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CUBIC LIQUID CRYSTALLINE NANOPARTICLES (CUBOSOMES): A NOVEL CARRIER FOR DRUG DELIVERY

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ABSTRACT: Lyotropic liquid crystalline systems, such as reversed bicontinuous cubic phases acquire progressive attention because of their unique microstructure and physicochemical properties. Cubosomes were nanostructured liquid crystalline particles, formed from a certain group amphiphilic lipids in definite proportions in water and was stabilized with a triblock copolymer. Substances in use were biocompatible. Cubosomes are curved bicontinuous lipid bi-layers which were organized in three-dimensional structures resembling honeycomb-like structure with distinct amphiphilic, hydrophilic and hydrophobic regions. They serve as a carrier in drug delivery for various bioactive molecules such as chemicals, drugs, peptides, and proteins to protect them from hydrolysis, oxidation or any other way of degradation. Furthermore, several studies have demonstrated the benefits of cubosomes in nanoparticle drug delivery, sustained release, controlled release, and also to provide improved bioavailability. This article gives an overview of initial work that took advancements till drug delivery, cubosomes types, structure, methods of preparation and primarily the applications of cubosomes in the formulation from the past in various categories drugs and pharmaceuticals.

INTRODUCTION: Liquid crystals were stated that can be considered as the fourth amongst the states of matter along with solids, liquids, and gases. It is an intermediate state that exists between solids and liquids that is they have both solid and liquid properties [1]. For a much better understanding they exhibit regular orientation of the molecules as in solid, and like liquids, they exhibit fluidity and flow like liquids [2]. Solvent molecules were filled in the space around imparting fluidity According to K. Hiltrop [3].

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A liquid crystal is a mesophase which has partially or completely lost the long-range positional order of ordinary crystals, but still possesses one- or more-dimensional long-range orientation order of certain isometric structural units".

Liquid crystals are of two types, thermotropic and lyotropic [3], the former, which is temperature dependent, *i.e.*, phase transition occurs into liquid crystalline phase as the temperature changes. The later, lyotropic liquid crystals (LLC) in which phase transition occurs as a function of the concentration of the mesogen in a solvent which is typically water [5]. Lyotropic liquid crystals have importance in drug delivery application. Many amphiphilic molecules that have distinct polar and non-polar units which may be ionic, non-ionic or cationic shows lyotropic liquid crystal phase sequence.

When an amphiphile is dissolved in water, due to the polar head and nonpolar tail, the molecules self-assemble forming micelles, a similar phenomenon is observed even to surfactants in soap formation. Many amphiphilic molecules show LLC phase sequences based on the volume balance, hydrophilic and hydrophobic regions. When the molecules self-assemble, solvent molecules fill the space around the compounds to provide fluidity to the system [4]. Structure of the molecule depends on the content of the solvent. Micelles formed essentially were amphiphilic monolayer in which aggregates are distributed randomly in the solvent creating an isotropic micellar solution. As the concentration of amphiphile changes, it produces different structured LLC [1, 4].

Molecules are randomly distributed without any order at low concentration of amphiphile. When the concentration is slightly increased, they tend to arrange themselves into micelles or vesicles. At high concentration, assembly becomes ordered, some structures to hexagonal columnar phase, cubic or lamellar [1, 4]. In these binary systems, if the concentration of amphiphile is increased beyond the lamellar phase, they tend to form reverse hexagonal, reversed cubic and reverse micellar cubic phases, *etc*.

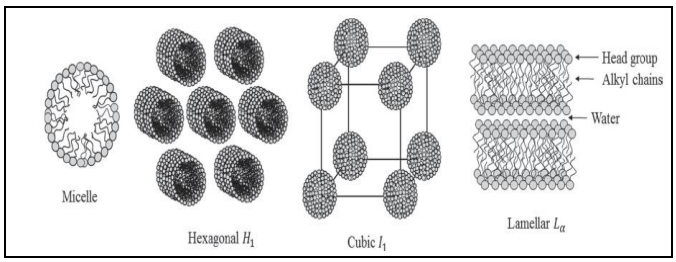


FIG. 1: STRUCTURES REPRESENTING AGGREGATION OF AMPHIPHILES INTO THE MICELLE, AND LLC PHASES SUCH AS HEXAGONAL, CUBIC, AND LAMELLAR PHASES

Thus, formed structures have highly organized structures and are capable of being used in drug delivery. The principal may be simply by dissolving the drug in the liquid crystal matrix which carries the drug to the site of action. In general, such a drug delivery might take place in two stages: first, preparation of liquid crystal and the drug solutions and later dissolving the drug in the liquid crystal [6]. Incorporation of the drug into these structures shows some unique advantageous like, protection from chemical and physiological degradation, *in-vivo*, drug release in a controlled manner and improving the bioavailability of drug while reducing the side effects [7, 8].

Cubic Phases: The structures that show cubic symmetry were known as cubic phases. The existence of cubic structures was first observed by V. Luzzati F, Husson [9] and later Luzzati *et al*., [10] during X-ray scattering study of lipid-water systems with concentration and temperature as a function, has confirmed the appearance of several liquid crystalline structures. This lead the interest in the investigation on simple lipids either alone or in the presence of water, lipophilic solvents or both shows the presence of many liquid crystalline structures, to the fact that lamellar structure being one among all, but it is the one which has drawn the major attention in the early investigations. Initial reports of cubic phases characterize them as, optically isotropic, contains 4.5 Å diffuse band typically of a liquid, two sharp and small angles reflections the Braggs spacing ratio of which is √3: √4. The first cubic structure was proposed by Luzzati consist of the close-packed spheres filled in with the liquid spaces.

Cubosomes: The term ‘cubosomes’ is derived by their structure, since ‘phases’ suffixed as ‘some’ and they have cubic crystal lattice, were called as cubosomes [11]. One of the first published instances of the term is found in a review published by Larsson [12]. Patrick T Spicer *et al*., [13] have mentioned the term ‘cubosome’ being a USPTO trademark of GS development AB Corp. Sweden. Cubosomes are the nanoparticles of bicontinuous, lyotropic cubic phases, comprised of curved lipid bilayers organized into a three-dimensional honeycomb (cavernous) like structures separating two internal aqueous channels and large interfacial area [14]. Cubic phases are optically isotropic, very viscous, and solid like (crystalline) with cubic crystallographic symmetry. Bicontinuous cubic phases have nonintersecting hydrophilic regions separated by a lipid bilayer that is contorted into a periodic minimal surface with zero curvature; hence they were called as viscous isotropic phases. Lutton *et al*., studied the aqueous phase behavior of monoglycerides. Monoglycerides are polar lipids also have poor aqueous solubility and exhibit aqueous phase behavior.

Larsson [15] examined the structure of aqueous monoglyceride cubic phases using X-ray diffraction, and NMR found cubosomes has continuous regions of both hydrophobic and hydrophilic nature, which leads to a conclusion that the cubic phase structures explained with the concept of differential geometry and periodic minimal surfaces [16]. The critical features of cubic liquid phases were their interfacial area (~400 m^2), the thickness of bilayers (3.5 mm) and the diameter of pores (5 mm) [17]. The structural illustrations of Luzzati and Husson [9] revealed that these phases are square shaped and have spherical dots. In the observation of lipid-water binary systems, the cubic phase is formed between the lamellar and hexagonal phases. The most studied binary phase monoolein-water system (GMO/Water), with increased hydrocarbon chain disorder aided by heating or increasing water content, there is a transition from L_∞ to the cubic phase (Q or V) and finally to H_{II-} phase [18].

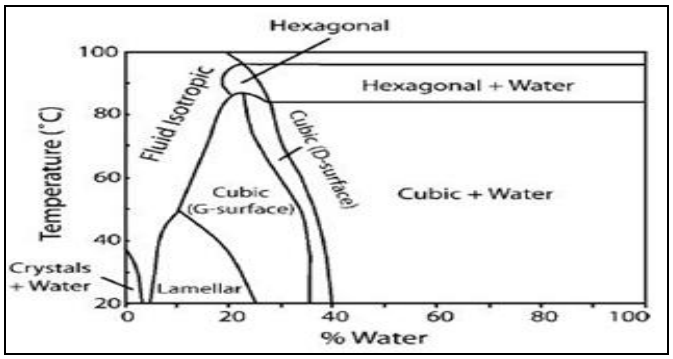


FIG. 2: BINARY PHASE DIAGRAM OF GMO-WATER SYSTEM DEPICTING THE LAMELLAR, TWO CUBIC, AND HEXAGONAL PHASES

Cubic phases were observed to have three structures: Diamond (Pn3m, Q224) or D surface, primitive surface (Im3m, Q299) or P surface and Gyroid surface (Ia3d, Q230) G surface [19]. D surface and P surface were first described by Schwarz and his students in 1980 while G surface was discovered by Schoen in 1960 [20]. In cubic phases, the minimal surface is formed by self-assembled bilayer occur as hydrophobic and hydrophilic portions of surfactant molecules minimize their interaction with the opposite. The three structures found were bicontinuous and has two separate regions of hydrophilic material (water channels). Based on Scriven's [21] suggestions, the minimal surfaces could explain the structure of a liquid crystal. Larsson *et al*., [22] applied the minimal surface description to the cubic phase observed in the monoolein-water system and noted the connection to the structures formed in plastid systems.

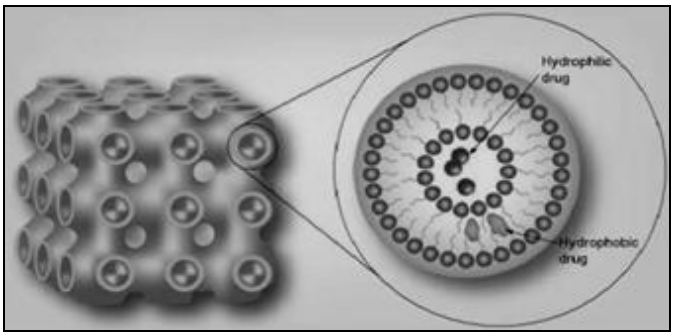
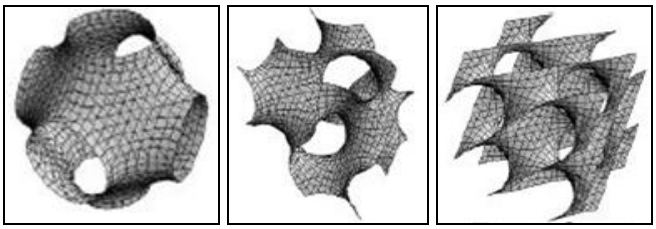


FIG. 3: STRUCTURE OF CUBOSOMES SHOWING HYDROPHILIC AND HYDROPHOBIC REGIONS

Longley and Mcintosh [23] found evidence of an alternative symmetry in the monoolein-water cubic phase, leading to Larsson [24] to realize that two cubic phases are formed, both with minimal surface structures. The monoolein-water system forms the D-surface at high water levels and the G-surface at lower levels, as shown in the phase diagram [25]. Qiu and Caffrey [26] later updated elements of the monoolein-water phase diagram. The P-surface is formed in the monoolein-water system, but only when a third component, such as caseins [27] or amphiphilic block copolymers are added [28].



P-Surface **G-Surface** **D-Surface**

FIG. 4: CUBIC UNIT STRUCTURES REPRESENTING P-SURFACE, G-SURFACE, AND D-SURFACE

Components of Cubosomes: Preparation of cubosomes as mentioned in the literature is simple since they were composed of three major components. Amphiphilic lipids, stabilizer, and water. The important components to discuss amongst are amphiphilic lipids and stabilizer. It is said that amphiphilic upon hydration produce cubic liquid crystalline phases. Stabilizers are polymeric substances that prevent the reconstitution to bulk cubic phase. Some of the most investigated molecules that can form lyotropic liquid crystals are monoglycerides, ethylene oxide amphiphiles [29,

[30], glycolipids [31, 32], phosphatidylethanolamine amphiphiles, urea amphiphiles[33], phytantriol [34, 35,] *etc*.

Amphiphilic Lipids: The most commonly used lipids for the preparation of cubosomes as per the literature are glyceryl mono-oleate (GMO) and phytantriol (PHYT). GMO is a synthetic compound made of glycerides of oleic acid and other fatty acids; the principal component is GMO which belongs to the class amphiphilic lipids [36]. GMO is a food emulsifier used in the food industry is found to produce cubic lipid phases in an unusual place; initial observations during the study of polar lipids such as monoolein [37, 38]. As mentioned change in temperature and concentration leads to the formation of cubic phases. GMO has a hydrophilic head and a hydrophobic tail. Based on Lutton's results monoglycerides with a chain length between 12-22. Have a greater tendency to form cubic phases. GMO is biodegradable and biocompatible recognized safe by GRAS to be used in the food industry as an emulsifier.

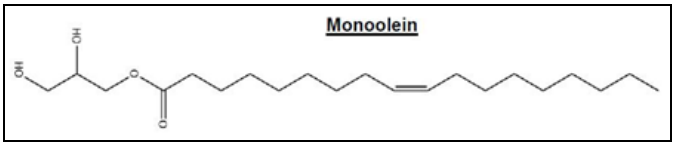


FIG. 5: STRUCTURE OF GLYCERYL MONOOLEATE

Another known substance which is a good alternative for GMO that is used to prepare cubosomes is phytantriol (PHYT), a molecule that contains phytanyl chain. Phytantriol, 3, 7, 11, 15-tetramethyl-1,2,3-hexadecane thiol ($C_{20}H_{42}O_3$) is a key component used in the cosmetic industry [39]. PHYT is a fatty acid based substance susceptible to esterase-catalyzed hydrolysis and offers higher structural stability [40]. Although the two substances differ in their molecular structure and properties, they show similar phase behavior with increased water content and temperature.

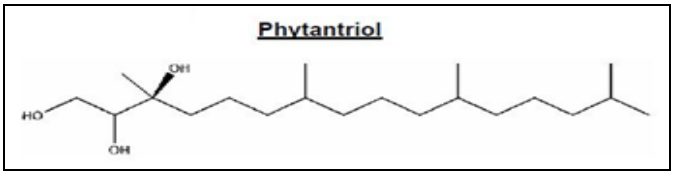


FIG. 6: STRUCTURE OF PHYTANTRIOL

Based on the PHYT-water phase diagram upon increase of concentration at room temperature the structures obtained are reverse micellar, lamellar, Q230 and Q224 respectively. At an elevated temperature of 44 ºC cubic phase turns to a hexagonal structure. PHYT cubosomes exist in equilibrium with water which is a required condition for cubosomes formation [41]. Rizwan *et al*., [42] showed the PHYT made dispersion are stable which incorporating hydrophilic additives and preserve the internal Pn3m nanostructure, while GMO colloidal dispersions show hexosomes that co-exist with Pn3m cubic structure. The purity of the compounds also affects the phase transition [43].

Stabilizer: Surfactants provide colloidal stability to prepared cubosomes. Cubosomes by nature re-coalesce to the bulk cubic phase. Ideal stabilizer for cubosomes prevents unfavorable interactions between hydrophobic domains but encounters between particles, without causing any disruption to the cubic structure. This occurs due to the electrostatic- repulsive barrier between the approaching particles. Hence, these stabilizers were considered to be the essential components of the cubosome formation. Due to the high internal surface area, which leads to stabilizer sequestration [44]. There is so much of work going on using different surfactant materials to stabilize cubosomes.

Of all, the most widely used substance to stabilize cubosomes is the poloxamer 407 (BASF trade name Pluronic® F127), PEO_{99}-PPO_{67}-PEO_{99} a tri-block copolymer, with its PPO portions on either side or within the bilayer and PEO chain exposed to the surrounding water phase [45] were added to stabilize the cubosomal dispersion. It stabilizes by participating within the structure of dispersed particles and manipulates the phase behavior. Usually, poloxamer 407 concentration is applied at a concentration up to 20% w/w with reference to dispersed phase, while the concentration of the monoglyceride- polymer mixture is usually between 2.5 and 10% w/w.

Worle *et al*., [46] investigated the effect of different concentrations of P407 on the properties of cubosomes. Higher concentration of P407 promote the formation of smaller particles but at this state vesicular particles are formed than nanostructure cubic phases. An adequate amount of P407 yields cubic structured nanoparticulate dispersions. The occurrence of the type of cubic crystal depends on

the internal crystalline structure and composition. P407 adsorbed to the surface of the bulk PHYT cubic phase, while for monoolein cubic phase P407 was integrated into the liquid crystalline structure[47].

Wadsten-Hindrichsen *et al*., studied the effect of three water-miscible solvents including propylene glycol (PG), polyethylene glycol 400 (PEG400) and 2-methyl-2,4-pentanediol (MPD) on PHYT based systems. They showed that MPD produces a sponge phase whereas, with PG and PEG400, only cubic, lamellar and non-ordered liquid phases were identified. Zhain *et al*., [48] substituted *β*-casein with P407 as the stabilizer were studied The GMO–*β*-casein cubosomes display a Pn3m phase structure and a QII to HII phase transition at 60 °C. In comparison, P407–GMO dispersion had an Im3m phase structure, and the HII phase only appeared at higher temperatures, that is 70 °C.

In the case of PHYT systems, only the Pn3m phase structure was detected irrespective of the type and concentration of the stabilizer. By contrast, the *β*-casein-PHYT system displayed a QII to HII to Lα transition behavior upon heating, whereas P407-PHYT dispersion displayed only a direct QII to Lα conversion. The *β*- casein gives steric stabilization to dispersions of lipid nanostructure particles and avoids the transition to the Im3m structure in nanoparticles. The poly (ethylene oxide) stearate stabilizers (also called; Myrj) were found to be effective as steric stabilizers in cubosomes. Myrj 59, with an average of 100 poly (ethylene oxide) proved to be more effective than P407 for PHYT cubosomes at a concentration fivefold lower than that achievable with P407 [49]. Uyama M *et al*. used modified cellulose materials such as hydroxypropyl methylcellulose acetate succinate (HPMCAS) also showed roughly equal stability to GMO-based cubosomes with P407 [50]. Zhai *et al*., [51] explored the ability of 1, 2-distearoyl-sn-glycerol-3-phosphate-ethanolamine conjugated with PEG (DSPE–PEG) on PHYT-based cubosomes, because bio-compatibility depends on the selected stabilizers and selected lipid. The cubosomes prepared using DSPE–PEG showed reduced cytotoxicity.

Josephine Y.T. Chong *et al*., [52] have evaluated the triblock co-polymers series on steric stabilization of cubosomes. Accordingly, 20 different types of polymers were studied for having the property of steric stabilization. It is shown that pluronic F108 is superior to pluronic F127 as a stabilizer for the monoolein based particle as it is said to preserve the integrity of the diamond inverse bicontinuous cubic phase internal structure. Few polymers in the pluronic series were found useful in the formation of lyotropic liquid crystals. Of all, F108 produces Pn3m structured crystals, pluronic F 68, F87, P104, P105 and F127 gives Im3m crystal structures.

Preparation Methods: Liquid crystals can be made simply by mixing the aqueous phase with the lipid phase using vortex or ultra sonification [1, 42]. Bulk cubic gels were made easier than their dispersions. It is a critical concern of any method is cost, time and energy efficiency. The method needs to be scalable and adaptable to bulk production. There are two main approaches to produce cubosomes; they are top-down and bottom-up approaches.

Top-down Approach: This is the most commonly used method of preparation [53] initially reported by Ljusberg-Wahren (1996) [21]. This process is carried out in two steps. First is the formation of viscous bulk cubic phase by mixing lipid(s) with stabilizer(s); thus aggregation takes place. The second step is derived from step one. Here bulk cubic phase will be dispersed into the aqueous medium through the application of high-pressure homogenization or sonication / high energy dispersions [54] to form cubosomes dispersions (nanoparticles). Bulk cubic phase is like cross-linked clear gel-like polymer which is swollen by water. Cubosomes obtained through this approach always coexist with vesicles or vesicle-like structures of dispersed nanoparticles of the lamellar liquid crystalline phase [55].

Worle *et al*., [56] studied the effect of temperature during homogenization on the particle size distribution of the cubic phases. According to the study it is found that between 40-60 ºC colloidal dispersions can achieve, at a higher temperature at 60 ºC it is observed that particle size will be less and at a much higher temperature at 80 ºC the quality of cubic dispersions were poor but at this temporary temperature formation of D type, cubic structure is observed. Although cubosomes obtained in this process are stable, the Large-scale production using this process is a major drawback.

This high process energy required to homogenize the bulk phase requires more energy input which in large scale is nearly not possible, and it is difficult to incorporate thermo-labile ingredients, peptides, and proteins.

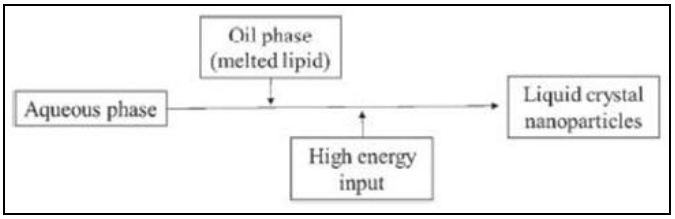


FIG. 7: SCHEMATIC REPRESENTATION OF THE TOP-DOWN PROCESS

Bottom-up Approach: Another alternative approach in the preparation of cubosomes at room temperature is by crystallization from the precursor. Scale up of the top-down approach is found to be very difficult with the high energy requirements to form the dispersion of cubosomes from the viscous bulk cubic phase. To solve these problems Patric T. Spicer *et al*., [57] studied cubic phase formation in the presence of a hydrotrope. Hydrotrope here is a molecule that is hydrophilic or hydrophobic but incapable of exhibiting surfactant behavior (Micelle formation). Although it was reported that some hydrotropes disrupt the Liquid crystals, but few functions as facilitators of dispersed liquid crystalline particle formation. The key role of a hydrotrope is making a liquid precursor by dissolving the lipids and thus prevent the formation of a viscous liquid crystal [58].

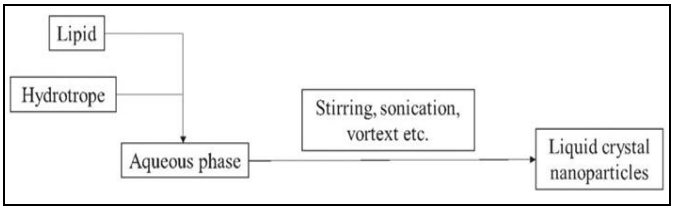


FIG. 8: SCHEMATIC REPRESENTATION OF THE PROCESS INVOLVING LIQUID PRECURSOR

Hydrotropes do not produce LLC, but they increase the solubility of the lipids and exhibit a phenomenon called 'salting out' precursor may be of liquid or a solid. The liquid precursor is made from adding ethanol to the lipid (monoolein) ethanol. When the precursor is diluted, cubosomes are produced. To produce cubosomes in this unique process, there is primary prerequisite to study the ternary Phase diagram of lipid-water- hydrotrope system enables to understand the full phase behavior to know the extent of dilution which is a crucial factor.

Powdered precursors were composed of a dehydrated substance coated with polymer upon hydration forms cubosomes. Powdered precursor has some advantage to liquid precursor cubosomes. Kim *et al*., [59] attempted to create powdered precursor by freeze-drying; however, it was unclear if cubosomes were produced or not due to the lack of the data. In the preparation of drug-containing vesicles prepared by freeze-drying technique, Freitas & Muller [60] produced solid lipid nano-particles using spray drying technology. Patrick T. Spicer *et al*., [61] has worked on producing starch, and dextran powder precursors using a spray drying technique upon addition of water produce cubosomes. Monoolein encapsulated in aqueous star paste is difficult to be sprayed in spray dryer due to the Immediate formation of cubic phases. Hence, hydrophobically modified starch is used to encapsulate monoolein. Starch-monoolein-water system can be characterized by a 'pseudo-ternary equilibrium phase diagram.'

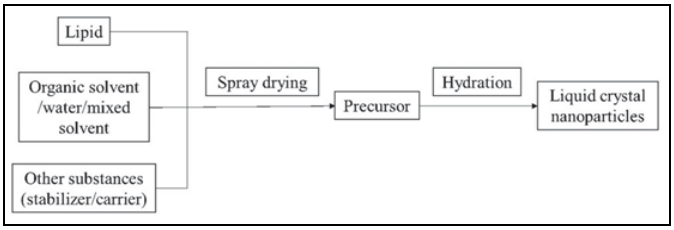


FIG. 9: SCHEMATIC REPRESENTATION OF THE PROCESS USING POWDER PRECURSOR

Another alteration of producing dry powder Precursor is with dextran with an additional dispersion step. Ethanol is used to dissolve a cubic liquid crystalline phase, and it acts as hydrotrope [62]. Dextran is a substitution for starch and is used as a film former. Upon addition of monoolein-dextran-water system an emulsion is formed quickly and is easy to spray dry removing water and ethanol. Dry particles produced by both ways are 24 µm in diameter on hydration cubosomes produced are of 0.6 µm size.

Drug Release from Cubic Phases: Due to their unique structure, Hyde *et al*., [63] have studied the controlled release application. Further investigation of the structure of these phases found that its distinct structure provides a tortuous diffusion pathway for controlled release [64, 65].

Diffusion is the general mechanism of drug release as the drug concentration gradient is the driving force across the cubosomes [64]. Certainly, there are many factors influencing the drug release rate, such as (1) drug solubility, diffusion coefficient, partition coefficient, *etc*. (2) cubic liquid crystalline geometry, pore size and distribution, and the interface curvature; (3) temperature, pH, and ionic strength of the release medium [65, 66].

Potential of Cubosomes in Drug Delivery Application: Cubic phases are discrete particles which serve as carriers in the drug delivery systems. Cubosomes have similar micro-structure like the bulk cubic phase and also contains the larger surface area and much lower viscosity. Cubosomes are relatively insoluble in any dilution and is easily incorporated into the product formulations. Formulation with cubosomes has shown some advantages: They prove to improve the absorption, serve as delivery vehicles for poorly water-soluble drugs, bioadhesive and lipid-based nanoparticles they are biocompatible with the biological environment. Bicontinuous structure makes it possible to incorporate hydrophilic, hydrophobic or amphiphilic drugs into cubosomes. After formation of cubosomes, the dispersions were formulated into a product and then applied to the substrate. Landh and Larsson [68] filed the first patent explaining cubosomes usage, specifying numerous medical and controlled release applications.

Cubosomes for the Oral Route: Oral drug delivery is one of the conventional routes of administration and most common. Cubosomes a novel nano-carrier system with many advantages drew the interest of researchers to formulate oral dosage forms. Chung *et al*., [68] succeeded to improve oral absorption of insulin by GMO-based cubosomes, poorly water-soluble drugs would meet a different fate in the gastrointestinal (GI) tract. YS Tu *et al*., [69] formulated cubosomal nano-particles with piperine and curcumin with phytantriol, made into a liquid precursor stabilized by pluronic ® F127 and also vit E has found to have improved the bioavailability than the suspension. Amphotericin B shows poor bioavailability. ZhiwenYang *et al*., [70, 71] worked on the preparing cubosomes in solemuls technology for the enhancement of the bioavailability. A pharmacokinetic study of ibuprofen-incorporated cubosomes made of PHYT and P407 indicated improved absorption of ibuprofen from cubosomes compared with conventional ibuprofen with a longer half-life and appropriate relative oral bioavailability [72]. Clotrimazole antifungal activity has been improved in ribosomal formulation than the suspension of clotrimazole against *Candida albicans* [73]. Efavirenz (EFV) cubosomal formulation provided sustained action and also improved Bioavailability[74]. Elnaggar, Y.S. *et al*., [75] monoolein cubosomes modified with (T-cubs) loaded with piperine orally targeting the brain parenchyma. *In-vivo* study results showed the drug-loaded (T-cubs) produce potential anti-inflammatory and anti-apoptotic activity of piperine, indicating the potential to stop Alzheimer's disease (AD). glibenclamide cubo-some were prepared by a top-down approach and administered as capsules. *In-vitro* release kinetics exhibited the drug release up to 7 h [97]. 5-Fluorouracil (5-FU) hydrophilic anticancer drug is formulated into cubosomal dispersions to target liver found to have better bio-distribution and delayed drug release [98].

Cubosomes for the Topical Route: Drug delivery through the skin is limited because of the external layer of the skin stratum corneum. Several approaches have been presented to improve the skin permeation such as chemical modification of the active molecule, applying a skin permeation enhancer and iontophoresis. The crucial issue in topical formulations is to increase the thermodynamic activity of the active molecule in the vehicle while decreasing it in the skin, which results in increasing the partition of the molecule from vehicle to skin and decreasing the barrier function of the skin.

Sung Kyeong Hong *et al*., [76] prepared a hot water extract KIOM-C from plant sources and compared the conventional suspension with cubosomal suspension and concluded that stability and sedimentation rate had been improved. Nadia M. Morsi *et al*., [77] prepared cubosomal hydrogels for the treatment of burns with silver sulfadiazine and reported that cubosomes formulation treats second-degree burns in rats. It is in practice to use herbal drugs for the treatment of various alignments for therapeutic and cosmetic purpose. Various cubosomal herbal drugs like Hinokitiol [78], soluble extracts of Korean barberry [79] Tacrolimus [80] and

herbal extracts from various plants [81] were formulated and tested for enhanced skin permeation and enhanced the therapeutic effect. Synthetic drugs like diclofenac sodium [82], triclosan [83], fluconazole [84], miconazole [85], curcumin [86], indomethacin [87], *etc.* were formulated as topical drug delivery systems using cubosomes as a carrier, the formulations entrapment efficiency, skin permeation, improved stability, and therapeutic action.

Cubosomes in Intravenous Route: Intravenous administration have special considerations to maintain the particle sizes in the colloidal range, to avoid problems that could occur from capillary blockage by outsized particles and interaction between the particles and plasma components is important for the stability of carriers although the surface modification can potentially minimize the interactions of the carrier with blood components, thus extend the lifespan in the blood circulation. Leesajakul *et al*., [88] investigated the effects of some plasma components such as high-density lipoprotein (HDL), low-density lipoprotein (LDL) and albumin on the integrity and stability of GMO-based cubosomes as well as the *in-vivo* behavior of particles after intravenous injection.

Bode *et al*., [89] studied 407, a steric stabilizer, not useful in the protection of ribosome structure interactions with blood compounds and also found the cubosomes based on GMO-P407 have a low but detectable tendency toward hemolysis. They suggested P188 instead of P407 produce stable cubosomes for parenteral use. Sterility is another important concern for parenteral usage; autoclaving is a standard sterilization method for aqueous pharmaceutical formulations. Worle *et al*., [90] worked on the effect of autoclaving on the structure and Stability of cubic-phase dispersions of GMO. After autoclaving, the majority of the particles in two different colloidal systems became larger with cubic matrix and only a few small non-cubic particles remained whereas vesicular particles almost completely vanished. Therefore, the heat treatment of GMO-based dispersions can convert vesicular dispersions into cubosomes as well. Esposito *et al*., [91] presented a comparative study of the anti-Parkinson's drug bromocriptine (BC), including monoolein cubosome and nanostructured lipid carriers (NLCs). Cubosomes and NLC were shown to encapsulate BC with high entrapment efficiency of the drug test to a much lesser degree than those attained with the other preparations.

Cubosomes in Nasal route: Direct nose-to-brain delivery of therapeutics, bypassing the blood-brain barrier (BBB), has provided a noninvasive and effective route in the treatment of central nervous system (CNS) disorders. Wu *et al*., [92] engineered PEGylated cubosomes with functional molecules of odorranalectinwere studied using coumarin as a marker and its relative uptake were about 3.46-fold in the brain compared with untreated cubosomes. Further, Gly14-human (S14G– HN) was incorporated into cubosomes and investigated for its therapeutic effect in the AD. The results showed that using odorranalectin cubosomes could improve the effects of S14G-HN in AD. Mayuri Ahirrao *et al*., [93], studied the delivery of resveratrol targeting brain in nasal route by cubosomes to treat Alzheimer's disease. GMO P407 cubosomes were made by probe sonication method. *In-vitro* drug release showed a controlled pattern for almost about 24 h.

Cubosomes for Ophthalmic Drug Delivery: Drugs were administered to the eyes as drops in general because of the blinking, tears, nasolacrimal drainage drug removal is often. pH, the lipophilicity of the drug and corneal epithelium were the considerable facts that affect poor bioavailability of the drugs. Shun Han *et al*., [94] studied cubosomes as an ophthalmic drug delivery carrier for flurbiprofen (FB). The cubosomes showed low ocular irritation as evaluated by the Draize method and histological examination. *In-vitro* corneal penetration, evaluation proved their capability of increasing the transcorneal permeation of FB. Cubosomes were loaded by dexamethasone (DEX) [95] to enhance pre-ocular retention and ocular bioavailability. The drug is incorporated in cubosomes exhibited about 3.5- and 1.8- fold increase in comparison with free DEX eye drops.

Moreover, after incubation with drug cubosomes, corneal cross-sections confirmed an unaffected corneal structure and tissue integrity, indicating the good biocompatibility of cubosomes. Zubair Ali *et al*., loaded Ketorolac in cubosomes by using GMO and P.407.

The formulation found to have transcorneal permeation and retention of ketorolac was achieved by the developed cubosomal formulation. Histopathology study revealed that ketorolac loaded cubosomes were safe for ocular use. In conclusion, from the studies in ophthalmic drug delivery using cubosomes, it is obvious that this system can be used as a promising vehicle for effective ocular drug delivery [96].

CONCLUSION: Cubosome nanoparticle is lyotropic liquid crystalline materials and has found to be a potential advantage in drug delivery through various routes. Cubosomes are nontoxic, biocompatible, bioadhesive, larger surface area and flexible to incorporate hydrophilic hydrophobic or amphiphilic drugs have drawn the interest of the researchers to apply in drug delivery as carriers. Although there is much research on cubic phases in formulation studies, there is still more to explore this application for development of newer methods of production and also for applying this nanoparticulate carrier in various other fields of drug delivery.

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