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ABSTRACT: Cubosomes are particles that are square or spherical and have visible cubic lattices inside. The fascinating story of how the cubosome was discovered involves differential geometry, biological membranes, digestion, and food science. Cubosomes are thermodynamically stable and have a structure that looks like honeycomb. Amphiphilic lipids are the building blocks of cubosomes, which are joined by a polymer. Cubosomes can be utilized to treat skin, hair, and other substantial tissues in various ways, including parenteral, oral, mucosal, and transdermal. Polymers can be utilized to target the outer circle, and cubosome formation can be manipulated to design pore size or include bioactive lipids. Additionally, they are quite secure in physiological conditions. Due to their network topology, they can catch more drugs. Cubosomes are liquid crystalline nanoparticles with a unique internal cubic structure and content that self-assemble. Cubosomes are made by dispersing a solid-like phase into smaller particles after hydrating a surfactant or polar lipid into a cubic phase. They have strong like rheology with one-of-a-kind elements that are valuable practically speaking. Cubosomes can contain molecules that are hydrophobic, hydrophilic, or amphiphilic. Cubosomes can make drugs that are hard to dissolve more soluble. Treatment of skin, hair, and other body tissues with cubosome-like vehicle activity of biological substances and controlled release of solubilized chemicals are examples of cubosome applications. Melanoma (malignant growth) treatment in view of a size conveyance framework is the way to successfully focusing on melanoma because of expanded porousness and maintenance.

KEY WORDS: Cubosomes, Drug-loading hydrophilic, Hydrophobic, Amphiphilic, Lyotropic liquid crystals, Biocontinuous, Nanoparticles, Honeycomb

INTRODUCTION

Cubosomes are discrete, nanostructured particles of the bicontinuous cubic fluid translucent stage that are short of what one micron in size. Larsson came up with the term "Cubosomes," which refers to the cubic crystallography of the molecules and their similarity to liposomes. These are nanoparticles that have a proper water-to-microstructure ratio and are self-assembled liquid crystalline particles of certain surfactants. Cubosomes are nanoparticles yet rather than the strong particles generally experienced, these are self-gathered fluid translucent particles with a strong like rheology that gives exceptional properties of viable interest(1). Cubosomes

are probably made of polymers, lipids, and surfactants that are both polar and non-polar, which is why they are called amphiphilic. The amphiphilic particles are driven by the hydrophobic impact into polar dissolvable to incautiously recognize and collect into a fluid gem of nanometer scale. As a result, cubosomes have a cubic, bicontinuous liquid phase that is divided by surfactant-controlled bilayers into two distinct regions of water. In addition, they are optically isotropic, viscous, and solid, and have cubic crystallographic symmetry, making them resemble liquid crystals[2]. The cubic phase is capable of fracturing into particulate dispersions that are thermodynamically and colloidally stable. Cubosomes are bicontinuous cubic liquid crystalline phase formations produced by hydrating a mixture of monoolein and poloxamer 407. They play a significant role in the formulation of nanodrugs. Dots with a square or slightly spherical shape and a diameter of 10 to 500 nm. Chemical bonds bind the polar head of the phospholipids to the active chemical constituent molecules in cubosomes. Depending on the substance, a 1:1 or 2:1 complex is formed between the polymer and the individual drug compound. Despite their early recognition (in 1980), cubosomes' complex phase behavior and viscous properties made large-scale production challenging[3]. When mixed with water at a certain concentration, some surfactants spontaneously form cubic phases. To produce cubosomes on a large scale, scalable processes are currently being developed. A couple of anticancer medications have been effectively epitomized in cubosomes and portrayed[4].

CUBOSOME CHARACTERISTICS[5-7]

- Cubosome dispersions have a significantly lower viscosity.
- Cubosomes are distinct, bicontinuous cubic liquid crystalline particles with a nanostructure of less than one micron.
- Cubosomes may be the most fascinating. Cubic liquid crystals, which are transparent and isotropic, are physically stable in excess water.
- Cubosomes are appealing for controlled release due to their small pores.
- It is biodegradable and capable of solubilizing hydrophobic, hydrophilic, and amphiphilic compounds.

CUBOSOME ADVANTAGES [6, 8, 9]

- Cubosomes are non-irritating, biocompatible, and biodegradable.
- The method of preparation is straightforward.
- As a result of their huge inside surface region, they have a high medication stacking limit. for a more drawn out timeframe, they are thermodynamically steady.

- They can epitomize hydrophobic/lipophilic (cinnarizine) and hydrophilic (cyclosporine) atoms.
- The use of a particular polymer considers the directed and designated arrival of bio-actives.
- Health care costs less overall because there is less recurring administration.
- They reduce the adverse effects of injections brought on by burst release.
- The ratio of particle volume to bilayer area is higher than in liposomes.
- When compared to other typical carriers (lipid-based), cubosomes are excellent solubilizers. They demonstrated that medications that are barely soluble in water can be encapsulated. The sensitive drug moiety (proteins, peptides) that has been enzymatically degraded is carried by them as a carrier. They roughly 20 to 100 percent up the bioavailability of water-soluble peptides.
- The use of organic solvents is not required for cubosome preparation methods like shear and homogenization.

CUBOSOME DISADVANTAGES[8, 9]

- Water-soluble drugs are less likely to be trapped in cubosomes because they contain a lot of water.
- Large-scale cubosome manufacturing is challenging because of its high viscosity.
- Without the utilization of a particular polymer, managed drug conveyance is beyond the realm of possibilities. They could leak during storage or transmission in real time.
- At the point when particles are abandoned for quite a while, they might develop. In the event that the outside climate changes, cubosomes can deliver a stage change (elements).

STRUCTURE OF CUBOSOMES[10]

A large interfacial area and honeycomb-shaped (carvenous) structures that separate the two internal aqueous channels make up cubosomes' fundamental structure. Cubosomes are nanoparticles with a diameter of 10–500 nm. They are likely to be spherical, resembling dots, but they are actually nanostructured particles of liquid crystalline phases that are formed by the self-assembly of molecules that are either surfactant-like or amphiphilic. Cubosomes have the amphiphilic transporter framework that has the capacity to exemplify both hydrophilic and lipophilic medications. The lipophilic drug is divided between the hydrophilic domains, whereas the hydrophilic drug is contained within the vesicles. Cubosomes, which structures

bicontinuous water and oil channels as they are Amphiphilic particles, though 'bicontinuous' alluded as two particular (constant, yet non-crossing) hydrophilic districts that are isolated by the bilayer. The interconnections of the construction brings about a reasonable, gooey gel which are comparable for all intents and purposes and rheology to be cross-connected polymer hydrogels.

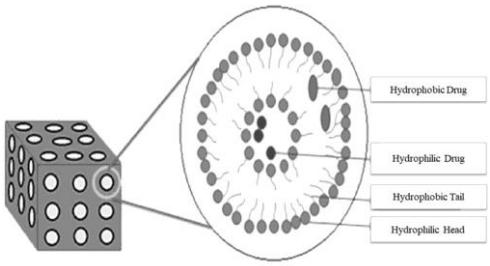

Figure 1 Structure of Cubosomes

TYPES OF CUBOSOMES[7]

Liquid cubosome precursors: The goal of the hydrotropic dilution procedure is to produce cubosomes that are both smaller and more stable. The nucleation process, which enables the growth of particles under precipitation and crystallization conditions.

Powdered cubosome precursors: These are made of a polymer-coated, dehydrated surfactant. Hydrotropic cubosome precursors in the liquid phase can benefit from these powders in some ways. Cryo-TEM and light scattering demonstrate that cubosomes with a mean particle size of 600 nm are formed when the precursor powders are hydrated.

COMPONENTS OF CUBOSOMES

The parts of cubosomes made out of fundamentally three significant parts Amphiphilic lipids, stabilizer, and water. During the hydration process, the cubic liquid crystalline phases are produced by the amphiphilic lipids, while the polymeric stabilizers prevent the bulk cubic phase from forming.

- **Amphiphilic lipids:** Glyceryl monooleate GMO, also known as monoolein or phytantriol (PHYT), and glyceryl monooleate GMO are the primary amphiphilic lipids utilized in the production of cubosomes. GMOs are mixtures of glycerides of oleic acid and other fatty acids, most of which are monooleates. These glycerides belong to the amphiphilic lipids group and have the ability to form various lyotropic liquid crystals.

GMOs with hydrocarbon chains ranging from 12 to 22 have a greater propensity to form cubic phases[11]. Moreover, it is a biocompatible and biodegradable material for the most part perceived as protected (GRAS) classification by FDA, which is basically utilized as emulsifier in the food business. PHYT is a compound material having a phytanyl chain displays the development of cubic stages by expanding the temperature and water content. PHYT, whose chemical name is 3,7,11,15-tetramethyl-1,2,3-hexadecanetriol, is primarily found in cosmetics[12].

- Glycerol monooleate (GMO): The most common amphiphilic lipid used to make cubosomes is glyceryl monooleate (GMO), which is also known as monoolein. GMO is a polar unsaturated monoglyceride that appears clear and colorless and has a melting point of 35-37 °C, a storage temperature of 20 °C, and a HLB value of 3. It is a manufactured combination of glycerides ester of oleic corrosive and other unsaturated fats and basically comprises of monooleate which ready to self-collect in water into bicontinuous cubic designs. The chemical structure of a GMO reveals that it has both hydrophilic and hydrophobic characteristics simultaneously (amphiphilic molecule). This is due to the presence of hydrocarbon chains in the tail and hydroxyl groups in the head, which are responsible for the formation of H-bonds with water. It was first recommended as a biocompatible encapsulating material in 1984 and is frequently used as an emulsifier in the food industry. It is safe, nontoxic, biodegradable, and biocompatible[13].
- **Phytantriol (PHYT):** In the preparation of cubosomes, phytantriol, a common ingredient in cosmetics, is regarded as an excellent alternative to GMO. Under physiological conditions and temperatures, Phytantriol (3, 7, 11, 15-tetramethyl-1, 2, 3-hexadecantriol) can form a bicontinuous cubic structure in aqueous media. It has recently attracted more attention in the biomedical field than monoglycerides due to its enhanced skin penetration properties, improved moisture retention, and its high chemical stability (95 percent) in comparison to monoglycerides. In contrast, monoglycerides have varying purity levels because they are produced from a variety of sources. As a remarkable sustained drug delivery system, PHYT-based liquid crystalline matrices are thought to be able to sustain the release of various drug molecules, particularly those with hydrophilic properties[14].

- **Stabilisers:** Surfactants were found to play a crucial role in protecting cubosomes from the coalescence of the bulk cubic phase, according to the researchers. Poloxamer 407

(P407) is a PEO-PPO-PEO tri-block copolymer that is mostly used as a surfactant in the preparation of cubosomes. It has specific PPO portions that are either on the surface of the cubosomes or within the bilayer structure, and the PEO chains are exposed to the water phase that is surrounding them[15]. Typically, P407 is used up to a concentration of 20% w/w, but this depends on the amount of dispersed phase. Wadsten-Hindrichsen looked into how propylene glycol (PG), polyethylene glycol 400 (PEG400), and 2-meth-yl-2, 4-pentanediol (MPD) affected a phytosome-based cubosomal system. Poly (ethylene oxide) stearate stabilizers outperformed steric stabilizers in the cubosomes, it was found[16].

SELECTION CRITERIA FOR DRUGS AND EXCIPIENTS

Delivering lipophilic medications like diazepam, rifampicin, propofol, and griseofulvin to the target region was the fundamental idea behind the cubosome design. The phospholipid coat makes the target region more permeable by making the lipophilic moiety less soluble. If the porousness of hydrophilic glucose and insulin moieties regardless of the way that the biomembrane is restricted, this can be achieved effectively by incorporating them into lipid parts, they can be relieved. As a consequence of this, both kinds of pharmaceuticals are capable of being incorporated into cubosomes; however, lipophilic drug encapsulation has been reported to be more prevalent up until this point[17]. Peptides were efficiently dispersed by cubosomes, and the peptides' stability was enhanced by reducing their exposure to various pH environmental conditions. Subsequently, the downsides of elective site-explicit/designated drug conveyance techniques could be relieved via cautious choice of a cubosome transporter that permits drug moiety circulation to indicated tissues/organs. When choosing excipients, two physicochemical factors to take into account are the drug's compatibility with the polymer and its distribution within the solid lipid matrix[18].

PREPARATION METHODS OF CUBOSOMES

There are three macroscopic forms of cubic lipid phases found in cubosomes: bulk phase gel, particulate dispersion, and particle dispersion. Cubosome nanoparticles made easier to disperse than their dispersions are bulk phase cubic gels that are rigid, strong, optically isotropic, and solid like particles. They form cubosome nanoparticles and are in equilibrium with water. Spray drying, sonication, high pressure homogenization, and spontaneous emulsification are all methods that can be used to create the cubosome-prepared nanoparticle dispersions. Sonication and high pressure homogenization, on the other hand, result in the formation of complex

dispersions with vesicle-like structures and cubosomes containing time-dependent ratios of each type of particle[19].

There are two distinct technologies that can be used to produce cubosomes. They are:

1. Top-down approach
2. Bottom-up approach

1. Top-down approach: It was first described by Ljusberg-Wahren in 1996 and is the most widely used procedure. This technology is implemented in two phases. Lipids and stabilizers are first combined to form the viscous bulk cubic phase, causing aggregation. The second step involves using high-energy processing, such as high-pressure homogenization or sonication/high energy dispersions, to disperse the bulk cubic phase into an aqueous medium, resulting in the formation of lyotropic liquid crystal (LLC) nanoparticles (cubosome dispersions). resembles the bulk cubic phases in that it is a single thermodynamic phase with a periodic liquid crystalline structure and is formed by water-swollen cross-linked polymer chains. Incorporating thermo-labile components like peptides and proteins is extremely challenging, and the high energy input process required to homogenize the bulk phase is nearly impossible on a large scale. During dispersion, cubic phases behave like lamellar phases: vesicles form at intermediate shear rates, and a defect-free bulk phase re-forms at higher shear rates. At high oscillatory frequencies, cubic phases become highly elastic. In the process of making LLC nanoparticles, HPH is the method that is used the most frequently. Vesicle-like structures are observed to coexist with prepared cubosomes[20].
2. Bottom-up approach: It is the most recent cubosome development method, an alternative method for preparing cubosomes at room temperature that allows cubosomes to form crystallization from molecular scale-length precursors. In this sort of procedure, it at first structures the structure blocks in nanostructure and afterward collects them into the eventual outcome. The high process energy required to form the cubosome particle dispersions from the viscous bulk cubic phase makes scaling this method extremely challenging. To stay away from these issues Patric T. Spicer concentrated on the development of cubic stage within the sight of a hydrotrope. In this context, a hydrotrope is a molecule that is either hydrophilic or hydrophobic but does not behave like a surfactant (Micelle formation). Hydrotropes don't deliver LLC, however they increment the lipid dissolvability and afterward show a peculiarity called "salting out" forerunner might be both of a fluid or a strong. Ethanol is added to the

lipid (monoolein) ethanol to make the liquid precursor. When the precursor is diluted, cubosomes are made. Powdered precursors are composed of a polymer-coated, dehydrated substance that, upon hydration, forms cubosomes. Liquid-precursors are produced by dissolving the input factor hydrotrope in water-insoluble lipids using this method. Powdered antecedents enjoy some benefit contrasted with fluid forerunner cubosomes. When compared to the top-down approach, producing cubosomes at high concentrations to prevent the formation of liquid crystals requires less energy. The scattering of backwards micellar ease beads prompts the cubosomes development in water at 80 °C, and afterward permit them to gradually cool and drops to continuously solidify into cubosomes. After that, the monoolein-ethanol mixture is diluted with an aqueous solution of poloxamer 407, which is made at room temperature from cubosomes. Emulsification thus results in the formation of cubosomes. Through cryo-TEM, this method cannot prevent the formation of vesicles; numerous structures with the shape of vesicles are also observed to coexist with cubosomes. In the planning of medication containing vesicles utilized by freeze-drying method. Utilizing spray drying technology, Freitas and Muller produced solid lipid nanoparticles. T. Patrick Spicer was worked by spray drying starch and dextran powder precursors, which, when added to water, produced cubosomes. Monoolein can be encased in hydrophobically modified starch as a result. Starch-based monoolein-water framework is then described by a "pseudo-ternary balance stage graph". Sonication, high pressure homogenization, spontaneous emulsification, spray drying, and sonication and high pressure all contributed to the cubosome dispersion of the nanoparticles[21].

The cubosome dispersion is carried out by two methods:

- **Fabrication method:** In a hot water bath, P407 cubic gel GMO 5% or P407 and GMO 1.0% are melted at 60 °C. The required quantity of the drug is then added, and the mixture is continuously stirred until it dissolves. Drop by drop, deionized water is added, and the vortex region is set to homogenize. It forms the optically isotropic cubic gel after being kept at room temperature for about 48 hours and is completely distributed by mechanical stirring. Typically, crude dispersion is fragmented using a 200W sonicater probe at 20 °C in a water bath for about 20 minutes at a cool temperature[22].
- **Emulsification method:** GMO and P407 are added to water during this procedure, and the ultrasonication method is used to extract 1% P407, 5% GMO, and 5% ethanol from

89% water. GMO and P407 are softening at 60° and afterward blended in with the ethanolic arrangement that was added to the dissolving. The resultant combination is added dropwise to deionized water preheated at the 70 °C, it ultrasonicated at the most extreme force of 130kW for around 50 min at a similar temperature as the scatter blend kept at the encompassing temperature and shielded from direct daylight[23].

Researcher Name & Year	Title	Drug Name	Method of Preparation	Publication
Narendar Dudhipala et. al. (2015)	Formulation and characterization of Liquid Crystalline Hydrogel of Agomelatin: In vitro and Ex vivo evaluation	Agomelatin	Top-down technique	Journal of Applied Pharmaceutical Science
Popat S. KUMBHAR et. al. (2023)	Ifosfamide-Loaded Cubosomes: An Approach to Potentiate Cytotoxicity against MDA-MB-231 Breast Cancer Cells	Ifosfamide	Top-down technique	Journal of Pharmaceutical Sciences
Leilei Zhang et. al. (2020)	Theranostic combinatorial drug-loaded coated cubosomes for enhanced targeting and efficacy against cancer cells	Bovine serum, Penicillin, and Streptomycin	Bottom-up approach	Cell Death & Disease
Rasha S. Younus Alkwak et. al. (2021)	Lornoxicam-Loaded Cubosomes: Preparation and In vitro Characterization	Lornoxicam	Solvent dilution method	Iraqi Journal of Pharmaceutical Science
Dr. P. Rajesh Kumar et. al. (2021)	Formulation Design and In-vitro Characterization of Docetaxel Cubosomes for Gastric Cancer therapy	Docetaxel	Bottom-Up Method technique	Research Journal of Pharmaceutical Dosage Forms and Technology
Maha KA Khalifa (2015)	Miconazole Nitrate based cubosome hydrogels for topical application	Miconazole Nitrate	Emulsification method	International Journal of Drug Delivery

Ananda Kumar Chettupalli et. al. (2021)	Design, Formulation, In Vitro and Ex Vivo Evaluation of Atazanavir Loaded Cubosomal Gel	Atazanavir	Homogenization processes	Biointerface Research in Applied Chemistry
Arindam Pramanik et. al. (2022)	Hyaluronic-Acid-Tagged Cubosomes Deliver Cytotoxics Specifically to CD44-Positive Cancer Cells	Hyaluronic-Acid	Tip sonicating Method	Molecular Pharmaceutics
Valeria Castelletto et. al. (2019)	Self-Assembly of a Catalytically Active Lipopeptide and Its Incorporation into Cubosomes	Lipopeptide PRW-NH-C_{16}	Solvent dilution method	ACS Publication
Fahima Hashem et. al. (2017)	Formulation and Characterization of Cubosomes Containing REB for Improvement of Oral Absorption of the Drug in Human Volunteers	Rebamipide	Disrupting a cubic gel phase Method	Journal of Advance Pharmacy Research
Sergio Murgia et. al. (2015)	Cubosome formulations stabilized by a dansyl-conjugated block copolymer for possible nanomedicine applications	Dansyl-conjugated F108	Dispersion Method	Colloids and Surfaces B.
Amal A Sultan et. al. (2022)	Cubosomes for Enhancing Intestinal Absorption of Fexofenadine Hydrochloride: In situ and in vivo Investigation	Fexofenadine Hydrochloride	Self-assembled from amphiphilic lipids	International Journal of Nanomedicine
Laura Deruyver et. al. (2023)	In vitro Evaluation of Paliperidone Palmitate Loaded Cubosomes Effective for Nasal-to-Brain Delivery	Paliperidone Palmitate	Bottom-up method	International Journal of Nanomedicine
Rasha S. Younus Alkwak et. al. (2022)	Lornoxicam-Loaded Cubosomes: Preparation and In vitro Characterization	Lornoxicam	Solvent dilution method	Iraqi Journal of Pharmaceutical Science

Lukas Boge et. al. (2017)	Cubosomes post-loaded with antimicrobial peptides: characterization, bactericidal effect and proteolytic stability	AP114, DPK-060 and LL-37 antimicrobial peptides	Bottom-up approach	International Journal of Pharmaceutics
Karthika V T et. al. (2018)	Fabrication & Evaluation of Ketoprofen Loaded Cubogel for Topical Sustained Delivery	Ketoprofen	Top-Down Technique	International Journal of Research & Review
Yosif Almoshari et. al. (2022)	Formulation, Characterization, and Evaluation of Doxorubicin-loaded Cubosome as a Cytotoxic Potentiator against HCT-116 Colorectal Cancer Cells	Doxorubicin	Bottom-up approach	Indian Journal of Pharmaceutical Education and Research
N. Vishal Gupta et. al. (2023)	Development, Characterization and Evaluation of Cubosomes Loaded Smart Gel for the Treatment of Osteomyelitis using 32 Factorial Design	Pluronic F-127 and Pluronic F-68	Hydrotrope dilution Method	Indian Journal of Pharmaceutical Education and Research
Carlos Fitzgerald Grandes Reyes et. al. (2023)	Synthesis and applications of polymer cubosomes and hexosomes	Block copolymer	co-solvent method	Journal of Polymer Science
Masao Nagao et. al. (2023)	Preparation of Cubosomes with Improved Colloidal and Structural Stability Using a Gemini Surfactant	Phytantriol	Probe-sonication Method	Molecular Pharmaceutics
Bizhan Malaekeh-Nikouei et. al. (2023)	Preparation and in-vitro evaluation of fluorometholone cubosomes for ocular delivery	fluorometholone	Homogeneous solution Method	Nanomedicine journal
Nabil A. Shoman et. al. (2023)	Optimization of hyaluronan-enriched cubosomes	Bromfenac Sodium	Emulsification method	Drug Delivery

	for bromfenac delivery enhancing corneal permeation: characterization, ex vivo, and in vivo evaluation			
Von Halling Laier, Christoffer et. al. (2024)	Spray dried cubosomes with ovalbumin and Quil-A as a nanoparticulate dry powder vaccine formulation	Ovalbumin and Quil-A	Probe-sonication Method	International Journal of Pharmaceutics
Leilei Zhang et. al. (2020)	Theranostic combinatorial drug-loaded coated cubosomes for enhanced targeting and efficacy against cancer cells	Cisplatin and Paclitaxel	Homogeneous solution Method	Cell Death & Disease
Xiangfeng Lai et. al.	A polytherapy based approach to combat antimicrobial resistance using cubosomes	Polymyxins	Emulsification method	Nature Communications
Poorvika Badiger et. al. (2024)	Dual drug-loaded cubosome nanoparticles for hepatocellular carcinoma: a design of experiment approach for optimization and in vitro evaluation	Piperine and Quercetin	Top-down method	Future Journal of Pharmaceutical Sciences
Ruksar Fatima et. al. (2022)	Preparation of Daruavir Cubosomal Gel to Treat HIV Infections	Darunavir	Emulsification method	Saudi Journal of Medical and Pharmaceutical Sciences

EVALUATION OF CUBOSOMES

1. **Photon Correlation Spectroscopy:** By utilizing zeta-sizer (photon connection spectroscopy) molecule size dispersions in not entirely settled with dynamic laser light dissipating. The example is weakened with appropriate dissolvable and acclimated to light dissipating force of around 300 Hz and estimated at 25°C in three-fold. The collected data can be shown in general by using the average weight

size and volume. The zeta potential and polydispersity list can likewise be recorded[24].

2. **Polarized Light Microscopy:** The polarized light microscopy method can be used to reveal the cubosomes' possible surface coating. Additionally, this can be utilized to differentiate between isotropic and anisotropic substances[25].
3. **HPLC Procedure:** The samples were analyzed using a HPLC densitometry technique that was proven to work. Created plates were stained with a versatile stage which is cupric sulfate (penta hydrate): phosphoric acid: water and measured utilizing an UV light source set at regarded frequency[26].
4. **Entrapment Efficiency:** Each of the dispersions was diluted with 4 ml of deionized water to determine its entrapment efficiency. Once more, 1 milliliter of the diluted dispersion is taken and diluted with 4 milliliters of deionized water. A syringe filter with a pore size of 0.1 m was used to filter this formed dispersion, and the filtrate was analyzed spectrophotometrically at 250 nm. Taking into account the weakening component, this acquired fixation was duplicated by the complete volume of the scattering delivered. This gives the free centralization of medication (Cf) which when diminished from the absolute medication fixation (Ct) gives how much medication entangled in the cubosomes to get all the more precisely, each trial was rehashed multiple times[27].
5. **Particle Size Distribution Measurements:** Portrayal of both splash dried powders and the fluid scatterings of cubosomes is completed by utilizing laser diffraction[28].
6. **Cryo-Transmission Electron Microscopy:** At ambient temperature, a small amount of the prepared sample is placed on a pure thin bar 600-mesh transmission electron microscopy grid. A thin film was created by blotting the solution with filter paper to span the transmission electron microscopy grid's holes. Presently checks of test are finished by submerging into fluid ethane close to its edge of freezing over. Using a cryo holder, this is transferred to TEM for imaging at a temperature of -180°C. Digital images are recorded[29].
7. **Pressure Ultra-filtration Method:** By pressure ultra-filtration strategy drug discharge estimation from cubosomes is finished. At a temperature of (22±2) °C, it is based on an Amicon pressure ultrafiltration cell with a Millipore membrane[30].
8. **Thermal Analysis:** DSC was used at temperatures ranging from 37°C to 56°C to assess the drug's physical state within the cubosome. At these temperatures,

cubosome components appear to melt together, which could lead to plasticization of glycerol monooleate. Due to the absence of a distinct drug melting peak around 200°C, the thermal events occurring between 200°C and 300°C may be connected to the degradation of glycerol monooleate[31].

9. **Light Microscopy:** After being diluted with deionized water, the prepared cubosomes are examined under an optical microscope that has been calibrated with a micrometer slide at magnifications of 400x and 1000x[32].
10. **Drug content of dispersions:** The filtered dispersion sample is diluted in methanol (1:9 v/v) and analyzed by HPLC to determine its effectiveness[32].
11. **Transmission Electron Microscopy:** It tends to be utilized to see the shape and interior design of the cubosomes. After being negatively stained with a pH 6.8 solution of 2% phosphotungstic acid, the suspension of cubic phase nanoparticles (Cubosomes) was transferred to a 200-mesh carbon-coated grid and air dried at room temperature. Electron micrographs were taken with an electron microscope[27].
12. **X-Ray Diffraction Measurements:** Using a Philips PW 1830 X-ray generator, XRD is used to determine the spatial arrangements of the various sample groups[25].
13. **Gel permeation chromatography:** Gel permeation chromatography enables us to determine cubosome entrapment efficiency and drug loading. The unentrapped drug concentration, which is subtracted from the total amount of drug added, is determined using the ultra-filtration technique[28].
14. **Viscosity:** At various angular velocities and 25°C, the prepared formulation of cubosomes' viscosity was measured using a Brookfield rotary viscometer. The viscometer rotated at 20 rpm and spindle number 18 An average of three readings was taken in order to determine the formulation's viscosity[17].
15. **Visual Inspection:** After being prepared, the Cubosomes were visually examined for optical properties like color, turbidity, homogeneity, and the presence of macroscopic particles for approximately six to ten days[8].
16. **Stability Studies:** Physical stability studies can be conducted by examining the organoleptic and morphological characteristics over time. Over time, drug content and particle size distribution can be evaluated[32].

APPLICATION OF CUBOSOMES:

Melanoma therapy: As of late, a couple of anticancer medications have been epitomized in cubosomes and physico-synthetically described. The unique structure of this promising nanocarrier suggests that it could be used to treat melanoma. In both preclinical and clinical studies, it has been demonstrated that both passive and active targeting of cancer cells are effective strategies for specifically targeting nanomedicines at tumors. The pathophysiological nature of the tumor vasculature, which typically has large gap junctions between endothelial cells and impaired lymphatic drainage, enables the extravasation of nanocarriers with sizes ranging from a few hundred nanometers to a few hundred micrometers, making passive targeting advantageous. The endothelial cell lining of healthy tissue vessels has tight junctions that prevent objects of this size from passing through. The most well-known adjustment used to stay away from recognition is Catch and extension of macrophages. By coating the surface of the nanoparticles with polyethylene glycol (PEG), which is hydrophilic, the circulation time is increased. In clinical trials and development, the vast majority of nanoparticle drug formulations are primarily based on passive targeting. Specific ligands that bind to molecules that are expressed or are overexpressed in target cells include peptides and antibodies. As a result, active Targeting has no effect on overall performance accumulation at the site of the tumor, but rather improves the cellular uptake of particles after passive extravasation due to the leaky vasculature Transferrin and its derivatives Two examples of commonly used ligands are folate ligands and in nanomedicine, active targeting moieties are used[33].

Oral Drug Administration: Cubosomes faces issues like poor watery dissolvability, unfortunate assimilation, and huge sub-atomic size in the oral conveyance of many promising mixtures. An alternative method for achieving local activity in the gastrointestinal tract has involved the encapsulation of large proteins. Controlled release and targeting capabilities can be combined with carriers based on liquid crystalline nanoparticles technology. The particles are effective for drug distribution in vivo because they are designed to form at a controlled rate in situ. For drugs with a limited regional absorption window, cubosome carriers must also be released at various absorption sites, such as the upper or lower intestine[34].

Intravenous Drug Administration Systems: Lipid nanoparticles with inside fluid crystal structures of bended lipid films are utilized to solubilize, typify, and convey meds to infection destinations all through the body. Liquid crystal nanoparticle structures have increased payloads of peptides, proteins, and many insoluble small molecules, making them ideal carriers

for injection or infusion of many actives. In contrast, emulsions and liposomes have been used as intravenous carriers in drug products[5].

Topical Drug Delivery Systems: Because of their bioadhesive nature, cubic phases are ideal for drug delivery and deposition on the skin and mucosa. The one of a kind properties of fluid precious stone (LC) and fluid gem nanoparticle (LCNP) innovations are utilized to make effective conveyance frameworks. Topical drug delivery systems are unique in that they form bio-adhesive LC systems in situ, making it possible to deliver drugs to mucosal surfaces (such as buccal, ophthalmic, and vaginal surfaces) in a controlled and efficient manner. The nanostructure of this fascinating system, which is composed of a liquid crystal matrix and forms a thin surface film at mucosal surfaces, can be controlled to achieve an optimal delivery profile. It also provides good temporary protection for sore and sensitive skin. Because cubosomes and stratum corneum share a cubic phase structure, the cubosomes' lipid component mixes with the lipids of the stratum corneum to enhance penetration into the skin. Additionally, cubosomes are known to be skin adhesive consequently these medication transporters are promisingly administrable by transdermal course[35].

Vehicle for Drug Delivery: Drug delivery vehicles are a common use for these new materials. It is anticipated that the previously "exotic" delivery vehicles and ingredients will be pushed into broader markets like personal care and consumer goods as a result of the life sciences industry's rapid expansion. Consequently, self-assembled surfactant phases have undergone extensive testing to ensure that they are compatible with a wide range of medical active ingredients and applications. Cubosome particles are being tested in cosmetics as pollutant absorbents and oil-in-water emulsion stabilizers in a number of studies conducted in collaboration with L'Oreal and Nivea. In addition, these researchers discovered that phytantriol, a second amphiphile, can form cubosomes in similar conditions thanks to its aqueous phase behavior that is comparable to that of monoolein[8].

Sustained Drug Release Behaviour: There has been a lot of patent activity recently by. Utilization of cubosomes in cosmetics, skin care, hair care, and other personal care products, including antiperspirants. There is still a lot of work to be done, despite recent efforts. The necessary features for being a leader, such as material scalability and manufacturing scalability customization, are still lacking. The cubic phase has been demonstrated to be a carrier for various in vivo experiments depot, transdermal, and other delivery methods ophthalmic adhesion and mucoadhesion as a result of Monoolein's fusogenic property increasing the

macromolecular penetration. Formulators ought to take Cubosomes into consideration for commercially available goods. Furthermore, it enhances macromolecule penetration. Cubosomes have been used to integrate a variety of physicochemical drugs, and their sustained release behavior has been studied. The long-term activity of the cubosomes was due to residual particles. Effective use of monoglyceride-based cubosome scattering, for example, for perctuneous or mucosal applications, is conceivable[8].

In The Treatment of Viral Infections: Monoglycerieds could be used to develop intravaginal treatments for viruses that cause sexually transmitted diseases (such as HSV, HIV), bacteria (such as Chlamydia trachomatis and Neisseria genorrticae) due to their microbicidal attributes. Due to the similarity between the cubic phase structure and the stratum corneum structure, it is reasonable to combine cubosomalmonolein and stratum corneum lipids. This interaction may lead to the formation of a cubosome depot in this layer, from which controlled drug delivery could occur. A synthetic vernix, the cheesy white fluid that covers children in late pregnancy, is being made using the cubosome method to help premature babies born without it. Lipids (fats), proteins, and water make up the vernix in a complicated way. It grows late in pregnancy and plays a significant capability in proper skin advancement[36].

In Topical and Mucosal Dispositions: Cubic stages are more bio-adhesive in nature in skin and mucosal testimonies, making them more reasonable to use in skin and mucosal affidavits and medication conveyance[18].

In Materials Synthesis: From the point of view of materials science, the nanoscale creation of coordinated structures Many individuals are keen on pore geometries. Electronics, photonics, and catalysis are a couple examples.as well as drug developing solid structures Commonly, cubic stages are utilized as a layout. either polymerization or a response to create solids got from solubilized forerunners in, or the cubic stage grid is comprised of. Among the components made in the earliest and best the aluminosilicate is a cubic stage format. MCM-48 zeolite for reactant handling of oil. The project was completed successfully by Yang et al. Polymerization takes place within cubosomes, resulting in the symmetry of cubic solid nanostructured particles. The use of such particles could be beneficial to semiconductor and photonic applications. Lu et al. have made exceptional spray strategies that produce nanometer-scale particles by dissipating dissolvable from isotropic stage fluid beads, driving them into cubic stage designs, and solidifying the particles. Structure optimization will become a major focus as the cubic phase template area gets more sophisticated. Larson contends that steady or

large-amplitude oscillatory shearing could have aligned the cubic phases prior to templating, producing materials with distinctive and highly anisotropic properties[37].

Controlled-Release Drug Delivery: Controlled release of solubilized actives is the most common application investigated by cubosome researchers. There are also comprehensive evaluations of pharmaceutical actives that have been solubilized in bulk cubic phase and cubosomes and attempted delivery applications. Cubic phase is appealing for controlled release due to its ability to solubilize hydrophobic, hydrophilic, and amphiphilic compounds, biodegradability by simple enzyme activity, and small pore size (5–10 nm). Cubic stage is profoundly bioadhesive and is thought to be a skin entrance enhancer, inferring extraordinary similarity with effective and mucosal statement and dynamic fixing organization. Late exploration has tracked down matches between the bicontinuous structures made in human skin layers and those tracked down in cubic stages, promising a superior comprehension and treatment of skintransport. Cubic stage's convoluted design is great for easing back diffusive arrival of solubilized actives. Theoretically, the free solution diffusivity of a solute will decrease by 33%. In experiments, the diffusivity of small molecules in cubic phases is about 10 m2/sec. Cubic phase delivery vehicles have no known commercial applications aside from a periodontal disease treatment based on triglyceride–monoolein and metronidazole. The drug-lipid mixture hydrates to form a bulk cubic phase when applied to the gums and comes into contact with saliva. This distributes the drug to the gums. Despite its potential as a delivery vehicle, the bulk cubic phase's extremely high viscosity necessitates the use of cubosomes in a number of applications. Although small molecule solutes and unmodified cubosomes are subject to the aforementioned controlled-release limits, cubosomes may have distinct controlled-release pathways. Large poly(amidoamine) dendrimer molecules lose 100 percent of their free diffusivity when trapped in cubic phases[38].

Biologically Active Substances: Cubic stage is delivered at 25 ºC in water monoolein and liquor blends. It was determined that ethanol was more suitable than propanol and butanol. A new transparent, low-viscosity phase known as OL was discovered in the composition range of 49 to 56 weight percent water, 31 to 40 weight percent mono oleine, and 10 to 13 weight percent ethanol. Bright field and polarized light microscopy revealed no structures, indicating that OL is an isotropic phase. CryoTEM revealed extensive domains of this ordered phase, which was identified as a cubic phase through Fast Fourier Transformation[39].

Treatment of Skin, Hair and Body Tissue: Cubic stage materials can be shaped by a straightforward blend of organically viable lipids and water, making them ideal for use in skin, hair, and other body tissue medicines. Cubosomes contain mono-olein, or monoglycerides. Monoglycerides with microbicidal properties Cubosomes contain ethanol, which disrupts the skin. There is more penetration through the skin as a result of the increased fluidity of the lipids. Drugs can enter the skin, bind to skin lipids, and be released into the deep layers of the skin thanks to cubosomes[(40)].

Brain targeting: The BBB prevents drugs used to treat CNS diseases from reaching the brain. The administration of both small and large drug molecules is significantly hampered by this barrier. Cubosomes, a type of lipid-based nanoparticle, have been studied as a means of increasing drug delivery to the brain. Enhancing cubosome-mediated transnasal delivery of resveratrol to the brain is one example. Glycerol monooleate lipid and LutrolR F 127 were used in the probe sonication process to make these. It was dispersed into Poloxamer 407 polymer to create in situ nasal gel after achieving optimal cubosomal dispersion. It had better distribution and transnasal penetration than the drug solution[(41)].

Increasing the corneal permeability: Ocular drug delivery faces a number of difficulties due to the low bioavailability and permeability of the cornea. In a study with the assistance of glycerol monooleate and Poloxamer 407, a cubosome drug delivery system for Timolol Maleate (TM) was developed for the treatment of glaucoma. The penetration of TM cubosomes was found to be higher than that of commercially available eye drops[(42)].

Cosmetics: Cubosomes have been used to make antiperspirants, hair care, skin care, and other cosmetics. A powerful antioxidant, alpha-lipoic acid (ALA) is a naturally occurring fatty acid found in mitochondria. This ALA in cubosome dispersions has excellent results in improving skin texture and color while also reducing facial lines[(16)].

CONCLUSION: Amphiphilic lipids, specifically GMO and PHYT, are the building blocks of cubosomes, which are self-assembling liquid crystals. Cubosomes can encapsulate hydrophilic, lyophobic, and amphiphilic compounds as drug delivery vehicles and range in size from 5 to 10 nm. The production of cubosomes using ultrasonication high-pressure homogenization can take place primarily in one of two ways: either top-down or bottom-up. There is a lot of room for product development given the ability to shape cubosomes in use, during formulation, and during manufacturing. Cubosomes can be given via intravenous, topical, intranasal, ophthalmic, and oral routes, among others, because of their unique properties. One of the most

important and distinctive features of cubosomes is their bioadhesiveness, which enables their use in topical and mucosal depositions for the delivery of various actives. The cubosome technology is new and produces a lot, so there is a lot of room for research into developing efficient formulations for use in business and industry.

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