Bulletin of Environment, Pharmacology and Life Sciences
Bull. Env. Pharmacol. Life Sci., Vol 15 [9] August 2026. 95-104

Online ISSN 2277-1808
Journal's URL: http://www.bepls.com
CODEN: BEPLAD

REVIEW ARTICLE **OPEN ACCESS**

Cubosomes: A Multipurpose Drug Delivery Carrier

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ABSTRACT

The abstract consists of detailed information regarding cubosomes including its basic introduction, history, structure, classification, components production and its applications. Cubosomes are biocompatible carriers in drug delivery that are nanostructured liquid crystalline particles formed of specific amphiphilic lipids in specific proportions. They have a three-dimensional "honeycomb" shape and are mostly made up of amphiphilic lipids that are disseminated in water with the help of stabilisers. Generally, range in size from 10 to 50 nanometres' in diameter. They resemble square dots that are slightly round. In the X-ray scattering technique, each dot represents the presence of a pore containing aqueous phase cubic phases in a lipid water system. Cryo-Transmission Electron Microscopy (CryoTEM), Small-Angle X-ray Scattering (SAXS), and Particle Size Distribution are some of the methods used to manufacture cubosomes, as well as their characterization methods (PSD). The most prevalent mode of drug transport is transcellular migration, which involves drug transit across cells. Some medications, though, are too polar to pass through the lipoidal cell membrane, and therefore must rely on the paracellular route, which connects the cells. In the future, blood compatibility should be considered early in the development of cubosome-based intravenous nanomedicines. The cubosomes for use in IV drug administration is inventive; nevertheless, those nanocarriers may find rapid usage for the delivery of poorly water-soluble drugs via oral, ocular, and topical routes, giving a cost-effective choice in formulation research.

Keywords: *Cubosomes, Cyro-Transmission, Honeycomb, PSD, Small angle X-ray scattering.*

Received 02.02.2026 Revised 11.07.2026 Accepted 29.07.2026

INTRODUCTION

Cubosomes are biocompatible carriers in drug delivery that are nano - structured liquid crystals particles made up of a specified proportion of amphiphilic lipids. These are honeycombed-like structures made up of curved discontinuous lipid bilayers categorized in 2 internal water channels, which could be created through a variety of bioactive substances including chemical medications, proteins, and peptides [1]. Also, cubosomes are lipid-based nano systems that are analogous to well-known vesicular systems like liposomes and niosomes. Certain amphiphilic lipids such as glyceryl monooleate and phytantriol with an appropriate stabilizer have been frequently used to make cubosomes. They could be used as part of a unique drug delivery system that includes hydrophilic (water loving), lipophilic (lipid loving), and amphiphilic drug molecules. They're frequently employed in a variety of drug delivery applications, including oral, ocular, transdermal, and chemotherapy [2]. With diverse drug-loading techniques, cubosomes have varying interior cubic structure and composition. It has a large interior surface area and cubic crystalline structures, as well as the capacity to encapsulate hydrophobic, hydrophilic, and amphiphilic molecules and biodegradability of lipids., and the ability to target and control the release of bioactive chemicals. Now a days cubosomes are getting more attention to the researchers as they have numerous applications in many fields that can be characterized by different evaluation parameter and comparatively simple method of preparation that will help to improve effectivity of novel drug delivery systems in upcoming days [3].

HISTORY OF CUBOSOMES

Despite its early recognition (in 1980), cubosomes were challenging to mass produce because of their complicated phase behaviour and viscous qualities. The Cubic phases are remarkable in that they have a

strong solid-like quality such as viscosities which are fascinating because of their bicontinuous nature [4] and Hyde [8]. determined the "honeycomb" like structure of cubosomes. To create colloidally or possibly thermodynamically stable particulate dispersions with either a longer lifetime, cubic phases can be broken up and dispersed. When some surfactants are combined with water above a particular concentration, they spontaneously produce cubic phases. [6,7]
Larsson developed the name "cubosomes," which refers to the cubic molecular crystallography and similarities to liposomes. Efforts are being made to develop scalable procedures for producing cubosomes on a big scale. Several anticancer medicines have been effectively encapsulated and described in cubosomes [9].

STRUCTURE OF CUBOSOMES

When dispel in water into submicron particles, cubosomes may be formed from bulk cubic structures, according to Larsson's pioneering research on the subject. The internal structures of the cubosomes are similar to the original cube like structure. Cubosomes have a 3-dimensional "honeycomb" shape and are mostly made up from amphiphilic lipids that are disseminated in aqueous media with help of stabilisers.

Amphiphilic lipids:

Glycerol monooleate:

Glyceryl monooleate is the most often utilised amphiphilic lipid in cubosome preparation, and it is also known as monoolein [10,11]
It is a polar unsaturated monoglyceride with a M.P of 35-37 degrees Celsius, a storage temperature of -20 degrees Celsius, and an HLB value of 3[12] and is generally clear and colourless. Also, it is a man-made mixture of acylglycerol esterified with oleic acid as well as other fatty acids. with monooleate being the primary component that can self-assemble into bicontinuous cubic structures in water [13]. It's commonly used as an emulsifier in the food business, and it's safe, nontoxic, biodegradable, and biocompatible. In 1984 it was originally accepted as a biocompatible encapsulating material [14]

Phytantriol:

Under physiological conditions and temperature, phytantriol (15-tetramethyl-1, 2, 3-hexadecantriol) can form a bicontinuous cubic structure in aqueous mediums. Because of its outstanding chemical stability especially in comparison to monoglycerides due to the lack of an ester group, it has previously piqued the interest of researchers in the biomedical field [15].

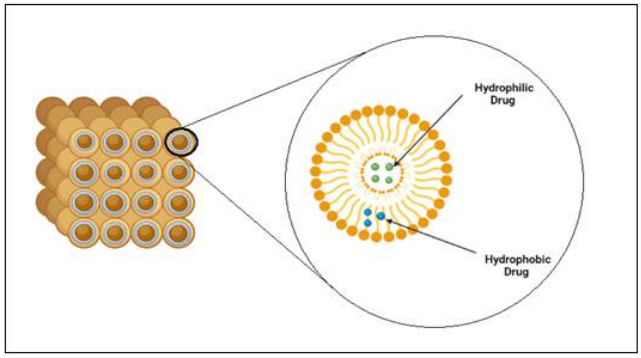

Figure 1: Structure of cubosomes

Component of cubosomes:

Numerous lipids have been used to create cubosomes as well as other liquid cubic phase; for example, a comprehensive overview, see Yaghmur's study [16]. Although the aggregate mesomorphic phase are thermally stable, since distributed, particles are not highly stable as compared to a colloid stability stand point, and they tend to agglomerate owing to the aqueous domains being exposed to the external aqueous environment [17]. The choice of a stabilising or dispersed agent is critical, as it must cooperate in the cubosome while preserving the structure's cubic liquid crystallinity [18]. Larsson's early cubosome research employed bile salts to stabilise dispersions of cubic phase [19]. Hydrophilic and hydrophobic co-polymers are most frequently used stabilizing agents. Pluronic's, in particular F 127, are considered to be the 'gold standard' of Pluronic's [20]. Stabilizing agents are essential in order to avoid aggregation [21]. The stabilizer agent's primary function is to full fill an electrostatic or stearic buffer between particles to avoid close particle [22]. The (D-type) cubic phases dominates in GMO formulations at relatively small concentrations (3%) with reduce regional of the P-type cubic spinel structure. The proportion of the (P-type) cubic crystal increases as the polymer concentration grows [23]. The percentage of F 127 employed in relation to the crystalline forming lipid can influence the formation type of the dispersions [20]. Chong et al. recently evaluated the capacity of a variety of non-ionic molecules to stabilise phytantriol and GMO

dispersions and comparing them to F 127[24]. The interior cubic structure of cubosomes that are based on phytantriol seems to be unchanged by high F127 levels. This is because at low exposure levels to the chemical agent, relatively less polymers are expected to be implicated in the inside cubic configurations of such particles [25]. When comparing the "gold-standard F 127" to the poly (ethylene oxide) stearate family of stabilizer, they identified that (Myrj 59 [100 units of (polyethylene oxide]) was somewhat more successful in stabilising phytantriol cubosomes. The cause of the greater stability is unknown.

Production of cubosomes:

In the presence of high concentration of water, microfludization, ultra-sonication, and homogenized of the thick cubic structure are performed. Although significant progress has been achieved, there is still no agreement on the best approach for producing cubosomes. Stability, biodegradability, and optimum drug release are all issues that have yet to be tackled. Cubosomes have been described in the literature to be made using one of following techniques [27]. When dry chemical precursor is hydrated with a solvent, they form cubosomes [28]. Micro fluidization of a lecithin mixture, followed by high-temperature heat treatment and cooling, yields liquid crystal colloids with a limited size distribution [29]. Using mechanical mixing processes such as homogeneity, dry lipid film of lecithin is created, rehydrated, and then dispersed in extra water and broken into cubosomes [30]. Excess liquid (the fluid of choice) disperses combinations of liquid crystals producing lipid in alcohol or organic solvents (wet substrates), resulting in the spontaneously production of cubosomes [31,32,33,34].

Table 1: Drugs with and without cubosomes are compared

Drug alone	**Drug enclosed in cubosomes**
Low efficacy	More effectiveness
Biodistribution is low	More biodistribution
Critical side-effects(toxicity)	Reduced side-effects.
Healthy tissues is affected	Prevent affecting healthy tissues
Fail to differentiate normal cells from cancer cells	Distinguishes normal cells from cancer cells

PREPARATION OF CUBOSOMES

There are two techniques to cubosome preparation in general 1) top-down 2) bottom-up Both require the use of a suitable stabiliser, such as F127, to prevent cubosome dispersion aggregation. However, biocompatibility, stability and optimal drug release remain the primary goals in selecting the best preparation method [35].

Top-down approach:

The most popular approach for manufacturing cubosomes is top-down approach, and mainly it is divided into two major steps. To begin, to generate bulk viscous cubic aggregates, mix the lipid-forming cubosomes with an appropriate stabiliser. Secondly, high energy is used to disperse the resulting viscous cubic aggregates in aqueous fluids as a such as sonication, resulting in the formation of cubosomes [35]. Preparation of cubosomes using the top-down method, on the other hand, have been found to be stable preventing from aggregation for up to a one year. However, this method has drawbacks in large-scale production because the formation of viscous cubic aggregates requires a more energy input to be dispersed into cubosomes, which may be a problem when temperature-sensitive bioactive agents, particularly peptides and protein, are required.

Bottom-up approach:

The solvent dilution method involves dispersing a combination including cubosomes producing lipid, a stabilizer, and a hydrotrope in amounts of water with low energy input. The bottom-up strategy is based on the addition of hydrotrope to breakdown water-insoluble lipid in order to form lipid precursors hence avoid the development of crystalline liquid at large concentrations [36,37]. A hydrotrope is a compound that may emulsify poorly water - soluble molecules in aqueous conditions by enhancing the dissolution of one solute by mixing another. Ammonia, sodium benzoate and sodium alginate are three of the most often utilised hydrotrope. The creation of a bond between both the hydrotrope as well as the hydrophobic (water hating) substance is involved in the hydrotrope solubilizing process [38,39]. The bottom-up technique outperforms the top-down approach because it requires less energy input and thus can be used safely to prepare cubosomes loaded with temperature-sensitive agents. Furthermore, due to the homogenous dispersion of stabilizing agents onto the surface of the created non-vesicles, the given cubosomes demonstrate long-term stability [40].

Preparation of ALA containing cubosome dispersions.

The first procedure included emulsifying GMO and P407 in water and then ultrasonically separating them. The dispersion is 5 percent glyceryl monooleate in 89 percent water {with 1 percent poloxamer (P407) and

5 percent ethanol}. glyceryl monooleate and poloxamer (P407) were gently melted and combined at 60°C, followed by the addition of an ALA ethanolic solution should be melted. The resulting mixture then was dropped into distilled water that had been prepared to 70-degree Celsius and ultrasonicated for 15 minutes at same temperature at a maximum power of 130 kW. All dispersions were reserved at room temperature i.e. 23°C in light-resisted glass vials.

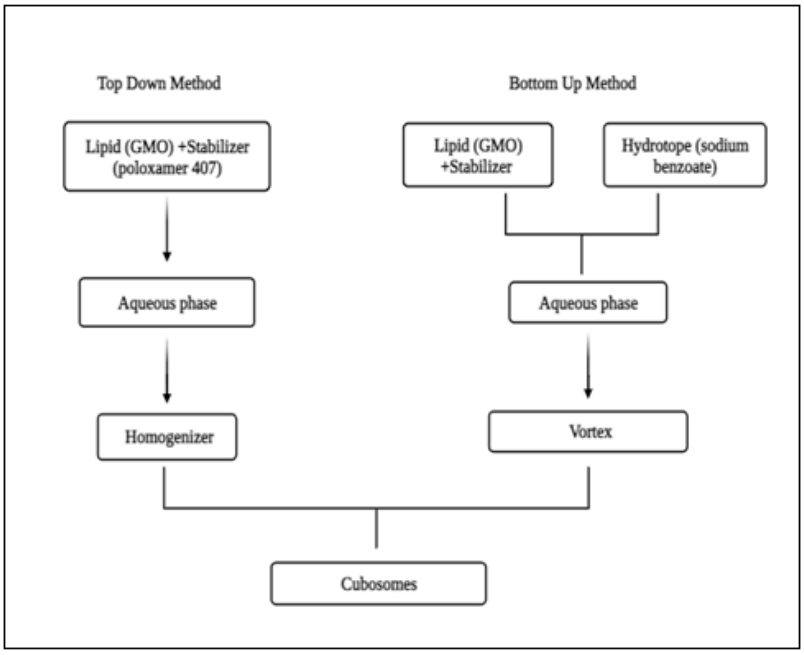

Figure 2: Method of Preparation

By pseudo-Binary Systems [32].

At very first time cubosomes were created utilising the traditional process of bulk cubic gel energy dispersion in a monoolein-water pseudo-binary solution (containing polymer at low levels). To make a homogenous solution, poloxamer 407 (8 percent w/w) is melted then monoolein (92 percent w/w) was mixed with it. The solution of monoolein-polymer was then mixed with demineralized water to make a 1.8 percent monoolein solution that contained 98 percent of water and 0.2 percent Poloxamer 407. To disseminate cubic liquid crystalline gel, the mixture was sonicated for 60 minutes at 25°C in a regulated temperature ultrasonic bath. According to Fourier analysis, the periodicity is 150, that is compatible with small angle X ray scattering for of cubic phases monoolein water. The aggregates' three-dimensional shape, on the other hand, remains a mystery. Stereographic pictures produced at 0 and 15 degrees from normally indicate minor blurring in the matrix of water channels as a result of observing successive layers beneath the top layer. Cryo-TEM indicated predominantly square cubosomes with an edge length of 100-300 nm. Water (light grey dots) and oil (dark grey dots) channels alternate, revealing the unit cell structure (dark matrix). The length of the particle edge, on the other hand, does not alter when it is tilted. This is strange because rotating a cube by angle of 15 degrees should increase its size by 22% in the rotating direction. Although cubic cubosome aggregate has been reported, this shows that the aggregation is more sphere like or generally flat

In the Presence of Hydrotrope [32].

Sonication-based approaches were also used to create cubosomes in the presence of substantial quantities of hydrotrope. A low-viscosity isotropic liquid was created by combining molten monoolein (92.9percent w/w) with ethyl alcohol (7.1 percent w/w) to make a bulk cubic gel. In order to create a viscous, crystalline gel with a cubic structure, a solution of Poloxamer 407 at 1.2 percent was added to the liquid (final composition: 68 percent monoolein, 26.7 percent H_2O, 5 percent ethyl alcohol, with 0.3 percent Poloxamer 407). Then for 5 minutes, the mixture was sonicated. The size and shape of these cubosomes are comparable to those generated without ethanol, except they are more circular than square. There is also a larger patch of cubic crystalline material that is attached to the supporter with an incredibly distinct cubic lattice. Due to the uneven dispersion brought on by the brief entrance of ultrasonic energy, which was macroscopically more opaque, larger cubic gel fragments form (a dispersion generated after 1 hour of sonication). At last, one of the cubosomes borders has a hemispheric vesicle spreading from it. When the cubic liquid crystal gel is split during dispersion, the creation of a vesicular covering on cubosomes have

now reported as a thermodynamic method for preventing the chain lipid hydrocarbons that to be exposed. SAXS tests on ethyl-alcohol containing cubic phase gels validated the generation of cubic liquid crystals in the setting of hydro tropes. Small angle X Ray scattering measures are performed on cubic phase gels containing 2% ethyl alcohol (50 percent monoolein, 48 percent H_2O, and 2% ethyl alcohol), and the results were correlated with this that did not (50 percent monoolein and50 percent water).

TYPES OF CUBOSOMES

Liquid cubosome precursor:

The dilution of hydrotrope has been identified to build better smaller and more stable cubosomes. The nucleation process enables particles to form, which then grow in size as a result of crystallisation or precipitation.

Monoolein is effectively dispersed in a hydrotrope like ethyl alcohol, preventing liquid crystal formation. As a result, diluting this combination leads the cubosomes to crystallise or precipitate spontaneously. Quid precursor approach enables for speedier cubosomes preparation scale-up while eliminating the handling of bulk solids and potentially destructive high-energy activities [42]

Cubosome precursor in powdered form

Dehydrated surfactant coated in polymer makes up powdered cubosome precursors. Relative to liquid phases hydrotropic cubosome precursors, such powders have a number of benefits. Light scattering and cryo-TEM confirmed that the powdered precursor is hydrated formed cubosomes with a 600 nanometre (nm) average size [43]. Cubosomes are lipid-based solids that are waxy and sticky. Water-soluble waxy lipid coating non-cohesive starch inhibits accumulation and regulates particle size in most cases. Spray drying is a wonderful method for his needs.

Drug loading in cubosomes:

As a feasible drug delivery vehicle, enough quantities of comparatively tiny medications, peptide, biologic drugs, or bioactive components must be deposited onto the generated cubosomes. The three basic stages for delivering the cargo include loading into the phospholipids, connecting to the lipid membrane, and localising the drug inside the water pathways in the cubic phase [44].

The drug constituents might be injected into the bilayer film by pouring the pharmaceutical active ingredient to the molten lipid or by injecting the therapeutic agent into the lipid film[45] or preceding dispersion, by freeze drying the latter along the lipid membrane [46,47] The incubation approach[48,49] could potentially be used to load drug moieties after dispersion onto already produced cubosomes, relatively tiny medicines, proteins and peptides are loaded within the lipid bilayer, despite the fact that there are a variety of techniques for doing so. Additionally, single or binary lipid compositions, primarily phytantriol and monoolein, are used to make these cubosomes. Several research [50,51,52] have reported the use of cubosomes for anti-cancer drug delivery. Encapsulation efficiencies range between 71 and 103 %. Despite the fact that drug loading can be calculated in a several ways, “small-angle X-ray scattering” is still the most commonly utilized. As a result, these studies point to cubosomes' potential as a medication delivery mechanism, notably for anti-cancer medicines.

Mechanism of drug transport:

The nature of the carrier's activity and composition, as well as the structure and physiology of the skin, all influence drug transport through the biological membrane. Small ions are transferred without much complexity through hair follicles, epidermal membrane pores, and tight junctions. Intra (trans) and inter (para) cellular transports are both involved in skin membrane transport mechanisms. Drugs can be introduced into the core or as an inherent part of the vesicles by altering transporters [9].

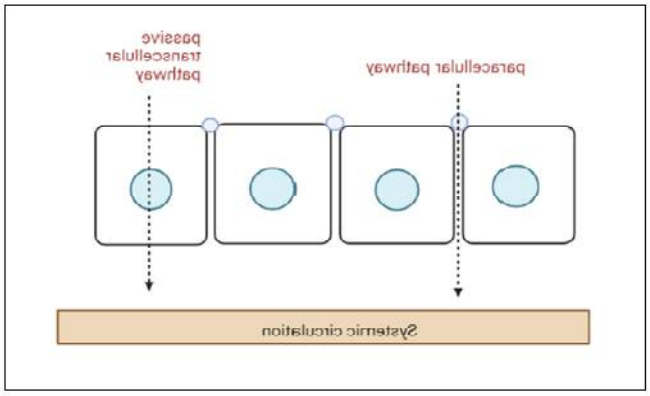

Figure 3: Mechanism of drug transport

The passage of a substance across a membrane by travelling between, rather than between, two cells is known as paracellular diffusion. By definition, this is a passive process that is influenced by pore size as well as the size and form of the xenobiotic. The passage of a drug across a cell is known as transcellular diffusion. The drug is introduced to the enzymes within the cell, as well as any efflux pumps present on the apical area of the membrane, when intestinal absorption proceeds by transcellular diffusion. As a result, the amount of medication that reach the systemic circulation may be reduced. Diffusion between cells can be passive, assisted, or active [53].

The most prevalent mode of drug transport is transcellular migration, which involves drug transit across cells. Some medications, though, are too polar to pass through the lipoidal cell membrane, and therefore must rely on the paracellular route, which connects the cells [53].

CryoTransmission Electron Microscopy (CryoTEM) [55].

It is a microscopic approach in which the stream of electrons is passed by an incredibly thin object in which electrons interaction passing within a specimen creates a picture that is focused and magnified on the device like a fluorescent screen, that is a photographic film layer, that should be detected. Because electrons have such a short wavelength, cryo-TEMs can image at a far better resolution than light microscopes.

Small-Angle X-ray Scattering (SAXS) [55]

SAXS is an approach that detects the elastic scattering of X rays (wavelength-.1-0.2 nm) by a sample with non - uniformity in the nm range at very extreme closeups (generally 0.1- 10°). This angular range comprises data on macromolecule shape and size, partially ordered material characteristic distances, pore diameters, and other data. SAXS can offer structural information on macromolecules with a diameter of 5 to 25 nm, as well as repeat spacing in partially ordered systems up to wavelength of 150 nm.

Particle Size Distribution [56]

Using photon correlation spectroscopy, the particle size distribution of the colloidal was identified. At 250°C, measures of Cubosomes' refractive index (RI) were taken at 100-second intervals. To modify the signal level, samples were diluted with water. The poly dispersity index and average particle size (z-average) were calculated.

Polarized light microscopy:

It can disclose the cubosomes' optically birefringent (potentially vesicular) surface covering as well as identify anisotropic and isotropic substances [57].

Gel permeation chromatography:

Gel permeation chromatography or ultra-filtering techniques can be used to measure the entrapment efficiency and drug loading of cubosomes. The concentration of entrapped drug is determined in the latter procedure, and it is deducted from the total drug added. A UV spectrophotometer or HPLC analysis is used to determine the amount of medication [58].

Table 2: Advantages and disadvantages of Cubosome**s.**

Advantages	Disadvantages
It is non-toxic and biocompatible.	There is less trapping of water-soluble medicines inside cubosomes due to the significant amount of water present.
It has excellent bio adhesive properties	Due to high viscosity large scale production is somewhat difficult.
It has skin permeation enhancement	It has limited stability.
Target specific and control release of bioactive agents	It has complex fabrication.
It is economic	It has limited scalability.

APPLICATIONS OF CUBOSOMES

Topical drug delivery approach:

Cubic phases are mostly extra bioadhesive, that makes them perfect for topical and mucosal medication administration. Crystalline liquid and its nanoparticle technologies are used to produce topical delivery systems because of their distinct characteristics. Topical drug delivery systems are different in as they create bioadhesive liquid crystals systems on the mucosal surfaces, enabling for effective and controlled drug delivery including buccal, ophthalmic, vaginal etc. The technique coats mucosal surfaces with a thin layer of liquid crystal matrix along a nanostructure that may be modified for a specific delivery profile and gives a detailed overview relief for sore and sensitive skin [59].

IV drug delivery approaches:

Nanoparticles of lipids having internal crystalline liquid structures and curved lipid membranes are utilised to liquefy, encapsulate, and distribute drugs to illness areas throughout the body. Although liposomes and emulsions have been employed in medicinal goods as intravenous carriers, liquid crystal nanoparticle

forms have improved the work capacity of proteins, peptides and many tiny molecules, that are less soluble making them excellent transporters for infusion of a wide range of actives [60].

Oral drug delivery:

Cubosomes solve a number of difficulties that afflict oral drug delivery, including low water solubility, low absorption, and huge molecular size. Our liquid crystalline nanoparticles self-emulsifying technology is employed in both liquid and powder capsule form (LCNP). In a different application, comparatively large protein molecules were enclosed in the GIT for local activation. Controlled release can be achieved using liquid crystalline nanoparticle technology carriers. The molecules are engineered to develop at a pre - determined rate in situ, allowing for successful in vivo medicine delivery. Nanoparticles made of liquid crystalline liquid Technological transporters can even be delivered at several sites of absorption, including the lower or upper part of stomach, which is essential for drugs with a small regional window of absorption [61].

Melanoma(cancer)therapy:

Cubosomes were successfully employed as a novel drug delivery method for targeted delivery of chemotherapeutic medicines, with better bioavailability, pharmacokinetics, and safety characteristics of the loaded pharmaceuticals [62]. Cubosomes' unique shape and features are being used to improve the oral bioavailability of medications delivered. Cubosomes improved the oral bioavailability of 20(S) protopanaxadiol (PPD), an anticancer medication with low oral absorption, according to studies. This could be related to the action of cubosomes on the improvement of absorption due to its bio adhesive qualities [63]. When compared to currently available 5-FU formulations, it was also reported that targeted and sustained administration of 5-Fluorouracil to the tumour site not only improves anticancer effectiveness but also reduces side effects [64]. Also, Cubosomes were successfully employed to deliver 5-Fluorouracil (5-FU), a water-soluble medication, to liver tissue selectively.

In cosmetics:

Hair care, skin care, antiperspirants, and other cosmetics have all been made with cubosomes. Alpha-lipoic acid (ALA) is a strong antioxidant fatty acid found in mitochondria. This ALA cubosome dispersion has remarkable effectiveness in reducing facial wrinkles and enhance skin texture and colour [64].

In Nasal route:

Medicines sent directly from the nose to the brain, bypassing the blood-brain barrier (BBB), have proven to be a non-invasive and effective technique of treating central nervous system disorders. Problems with the central nervous system (CNS). PEGylated PEGylated Polyfunctional odorant pectin molecules were found in cubosomes. The use of coumarin as a marker was examined, as well as their relationship. In the brain, absorption was around 3.46-fold higher than in the rest of the body. According to Wu et al., Gly14-human cubosomes were found in untreated cubosomes. (S14G– HN) was also investigated after being introduced into cubosomes for its Alzheimer's disease therapeutic efficacy. The odorranalectin cubosomes were discovered to have the ability toS14G-effects HN's in Alzheimer's disease can be improved. Cubosomes were used to carry resveratrol to brain via nasal route in the treatment of Alzheimer's disease, according to Mayuri Ahirrao et al. GMO P407 cubosomes were created using the probe sonication method. For over 24 hours, in-vitro drug release continued a constant pattern [65].

Table 3: Drugs used in cubosomes

Sr. no	Analyzer	API	Uses	Associate disorder
1	Boyd.	Rifampicin	Bactericidal Antibiotic	Tuberculosis
		Propofol	Hypnotic	Procedural sedation
		Griseofulvin	Antifungal	Skin fungal infection
2	Damani N.	Clindamycin phosphate	Antibiotics	Peritonitis, staphylococcal bone, joint infection
3	Nielsen	Indomethacin	NSAIDS	Gout, rheumatoid arthritis
4	Sadhale	Cefuroxime	Antibiotics	Meningitis, soft tissue and bone infection
		Cefazolin	Antibiotics	Genito-urinary and respiratory tract infection
		Prilocaine	Local Aesthetics	In Dentistry
5	Engstrom	Clomethiazole	Psychotropic	Insomnia
6	Engstrom	Clotrimazole	Antifungal	Oral, vaginal, and skin infection
7	Engstrom	Gramicidin	Topical Steroid	Corticosteroids prone dermatoses
		Insulin	Hypo / Hyper Glycemic	Diabetes mellitus
8	Engstrom	2-amino-1-phenylpropanol HCl	Antidepressant	Mania, depression

CONCLUSION AND FUTURE SCOPE

Cubosome nanoparticles show potential in terms of sustained release and delivery of drug, but also more work is needed, based on the frequency of dosing, route of administration and manner of release of drug, before those nanocarriers may really realise their therapeutic ability in a variety of disorders.[66] Also they are intriguing nano vehicles for booting and delivering peptides and proteins, but the studies that are reported are even now at a fundamental level [65], and various aspects of morphological and structural characteristics of these soft nanocarriers, along with their capacity of loading and release, should be noticed. In the future, blood compatibility should be considered early in the development of cubosome-based intravenous nanomedicines. Furthermore, little is known about their stability in biological fluids and the biological parameters that control, to name a few, drug deliverance from cubosomes, structural alterations brought on by interactions with cell membranes, plasma contact, and infusion-related responses [67]. The cubosomes for use in IV drug administration is inventive; nevertheless, those nanocarriers may find rapid usage for the delivery of poorly water-soluble drugs via oral, ocular, and topical

DECLARTION OF COMPITING INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

ACKNOLEDEGEMENT

The authors wish to acknowledge the help provided by the technical and support staff of GES's Sir Dr. M. S. Gosavi College of Pharmaceutical Education and Research, Nashik.

REFERENCES

1. Karami, Z., & Hamidi, M. (2016). Cubosomes: Remarkable drug delivery potential. Drug Discovery Today, 21(5), 789–801.
2. Gaballa, S. A., El Garhy, O. H., & Abdelkader, H. (2020). Cubosomes: Composition, preparation, and drug delivery applications. Journal of Advanced Biomedical and Pharmaceutical Sciences, 3(1), 1–9.
3. Dhadwal, A., Sharma, D. R., Pandit, V., Ashawat, M. S., & Kumar, P. (2020). Cubosomes: A novel carrier for transdermal drug delivery. Journal of Drug Delivery and Therapeutics, 10(1), 123–130.
4. Scriven, L. E. (1976). Equilibrium bicontinuous structure. Nature, 263(5573), 123–125.
5. Luzzati, V., & Husson, F. (1962). The structure of the liquid-crystalline phases of lipid-water systems. The Journal of Cell Biology, 12(2), 207–219.
6. Luzzati, V., Tardieu, A., Gulik-Krzywicki, T., Rivas, E., & Reiss-Husson, F. (1968). Structure of the cubic phases of lipid-water systems. Nature, 220, 485–488.
7. Larsson, K. (1983). Two cubic phases in monoolein-water system. Nature, 304(5927), 664.
8. Hyde, S. T., & Andersson, S. (1984). A cubic structure consisting of a lipid bilayer forming an infinite periodic minimum surface of the gyroid type in the glycerolmonooleat-water system. Zeitschrift für Kristallographie - Crystalline Materials, 168(1–4), 213–219.
9. Krishnan, R. V. (2013). Tailoring active compounds across biological membranes by cubosomal technology: An updated review. Chinese Pharmaceutical Journal, 22(4), 303–313.
10. Montis, C., Castroflorio, B., Mendozza, M., Salvatore, A., Berti, D., & Baglioni, P. (2015). Magnetocubosomes for the delivery and controlled release of therapeutics. Journal of Colloid and Interface Science, 449, 317–326.
11. Murgia, S., Falchi, A. M., Meli, V., Schillén, K., Lippolis, V., Monduzzi, M., Rosa, A., Schmidt, J., Talmon, Y., Bizzarri, R., & Caltagirone, C. (2015). Cubosome formulations stabilized by a dansyl-conjugated block copolymer for possible nanomedicine applications. Colloids and Surfaces B: Biointerfaces, 129, 87–94.
12. Dumanli, I. (2002). Mechanistic studies to elucidate the role of lipid vehicles on solubility, formulation and bioavailability of poorly soluble compounds [Doctoral dissertation, University of Rhode Island].
13. Kulkarni, C. V., Wachter, W., Iglesias-Salto, G., Engelskirchen, S., & Ahualli, S. (2011). Monoolein: A "magic" lipid? Physical Chemistry Chemical Physics, 13(8), 3004–3021.
14. Milak, S., & Zimmer, A. (2015). Glycerol monooleate liquid crystalline phases used in drug delivery systems. International Journal of Pharmaceutics, 478(2), 569–587.
15. Rizwan, S. B., Hanley, T., Boyd, B. J., Rades, T., & Hook, S. (2009). Liquid crystalline systems of phytantriol and glyceryl monooleate containing a hydrophilic protein: Characterisation, swelling and release kinetics. Journal of Pharmaceutical Sciences, 98(11), 4191–4204.
16. Yaghmur, A., & Glatter, O. (2009). Characterization and potential applications of nanostructured aqueous dispersions. Advances in Colloid and Interface Science, 147, 333–342.
17. Dan, Y., & Poo, M. M. (2004). Spike timing-dependent plasticity of neural circuits. Neuron, 44(1), 23–30.

18. Larsson, K. (1989). Cubic lipid-water phases: Structures and biomembrane aspects. The Journal of Physical Chemistry, 93(21), 7304–7314.
19. Almgren, M. (2003). Alexander lecture 2003: Cubosomes, vesicles, and perforated bilayers in aqueous systems of lipids, polymers, and surfactants. Australian Journal of Chemistry, 56(10), 959–970.
20. Larsson, K. (2000). Aqueous dispersions of cubic lipid-water phases. Current Opinion in Colloid & Interface Science, 5(1–2), 64–69.
21. Nakano, M., Sugita, A., Matsuoka, H., & Handa, T. (2001). Small-angle X-ray scattering and ^13C NMR investigation on the internal structure of "cubosomes." Langmuir, 17(13), 3917–3922.
22. Almgren, M., Edwards, K., & Gustafsson, J. (1996). Cryotransmission electron microscopy of thin vitrified samples. Current Opinion in Colloid & Interface Science, 1(2), 270–278.
23. Gustafsson, J., Ljusberg-Wahren, H., Almgren, M., & Larsson, K. (1997). Submicron particles of reversed lipid phases in water stabilized by a nonionic amphiphilic polymer. Langmuir, 13(26), 6964–6971.
24. Chong, J. Y., Mulet, X., Waddington, L. J., Boyd, B. J., & Drummond, C. J. (2011). Steric stabilisation of self-assembled cubic lyotropic liquid crystalline nanoparticles: High throughput evaluation of triblock polyethylene oxide-polypropylene oxide-polyethylene oxide copolymers. Soft Matter, 7(10), 4768–4777.
25. Dong, Y. D., Larson, I., Hanley, T., & Boyd, B. J. (2006). Bulk and dispersed aqueous phase behavior of phytantriol: Effect of vitamin E acetate and F127 polymer on liquid crystal nanostructure. Langmuir, 22(23), 9512–9518.
26. Gabizon, A., Shmeeda, H., Horowitz, A. T., & Zalipsky, S. (2004). Tumor cell targeting of liposome-entrapped drugs with phospholipid-anchored folic acid-PEG conjugates. Advanced Drug Delivery Reviews, 56(8), 1177–1192.
27. Spicer, P. T., Small, W. B., Lynch, M. L., & Burns, J. L. (2002). Dry powder precursors of cubic liquid crystalline nanoparticles (cubosomes). Journal of Nanoparticle Research, 4, 297–311.
28. Barauskas, J., Johnsson, M., Joabsson, F., & Tiberg, F. (2005). Cubic phase nanoparticles (cubosome): Principles for controlling size, structure, and stability. Langmuir, 21(6), 2569–2577.
29. Wörle, G., Siekmann, B., & Bunjes, H. (2006). Effect of drug loading on the transformation of vesicular into cubic nanoparticles during heat treatment of aqueous monoolein/poloxamer dispersions. European Journal of Pharmaceutics and Biopharmaceutics, 63(2), 128–133.
30. Nakano, M., Teshigawara, T., Sugita, A., Leesajakul, W., Taniguchi, A., Kamo, T., Matsuoka, H., & Handa, T. (2002). Dispersions of liquid crystalline phases of the monoolein/oleic acid/Pluronic F127 system. Langmuir, 18(24), 9283–9288.
31. Rizwan, S. B., Assmus, D., Boehnke, A., Hanley, T., Boyd, B. J., Rades, T., & Hook, S. (2011). Preparation of phytantriol cubosomes by solvent precursor dilution for the delivery of protein vaccines. European Journal of Pharmaceutics and Biopharmaceutics, 79(1), 15–22.
32. Spicer, P. T., Hayden, K. L., Lynch, M. L., Ofori-Boateng, A., & Burns, J. L. (2001). Novel process for producing cubic liquid crystalline nanoparticles (cubosomes). Langmuir, 17(19), 5748–5756.
33. Zheng, L. Q., Um, J. Y., Chung, H., Kwon, I. C., Li, G. Z., & Jeong, S. Y. (2003). Microstructure of dispersed colloidal particles of a bilayer cubic phase. Journal of Dispersion Science and Technology, 24(1), 123–128.
34. Chung, H., Kim, J. S., Um, J. Y., Kwon, I. C., & Jeong, S. Y. (2002). Self-assembled "nanocubicle" as a carrier for peroral insulin delivery. Diabetologia, 45, 448–451.
35. Rizwan, S. B., & Boyd, B. J. (2014). Cubosomes: Structure, preparation and use as an antigen delivery system. In Subunit vaccine delivery (pp. 125–140). Springer.
36. Um, J. Y., Chung, H., Kim, K. S., Kwon, I. C., & Jeong, S. Y. (2003). In vitro cellular interaction and absorption of dispersed cubic particles. International Journal of Pharmaceutics, 253(1–2), 71–80.
37. Mezzenga, R., Meyer, C., Servais, C., Romoscanu, A. I., Sagalowicz, L., & Hayward, R. C. (2005). Shear rheology of lyotropic liquid crystals: A case study. Langmuir, 21(8), 3322–3333.
38. Maheshwari, R. K., Chaturvedi, S. C., & Jain, N. K. (2007). Novel application of hydrotropic solubilization in the analysis of some NSAIDs and their solid dosage forms. Indian Journal of Pharmaceutical Sciences, 69(1), 101–106.
39. Dandekar, D. V., & Gaikar, V. G. (2003). Hydrotropic extraction of curcuminoids from turmeric. Separation Science and Technology, 38(5), 1185–1205.
40. Zakaria, F., Ashari, S. E., Azmi, I. D., & Rahman, M. B. (2022). Recent advances in encapsulation of drug delivery (active substance) in cubosomes for skin diseases. Journal of Drug Delivery Science and Technology, 67, 103097.
41. Luzzati, V., Gulik-Krzywicki, T., Rivas, E., Reiss-Husson, F., & Rand, R. P. (1968). X-ray study of model systems: Structure of the lipid-water phases in correlation with the chemical composition of the lipids. The Journal of General Physiology, 51(5), 37–54.
42. Almeida, J., Edwards, D. C., Brand, C., & Heath, T. (1975). Formation of virosomes from influenza subunits and liposomes. The Lancet, 306(7941), 899–901.
43. Barriga, H. M. G., Holme, M. N., & Stevens, M. M. (2019). Cubosomes: The next generation of smart lipid nanoparticles? Angewandte Chemie International Edition, 58(10), 2958–2978.
44. Elnaggar, Y. S. R., Etman, S. M., Abdelmonsif, D. A., & Abdallah, O. Y. (2015). Novel piperine-loaded Tween-integrated monoolein cubosomes as brain-targeted oral nanomedicine in Alzheimer's disease: Pharmaceutical, biological, and toxicological studies. International Journal of Nanomedicine, 10, 5459–5473.
45. Caltagirone, C., Falchi, A. M., Lampis, S., Lippolis, V., Meli, V., Monduzzi, M., Prodi, L., Schmidt, J., Sgarzi, M., Talmon, Y., & Bizzarri, R. (2014). Cancer-cell-targeted theranostic cubosomes. Langmuir, 30(21), 6228–6236.
46. Aleandri, S., Bandera, D., Mezzenga, R., & Landau, E. M. (2015). Biotinylated cubosomes: A versatile tool for active targeting and codelivery of paclitaxel and a fluorescein-based lipid dye. Langmuir, 31(46), 12770–12776.

47. Simon, K. A., Mosadegh, B., Minn, K. T., Lockett, M. R., Mohammady, M. R., Boucher, D. M., Hall, A. B., Hillier, S. M., Udagawa, T., Eustace, B. K., & Whitesides, G. M. (2016). Metabolic response of lung cancer cells to radiation in a paper-based 3D cell culture system. Biomaterials, 95, 47–59.
48. Alcaraz, N., Liu, Q., Hanssen, E., Johnston, A., & Boyd, B. J. (2018). Clickable cubosomes for antibody-free drug targeting and imaging applications. Bioconjugate Chemistry, 29(1), 149–157.
49. Murgia, S., Bonacchi, S., Falchi, A. M., Lampis, S., Lippolis, V., Meli, V., Monduzzi, M., Prodi, L., Schmidt, J., Talmon, Y., & Caltagirone, C. (2013). Drug-loaded fluorescent cubosomes: Versatile nanoparticles for potential theranostic applications. Langmuir, 29(22), 6673–6679.
50. Meli, V., Caltagirone, C., Falchi, A. M., Hyde, S. T., Lippolis, V., Monduzzi, M., Obiols-Rabasa, M., Rosa, A., Schmidt, J., Talmon, Y., & Murgia, S. (2015). Docetaxel-loaded fluorescent liquid-crystalline nanoparticles for cancer theranostics. Langmuir, 31(35), 9566–9575.
51. Stephenson, J., Celorrio, V., Tiwari, D., Hall, S. R., Green, D. C., & Fermín, D. J. (2018). Photoelectrochemical properties of BiOCl microplatelets. Journal of Electroanalytical Chemistry, 819, 171–177.
52. Bhosale, R. R., Osmani, R. A., Harkare, B. R., & Ghodake, P. P. (2013). Cubosomes: The inimitable nanoparticulate drug carriers. Scholars Academic Journal of Pharmacy, 2(6), 481–486.
53. Rowland, M. (2011). Membranes and distribution. In Clinical pharmacokinetics and pharmacodynamics: Concepts and applications (pp. 73–110).
54. Rizwan, S. B., Dong, Y. D., Boyd, B. J., Rades, T., & Hook, S. (2007). Characterisation of bicontinuous cubic liquid crystalline systems of phytantriol and water using cryo field emission scanning electron microscopy (cryo FESEM). Micron, 38(5), 478–485.
55. Ma, X. Y., & Hao, Q. (2011). Biodegradable methoxy poly (ethylene glycol)-poly(lactide) nanoparticles for controlled delivery of dacarbazine: Preparation, characterization and anticancer activity evaluation. African Journal of Pharmacy and Pharmacology, 5(11), 1369–1377.
56. Pitzalis, P., Monduzzi, M., Krog, N., Larsson, H., Ljusberg-Wahren, H., & Nylander, T. (2000). Characterization of the liquid-crystalline phases in the glycerol monooleate/diglycerol monooleate/water system. Langmuir, 16(15), 6358–6365.
57. Wu, H., Li, J., Zhang, Q., Yan, X., Guo, L., Gao, X., Qiu, M., Jiang, X., Lai, R., & Chen, H. (2012). A novel small Odorranalectin-bearing cubosomes: Preparation, brain delivery and pharmacodynamic study on amyloid-β25–35-treated rats following intranasal administration. European Journal of Pharmaceutics and Biopharmaceutics, 80(2), 368–378.
58. Hundekar, Y. R., Saboji, J. K., Patil, S. M., & Nanjwade, B. K. (2014). Preparation and evaluation of diclofenac sodium cubosomes for percutaneous administration. World Journal of Pharmacy and Pharmaceutical Sciences, 3(1), 523–539.
59. Patni, P., Varghese, D., Balekar, N., & Jain, D. K. (2006). Needle-free insulin drug delivery. Indian Journal of Pharmaceutical Sciences, 68(1), 7.
60. Potphode, V. R., Deshmukh, A. S., & Mahajan, V. R. (2016). Self-micro emulsifying drug delivery system: An approach for enhancement of bioavailability of poorly water-soluble drugs. Asian Journal of Pharmacy and Technology, 6(3), 159–168.
61. Han, S., Shen, J. Q., Gan, Y., Geng, H. M., Zhang, X. X., Zhu, C. L., & Gan, L. (2010). Novel vehicle based on cubosomes for ophthalmic delivery of flurbiprofen with low irritancy and high bioavailability. Acta Pharmacologica Sinica, 31(8), 990–998.
62. Lai, L. F., & Guo, H. X. (2011). Preparation of new 5-fluorouracil-loaded zein nanoparticles for liver targeting. International Journal of Pharmaceutics, 404(1–2), 317–323.
63. Cheng, M. R., Li, Q., Wan, T., He, B., Han, J., Chen, H. X., Yang, F. X., Wang, W., Xu, H. Z., Ye, T., & Zha, B. B. (2012). Galactosylated chitosan/5-fluorouracil nanoparticles inhibit mouse hepatic cancer growth and its side effects. World Journal of Gastroenterology, 18(42), 6076–6084.
64. Divekar, S. R., & Vaidya, V. R. (2019). Cubosomes—An advanced drug delivery system—A. [Journal details not provided in the supplied reference].
65. Angelova, A., Angelov, B., Lesieur, S., Mutafchieva, R., Ollivon, M., Bourgaux, C., Willumeit, R., & Couvreur, P. (2008). Dynamic control of nanofluidic channels in protein drug delivery vehicles. Journal of Drug Delivery Science and Technology, 18(1), 41–45.
66. Angelova, A., Angelov, B., Drechsler, M., Garamus, V. M., & Lesieur, S. (2013). Protein entrapment in PEGylated lipid nanoparticles. International Journal of Pharmaceutics, 454(2), 625–632.
67. Wibroe, P. P., Azmi, I. D., Nilsson, C., Yaghmur, A., & Moghimi, S. M. (2015). Citrem modulates internal nanostructure of glyceryl monooleate dispersions and bypasses complement activation: Towards development of safe tunable intravenous lipid nanocarriers. Nanomedicine: Nanotechnology, Biology and Medicine, 11(8), 1909–1914.

CITATION OF THIS ARTICLE

Pratik S. K, Prashant L. P, Sahebrao S. B, Dattatraya M. S, Sunil V. A. Cubosomes: A Multipurpose Drug Delivery Carrier. Bull. Env. Pharmacol. Life Sci., Vol 15 [9] August 2026. 95-104