermal absorption (12).

Disadvantages

1. **Low entrapment of hydrophilic drugs:** Due to their high-water content, water-soluble drugs may not be efficiently encapsulated within cubosomes.
2. **High viscosity issues:** Their viscous nature poses challenges for large-scale manufacturing and processing.
3. **Dependence on polymers:** Without specific polymers, controlled or targeted drug release becomes difficult to achieve.
4. **Risk of leakage:** Cubosomes may experience drug leakage during storage or in vivo application.
5. **Particle instability:** Over time, particle aggregation or an increase in particle count may occur, affecting stability.
6. **Environmental sensitivity:** Changes in temperature, pH, or ionic strength can alter cubosome phase behaviour, potentially leading to phase transitions or instability (13).

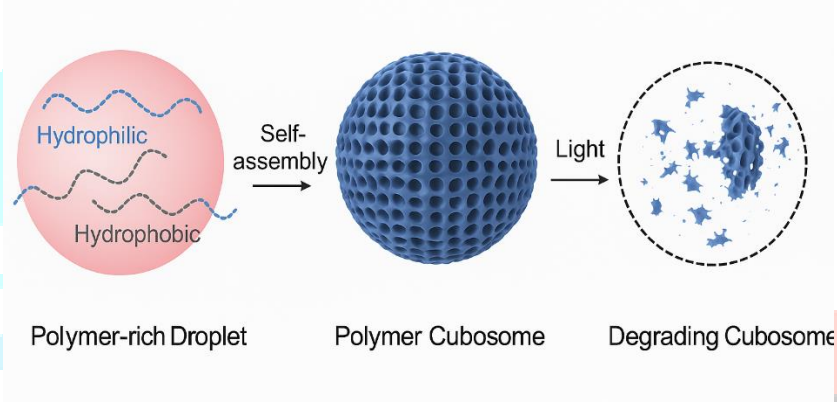

Figure 2. Light Effect

Theories on Cubic Phase Structure

Cubosomes, also known as bicontinuous cubic phase liquid crystals, possess several unique characteristics that make them highly promising as universal drug delivery systems. Structurally, they are composed of surfactant bilayers arranged into a three-dimensional, periodic minimal surface, creating a densely packed and highly ordered architecture. These structures form an optically transparent, viscous, bicontinuous liquid-crystalline phase with nanoscale organization.

Cubosomes are relatively simple to prepare, and their lipid-based composition enhances emulsification and penetration properties, allowing them to efficiently encapsulate hydrophilic, hydrophobic, and amphiphilic compounds. This enables controlled and targeted release of bioactive molecules, improving therapeutic efficacy and stability.

During cubosome formation, three distinct microscopic phases are typically observed:

1. **Precursor phase** – a solid or semi-solid material that forms the cubic phase when exposed to stimuli such as contact with a liquid.
2. **Bulk gel (cubic phase)** – a rigid, isotropic structure that can be processed into nanoparticulate form.
3. **Particle dispersion phase** – the final stage, where the bulk cubic phase is dispersed into smaller, stable nanoparticles known as cubosomes.

These structural and functional features make cubosomes a versatile and efficient nanocarrier platform for advanced drug delivery applications.

1. Fontell & Drew Theory

Cubic phases occur in ternary systems consisting of amphiphiles, oil, and water, often involving various monoglycerides. These monoglycerides are polar lipids with low water solubility and exhibit aqueous phase behaviour similar to non-ionic surfactants. According to Lutton's findings, monoglycerides with hydrocarbon chain lengths between C-12 and C-22, especially monoolein, form larger cubic phase regions. Monoolein (C-18 monoglyceride) is an unsaturated fatty acid commonly used for cubic phase formation.

2. Gustafson et al. Theory

Cubosomes are single crystal structures containing unilamellar vesicles dispersed within lamellar liquid crystalline phase particles. Increasing the polymer to monoolein ratio promotes the formation of larger vesicles. Due to slow transport processes and the high energy needed for fragmentation, ultrasonication of bulk cubic phases mainly produces vesicles that gradually transform into cubosomes through membrane fusion over time. This metastability is a key feature of bulk cubic phase systems, with cubosomes being colloidally stabilized by vesicles.

3. Schwarz, Jacob & Anderson Theory

In non-ionic surfactant systems, cubic phases often appear between lamellar and hexagonal liquid crystalline phases. The monoolein water system is notable for exhibiting a broad cubic phase region across varying compositions and temperatures. Based on surfactant packing principles, monoolein molecules with hydrophilic heads and hydrophobic tails form reversed (inverted) cubic phases, indicating polar medium phases. These structures can be described through differential geometry and periodic minimal surfaces, similar to soap films.

Three types of minimal surfaces are identified in cubic phases based on curvature: at high water content, the D surface forms; at lower water levels, the G-surface appears; and the P surface develops only when a third component, such as casein, amphiphilic molecules, or block copolymers, is added. The presence of cubic phases can be confirmed through X ray scattering, while their morphology and structural details are visualized using transmission electron microscopy (TEM) and freeze fracture electron microscopy (FFEM).

4. System Forming Theory

Cubosomes can form in both binary and ternary systems when there is a significant miscibility gap between the cubic phase and the solvent. The use of Poloxamer 407 helps prevent aggregation and flocculation, providing excellent colloidal stability. Cubosomes may also be enclosed within lamellar bilayer caps, which seal the openings in the cubic bilayer formed during fragmentation and prevent hydrocarbon chains from contacting water, thereby enhancing stability.

Cubosomes coated with a solid crystalline bilayer show superior colloidal stability, while those with lamellar liquid crystalline coatings tend to be more rigid. Additionally, sponge phase coatings have been proposed as effective stabilizing layers for cubosomes. Another promising molecule for cubosome formation is phytonadione (vitamin K1), which has shown high potential in improving their structural and functional properties (14).

Components of Cubosome

1. Glyceryl Mono-Oleate (GMO)

GMO is an amphiphilic lipid derived from glycerides of oleic acid and other fatty acids. It consists of a hydrophilic head and a hydrophobic tail, enabling the formation of cubic lipid phases. Besides pharmaceutical applications, GMO is also widely used in the food industry as an emulsifier. It is a transparent, colourless, polar, unsaturated monoglyceride with a melting point of 35–37 °C and is typically stored at –20 °C. GMO has a hydrophilic lipophilic balance (HLB) value of 3, indicating its strong lipophilic nature.

2. Phytantriol (PHTY)

Phytantriol, a compound containing phytanyl chains, serves as an excellent alternative to GMO due to their similar phase behaviour, though they differ in structural, physical, and chemical properties. It is an important component in the cosmetics industry, chemically known as 3,7,11,15-tetramethyl-1,2,3-hexadecanetriol. Under physiological conditions, it forms bicontinuous cubic structures in aqueous environments. Because it lacks an ester group, phytantriol exhibits greater chemical stability than monoglycerides, making it increasingly attractive for biomedical applications. Phytantriol-based liquid crystalline matrices have been shown to sustain the release of various drugs, particularly hydrophilic molecules, making it an excellent system for controlled and sustained drug delivery.

3. Stabilizers

Surfactants play a vital role in providing colloidal stability, which is essential for cubosome formation. During this process, cubosomes tend to aggregate into a bulk cubic phase. The stabilizer creates an electrostatic repulsive barrier between particles, preventing unwanted interactions between the hydrophobic regions of cubosomes while maintaining their structural integrity. Hence, the stabilizer is a key component in cubosome formulation.

Among stabilizers, Pluronic's, especially F127 (Poloxamer 407), are considered the gold standard. Pluronic's are self-assembling triblock copolymers consisting of polypropylene oxide (PPO) and polyethylene oxide (PEO) arranged in a PEO PPO PEO configuration. These polymers possess both hydrophilic and hydrophobic characteristics, making them highly effective and water-soluble stabilizing agents (12).

Mechanism of Drug Release from Cubosomes

One of the major advantages of cubosomes as drug delivery carriers is their ability to provide controlled and sustained drug release. The release mechanism is primarily influenced by the physicochemical properties of the lipids, the nature of the encapsulated drug, and the surrounding environmental conditions. The main mechanisms governing drug release from cubosomes include:

Diffusion-Controlled Release

The most common mechanism of drug release from cubosomes is diffusion. Owing to the interconnected aqueous channels within the bicontinuous cubic phase, drugs encapsulated in the aqueous domains gradually diffuse into the surrounding medium. Similarly, hydrophobic drugs embedded in the lipid bilayer diffuse outward over time. Since diffusion is a slow and sustained process, cubosomes are ideal for prolonged drug release.

The rate of diffusion is influenced by several factors:

Particle size: Smaller cubosomes have a higher surface area-to-volume ratio, resulting in faster diffusion.

Lipid composition: The type and ratio of lipids determine the bilayer fluidity, which affects the diffusion rate.

Drug properties: Hydrophilic drugs diffuse more easily through aqueous channels, whereas hydrophobic drugs take longer to release as they move through the lipid bilayer.(15)

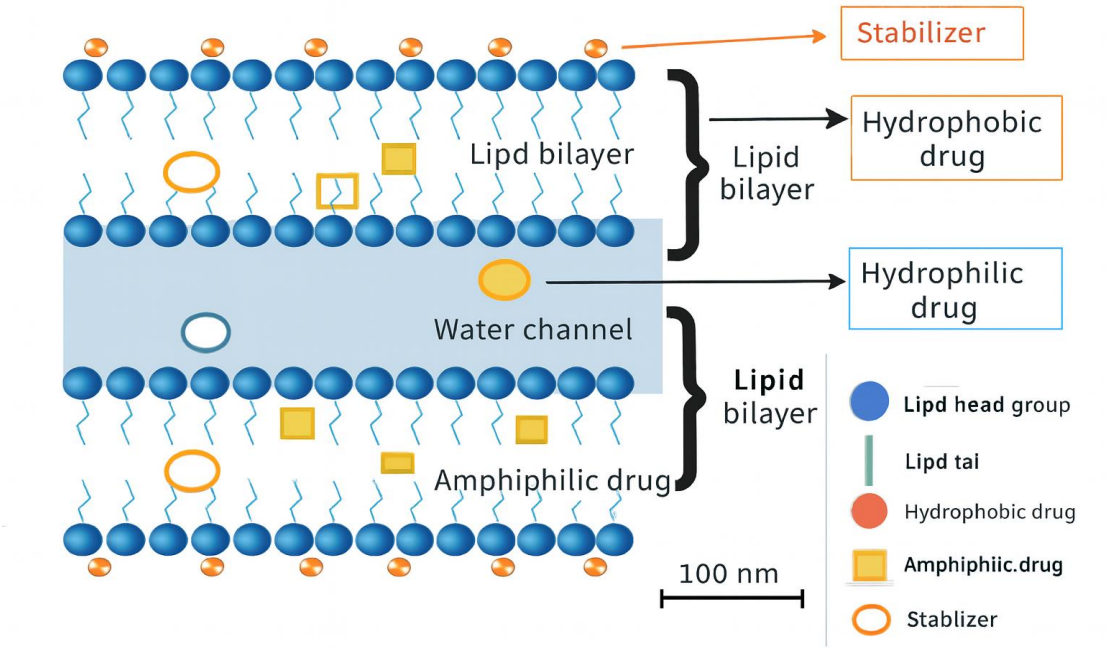

Figure 3. Mechanism of Drug Transport

Self-Assembling of amphiphilic lipids

In aqueous environments, amphiphilic lipids spontaneously self-assemble into various structures such as micelles, inverted micelles, open lipid bilayers, and closed lipid bilayers. This behaviour can be explained by two key concepts: opposing forces and packing parameters.

According to the first hypothesis, amphiphilic molecules organize in a polar solvent to minimize free energy. The hydrophilic heads orient toward the solvent, while the hydrophobic tails are shielded from it. This creates opposing forces between the two regions, a phenomenon known as the hydrophobic effect (16).

The packing parameter (P) determines the structure of the resulting mesophase and is defined by the ratio between the hydrophobic chain volume (v), its length (l), and the surface area of the polar head group (a_0). The values of P indicate different structural formations:

- **P < 1/2:** typical micelles
- **1/2 < P < 1**: closed lipid bilayers
- **P = 1:** open bilayers with zero curvature
- **P > 1:** inverted micelles

Thus, the packing parameter is a crucial determinant of the architecture and curvature of lipid assemblies (17).

Preparation methods of cubosomes:

Main preparation method

- Top-down method
- Bottom-up method

Others method which used for cubosome preparation

- Gel preparation
- Shearing
- High-pressure homogenization
- Automated cubosome preparation
- Probe ultra sonication

- Emulsification
- High-shear homogenization technique
- Spray-dried technique

Top-down method

The top-down method is the most widely used technique for producing cubosomes and involves two main stages. First, a viscous bulk cubic phase is formed by mixing a lipid with a stabilizer to prevent aggregation. In the second step, this bulk phase is dispersed into an aqueous medium using high energy processes such as high-pressure homogenization or sonication, resulting in the formation of cubosomes. Although the bulk cubic phase appears as a translucent, stiff gel similar to a cross-linked water swollen polymer, it is actually a thermodynamically stable liquid crystalline phase with a periodic internal structure. This method produces cubosomes with excellent stability, resistant to aggregation for up to one year. However, vesicles or lamellar nanoparticles often coexist with cubosomes generated through this approach. Notably, at high oscillation frequencies, cubic phases exhibit increased elasticity (14).

Bottom-up method

This alternative method enables cubosome formation from precursors, where crystallization occurs at the molecular scale and can be performed at room temperature. It is considered the most advanced approach for cubosome production. In this method, nanostructured building blocks are first created and then self-assemble into the final product. However, producing particle dispersions from viscous cubosomes requires significant process efficiency, making large scale production challenging in bulk cubic phases. To overcome these limitations, Thomas T. Spicer investigated cubic phase formation in the presence of a hydrotrope a compound that may be water soluble or water insoluble but lacks surfactant properties like it does not form micelles. Hydrotropes enhance lipid solubility without forming liquid crystalline phases, resulting in a process known as “salting out.”

In the liquid precursor method, monoolein is dissolved in ethanol, and upon dilution with an aqueous solution of poloxamer 407, cubosomes form. Alternatively, powdered precursors, consisting of polymer coated dried material, hydrate to form cubosomes upon contact with water. These powdered precursors offer advantages such as better stability and easier handling compared to liquid ones. During the process, the lipid hydrotrope mixture cools gradually, leading to cubosome condensation at room temperature (18).

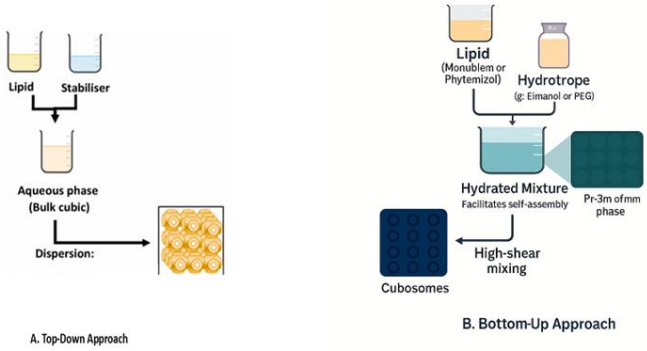

Figure 4. Methods of Preparation

Phase formation

Cubic phase formation occurs through the interaction of a bicontinuous lipid bilayer with an aqueous environment, producing a three-dimensional network that separates two continuous hydrophilic regions. The thermodynamic stability of this cubic structure mainly depends on two types of free energies: the stretching energy of the lipid chains and the curvature energy of the monolayer. Key structural parameters of the cubic phase include bilayer thickness, interfacial tension, and pore diameter is approximately 3-5 nm under hydrated conditions. Lipids are classified into two types: lamellar (Lα) lipids, which form planar bilayers, and non-lamellar lipids, which promote the formation of bicontinuous cubic (QII) and hexagonal (HII) phases. The cubic phase, positioned between the hexagonal and lamellar phases, exhibits lower frustration energy (19). All these structures are collectively referred to as lyotropic liquid crystals (LLCs).

The structure and stability of these lipids depend on temperature, pressure, hydration level, and lipid composition. Three primary types of lipid bicontinuous cubic phases are generally identified: the gyroid ($Ia3d/QII^{g}$, G-surface), double diamond ($Pn3m/QII^{D}$, D surface), and primitive ($Im3m/QII^{P}$, P-surface). Most cubosomes exhibit simple or double diamond structures. In the GMO–water system, the G-surface tends to transform into a D surface at higher water levels, while the P surface can only form with the addition of a third component that modifies the system's surface energy (20).

Cubosomes As Transdermal and Topical Drug Delivery System

Cubic phases exhibit strong bio adhesive properties, making them highly effective for drug delivery, particularly in topical and mucosal applications. The unique characteristics of liquid crystal (LC) and liquid crystal nanoparticle (LCNP) systems enable the development of bio adhesive LC matrices in situ, allowing for controlled and efficient drug delivery across mucosal surfaces such as buccal, ophthalmic, and vaginal tissues. These systems can also form a protective liquid-crystal coating on irritated or sensitive skin, which temporarily shields the surface while providing a tailored drug release profile (21).

Cubosomes show great potential as mucosal and transdermal delivery systems owing to their well-defined nanostructure, biocompatibility, and efficient tissue penetration. Their structural resemblance to epithelial cells enhances skin and mucosal permeability, thereby improving drug bioavailability (22). Transdermal delivery offers an attractive alternative to conventional routes because it leverages the large surface area of the skin and bypasses first-pass metabolism, which enhances drug bioavailability and reduces systemic side effects. However, the stratum corneum (SC) the outermost skin layer acts as a major barrier to drug permeation due to its complex composition and structure. Cubosome based systems effectively overcome this limitation by facilitating deeper penetration and sustained release of therapeutic agents.

Overall, lipid based crystalline nanoparticles, including cubosomes, have proven beneficial for the topical administration of a variety of bioactive compounds such as peptides, vitamins, and vaccines, offering a promising platform for targeted and efficient dermal therapy (23).

Drug permeation through stratum corneum

Percutaneous (dermal) absorption is the physicochemical process through which molecules traverse the stratified layers of the skin. It encompasses three distinct phases:
(1) **Penetration** – the entry of molecules into the outermost layer of the skin.
(2) **Permeation** – diffusion across successive layers of the epidermis.
(3) **Reabsorption** – systemic uptake of permeated molecules into the circulation.

Following release from the carrier matrix, the drug permeates the SC primarily via passive diffusion, which occurs through three established routes:

(1) the transcellular (intracellular) route,
(2) the intercellular (paracellular) route, and
(3) the appendageal (trans appendageal) route, involving eccrine glands and pilosebaceous units (24).

In the transcellular pathway, molecules diffuse through keratinized corneocytes; however, the low diffusion coefficient of this layer presents a significant barrier. The intercellular route is generally considered the predominant pathway, wherein diffusion occurs through the lipid matrix between corneocytes. The interlamellar spacing within the SC ranges from 19–75 nm, with an effective diffusion path length of approximately 900 µm. For optimal permeation, molecules typically exhibit a molecular weight <500 Da and a log P between 1 and 4, enabling partitioning between hydrophilic and lipophilic domains.

The appendageal route contributes minimally to overall absorption due to its limited surface area coverage; nonetheless, it can facilitate the permeation of macromolecules and nanoparticles under specific conditions (25).

Advancement in cubosome structure and modification in its effect

Recent advancements in nanotechnology have focused on surface modification of nanocarriers to enhance their targeting efficiency and therapeutic performance at the desired site of action (26). Various

modification strategies employ polymers, ligands, surfactants, and fatty acids to functionalize the nanocarrier surface, thereby improving biocompatibility, stability, and site-specific delivery.

Compared to conventional liposomes, cubosomes offer superior physical stability, simpler fabrication, and unique liquid-crystalline characteristics. However, despite their ability to achieve sustained in vivo drug release, cubosomes may undergo enzymatic degradation in the gastrointestinal tract (GIT) due to lipase activity, which disrupts their liquid-crystalline architecture and compromises their release profile.

To overcome this limitation, surface modification with chitosan has been shown to significantly enhance cubosome stability and performance. Chitosan-coated cubosomes exhibit resistance to lipase-mediated degradation, prolonged drug release, and improved cohesion. Notably, this modification resulted in a five-fold increase in bioavailability, a 2.2-fold extension in mean residence time, and a delayed Tmax, compared to unmodified cubosomes, highlighting its potential for controlled and sustained oral drug delivery (27).

CONCLUSION

Cubosomes are advanced nanostructured lipid carriers with a unique cubic crystalline architecture that allows the encapsulation of hydrophilic, hydrophobic, and amphiphilic drugs. Their high biocompatibility, stability, and controlled-release capability make them superior to conventional systems like liposomes. Lipids such as glyceryl monooleate and phytantriol, stabilized by Pluronic F127, form the basis of their structure, while surface modification (e.g., with chitosan) enhances stability and targeted delivery.

Cubosomes show great promise in transdermal, topical, and cancer drug delivery due to their strong bio adhesion and sustained release behavior. Although challenges such as high viscosity and limited hydrophilic drug loading remain, ongoing improvements in formulation and scale-up methods continue to enhance their potential as next-generation nanocarriers for efficient and precise drug delivery.

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