International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 32, Issue 3, March 2026 ijppr.humanjournals.com ISSN: 2349-7203

Cubosomes: The Next-Generation Lipid Nanoplatform for Advanced Topical Drug Delivery

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Received: 25 January 2026 Revised: 10 February 2026 Accepted: 26 February 2026

ABSTRACT:

Topical delivery of medicines is frequently used to treat dermatological conditions because it allows the medicine to be applied directly to the site of action, lowers systemic exposure, and increases patient compliance. Despite these benefits, the therapeutic benefits of traditional topical dose forms such creams, ointments, and gels are frequently restricted. This is mostly caused by inadequate drug retention at the target location, poor drug penetration through the stratum corneum, and the requirement for repeated administration, especially for lipophilic and poorly soluble medications. Lipid-based nanocarriers have drawn a lot of interest lately as cutting-edge drug delivery methods that can get beyond the drawbacks of traditional formulations. Cubosomes, which are nanostructured particles made of bicontinuous cubic liquid crystalline phases, have shown promise as topical drug delivery vehicles. In addition to providing high surface area, physicochemical stability, and controlled drug release, their distinctive three-dimensional interior structure enables the effective encapsulation of hydrophilic, lipophilic, and amphiphilic medications. Cubosome-based topical formulations have been shown in several trials to improve treatment effects, increase skin penetration, and extend drug residence time in a variety of dermatological illnesses, such as inflammatory skin disorders and fungal infections. The promise of cubosomes as cutting-edge nanocarriers for topical drug administration is the main theme of this article, which also highlights current advancements, formulation issues, and their benefits over traditional topical therapy methods.

Keywords: Topical drug delivery; Cubosomes; Lipid nanocarriers; Skin penetration; Controlled drug release; Dermatological therapy

2. INTRODUCTION:

The skin is a promising drug delivery system due to its accessibility and ability to provide tailored treatment. Topical drug delivery systems are frequently used to treat inflammatory diseases, wound healing, psoriasis, acne, bacterial infections, and fungal infections. However, the stratum corneum functions as a robust barrier that limits medication penetration, which is the fundamental reason why traditional topical formulations continue to have limited efficacy. limited drug stability, limited bioavailability at the target location, and the requirement for frequent administration are additional difficulties that may have an adverse effect on patient adherence.

Drug distribution is made more difficult by the intricate structure of the skin, which goes beyond the stratum corneum's barrier role. Each of the many diffusion channels produced by the epidermis, dermis, and related appendages like hair follicles and sebaceous glands has unique permeability properties. Subtherapeutic concentrations in deeper layers or fast drug depletion from the application site are the results of the unregulated drug release seen in the majority of conventional creams, ointments, and gels. Furthermore, hydrophilic medications have difficulty partitioning into the lipid-rich stratum corneum, whereas lipophilic medications frequently show restricted solubility in aqueous vehicles. Recent developments in carriers based on nanotechnology, including cubosomes, solid lipid nanoparticles, liposomes, nanofibers, and nanoemulsions, have demonstrated encouraging promise in tackling these issues. These methods can decrease systemic exposure, increase skin retention, improve regulated and sustained release, and improve drug solubility. Thus, the creation of innovative topical administration systems is a targeted field of study meant to increase patient compliance, decrease dosage frequency, and improve therapeutic efficacy.[1, 2]

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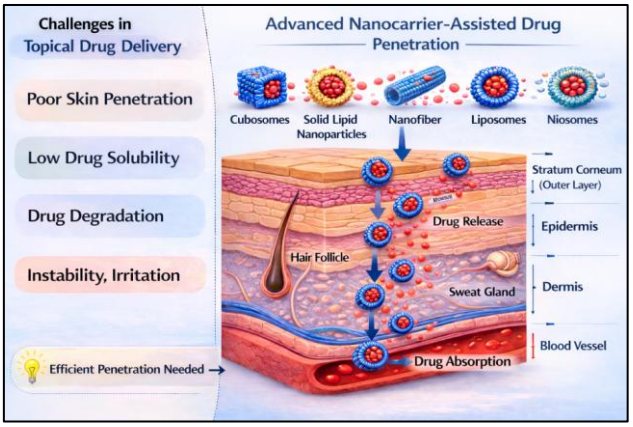

Fig. No.1.Schematic Representation of Nanocarrier-Assisted Drug Penetration Across Skin Layers

2.1. Conventional Topical Treatment Options and Their Limitations:

Conventional topical drug delivery methods principally include creams, gels, ointments, lotions, suspensions and ophthalmic solutions, which are widely used for the management of dermatological and ocular illnesses due to ease in use and good patient compliance. These systems typically function by releasing the medication onto the skin or ocular surface, from where the drug must permeate across biological barriers to reach the target site. However, low permeability across the stratum corneum or corneal epithelium, quick evacuation from the application site due to perspiration, washing, or tear drainage, and poor drug retention at the application site severely limit the therapeutic efficacy of standard topical formulations. As a result, only a small percentage of the administered dose, often less than 5%, penetrates the deeper tissues, resulting in low bioavailability and the requirement for frequent dosing.

Additionally, frequent use of traditional topical formulations frequently results in systemic side effects, hypersensitivity reactions, and local irritation, especially when corticosteroids, antifungals, and antibiotics are used. These drawbacks emphasize the necessity of sophisticated drug delivery systems that can increase drug residence time, improve penetration, and provide controlled release at the intended location.[3,4]

2.2. Cubosomes:

Drug delivery techniques based on nanotechnology have been thoroughly investigated to overcome these issues; lipid-based nanocarriers have shown particular promise. These systems can facilitate regulated medication release, increase drug solubility, and improve interaction with skin lipids. Cubosomes have drawn more attention than other lipid nanocarriers because of their remarkable thermodynamic stability and bicontinuous cubic form. In order to preserve their nanoscale structure and avoid aggregation, cubosomes are usually made with amphiphilic lipids like glyceryl monooleate or phytantriol stabilized with polymers like Poloxamer 407.

The structure of cubosomes features two continuous, non-intersecting aqueous channels divided by a lipid bilayer, which creates a remarkably large internal surface area. This unique structure enables cubosomes to hold a variety of drug molecules with differing physicochemical characteristics. Additionally, cubosomes can shield encapsulated drugs from degradation and ensure sustained drug release, making them ideal for topical applications that demand extended therapeutic effects.

Compared to traditional dosage forms, cubosomes provide a number of benefits for topical drug administration. Because their lipid composition is so similar to that of the skin's natural lipid matrix, they interact with the stratum corneum more effectively and improve drug penetration into the deeper layers of the skin. Cubosomes may also create drug depots in the epidermis, which could result in decreased frequency of dosage and extended drug retention.

Antifungal and anti-inflammatory drugs administered via cubosome-based topical systems have demonstrated enhanced therapeutic efficacy in recent investigations, indicating its promise as a cutting-edge substitute for traditional topical formulations.

Despite extensive research on cubosomes for ophthalmic, parenteral, and oral drug administration, their use in topical medicine is still developing. More research is necessary to address problems with clinical translation, long-term stability, and large-scale production. Thus, the purpose of this study is to present a thorough analysis of cubosomes as cutting-edge nanocarriers for topical

drug administration, highlighting their benefits, present state of research, and potential for enhancing traditional topical treatment approaches in the future.[5,6]

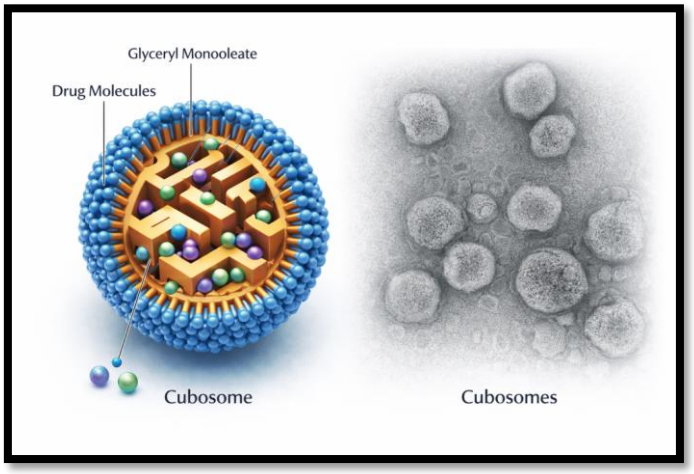

Fig. No.2.Internal Cubic Structure and Microscopic Appearance of Cubosomes

2.3 Types of cubosomes:[5,31]

Cubosomes are commonly classified based on their precursor form.

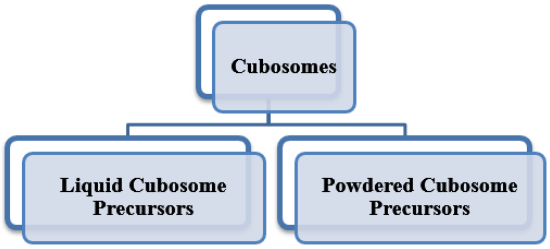

Fig. No.3. Structural Variants of Cubosomes

a. Liquid Cubosome Precursors:

In order to create a homogenous lipid solution, monoolein or other lipid-forming chemicals are dissolved in hydrotropic solvents like ethanol to create liquid cubosome precursors. Cubosomes are created by a series of nucleation, crystallization, and precipitation processes that result in the spontaneous creation of cubic liquid crystalline nanostructures when the substance is gradually diluted with water. High shear homogenization and probe sonication are used in the majority of pharmaceutical applications to further process the resultant liquid systems. This reduces particle size, enhances dispersibility, and produces stable nanosized cubosomal dispersions with a restricted size distribution. These high-energy methods are essential for transforming the viscous cubic phase into homogeneous nanocarriers that can be used to deliver drugs.

b. Powdered Cubosome Precursors:

Dehydrated surfactant systems, usually coated with polymeric stabilizers to inhibit aggregation, make up powdered cubosome precursors.

Typically, spray drying methods are used to create these powdered systems, turning the liquid cubosomal dispersion into a dry solid. Powdered precursors for cubosomes rehydrate to form cubosomes with particle diameters typically approximately 600 nm. Powdered cubosomes are especially well-suited for large-scale production and long-term storage applications in pharmaceutical formulations because they provide a number of useful benefits, including increased physical stability, ease of handling, decreased risk of microbial contamination, and improved shelf life.

2.4. Evolution of Lipid Nanocarriers: From Liposomes to Cubosomes:[10-13]

The first generation of lipid-based nanocarriers, liposomes, were developed to address theshortcomings of traditional formulations. They have been thoroughly investigated for topical and transdermal distribution and are composed of spherical phospholipid bilayers that can encapsulate both hydrophilic and lipophilic medicines. Liposomes increased medication solubility and decreased systemic toxicity, but their short shelf life, low physical stability, drug leakage, and phospholipid oxidation hampered their clinical application. Moreover, liposomes quickly destabilize structurally in biological settings and have a comparatively low drug loading capacity.

Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) were created as second-generation solutions to address these concerns, but they still had drawbacks such poor encapsulation efficiency and drug expulsion during storage.

Cubosomes, the third generation of lipid-based nanocarriers, are thought to be a significant improvement over SLNs and liposomes. The distinctive bicontinuous cubic liquid crystalline structure of cubosomes is defined by a network of three-dimensional lipid bilayers encapsulating interconnecting water channels. High drug loading and prolonged release behavior are made possible by the very high interior surface area provided by this architecture. Because of their stiff interior structure, cubosomes exhibit less drug leakage than liposomes and maintain thermodynamic stability even in the presence of abundant water.Cubosomes structural resemblance to biological membranes and bioadhesive qualities allow them to penetrate skin and ocular barriers more easily when applied topically. Therefore, cubosomes are better carriers for contemporary topical drug delivery systems because they provide longer drug residence duration, enhanced therapeutic efficacy, and decreased dose frequency.

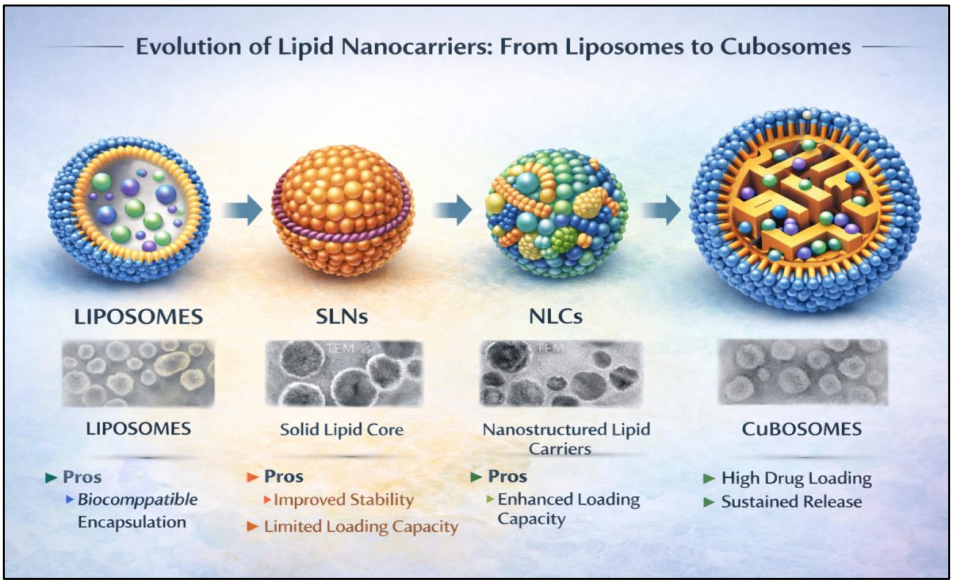

Fig. No.4.Structural Progression of Lipid-Based Nanocarriers

2.5. Structural Organisation of Cubosomes:[21,22]

Cubosomes are nanostructured lipid carriers that differ from traditional vesicular systems due to their highly organized bicontinuous cubic liquid crystalline internal structure. Cubosomes are structurally composed of a single continuous lipid bilayer that occasionally folds in three dimensions to produce two distinct but interconnected networks of water channels. These water channels are continuous throughout the particle but do not join because they are separated by a highly curved lipid membrane placed on a periodic minimum surface. Three primary cubic symmetries the gyroid (Ia3d), diamond (Pn3m), and primitive (Im3m) lattices are frequently used to characterize the internal geometry of cubosomes. These symmetries maximize surface area while minimizing interfacial energy.

Because of their special structure, cubosomes have a remarkably large internal surface area, which makes it possible to effectively encapsulate hydrophilic medications in aqueous channels and lipophilic medications in lipid bilayers. Amphiphilic compounds can also locate at the lipid–water interface. Moreover, cubosomes isotropic and crystalline structure contributes solid-like mechanical strength, optical clarity, and prolonged drug release behavior, which makes them very appealing for cutting-edge drug delivery schemes.

2.6. Composition:

Cubosomes consist of three primary components: amphiphilic lipids, an aqueous phase, and stabilizing chemicals, all of which play a role in the creation and stability of the cubic nanostructure.

a. Amphiphilic Lipids: Amphiphilic lipids form the structural backbone of cubosomes.

1. GMO: Glyceryl monooleate (GMO), a monoacylglycerol made of glycerol esterified with oleic acid, is the most commonly utilized lipid. At normal temperature and physiological temperature, GMOs spontaneously form cubic phases and have exceptional biocompatibility. The hydrophobic tail creates the membrane curvature required for the development of a cubic lattice, while the hydroxyl groups in the polar head region encourage hydrogen bonding with water.[14]

2. Phytantriol (PHYT): Which, because of its greater structural stability and resistance to enzymatic degradation, is frequently used. PHYT is very helpful for formulations involving sustained drug release and generates highly organized cubic phases throughout a broad temperature range. Phytantriol-based cubosomes have a longer shelf life and greater physical stability than GMOs.

The cubic lattice is formed by the amphiphilic lipids, which also regulate the system's general biocompatibility, drug solubility, and membrane permeability.[1

b. Aqueous Phase:

The cubic lattice's interconnecting water channels are occupied by the aqueous phase. Hydrophilic medicines, peptides, proteins, and nucleic acids are all stored in these channels. Drug transport behavior, pore diameter, and lattice swelling are all significantly influenced by the degree of hydration.

Drug mobility is improved by higher water content, although entrapment efficiency for water-soluble medicines may be decreased.

The aqueous phase controls diffusion-controlled drug release kinetics, facilitates the solubilization of hydrophilic medications, and promotes cubic lattice swelling.[16]

c. Stabilizers:

In order to keep cubosomes dispersion stable and stop particle aggregation, stabilizers are necessary. Non-ionic triblock copolymers poloxamer 407 (Pluronic F127) and poloxamer 188 are the most widely used stabilizers. By providing steric stability through adsorption on the cubosome surface, these stabilizers lessen interparticle attraction and regulate the distribution of particle sizes. Additionally, they increase formulation toughness and shelf-life during storage.

Stabilizers improve physical stability, keep particles at the nanoscale, stop aggregation, and guarantee the cubosomal formulations' long-term storage performance.[17]

2.7. Effect of Lipid and Stabilizer on Cubosomes:[18,19,20]

The form and quantity of lipid and stabilizer utilized in the formulation have a significant impact on the cubosomes' physicochemical characteristics and functionality.

I. **Monoolein (glyceryl monooleate):** In cubosomal systems, it is the most frequently used lipid because of its potent capacity to self-assemble into bicontinuous cubic liquid crystalline phases when water is present. According to research on lipid-based cubosomes, the formation and stability of the cubic phase are strongly influenced by the monoolein content. The formation of incomplete or loosely structured cubic structures at lower lipid concentrations can lead to decreased stability and drug encapsulation efficiency. Increased monoolein content results in the development of a well-organized internal cubic lattice, which increases drug loading capacity and provides a high interfacial surface area.Moreover, drug release behavior is also controlled by monoolein concentration; a denser lipid bilayer network created by a higher lipid content slows down drug diffusion and encourages persistent release. Overly high monoolein concentrations, however, can raise system viscosity, which can complicate processing and occasionally result in particle aggregation or poor dispersion stability.

II. **Stabilizers:** Maintaining the cubosomes colloidal stability and physical integrity is equally crucial. With its ability to adsorb on the surface of cubosome particles and create a steric barrier that inhibits aggregation and coalescence, poloximer 407 is the most

commonly employed stabilizer. According to published research, a stable concentration guarantees consistent nanoscale particle size, enhanced dispersibility, and sustained stability. Instead, too much stabilizer can disrupt the internal cubic structure, decrease lipid packing, and impair drug entrapment efficiency. Insufficient stabilizer, on the other hand, results in unstable systems with a high propensity for aggregation. Additionally, stabilizer concentration affects drug release properties; balanced levels promote regulated or sustained release behavior and preserve the cubic design. Therefore, to create stable cubosomes with the desired drug loading, release, and storage characteristics, rigorous lipid and stabilizer optimization is required.

2.8. Physicochemical Properties of Cubosomes:

Cubosomes have a special set of physicochemical characteristics that make them exceedingly appealing as cutting-edge drug delivery vehicles. Their internal nanostructure, which is generated from bicontinuous cubic liquid crystalline phases, offers unique benefits with regard to biological compatibility, stability, release behavior, and drug loading.

Fig No.5.Critical Physicochemical Attributes of Cubosomes

a. High Internal Surface Area:

One of the most remarkable features of cubosomes is their incredibly large internal surface area, which typically varies between 300 and 800 m2/g. A continuous lipid bilayer regularly folds to create a huge interfacial network between the lipid and aqueous domains in their highly organized three-dimensional cubic lattice, which is the source of this feature. By providing a vast number of locations for drug entrapment, the interior surface's size greatly increases drug loading capacity. Furthermore, effective mass transfer is made possible by this wide contact, which permits controlled drug molecule diffusion from the carrier into the surrounding biological environment. Cubosomes are therefore very good at maintaining medication release over extended periods of time.

b. Bicontinuous Aqueous Channel Network:

A continuous lipid bilayer separates the two interpenetrating but non-mixing aqueous channel networks that make up the remarkably unique internal architecture of cubosomes. Because of its bicontinuous shape, cubosomes can hold both lipophilic and hydrophilic drugs in one nanocarrier at the same time. Drugs that are hydrophilic are found in aqueous channels, whereas those that are hydrophobic are integrated into the lipid bilayer. Compared to traditional administration methods, this dual-loading capability provides a substantial benefit and increases formulation flexibility, particularly for combo medicines.

c. Thermodynamic Stability in Aqueous Environment:

Cubosomes exceptional thermodynamic stability in excess water is another crucial feature. Even in extremely watery conditions, cubosomes maintain their internal cubic structure, in contrast to other liquid crystalline systems that have a tendency to break down upon dilution. This stability results from the natural equilibrium between hydration forces and hydrophobic lipid interactions in the aqueous channels. Cubosomes are therefore extremely dependable carriers for in vivo drug administration since they maintain their structural integrity in physiological fluids like blood, gastrointestinal secretions, and mucosal surfaces.

d. Uniform and Narrow Pore Size:

Cubosomes have extremely homogeneous nanochannels, typically with a diameter of 5-10 nm. The cubic phase's crystalline symmetry directly contributes to the uniformly small and narrow pore size. By controlling molecular transport and serving as diffusion barriers, these nanochannels enable exact control over the kinetics of drug release. Mechanistically speaking, Fickian diffusion via convoluted internal channels primarily controls drug release from cubosomes, producing consistent and long-lasting release behavior.

e. High Drug Loading Capacity:

The three-dimensional lipid bilayer network of cubosomes provides a large internal volume that allows for substantial drug loading without sacrificing structural integrity. Peptides, proteins, and other macromolecules as well as tiny compounds can be effectively integrated into cubosomal systems. Cubosomes, in contrast to solid lipid nanoparticles, maintain a semi-fluid liquid crystalline form that enables flexible drug molecule accommodation. This characteristic is especially helpful for combination treatments and high-dose formulations.

f. Solubilization of Poorly Water-Soluble Drugs:

Drugs that are poorly soluble in water, particularly those in BCS Classes II and IV, can be made more soluble with the help of cubosomes. Hydrophobic medicinal molecules can dissolve in the lipophilic environment produced by the curved lipid bilayers inside cubosomes. Better protection against precipitation, increased dissolve rate, and greater apparent solubility result from this. Consequently, the bioavailability of numerous medicinal drugs that are poorly soluble is greatly enhanced by cubosome-based formulations.

g. Controlled and Sustained Drug Release:

Significant diffusion resistance is produced by the intricate internal geometry of cubosomes, allowing for regulated and prolonged drug release. The Higuchi-type or zero-order models may be used to describe release kinetics, depending on formulation factors and drug localization. Drugs that are hydrophilic move slowly across aqueous channels, whereas those that are lipophilic move across lipid bilayers. The therapy of chronic diseases greatly benefits from this controlled release characteristic since it reduces burst effects and sustains therapeutic drug levels for longer periods of time.

h. Bioadhesive and Biocompatible Nature:

Cubosomes made with biocompatible lipids like phytantriol and monoolein have good biological compatibility and great bioadhesive qualities. Their lipid makeup is quite similar to that of real biological membranes, which allows for improved cellular absorption and close contact with epithelial tissues. Additionally, cubosomes are often well tolerated, biodegradable, and non-toxic, which makes them appropriate for delicate delivery methods such topical, pulmonary, nasal, and ocular administration. Their bioadhesive properties also lengthen the residence time at the application site, which enhances medication absorption and therapeutic effectiveness.

- **Advantages**[7,8]

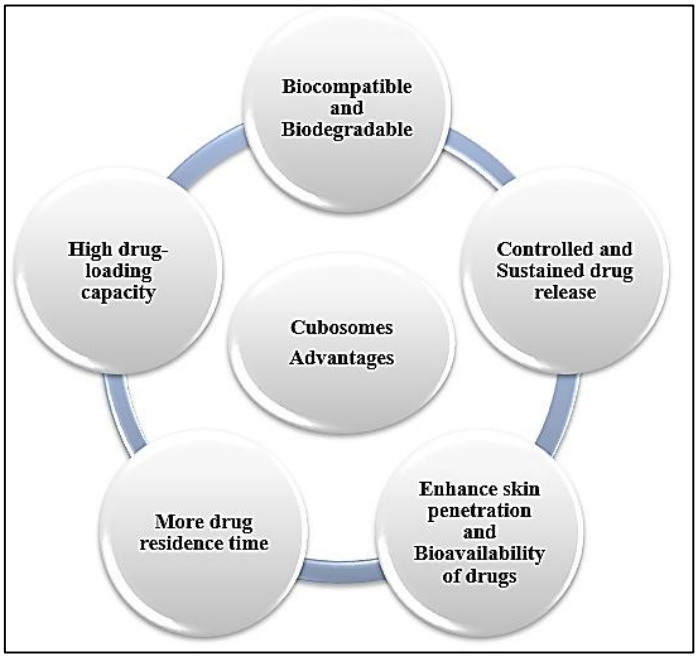

Fig. No.6.Key Advantages of Cubosomal Drug Delivery System

- **Disadvantages**[8,9]

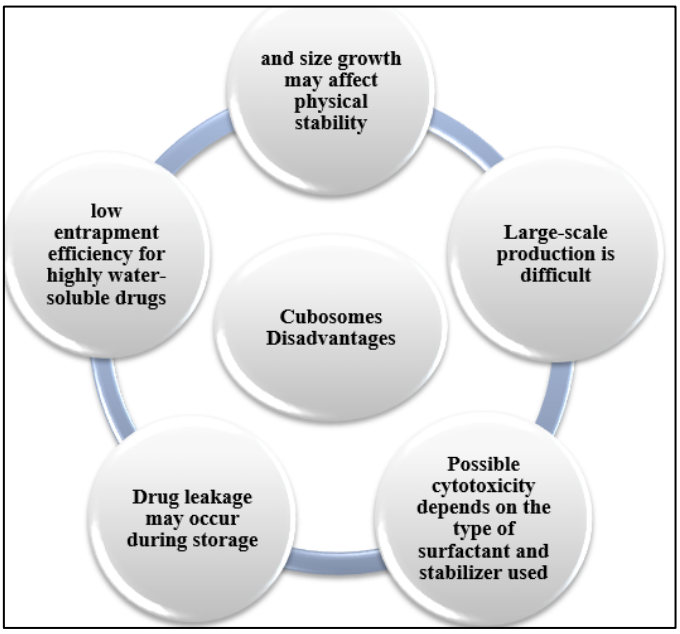

Fig. No.7.Limitations of Cubosomal Drug Delivery Systems

4. Drug Release Mechanism from Cubosomes:[32,33]

Cubosomes distinct bicontinuous cubic liquid crystalline structure, which is made up of two continuous and interpenetrating aqueous channel networks formed by a highly organized lipid bilayer, is largely responsible for controlling their drug release behavior. This complex three-dimensional internal structure is crucial in regulating the release profile because it generates numerous diffusion paths for medication molecules. In contrast to hydrophobic pharmaceuticals, which are kept inside the lipid bilayer and released more slowly through partitioning and lipid matrix relaxation, hydrophilic drugs are mostly confined within the aqueous channels and are released through diffusion along these interconnected pathways. Biphasic or prolonged release patterns can be produced by amphiphilic medications distributing between both domains.

The fragility and length of the aqueous channels, which considerably slow down molecular diffusion in comparison to traditional vesicular systems, also affect drug release from cubosomes. Long-term, regulated, and sustained drug release is made possible by cubosomesconvoluted diffusion mechanism. Drug release is also influenced by structural rearrangement or slow degradation of the lipid matrix, in addition to diffusion. This is especially true in physiological settings where temperature and enzymatic activity can alter lipid architecture.Additionally, formulation factors like particle size, stabilizer content, and lipid concentration have a significant impact on drug release. While smaller particle size offers shorter diffusion paths and somewhat faster release, higher lipid content creates a tighter bilayer network that limits drug mobility and causes slower release. Stabilizers are also essential for preserving the integrity of the cubic structure, which guarantees consistent and repeatable release behavior. Overall, cubosomes drug release mechanism is primarily driven by diffusion through networked aqueous channels in conjunction with lipid matrix remodeling, which makes them ideal for applications requiring regulated and prolonged drug delivery.

5. Methods of Preparation of Cubosomes:[29-38]

Cubosomes are often made by using energy-assisted or self-assembly methods to convert a bulk bicontinuous cubic liquid crystalline phase into stable nanoparticles. In general, there are two types of preparation strategies: top-down and bottom-up.

i. Top-Down Approach (High Energy Dispersion Method)

The most popular and traditional way for preparing cubosomes is the top-down approach. This process starts with the formation of a bulk cubic phase and uses high mechanical energy to break it up into nanoparticles.

Principle: The top-down method breaks down a pre-formed bulk cubic liquid crystalline phase into nanoparticles by applying high mechanical energy.

While the stabilizer (such as Poloxamer 407) adsorbs onto the particle surface to prevent aggregation and ensure the creation of stable cubosome nanoparticles, the high shear forces produced by homogenization or ultrasonication split the viscous cubic gel into tiny fragments.

Method: First, a stabilizer like Poloxamer 407 is melted together with an amphiphilic lipid, usually glyceryl monooleate or phytantriol. Water is added gradually while being constantly stirred to create a very viscous cubic gel. Cubosome nanoparticles are created by dispersing this bulk cubic phase in an excess aqueous phase and then undergoing probing ultrasonication or high-pressure homogenization.

This technique is still the gold standard for producing cubosomes on a laboratory scale and has been thoroughly documented in pharmaceutical literature.

ii. Bottom-Up Approach (Self-Assembly / Hydrotrope Dilution Method)

A recent and energy-efficient method for preparing cubosomes is the bottom-up strategy, which uses molecular self-assembly rather than mechanical fragmentation to create nanoparticles. This technique is more suited for delicate medicinal compounds since it creates cubosomes directly from molecular building blocks through regulated solvent exchange.

Principle: The bottom-up approach's fundamental concept is that lipids dissolve in hydrotropic solvents and then spontaneously self-assemble into cubic nanoparticles when diluted with water. The lipid molecules are first dissolved by the hydrotrope in a condition of molecular dispersion. The hydrotrope diffuses out of this solution when it is diluted with an aqueous phase, decreasing lipid solubility and causing the lipid molecules to reorganize into a bicontinuous cubic liquid crystalline structure. In the presence of a stabilizer, stable cubosomes are formed.

Method: To create a low-viscosity precursor solution, the lipid is first dissolved in a hydrotrope (such as ethanol or propylene glycol). Cubosomes are created when the system spontaneously nucleates and crystallizes after being diluted with a water-containing stabilizer (Poloxamer 407).

Because bottom-up approaches are more scalable and require less harsh processing conditions, they are becoming more and more popular in industrial settings.

iii. Heat Treatment Method (Thermal Induction Method)

The heat treatment method is a temperature-driven process that uses thermal energy to cause lipids to change into cubosomal structures. This method forms cubosomes without the need of high mechanical force or organic solvents.

Principle: The thermally induced phase transition of lipids serves as the foundation for this technique. At high temperatures, lipids like phytantriol and glyceryl monooleate experience structural reconfiguration. Lipid chains become more flexible and mobile when heated, which facilitates the transition from lamellar or micellar configurations to a bicontinuous cubic phase. These cubic structures stable as cubosomes when cooled under regulated conditions with a stabilizer.

Method: To create a dispersion, the lipid and stabilizer (such as Poloxamer 407) are first combined with water. After that, this mixture is heated (usually between 60 and 80 °C) while being stirred constantly. Phase transition and molecular mobility are facilitated by the heat. Stable cubic nanostructures are formed when the system is gradually cooled to room temperature after a predetermined amount of time has been consumed maintaining the temperature.

iv. Solvent Evaporation Method

By evaporating a volatile organic solvent from a lipid solution, cubosomes are created via the solvent evaporation method, a bottom-up self-assembly process.

Principle: The solvent evaporation method's basic concept is to use a rotary evaporator to carefully remove a volatile organic solvent, which causes lipids to self-assemble. First, lipids are dispersed in an aqueous phase after being dissolved in an organic solvent. Lipid solubility reduces and lipid molecules reorganize into a bicontinuous cubic liquid crystalline structure, creating stable cubosomes, when the solvent is evaporated using a rotavapor at lower pressure.

Method: Using a volatile organic solvent like ethanol or chloroform, the drug and lipid are first dissolved. Then, under constant stirring or sonication, this organic phase is introduced to an aqueous phase that contains a stabilizer. After that, the organic solvent

evaporates under low pressure using a rotavapor, a rotary evaporator. Lipid solubility reduces as the solvent evaporates, and the lipid molecules self-assemble spontaneously to create stable cubosomes by creating bicontinuous cubic liquid crystalline nanoparticles.

v. Emulsification Method

Lipid is dissolved in ethanol and then emulsified into an aqueous stabilizer solution while being stirred or sonicated in this process.

Principle: Lipids self-assemble into cubic nanoparticles when ethanol evaporates or is diluted. This method prevents the formation of bulk cubic gel and is especially helpful for lipophilic drug loading.

Method: The process involves dissolving the drug and lipid in ethanol and emulsifying them into an aqueous stabilizer solution while being stirred or sonicated. Cubosomes are created via self-assembly when ethanol is removed.

6. Characterization:[39-41]

Table. No.1. Characterization and Evaluation of Cubosomes

Sr. No.	Characterization Parameter	Purpose	Procedure	Instrument
1.	Particle size & PDI	Todeterminenanoscale size and uniformity ofcubosomes	Cubosome dispersion is diluted with distilled water and analyzed for average size and distribution	Dynamic Light Scattering (DLS), Zetasizer
2.	Zeta potential	To evaluate surface charge and predict physical stability	Diluted sample is placed in electrophoretic cell and surface charge is measured	Zetasizer with electrophoretic mobility cell
3.	Morphology	To examine shape and surface characteristics	A drop of sample is placed on copper grid, stained and observed	Transmission Electron Microscope (TEM) /SEM
4.	Internal structure	Toconfirmbicontinuous cubic architecture	Scattering pattern of formulation is recorded	Small-Angle X-ray Scattering (SAXS)
5.	Structural phase	To identify cubic phase type (Pn3m, Im3m)	Diffraction peaks are analyzed for phase confirmation	SAXS / Powder XRD
6.	Drug loading & Entrapment efficiency	To quantify drug incorporated within cubosomes	Free drug is separated by centrifugation and supernatant is analyzed by UV.	Centrifugation then by UV
7.	In vitro drug release	To study controlled and sustained release behavior	Formulation is placed in dialysis membrane and samples withdrawn at intervals and then anlysed by UV.	Franz diffusion cell / Dialysis method
8.	FTIR analysis	To detect drug–excipient compatibility	Spectra of pure drug and formulation are compared	FTIR spectrophotometer
9.	Thermal analysis	To study thermal behavior and drug dispersion	Sample is heated at controlled rate and thermogram recorded	Differential Scanning Calorimetry (DSC)
10.	pH measurement	To ensure physiological compatibility (5.5–7.4)	pH electrode is dipped directly in formulation	Digital pH meter
11.	Stability studies	To evaluate shelf life and formulation robustness	Samples stored at different temperatures and evaluated periodically	Stability chamber
12.	Powder X-ray diffraction (PXRD)	To determine crystalline/amorphous nature of drug	Dried sample is scanned over 2θ range	X-ray Diffractometer
13.	Ex vivo skin permeation	To evaluate drug penetration through skin	Formulation is applied on excised animal skin mounted on diffusion cell.	Franz diffusion cell + animal skin

7. Future Aspects of Cubosomes:[30,42,43]

Cubosomes have become very promising drug delivery nanocarriers, although their full potential has not yet been fully realized. The main goal of future research should be to optimize cubosome formulations for various administration routes, including oral, topical, ocular, and parenteral delivery. For each route to guarantee optimal treatment efficacy and patient compliance, precise control over particle size, surface characteristics, and drug release behavior is necessary.

Enhancing drug loading and controlled release of delicate biomolecules, such as proteins, peptides, and nucleic acids, is another crucial future path. Despite their superior structural qualities, cubosomes still have issues with stability and encapsulation effectiveness when used to transport big biological molecules. Therefore, more research is needed to improve the efficacy of stabilizer systems and lipid composition for improved biological therapies.

Systemic and intravenous cubosome applications require particular consideration for clinical translation. To understand their hemocompatibility, interactions with blood components, and long-term safety profiles, thorough research is required. The behavior of cubosomes in actual biological settings is still poorly understood, especially with regard to their stability in plasma, enzymatic breakdown, and possible immunological reactions.

Future studies should also look into challenges related to commercialization and large-scale manufacturing. Cubosome manufacturing on an industrial scale is still difficult because of its high viscosity, intricate processing, and stability issues, despite the fact that laboratory-scale production is well established. The creation of scalable and energy-efficient technologies, such bottom-up approaches, could greatly increase their viability in the industrial setting.

All things considered, cubosomes are a cutting-edge drug delivery system with an extensive range of therapeutic applications. Cubosomes could soon become a therapeutically and commercially viable nanocarrier system with the help of enhanced formulation techniques, regulatory standardization, and rigorous in vivo research.

8. Applications:[44-50]

Cubosomes have demonstrated promising applications in the treatment of various infectious, ocular, and oncological disorders.

Fig. No.8. Different Therapeutic Applications of Cubosomes

1. Bacterial Skin Diseases

Bacteria like Staphylococcus aureus and Streptococcus pyogenes are frequently responsible for bacterial skin diseases such impetigo, cellulitis, folliculitis, and abscesses. Successful treatment of these infections requires on preserving a sufficient concentration of antibiotics at the site of infection, which may stay superficial or spread to deeper tissues. Traditional topical preparations may not adequately penetrate deeper layers of the epidermis or hair follicles and are usually rapidly removed from the skin's surface.

In this sense, cubosomes present a potential theoretical approach. Their lipid-based nanostructure may enhance penetration into infected areas because it interacts favorably with the stratum corneum's endogenous lipids. They can settle inside hair follicles, which are often home to germs, due to their small size. They are flexible carriers because of their internal structure, which enables the integration of both lipophilic and hydrophilic antibiotics. Crucially, cubosomes release medications gradually, which may lessen the need for frequent doses and help maintain steady local levels. In addition to reducing systemic absorption and local discomfort, this consistent exposure may also reduce the likelihood of resistance.

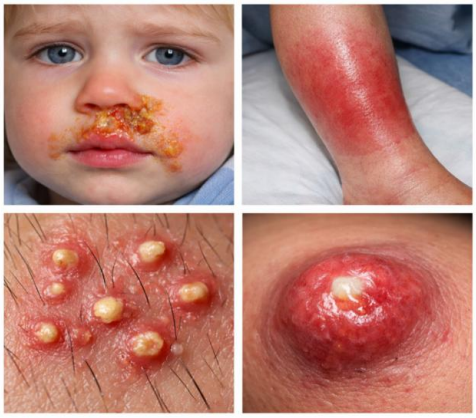

Fig. No.9.Representative Image of Bacterial Skin Disease

2. Fungal Skin Diseases

Keratinized tissues including the stratum corneum, hair, and nails are the main targets of fungal diseases such dermatophytosis, cutaneous candidiasis, and pityriasis versicolor. Antifungal medications frequently fail to adequately penetrate the outer layers of the epidermis, which is why these infections frequently persist. The effectiveness of many antifungal medicines in traditional creams and gels is further limited by their poor water solubility.Cubosomes offer a rational theoretical answer to these problems. Because of their special cubic shape, which combines lipid bilayers and aqueous channels, a variety of antifungal medications can be effectively included. Interactions between the lipid-rich surface and skin lipids may improve intercellular penetration through the stratum corneum. The lipid-based nature of fungal cell membranes makes it feasible for better medication partitioning into fungal cells. Sustained medication release, which keeps therapeutic doses at the infection site for extended periods of time, is an additional benefit.In cases of persistent or recurring infections, this extended exposure is especially crucial. Cubosomes may enhance the overall effectiveness of antifungal treatment by improving solubility, penetration, and retention.

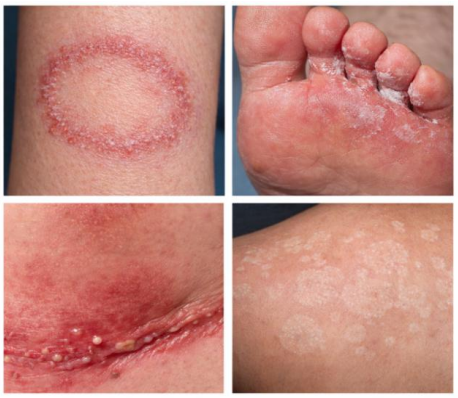

Fig. No.10.Representative Image of fungal Skin Disease

3. Ocular Diseases

Drug delivery to the eye is difficult due to defensive mechanisms include nasolacrimal drainage, blinking, and tear turnover. Because of this, the majority of traditional eye drops are quickly removed, which results in extremely poor medication availability at the intended location. One of the biggest challenges in eye therapy is maintaining therapeutic levels without frequent doses.

Theoretically, cubosomes can help get beyond these obstacles. Their lipid-based nanostructure has the ability to interact with the tear film's mucin layer, extending the precorneal residency duration. This indicates that the medication stays in contact with the surface of the eye for extended periods of time. Cubosomes dual hydrophilic and lipophilic structure complements the cornea's biphasic structure, which may improve drug penetration. Furthermore, controlled and sustained release is provided by the cubic matrix, which aids in preserving more consistent drug concentrations in the anterior chamber. These characteristics may increase antibiotic efficacy in ocular infections, decrease dosage frequency, and enhance patient compliance in chronic disorders like glaucoma or uveitis.

Fig. No.11.Representative Image of Ocular Disease

4. Cancer Therapy

Cancer treatment can frequently be difficult by poor selectivity, systemic toxicity, and medication resistance. Conventional chemotherapy passes throughout the body, killing both healthy tissues and malignant cells. Improving targeted delivery while minimizing side effects remains a primary goal in oncology.

Cubosomes present a speculative nanocarrier framework for addressing these difficulties. Their interior cubic structure allows for the simultaneous loading of hydrophilic and lipophilic anticancer medicines, which improves the solubility and stability of poorly water-soluble compounds. Because of their nanoscale size, cubosomes can accumulate in tumor tissue via the increased permeability and retention effect, where leaky tumor vasculature facilitates nanoparticle deposition. Once inside cancer cells, medicines can be released gradually, resulting in persistent intracellular concentrations. This regulated release may increase cytotoxic efficiency while lowering peak systemic exposure. Furthermore, nanoparticle uptake via endocytosis may aid in overcoming certain drug resistance pathways. Overall, cubosomes offer a solid theoretical framework for more precise and effective cancer treatment.

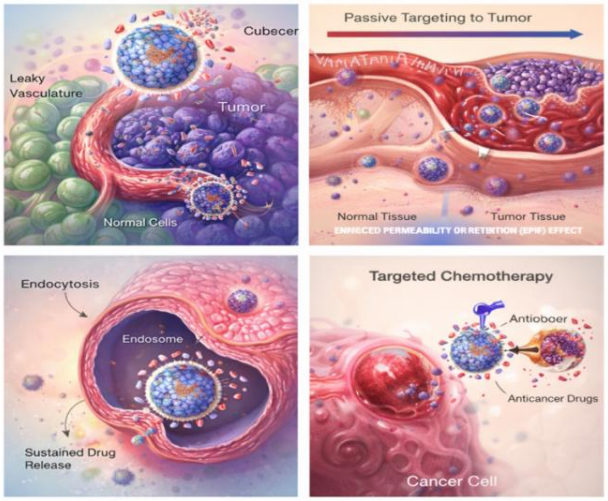

Fig. No.12.Representative Image of Cancer Disease

9. Conclusion:

Cubosomes are an effective lipid-based nanocarrier system due to their distinct bicontinuous cubic shape, high drug-loading capacity, and ability to encapsulate both hydrophilic and lipophilic medicines. Evaluation studies employing criteria such as particle size, zeta potential, entrapment efficiency, in vitro drug release, stability, and permeation profiles show that cubosomal formulations outperform traditional methods.

When compared to typical dose forms such creams, gels, suspensions, and eye drops, cubosomes have better penetration, longer drug residence duration, controlled release behavior, and higher bioavailability. These advantages lead to lower dosing frequency and, perhaps, improved patient compliance.

Although cubosomes have apparent advantages over traditional drug delivery methods, obstacles such as large-scale production, stability, and regulatory acceptability exist. Cubosomes have a high potential to replace or enhance current formulations in future pharmaceutical applications with more optimization and clinical testing.

10. REFERENCES:

1. Karami Z, Hamidi M. Cubosomes: Remarkable drug delivery potential. Drug Discov Today. 2016;21(5):789–801. doi:10.1016/j.drudis.2016.01.004
2. Balakrishnan P, Gopi S. Revolutionizing transdermal drug delivery: unveiling the potential of cubosomes and ethosomes. J Mater Chem B. 2024;12:4335–4360.
3. Gowri Nath A, Dubey P, Kumar A, Vaiphei KK, Rosenholm JM, Bansal KK, et al. Recent advances in the use of cubosomes as drug carriers with special emphasis on topical applications. J Lipids. 2024;2024:2683466.
4. Shukla MK, Pandey R, Pratap S. A comprehensive review on cubosomes. Int J Pharm Phytopharmacol Res. 2022;26(1):1–12.
5. Kamble SN, Subhedar R, Chougule NB. A comprehensive review on cubosomes. Int J Pharm Sci. 2024;2(5):1728–1739.
6. Waghmode RR, Jadhav SL, Patil SS. Advancement of cubosomes and their pharmaceutical applications. Curr Pharm Biotechnol. 2025;26(3):245–260. doi:10.2174/1389201025666241120114238
7. Sivadasan D, Sultan MH, Almoshari Y, et al. Cubosomes: Structure, preparation and pharmaceutical applications. Biomedicines. 2023;11(4):1114.
8. Patel R, Jain A, Mishra A. Cubosomes: A promising drug delivery system. Int J Pharm Sci Res. 2022;13(2):444–457.
9. Shinde PB, Devarajan PV. Cubosomes: An emerging platform for drug delivery. Int J Creat Res Thoughts. 2021;9(11):423–432.
10. Attri N, Das S, Banerjee J, Shamsuddin SH, Dash SK, Pramanik A. Liposomes to cubosomes: The evolution of lipidic nanocarriers and their cutting-edge biomedical applications. ACS Appl Bio Mater. 2024;7(5):2677–2694. doi:10.1021/acsabm.4c00153
11. Xing H, Hwang K, Lu Y. Recent developments of liposomes as nanocarriers for theranostic applications. Theranostics. 2016;6(9):1336–1352. PMID:27375783; PMCID:PMC4924503.
12. Sreelaya P, Bhattacharya S. Synoptic update on smart lipid nanocarrier: Cubosomes, their design development, and recent challenges. Curr Pharm Biotechnol. 2024;25(4):434–447.
13. Bhatt AH, Patel HP, Patel PR, Rathod HG, Hirawala JH, Shaikh PS, et al. Cubosomes in non-oral drug delivery: Advancing precision therapeutics from bench to bedside. Int J Pharm. 2025;684:126108. doi:10.1016/j.ijpharm.2025.126108
14. Iqbal S, Zaman M, Waqar MA, Sarwar HS, Jamshaid M. Vesicular approach of cubosomes: its components, preparation techniques, evaluation and appraisal for targeting cancer cells. J Liposome Res. 2024;34(2):368–384.
15. Patil SM, Mulla JAS. Cubosomes uncovered: Insights into their types, preparation techniques, evaluation methods and emerging applications. Indian J Novel Drug Deliv. 2024;16(2):104–112.
16. Valarmathi S, Abarna S, Dharshini J, Vijai S. Cubosomes as advanced nanocarriers for drug delivery. J Pharma Insights Res. 2025;3(1):35–42. doi:10.69613/22seee98
17. Fatima AF, Gandla K. Cubosomes in drug delivery: A comprehensive overview of mechanisms, applications, and future direction. Saudi J Med Pharm Sci. 2025;11(6):444–451. doi:10.36348/sjmps.2025.v11i06.001
18. Parkin HC, Swietach P, Townley H. Lipid cubosome nanoparticles for drug delivery. Nanomedicine. 2025;20(24):2909–2912.
19. Garg G, Saraf S, Saraf S. Cubosomes: An emerging lipid-based nanocarrier for drug delivery. Biomedicines. 2022;10(4):821.
20. Vahab SA, Nair A, Raj D, et al. Cubosomes as versatile lipid nanocarriers for neurological disorder therapeutics: a comprehensive review. NaunynSchmiedebergs Arch Pharmacol. 2024;397(6):3729–3746. doi:10.1007/s00210-023-02879-7
21. Rizwan SB, Dong YD, Boyd BJ, Rades T, Hook S. Characterization of bicontinuous cubic liquid crystalline systems of phytantriol and monoolein for drug delivery. Int J Pharm. 2017;509(1–2):336–345.
22. Yaghmur A, Mu H. Recent advances in drug delivery applications of cubosomes, hexosomes, and solid lipid nanoparticles. Adv Drug Deliv Rev. 2021;178:113956.
23. Teba HE, Khalil IA, El Sorogy HM. Novel cubosome-based system for ocular delivery of acetazolamide. Drug Deliv. 2021;28(1):2177–2186. doi:10.1080/10717544.2021.1989090

24. Barriga HMG, Holme MN, Stevens MM. Cubosomes: The next generation of smart lipid nanoparticles? Angew Chem Int Ed. 2019;58(10):2958–2978.
25. Miranda I, Misra B, Manjunath MC, Nayak G, Likhitha U, Nayak UY. Responsive nanostructured cubosomes: Advancements and therapeutic applications. Adv Pharm Bull. 2025;15(2):284–292. doi:10.34172/apb.025.43330
26. Joshi VC, Bhardwaj M, Bisht M, Bhatt V. A review on cubosome: An overview of a novel drug delivery approach. Afr J Biomed Res. 2024;27(4S):14330–14337. doi:10.53555/AJBR.v27i4S.7248
27. Kumari P, Shrivastava P, Gupta K, Pandey R, Tiwari SP. A review on novel cubosomal drug delivery system. Asian J Pharm Educ Res. 2024;13(3):221–232.
28. Singh S, Sachan K, Verma S, Singh N, Singh PK. Cubosomes: An emerging and promising drug delivery system for enhancing cancer therapy. Curr Pharm Biotechnol. 2024;25(6):757–771. doi:10.2174/0113892010257937231025065352
29. Gawari VA, Choudhary BN, Gaikwad SM, Dhasade PV. A review on cubosome: An innovative drug delivery technology. Int J Creat Res Thoughts. 2023;11(11):624–633.
30. Rao SV, Sravya BN, Padmalatha K. A review on cubosome: The novel drug delivery system. GSC Biol Pharm Sci. 2018;5(1):76–81. doi:10.30574/gscbps.2018.5.1.0089
31. Tekade AR, Avhad GD. A review on cubosome: A novel approach for drug delivery. Int J Pharm Sci Res. 2022;13(2):579–588. doi:10.13040/IJPSR.0975-8232.13(2).579-588
32. Chaudhary K, Sharma D. Cubosomes: A potential drug delivery system. Asian J Pharm Res Dev. 2021;9(5):93–101. doi:10.22270/ajprd.v9i5.981
33. Neena S, et al. Cubosomes: A novel drug delivery system. J Pharm Res Int. 2021;33(1):45–58.
34. Yalavarthi LP, Jonnadula PK, Manthina MV, Addagalla A. Cubosomes: A novel drug delivery system overview. Int J Res Ayurveda Pharm. 2020;11(5):38–44. doi:10.7897/2277-4343.1105169
35. Sunduru P, Sunkari KR, Begum MI. A review on cubosomes as a novel carrier for drug delivery. World J Pharm Res. 2020;9(11):1201–1214.
36. Umar H, Wahab HA, Gazzali AM, Tahir H, Ahmad W. Cubosomes: Design, development, and tumor-targeted drug delivery applications. Polymers. 2022;14(15):3118. doi:10.3390/polym14153118
37. Kaur SD, Singh G, Singh G, Singhal K, Kant S, Bedi N. Cubosomes as potential nanocarrier for drug delivery: A comprehensive review. J Pharm Res Int. 2021;33(31B):118–135. doi:10.9734/JPRI/2021/v33i31B31698
38. Saritha M, Harshini B, Kamala Kumari PV, Srinivasa Rao Y. A review on cubosomes. Asian J Pharm Clin Res. 2021;13(6):32–38.
39. Abo El-Enin H, Al-Shanbari AH. Nanostructured liquid crystalline formulation as a remarkable new drug delivery system of anti-epileptic drugs for treating children patients. Saudi Pharm J. 2018;26(6):790–800. doi:10.1016/j.jsps.2018.04.003
40. Oliveira C, Ferreira CJO, Sousa M, Paris JL, Gaspar R, Silva BFB, et al. A versatile nanocarrier—Cubosomes, characterization, and applications. Nanomaterials. 2022;12(13):2224. doi:10.3390/nano12132224
41. Shoman NA, Gebreel RM, El-Nabarawi MA, Attia A. Optimization of hyaluronan-enriched cubosomes for bromfenac delivery enhancing corneal permeation: Characterization, ex vivo, and in vivo evaluation. Drug Deliv. 2023;30(1):2162162. doi:10.1080/10717544.2022.2162162
42. Satheesan S, Kamath KK, Shabaraya AR. Cubosomes and its applications – A review. Eur J Biomed Pharm Sci. 2022;9(7):111–118.
43. Mathias A, Monika R. Cubosomes – an emerging platform for drug delivery. World J Pharm Sci Res. 2024;3(6):109–121. doi:10.5281/zenodo.14252556
44. Lakic B, Beh C, Sarkar S, Yap SL, Cardoso P, Valery C, et al. Cubosome lipid nanocarriers for delivery of ultra-short antimicrobial peptides. J Colloid Interface Sci. 2021;586:701–713. doi:10.1016/j.jcis.2020.11.073
45. Villalva DG, Otoni CG, Loh W. Cubosome-carrying bacterial cellulose membrane as a versatile drug delivery platform. J Colloid Interface Sci. 2019;544:106–114. doi:10.1016/j.jcis.2019.02.078
46. Nath AG, Vaiphei KK, Kumar A, Basrani S, Jadhav A, Chakravarti R, Ghosh D, Bansal KK, Gulbake A. Dual drug loaded topical cubosomal gel against Candida albicans: An in vitro and in vivo proof of concept. AAPS PharmSciTech. 2025;26(3):77. doi:10.1208/s12249-025-03070-2
47. Narula H, Devi N, Singh TG, Kumar P, Dhiman S, Dora CP. Unleashing the potential of cubosomes to overcome ocular barriers in precision drug delivery. Adv Drug Technol Pharm Dev. 2025. doi:10.1002/adtp.202500267
48. Nezhad NM, Kamali H, Sarchahi AA, Jalalifar S, Amani A, Oroojalian F. Investigating the efficacy of liquid crystal nano cubosomes containing dorzolamide and timolol for drug delivery to the cornea. J Drug Deliv Sci Technol. 2023;78:104025.
49. Varghese R, Salvi S, Sood P, Kulkarni B, Kumar D. Cubosomes in cancer drug delivery: A review. Mater Today Proc. 2023;72(2):194–201. doi:10.1016/j.matpr.2022.09.410
50. Garnipudi DK, Varalakshmi S, Mallikarjuna BP. Cubosomes and their role in various types of cancer treatment. Oncol Radiother. 2024;18(10):001–004.

International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 32, Issue 3, March 2026 **ijppr.humanjournals.com** ISSN: 2349-7203

How to cite this article:
Bhimashankar Hucche et al. Ijppr.Human, 2026; Vol. 32 (3): 326-341.

Conflict of Interest Statement: All authors have nothing else to disclose.