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CUBOSOMAL HYDROGELS: A PROMISING HYBRID NANOSTRUCTURED PLATFORM FOR CONTROLLED DRUG DELIVERY

Khadkutkar V. K.*[1], Vaishnavi Munde[1], Rutuja Dasre[1], Maheshwari Kapale[1], Dr. Dudhamal S. S.[2]

[1]Department of Pharmaceutics, Channabasweshwar Pharmacy College (Degree), Latur.
[2]Maharashtra Pharmacy Diploma Institute Nilanga, Dist. Latur.

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***Corresponding Author: Khadkutkar V. K.**
Department of Pharmaceutics, Channabasweshwar Pharmacy College (Degree), Latur.
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ABSTRACT

Cubosomal hydrogels have emerged as an advanced hybrid drug delivery system combining the unique nanostructured architecture of cubosomes with the bioadhesive and viscosity-enhancing properties of hydrogels. Cubosomes are bicontinuous cubic phase lipid nanoparticles capable of encapsulating hydrophilic, lipophilic, and amphiphilic drugs within their highly ordered internal structure. However, their low viscosity and limited retention at the site of application restrict their direct topical use. Incorporation into hydrogel matrices overcomes these limitations by improving formulation stability, residence time, spreadability, and patient compliance. This review provides a comprehensive overview of cubosomal hydrogels, including their structural characteristics, composition, preparation techniques, and physicochemical evaluation parameters. The synergistic interaction between lipid nanocarriers and polymeric gel networks is discussed in detail, highlighting its influence on drug release kinetics, permeation enhancement, and therapeutic performance. Various formulation approaches and characterization methods such as particle size analysis, entrapment efficiency, rheological assessment, in vitro drug release, and ex vivo permeation studies are critically summarized. Furthermore, the therapeutic applications of cubosomal hydrogels in dermatological disorders, wound healing, antifungal therapy, anti-inflammatory treatment, and transdermal drug delivery are analyzed. Despite significant advancements at the preclinical level, challenges related to physical stability, large-scale manufacturing, drug loading variability, and limited clinical validation remain. Overall, cubosomal hydrogels represent a promising next-generation platform for controlled and localized drug delivery. Continued research focusing on stability optimization, scalable production techniques, and clinical evaluation may facilitate their successful translation into commercial pharmaceutical products.

KEYWORDS: Cubosomes, Hydrogels, Nanostructured lipid carriers, Controlled drug delivery, Topical drug delivery.

1. INTRODUCTION

In recent years, advanced drug delivery systems have gained significant attention as effective approaches to overcome the limitations associated with conventional therapeutics, including poor solubility, low permeability, rapid drug clearance, and reduced therapeutic efficiency. Among various novel carriers, lipid-based nanocarriers have emerged as promising systems due to their biocompatibility, ability to encapsulate a wide range of drug molecules, and potential to provide controlled and sustained drug release. In this context, cubosomes—nanostructured particles derived from bicontinuous cubic liquid crystalline phases—have attracted considerable interest as versatile drug delivery vehicles.[1,2]

Cubosomes are formed through the self-assembly of amphiphilic lipids such as glyceryl monooleate or phytantriol in the presence of stabilizers like poloxamer 407. Structurally, they consist of a three-dimensional lipid bilayer network that separates two continuous aqueous channels, resulting in a highly ordered internal architecture with a large interfacial surface area. This unique structure enables the simultaneous incorporation of hydrophilic, lipophilic, and amphiphilic drugs, thereby

offering high drug loading capacity and controlled release characteristics.[1,2] These properties make cubosomes suitable for a variety of drug delivery routes, including topical, oral, and parenteral applications.

However, conventional cubosomal dispersions often suffer from certain practical limitations such as low viscosity, poor retention at the site of application, and potential instability during storage. These drawbacks can reduce their effectiveness, particularly in topical and localized drug delivery systems where prolonged contact with the target tissue is essential.[3] To overcome these limitations, the incorporation of cubosomes into hydrogel matrices has emerged as a promising strategy.

Hydrogels are three-dimensional crosslinked polymeric networks capable of absorbing large amounts of water while maintaining their structural integrity. They are widely used in pharmaceutical formulations due to their biocompatibility, ease of application, and ability to provide sustained drug release. When cubosomes are embedded within a hydrogel system, the resulting formulation—commonly referred to as a cubosomal hydrogel or cubogel—combines the advantages of both nanostructured lipid carriers and polymeric gels.[3,4] The hydrogel matrix improves the viscosity and mechanical strength of the formulation, enhances residence time at the site of application, and provides an additional barrier for controlled drug diffusion.

Recent studies have highlighted the therapeutic potential of cubosomal hydrogels in topical drug delivery. For example, drug-loaded cubogels have demonstrated improved skin permeation, prolonged release profiles, and enhanced therapeutic outcomes compared to conventional formulations. Applications such as wound healing, anti-inflammatory therapy, and dermatological treatments have shown particularly promising results, indicating the effectiveness of this hybrid system.[5–7] These findings suggest that cubosomal hydrogels can serve as efficient platforms for localized and controlled drug delivery.

Despite these advancements, a comprehensive understanding of formulation strategies, characterization techniques, and drug release mechanisms of cubosomal hydrogels is still evolving. Therefore, this review aims to provide a critical overview of cubosomal hydrogel systems, focusing on their structural characteristics, formulation approaches, evaluation methods, and potential pharmaceutical applications, along with current challenges and future prospects.

2. CUBOSOMES: STRUCTURE, COMPOSITION AND PREPARATION APPROACHES

Cubosomes are nanostructured lipid carriers derived from bicontinuous cubic liquid crystalline phases formed by the self-assembly of amphiphilic lipids in aqueous media. These systems possess a highly ordered internal nanostructure consisting of a three-dimensional lipid bilayer network that separates two continuous aqueous channels.[2,7] This unique architecture provides a large internal surface area, making cubosomes highly suitable for controlled and sustained drug delivery.

2.1 Structural Organization

Cubosomes exhibit a periodic minimal surface geometry, typically classified into primitive (Im3m), double diamond (Pn3m), and gyroid (Ia3d) cubic phases. These structures differ in lattice arrangement and channel size, which influence drug loading and release behavior.[2]

The presence of interconnected aqueous channels allows encapsulation of hydrophilic drugs, while the lipid bilayer accommodates lipophilic molecules. Amphiphilic drugs can localize at the lipid–water interface, enhancing formulation versatility.[2,8]

Additionally, the tortuous diffusion pathways within the cubic phase act as a barrier to drug movement, resulting in sustained release profiles compared to conventional vesicular systems such as liposomes.[8]

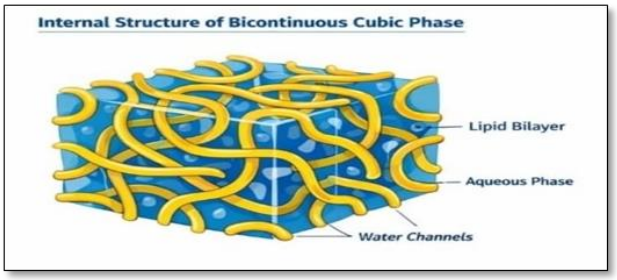

Figure 1: Schematic representation of bicontinuous cubic phase showing lipid bilayer and interconnected aqueous channels.

2.2 Lipid Components and Stabilizers

Cubosomes are primarily composed of amphiphilic lipids capable of forming inverse cubic phases. Glyceryl monooleate (monoolein) and phytantriol are the most commonly used lipids due to their biocompatibility and ability to spontaneously form stable cubic structures upon hydration.[2,7]

To maintain colloidal stability in dispersion form, stabilizers such as poloxamer 407 are incorporated. These surfactants adsorb onto the surface of cubosomes, preventing aggregation and improving stability during storage.[2,9] The concentration of stabilizer plays a critical role in determining particle size, zeta potential, and overall formulation stability.

Table 1: Composition of Cubosomes and Their Functional Roles.

Component	Examples	Typical Concentration Range	Functional Role	Key Notes
Lipid (Cubic Phase Former)	Glyceryl Monooleate (GMO), Phytantriol	2–10% w/w	Forms bicontinuous cubic phase structure	GMO most widely used; Phytantriol more oxidatively stable
Stabilizer / Surfactant	Poloxamer 407	0.2–2% w/w	Prevents aggregation, stabilizes nanoparticles	High concentration may alter cubic phase
Aqueous Phase	Purified Water	q.s.	Hydration medium	Required for self-assembly
Drug (Hydrophilic / Lipophilic)	Tretinoin, Diclofenac, Miconazole	As per dose	Encapsulated in lipid bilayer or water channels	Drug nature determines entrapment location
Antioxidants (Optional)	BHT, α-Tocopherol	0.01–0.1%	Prevent lipid oxidation	Required for long-term stability

2.3 Preparation Methods

Cubosomes are typically prepared using two approaches: top-down and bottom-up methods. In the **top-down approach**, bulk cubic phase gel is formed by hydrating lipids, followed by fragmentation into nanoparticles using high-pressure homogenization or sonication [2,9]. Although widely used, this method requires high energy input.

In the **bottom-up approach**, lipids are dissolved in a hydrotropic solvent, and cubosomes are formed spontaneously upon addition of water [9]. This method is advantageous due to lower energy requirements and potential scalability.

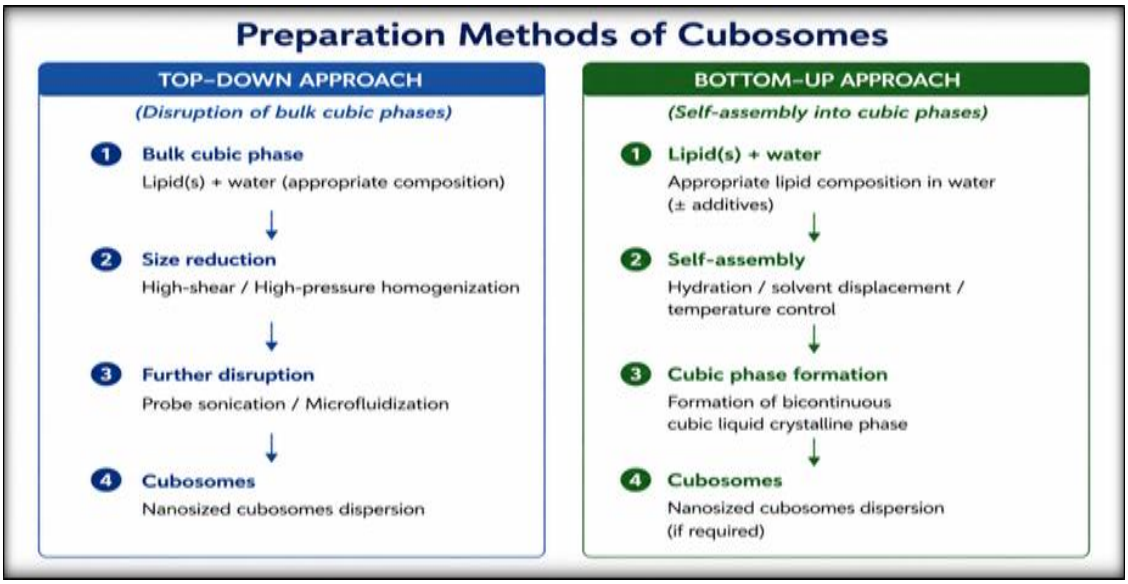

Figure 2: Preparation methods of cubosomes illustrating top-down and bottom-up approaches.

3. HYDROGELS IN DRUG DELIVERY SYSTEMS

Hydrogels are three-dimensional crosslinked polymeric networks capable of absorbing large amounts of water while maintaining structural integrity, making them suitable for drug delivery applications.[10] They are formed by physical or chemical crosslinking of hydrophilic polymers and can be derived from natural or synthetic sources.[10,11] Drug release from hydrogels occurs through diffusion, swelling, or degradation mechanisms, enabling controlled delivery [10,12]. Hydrogels offer advantages such as biocompatibility and prolonged residence time but may show limitations like poor loading of lipophilic drugs and burst release.[1,10] To overcome these issues, hydrogels are combined with nanocarriers like cubosomes to achieve enhanced stability and dual-controlled drug release.[1,3]

4. FORMULATION STRATEGIES AND CHARACTERIZATION OF CUBOSOMAL HYDROGELS

Cubosomal hydrogels (cubogels) are hybrid systems formed by incorporating cubosomal nanoparticles into a three-dimensional hydrogel matrix. This combination integrates the nanostructured drug delivery capability of cubosomes with the viscosity, stability, and bioadhesive properties of hydrogels, resulting in improved drug retention and controlled release.[1,13]

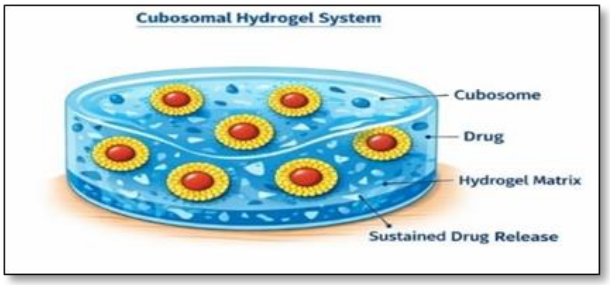

Figure 3: Schematic representation of cubosomes embedded within hydrogel matrix for sustained drug release.

4.1 Formulation Strategies

The preparation of cubosomal hydrogels generally involves two key steps:

(i) Preparation of cubosomal dispersion and
(ii) Incorporation into a suitable hydrogel base.

Initially, cubosomes are prepared using optimized conditions involving appropriate lipid type (e.g., monoolein or phytantriol), stabilizer concentration (e.g., poloxamer 407), and processing parameters such as homogenization or sonication.[2,9] These factors influence particle size, stability, and drug entrapment.

The prepared cubosomal dispersion is then incorporated into a preformed hydrogel under gentle stirring to ensure uniform distribution without disrupting the internal cubic structure. Commonly used gelling agents include Carbopol, HPMC, chitosan, hyaluronic acid, and poloxamer-based systems.[13]

Polymer concentration plays a critical role in determining viscosity, spreadability, and drug release behavior. Proper optimization is required to achieve a balance between mechanical strength and drug diffusion.

Table 2: Methods of Preparation of Cubosomes and Cubosomal Hydrogels.

Method	Principle	Advantages	Limitations
Top-Down Method	High-energy dispersion of bulk cubic phase	Produces uniform nanoparticles	Energy-intensive
High-Pressure Homogenization	Mechanical size reduction	Scalable	Expensive equipment
Ultrasonication	Acoustic cavitation	Simple lab-scale method	Risk of overheating
Bottom-Up Method	Controlled self-assembly from molecular dispersion	Lower energy requirement	Process-sensitive
Hydrogel Incorporation	Mixing cubosomal dispersion with polymer gel base	Improves viscosity & retention	Possible alteration of nanostructure

4.2 Physicochemical Characterization

Characterization of cubosomal hydrogels is essential to ensure stability, uniformity, and performance.

4.2.1 Particle Size and Zeta Potential

Particle size and polydispersity index (PDI) are measured using dynamic light scattering. These parameters indicate dispersion stability and uniformity. Zeta potential helps predict colloidal stability.[2]

4.2.2 Structural Analysis

Techniques such as small-angle X-ray scattering (SAXS) and transmission electron microscopy (TEM) are used to confirm the internal cubic structure. These methods ensure that the cubosomal architecture is retained after incorporation into the hydrogel.[3,13]

4.2.3 Rheological Properties

Rheological studies evaluate viscosity and flow behavior. Cubosomal hydrogels generally exhibit pseudoplastic (shear-thinning) behavior, which is desirable for topical application as it allows easy spreading with good retention at the site.[13]

4.2.4 Drug Content and Entrapment Efficiency

Drug content uniformity ensures even distribution of cubosomes within the gel. Entrapment efficiency reflects the drug-loading capacity of the system and is influenced by lipid composition and formulation conditions.[2]

4.2.5 In Vitro Drug Release Studies

Drug release is commonly studied using Franz diffusion cells. Cubosomal hydrogels typically show a controlled release pattern due to a dual mechanism: release from the cubic phase followed by diffusion through the hydrogel matrix [1,3].Release kinetics are often analyzed using models such as Higuchi and Korsmeyer–Peppas equations.[12]

Table3: Characterization Parameters of Cubosomal Hydrogels.

Parameter	Technique Used	Ideal Range / Observation	Significance
Particle Size	Dynamic Light Scattering (DLS)	100–300 nm	Influences permeation & stability
Polydispersity Index (PDI)	DLS	<0.3	Indicates uniformity
Zeta Potential	Electrophoretic mobility	±20–30 mV	Stability indicator

Entrapment Efficiency (%)	Centrifugation method	>60% desirable	Drug loading capacity
Rheological Behavior	Brookfield Viscometer	Pseudoplastic flow	Spreadability
pH	Digital pH meter	5.5–7 (topical use)	Skin compatibility
In vitro Drug Release	Franz Diffusion Cell	Sustained release	Release kinetics evaluation
Ex vivo Permeation	Animal skin model	Higher flux vs conventional gel	Transdermal potential

4.3 Advantages of Cubosomal Hydrogels

Cubosomal hydrogels offer several advantages over conventional systems:

- Improved formulation stability
- Enhanced drug retention at the application site
- Reduced burst release
- Controlled and sustained drug delivery
- Better permeation, especially for lipophilic drugs

These systems combine the benefits of both nanocarriers and hydrogels, making them highly effective for topical and transdermal applications.[1,13]

4.4 Disadvantages of Cubosomal Hydrogels

Despite their numerous advantages, cubosomal hydrogels also exhibit certain limitations:

- Complex formulation process
- High production cost
- Possible aggregation and physical instability
- Scale-up difficulties
- Limited drug loading for some drugs
- Sensitivity to temperature and pH changes
- Limited clinical studies available

These limitations highlight the need for further optimization and large-scale studies to improve the stability, scalability, and clinical applicability of cubosomal hydrogel systems.[1,2,13]

4.5 Stability Considerations

Stability studies include evaluation of physical appearance, pH, viscosity, particle size, and drug content over time. Environmental factors such as temperature and storage conditions may affect the internal cubic structure and overall performance.[2]

Incorporation into hydrogels improves stability by reducing particle aggregation and enhancing structural integrity during storage.[13]

5. Applications of cubosomal hydrogel

The integration of cubosomes into hydrogel matrices has significantly expanded their applicability in localized and controlled drug delivery. The hybrid structure enables prolonged drug residence time, enhanced permeation, and sustained therapeutic action. Recent studies have demonstrated promising results across dermatological, wound healing, anti-inflammatory, and transdermal applications.[1,13]

5.1 Topical and Dermatological Applications

Cubosomal hydrogels improve skin penetration and retention, making them highly effective for dermatological conditions. Formulations such as tretinoin and miconazole-loaded cubogels have demonstrated enhanced permeation and prolonged antifungal activity compared to conventional formulations.[4,15]

5.2 Wound Healing Applications

These systems provide sustained drug release, maintain a moist environment, and enhance antimicrobial activity. Studies using silver-based and benzimidazole-loaded cubogels have shown faster wound healing and improved tissue regeneration.[5,6,14]

5.3 Anti-inflammatory and Analgesic Applications

Cubosomal hydrogels enable prolonged localized drug action with reduced dosing frequency. Diclofenac-loaded cubogels have demonstrated controlled release and improved therapeutic efficacy in inflammatory conditions.[3]

5.4 Transdermal Drug Delivery

The lipidic nature of cubosomes enhances drug permeation across the skin, while the hydrogel matrix ensures prolonged contact, resulting in improved transdermal drug delivery and sustained systemic absorption.[2,8]

5.5 Ocular and Mucosal Applications

Cubosomal hydrogels offer improved bioadhesion and prolonged residence time on mucosal surfaces, making them promising for ocular and mucosal drug delivery, though further research is needed.[2,13]

5.6 Comparative Therapeutic Advantages

Cubosomal hydrogels provide enhanced permeation, reduced burst release, improved stability, and prolonged drug action, making them superior to conventional gel systems.[1,13]

6. CHALLENGES, LIMITATIONS, AND FUTURE PERSPECTIVES OF CUBOSOMAL HYDROGELS

Despite their promising advantages, cubosomal hydrogels face several challenges including physical instability of cubosomes, such as aggregation and phase transitions, difficulties in large-scale manufacturing, variability in drug loading efficiency, and potential interactions between lipid nanoparticles and polymer networks that may influence rheology and drug release behavior [2,8,12]. Furthermore, limited clinical studies and

regulatory concerns associated with nanostructured delivery systems restrict their commercial translation [18]. Nevertheless, cubosomal hydrogels possess significant future potential, particularly in the development of targeted and stimuli-responsive delivery systems, advanced wound care formulations, and personalized medicine approaches. The use of scalable manufacturing techniques such as microfluidization and spray-drying may improve industrial reproducibility and product stability.[17]

With continued optimization and regulatory validation, cubosomal hydrogels may emerge as next-generation systems for topical and transdermal drug delivery.

7. CONCLUSION

Cubosomal hydrogels represent a promising hybrid drug delivery platform that integrates the nanoscale structural advantages of cubosomes with the macroscopic stability and bioadhesive properties of hydrogels. The unique bicontinuous cubic phase structure of cubosomes enables the encapsulation of hydrophilic, lipophilic, and amphiphilic drugs, while the hydrogel matrix enhances formulation viscosity, spreadability, residence time, and patient compliance.

The combination system successfully addresses several limitations associated with conventional topical and transdermal formulations, including rapid drug release, poor skin permeation, and limited drug retention at the site of application. Incorporation into hydrogel matrices significantly reduces burst release, improves rheological characteristics, and enhances sustained drug delivery performance.

Extensive in vitro and preclinical investigations have demonstrated the therapeutic potential of cubosomal hydrogels in dermatological disorders, wound healing, anti-inflammatory therapy, antifungal treatment, and transdermal drug delivery. Particularly in chronic wound management and diabetic ulcer therapy, this system offers controlled drug release, improved tissue penetration, and enhanced therapeutic outcomes.

However, despite encouraging laboratory findings, several challenges remain. Physical stability concerns, scale-up limitations, variability in drug loading efficiency, and insufficient clinical evidence currently restrict widespread commercialization. Furthermore, regulatory pathways for nanostructured hybrid systems require comprehensive safety and toxicological evaluation.

Future research should focus on:

- Long-term stability optimization
- Scalable manufacturing technologies
- Detailed clinical investigations
- Development of stimuli-responsive and targeted cubosomal hydrogels
- Exploration of multifunctional systems incorporating bioactive agents

With continued scientific advancement and industrial optimization, cubosomal hydrogels have the potential to emerge as next-generation platforms for localized and controlled drug delivery.

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