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CUBOSOME: A NOVEL VESICULAR DRUG DELIVERY SYSTEM

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ABSTRACT: Cubosomes are square and rounded particles with internal cubic lattice. Cubosomes are thermodynamically stable and consist of honeycombed (cavernous) structures separating two internal aqueous channels and a large interfacial area. Cubosomeisa novel biocompatible drug delivery system whose diameter size range from 10–500 nm. *Cubosomes possessa* great significance in the field of cosmeceuticals and Pharmaceuticals due to their unique features and become an attractive choice of vehicle for *in-vivo* drug delivery due to their low cost, safety, efficacy, and versatility for controlled release application and functionalization. Cubosomes have a very simple method of preparation. Cubosomes are nanoparticles that are self-assembled liquid crystalline particles of certain surfactants with a proper ratio of water with a microstructure that provides unique properties of practical interest. The word bicontinuous refers to the division of the two continuous but non-intersecting aqueous regions by a lipid bilayer that is twisted into a space-filling structure. The controlled release application of these nanoparticles is of great significance in cosmeceutical and pharmaceutical fields, and they can be characterized by various evaluation parameters. The low cost of the raw materials, versatility, and the potential for controlled release through functionalization make them an attractive vehicle for several *in-vivo* drug delivery routes. This review article other than this mainly focuses on the history, structure, types, advantages, disadvantages, and applications of cubosomes.

INTRODUCTION: A drug delivery system is a device that safely brings a therapeutic agent to the specific body site at a certain rate to achieve an effective concentration at the site action.

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The release of drugs in a predesigned manner is termed controlled drug release (CR), which is used to promote therapeutic benefits while minimizing toxic side-effects.

Surfactants and polymers are generally used in the controlled drug delivery systems. Sustained release over an extended period may reduce the need for multiple dosing which will be a benefit in terms of reduced cost and increased patient compliance [1-3]. To achieve targeted drug delivery by encapsulating

the drug within a vesicular structure such a system is known to be a vesicular drug delivery system. In this system, if the vesicles behave as a carrier system it will transport the high molecular weight of drugs, and if behave as a penetration enhancer it will increase the drug transport rate across the skin [4, 5].

There is a huge number of vesicular drug delivery systems that allow drug targeting and the sustained or controlled release of conventional medicines. Surfactant and polymer systems form supra-assemblies, which are extensively exploited as active delivery vehicles. These systems include liquid crystalline aggregates (*e.g.*, liposomes and cubosomes), dehydrated form niosomal dispersion (proniosome), orcross-linked gel networks (hydrogels) that load, stabilize, and eventually deliver active ingredients.

The potential for utilizing a particular activity with a vehicle depends on the physicochemical properties of both. To achieve therapeutic effects, it must be possible to load sufficient amounts of the active, which largely depends on the interaction of the vehicle and active. Further, the integrity of the action must be retained through all stages: preparation, storage, and use. The release rate of actives must be controlled to achieve optimal drug release profiles, while ease of preparation and vehicle stability must also be considered. An optimal delivery vehicle must successfully encompass all these properties [6].

Lipids, surfactants, and polymer molecules have both polar and non-polar components are termed amphiphilic. Amphiphilic molecules play an important part in drug delivery owing to their self-assembly ability under certain conditions, eventually leading to highly organized structures capable of being used in drug delivery systems. Protecting loaded actives against chemical and/or physiological degradation in vivo, drug release in a temporally and/or spatially controlled manner, as well as improving the bioavailability of the drug while reducing side-effects observed upon drug administration are some unique advantages this class of nanocarriers offers [7, 8]. 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 [9]. 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 [10].

Solvent molecules were filled in the space around imparting fluidity [11]. A liquid crystal is a mesophase that 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 a certain isometric structural unit. Liquid crystals are of two types, thermotropic and lyotropic [11], the former, which is temperature-dependent, *i.e., a* 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 mesogenic in a solvent which is typically water [13]. Lyotropic liquid crystals have importance in drug delivery applications. Many amphiphilic molecules that have distinct polar and non-polar units which may be ionic, non-ionic, or cationic show 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 [12]. The 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 [9, 12]. Molecules are randomly distributed without any order at a 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 [9, 12].

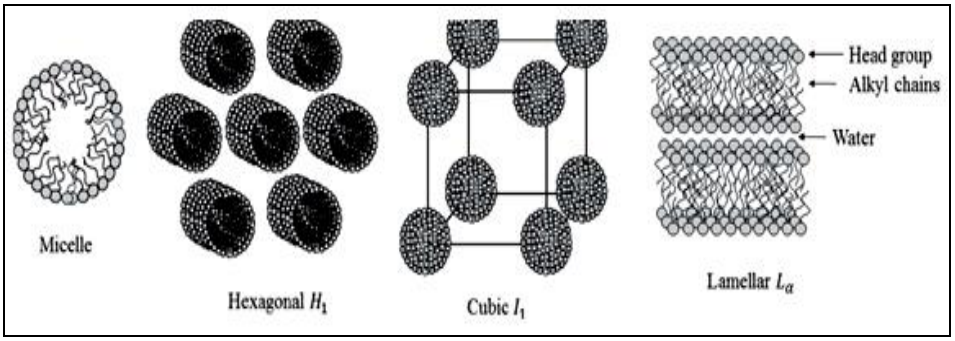

FIG. 1: STRUCTURES REPRESENTING AGGREGATION OF AMPHIPHILES INTO THE MICELLE, AND LLC PHASES SUCH AS HEXAGONAL, CUBIC, AND LAMELLAR PHASES

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*. 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 [14]. Incorporation of the drug into these structures shows some unique advantages 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].

These structures have gained considerable interest in recent years owing to their unique physicochemical properties, in particular, their strong ability to encapsulate diverse active molecules from hydrophilic, hydrophobic, and amphiphilic classes. In the following sections, we briefly introduce the bicontinuous cubic phase and its potential applications in drug delivery. In particular, the structure, chemistry, preparation methods, and current applications of cubosomes in drug delivery will be discussed based on the recent literature published in the field. In another way, among the variety of amphiphilic molecules, the self-assembly of amphiphilic lipids as a result of the hydrophobic effect could potentially lead to some well-defined, thermodynamically stable structures such as lamellar (La), hexagonal (HII), and bicontinuous (QII) cubic phases, collectively known as lyotropic liquid crystal (LLC) systems shown in **Fig. 1**, all of them having a sufficient average degree of molecular orientation and structural symmetry [15, 16]. By dispersion of these poorly water-soluble structures in aqueous media, the main typically obtained nanostructures are liposomes, as a result of the dispersion of a huge lamellar phase; cubosomes, formed by reversed bicontinuous cubic phase; and hexosomes, from the reversed hexagonal phase [17, 18]. In such a system cubosomes are also part of the vesicular drug delivery system or lipid-based colloidal system which were discovered in 1980. The term “Cubosomes” reflects the cubic molecular crystallography and similarity to liposomes [3, 19].

History: Despite the early recognization (1980) large-scale manufacture of cubosomes was difficult due to their complex phase behavior and viscous properties. Thecubic phases are unique as possess very high solid-like viscosities because of their intriguing bicontinuous structures [20]. Among the liquid crystalline structures self-assembled from aqueous surfactant systems, bicontinuouscubic phases possess a special status. Bicontinuous cubic phase liquid crystals are newly discovered exotic materials originally found in the most unexpected places. The original observations of the cubic liquid crystalline phase came during the study of polar lipids, such as monoolein **Fig. 1**, that are used as food emulsifiers [21, 22]. Cubic phases can be fractured and dispersed to form particulate dispersions which are colloid ally and/or thermodynamically stable for a longer period. Certain surfactants spontaneously form cubic phases when mixed with water above a certain concentration. Determination of their “honeycomb” structure was carried out using X-ray scattering measurement [23, 24, 25, 26] between 1960 and 1985. An effort to develop scalable processes to produce cubosomes on large scale is under development.

A few anticancer drugs have been successfully encapsulated in cubosomes and characterized [27]. Cubic phase in ternary systems of amphiphiles, oils, and water in parallel although without apparent awareness of the lipid work [28]. Around the same time, a comprehensive study of the aqueous phase behavior of monoglycerides was published. Monoglycerides are polar lipids with poor water solubility that exhibit aqueous phase behavior reflecting their structural similarity tonon-ionic surfactants. The preparation of colloidal dispersions of no lamellar lyotropic crystalline phases and have termed the particles "cubosomes" [29]. Cubosomes usually have been produced using time-consuming methods involving high-energy input. For instance, The production and structure of aqueous dispersions of lipid-based lyotropic liquid crystalline phases. The dispersions were based either on glycerylmonooleate /sunflower oil orglycerylmonooleate/ retynilpalmitate mixtures plus a nonionictriblock polymer (Poloxamer 407) in water. Dispersions were produced by dropwise addition of a melt of lipids and poloxamer in water, followed by reduction of size by homogenization under high pressures at 80 °C [30]. The preparation and characterization of dispersions constituted of monoolein-rich monoglycerides with or without purified soya phospholipids Dispersions were prepared by equilibration of the monoglyceride/ phospholipid/water cubic phase, subsequent fragmentation by a solution of Poloxamer 407, predispersing by probe sonication, and finally high-pressure homogenization [31]. Moreover, some authors have developed experimental protocols for cubosome production based on the use of organic solvents. In particular, a method based on a dilutionprocess of an ethanolic solution of monoolein with an aqueous solution of poloxamer was proposed. Ethanol was used as a hydrotropeto create a liquid precursor, spontaneously forming cubosomes after dilution. A method to produce cubosomes based on the hydration of a dry film of monoolein/poloxamer with an aqueous buffer [32].

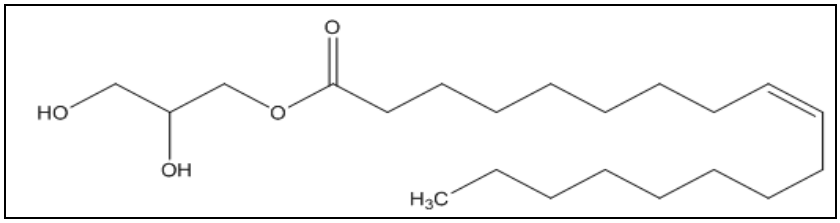

FIG. 2: STRUCTURE OF MONOOLEIN

Cubosome: The term "cubosomes" is derived by their structure, since "phases" suffixed as "some" and they have cubic crystal lattice, were called as cubosomes [33]. Cubosomes are nanoparticles, more accurately nanostructure particles of a liquid crystalline phase withcubic crystallographic symmetry formed by the self-assembly of amphiphilic or surfactant-like molecules [34]. Cubosomes possess a larger surface area and have the same microstructure as that parent cubic phase and the prepared cubosomes dispersions have much lower viscosity compared with the bulk cubic phase [35]. Due to its amphiphilic nature molecules progress by the hydrophobic effect into a polar solvent to spontaneously recognize and unite into a liquid crystal of nanometer scale. Thus, Cubosomes are bicontinuous cubic liquid phases surrounded by two different regions of water separated by surfactant-controlled bilayers [36]. Further, these are parallel to a liquid crystalline substance with cubic crystallographic symmetry and are visually isotropic, viscous, and solid too. The cubic phase can split and form thermodynamically stable particulate dispersions [37]. Cubosomes are defined as discrete, sub-micron, nanostructured particles of bicontinuous cubic liquid crystalline phase [38]. These nanostructured particles [39], of a liquid crystalline phase with cubic crystallographic symmetry, are liquid instead of solid. Cubosomes are typically produced by high-energy dispersion of bulk cubicphase, followed by colloidal stabilization using polymeric surfactants. After the formation of the cubosomes, the dispersion is formulated into a product and then applied to a substrate of interest, usually bodily tissue [40]. However, at present cubosomes do not offer controlled release on their own [41]. They have also been modified using proteins [42, 43]. Bulk cubic phase is formed by hydration of monoolein at levels between 20-40% w/w. The cubic phase is unique and desirable as a

result of its mesoscale structure: a contorted lipid bilayer separating two continuous but nonintersecting water regions [20, 44]. The tortuous structure of the bulk cubic phase provides a controlled release of solubilised active ingredients [45], while cubosomes exhibit burst release because of their sub-micron length scales [41]. Cubosomes have great potential in drug nanoformulations. In cubosomes active chemical constituent molecules are anchored through chemical bonds to the polar head of the phospholipids. The polymer and the individual drug compound form a 1:1 or 2:1 complex depending on the substance. Despite the early recognization (in 1980) large-scale manufacture of cubosomes was difficult due to their complex phase behavior and viscous properties. Certain surfactants spontaneously form cubic phases when mixed with water at a certain concentration [46]. Cubosomes have been patented for use as active delivery vehicles [30], emulsion stabilizers [47], and pollutant scavengers [48, 49] in various pharmaceutical and personal care products [50-53]. In recent years, cubosomes (cubosome dispersions) were considered as the drug nanocarrier due to their great potential as an alternative drug delivery system relative to liposome.

Cubic Phase: The structures that show cubic symmetry was known as cubic phases. The existence of cubic structures was first observed [23] 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[24]. 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 cubic liquid crystalline phase has been evaluated for mucosal, periodontal, transdermal, and local drug delivery mainly owing to its bioadhesion properties. Some reported studies on applying cubic phase as a drug delivery system with various aims are listed in **Table 1**. They developed the cubic phase as a sustained release system as well as an embolization agent. The *in-vivo* embolization study was carried out with normal rabbits using trans-catheter arterial embolization. The angiographical results showed that the hepatic artery was effectively embolized with cubic phase to provide sustained release. In another study, the cubic phase was presented as a promising carrier to shield insulin from agitation-induced aggregation and precipitation.

TABLE 1: CUBIC PHASE AS DRUG VEHICLES REPORTED IN RECENT YEARS

Composition of cubic phase	Therapeutic agent	Route of administration	Refs.
Lauric acid–monolaurin	Cinnarizine	Intraduodenal	54
Phytantriol	Docetaxel	Intravenous	55
Glyceryl monooleate	Cinnarizine	Oral	56
Oleyl glycerate	Cinnarizine	Oral	
Glyceryl monooleate	Clonidine	Intraarticular	57
Glycerol monooleate–PEG200–oleic acid	[D-Ala2,D-Leu5]enkephalin	Buccal	58
Glycerol monooleate	Cyclosporin A	Topical	59
Phytantriol	Sulforhodamine B	Topical	60
Glycerol monooleate	Bovine serum albumin	Mucosal	61
Glyceryl monooleate	δ-Aminolevulinic acid	Topical	62
Glycerol monooleate	Oligonucleotide	Intravenous	63
Glycerol monooleate	magnesium trisilicate Diclofenac sodium	Oral	64
Glycerol monooleate	Paclitaxel	Oral	65

Structure: Cubosomes consist of honeycombed (cavernous) structures separating two internal aqueous channels and a large interfacial area. Self-assembled cubosomes as active drug delivery systems are receiving much more attention and interest after the first discovery [3, 66]. Cubosomes are nanoparticles whose size ranges from 10–500 nm in diameter and appear like dots, which are likely to be spherical. Each dot corresponds to the presence of a pore containing an aqueous cubic phase in the

lipid water system. The Ternary systems of amphiphiles, oil, and water, some monoglycerides will exhibit cubic phases. Monoglycerides are polar lipids and have poor water solubility that exhibits aqueous phase behavior, which is structurally mimicking to non-ionic surfactants [24, 28]. Cubosomes are amphiphilic carrier system which can encapsulate both hydrophilic and lipophilic drugs. The hydrophilic drug is encapsulated inside the vesicles whereas the lipophilic drug is partitioned between the hydrophilic domains. Chemical instability like oxidation of phospholipids was not avoided [67]. These pave the way for the discovery of non-ionic surfactant vesicles known as cubosomes [68].

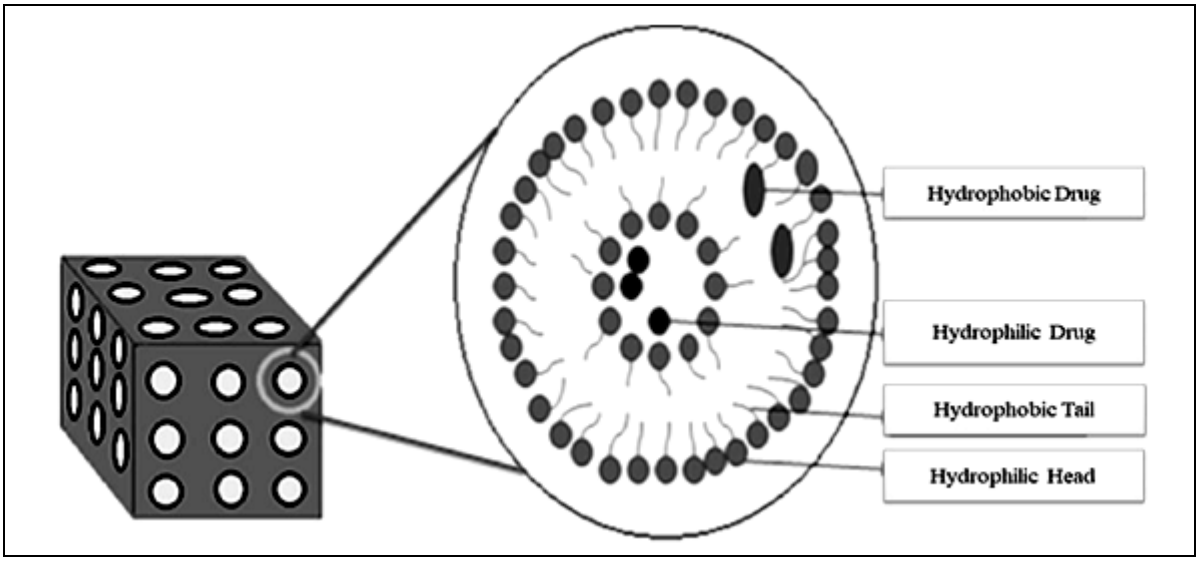

FIG. 3: STRUCTURE OF CUBOSOME

The inimitable microstructure of cubosomes confers some desirable characteristics as far as controlled release is concerned. Firstly, the drugs of varying polarities and sizes can be entrapped in the cubic phases [69]. Because of the dual polar/nonpolar nature of the cubic phase, hydrophilic drugs are trapped in the aqueous channels while their hydrophobic counterparts will partition into the lipid bilayer compartment which will be the rate-limiting step [26, 70]. Secondly, the unique microstructure of the cubic phase controls the degree of drug release. Thus, the drug must diffuse from the three-dimensional network in which both tortuosity and pore size of the aqueous nanochannels contribute to delayed/controlled release. Thirdly, the cubic mesophases are stable *in-vitro* and may be subjected to lipolysis which facilitates ultimate dissolution *in-vivo*. Finally, the cubic phase exhibits a bioadhesive property [71], which makes it useful for the delivery of gastrointestinal, lung, nasal, oral, buccal, rectal, and vaginal drugs [72]. Three structures of cubosomes have been proposed [73] (i) P*n*3*m* (D-surface) (Diamond surface), (ii) I*a*3*d* (G-surface) (Gyroid surface), and (iii) Im3m (P-surface) (Primitive surface), in terms of nodal surfaces. The structure generally maintains the efficacy; stability of actives such as vitamins and proteins. Cubosomes are thermodynamically stable, lasting indefinitely.

FIG. 4: TYPES OF STRUCTURES OF CUBOSOMES

Advantage [74-77]:

1. It is economic.
2. It is non-toxic and biocompatible and digestible.
3. The method of preparation is simple.
4. It has excellent bioadhesive properties.
5. It has skin permeation enhancement.
6. For a longer time, they are thermodynamically stable.
7. The capability of encapsulating hydrophilic, hydrophobic, and amphiphilic substances.
8. Targeted release and controlled release of bioactive agents
9. Due to high internal surface area & cubic crystalline structures, there is high drug loading.
10. Cubosomes are useful over other drug delivery systems due to their bioavailability improvement of poorly soluble drugs and enhances skin permeation, by this it reduces the cost of therapy.
11. The surfactant used in cubosomes does not require any special handling and storage conditions.
12. One of the reasons to select cubosomes as carrier systemsare that it possesses high physicochemical stability of surfactant and emulsifiers than that of phospholipids which are used in the preparation of liposomes.

Disadvantages [66, 78, 79]:

1. Due to the presence of large amounts of water inside cubosomes there is low entrapment of water-soluble drugs.
2. Large-scale production is difficult sometimes because of high viscosity.
3. Cubosomes and when compared with polymer-based drug delivery cubosomes do not offer controlled drug delivery on their own.

Types of Cubosomes:

A. **Liquid Cubosome Precursors:** The hydrotrope dilution process is found to produce more stable and smaller cubosomes. The nucleation process allows the formation of particles whose growth is seen under crystallization and precipitation processes. Monoolein is properly dissolved in a hydrotrope, such as ethanol, which prevents it from the liquid crystalline formation. Thus, dilution of this mixture spontaneously "crystallizes" or precipitates the cubosomes. The liquid precursor process is allowed for easier scale-up of cubosome preparations and avoids the bulk solids handling and potentially damaging high energy processes [73, 80, 81].

B. **Powdered Cubosome Precursor:** Powdered cubosome precursors are composed of dehydrated surfactant coated with a polymer. Such powders offer advantages to liquid phase hydrotropic cubosome precursors. Cubosomes with a mean particle size of 600 nm are formed by the hydration of the precursor powders, as confirmed by light scattering and cryo-TEM. Cubosomes which are made up with the use of lipids are waxy and sticky solids. Coating of the waxy lipid on water-soluble non-cohesive starch generally prevents agglomeration and controls the size of the particle. An excellent process for his purpose is spray drying [82, 83].

Manufacturing Techniques of Cubosomes: Cubosomes can be manufactured by two distinct methods [84]:

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

In the Bottom-up technique, cubosome dispersion is formed by dilution of an isotropic solution, [85] whereas in the top-down technique powder cubosome precursors can be achieved [82]. Liquid crystalline dispersions are prepared by selected techniques like.

a) Cubosomes from pseudo-binary systems.

b) Cubosomes by nucleation.

c) Cubic liquid crystalline phase in the presence of hydrotropes.

d) Dry powder precursor [86].

Top-down Technique: This process is carried out in two steps.

First is the formation of viscous bulk cubic phase by mixing lipid(s) with the stabilizer(s); thus, aggregation takes place. The second step is derived from step one. It is the most frequently used procedure initially reported in 1996 [87]. The bulk cubic phase is first produced and by application of high energy such as high-pressure homogenization it is processed into cubosomes nanoparticles. The bulk cubic phase resembles a clear rigid gel formed by water-swollen cross-linked polymer chains. The cubic phases differ in that they are a single thermodynamic phase and have the periodic liquid crystalline structure [82]. Cubic Phases ruptures in a direction parallel to the shear direction, the energy required is proportional to the number of tubular network branches that rupture [88].

Here bulk cubic phase will be dispersed into the aqueous medium through the application of high-pressure homogenization or sonication / high energy dispersions [86] to form cubosomes dispersions (nanoparticles). The bulk cubic phase is like a cross-linked clear gel-like polymer that 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 [89]. 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 was poor but at this temporary temperature formation of D type, a 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 on large scale is nearly not possible, and it is difficult to incorporate thermo-labile ingredients, peptides, and proteins.

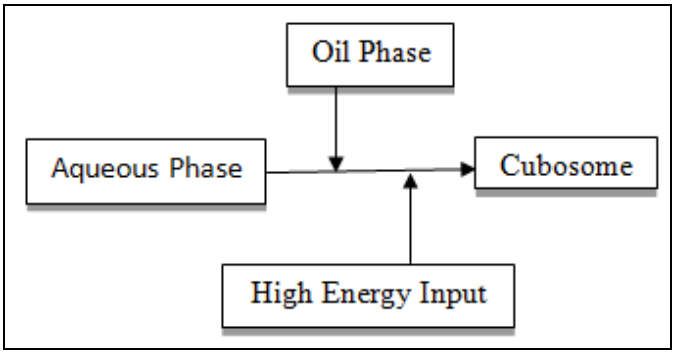

FIG. 5: TOP-DOWN APPROACH

Bottom-up Technique: In this cubosomes are allowed to form or crystallize from precursors. The bottom-up approach first forms the nanostructure building blocks and then assembles them into the final material. It is more recently developed the technique of cubosome development, allowing cubosomes to form and crystallize from precursors on the molecular scale length. The input factor of this technique is hydrotrope that can dissolve water-insoluble lipids into liquid precursors. This is a dilution-based approach that produces cubosomes with less energy input when compared to the top-down approach [91].

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 [92] 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 [93].

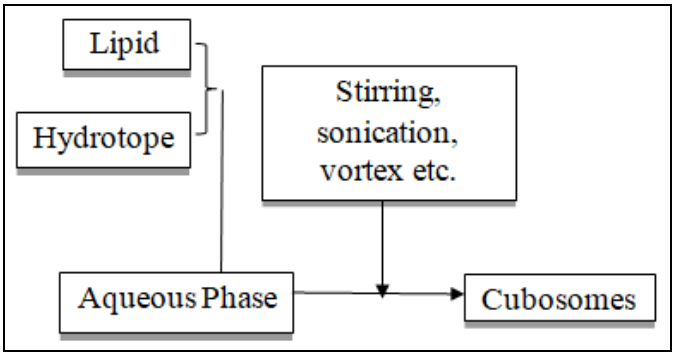

FIG. 7: BOTTOM-UP TECHNIQUE

Dispersion of the nanoparticles produced in the cubosomes formation by several techniques [94].

A. Sonication

B. High-pressure homogenization

C. Spontaneous emulsification

D. Spray drying

E. Sonication and high-pressure.

Homogenization suggests the formation of complex dispersions containing vesicles and cubosomes with time-dependent ratios of each particle type. Coarse cubosomes on the micron scale possess the same D-surface cubic structure as their originating bulk cubic phase [31] but after homogenization, the P-surface dominates, either because of the added polymer or other factors [82]. Large-scale production of cubosomes and products containing them requires more robust processes. Smaller and more stable cubosomes are produced than those by high-energy processes, but some vesicles are also produced. A process was also developed to allow cubosome production from a powdered precursor [95]. Spray-dried powders comprising monoolein coated with starch or dextran form cubosomes on simple hydration. The polymers immediately provide colloidal stabilization of the cubosomes.

Structural Components of Cubosomes:

Amphiphilic Lipids: Bicontinuous cubic phases are found in natural lipids, cationic [96] and nonionic surfactants [97], and polymer systems, although the lipid most widely used to construct bicontinuous cubic phases is the monoglyceride monoolein, monoglycerides spontaneously formbicontinuous cubic phases upon the addition of water, are relatively insoluble, and are resistant to changes in temperature. The main precursor of cubosome formation is monoolein. Monoolein or glyceryl monooleate is a mixture of the glycerides of oleic acid and other fatty acids, consisting mainly of the monooleate [98, 99]. The glycerol moiety may form hydrogen bonds with water in an aqueous environment and is commonly referred to as the head group. The hydrocarbon chain gives hydrophobic characteristics to monoolein and is often termed the tail. Commercially available monoolein may be obtained in two forms, a mixed glyceride form or as distilled monoolein; the distilled monoolein is preferred for pharmaceutical applications because of its high purity. It swells in water, giving rise to several lyotropic liquid crystalline structures. When a lipid molecule is heated, instead of melting directly convert into an isotropic liquid.

The widely used amphiphilic lipids to prepare cubosomes are glyceryl monooleate GMO, usually discussed as monoolein and phytantriol (PHYT) [82, 100]. GMO consists of a mixture of the glycerides of oleic acid and other fatty acids, containing mostly monooleate which fits the group of amphiphilic lipids with a capacity to form various lyotropic liquid crystals [101, 102]. It has been reported that GMOs with hydrocarbon chain lengths in the range of12-22 have a greater tendency to form cubic phases [103]. Further, GMO is a biocompatible and biodegradable material under as generally recognized as safe (GRAS) category by FDA, mainly used as an emulsifier in the food industry. PHYT is a material with a phytanyl chain, also exhibits the formation of cubic phases upon increasing the water content. PHYT, chemically 3,7,11,15-tetramethyl-1,2,3-hexadecanetriol, is a frequently used component in cosmetic products. It has been recommended as a good alternate for GMOs in the manufacturing of cubosomes. As compared to GMO, PHYT has an added advantage in that it shows greater structural stability. The GMO is more prone to ester hydrolysis [104]. Although PHYT and GMO have different molecular structures, these two materials show many related phase transition behaviors with increasing water content and temperature.

Stabilizers: The research scientists have suggested an important role for the surfactants as stabilizers for improved stability of cubosomes against coalescence to the bulk cubic phase.

Surfactants, which are used in the production of cubosomes, are poloxamer 407 in a concentration range between 0% and 20% w/w with respect to the disperse phase. The concentration of the monoglyceride/surfactant mixture generally takes between 2.5% and 10% w/w with respect to the total weight of the dispersion. Polyvinyl alcohol (PVA) was used in addition to poloxamer as a stabilizing agent of the dispersion.

Poloxamer 407 (P407), a PEO-PPO-PEO tri-block copolymer, is a mostly investigated surfactant in the preparation of cubosomes with its PPO portions being located either at the surface of the cubosomes or within the bilayer structure, whereas the PEO chains are exposed to the surrounding water phase [33, 105]. P407 is usually applied upto a concentration of 20 %w/w depending on the quantity of dispersed phase. The effect of three water-miscible solvents i.e propylene glycol (PG), polyethylene glycol 400 (PEG400), and 2-meth-yl-2,4-pentanediol (MPD) on a PHYT-based cubosomalsystem [106]. They showed that MPD produced a sponge phase whereas with the two other solvents, PG and PEG400, only cubic, lamellar, and non-ordered liquid phases were identified. The main reasons attributed tothe difference in phase behavior were the more hydrophobic nature of PHYT as compared to GMO and the branched hydrocarbon chain of PHYT, which makes PHYT less flexible than GMO.

On substituting b-casein with P407 as the stabilizer, the stabilizer to GMO and PHYT based cubosomes, its internal structure as well as its morphology was studied [107]. A Pn3 m phase structure was displaced by the GMO-b-casein cubosomes and at 60˚C a QII to HII phase transition.WhereasIm3 m phase structure has P407-GMO dispersion and at higher temperatures, that is, 70°C the HII phase gets appeared. The concentration of the stabilizer and the Pn3m phase structure was detected in the case of PHYT systems.

P407-PHYT dispersion displayed only a direct QII to La conversion, whereas upon heating the b-casein-PHYT system displayed a QII to HII to La transition behavior. Steric stabilization to dispersions of lipid nanostructured particles gives the b-casein and Im3m structure in nanoparticles avoids the transition. In cubosomes, it was discovered that the poly (ethylene oxide) stearate stabilizers (commercially known as Myrj) were more effective as steric stabilizers. In contrast, Myrj 59 was proven to be more effective than P407 for PHYT cubosomes with an average of 100 poly (ethylene oxide) units at a concentration of fivefold lower than that of P407. To GMO-based cubosomes with P407 the hydroxypropyl methylcellulose acetate succinate (HPMCAS) showed roughly equal stability [108].

Methods for Characterization and Evaluation of Cubosomes:

Visual Inspection: The cubosomes are visually assessed for optical appearance (e.g color, turbidity, homogeneity, presence of macroscopic particles)

Photon Correlation Spectroscopy: Particle size distributions of cubosomes are mainly determined by dynamic laser light scattering using Zeta sizer (Photon correlation spectroscopy). The sample diluted with a suitable solvent is adjusted to light scattering intensity of about 300 Hz and measured at 25°C in triplicate. The data can be collected and generally shown by using average volume weight size. The zeta potential and polydispersity index can also be recorded [72, 31].

Zeta Potential: The magnitude of zeta potential indicates the degree of electronic repulsion between adjust, similarly charged particles. Zeta potential is a key indicator of the stability of the formulation.

Polarized Light Microscopy: Polarized light microscopy can be used to reveal the optically birefringent (possibly vesicular) surface coating of the cubosomesand can distinguish between anisotropic and isotropic substances [109].

Gel Permeation Chromatography or Ultrafiltration Techniques & UV Spectrophotometer or HPLC Analysis: Entrapment efficiency and drug loading of cubosomes can be determined using gel permeation chromatography or ultrafiltration techniques. In the latter technique, the unentrapped drug concentration is determined, which is subtracted from the total drugadded. The amount of drug is analyzed by using a UV spectrophotometer or HPLC analysis [108].

X-ray Scattering: Small-angle X-ray scattering (SAXS) can be used to identify the spatial arrangements of different groups in the sample. The diffraction patterns obtained are converted to plots of intensity versus q value, which enables the identification of peak positions, and their conversion to Miller Indices. The Miller Indices could then be correlated with known values for different liquid crystalline structures and space groups to identify the dominant internal nanostructure of the sample [110].

Small-angle X-ray scattering (SAXS) is a small-angle scattering (SAS) technique where the elastic scattering of X-rays (wavelength 0.1- 0.2 nm) by a sample that has in homogeneities in the nm-range, is recorded at very low angles (typically 0.1- 10°). This angular range contains information about the shape and size of macromolecules, characteristic distances of partially ordered materials, pore sizes, and other data. SAXS can deliver structural information of macromolecules between 5 and 25 nm, of repeat distances in partially ordered systems of up to 150nm [46].

Transmission Electron Microscopy: Transmission electron microscopy can be used to view the shape of the cubosomes. Kim et al. described that the suspensions of cubic phase nanoparticles were negatively stained with a freshly prepared phosphotungstic acid solution (2%, pH 6.8) and were transferred onto a formvar/carbon-coated grid (200 mesh), air-dried at room temperature. The electron microphotographs were taken on an electron microscope [111].

Cryo-Transmission Electron Microscopy (Cryo-TEM) [112]: Cryo-Transmission electron microscopy (Cryo-TEM) is a microscopy technique whereby a beam of electrons is transmitted through an ultrathin specimen, interacting with the specimen as it passes through. An image is formed from the interaction of the electrons transmitted through the specimen; the image is magnified and focused onto an imaging device, such as a fluorescent screen, on a layer of photographic film, or to be detected by a sensor.

Cryo-TEMs are capable of imaging at a significantly higher resolution than light microscopes, owing to the small wavelength of electrons. SEM analysis may not be performed on cubosomes or some vesicular systems since the integrity and robustness of the formulation may be lost during the procedure while exposing to an electron array.

Pressure Ultrafiltration Method: Drug release measurement of cubosomes can be done by a pressure ultrafiltration method. It is based closely on that proposed by Magenheim *et al.* using an Amicon pressure ultrafiltration cell fitted with a Millipore membrane at ambient temperature (22±2) °C [113].

Entrapment Efficiency: The entrapment efficiency of cubosomes can be determined using ultrafiltration techniques. In the later technique, the unentrapped drug concentration is determined, which is subtracted from the total drug added. The amount of drug is analyzed by using a spectrophotometer.

Measurement of Drug Release: Drug release from cubosomes can be done by the pressure ultrafiltration method. It is based on that proposed by Magenheim *et al.* using an Amicon pressure ultrafiltration cell fitted with a Millipore membrane at ambient temperature (22±2) °C.

Stability Studies: The physical stability can be studied by investigation of organoleptic and morphological aspects as a function of time. Particle size distribution and drug content can be assessed at different time intervals can also be used to evaluate the possible variations by the time [114].

Cubosome Applications: Drug delivery vehicle is a common application for such new materials. The rapid expansion of the life-sciences industry is expected to drive previously "exotic" delivery vehicles and ingredients into broader marketplaces, such as personal care and consumer products. The cubosome usage in numerous medical and controlled release applications. Some researchers specify that controlled release is usually possible only for bulk cubic phases. Consequently, self-assembled surfactant phases have been extensively examined for compatibility with numerous medical active ingredients and their applications [48].

The number of research in association with cosmetic companies like L'Oreal and Nivea are trying for the use of cubosome particles as oil-in-water emulsion stabilizers and pollutant absorbents in cosmetics [3, 48, 49, 115-118].

In Cancer Therapy: Recently some anticancer drugs have been successfully encapsulated in cubosomes and characterized physicochemical properties [119]. The unique structure of this promising nanocarrier suggests its application in melanoma therapy. To specifically target nanomedicines to tumors, different approaches have been envisaged, with passive and active targeting of cancer cells being valid approaches in preclinical and clinical studies.

Oral Drug Delivery: Cubosomes direct the varied challenges in oral delivery of numerous compounds including poor aqueous solubility, poor absorption, and large molecular size. In an application, large proteins have been encapsulated for local activity in the gastrointestinal tract [120]. Cubosomes technology provides drug release at different absorption sites, for example in the upper or lower intestine, which is important for the drugs that have a narrow absorption window.

Intravenous Drug Delivery Systems: Lipid nanoparticles comprising interior liquid crystal structures of curved lipid membranes are used to solubilize encapsulate and deliver medications to disease areas within the body [121]. Compare to emulsions and liposomes the cubosomes nanoparticle shows increased payloads of peptides, proteins, and many insoluble small molecules, and are ideal carriers for injection.

Topical Drug Delivery Systems: Cubosomes are more bioadhesive in nature so that they can conveniently use in topical and mucosal delivery of different drugs. Topical delivery systems are based on the exploitation of unique properties of liquid crystal and liquid crystal nanoparticle technologies. Topical drug delivery systems are unique *in-situ* forming bioadhesive liquid crystal systems that facilitate controlled and effective drug delivery to mucosal surfaces like buccal, ophthalmic, and vagina.

Drug Delivery Vehicle: It is a common application for such new materials. The research in association with cosmetic companies like L'Oreal and Nivea is trying for the use of cubosome particles as oil-in-water emulsion stabilizers and pollutant absorbents in cosmetics [122].

Controlled or Sustained Release Behavior: A number of drugs with different physicochemical properties has been incorporated in cubosomes and their sustained drug release behavior was also studied. The sustained behavior of cubosomes was because of cubosome remnant particles. Monoglyceride-based cubosome can be proposed for topical use, such as for percutaneous or mucosal application.

In the Treatment of Viral Diseases: Because of the microbicidal properties of monoglycerieds, could be used to design intravaginal treatment of sexually transmitted diseases caused by viruses (e.g. HSV, HIV) or by bacteria like Chlamydia trachomatis and Neisseria genorrticae [123].

TABLE 2: LIST OF DRUGS INCORPORATED IN CUBOSOME

Drug	Category	Associated disease	Ref.
2-amino-1-phenylpropanol HCl	Antidepressant	Mania, depression	124
Nitroglycerin	Anti-anginal	Angina pectoris	
Oestriol	Hormonal therapy	Atrophic aginitis, pruritus	
Cefazolin	Antibiotics	Genito-urinary, respiratory tract infection	125
Cefuroxime	Antibiotics	Meningitis, bone and soft tissue infection	
Prilocaine	Local anesthetic	In Dentistry	
Clindamycin phosphate	Antibiotics	Peritonitis, staphylococcal bone andjoint infection	126
Clomethiazole	Psychotropic	Insomnia	127
Clotrimazole	Antifungal	vagina, mouth, and skin infection	128
Gramicidin	Topical steroid	Corticosteroid sensitive dermatoses	129
Insulin	Hypo/Hyper glycaemics	Diabetes mellitus	
Indomethacin	NSAIDs	Gout, rheumatoid arthritis	130
Isosorbide mononitrate	Anti-anginal	Angina pectoris	
Lidocaine hydrochloride	Aural prepration	Fungal infection of external ear	
Diazepam	Sedative-hypnotic	Anxiety, insomnia, seizures	41
Rifampicin	Bactericidal antibiotic	Tuberculosis	
Griseofulvin	Antifungal	Fungal infection of skin	
Propofol	Hypnotic	Procedural sedation, to induce and maintain General Anesthesia	
Dexamethasone	glucocorticoid steroidal drug	Inflammatory and autoimmune conditions like Rheumatoid arthritis, edema, nasal and opthalmic allergies	131
Flurbiprofen	NSAIDs	inhibition of intra-operative miosis, management of post-operative inflammation, treatment of seasonal allergic conjunctivitis, prevention and	132

		treatment of cystoid macular edema and control of pain after photo refractive keratectomy	
colchicine	alkaloid	Familial editerranean fever, psoriasis, and actinic keratosis	133
Miconazole nitrate	antifungal agent	Opical treatment for cutaneous mycoses	134
Ketorolac	NSAID	conjunctivitis, uveitis, endophthalmitis, glaucomatous conditions and post-operative pain.	135
Amphotericin B	antifungals	fungal infections for cancer, organ, or bone marrow transplant patients	136
Glimepiride	oral hypoglycemic agent	Type II diabetes mellitus	137
Dacarbazine	Anticancer	melanoma	138
rebamipide	antiulcer	ulcer healing	139
Ketoprofen	NSAID	acute and chronic arthritic conditions	140
Capsaicin	alkaloid	psoriasis, pruritus, a pocrine chromhidrosis, and contact allergy	141
Miconazole nitrate	antifungal	Superficial Candidiasis, Dermatophysis and Pityriasis versicolor	142

CONCLUSION: Cubosomes offer increased flexibility for product development and act as excellent solubilizers, compared with conventional lipid or non-lipid carriers. When compared with conventional carrier systems overall, Cubic phase materials can be formed by a simple combination of biologically compatible lipids and water and have great potential in drug nanoformulations for different diseases and disorders. The precursor forms enhance its further scope in the technological field. Cubosomes are too small and have a high surface area for such performance, exhibiting instead burst release. It is expected that in the next years, cubosomes containing protein and peptide-based drugs will constitute more than half of the new drugs introduced into the market. Further specialized studies are required to confirm this fascinating hypothesis and to better investigate the role of vesicles and cubosomes in controlling the release of the drug.

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