International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 30, Issue 10, October 2024 **ijppr.humanjournals.com** ISSN: 2349-7203

Exploring the Fascinating World of Cubosomes: A Comprehensive Review

Hasnamol[1], Sijamol C.S.[2], Mr. S. Mahendran[3]

1,2- M. Pharm Students, Department of Pharmaceutics, Nehru College of Pharmacy, Pampady, Thrissur, Kerala, India.

3-Associate Professor, Department of Pharmaceutics, Nehru College of Pharmacy, Pampady, Thrissur, Kerala, India.

Received: 2024-10-11 Revised: 2024-10-17 Accepted: 2024-10-22

ABSTRACT

Cubosomes are sized between 100 and 300 nm, are stable colloidal dispersions, and have an intricate nanostructure. Larsson coined the name "cubosome," which mimics the cubic molecular crystallography, analogous to liposomes. Their three-dimensional structures exhibit liquid-crystalline patterns that are bicontinuous cubic. Unsaturated monoglycerides (amphiphilic lipids like glyceryl monooleate or phytantriol) self-organize to generate these patterns, which are then stabilized by the using of steric polymers (poloxamers). Cubosomes have been shown to have a higher entrapment efficiency for hydrophobic drugs than liposomes due to their bicontinuous structure and steric polymer-based stabilization. They also showed higher stability. They are used in the treatment of skin conditions, fungus infections, cancer, and other ailments. This review examines the cubosome's composition, methods of production, and uses.

Keywords: Cubosomes, Hydrophobic, Amphiphilic.

INTRODUCTION

Lyotropic liquid crystals are a class of mesophase, self-assembling, non-lamellar nanostructured materials that have attracted a lot of interest in the pharmaceutical industry as drug carriers. Cubosomes are a kind of lyotropic liquid crystalline nanoparticles where the liquid-crystalline patterns are bicontinuous and arranged in three dimensions. Unsaturated monoglycerides (amphiphilic lipids like glyceryl monooleate or phytantriol) self-organize to generate these patterns, which are then stabilized by the using of steric polymers (poloxamers). Cubosomes have been shown to have higher stability and entrapment efficiency for hydrophobic drugs than liposomes because of their bicontinuous structure and steric polymer-based stabilization [1].

On the basis of differences in nodal surfaces, three structures of cubosomes have been recognized, namely: Im3m/QIIP (Primitive, Schwarz, or P-surface), Pn3m/QIID (Diamond or D-surface), and Ia3d/QIIG (Gyroid or G-surface) [2].

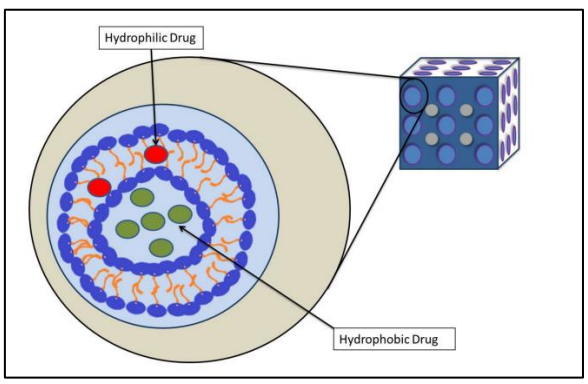

Fig 1: The structures of cubosome [17].

Cubosomes are sized between 100 and 300 nm, are stable colloidal dispersions, and have an intricate nanostructure. Cubosomes have remained the preferred approach for prolonged release, controlled release, and targeted release dosage forms as a new drug delivery technique for better drug release because of its unique advantages in biocompatibility and thermodynamic stability [4]. Larsson coined the word "cubosomes," which mimics the cubic molecular crystallography, akin to liposomes [3,5].

COMPONENTS

1. AMPHIPHILIC LIPIDS:

GLYCERYL MONOOLEATE

Polar unsaturated monoglyceride, or GMO, has certain chemical and physical characteristics that are essential for the formation of hexosomes and cubosomes. With an HLB value of three, it is a colorless, non-toxic, biodegradable, and GRAS molecule that has an MP of 35–37 ◦C and a storage temperature of 20–30 ◦C. It has a hydrocarbon tail and a hydroxyl head as its structural components. Water molecules and hydroxyl groups typically create hydrogen bonds. But there are disadvantages as well, like oxidation of unsaturated bonds in the hydrocarbon chain or ester hydrolysis in the GMO headgroup, which reduce long-term stability and storage [6]. As a synthetic molecule, GMO is a blend of fatty acid glycerides, mostly oleic acid glycerides and other fatty acids belonging to monooleates which is primarily a member of the amphiphilic lipid class, which is capable of forming different types of lyotropic liquid crystals [7].

PHYTANTRIOL

Because of its superior emulsification feature and stronger penetration power, phytantriol (PHY) is another amphiphilic contender that is used. Because it has a phytanyl backbone devoid of ester and unsaturated linkages, it is also more stable than GMO. Its moisture retention is also quite high. Its commercial purity is 95%, although the GMO content fluctuates according to purity [6].

It is often used in skincare products because of its capacity to generate a cubic structure in aqueous environments with physiological parameters and temperatures [7].

Due to their claims of prolonged drug release, particularly for hydrophilic moieties and hydrophilic medicines, PHY-based liquid nanocarriers are attracting a lot of attention. When making cubosomes, it works well as a GMO alternative. However, since GMO has a lesser probability to cause hemolysis at dose-relevant concentrations than PHY, it is preferred [6].

2. STABILIZERS

For cubosomes to remain colloidally stable and avoid re-coalescing into the bulk cubic phase, a surfactant is necessary. The stabiliser maintains the dispersed particles in a highly stable condition by creating an electric barrier between them to avoid close interaction [8].

The stabilizers also help to preserve the amphiphilic molecules' integrity under different circumstances, guaranteeing their long-term stability and functioning [6]. It is known that the amphiphilic block copolymers, the pluronics function as the best stabilizers. Triblock copolymer Poloxamer 407 (P407, Pluronic F-127) and poly (ethylene glycol)-block-poly (propylene glycol)-block-poly(ethylene glycol) (Pluronic F-108) are mostly used. Polymeric stabilizers must have a hydrophobic domain with at least 40 PPO units and a hydrophilic domain with at least 19 PEO units in order to effectively stabilize LCN by providing steric shielding [6,8].

P407 is often applied at a concentration of up to 20% w/w depending on the dispersed phase, whereas the monoglyceride–polymer combination concentration typically ranges from 2.5 to 10% (w/w) depending on the dispersion's total weight [5]. Rather than a nanostructured cubic matrix, Worle et al. showed that a greater concentration of P407 was able to effectively form smaller vesicular particles [7].

ADVANTAGES

- Cubosomes are thermodynamically stable, non-irritating, biocompatible, and biodegradable [8].

- Drugs that are hydrophilic, lipophilic, or amphiphilic may all be loaded into cubosomes [8].
- Their huge inner surface area contributes to their great drug-loading capacity [8].
- Its bio-adhesive qualities are exceptional. Because of its greater surface area and cubic crystalline phase, it provides a large area for drug loading [7].
- They have improved skin penetrating capabilities and long-term thermodynamic stability [7].

DISADVANTAGES [7,8]

- Due to their high viscosity, cubosome manufacture on a wide scale is difficult.
- Water-soluble medicines have a lower chance of entrapment since they include a considerable quantity of water.
- Possibility of leakage during storage or in vivo transmission.
- When cubosomes are exposed to their surroundings, a phase shift might occur.
- If particles are left alone for an extended period, there may be a chance of particle growth.

TECHNIQUES OF PREPARATION

- Generally, one encounters three macroscopic forms of cubic phase: particulate dispersion, bulk gel, and precursor.
- When a substance is stimulated, as by coming into contact with liquid, it transforms from a solid or liquid into a cubic phase. When in equilibrium with water, bulk cubic phase gel is an optically isotropic, rigid, and solid-like substance that may be dispersed into cubosome-like particles. [9]

TOP-DOWN TECHNIQUE

Top-down approaches begin with a suitable starting material that is shaped into the required structures by the application of high energetic inputs. First, a bulk cubic phase is created for cubosome synthesis. The cubosomes are then formed by sonication or high-pressure homogenization of this initial material in an aqueous solution [10].

The most popular technique for manufacturing cubosomes, the top-down approach, is done in two phases. To prevent aggregation, the first step involves forming the viscous bulk cubic phase by combining lipid(s) and stabilizer(s). The second step involves dispersing the first step's resultant into an aqueous medium using high energy, such as high-pressure homogenization or sonication, which eventually forms cubosomes. By co-melting the required lipid mixtures in slight volumes of water and letting it equilibrate, the selected lyotropic phases may be created. Dissolving the lipid mixture in a hydrotrope for subsequent evaporation is an additional method. Before the dispersion step whether by homogenization or sonication, a stabilizer that has been dissolved in water must be added in both cases. Variations in the process like adding of heat cycling stages might be added to certain rounds of this procedure to increase dispersity and reduce the quantity of vesicles that form. Despite being the most often used approaches, both have several disadvantages, including the need for a high energy input, heat production, and vesicle formation. Furthermore, additional care must be taken if a different solvent is employed in the first stages. This process may result in elevated toxicity, which would restrict its applicability in biological contexts [5,10].

MERITS

- Most common one
- The approach produced reproducible and stable cubosomes that are stable upto an year. [5,10]

DEMERITS

- Formation of the viscose cubic structure [5]
- Heat-sensitive components, such as peptides and proteins, cannot be added to nanocubosomes because of the high energy needed to disperse the cubic phase into them. [5]
- Long and tedious process [10]
- Generation of heat [10]
- Always exist alongside vesicles, such as vesicle-like structures or dispersed nanomaterials of the lamellar liquid crystalline phase. [5]

A significant quantity of P407 causes the emergence of a P-type cubic phase under conventional homogenization conditions, which seems to favor the production of a stable dispersion of colloidal cubic particles. The presence of D-type cubic phase during the fragmentation process seems to stimulate the development of large, non-colloidal particles. The presence of an adequate quantity of P407 guarantees the emergence of a P-type cubic phase under conventional homogenization conditions, which seems to facilitate the creation of a stable dispersion of colloidal cubic particles. The presence of the D-type cubic phase during the fragmentation process seems to promote the development of big, non-colloidal particles. Cubic particle colloidal dispersions were only achievable between 40 and 60 ◦C for the examined composition, with homogenization at 60 ◦C resulting in the lowest average particle sizes. The poor standard of a dispersion produced at 80 ◦C may be linked to the temporary emergence of a D-type cubic structure during homogenization, whereas the reasons for the challenges in dispersing samples at 20 ◦C have yet to be clarified. The kind of homogenization equipment had no impact on the dispersion characteristics, whereas an increase in homogenization pressure resulted in a slight decline in the proportion of micrometer-sized particles compared to the standard pressure of 350 bar. [11]

BOTTOM-UP TECHNIQUE

Cubosomes may be produced through an alternate approach at ambient temperature via the crystallization of precursors. This technique is referred to as the liquid precursor or solvent dilution method, solvent exchange method, sometimes termed solvent shifting and nanoprecipitation [5].

Bottom-up techniques depend on the initial creation of nanostructure building blocks, which then combine into the final structure [10].

The process entails the dispersion of a mixture consisting of liquid-crystal-forming lipid, polymer, and hydrotrope in excess water with low energy input to produce discrete nanoparticles. The primary function of the hydrotrope is to generate liquid precursors by dissolving lipids and to inhibit the development of a viscous liquid crystal phase at elevated concentrations [5].

MERITS

- Less energy [5]
- Facilitates the handling of temperature-sensitive products [5]
- Due to the distinct production process of cubosomes, this method is much more effective in producing tiny particles. [5]
- The preparation procedure is simplified by the use of hydrotrope, which results in cubosomes that exhibit comparable or superior properties to those produced through the top-down approach. [5]
- Better suited for scaling up to commercial production [5]
- Sherif et al. conducted a comparison of the two techniques and demonstrated that the bottom-up technique is superior in producing smaller cubosomes with enhanced encapsulation efficiency and slower release rates. [5]

DEMERITS

- A disadvantage of the bottom-up method of cubosome synthesis is that it often relies on organic solvents, such as ethanol, as diluents. This can lead to the formation of liposomes at the same time. [12]

Still, the discovery of new and better techniques for the low-energy production of cubosomes, eliminating the need for high-energy inputs like sonication or homogenization, is much looked for.

Recent research has introduced novel techniques to overcome the identified constraints. Muir et al. described the creation of cubosomes by the incorporation of PBS into the binary lipid system comprising the charged lipid dodecyl dimethyl ammonium bromide (DDAB) and PHYT. The incorporation of PBS using this approach generated a charged shield on the DDAB, thus altering the bilayer curvature and restoring the bicontinuous cubic phase. The creation of cubosomes by the charge-shielded approach may be optimized by adjusting the quantity of charged lipids and the concentration of PBS, allowing for size-specific integration of active compounds [7]. A different technique for cubosome preparation is the spray-drying approach. Spray-dried encapsulated particles are produced from an emulsion of liquid droplets or dispersions of solid particles in concentrated water-polymer solutions [13].

DRUG LOADING IN CUBOSOMES

For an effective drug delivery system, sufficient quantities of small-molecule medicines, peptides, biologics, or bioactives must be included into the produced cubosomes. The primary processes for cargo loading consist of incorporation into the lipid bilayer, attachment to the lipid membrane, or localization of the drug inside the aqueous channels of the cubic phase [3]. The drug moieties may be loaded by either incorporating the therapeutic agent into the molten lipid [22] or by colyophilizing it with the lipid film prior to dispersion [23,24].

APPLICATIONS

CUBOSOMES IN CANCER THERAPY

Cancer is a highly prevalent illness that presents a significant therapeutic challenge due to its elevated incidence rates. Nanobiotechnological modalities depend only on the release of active ingredients triggered by specific stimuli such as enzymes, temperature, pH, redox potential, or other external factors, according to their unique physicochemical properties. The synergistic integration of diverse nanoparticles with target ligands accelerates the development of highly effective active drug carrier systems. Furthermore, the integration of nanotechnology with a contrast agent may significantly enhance the sensitivity of in vivo real-time diagnostics for next-generation precision medicine [2].

Clinically approved Poly (Ethylene Glycol)-Polylactide (PEG-PLA) copolymer micelles for malignancy treatment; PEG-based Platinum (II) nanoformulation for multidrug-resistant cancer therapy; conjugated PEG and β-cyclodextrin (PEGCD) for efficient delivery of Sorafenib and Doxorubicin, along with various nanocarriers have been developed for cancer treatment [14].

The use of innovative drug delivery systems for the effective and patient-compliant administration of biomacromolecular drugs significantly enhances bioavailability, extends drug half-life, and improves patient adherence, thereby augmenting their effectiveness and potential for clinical applications [15]. A multitude of articles have been published about the potential applications of cubosomes as nanocarriers for cancer therapies. Doxorubicin, cisplatin, paclitaxel, curcumin, and quercetin are examples of chemical substances that have been effectively encapsulated in cubosomes, either individually or by simultaneous encapsulation [10].

International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 30, Issue 10, October 2024 ijppr.humanjournals.com ISSN: 2349-7203

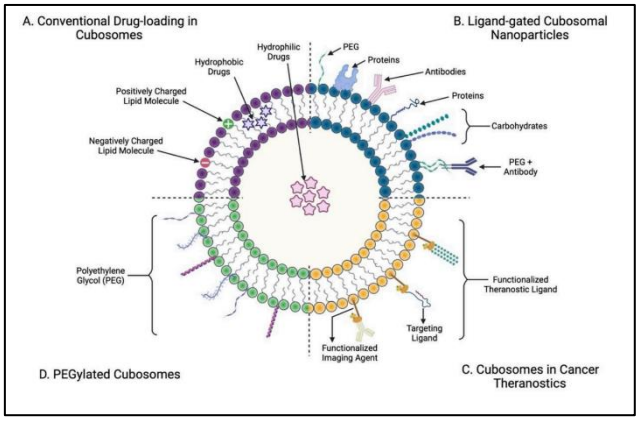

Fig 2: various utilities of cubosomes in the treatment and theranostics of various cancers [2]

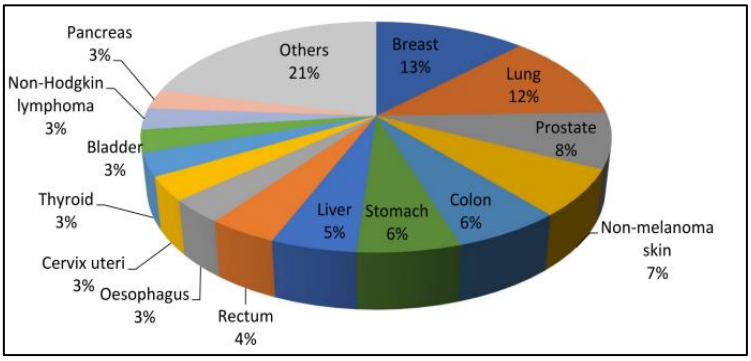

Fig 3: Worldwide distribution of the estimated new cases of cancer in 2020. The data were extracted from earlier published data [16]

Table 1: Cubosomes for various cancers

Cancer/Cells Type	Chemicals/ Drugs	Polymer Used	Stabilizer	Findings	Ref
Colorectal/HCT-116	Cisplatin	GMO	Pluronic F127	Cisplatin-loaded nano-cubosomes decreased the cell viability of HCT 116 and augmentation of their cytotoxicity in the presence of metformin	[18]
Hepatic/HepG2	5-Fluorouracil	GMO	Pluronic F127	5-FU-loaded cubosomes performed well in vitro cell culture. In vivo, biodistribution studies of 5-FU in rat liver indicated that the cubosomal formulation significantly increased 5-FU liver concentration (nearly 5-fold) as compared to that of a 5-FU solution	[19]
Cervical/Hela	Paclitaxel	GMO	PF108-B	The biotinylated cubosome facilitated drug uptake at the cellular level	[20]
T98G glioblastoma cells	Doxorubicin (DOX)	Monoolein	Pluronic F-127	DOX incorporated into cubic nanoparticles at a concentration of 2.3µg/mL exerted higher cytotoxicity than direct DOX delivery.	[21]
HCT116	Curcumin	Polyethylene glycol 400 (PEG-400), RH40, and Monoolein (MO)	Pluronic F-127	Cell growth inhibition was significantly higher when the cells were treated with curcumin as LCN	[22]

TOPICAL DRUG DELIVERY

Transdermal drug delivery facilitates a painless administration of medication that avoids first-pass metabolism, hence allowing a reduced dose. Nonetheless, several challenges exist in the use of this administrative technique. The stratum corneum, a layer of the skin, functions as a barrier that hinders molecular penetration [5].

Cubosomes may serve as a potential vehicle for the delivery and transport of medications to and through the skin. Furthermore, cubosomes has significant potential for use in antimicrobial treatment, augmenting the efficacy of drugs against infections [10].

Boge *et al*. investigated the capacity of cubosomes to transport LL-37, an antimicrobial peptide (AMP), by topical application. LL-37 was incorporated into monoolein cubosomes using three distinct methods: pre-loading, post-loading, and hydrotrope-loading, which refer to the encapsulation of the chemical before, after, and during the production of the cubosomes, respectively. The results indicated that the encapsulation method influenced the sizes and architectures of the cubosomes, with hydrotrope-loading yielding the smallest cubosomes. Neither formulation demonstrated skin irritation. No release of LL-37 was detected from the cubosomes, leading to enhanced protection of LL-37 against enzymatic degradation. Under physiological conditions, several antimicrobial peptides are prone to proteolytic degradation.

Upon exposure to Pseudomonas aeruginosa elastase or human neutrophil elastase, pure LL-37 was entirely destroyed, however LL-37 encapsulated inside the cubosomes remained unaltered. Moreover, the encapsulated LL-37 exhibited bactericidal properties against E. coli and S. aureus, even after enzyme exposure [23].

Mohammed Gulzar Ahmed *et al*. investigated cubosomes containing dexamethasone (DMS). Cubosomes were integrated into hydrogel for prolonged administration of DMS to address vitiligo. Cubosomes were synthesized utilizing a top-down approach with varying quantities of glyceryl monooleate (GMO) as the lipid phase, poloxamer 407 (P 407) as the non-ionic surfactant, oleic acid as the fatty acid, and water as the aqueous phase. The drug-loaded cubogel demonstrated increased drug content, optimal pH, enhanced spreadability, and an excellent sustained release profile after 12 hours. The formulated cubogel may serve as a promising topical continuous medication delivery strategy for vitiligo therapy [28].

OCULAR APPLICATIONS

Cubosomes have a longer residence time on the corneal surface and demonstrate good ocular bioavailability for the incorporated drugs. Cubosomes containing GMOs have mucoadhesive characteristics that improve ocular permeability, hence increasing medication bioavailability [25]. Cubosomes containing dexamethasone are extensively researched for their *in vitro* permeability through excised rabbit corneas. DEX cubosome particles were generated by breaking down a cubic crystalline phase of monoolein and water with the stabilizer Poloxamer 407. *In vitro*, the apparent permeability coefficient of DEX delivered via cubosomes demonstrated a 4.5-fold (F1) and 3.5-fold (F2) enhancement relative to Dex-Na phosphate eye drops. The precorneal residence time test and pharmacokinetic analysis of aqueous humor samples indicated that the preocular retention time is enhanced in comparison to Dex-Na Phosphate eye drops resulted in a simultaneous elevation in dexamethasone content in the aqueous humor [26].

Glaucoma is a serious worldwide health issue that may result in permanent blindness. In a glaucoma emergency, acetazolamide is the preferred medication. Nevertheless, the only feasible administration method is by systemic pills. Teba et al. presented a cubosome-based method for the topical administration of acetazolamide. The findings indicated that the improved formulation of acetazolamide-loaded monoolein cubosomes was non-irritating to the eye and provided prolonged and effective therapeutic effects compared to other commercially available pharmacological solutions. ACZ-loaded cubosomes provide an innovative topical drug delivery strategy for glaucoma treatment, demonstrating significant intraocular pressure reduction for over 9 hours while substantially decreasing the required dosage. This innovative drug delivery technology provides localized inhibition of the carbonic anhydrase enzyme in the eye, resulting in a significant decrease or elimination of severe systemic side effects associated with the marketed medication, CidamexVR tablets [27].

Bessone *et al*. synthesized latanoprost-loaded phytantriol cubosomes (CubLnp) by a top-down approach. The cubosomes exhibited a markedly slow release of Latanoprost, an anti-glaucoma medication, demonstrating a prolonged release profile. A single subconjunctival application of CubLnp has been shown to significantly reduce intraocular pressure [36].

ORAL DELIVERY

While oral route of drug delivery is the most convenient and traditionally used approach, it often poses challenges for administering poorly water-soluble medicines. A research was carried out to orally give insulin-loaded cubosomes to fasting streptozotocin-induced diabetic rats. This investigation included microfluidizing water, emulsifier, and GMO at 80 ◦C, followed by cooling to ambient temperature. To maintain insulin stability under challenging conditions, the formulation was manufactured at ambient temperature, and big aggregates were gathered. The mucoadhesive properties of GMO and the biocompatibility of cubosomes, together with a consistent hypoglycemic effect and improved adsorption on intestinal epithelia, are attained. Moreover, cubosomes may serve as an essential medium for the oral administration of weakly water-soluble compounds. The oral administration of pharmaceuticals is incorporated in a solubilized state inside the lipid bilayer of their structure, which inhibits drug precipitation in the gastrointestinal system and improves intestinal absorption owing to the mucoadhesive properties of GMO [25][28].

CUBOSOME IN BURNS

Vaishali Thakkar *et al.* created a cubogel involving Silver Sulfadiazine and Aloe Vera for the treatment of severe burn wounds. The findings of this research indicate that the formulation of cubosome dispersions containing SSD inside cubic liquid crystalline nanoparticles facilitates regulated release of SSD, hence mitigating the cytotoxic effects of silver [29].

CUBOSOME IN WOUND HEALING

Lamiaa M. Ahmed *et al*. produced cubosomes with beneficial physicochemical features, successfully encapsulating simvastatin into cubosomal nanoparticles. The HPMC-based cubogel exhibited enhanced properties for topical application and demonstrated greater permeability of simvastatin through the skin compared to the free drug hydrogel. This has been attributed to the penetration enhancing effect of Cubosomes and additional permeation enhancers. The effectiveness of simvastatin in promoting wound healing was assessed using histopathological analysis. These findings suggest that cubic nanoparticles may serve as an effective means for delivering simvastatin to the dermal layers [30].

CUBOSOME IN AGING

Mohamed El-Komy *et al*. assessed the effectiveness of 5% Cubosomal ALA as an anti-aging compound. This single-blinded, placebo-controlled comparative research included 20 females. Patients were directed to apply a gel formulation containing the active component to the right half of their face and a placebo gel to the left half twice daily for a duration of 6 months. The Global Aesthetic Improvement Scale (GAIS) was used as an indicator of clinical advancement. The epidermal and dermal thicknesses were evaluated pre- and post-treatment using an ultrasonic biomicroscope [31].

CUBOSOME IN INFECTIONS

Khaled M. Hosny *et al*. created an ophthalmic in situ gel formulation using NT-loaded cubosomes to boost ocular permeability, improve antifungal efficacy, and extend retention time in the eye. The in vivo ocular irritation test demonstrated that the optimal formulation is less irritating than a commercial NT formulation. This indicates that the formulated product results in less ocular irritation and may decrease the needed frequency of administration [32].

Mahmood, A *et al*. produced LUL-loaded lyotropic liquid crystalline nanoparticles (LCNP) and characterized them utilizing a three-factor, five-level Central Composite Design of Response Surface Methodology. The in vitro data demonstrated a ninefold longer release profile of LUL-LCNP compared to the pure drug solution. Upon determining the flux, the synthesized LUL-LCNP exhibited a two-fold increase in transdermal flux and a two-fold enhancement ratio compared to the commercial cream [33].

Thomas *et al*. developed a number of cubosomes containing silver (Ag) nanocrystals, copper oxide (Cu2O), and magnetite (Fe3O4) for extensive applications in therapies, including antibacterial efficacy. The study's results demonstrated a significant enhancement in the antibacterial efficacy of silver nanocrystals against both gram-positive and gram-negative bacteria [34]. Another research successfully generated cubosomes loaded with the antimicrobial peptides AP114, DPK-060, and LL-37, demonstrating enhanced antibacterial efficacy of the peptides [35].

CONCLUSION

The advancement of nanocarriers has resulted in significant advances across several research domains, especially within the medical sector. Cubosomes have garnered significant interest in recent years among the many developed and described nanocarriers. This article had reviewed the primary composition, preparation methods, and applications of cubosomes. The advancement of cubosome development had facilitated the emergence of novel and more effective therapies with less side effects. Cubosomes may be given via several methods, including intravenous, intranasal, oral, ocular, and topical, owing to their outstanding characteristics. Cubosomes are notably characterized by their bioadhesive properties, enabling their use in both topical and mucosal formulations for drug delivery.

REFERENCES

1. Gowda BHJ, Ahmed MG, Alshehri SA, Wahab S, Vora LK, Singh Thakur RR, Kesharwani P. The cubosome-based nanoplatforms in cancer therapy: Seeking new paradigms for cancer theranostics. Environ Res. 2023 Nov 15; 237(1):116894.
2. Ryan Varghese, Sahil Salvi, Purab Sood, Bhargavi Kulkarni, Dileep Kumar. Cubosomes in cancer drug delivery: A review. Colloid and Interface Science Communications. 2022; 46: 100561.
3. Francesca Damiani Victorelli, Livia Salvati Manni, Stefania Biffi, Barbara Bortot, Hilde Harb Buzza, Viviane Lutz-Bueno, Stephan Handschin, Giovana Calixto, Sergio Murgia, Marlus Chorilli, Raffaele Mezzenga. Potential of curcumin-loaded cubosomes for topical treatment of cervical cancer. Journal of Colloid and Interface Science. 2022; 620:419-430.
4. Garg M, Goyal A, Kumari S. An Update on the Recent Advances in Cubosome: A Novel Drug Delivery System. Curr Drug Metab. 2021; 22(6):441-450.
5. Karami Z, Hamidi M. Cubosomes: remarkable drug delivery potential. Drug Discov Today. 2016 May; 21(5):789-801.
6. U. Likhitha, Usha Y. Nayak. Advances in tailored drug delivery systems: Amphiphilic lyotropic mesomorphs for targeted therapeutic intervention. Journal of Molecular Liquids. 2024; 403: 124738.
7. Madhukar Garg, Anju Goyal, Sapna Kumari. An Update on the Recent Advances in Cubosome: A Novel Drug Delivery System. Current Drug Metabolism. 2021; 22:441-450.
8. Sivadasan D, Sultan MH, Alqahtani SS, Javed S. Cubosomes in Drug Delivery-A Comprehensive Review on Its Structural Components, Preparation Techniques and Therapeutic Applications. Biomedicines. 2023 Apr 7; 11(4):1114.
9. Gopal Garg, Shailendra Saraf, Swarnlata Saraf. Cubosomes: An Overview. Biol. Pharm. Bull. 2007; 30(2): 350-353.
10. Oliveira C, Ferreira CJO, Sousa M, Paris JL, Gaspar R, Silva BFB, Teixeira JA, Ferreira-Santos P, Botelho CM. A Versatile Nanocarrier-Cubosomes, Characterization, and Applications. Nanomaterials (Basel). 2022 Jun 29; 12(13):2224.
11. Worle G, Drechsler M, Koch MH, Siekmann B, Westesen K, Bunjes H. Influence of composition and preparation parameters on the properties of aqueous monoolein dispersions. Int J Pharm. 2007 Feb 1; 329(1-2):150-7.
12. Saffron J. Bryant, Elly K. Bathke, Karen J. Edler. Bottom-up cubosome synthesis without organic solvents. Journal of Colloid and Interface Science. 2021; 601:98-105.
13. Hafez IM, Ansell S, Cullis PR. Tunable pH-sensitive liposomes composed of mixtures of cationic and anionic lipids. Biophys. J. 2000; 79:1438–1446.
14. Qi B, Wang C, Ding J, Tao W. Editorial: Applications of Nanobiotechnology in Pharmacology. Front Pharmacol. 2019 Dec 4; 10:1451.
15. Qin Guo, Chen Jiang. Delivery strategies for macromolecular drugs in cancer therapy. Acta Pharmaceutica Sinica B. 2020; 10(6):979-986.
16. Ferlay J, Colombet M, Soerjomataram I, Parkin M, Pineros M, Znaor A, Bray F. Cancer statistics for the year 2020: An overview. Int. J. Cancer. 2021; 149: 778–789.
17. Almoshari Y. Development, Therapeutic Evaluation and Theranostic Applications of Cubosomes on Cancers: An Updated Review. Pharmaceutics. 2022 Mar 9; 14(3):600.
18. Saber, MM, Al-mahallawi, AM, Nassar NN, *et al.* Targeting colorectal cancer cell metabolism through development of cisplatin and metformin nano-cubosomes. BMC Cancer. 2018; 18:822.
19. Nasr M, Ghorab MK, Abdelazem A. In vitro and in vivo evaluation of cubosomes containing 5-fluorouracil for liver targeting. Acta Pharm Sin B. 2015 Jan; 5(1):79-88.
20. Aleandri S, Bandera D, Mezzenga R, Landau EM. Biotinylated Cubosomes: A Versatile Tool for Active Targeting and Codelivery of Paclitaxel and a Fluorescein-Based Lipid Dye. Langmuir. 2015 Nov 24; 31(46):12770-6.

21. Nazaruk E, Majkowska-Pilip A, Bilewicz R. Lipidic Cubic-Phase Nanoparticles-Cubosomes for Efficient Drug Delivery to Cancer Cells. Chem Plus Chem. 2017; 82(4): 570–575.
22. Baskaran R, Madheswaran T, Sundaramoorthy P, Kim HM, Yoo BK. Entrapment of curcumin into monoolein-based liquid crystalline nanoparticle dispersion for enhancement of stability and anticancer activity. Int J Nanomedicine. 2014; 9(1):3119-3130.
23. Boge, Hallstensson K, Ringstad L, Johansson J, Andersson T, Davoudi M, Larsson PT, Mahlapuu M, Håkansson J, Andersson M. Cubosomes for topical delivery of the antimicrobial peptide LL-37. Eur J Pharm Biopharm. 2019 Jan; 134:60-67.
24. Demurtas D, Guichard P, Martiel I. *et al.* Direct visualization of dispersed lipid bicontinuous cubic phases by cryo-electron tomography. Nat Commun. 2015; 6:8915.
25. Umar H, Wahab HA, Gazzali AM, Tahir H, Ahmad W. Cubosomes: Design, Development, and Tumor-Targeted Drug Delivery Applications. Polymers. 2022; 14:3118.
26. Gan L, Han S, Shen J, Zhu J, Zhu C, Zhang X, Gan Y. (). Self-assembled liquid crystalline nanoparticles as a novel ophthalmic delivery system for dexamethasone: Improving preocular retention and ocular bioavailability. International Journal of Pharmaceutics. 2010; 396(1-2):179–187.
27. Teba HE, Khalil IA, El Sorogy HM. Novel cubosome based system for ocular delivery of acetazolamide. Drug Deliv. 2021 Dec; 28(1):2177-2186.
28. Chung H, Kim J, Um J, et al. Self-assembled "nanocubicle" as a carrier for peroral insulin delivery. Diabetologia. 2002; 45:448–451.
29. Thakkar V, Korat V, Baldaniya L, Gohel M, Gandhi T, Patel N. Development and characterization of novel hydrogel containing antimicrobial drug for treatment of burns. Int J Pharm Investig. 2016 Jul-Sep; 6(3):158-68.
30. Ahmed LM, Hassanein KMA, Mohamed FA, *et al.* Formulation and evaluation of simvastatin cubosomal nanoparticles for assessing its wound healing effect. Sci Rep. 2023; 13:17941.
31. El-Komy M, Shalaby S, Hegazy R, Abdel Hay R, Sherif S, Bendas E. Assessment of cubosomal alpha lipoic acid gel efficacy for the aging face: a single-blinded, placebo-controlled, right-left comparative clinical study. Journal of Cosmetic Dermatology. 2016; 16(3):358–363.
32. Hosny KM, Rizg WY, Alkhalidi HM, Abualsunun WA, Bakhaidar RB, Almehmady AM, Alghaith AF, Alshehri S, El Sisi AM. Nanocubosomal based *in situ* gel loaded with natamycin for ocular fungal diseases: development, optimization, *in-vitro*, and *in-vivo* assessment. Drug Deliv. 2021 Dec; 28(1):1836-1848.
33. Mahmood A, Rapalli VK, Waghule T, Gorantla S, Singhvi G. Luliconazole loaded lyotropic liquid crystalline nanoparticles for topical delivery: QbD driven optimization, in-vitro characterization and dermatokinetic assessment. Chem Phys Lipids. 2021 Jan; 234:105028.
34. Meikle TG, Dyett BP, Strachan JB, White J, Drummond CJ, Conn CE. Preparation, Characterization, and Antimicrobial Activity of Cubosome Encapsulated Metal Nanocrystals. ACS Appl Mater Interfaces. 2020 Feb 12; 12(6):6944-6954.
35. Martin-SerranoA, Gomez R, Ortega P, De la Mata FJ. Nanosystems as Vehicles for the Delivery of Antimicrobial Peptides (AMPs). Pharmaceutics. 2019 Sep 2; 11(9):448.
36. Bessone CDV, Akhlaghi SP, Tartara LI, Quinteros DA, Loh W, Allemandi DA. Latanoprost-loaded phytantriol cubosomes for the treatment of glaucoma. Eur J Pharm Sci. 2021 May 1; 160:105748.

How to cite this article:
Hasnamol et al. Ijppr.Human, 2024; Vol. 30 (10): 270-279.
Conflict of Interest Statement: All authors have nothing else to disclose.