CUBOSOMES- AN EMERGING PLATFORM FOR DRUG DELIVERY

Avril Mathias* and Monika R.

Department of Pharmaceutics, Nitte College of Pharmaceutical Sciences, (Nitte Deemed to be University) Yelahanka, Bengaluru.

*Corresponding Author: Avril Mathias
Department of Pharmaceutics, Nitte College of Pharmaceutical Sciences, (Nitte Deemed to be University) Yelahanka, Bengaluru.
DOI: https://doi.org/10.5281/zenodo.14252556

ABSTRACT

Due to their unique properties and wide variety of applications, cubosomes—nanoscale cubic liquid crystalline formulations—have garnered a lot of attention recently. Self-assembling cubic phase nanoparticles are created when lipid molecules arrange themselves in a three-dimensional cubic lattice. These self-assembled nanoparticles have a large surface area and excellent stability due to their well-defined cubic lattice structures and amphiphilic surfactant composition. They are appealing choices for gene therapy, drug delivery, and other biological applications due to their special properties, which include their ability to encapsulate molecules that are both hydrophilic and hydrophobic. Presenting a comprehensive overview of the latest advancements in cubosome research, including their structural characterisation, synthesis methods, and functional applications, is the aim of this work. Among the key topics covered are the many methods for creating cubosomes, the manner in which lipid content influences their structural properties, and the mechanisms underlying their drug release profiles. Additionally, it will examine the difficulties and potential paths forward in refining cubosome formulations for enhanced clinical efficacy.

KEYWORDS: Cubosomes, applications, liposomes, nanoparticles, bioactive lipids.

INTRODUCTION

A specific, relevant, and adequate drug delivery system is required for the treatment and cure of any disease involving a medication molecule or product. In order to establish an effective concentration at the site of action, a drug-delivery system (DDS) is a device that distributes a pharmacological substance at a predefined rate at a specified area in the body. Long-term release can lower the requirement for a number of drugs, which can save money and increase patient adherence.[1] The technique of releasing drugs in accordance with a preset schedule in an attempt to optimise

therapeutic advantages and minimise adverse effects is known as controlled drug release, or CR.[2] Biomedical nanotechnology has advanced significantly during the last few decades, converting traditional drug delivery techniques into stimuli-responsive smart drug delivery systems.[3] Through a variety of methods, nanotechnology can increase the therapeutic potency of bioactive chemicals and enable the creation of intricate nano-systems with great selectivity to the target efficacy. Nanoparticles may now hold many molecules at once thanks to developments in nanocarriers.[4] Nanoparticles can generally be categorised according to their size, shape, and composition. However, nanoparticles can also be categorised as either organic or inorganic; the former include dendrimers, liposomes, polymeric nanoparticles, and cubosomes, while the latter include fullerenes, quantum dots, and gold nanoparticles.[5] Nanotechnology has recently drawn interest for improving the oral bioavailability of drugs in their dosage form, especially those that are lipophilic. 'Cubosomes' are nanostructured systems with dimensions between 100 and 500 nm that are created by colloidally dispersing bi-continuous cubic liquid crystalline structures in water with the help of appropriate surfactants.

HISTORY OF CUBOSOMES: Bicontinuous inverse cubic dispersion was originally reported by Larsson et al. in the late 1990s (Longley and McIntosh, 1983; Gustafsson et al., 1997), which paved the way for cubosome history and implementation.[7] Despite early recognition (1980), large-scale manufacturing of cubosomes was challenging due to their complicated phase behavior and viscosity properties. Cubic phases have strong solid-like viscosity due to their bicontinuous structure. Bicontinuous cubic phases are unique liquid crystalline formations that self-assemble from aqueous surfactants. Bicontinuous cubic phase liquid crystals are a novel substance encountered in unexpected places. The cubic liquid crystalline phase was first seen while studying polar lipids like monoolein, which are utilized as food emulsifiers.[2]

Simple amphiphiles can self-assemble into the structures listed below: Lipids form the structural underpinnings of life, such as cell membranes and organelles. Nature contains a wide variety of intricate biological membranes. In reaction to hunger or stress, biomembranes transition from simple bilayers to cubic phases. This liquid cubic phase, which is stabilised by an outer corona composed of polymers because of their inherent instability, is used to form lipid cubosomes.[8] Since they may be loaded with both lipophilic and hydrophilic medications and have the potential for on-demand reversible release, self-assembled lipid-based liquid crystalline nanoparticles [LCNP] with an internal cubic phase structure, also known as cubosomes, have attracted interest as a drug delivery technique. For this reason, they are superior to the more widely utilised liposomes.[9]

Because of their various qualities, cubosomes—bi-continuous cubic phase liquid crystals—are attractive as a generic drug delivery system.[10] Nanotechnology has proven remarkable advantages in the field of diagnosing, images, monitoring, even delivering the drug to target sites.[11]

Cubic phase: Larsson designated these nanoparticles 'cubosomes' due to their cubic molecular crystallographic symmetry and similarities to liposomes.[11] Cubosomes are named after this kind of three-dimensional network of water channels encircled by lipid bilayers because they exhibit cubical crystallography, which is attributed to amphiphilic molecules and a self-assembling surfactant. They were found to be square and spherical in shape after morphological characterisation using cryo-TEM (cryo-TRANSMISSION electron microscopy) and small-angle X-ray scattering (SAAXS) particles with a nanoscale size.[12] X-ray scattering analysis of lipid-water systems with varying concentration and temperature revealed the presence of liquid crystalline formation.[2]

Components: When we come to the structural aspects they contain similar microstructures to liquid crystalline phases, but have a higher surface area and lower viscosity, making them suitable for injectable drug delivery and imaging (9). Cubosomes' tiny pore diameters allow for controlled drug release and help maintain the stability and efficacy of physiologically active molecules like proteins and vitamins.[3]

They have a distinct architecture, making them excellent for controlled release. First, medicines of varying polarity and sizes can be confined in cubic phases. Second, the cubic phase's microstructure influences drug release. Third, cubic mesophases are stable in vitro and can be broken down by lipolysis in vivo. Cubosomes are amphiphilic carrier systems that can transport both hydrophilic and lipophilic drugs. The hydrophilic medication is kept within the vesicle, while the lipophilic drug is disseminated between the hydrophilic domains. The cubic phase's bioadhesive qualities makes it appropriate for delivering drugs to a variety of sites, including the gastrointestinal, lung, nasal, oral, buccal, rectal, and vaginal.

Stabilizers: A periodic, three-dimensional structure with a minimum surface that resembles a "honeycombed" pattern with bi-continuous domains of liquid and fat is formed by the surfactant-phospholipid bilayer. They exhibit eternal stability when seen via a thermodynamic lens. Polymers can be added to Cubosome colloidal dispersions to increase their stability. They also offer the possibility of controlled active delivery, where diffusion is controlled by the active's winding path through the "regular" channel form of the cubic phase.[10] The stabiliser keeps the dispersed particles in a stable condition by acting as an electrical barrier between them, preventing them from making close contact. Choosing the right stabiliser is a crucial step since the impact is produced by the stabilizer's participation in the lipid water assembly without affecting the cubic liquid crystallinity. Pluronics, especially F127 (Poloxamer 407), which were regarded as the "gold standard"[13], are the most commonly utilised stabilising agents.

STRUCTURE

Three cubosome structures have been proposed: Pn3m (Diamond surface), Ia3d (Gyroid surface), and Im3m (Primitive surface).[2] Using cryo-TEM, the cubosomes' internal structure and shape were examined. Based on SAXS results, cubosomes generated at DLGL/PHY of 2% w/w were chosen as representative of Pn$\bar{3}$m cubosomes and cryo-TEM was performed on them. As an example of Im$\bar{3}$m cubosomes, cubosomes generated at DLGL/PHY of 10% w/w with PBS were also chosen. It was confirmed that cubosomes with a cubic phase at a solid ratio of 2% w/w of DLGL/PHY were about 200 nm in size. This observation aligned with SAXS-confirmed particle size and internal structural data. At a solid ratio of 10% w/w with PBS, cubosomes with particle sizes ranging from 100 to 200 nm were verified to exhibit a cubic phase. These results were in line with the internal structure and particle size data that SAXS verified.[14]

FACTORS AFFECTING THE STRUCTURE OF CUBOSOMES

Researchers investigated how temperature and pressure affected the cubic phases in nanoparticles. Salts and buffering agents have an impact on the bilayer membrane's electrostatic behaviour, which in turn influences the diameters of swelling water networks and load release. It has previously been investigated how salts affect the cubic forms in the bulk phases of mixtures that contain monoolein and either DOPG or DOPE. Phase transitions between the Im3m and Pn3m cubic phases resulted from the addition of salt, which changed the phase geometry of charge-bearing cubic phases containing DOPG. The bilayer membrane's hydration may be affected by a number of methods. The most inflated versions are produced by adding phospholipids with charged polar heads.

Electrostatic swelling causes the cubic phases to expand. Despite persistent concerns regarding the rational design of cubosomes, current understanding and characterisation of these structures enable the development of bioengineering platforms modifying cubosomes for a range of biological uses. The oral route is the most popular way to administer all drugs. Numerous medications with large molecular weights and poor solubility can have their bioavailability increased by using cubosomes. There are some examples of cubosomes being used orally to improve their properties. For example, a pharmacokinetic study in beagle dogs found that ibuprofen-loaded cubosomes had better absorption from cubosomes than from regular ibuprofen, with a longer half-life and adequate relative oral bioavailability.[6]

When a drug is administered intravenously, it must be loaded onto an effective carrier, kept in circulation for a long enough period of time, held in the proper locations, and then released to guarantee its efficacy.[3] Because of their ability to change permeability, cubosomes have gained interest as a possible topical delivery mechanism. This has applications in burn therapy, rheumatoid arthritis, post-operative pain management, and ocular administration.[12] With an emphasis on cubosomes' advantages, composition and structure, manufacturing techniques, and drug delivery applications, this study will critically assess the existing research on the subject.

Characterization of cubosomes: DOPE was employed in this system, DOPE/PEG(660)-GMO/water[4], since it is more appropriate for parenteral pharmaceutical applications than cubic phase materials based on unsaturated monoglycerides (uMGs), which are hazardous when administered in vivo at high concentrations.

By using the diffusion coefficient of cubosome particles in Brownian motion, photon correlation spectroscopy can be utilised to study the interaction between light and matter. Second, the vesicular optical birefringence of the refractive index brought on by the surface coating of cubosome materials can be investigated using polarised light microscopy. By splitting cross-polarized light, this technique has been used in the past to find crystals in colloidal systems. Three further approaches are essential in addition to these two cubosome characterisation techniques. These include energy-dispersive X-ray analysis (EDAX), cryo-TEM (cryo TEM), and small-angle X-ray scattering (SAXS). The high-energy X-rays produced by SAXS's electrons are subsequently directed at cubosome samples in a wavelength-independent manner. The distinctive characteristics of the ring are ascertained by converting the diffracted patterns into intensity plots versus a q value. A useful technique for examining the morphology of biological materials, polymeric nanoparticles, and soft matter dispersions is cryo transmission electron microscopy, or cryo-TEM. EDAX is a SEM-based method for quantifying nanoparticles.[15] Atomic force microscopy (AFM), small-angle diffraction of X-rays (SAXD), and cryo transmission electron microscopy (cryo-TEM) are used to assess the internalised properties of crystalline nanoparticles prepared with different lipids and polymeric excipients.[16] Stability analysis: Physical stability can be studied by looking at the morphological and organoleptic properties as a function of time. The drug content and particle size distribution can be evaluated at different intervals to investigate possible variations over time.[17]

Toxicological aspects

Nanotoxicology of colloidal carriers relies on their ability to self-assemble into supramolecular structures. Surfactants are commonly found in high concentrations at membrane contacts. In the recent decade, hazardous consequences of liquid crystals have been thoroughly explored, with efforts mostly focusing on the environmental impact of liquid crystals utilized in many technical domains.[18] It is worth noting that cubosome cytotoxicity is dependent on various parameters, including internal nanostructures, lipid chemistry, and the type of stabilizers used.[4] Toxicity experiments on PHYT and GMO-based cubosomes demonstrate that PHYT-based cubosomes are more harmful than GMO-based

cubosomes. Despite their differing structures, phytantriol and GMO exhibit similar phase changes with increased water content and temperature. Toxicity studies on based cubosomes have revealed that PHYT based cubosomes include more based cubosomes, resulting in the onset of a sustained-release inflammatory response that is not evident in GMO cubosomes.[16] There is evidence that cubosome cytotoxicity and uptake can be influenced by surface architecture and phase shape.[54]

Mechanism of drug release from cubosomes

Generally speaking, the Higuchi-diffusion-controlled kinetic law governs how medicines are released from CBs.[19]

$$Q = [Dm\,Cd\ (2A - Cd)\,t]^{1/2}$$ ……………………………………(Eq1)[19]

Where Q is the number of agents released per unit area of the matrix, Dm is the diffusion coefficient of the agent, Cd is the solubility of agents in the matrix, A is the concentration of agents present in the matrix per unit volume, and t is the time, the equation indicates that the square root of time influences how agents are released from the matrix (19). Cubosomes exhibited faster release rates than bulk cubic phases when comparing release rates from cubic phases and cubosomes. Understanding the underlying release mechanisms is aided by the Korsmeyer-Peppas equation's ability to fit nearly all of the curves in both lipid systems.[20]

Preparation techniques of cubosomes: Depending on the energy sources employed to separate the bulk phases, cubosome manufacturing techniques can be categorised as either top-down or bottom-up. While bottom-up approaches use hydrotropes to lower energy inputs, top-down approaches involve sonication and high-pressure homogenisation.[21\]

Top down technique: This technique requires a significant amount of energy and is most effective when used in bulk with cubic stages. The product is made by combining amphiphilic and lipid surfactants. After being homogenised under high pressure, the aforementioned mixture is sonicated to distribute it across an aqueous media. Liquid crystal nanoparticles are the result of this.[10]

Bottom up technique: Cubosomes can be effectively made using this technique. It is very effective in producing little particles. It takes comparatively little energy to do anything. Cubosomes are produced spontaneously as a result of the emulsification process. The hydrotrope is an essential part of this strategy. Small particles combine to form larger ones during this process. Consequently, they exhibit constancy over an extended duration.[10] Compared to cubosomes produced by top-down sonication, the resultant cubosomes showed decreased vesicle formation and polydispersity. Other advantages of the bottom-up approach over the top-down one include consuming less energy due to the avoidance of time-consuming fragmentation.

The creation of tiny particle cubosomes and the addition of thermolabile components are examples of novel techniques. The production of long-term stable cubosomes and the ability to scale up to industrial batches are brought about by the uniform dispersion of stabilisers used in this process.[15] Five different self-assembly methods have been proposed to create polymer cubosomes: solvent diffusion evaporation mediated self assembly (SDEM), polymerisation induced self assembly (PISA), evaporation induced self assembly (EISA), flash nanoprecipitation, and co-solvent approach.[14]

Preparation methods	Advantages	Disadvantages
Co-solvent method	Most used technique for producing polymer cubosomes.	Makes it possible to manufacture colloids at low weight fractions (0.1–2%).
Flash nanoprecipitation	Mixing an organic solution on a millisecond scale. Promotes consistent precipitating solute nucleation growth.	Requires sophisticated machinery, including mixers for impingement jets (CIJ).
Evaporation-induced self-assembly (EISA)	A quick and easy way to create porous monoliths or films.	Depends on the concentration of crucial micelles.
Solvent-diffusion-evap-oration-mediated self-assembly (SDEMS).	Practical technique for block copolymers with high Tg and molecular weight. BCPs self-assemble without being physically disturbed.	Unregulated solvent exchange rate of diffusion.
Polymerization– induced self assembly (PISA).	Permits the manufacture of colloids at high weight fractions (40 wt%). The polymerisation and self-assembly processes occur simultaneously.	Alcohols are the only solvents available. Limited monomer selection because of solubility problems. High solid content plasticiser need. Poor internal conformation has been revealed by SAXS data.

Approaches for encapsulation of drugs into cubosomes: Approaches to encapsulating different medications. Currently, there are three techniques for encapsulating pharmaceuticals in cubosomes.

Pre-loading: Pre-loading involves incorporating the medicine into a liquid-crystalline gel first, then dispersing it into nanoparticles. Incorporating drugs into LC frameworks can improve encapsulation efficiency and add value to pre-loaded cubosomes.[1]

Post-loading Drugs are adsorbed onto cubosomes that have been previously modelled during post-loading. Using this technique, the post-incorporated particles are heated before the drug is added, creating a sterile cubosome dispersion. The final product of sonication usually contains fewer vesicles.[1]

Hydrotrope loading: Hydrotrope-loading involves putting a medication into cubosomes as they form naturally.[1]

Applications of Cubosomes

In Oral Drug Delivery System

The low oral bioavailability of poorly water-soluble medicines remains one of the most difficult elements of therapeutic development. Cubosomes have lately grabbed the interest of formulation scientists for their prospective use as drug delivery vehicles due to their highly organized, segregated internal architecture, high lipid content, and vast surface area.[22] The cubosome (CUB) is a potential delivery method that can encapsulate both hydrophilic and hydrophobic medicines, increase absorption, and preserve them from degradation.[23] They have garnered particular attention for

their potential to improve the oral delivery of a variety of substances, including large-molecule medicines and poorly soluble pharmaceuticals. Through their entrapment within the mixed micelles generated by cubosome digestion, cubosomes in the gastrointestinal tract (GIT) maintain the medication encapsulated in a solubilized condition. As a result, they increase the medication's oral bioavailability through improved drug absorption. Cubic nanoparticles, on the other hand, were assessed as efficient means of increasing the oral bioavailability of cyclosporine A, a more difficult BCS IV medication with low water solubility and permeability. They were able to boost the oral bioavailability by 178% by using their permeation-enhancing effect.[24,25] By encasing medications in mixed micelles during digestion, cubosomes can maintain their solubility in the gastrointestinal tract. Increased oral bioavailability results from improved drug release and absorption.[26]

Cubosomes could significantly improve drug absorption after oral administration. For example, oral delivery of cubosomes laden with insulin led to a prolonged reduction in blood glucose levels in rats.[27]

Cubosomes encapsulating ovalbumin demonstrated high entrapment ratio and slow release in vitro, indicating its potential as a vaccine delivery mechanism.[28]

Hence cubosomes play a vital role in oral drug delivery systems as it is having a wide area of applications.

In Ocular Drug Delivery System

The delivery of medications to the eye is a promising area for formulation developers. This is owing to the intricate anatomy and physiology of the eye. The most common method of drug administration is topical instillation of formulation into the cul-de-sac of the eye to treat ocular disorders such as conjunctivitis, uveitis, endophthalmitis, glaucoma, and post-operative discomfort.[29] Cubosomes have numerous advantages, making them a promising ocular medication delivery mechanism Nanoparticles with enhanced corneal penetrability, drug protection against chemical and physical deterioration, controlled drug release, biocompatibility, and biodegradability can be made using biodegradable lipids. Furthermore, because of the high ratio of lipid bilayer and the strong electrical repulsive forces, they might exhibit greater physical stability than liposomes.[30]

Cubosomes were chosen as a delivery mechanism for ACZ because they improve drug solubility and penetration in topical eye drops, addressing previously identified issues.[31]

- Glaucoma is a chronic and progressive ocular illness characterized by retinal ganglion cell death and neural tissue degradation. The greatest risk factor for the development of glaucoma is a rise in intraocular pressure (IOP), which causes progressive visual loss and irreversible blindness. Timolol, a non-selective beta-blocker, is a primary therapeutic option for glaucoma. Timolol reduces IOP by inhibiting the generation of aqueous humor by blocking sympathetic nerve terminals in the ciliary epithelium.[32] Latanoprost, a prosta-glandin analogue (derivative of prostaglandin F2α), is used to treat glaucoma by lowering intraocular pressure (IOP) and slowing disease development. Currently, it is the first-line treatment for primary open-angle glaucoma. Latanoprost is an esterified prodrug, which means it must be hydrolyzed to its biologically active form by the cornea's esterase.[32]

- Despite their remarkable efficacy as drug carriers, cubosomes' potential for ocular medication administration has not received much attention. Like the hormone the body's adrenal glands generate, dexamethasone is a lipophilic glucocorticoid steroid. Uveitis is one of the acute and chronic posterior segment eye conditions that this medication

successfully treats.[34] In the presence of stabiliser Poloxamer 407, a cubic crystalline phase of monoolein and water was broken up to create a dexamethasone (DEX) cubosome system.[35]

- It is reasonable to assume that some of the effects of niosomes and cubosomes in vivo are due to the molecular characteristics of their constituent parts rather than just their structural makeup.[36]
- To treat conjunctivitis and corneal ulcers, an in situ hydrogel containing ciprofloxacin-loaded cubic nanoparticles was developed to enhance carrier system retention.[16]

In Parenteral Drug Delivery Systems

Due to problems including inadequate solubility or penetration ability, high first-pass metabolism, or susceptibility to gastrointestinal degradation, the vast majority of oral medicines have restricted bioavailability. Because of the limited absorption, a greater dosage is required to attain the necessary plasma levels and therapeutic efficacy.[1] A successful course of treatment frequently requires long-term maintenance of systemic medication levels within the therapeutically optimal concentration range. This requires a large number of injections, which may cause discomfort and deter patients from complying.[37]

The solubility and bioavailability of drugs are improved when they are integrated into vesicular structures. The cubosomes' small size enables them to firmly attach to the gastrointestinal mucosa and enter intravascular spaces, improving therapeutic absorption.[1] The compatibility of the cubosomal components with blood fluids and commonly administered drugs in comorbid patients should be the primary focus of the early-phase formulation and development of cubosome-based intravenous nanomedicines in the near future.[38]

Therapeutic products frequently employ liposomes and emulsions as intravenous carriers. LCNP structures are ideal for injection or infusion because they can transport proteins, peptides, and other insoluble small molecules.[9]

Cubosomes, in particular, have been shown to enhance adjuvants' immunostimulatory qualities and potentiate them, making them a promising technology for vaccine development. Cubic and hexagonal nanosystems hold great promise. As a method for long-acting surgical pain management, the local anaesthetic bupivacaine hydrochloride was also created as an injectable in-situ gel-forming LLC-based sustained release system.[39] To help IPA patients receive better treatment outcomes, new nanoparticulate formulations are being created. Two extremely tortuous non-intersecting water channels and a twisted lipid bilayer serve as the basic unit of cubosomes, a dispersion of the bicontinuous cubic mesophase.[40]

Advantages of Cubosomes

- Cubic phase's tiny pore size makes it more suitable for control release.[41]
- Method of preparation is simple and It has excellent bio adhesive properties and has skin permeation enhancement.[42]
- For a longer time they are thermodynamically stable.[42]
- They have a declining toxicity profile, greatly enhanced absorption, and excellent pharmacokinetic and pharmacodynamic qualities.[43]
- Have two advantages over other lipid-based systems, including liposomes: the ability to encapsulate a sizable pharmacological payload and to allow for the prolonged release of the bioactive.[44]

- It is an excellent carrier for shielding delicate medications from peptide and protein breakdown caused by enzymes and in vivo. Because of their advantages, which include a high drug payload because of their huge interior surface area, low viscosity, and the capacity to exist at almost any dilution level, cubosomes hold great potential for the development of nano-sized particle systems for topical delivery.[45,46]

- This approach offers drug administration through safer and more effective channels with lower toxicity, such as the topical route.[47]

Disadvantages of Cubosomes

- During the shelf life, the particles may gel irregularly, Owing to modifications in the external surroundings, they possess the capacity to alter their dynamics, or phase shift.[48]

- Loading hydrophilic active chemicals into cubosomes is challenging due to the high water content used to disperse GMO and Poloxamer.[49]

- Cubosomes can reduce medication loading efficiency and cause leakage during preparation, storage, and transportation. In vivo, the main issue is their stability, which functions as a barrier, restricting their utilization.[50]

- Due to its high viscosity, it is not suitable for bulk manufacture.[51]

General Applications

Cubosomes have shown their versatile importance and advantages in various fields of drug delivery system such as mucosal, ocular, transdermal, intravenous, intraperitoneal, intramuscular etc drug delivery system, because of their potential, bioavailability, bio adhesiveness, solubilities profiles, target specificity, efficacy, biocompatibility, tolerance etc characteristics. Few of them are listed below:-

- Dermatological application: GMO-containing cubosomes can effectively distribute medications via mucosal and topical routes due to their bioadhesive qualities on the stratum corneum. Another promising topic such as the application of cubosomes is vaccination using transcutaneous immunization (TCI). Microneedles (MNs) and cubosomes work together to effectively administer vaccines through the skin. The microneedle improves peptide permeability through skin layers and leads to extended retention of peptide cubosomes. Combining microneedle and cubosome techniques effectively delivers antigens to targeted skin cells.[3]

- Anticancer application: Cubosomes, with encapsulation efficiencies ranging from 71 to 103%, have been used in a number of experiments to administer anticancer medications. Consequently, our investigations highlight the potential of cubosomes as a drug delivery system, particularly for anticancer medications.[21] One common anticancer drug that works particularly well against cervical cancer is doxorubicin.[15]

- Antifungal applications: Cubosomes' strong drug-loading capacity allows for successful encapsulation of antifungal medicines in their lipid bilayers. As Clotrimazole is the most widely recommended medication for treating fungal infections, its cubosome formulation resulted in enhanced skin retention and they pass through skin corneocytes via the paracellular pathway, resulting in rapid drug release in the first phase and sustained drug release in the second phase due to their ability to form a depot in the stratum corneum's lipid layer recommended medication for treating fungal infections topically.[52]

- Application in parenteral drug delivery system: Cervin found that injecting somatostatin cubosomes intravenously in rats significantly increased the terminal half-life by over six times compared to the matching somatostatin solution.[28]

● Present use: L'Oreal is now creating cubosome particles for use as pollution absorbents and stabilisers for oil-in-water emulsions in cosmetics.[17]

● Cubosomes have also been investigated for use in agri-food and agriculture, such as food preservation, nutrient delivery, and crop protection. Agrochemicals, including fertilisers, insecticides, and herbicides, can be encapsulated in cubosomes for controlled release and enhanced effectiveness.[53]

● Drug delivery vehicle: These innovative materials are frequently used in drug delivery vehicles. Cubosome particles are being researched for application as pollutant absorbers and stabilisers in oil-in-water emulsions in cosmetics by companies including L'Oreal and Nivea.[42]

CONCLUSION

The work highlights substantial advances and possibilities of cubosomes as a versatile platform for nanotechnology. Their unique cubic phase structure ensures outstanding stability and adaptability making them ideal candidates for a variety of applications in drug delivery, imaging and biosensing. Cubosomes future is bright with continuing development primed to open up new opportunities and advances in a variety of scientific and industrial sectors. Their distinct cubic crystalline structure provides increased stability and controlled release qualities, making them promising candidates for a wide range for medicinal applications. Overall, cubosomes show enormous promise for transforming medicine delivery and and increasing patients outocme.

REFERENCES

1. Abourehab MA, Ansari MJ, Singh A, Hassan A, Abdelgawad MA, Shrivastav P, Abualsoud BM, Amaral LS, Pramanik S. Cubosomes as an emerging platform for drug delivery: A review of the state of the art. Journal of Materials Chemistry B., 2022; 10(15): 2781-819.

2. Bachhav AA, Pingale PL, Upasani CD, Ahire SA. Cubosome: A Novel Vesicular Drug Delivery System. IJPSR, 2024; 15(2): 323-339.

3. Umar H, Wahab HA, Gazzali AM, Tahir H, Ahmad W. Cubosomes: design, development, and tumor-targeted drug delivery applications. Polymers, 2022 Jul 31; 14(15): 3118.

4. Oliveira C, Ferreira CJ, Sousa M, Paris JL, Gaspar R, Silva BF, Teixeira JA, Ferreira-Santos P, Botelho CM. A versatile nanocarrier—cubosomes, characterization, and applications. Nanomaterials, 2022 Jun 29; 12(13): 2224.

5. Huang Y, Chang Z, Xia X, Zhao Z, Zhang X, Huang Z, Wu C, Pan X. Current and evolving knowledge domains of cubosome studies in the new millennium. Journal of Nanoparticle Research, 2023 Sep; 25(9): 176.

6. Salem EM, Dawaba HM, Gad S, Hassan TH. Cubosomes as an oral drug delivery system. Records of Pharmaceutical and Biomedical Sciences, 2023 Jan 1; 7(3): 81-90.

7. Fornasier M, Murgia S. Non-lamellar lipid liquid crystalline nanoparticles: A smart platform for nanomedicine applications. Frontiers in Soft Matter, 2023 Mar 15; 3: 1109508.

8. Grandes Reyes CF, Ha S, Kim KT. Synthesis and applications of polymer cubosomes and hexosomes. Journal of Polymer Science, 2023 Jun 15; 61(12): 1196-213.

9. Garg G, Saraf S, Saraf S. Cubosomes: an overview. Biological and Pharmaceutical Bulletin, 2007; 30(2): 350-3.

10. Rights are reserved by Mukesh A, Shukla K. A Comprehensive Review on Cubosomes.

11. Gupta L, Mittal A, Katrolia A, Raizaday A, Kaushik L, Shukla BK. Cubosomes the pliant honeycombed nano-cargos in drug delivery applications. Nanomedicine Journal, 2024 Apr 1; 11(2).

12. Chandrakala V. Cubosomes: A Boon for Cosmeceuticals And Topical Drug Delivery. Int J Pharm Pharm Sci, 14(11): 13-17.

13. Gaballa SA, El Garhy OH, Abdelkader H. Cubosomes: composition, preparation, and drug delivery applications. Journal of advanced biomedical and pharmaceutical sciences, 2020 Jan 1; 3(1): 1-9.

14. Nagao M, Ranneh AH, Iwao Y, Yamamoto K, Ikeda Y. Preparation of Cubosomes with improved colloidal and structural stability using a Gemini surfactant. Molecular Pharmaceutics, 2023 Sep 19; 20(10): 5066-77.

15. Almoshari Y. Development, therapeutic evaluation and theranostic applications of cubosomes on cancers: An updated review. Pharmaceutics, 2022 Mar 9; 14(3): 600.

16. Kaur SD, Singh G, Singh G, Singhal K, Kant S, Bedi N. Cubosomes as potential nanocarrier for drug delivery: a comprehensive review. Journal of pharmaceutical research international, 2021 Jun 14; 33(31B): 118-35.

17. Bhosale RR, Osmani RA, Harkare BR, Ghodake PP. Cubosomes: the inimitable nanoparticulate drug carriers. Scholars Academic Journal of Pharmacy, 2013; 2(6): 481-6.

18. Tudose A, Celia C, Belu I, Borisova S, Paolino D. Effect of three monoglyceride based cubosomes systems on the viability of human keratinocytes. Farmacia, 2014 Jul 1; 62(4): 777-90.

19. Nath AG, Dubey P, Kumar A, Vaiphei KK, Rosenholm JM, Bansal KK, Gulbake A. Recent Advances in the Use of Cubosomes as Drug Carriers with Special Emphasis on Topical Applications. Journal of Lipids, 2024; 2024(1): 2683466.

20. Kulkarni CV, Vishwapathi VK, Quarshie A, Moinuddin Z, Page J, Kendrekar P, Mashele SS. Self-assembled lipid cubic phase and cubosomes for the delivery of aspirin as a model drug. Langmuir, 2017 Sep 26; 33(38): 9907-15.

21. 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.

22. Ali MA, Kataoka N, Ranneh AH, Iwao Y, Noguchi S, Oka T, Itai S. Enhancing the solubility and oral bioavailability of poorly water-soluble drugs using monoolein cubosomes. Chemical and Pharmaceutical Bulletin, 2017 Jan 1; 65(1): 42-8.

23. Alfagih IM, AlQuadeib B, Aldosari B, Almurshedi A, Badran MM, Eltahir E, Alnakhli KA. Cubosomes Dispersions as Enhanced Indomethacin Oral Delivery Systems: In vitro and Stability Evaluation. Journal of Pharmaceutical Research International, 2021 Apr 20; 33(25A): 24-35.

24. Mohsen AM, Younis MM, Salama A, Darwish AB. Cubosomes as a potential oral drug delivery system for enhancing the hepatoprotective effect of coenzyme. Journal of Pharmaceutical Sciences, 2021 Jul 1; 110(7): 2677-86.

25. Hashem F, Nasr M, Youssif M. Formulation and characterization of cubosomes containing REB for improvement of oral absorption of the drug in human volunteers. Journal of advanced pharmacy research, 2018 Apr 1; 2(2): 95-103.

26. El-Laithy HM, Badawi A, Abdelmalak NS, El-Sayyad N. Cubosomes as oral drug delivery systems: a promising approach for enhancing the release of clopidogrel bisulphate in the intestine. Chemical and Pharmaceutical Bulletin, 2018 Dec 1; 66(12): 1165-73.

27. Yang Z, Tan Y, Chen M, Dian L, Shan Z, Peng X, Wu C. Development of amphotericin B-loaded cubosomes through the SolEmuls technology for enhancing the oral bioavailability. AAPS PharmSciTech, 2012 Dec; 13: 1483-91.

28. Pan X, Han K, Peng X, Yang Z, Qin L, Zhu C, Huang X, Shi X, Dian L, Lu M, Wu C. Nanostructed cubosomes as advanced drug delivery system. Current pharmaceutical design, 2013 Oct 1; 19(35): 6290-7.

29. Ali Z, Sharma PK, Warsi MH. Fabrication and evaluation of ketorolac loaded cubosome for ocular drug delivery. Journal of applied pharmaceutical science, 2016 Sep 26; 6(9): 204-8.

30. 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 Delivery, 2023 Dec 31; 30(1): 2162162.

31. Teba HE, Khalil IA, El Sorogy HM. Novel cubosome based system for ocular delivery of acetazolamide. Drug Delivery, 2021 Jan 1; 28(1): 2177-86.

32. Huang J, Peng T, Li Y, Zhan Z, Zeng Y, Huang Y, Pan X, Wu CY, Wu C. Ocular cubosome drug delivery system for timolol maleate: preparation, characterization, cytotoxicity, ex vivo, and in vivo evaluation. Aaps Pharmscitech, 2017 Nov; 18: 2919-26.

33. Bessone CD, Akhlaghi SP, Tártara LI, Quinteros DA, Loh W, Allemandi DA. Latanoprost-loaded phytantriol cubosomes for the treatment of glaucoma. European journal of pharmaceutical sciences, 2021 May 1; 160: 105748.

34. 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 Aug 30; 396(1-2): 179-87.

35. Gan L, Wang J, Jiang M, Bartlett H, Ouyang D, Eperjesi F, Liu J, Gan Y. Recent advances in topical ophthalmic drug delivery with lipid-based nanocarriers. Drug discovery today, 2013 Mar 1; 18(5-6): 290-7.

36. Achouri D, Alhanout K, Piccerelle P, Andrieu V. Recent advances in ocular drug delivery. Drug development and industrial pharmacy, 2013 Nov 1; 39(11): 1599-617.

37. Rarokar NR, Saoji SD, Raut NA, Taksande JB, Khedekar PB, Dave VS. Nanostructured cubosomes in a thermoresponsive depot system: an alternative approach for the controlled delivery of docetaxel. AAPS pharmscitech, 2016 Apr; 17: 436-45.

38. Varghese R, Salvi S, Sood P, Kulkarni B, Kumar D. Cubosomes in cancer drug delivery: A review. Colloid and Interface Science Communications, 2022 Jan 1; 46: 100561.

39. Chavda VP, Dawre S, Pandya A, Vora LK, Modh DH, Shah V, Dave DJ, Patravale V. Lyotropic liquid crystals for parenteral drug delivery. Journal of Controlled Release, 2022 Sep 1; 349: 533-49.

40. Kazi M, Dehghan MH. Development of inhalable cubosome nanoparticles of Nystatin for effective management of Invasive Pulmonary Aspergillosis. İstanbul Journal of Pharmacy, 2020 Dec 1; 50(3): 224-37.

41. Rarokar NR, Khedekar PB. Cubosomes: a vehicle for delivery of various therapeutic agents. MOJ Toxicol, 2018; 4(1): 19-21.

42. Rao SV, Sravya BN, Padmalatha K. A review on cubosome: The novel drug delivery system. GSC Biological and Pharmaceutical Sciences, 2018; 5(1).

43. Wakaskar RR. General overview of lipid–polymer hybrid nanoparticles, dendrimers, micelles, liposomes, spongosomes and cubosomes. Journal of drug targeting, 2018 Apr 21; 26(4): 311-8.

44. Azhari H, Strauss M, Hook S, Boyd BJ, Rizwan SB. Stabilising cubosomes with Tween 80 as a step towards targeting lipid nanocarriers to the blood–brain barrier. European Journal of Pharmaceutics and Biopharmaceutics, 2016 Jul 1; 104: 148-55.

45. Rashi S, Singh D, Chanchal DK, Singh M, Anand S, Alok S. Cubosomes: a bicontinuous cubic crystalline phase. International Journal of Life Sciences and Review, 2015; 1(10): 291-301.

46. Rajani T, Mahesh G, Reddy BC. Formulation and evaluation of dexamethasone loaded cubosomes. Research Journal of Pharmacy and Technology, 2020; 13(2): 709-14.

47. Victorelli FD, Manni LS, Biffi S, Bortot B, Buzzá HH, Lutz-Bueno V, Handschin S, Calixto G, Murgia S, Chorilli M, Mezzenga R. Potential of curcumin-loaded cubosomes for topical.

48. M Lakshmi N, R Yalavarthi P, C Vadlamudi H, Thanniru J, Yaga G. Cubosomes as targeted drug delivery systems-a biopharmaceutical approach. Current Drug Discovery Technologies, 2014 Sep 1; 11(3): 181-8.

49. Chakorkar SS, Mulla JA. A novel corticosteroid cubosomes–For ocular drug delivery. Indo Am J Pharm Res, 2020; 10: 775-84.

50. Desai TB, Patil SB, Tipugade OB, Malavi SB. Cubosomes: The next generations of drug delivery in nanoparticles form. World Journal of Pharmaceutical Sciences, 2021 Jun 1: 222-31.

51. Shravani Y, Ahad HA, Haranath C,Poojitha B, Rahamathulla S, Rupasree A. Past Decade Work Done On Cubosomes Using Factorial Design: A Fast Track Information for Researchers, Int. J. Life Sci. Pharma Res.; 2021; 11(1): P124-135.

52. 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 Applied Bio Materials, 2024 Apr 13; 7(5): 2677-94.

53. Palma AS, Casadei BR, Lotierzo MC, de Castro RD, Barbosa LR. A short review on the applicability and use of cubosomes as nanocarriers. Biophysical Reviews, 2023 Aug; 15(4): 553-67.

54. Barkate AR, Gadekar DN. Cubosomes: the novel drug delivery system. World J. Pharm. Res, 2020 Jun 14; 9: 1170-85.