Cubosome An Overview

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ABSTRACT:
The purpose of the review article comprises manufacturing processes, systems for generating cubic phases, mechanisms, and cumbersome applications. In comparison to solid nanoparticles, cubosomes are self-assembled liquid crystalline particles of a specific surfactant with the right amount of water, and they have a microstructure that confers certain features of practical significance. The tale of the discovery of cubosomes is distinctive and involves aspects of biological membranes, differential geometry, food science, and digestive processesThey exhibitdifferent internal cubic structures and compositions with different drug-loading modalities. Overall, cubosome have great potential in drug nanoformulations for melanoma therapyowing to their potential advantages, including high drug payloads due to high internal surfacearea and cubic crystalline structures, relatively simple preparation method, th e biodegradability of lipids, the ability to encapsulate hydrophobic, hydrophilic and amphiphilic substances, targeting and controlled release of bioactive agents.

Keywords: Cubosomes, Cubic Phase, Mono-olein, nanoparticles, bicontinuous, bilayer,periodontal

INTRODUCTION:
A current trend in nanomedicine and drug delivery is to improve the specificity of the treatmentto in turn improve efficacy and avoid side effects. Nanoparticles have played a large role in this trend as they can accumulate in target tissues either passively [via the so-called Enhanced Permeation and Retention effect[1]] or actively using surface conjugated targeting ligands[2]. Self-assembled lipid-based liquid crystalline nanoparticles [LCNP] possessing an internal cubic phase structure, known as cubosomes, have been gathering attention as a drug delivery system as they can be loaded with both lipophilic and hydrophilic drugs and they have the potential for on-demand reversible release which offers advantages over more commonly used liposomes[3-6]. Amphiphilic lipids such as phytantriol and glycerol monooleate [GMO] can self-assemble in excess water to form thermodynamically stable liquidcrystalline phases such as the bicontinuous cubic phase [7, 8]. Cubosomes can then be formedby the dispersion of the ‗bulk' cubic liquid crystalline phase, usually with the aid of a polymer stabilizer, such as Pluronic F127 or F108. The internal structure of the particles, and approaches to modification for drug delivery or imaging capabilities by incorporation of other agents such as lipids, phospholipids, or metallic nanoparticles have been well studied [9-11], as influence the stabilizer [8]. The cubosomes often have the same microstructureas the bulk liquid crystalline phases but have a larger surface area and are much less viscous, enabling their potential deployment as injectable drug delivery or imaging systems [12-14]. The internal structure of the cubic phase particles makes them particularly interesting as MRI contrast agents, as the bound water behaves very differently to bulk water, providing a boost in relaxivity [15, 16]. The use of cubosomes as contrast agent enhancers was recently reviewed[17]. Active targeting of drug carriers is a challenge, with the most common approach involving the use of antibodies or ligands for a specific cell surface receptor. In cancer therapy, an antibody or folic acid group targeting a receptor overexpressed by the diseased cells is often conjugated to the surface of the carrier particle. Potential drawbacks of these approaches include being expensive, having poor stability, lack of specificity if the target receptor is common or can mutate in the target cells, competition with other ligands, and poor pharmacokinetic consequences for the particle after injection[18-20]. Metabolic labeling is gaining popularity as an approach to enable covalent attachments of probes' to cell surfaces. A cellular substrate [commonly a monosaccharide] is modified to contain a target functional group such as an azide. The modification needs to be small and inert to not interfere with or be recognized by the cell's natural metabolic pathway. The functionalized sugar is then processed like a natural monosaccharide and is expressed in surface glycoproteins which results in the target functional group being present at the cell surface. Following this surface expression, the functional group on the non-natural sugar can then be targeted by a probe molecule that contains the complementary functional group using biorthogonal chemical approaches. Bioorthogonal chemistry is defined as any chemical reaction that does not interfere with the native processes in a living system[21-31]. The benefits of bioorthogonal chemistry as an active targeting technique over other approachesare better stability, the materials are expectedly cheaper to synthesize than antibodies and the process is not reliant on overexpression of natural receptors to target non-functionalized cell populations [26, 30, 32]. Copper-

free click chemistry is one class of reaction that is particularly useful in combination with metabolic labeling. The azide group expressed on thecell surface will react rapidly with strained cyclooctynes under physiological conditions, withone of the more commonly used strained cyclooctyne systems being the dibenzocyclooctyne [DBCO]. The target group and the probe react covalently to form a triazole and the cell surface can thereby be imaged or targeted. Using this approach, imaging biological processes associated with sugars in cells and live animals, such as zebrafish, has been achieved [33- 38]. Early studies focussed on glycans such as sialic acid that can be incorporated into the cells natural metabolic machinery of cells, however, the field has expanded to DNA [39, 40] and protein [41, 42] labeling. Recently, nanoparticles have begun to be used as probes as opposed to simple dyes and imaging agents. Chitosan nanoparticles and liposomes have been covalently reacted to tumors that had metabolized azide-bearing sugars [43, 44].

Fig. 1. Different types of Cubosomes

Cubosomes are a novel colloidal dispersion with a bicontinuous cubic phase in water, which surfactants have stabilized to produce a unique, nanoscale, structured system. They aretypically between 10 and 300 nm in size and are primarily employed to transport various chemical compounds in living and non-living matter [45,46].

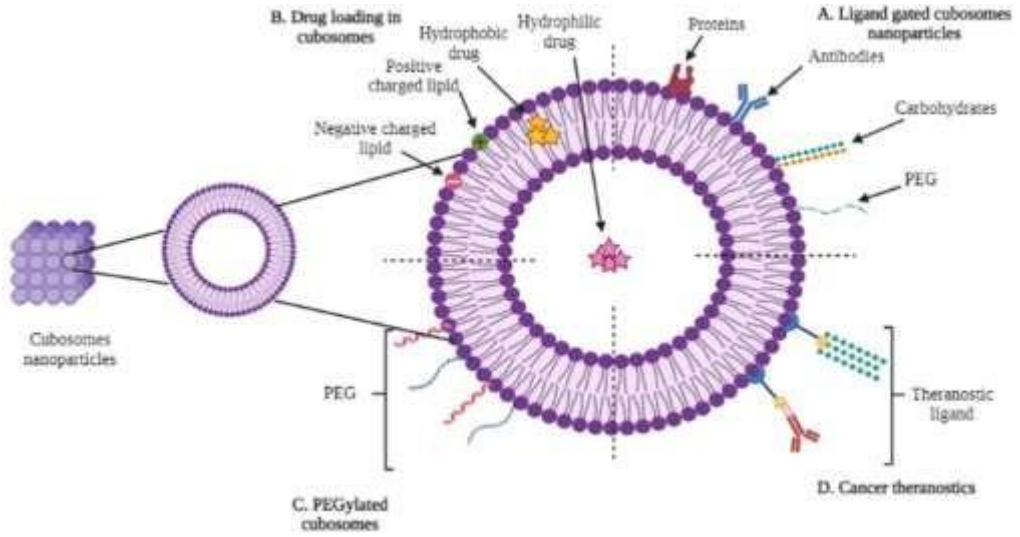

Fig.2.Structure of Cubosomes

In addition to their othernanoparticle properties, these cubosomes are unique in their ability to encapsulate lipophilic, hydrophilic, and amphiphilic molecules within their cubosome structure [47]. Figure 3 shows a cryogenic transmission electron microscopy (cryo-TEM) picture of a cubosome. Cubosomes, are more stable than liposomes and have a far greater potential to encapsulate hydrophobic molecules because of their liquid-crystalline membrane structure [48]. In addition to chemical compounds, cubosomes may also be utilized to transfer various proteins into biological systems, known as proteocubosomes. Peptides and nucleic acids can be delivered with expected loading and release [49]. Among cubosomes many benefits are the capacity to transport several proteins through the water channel of proteocubosomes, ensuring the stability and delivery of molecules to their intended biological targets without degradation by enzymes [50].

There are several benefits to using cubosomes over conventional cubic–phase drug delivery methods. This product has a long shelf life due to its high level of bio-adhesives, superior dermal penetration, ease of formulation, higher drug loading capacity, and greater stability at any dilution level, as well as its higher resistance to breakage and protection of enzyme attack-liable drugs within the cubic phase. It is economical, cost-effective, biologically compatible, and non-hazardous. Compared to other prominent categories of nanoparticles, cubosomes have various advantages. For instance, compared to liposomes in contact with cellular surfaces, the main benefit of cubosomes over liposomes is their liquid-crystalline arrangement, which may offer continuous drug release over lengthy periods [52]. Additionally, cubosomes possess a greater volume to accommodate increased quantities of drugs, resulting in better payload, less viscosity, and a less hydrophobic core than liposomes [53]. Cubosomes have a significant advantage compared to dendrimers.

Dendrimers have potential toxicity issues related to charges and the nature of the building blocks, while cubosomes use biodegradable, biocompatible, and bio-adhesive lipids. However, the formation of increased viscosity during large-scale manufacture and a few issues with the retention of hydrophilic drugs remain its principal drawbacks [54].

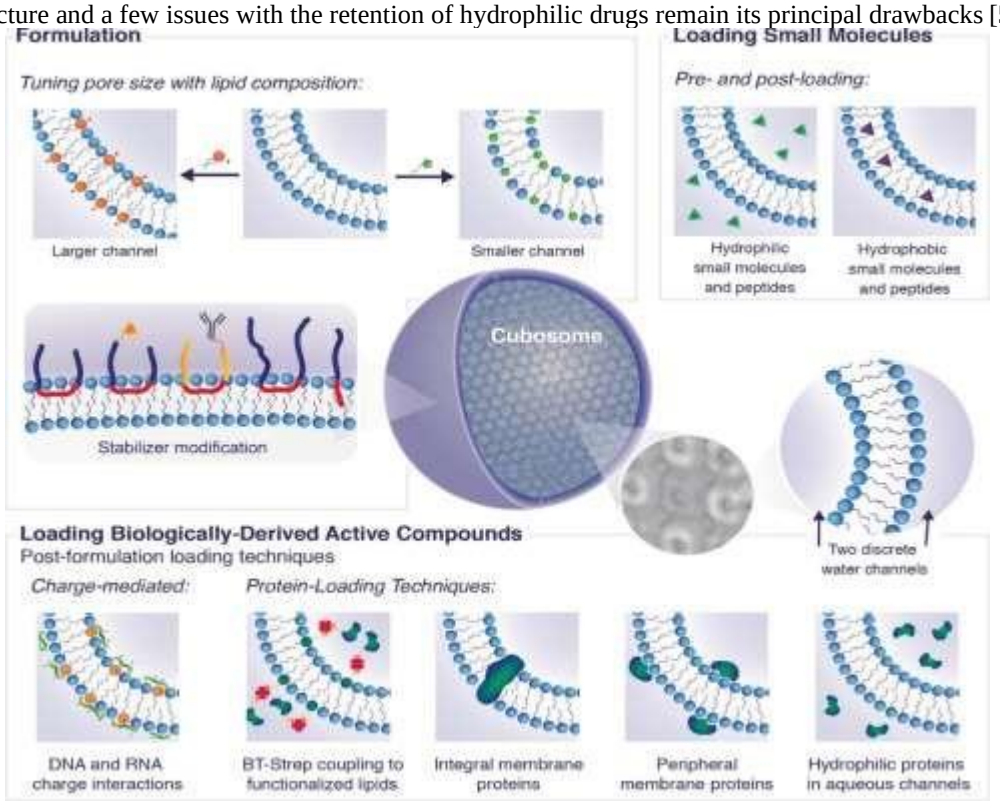

Fig. 3. Intelligent design of cubosomes for biomedical applications

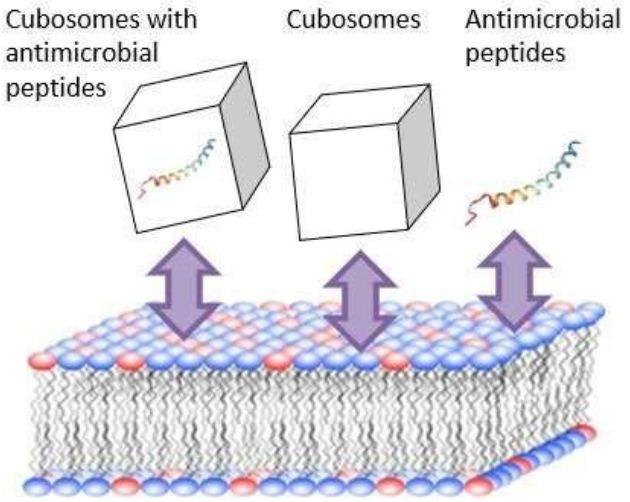

Fig. 4. Schematic of the exposure of bilayers to different drug delivery systems.

Even though there are some disadvantages, due to unique benefits among other nanomaterials, self-assembly capacity, better encapsulation of drugs, biological transportation, and applications in diagnosis, they have been used in a variety of applications for over two decades [55]. When a lipid bilayer is applied to a twisted three-dimensional surface with minimal surface formation comprising water and lipid phases, cubosome development occurs under exactly regulated temperature conditions. Cubosome formation may be divided into three types: primitive (P- surface), double diamond (D-surface), and gyroid (G-surface), all of which are in a favorable structural variation so that drug delivery to different biological targets is possible. Although these cubosomes have a microstructure comparable to their parent cubic phases, they are distinguished by their decreased viscosity as dispersions and their acquisition of a high surface area as equating [54]. This nanodispersion appears to be a potential approach for overcoming the major disadvantages of cubic phases.

Development of Cubosomes:

Self-Assembly of Amphiphilic Liquids

Self-assembly is a process in which disordered molecules come close together and spontaneously create a structurally orderly arrangement through reciprocal interaction. The theory behind the self-assembly of amphiphilic liquids is associated with two principles: opposing force and packing parameter [56-58]. According to the principle of opposing forces, molecular arrangements of amphiphilic molecules in a polar solvent reduce free energy. The solvent may pass through them and expose the hydrophilic regions to the aqueous environment while protecting the hydrophobicportions from the solvent. At this point, opposing forces begin to arise, as hydrophobic contacts occur at the interface between hydrophobic hydrocarbon tails and the hydrophilic head groups on the amphiphilic molecules. [59,60].

Amphiphilic Lipids for Cubosomes

Cubosomes are made up of three components that self-assemble to produce the lipid bicontinuous cubic phase: amphiphilic lipids, stabilizers, and drug molecules. GMOs are made up mostly of monooleate and glycerides of oleic acid and other fatty acids. They have a Pn3m cubic-phase structure and pass through inverted micellar and lamellar phases when exposed to excess water, and temperatures ranging from room temperature to 80 °C. Stabilizers The inclusion of stabilizers is a crucial component of the ribosome-makingprocess. They work by forming a protective layer over the ribosome structure, preventing aggregation and increasing dispersion stability by preventing amalgamation with the bulk cubic phase. It is evident that although the fundamental role is to control the phase morphology of lipid mixtures, a large proportion of the stabilizers remains on the surface of the ribosomes, with just a tiny amount intercalating into the phospholipid bilayers of thecells. The number of stabilizers that may intercalate into the lipid membrane varies dependingon the kind and quantity of the stabilizers. Block copolymers are the most often utilized stabilizers in the manufacture of ribosomes, accounting for more than half of all applications. F127 (Poloxamer 407), a triblock copolymer, has long been considered the gold standard for non-lamellar lyotropic liquid crystal (LLC) lipid nanoparticles. There are very few studies on the safety and biocompatibility of F127, which makes it hard to anticipate its protective nature and other related covert functions at the cellular level without more research. For instance, Cho and colleagues showed that binary blends of block copolymers may self-assemble into the required nanostructure in solution by varying their composition within the blend. They were able to accomplish this by manipulating the structural parametersof a binary block copolymer blend through composition control [61-74].

Preparation of Cubosomes

Cubosome preparation is relatively more common in the pharmaceutical industry than the preparation of the corresponding reverse non-lamellar phases, owing to the ease with which ribosomes can be prepared and their greater ability to deliver a broader range of pharmaceuticals, particularly those that are injectable. By adopting a two-step method, this approach begins with acceptable starting materials and then carves the usefulness out of them. Maintaining the optimal temperature throughout this phase is critical, since failure to do so may result in poor-quality cubosomes. Top-down sonication techniques have the major benefit of producing repeatable staribosomesomes without additional solvents. A re-examination of phase behavior is not necessary, and the risk of toxicity to cells is minor or non-existent. The second approach for synthesizing ribosomes is the bottom-up method, alsoreferred to as the solvent dilution method or the liquid precursor method. In this method, cubosome precursors may be transformed into the crystallized form on the molecular length scale while remaining at room temperature. Spicer et al. first described this process, wherein they made nanostructured building blocks and converted them into finished materials. The cubosomes formed exhibited less polydispersity and less vesicle formation than the cubosomes made using the top-down sonication approach. Furthermore, the bottom-up method has several advantages over the top-down method, including less energy due to avoiding strenuous fragmentation, the inclusion of thermolabile materials, and the generation of small particle cubosomes due to a unique technique.

The uniform dispersion of stabilizers used in this method leads to the development of long-term stable cubosomes and the ability toscale up to industrial batches [75-79].

Characterization of Cubosomes

- photon correlation spectroscopy(quasi-elastic light scattering) [80]
- polarized light microscopy [81]
- small-angle X-ray scattering (SAXS)[82]
- cryo-TEM (cryo TEM), and [83]
- Energy-dispersive X-ray analysis (EDAX) [84]

Physiological Properties and Drug Delivery of Cubosome

Cubosomes, according to the literature, have several other properties that make them attractive for use as drug-delivery vehicles. For example, they demonstrate biocompatibility; bio-adhesion; the protection of drug molecules against oxidation, hydrolysis, and deamidation processes; and the protection of protein molecules against denaturation, precipitation, aggregation, and surface adsorption. Additionally, they are an effective delivery method over an extended

period. These issues continue to be a barrier to achieving an optimal treatment response and patient compliance in the therapeutic region. Cubosome formulation, developed by Chung et al. previously, has successfully enhanced oral insulin absorption. Furthermore, it has been demonstrated that colchicine manufactured as a cubosome transdermal preparation improves topical medication absorption, compared to when the drug is administered orally Cubosomes have also shown considerable benefits in the delivery of drugs through intravenous and intranasal routes. Cubosomes may aid in the transfer of colloidal substances without obstructing capillaries. Additionally, they may minimize drug plasma–protein interactions, increasing drug molecules‘ bioavailability and stability. Intranasal cubosomes can deliver drugs directly to the central nervous system (CNS) by crossing through the blood–brain barrier. Cubosomes have been tested in many ways to exert their delivery capacity as nanoparticles with several disease models [91,103].

Methods Used in Cubosome Preparation

There are four main approaches to producing cubosome nanoparticles: top-down and bottom-up. Besides the differences, to prevent cubosome dispersion aggregation, both techniques require a colloidal stabilizer such as P407, as described. Top-down Technique It isthe most extensively utilized approach in the research field, with Ljusberg-Wahren first reporting it in 1996. [104]. The viscous bulk cubic phase is created by combining lipids with stabilizers and then dispersing the resulting mixture into an aqueous solution using high energy (such as High-Pressure Homogenization [HPH], sonication, or shearing) to produce Lyotropic Liquid Crystal (LLC) nanoparticles.HPH is the most widely used method for making LLC nanoparticles. Cubic phases vary from other thermodynamic phases in that they are a single thermodynamic phase with a periodic liquid crystalline structure [105]. Wörl et al.looked into the factors that influence the qualities of cubosomes made of glyceryl monooleate (GMO). The concentration of F127 and the temperature during HPH were regarded as crucially significant parameters based on the findings[106]. Vesicles (distributed nanoparticles of lamellar liquid crystalline phase) or vesicle-like structures are always detected coexisting with cubosomes made using a top-down technique.[107]

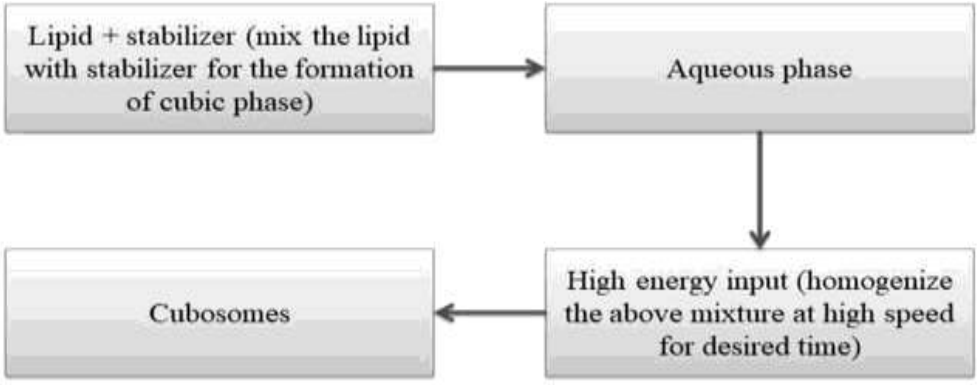

Fig. 5. Top-down technique

Bottom Up Technique

Cubosomes are permitted to develop or crystallize from precursors in this method. There are two types of precursors: liquid and powder. Monoolein and ethanol solution make up the liquid precursor. It is made by adding hydrotrope (ethanol) to molten monoolein at room temperature. The monoolein-ethanol solution is then emulsified with a solution of poloxamer 407, resulting in a viscous cubic liquid gel.[108] A Cubosomes nanoparticle is created by diluting the generated gel with water and sonicating it for five minutes. The powder precursor, on the other hand, is made up of monoolein powder that has been coated witheither starch or dextran. This precursor, which is made up of dehydrated surfactant that has been coated with a polymer, is then hydrated to produce a liquid droplet emulsion. Using the spray drying technique, the nanoparticle cubosomes are formed from these powder precursors[109].

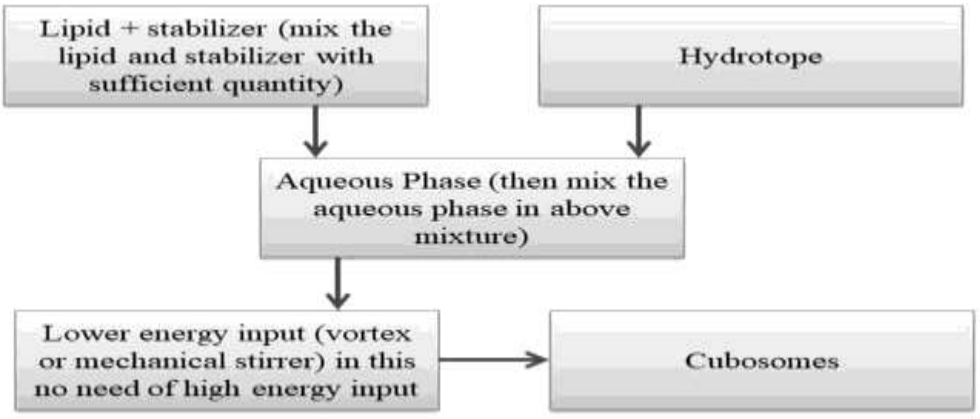

Fig.6.Bottom-UpTechnique

Heat treatment approach

This technique is not an integrated cubosome manufacturing process because it only promotes the transformation from non-cubic vesicles to well-ordered cubic particles via a homogenization and heat-treatment step, resulting in a decrease in the small particle size fraction that corresponds to vesicles and the formation of more cubic phases with narrow particle distribution and good colloidal stability. Spray drying Using a spray drying method Due to the limited flexibility of liquid precursors for cubosome production (Spicer et al), a dry powder precursor for cubosome preparation was devised. For the manufacture of starch-encapsulated monoolein precursor and dextran-encapsulated monoolein precursor, they useda spray drying process. Encapsulation with a high proportion of polymer (75 percent w/w for starch and 60 percent w/w for dextran) reduced the amount of active material loading, hence the method was limited to powerful medicaments, vitamins, flavors, or smells. Cuboidal preparation method in general Monoolein and water are frequently combined around 40° C tomake cubosomes. Mechanical or ultrasonic energy is used to disperse the resulting cubic liquid crystalline gel into particles. To make cubosomes, high-pressure homogenizers are frequently used. The cubosomes are finally secured against flocculation. Phase aqueous Inputof a lot of energy. [110]

Table. 1. cubosomes various findings and formulation

Drug/ Category	Type of formulation	Polymer	Routes of administration	Findings	Excipients	Size	References
Itraconazole[anti-fungal]	Oral cubosomal capsules	Poloxamer 407 (p-407)	Oral	Increased solubility and bioavailability	Starch powder, aerosil	479.2nm	111
Brimonidine tartrate (brt)[used in glaucoma]	Ocular brimonidine tartrate (brt) Formulation	Poloxamer 407	Ocular	Increased ocular bioavailability ,	Polyvinyl alcohol (PVA) or tween 80	157.2 ± 4.2 nm	112
Colchicine (col)[anti-gout]	Transdermal delivery of colchicine (col)-loaded cubosomes.	Surfactant (p407)	Topical /transdermal	Minimized potential side effects associated with its oral administration	Glyceryl monooleate (GMO), and surfactant (p407)	73.07 ± 2.18 nm	113
Gliclazide[anti diabetic]	Gliclazide-loaded cubosomal nanoparticles	Poloxamer 407(p407)	Oral	Improve bioavailability and activity of gliclazide.	Glyceryl monooleate (GMO) and poloxamer407 (p407)	220.60 ± 1.39 to 234.00 ± 2.90 nm	114
Tetrandrine (tet) [calcium channel blocker]	Liquid crystalline nanoparticles as an ophthalmic delivery system	Poloxamer 407	Ocular	Better Ocular bioavailability	Glyceryl monoolein, poloxamer 407, and water,	170.0 ± 13.34 nm	115
Dacarbazine- [anti cancer]	Dacarbazine-loaded cubosom	Poloxamer 407	Oral	Increased encapsulation efficiency of 6.9%	Monoolein, Polymer	104.7 nm	116
Phytantriol [cosmetics]	Phytantriol (20mg/ml),	Poloxamer 407	Topical	Improve skin penetration	Poloxamer 407 (3 mg/ml) and propylene glycol (53.7 mg/ml)	134–200 nm	117
Ketoconazole [anti-fungal]	Ketoconazole loaded cubosomes	Poloxamer 407	Topical	Increased absorption cumulative ketoconazole	Hydrogel containing ketoconazole	198 nm	118
Diclofenac sodium [anlgesic]	Diclofenac sodium cubosomes	Poloxamer 407	Topical	Better percutaneous administration	Gmo , poloxamer407	453±1.5	119

Docetaxel [anti-cancer]	Thermoresponsive depot system comprising of docetaxel-loaded cubosomes.	Poloxamer 407	Topical	Better controlled drug delivery.	Pluronic® f12 7 and pluronic® f68	170 and 280 nm	120
Norfloxacin [anti-bacetial]	Norfloxacin loaded nano-cubosomes	Poloxamer 407	Topical	Enhanced management of otitis external	Gmo (95%), cremophor (2.5%) and pluronic f108 (2.5%))	216.75 ± 2.47 nm	121
Valbumin and quil [vaccine]	subunit vaccine	--	S/c	Better absorption	--	257 ± 8 nm	122
Etodolac [analgesic]	Etodolac transdermal cubosome	Poloxamer 407	Transdermal	Improve skin penetration		135.95 to 288.35 nm	123
Voriconazole. [anti-bacterial]	Central composite optimization of ocular mucoadhesive cubosomes	Poloxamer 407	Ocular	Enhanced bioavailability and controlled delivery of voriconazole	15% monoolein and 1.2% pluronic f127	160 nm	124
Methotrexate [analgesic]	Development and characterization of sustained-release methotrexate-loaded cubosomes	Poloxamer 407	Topical	Sustained released achieved	Poloxamer 407 and glycerol monooleate (monoline,mo)	53.21 to 185.32 nm,	125
Sildenafil citrate [aphrodisiac]	In situ gelling vaginal sponges of sildenafil citrate-based cubosomes	Poloxamer 407	Viginal	Better bioavailability	Polyvinyl alcohol,	150.81-446.02 nm	126
Bedaquiline [anti-cancer]	Inhalable bedaquiline-loadedcubosomes	Poloxamer 407	Inhalation	Better absorption and targeted	--	150.2 ± 5.1 nm	127
Rebamipide (reb [anti gastric/anti ulcer]	Formulation and characterization of cubosomes containing reb	Poloxamer 407	Oral	Improvement of oral absorption	--	303.1 ± 4.9 to 444.9 ± 6 nm	128
Dexamethasone [anti-inflammatory]	Formulation and evaluation of dexamethasone-loaded cubosomes	Poloxamer 407	Ocular	Better absorption	Glycerine monooleate	119.4 nm	129
Clotrimazole [anti-fungal]	Formulation and evaluation of cubosome as skin retentive system clotrimazole	Poloxamer 407	Topical	Improve skin retentive system	Glyceryl monooleate (GMO) and poloxamer 407	133.23 nm	130

Oleoylethanolamide (oea), [neurodegenratve agent]	Oleoylethanolamide , into cubosomes	Poloxamer 407	Oral	Increased bioavailability	Polyvinyl alcohol,	200 nm	131
Clopidogrel bisulphate (cb) [used in haertdisases]	Cubosomes as oraldrug delivery systems	poloxamer 407(pl407)	Oral	For enhancing the release in the intestine	. Glyceryl monooleate (gmo) Polyvinyl alcohol (pva), poloxamer 407 (pl407)	115±6.47 to 248±4.63 nm)	132
Piperine [cns agent]	Novel piperine- loaded tween- integrated monoolein cubosomes	Poloxamer,	Oral	Oral nanomedicine for bioavailability	Tween 80, poloxamer, and cremophor	167.00±10.49 nm	133
Paclitaxel [anti cancer]	Paclitaxel-loaded cubosomes as a drug delivery	Poloxamer	Topical	Increased peneteration	(polyethylene glycol)]	---	134
Dexamethasone [anti inflammatory]	Development and evaluation of dexamethasone loaded cubosomes	Poloxamer	Oral	Increased absorption	Glyceryl monooleate (gmo) (lipid phase), poloxamer 407 (p 407) (non-ionic surfactant), oleic acid (fatty acid)	250.40 nm	135
Thymoquinone (tq), [anti cancer]	Anticancer activity of thymoquinone cubic phase	Poloxamer	Oral	Increased bioavailability	--	98.0 ± 4.10 nm	136
Oridonin [anti cancer]	Cubosomes containing oridonin	Poloxamer 407	Oral	Better absorbtion .	Glycerol monooleate lipid (gmo)- or phytantriol (pyt)– poloxamer 407– propyleneglycol	200 nm	137
Atazanavir [anti hiv]	Evaluation of atazanavir loaded cubosomal gel	Poloxamer 407	Topical/transdermal	To improve its bioavailability and curtail the adverse effects by the transdermal	Glyceryl monooleate (gmo), surfactant (pluronic f 127), and	100±7.9 - 345±6.4 nm	138
[antiviral]				route	cetyl trimethyl ammonium bromide (tab)		

Efavirenz [anti hiv] [antiviral]	Formulation and development of bicontinuous nanostructured liquid crystalline particles of efavirenz	Poloxamer 407	Oral	To improve oral bioavailability , Minimize side effects and drug resistance	Triglyceride vehicle	104.19 ± 0.21 nm	139
Raloxifene (rlx) [anti-cancer]	Optimization of raloxifene-loaded cubosomal formulation for transdermal delivery	Poloxamer	Transdermal	to improve its absorption, Subsequently, improve bioavailability .	Ethanol injectionmethod	110.6 nm	140
Agomelatine [anti-depressant]	Formulation and characterization of liquid crystalline hydrogel of agomelatine	Poloxamer 407	Topical	For improved topical application	Glyceryl monooleate (GMO) and poloxamer 407	187.6±3.97 nm to 225.8±7.54 nm	141
Fluconazole [anti-fungal]	Fluconazole encapsulated cubosomes	Poloxamer 407	Topical	Improve skin penetration	Glyceryl monooleate (GMO) and poloxamer 407	257.2 ± 2.94 nm	142
Resveratrol (rv) [anti-cancer]	Formulation and evaluation of resveratrol-loaded cubosomal nanoformulation	Poloxamer 407	Oral	Improve bioavailability	Glyceryl monooleate (GMO) and poloxamer 407	113±2.36 nm	143
Gatifloxacin [anti-bacterial]	Formulation for gatifloxacin delivery	Poloxamer 407	Occualr	Better absorption	Glyceryl monooleate (GMO) and poloxamer 407	197.46 ± 9.40 nm	144
Miconazole	Miconazole nitrate as a cubosomal	Poloxamer 407	Topical	Better skin	Glyceryl monooleate	88.7nm	145
[anti-cancer]	topical gel			penetration	(gmo) and poloxamer407		

Conclusion:

Cubosomes are among a special class of lipid-based nanovesicles characterized by the liquid crystalline nature of their nanostructure, prepared from amphiphilic lipids which self-assembled in water and the presence of stabilizer into cubosomes. Recently numerous published reports proved their potential uses as a novel drug delivery system. Cubosomes have been approved as an effective ocular drug delivery with enhanced ocular residence time, bioavailability, and no irritation to the eye. Oral application illustrated that cubosomes can be used effectively to increase absorption of poorly water-soluble drugs, protect the liable drug from enzymatic degradation, and in targeted drug delivery. They provide a promising vehicle for effective transdermal drug delivery with enhanced skin permeation and low irritation potential. Interestingly, cubosomes were applied for the delivery of anticancer drugs with reduced serious side effects of the chemotherapeutic agents and targeted drug delivery.

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