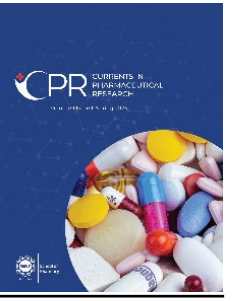
Currents in Pharmaceutical Research (CPR)
Volume 3 Issue 2, Fall 2025
ISSN$_{(P)}$: 3007-3235, ISSN$_{(E)}$: 3007-3243
Homepage: https://journals.umt.edu.pk/index.php/cpr

Article QR



Title:	**Cubosomes in Drug Delivery: Exploring Their Potential for Advanced Therapeutic Applications**
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DOI:	https://doi.org/10.32350/cpr.32.01
History:	Received: January 01, 2025, Revised: February 20, 2025, Accepted: March 15, 2025, Published: April 12, 2025
Citation:	Ali S, Farooq N, Rehman SU, Rehman FU. Cubosomes in drug delivery: exploring their potential for advanced therapeutic applications. *Curr Pharma Res*. 2025;3(2):01–30. https://doi.org/10.32350/cpr.32.01
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Conflict of Interest:	Author(s) declared no conflict of interest

A publication of
The School of Pharmacy
University of Management and Technology, Lahore, Pakistan

Cubosomes in Drug Delivery: Exploring Their Potential for Advanced Therapeutic Applications

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ABSTRACT

Cubosomes have become a subject of increasing significance because of their unique three-dimensional nano cubic lattice structure, which is composed of self-assembling lipid molecules like monoolein. A wide range of therapeutic agents, involving both hydrophilic and hydrophobic drugs, can be encapsulated within this stable and water-dispersible structure. Cubosomes' unique cubic lattice also facilitates surface modifications and lipid content adaptation, improving drug stability and resistance to degradation. This enables precise control over the kinetics of drug release and provides an intriguing framework for the development of controlled drug release systems. As a result, cubosomes can improve therapeutic efficacy while minimizing side effects of drugs molecules. In conclusion, this review explores the potential uses of cubosomes and highlights the specifics that emphasize their significance in improving drug delivery methods.

Keywords: cubosomes, monoolein, nanoparticles, poloxamer 407, targeted drug delivery

1. INTRODUCTION

The discipline of nanomedicine has greatly benefited from the emergence of nanotechnology, which has become a major actor in many areas of research. Its influence on medication distribution is particularly noteworthy. For example, nanotechnology has enabled the development of carriers that increase the potency of drug delivery, improving the overall success rate of therapies [1].

Cubosomes are distinguished by the fact that they are liquid crystals with bicontinuous cubic phase, exhibiting innate qualities that position them as a promising universal medium for transporting various drug

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actives [2]. These nanoparticles, like classic controlled drug delivery methods, use surfactant and polymeric systems, resulting in supramolecular assemblies known as active transport vesicles [3]. The surfactants produce three dimensional bilayers arranged limited surface-forming, periodic, tightly packed structures with bicontinuous lipid and water zones, suggesting a "honeycomb" shape [2]. Cubosomes are typically produced through labor-intensive processes, often involving high-energy input [4]. Initially, they are formed by disrupting the cubic,lipid-water phase inside a three-phase area that includes a dispersion of liposomes. These particles, however, are distinguished from ordinary liposomes by structural differences and their capacity to accept amphiphilic, lipid-soluble, and water-soluble actives [5].

Cubosomes are the particles composed of 2 internal aqueous channels, which are formed by curved bicontinuous lipid bilayers structured in three-dimensional honeycombed patterns. These channels can be effectively utilized for the incorporation of various bioactive ingredients, including peptides, proteins and chemical [6]. Due to their distinctive features such as stable thermodynamics, bio adhesion, the capability to entrap hydrophilic, lipophilic, and amphiphilic substances, as well as they have the capacity for controlling the release utilizing the specific functionalization. Cubosomes are recognized as a promising approach for multiple routes of administration [7]. Cubosomes are specifically liquid-crystalline nanostructured particles composed of various proportions of amphiphilic lipids. They are recognised as biocompatible carriers in medicine delivery. The physical and chemical features of these reversed bicontinuous cubic phases are distinct [8]. The basic structure of cubosomes is represented below Figure 1

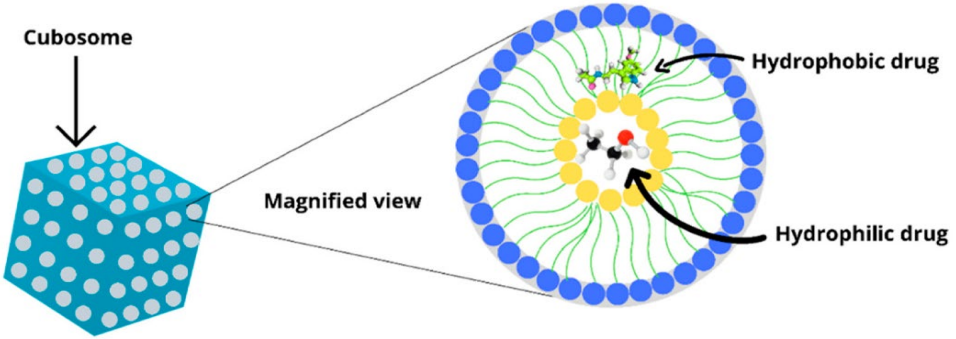

Figure 1. Structure of a Cubosome [9].

This review particularly highlights the fresh prospective of the potential use of cubosomes for targeted therapies, while previous reviews only cover the properties and general uses of cubosomes. It provides data regarding the stability and suitable method of formulation for controlled release mechanism, this prospective has not been explored in depth. This review also provides the list of successful formulations which have shown better results as compared to conventional formulations using top-up, top down and heating method. It also provides an insight of characterization methods including DLS, NMR, photon correlation which provides a very clear understanding to access the physiochemical properties of cubosomes.

1.1.Cubosomes and Their Types

Cubosomes are distinguished from liposomes by their ability to simultaneously retain lipid-soluble, water-soluble, and amphiphilic molecules [10]. Cubosomes are eternal and have thermodynamic stability. When loaded proteins, stabilizers, or the required chemical or medicine are combined with cubosomes, a lipid cubic bi-continous phase is formed by the self-assembly of lipid mixture [11]. Polymers can be used to stabilize cubosome colloidal dispersions. Diffusion is mediated by the tortuous diffusion of actives through the cubic phase's "regular" channel structure, making cubosomes an attractive choice for regulated active delivery. At high concentrations of amphiphiles in aqueous surfactant systems, these structures develop, with enough aligned molecules to be identified geometrically. Differential geometry allows for the distinction between two types of cubosome structures: an open cubosome, in which both water channels are exposed to the outside world, and a closed cubosome, in which only one water channel is present [12].

2. MATERIAL USED IN CUBOSOMES

For the formation of bicontinuous cubic phases the potential demonstration is represented by the natural lipids, nonionic surfactants such as Lynch ML18 and cationic Boretta-M17 [13]. While monoolein monoglyceride is typically utilized to produce bicontinuous cubic phases, other monoglycerides show spontaneous development of such phases when diluted. Monoglycerides are typically insoluble and resistant to the changes in temperature. Monoolein, also called glyceryl monooleate, is the principal precursor for cubosome synthesis. It is a complex made up

primarily of the glycerides of oleic acid and other fatty acids, with the monooleate being the dominating component [14].

2.1. Liquid Cubosome Precursors

To simplify large-scale manufacture of cubosomes, the liquid precursor approach is employed, which minimizes the dangers associated with working with bulk solids and decreases the destructive potential of high-energy operations. This strategy provides a less complicated and more productive way to prepare cubosomes for industrial use [15].

2.2. Cubosome Powdered Precursor

Lipid-made cubosomes have a characteristic waxy, sticky solidity texture. Waxy lipid coating is useful in preventing agglomeration and controlling particle size of water-soluble, non-cohesive starch. Spray drying stands out as a great method for accomplishing this goal [16].

2.3. Amphiphilic Bicontinuous Cubic Phases

Aggregation in various solvents produces morphologies as diverse as cylinders, vesicles (polymersomes), ribbons, spheres, films, tubules, fibers, and multi-geometry nanoparticles. These shapes form when unfavorable segment/solvent interactions are diminished. Bicontinuous mesostructured are an interesting subtype of these structures due to the percolating nature of their 3D phase structure [16]. Despite its notoriety, bicontinuous phase structures often have a constrained stability range. Low molecular weight surfactants and synthetic particles called cubosomes, which include bicontinuous cubic liquid-crystalline nanostructures, have been used to overcome this constraint. These nanostructured entities have the same cubic crystallographic symmetry as the parent phase, but with a much greater surface area and less viscosity thanks to their size and shape

3. PREPARATION OF CUBOSOMES

3.1. The Top Down Method

This approach, which entails two main phases, is by far the most commonly used methodology for manufacturing cubosomes. First, the lipid that forms cubosomes is added with a suitable stabilizer to produce large, viscous cubes. Next, high-energy methods, such as high-pressure homogenization or sonication, are used to disperse the resulting viscous

cubic aggregates in aqueous fluids, which ultimately results in the formation of cubosomes [17].

3.2. Bottom-up Approach

To create cubosomes, a mixture of the lipid, stabilizer, and hydrotrope is diluted in excess water using the solvent dilution method, also known as the bottom-up strategy. The hydrotrope is crucial to this strategy because it dissolves water-insoluble lipids, creates lipid precursors, and stops liquid crystals from forming at high concentrations [18]. Urea, sodium alginate, and sodium benzoate are all examples of hydrotropes that see regular application. The solubilization mechanism involves forming complexes between the hydrotrope and the hydrophobic substance. This technique has a number of advantages as that of the top-down technique, including lower overall energy expenditure. This allows for the creation of cubosomes that can safely house temperature-sensitive substances [19].

3.3. Heat Treatment

Heat treatment stands out as a practical option in this setting. Heat treatment is not, strictly speaking, the only process involved in making Cubosomes; rather, it aids in the transition from disordered vesicles to well-ordered cubic particles [20].

Cubosomes can be produced using a number of dispersion processes, including as sonication, spray drying, high-pressure homogenization, and spontaneous emulsification [21]. Their significant characteristics and advantages, including as a multicompartmental structure, high drug loading capacity, uncomplicated and convenient manufacturing procedures, and the utilization of biodegradable lipids like glycerol monooleate, position them as adaptable carriers for bioactive compounds. To facilitate targeted and controlled release, cubosomes allow for the encapsulation of hydrophilic, hydrophobic, and amphiphilic components [22]. Details about nano cubosomes are presented in Figure 2.

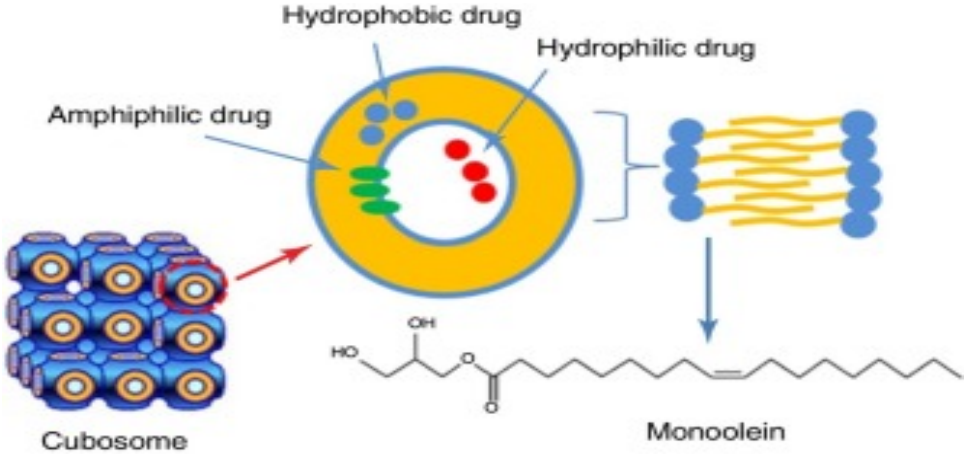

Figure 2. Scheme for Drug Entrapment in Cubosome [7].

3.4. Advantages

Efficient drug distribution is accomplished by using significant amounts of drugs and employing a simple method of preparation. Cubosomes have the capability to encapsulate lipophilic, hydrophilic, and amphiphilic medicines. Lipids have the potential to degrade naturally, this enables the precise and regulated delivery of bioactive substances [23].

3.5. Disadvantages

Cubosomes' high viscosity makes large-scale manufacturing difficult, requiring high-energy processes that can be detrimental to the temperature sensitivity of active components [24].

4. CUBOSOME CHARACTERIZATION

The physicochemical features of drug or gene delivery systems are essential, regardless of the production method used. Parameters such as particle size and structure are particularly important in this regard. Cubosomes are characterized by a variety of methods and can be categorized as following: direct techniques, which identify the phases, and indirect procedures, where measurements help describe the phases [17].

4.1. Methods for Characterization and Evaluation of Cubosomes

4.1.1. Nuclear Magnetic Resonance (NMR). It has the ability to give extensive information on the structure, dynamics, reaction state, and chemical environment of molecules. NMR may be used to identify the

physical and chemical characteristics of atoms and molecules. Pieter Cullis deserves special recognition for his noteworthy and inventive contributions to the field of NMR characterization of biological and synthetic lipidic systems [25, 26]. Rajesh et al. investigated the potential of substituting lipidic poly(2-methyl-2-oxazoline) (PMeOx) for F-127 in cubosome stabilization. The two lipopolymers, PMeOx80-OA: PMeOx40-OA were synthesized and their end-group efficiency evaluated using 1H NMR. These lipopolymers had different levels of polymerization. The 1H-NMR investigation indicated that polymers reflected a remarkably high degree of terminal-group functionalization approximately ≥95 percent, qualifying them for the production of PMeOx equilibrated cubosomes [27].

4.1.2. Photon Correlation Spectroscopy (PCS). The Zeta sizer is mostly utilized in dynamic laser light scattering to ascertain the particle size distributions of cubosomes. Three measurements are made by diluting the sample at a temperature of 25 °C after it has been adjusted to a light scattering intensity of around 300 Hz [28]. The data can be gathered and often displayed by utilizing the mean of volume, size, and weight. Also, the zeta potential and polydispersity index measurements can be verified [29].

4.1.3. Polarized Light Microscopy. Cubosomes' outer layer, which could show optical birefringence and a possible vesicular structure, can be recognized using this technique. Additionally, it is able to distinguish between substances that are anisotropic and isotropic [30].

4.1.4. Small Angle X-ray Scattering (SAXS). This methodology is utilized to ascertain the spatial configurations of distinct groups within the sample. The acquired diffraction patterns are transformed into plots displaying intensity as a function of the q value. These charts make it easier to identify peak positions and convert them into Miller Indices [31].

4.1.5. Transmission Electron Microscopy (TEM). It may be used to see how cubosomes are shaped. According to Kim et al., a technique involves transferring suspensions of cubic phase nanoparticles on negatively stained formvar/carbon-coated grid using freshly made phosphor tungstic acid solution (2%, pH 6.8) using 200 mesh [32]. The samples were then air dried at ambient temp. and microphotographs were employed using an electron microscope. However, SEM analysis for

cubosomes or vesicular systems might not be suitable, as the integrity of the formulation and its robustness may be affected during the procedure when exposed to the electron beam [33].

4.1.6. Pressure via Ultrafiltration Method. The rate of drug release from cubosomes can be measured by applying the pressure through ultrafiltration technique. It nearly adheres to the proposal made by Magenheim et al. Employing an Amicon pressure ultrafiltration cell equipped with a Millipore membrane at the prevailing temperature of 22±2 degrees Celsius [34].

4.1.7. Dynamic Light Scattering (DLS) and Zeta Potential. This is a widely used technique for analyzing the size and movement of particles in colloidal systems. This method is straightforward and does not require any intrusive procedures to analyze particles in a liquid or gas [16]. When a particle solution is exposed to a single-color, synchronized light, the light is dispersed in various directions, resulting in the formation of a mottling. The particles are not stationary in a solution. They show Brownian motion, causing their proximal density to change over time. This procedure is frequently employed to quantify the dimensions of the manufactured cubosomes. A significant limitation of DLS measurements is that the particles which are larger and heavier have a greater impact on the average decomposition rate of a polydisperse solution, usually resulting in an amplification of these huge particles [35]. The dimensions of cubosomes with a honeycombed structure have been quantified for a wide range of diverse systems intended for various purposes, spanning from 10 to 500 nm in diameter [36].

4.1.8. Differential Scanning Calorimetry (DSC). DSC is highly beneficial for investigating the thermotropic properties of various systems because it offers helpful information on transition temperatures and respective transition enthalpies. Liquid crystalline system refers to a state of thermodynamic equilibrium. DSC can be used to determine the endothermic or exothermic energy changes that typically occur during a phase transition. Mansour et al. conducted DSC experiments on dexamethasone-loaded cubosomes to examine how processing parameters and excipients influence the particles' physical stability. The experiments demonstrated that the characteristic dexamethasone's endothermic peak was no longer present in the lyophilized-cubosomes. This indicates that

the dexamethasone was trapped within the cubosomes and existed in an amorphous state [37].

4.1.9. Entrapment Efficiency. Cubosomes do have a lot of potential as drug delivery systems since they efficiently store large amounts of tiny drug molecules, peptides, biologics, or bioactive compounds. Various methods exist for incorporating the medication into cubosomes, all of which have been found to be successful in terms of entrapment-efficiency. The EE and loaded drug in the cubosomes are to be determined by employing chromatographic techniques, ultra-filtration procedures or small-angle X-ray scattering, dialysis [38]. The quantity of free drug can be assessed by using several methods such as UV spectrophotometry, fluorescence, HPLC analysis, Fluorescence Correlation Spectroscopy, or radioactivity. These techniques are employed to obtain a drug release profile, for instance.

4.1.10. Gel Permeation Chromatography. The utilization of ultrafiltration methods and UV spectrophotometer or by using HPLC analysis the entrapment efficiency and drug loaded in cubosomes, might be assessed through the utilization of gel permeation chromatography technique or other ultrafiltration methods. The later procedure involves determining the unentrapped drug concentration, which is then eliminated from the overall amount of drug that was added before. The quantity of drug is determined through the utilization of UV spectrophotometer or HPLC analysis [39].

4.1.11. Stability Studies. The examination of organoleptic and morphological aspects over time allows for the study of the physical stability of cubosomes. This includes assessing particle-size distribution and drug-content at different times to find any possible variations. Essentially, the methods described above can be employed to determine these aspects, including the confirmation of the distinct internal structural trait of cubosomes at various times. This comprehensive approach allows to determine the changes in particle size distribution and drug content over time, providing insights into the potential variations in the formulation's stability [40].

Table 1. Application of Cubosomes Through Different Routes for drug Delivery

Drug	Therapeutic Activity and Route of Administration	Ingredients (polymers and stabilizers)	Results and Conclusion
Fluconazole	Cutaneous candidiasis	Monoolein, poloxamer 407	76.86 percent of the total fluconazole produced from cubosomes was able to pass through a dialysis membrane having a molecular weight cutoff (MWCO) of 12–14 kd. In contrast, a fluconazole solution in phosphate-buffered saline (PBS) with a pH of 6.5 released up to 91.04 percent in just 24 hours. But after a day, cubosomes showed persistent release [40].
Ketorolac	Ocular drug delivery	Glyceryl mono-oleate, poloxamer 407	Ketorolac solution was found to have a high trans corneal penetration of 2.07 folds and a high corneal retention of 2.24 folds when compared to a cubosomal formulation (p<0.01) [40].
Dacarbazine	Melanoma	Poloxamer 407, (5-(3, 3-Dimethyl-1-triazeno) imidazole-4-carboxamide (DTIC)	The medication contained within the cubosomes existed in either an amorphous or molecular state [43].
Colchicine	Transdermal delivery	Glyceryl monooleate, and surfactant (P407)	The evidence in terms of relative bioavailability 4.6 times higher than that of oral COL solution suggests that medication absorption is enhanced as compared to oral COL solution [44].
Curcumin	Topical treatment of cervical cancer	Monooleoyl-*sn*-glycerol, Propylene glycol	The entrapment of curcumin into the cubosomes produced, as evidenced by the in-vitro cytotoxicity assay and cellular-uptake study, results in enhanced cytotoxic impact on the hela cell line [38].
Gliclazide	Oral Antidiabetic	Glyceryl monooleate, poloxamer 407	The bioavailability of gliclazide cubosomal formulation is twice as high as that of conventional gliclazide suspension [45].

Drug	Therapeutic Activity and Route of Administration	Ingredients (polymers and stabilizers)	Results and Conclusion
Resveratrol	Topical Delivery Anti- melanoma activity	Carbopol	RC-Gel exhibited superior drug penetration and deposition within the layers of mouse skin. The non-irritating nature of RC-Gel has been demonstrated on the skin of mice. The in vivo study on local bioavailability demonstrated the promising ability of RC-Gel to localize in the skin [39].
Erythromycin	Topical Delivery-Acne	Glyceryl monooleate Poloxamer 407, Carbopol 934	For treating and preventing acne, erythromycin-loaded cubosomes show promise in applying the medication topically for a prolonged time period in a non-invasive manner [46].
Norfloxacin	Otitis externa	Glyceryl monooleate, Cremophor EL, Pluronic F108/Pluronic F127	A greater quantity of drug was accumulated in the skin of rabbit's ear for the entire 10-hour research period, contrary to the drug suspension [47].
Methotrexate	Topical treatment of rheumatoid arthritis	Poloxamer 188	The mtcs that are generated have a painkilling impact. The paw thicknesses of rats with CFA-induced arthritis, which were inflamed, were measured and found to decrease [48].
5-fluorouracil	Liver targeting	Poloxamer 407	The cubosomal formulation crucially (p<0.05) results in the increase of 5-FU concentration in the liver, reaching a level about five times greater than that obtained with a 5-FU solution, according to the in vivo biodistribution experiments [49].
Paclitaxel	Skin Cancer Xenograft Model	Pluronic F127, 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N	Imaging investigations in vivo demonstrated that PTX-loaded cubosomes accumulated preferentially at the sites of tumors after i.e., injection, the

Drug	Therapeutic Activity and Route of Administration	Ingredients (polymers and stabilizers)	Results and Conclusion
			nanoparticle-based treatment group exhibited a reduction in average tumor size of around 50% when compared to the uninstalled PTX drug group [50].
Doxorubicin (DOX)	Anticancer Glioblastoma T98G cell line	Octyl glucoside detergent	On healthy cells, doxorubicin induces fewer cardiotoxic adverse effects. Thus, the drug can remain in circulation for extended durations, facilitating greater delivery of the drug to the cancer cells [26].
Aspirin	Antipyretic	Pluronic F127 Dimodan (DU)	In contrast to dispersed cubosomes, there was a continuous release from augmented lipid cubic phase, whereas the release in PBS was more effective than in water [51].
Latanoprost	Glaucoma	Phytantriol	The intraocular hypotensive impact was assessed in live subjects. Favorable outcomes as compared to a commercially available latanoprost formulation (0.005% w/v) [44].
Cisplatin-metformin	Colorectal cancer	Glyceryl-monooleate, polyvinyl-alcohol, Pluronic-F127	The cytotoxic effect of nano-cubosomal formulations was shown to be superior to that of unformulated cisplatin. Significant cytotoxicity was seen when metformin which is an indirect mTOR inhibitor, was introduced to cisplatin nano-cubosomes, Cells were made more apoptotic by blocking several pathways [52].
Etodolac	Transdermal	Poloxamer 407, monoolein	The pharmacokinetic study carried out on human subjects revealed that the etodolac-loaded cubosomes that were selected resulted in a

Drug	Therapeutic Activity and Route of Administration	Ingredients (polymers and stabilizers)	Results and Conclusion
			noteworthy 266.11 percent increase in etodolac's bioavailability when compared to oral capsules [53].
Flurbiprofen	Ophthalmic delivery	Glyceryl monooleate, Poloxamer 407	Histological analysis demonstrated that the cornea's structure and integrity remained unaffected following incubation with FB cubosomes. The area under the curveof FB, when administered as FB cubosome F2, was 486.36±38.93 ng·ml−1·min·μg−1. This value was much higher ($P<0.01$) than the AUC of FB Na eye drops. In contrast to FB Na eye drops, FB cubosome F2 exhibited a 1.6-fold increase in Tmax and a considerably longer MRT ($p<0.001$) [54].
Coq10 enzyme	Antioxidant	Poloxamer 407, glyceryl monooleate	An in-vivo study shown that coq10 cubosomes had an enhanced hepatoprotective impact by reducing liver enzymes, nitric oxide, and malondialdehyde levels, while simultaneously increasing phosphoinositide 3-kinase, catalase, and glutathione peroxidase activities [55].
Paliperidone Palmitate	Nasal-to-Brain Delivery for Schizophrenia	Dextran Kolliphor P407	The drug loading of this formulation was 70%, and it had an encapsulation efficiency of 99.7 ± 0.1%. ,the introduction of powder into a nasal cast created via 3D printing, approximately 51.47 ± 9.30% of the injected-powder was found in the olfactory region of right nostril, although in the left nostril 41.20 ± 4.59% was found determined [56].
Bedaquiline	Non-small cell lung cancer (NSCLC)	Glycerol Monooleate Poloxamer 188	The BQLC demonstrated improved cellular uptake and toxicity, with an approximately three-fold decrease in IC50 in contrast to free BQ, when

Drug	Therapeutic Activity and Route of Administration	Ingredients (polymers and stabilizers)	Results and Conclusion
			tested on NSCLC (A549) cells after 48 hours of treatment. In vitro, the BQLC hindered cell proliferation by activating the apoptotic pathway, additionally impeding colony formation and the spread of cancer. Furthermore, investigations using 3D-tumor modeling have demonstrated the superior effectiveness of cubosomal nanocarriers in treating cancer compared to free BQ [57].
Doxorubicin	Chemo and Internal Radiotherapy for Cancers	Monoolein	The cubosomes, which included both doxorubicin and the radionuclide complex, exhibited enhanced cytotoxicity as determined by the vitality of the treated hela cells. This impact was greater than that observed with cubosomes containing either one of the drugs, either DOX DOTAGA-OA or DOTAGA-OA-177Lu complex [58].
Amphotericin B	Chronic fungal infections.	Phytantriol	The HPLC assay revealed the encapsulation effectiveness, while UV spectroscopy and investigations of stability in (simulated) gastric secretions provided further confirmation that amb was successfully contained in cubosomes [59].
Simvastatin	MDA-MB-231 Breast Cancer Cell Line Orodispersible Anticancer Activity	Glyceryl monooleate, Pluronic F127 (PF-127)	Cubosomes formula F3 exhibited a significant reduction in MDA cell viability at dosages of 25 and 50 µg/ml, as compared to the dose of 12.5 µg/ml. SIM suspension and the drug-free cubosomes both untreated and at all doses, did not have a significant impact on MDA cell viability in contrast to the control [60].
Diclofenac sodium	Percutaneous administration	Poloxamer 407	A more advanced formulation of diclofenac-sodium with greater permeability may be beneficial for

Drug	Therapeutic Activity and Route of Administration	Ingredients (polymers and stabilizers)	Results and Conclusion
			managing pain and inflammation. The topical use of diclofenac-sodium mitigates the adverse effects associated with systemic distribution [61].
Beclomethasone Dipropionate	Trans corneal Uveitis	Poloxamer 407, solulan C24	Parameters related to the penetration of substances through the cornea. The Papp (permeability coefficient), flux, and AUC0-10h (area under the curve from 0 to 10 hours) were significantly increased by 4, 5.8, and 5.5-fold correspondingly, in contrast to the control formulation of BDP-suspension [62].
Dapsone	Topical	Glyceryl monooleate, poloxamer 407	The transdermal flow of dapsone, when encapsulated in cubic shaped lipid structures, was found to be the highest in contrast to the marketed formulation and dapsone-PBS [63].
Natamycin (NT)	*In situ* gel loaded with natamycin for ocular fungal diseases	Phytantriol	The ideal formulation significantly increases ex-vivo penetration of the drug by a factor of 3.3 in contrast to a commercial formulation and by a factor of 5.2 in contrast to the NT suspension [64].
Granisetron	In Situ Gel for Improved Management of Chemotherapy-Induced Emesis	Poloxamer 407	This formulation demonstrated safety and biocompatibility upon application on nasal mucosa. In contrast to a solution-medication , the nose-to-brain passage increased the amount of drug that was available for use by the body and improved its distribution in the brain [65].
Donepezil HCl	In situ nasal gel- controlled delivery to the brain	Glycerol mono-oleate Poloxamer 407	Comparatively, the trans nasal penetration of this substance was notably elevated, resulting in improved distribution to the brain, in contrast to the drug solution [66].

Drug	Therapeutic Activity and Route of Administration	Ingredients (polymers and stabilizers)	Results and Conclusion
Lamotrigine	In situ gelling system for intranasal delivery Antiepileptic- efficacy	Poloxamer 407	LTG cubogel and LTG cubosomes were found to have greater antiepileptic effectiveness in rats with pilocarpine-induced epilepsy in contrast to the free drug in in vivo studies. The activity of LTG cubogel was superior to that of LTG cubosomes [67].
Sildenafil citrate	Vaginal sponges for uterine targeting	Glyceryl monooleate, poloxamer 407	The pharmacokinetic analysis revealed that oral delivery shows larger AUC0–∞ and Cmax compared to intravaginal dosage forms [68].
Voriconazole	In-Situ Gel for Ocular Fungal Infection	Hyaluronic Acid-Poloxamer	The antifungal activity of the VZ-Cub-loaded in situ gel formulation was determined by assessing the inhibition zones of the fungal growth. The results revealed that the formulation showed 3.89-fold better antifungal activity compared to the VZ dispersion [69].
Atorvastatin-loaded eugenol	In-situ gel for the intra-pocket treatment of periodontitis as PEGylated cubosomes	Glyceryl monooleate Kolliphor, Poloxamer 407	The clinical assessment of the ISG demonstrated a significant decrease in probing depths, bleeding index, plaque index and gingival levels of transforming growth factor–β1 [70].
Sumatriptan succinate	In situ nasal gel for migraine	Glycerol monooleate	The sumatriptan succinate concentration in the brain was substantially greater when administered using this situ nasal gel in contrast to an intravenous solution [71].
Silver sulfadiazine	Topical For burns	Monoolein Poloxamer 407	The in vivo histopathology investigation shows that the manufactured cubogels have effectively treated deep second degree burns, leading to improved patient adherence and excellent healing outcomes [72].

Hyalcubosomes and cubosomes containing tenoxicam were developed by Elakkad et al. Cubosomes formulation and hyalcubosomes formulation were both put through a stability analysis, which compared their particle size, EE and zeta-potential before or after being stored for 3 months at 4 °C ± 1 [41]. Based on the results of this investigation, we can say that storing the manufactured vesicles in airtight amber glass containers at 4 °C has no ill effects on particle size and PDI but does have an effect on zeta potential and entrapment efficiency percentage. Phytantriol cubosomes loaded with Latanoprost were also produced by Bessone et al. for the treatment of glaucoma. Amber glass vials containing the processed samples were kept for 30 days in a thermostatically regulated humid chamber (25 degrees Celsius). Thus, the stability investigations showed that the latanoprost concentration in the cubosomes and the physicochemical parameters were stable for a full month [42].

5. APPLICATION OF CUBOSOMES

5.1. Controlled Release of Drugs

The predominant application of cubosomes lies in the controlled release of solubilized substances. The cubic phase is particularly well-suited for controlled release due to its diminutive pore size (5-10nm), capability to solubilize hydrophilic, hydrophobic, and amphiphilic molecules, as well as its biodegradability through an enzymatic processes [73].

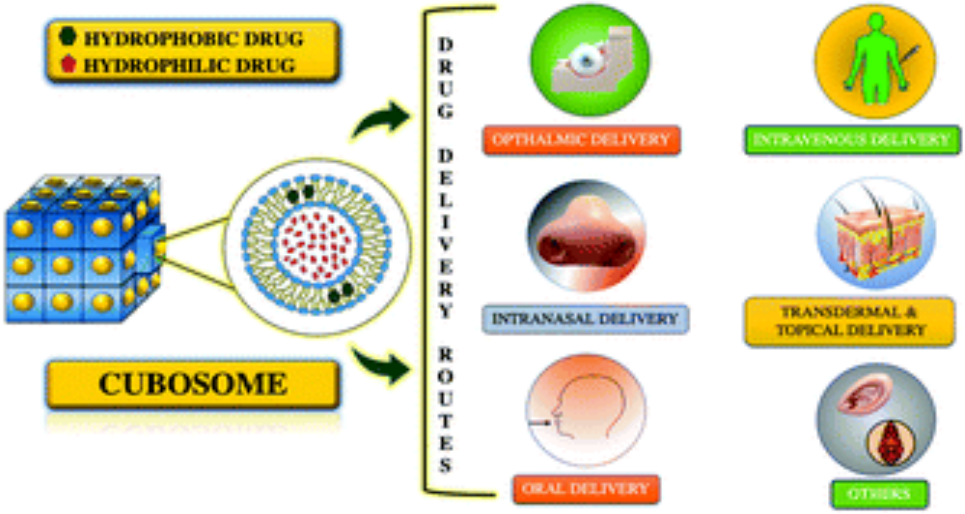

Figure 3. Graphical Representation of Cubosomes Application [74]

5.2. Cancer Therapy

Recently, several anticancer drugs have been effectively enclosed within cubosomes and subjected to thorough physicochemical characterization. The unique approach shows promising nanocarrier formation and indicates its potential application in the realm of cancer therapy. (Figure 3)

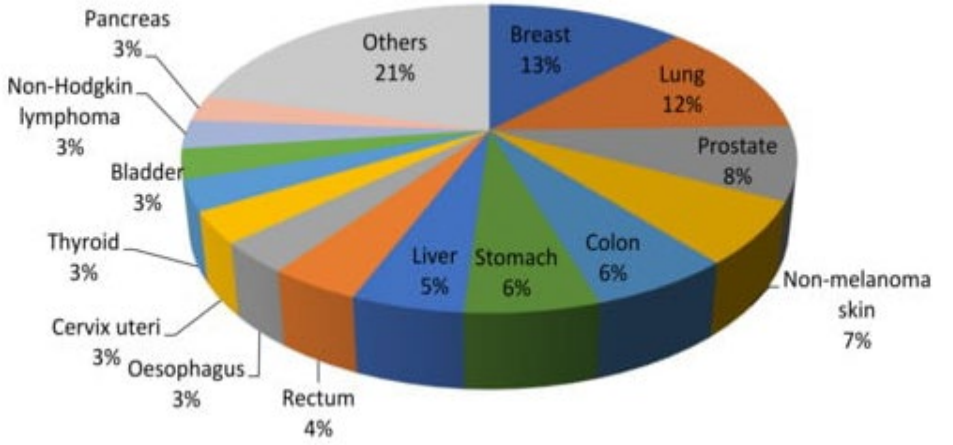

Figure 4. Worldwide Distribution of the Estimated New Cases of Cancer in 2020 [75]

5.3. Oral Drug Delivery

Cubosomes present a viable solution to the multifaceted challenges with respect to oral delivery of with a list of potential drugs, like poor aqueous solubility, inadequate absorption, and considerable molecular size [76]. These entities, available in liquid and powder forms both within capsule products, embody self-emulsifying liquid crystalline nanoparticles (LCNP)technology [77]. An alternative application involves the encapsulation of large proteins for localized gastrointestinal tract function. LCNP technology carriers can be strategically released at distinct sites of absorption, such as the upper or lower intestine, a critical consideration for the drugs with narrow absorption windows (NAW) [78].

5.4. Intravenous Drug Delivery Systems

Lipid based nanoparticles, which consist of curved lipid membranes with internal liquid crystal formations, used to dissolve, encapsulate, and

transport drugs to specific illness sites inside the body [79]. Emulsions and liposomes have been used as carriers for drug products administered intravenously. However, liquid crystal nanoparticle structures have shown to enhance the amount of peptides, proteins, and insoluble small molecules that can be delivered, making them optimal carriers for injection or infusion of various active substances [80].

5.5. Vaccines

Cubosomes have the potential to encapsulate antigens and/or adjuvants and then be transported to the desired location. An early example suggests that cubosomes have the potential to be utilized for protein-based vaccinations. The solvent precursor dilution approach was used to generate cubosomes containing monoolein and phytantriol [81]. The stratum corneum layer of skin can be a significant obstacle to this approach. Microneedles loaded with antigen and adjuvant were used to photograph skin penetration in piglets in vitro and in mice in vivo in one study [4].

5.6. Transdermal Drug Delivery

Lipid-based colloidal systems can facilitate the fluidization of epidermal lipids, hence promoting the enhanced penetration of molecules. Cubosomes have the ability to serve as a viable carrier for the delivery and transportation of pharmaceuticals over the skin [82].

6. CONCLUSION

This review highlights the importance of cubosomes as a drug delivery system for various routes. Their unique self-assembled structures make them favorable for the encapsulation of both hydrophilic and hydrophobic drugs leading to enhanced stability and better controlled release properties. These properties are crucial for improving the therapeutic efficacy and minimizing side effects. This review also provides an in-depth sight of the method of formulation and characterization including NMR, PCS, and DLS which is essential to determine the physiochemical properties of cubosomes for optimal drug delivery. However, ongoing research into innovative materials and alternative methods continuous to make progress in overcoming the barriers, leading to enhanced feasibility of cubosomes technology for clinical applications. Cubosomes are the major advancement in nanomedicine, they have an immense potential to revolutionize drug delivery systems. Continued research into their

preparation, characterization, and applications will be having significant improvements in targeted therapies, paving the way for better therapeutic outcomes across various diseases.

CONFLICT OF INTEREST

The authors of the manuscript have no financial or non-financial conflict of interest in the subject matter or materials discussed in this manuscript.

DATA AVAILABILITY STATEMENT

This is a review article. No data was generated or analyzed. All the findings in this review are based on already published data which has been appropriately cited.

FUNDING DETAILS

No funding has been received for this work.

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