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A REVIEW ON CUBOSOME: AN INNOVATIVE DRUG DELIVERY TECHNOLOGY

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ABSTRACT:

Cubosomes are extremely stable nanoparticles that have cavernous or honeycomb-like shapes. They are created of a particular class of amphiphilic lipids in a precise ratio in water, and they are then stabilized by biocompatible materials like triblock polymer. Cubosomes are flexible drug delivery methods because of their structural makeup. They are known as bicontinuous cubic phase liquid crystals. The two continuous but not intersecting watery zones that are separated by a lipid bilayer are referred to be bicontinuous. Cubosomes have a stable thermodynamic state, and the dispersions they form are both biocompatible and bioadhesive. Cubosomes can be administered orally, topically, mucosally, intravenously, or transdermally for the treatment of skin, hair, or other body tissues. In terms of drug delivery techniques, cubosomes are flexible devices. Targeted and regulated release of bioactive substances

KEYWORDS: Cubosomes, Drug-loading hydrophilic, Nanoparticles, Honeycomb, Self-assembly, Anti-cancer, Cubic Phase.

INTRODUCTION:

Larsson first used the word "*Cubosomes*," which is related to liposomes [1]. Discrete, sub-micron-sized, nano-structured cubosomes are a type of bicontinuous cubic liquid crystalline phase. Although having a greater specific surface area and substantially lower viscosity in contrast to the bulk cubic phase, cubosomes have the same microstructure as the parent cubic phase [2]. Amphiphilic molecules contain polar and non-polar parts and can be observed in lipid, surfactant, and polymer molecules. Amphiphilic molecules in polar fluids are induced by the hydrophobic effect to spontaneously self-assemble into a variety of thermodynamically stable liquid crystalline phases with lengths on the nanometer scale. A good illustration of this is the bicontinous cubic liquid crystalline phase. Bicontinous cubic phases are optically isotropic, highly viscous, and crystallized materials that behave like solids in liquids with cubic crystallographic symmetry [3]. Cubosomes are bicontinuous cubic liquid crystalline phases formed by hydrating a monoolein and poloxamer 407 mixture, and they play a significant role in nanodrug formulations [4]. Cubosomes' active chemical element molecules are coordinated with the polar head of the phospholipids through chemical bonds. Depending on the material, the complex ratio between the polymer and each therapeutic component is either 1:1 or 2:1 [5]. Cubosome-based chemotherapy drugs have been produced with a certain level of success. Cubosomes proved difficult to synthesize on large scales due to their viscosity and phase behavior. There is a spontaneous formation of the cubic phase when specific surfactants are mixed with water [6].When medicines get incorporated into the cubosomal vesicles, they are transported to the site of action (including high molecular weight pharmaceuticals). It enhances drug transport across skin and acts as a penetration enhancer [7].

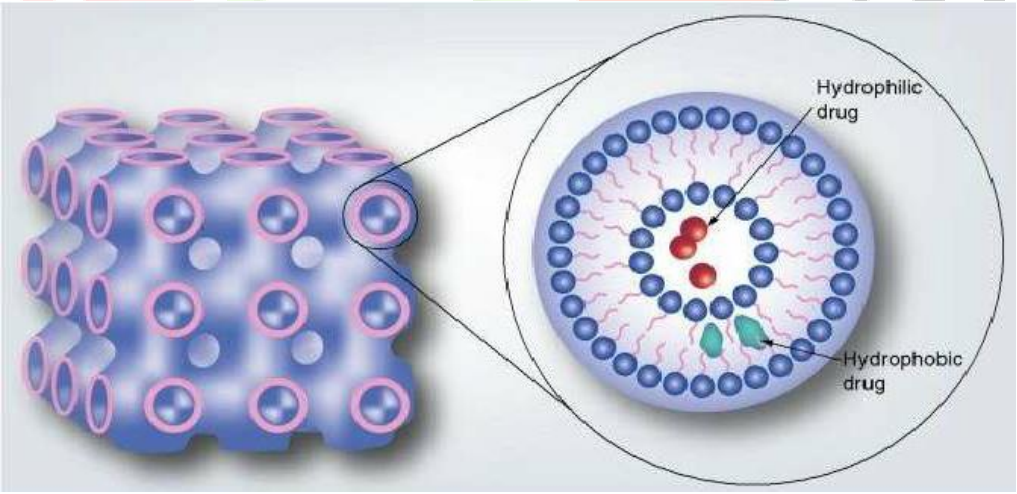

Fig No. 1: Structure of Cubosomes

❖ TYPES OF CUBOSOMES:

1. Liquid Cubosome Precursors

The objective of the hydrotropic dilution process is to generate cubosomes which are more stable and denser. The manufacturing of particles whose growth is apparent during precipitation and crystallization processes is made possible by the nucleation process. [8]

2. Powdered Cubosome Precursors

These are made of dehydrated surfactant that has been covered in polymer. These powders have some advantages over the hydrotropic cubosome precursors in the liquid phase. The hydration of the precursor powders results in cubosomes with a mean particle size of 600 nm, as demonstrated by light scattering and cryoTEM [9].

❖ COMPONENTS OF CUBOSOMES:

Amphiphilic lipids, stabilizers, and water make up the majority of the cubosome's components. When amphiphilic lipids are well-hydrated, they produce cubic liquid crystalline phases, although stabilizers, which are composed of polymers, inhibit them from reforming into bulk cubic phases [10].

1. Amphiphilic lipids:

Glyceryl monooleate GMO and phytantriol (PHYT) are the two amphiphilic lipids that are most frequently employed to create cubosomes, also known as monoolein. GMO comprised of combinations of glycerides of oleic acid and some other fatty acids, primarily monooleates, which belong to the amphiphilic lipids group and have the ability to crystallize into a variety of lyotropic liquid crystals, as seen in fig. 2. The likelihood for GMOs to form cubic phases is larger when the hydrocarbon chain length is between 12 and 22. [11, 12] Additionally, it falls under the FDA's generally recognized as safe (GRAS) category and is mostly employed as an emulsifier in the food business. PHYT is a chemical compound with a phytanyl chain that forms cubic phases when temperature and water content are elevated. Chemically speaking, PHYT is 3,7,11,15-tetramethyl-1,2,3-hexadecanetriol and is primarily employed in cosmetic applications [13, 14].

2. Stabilisers:

The scientists suggested that surfactants play an essential role as stabilizers to enhance the stability of cubosomes against the coalescence of the bulk cubic phase. PEO chains in Poloxamer 407 (P407), a PEO-PPO-PEO tri-block copolymer, are exposed to the surrounding water phase as shown in Figure 3. This copolymer is primarily used as a surfactant in the preparation of cubosomes with its distinct PPO portions being located either at the surface of the cubosomes or within the bilayer structure [20]. Depending on the amount of dispersed phase is utilized, P407 is typically applied up to a concentration of 20% w/w. Wadsten-Hindrichsen investigated at how a phytosome-based cubosomal system would respond to the impact of three water-miscible solvents: propylene glycol (PG), polyethylene glycol 400 (PEG400), and 2-meth-yl-2, 4-pentanediol (MPD). The poly (ethylene oxide) stearate stabilizers were found to be more efficient than the steric stabilizers in the cubosomes [14,15].

❖ **Advantages of Cubosomes** [16-25]:

- The cubosomes can enclose hydrophobic, hydrophilic, and amphiphilic molecules while maintaining longer-lasting thermodynamic stability.
- Cubosomes are non-allergic, non-irritating, and biodegradable.
- They have the ability to achieve sustained and targeted release profiles for drug delivery.
- They possess biocompatibility and bioadhesivity features. There is a high drug loading capacity because of the cubic crystalline structures and high interior surface area.
- They are cheap and non-toxic.
- Its size allows for exceptional bioavailability and physicochemical stability, especially in the presence of excess water.
- It reduces the overall cost of health care because there is less need for frequent administration.
- They lessen injection-related negative effects, which are associated with the burst release. When compared to liposomes, the ratio between the particle volume and the bilayer area is greater.
- They serve as a carrier of the sensitive drug moiety (proteins, peptides) from the enzymatic breakdown process.
- They increase the bioavailability of peptides that are soluble in water by roughly 20–100%. Shear and homogenization procedures, which are used to prepare cubosomes, do not
- necessitate using organic solvents.
- It has a straightforward production process and is lipid biodegradable.
- Cubosomes are utilized to treat skin, hair, and other bodily tissues because they are effective solubilizers.
- Even in excess of water, cubosomes of bicontinuous liquid cubic crystalline phases remain stable.

❖ **Disadvantages of Cubosomes**:

- Because cubosomes have a high viscosity, large-scale manufacture can occasionally be challenging.
- If the drug form inside the cubosome is polymer-based, then regulated drug delivery is not available.
- Because cubosomes contain a large amount of water, there is a low trapping of water-soluble medicines
- Cubosomes have a substantial stability issue that functions as a barrier, restricting their application. They may have low drug loading efficiency and cause drug leakage during manufacturing, preservation, and in vivo transport. Particle growth is possible after prolonged exposure.
- Cubosomes can do the following Trigger a phase shift in their dynamics in the event that the external environment changes.

❖ **METHODS OF PREPARATION OF CUBOSOMES:**

1) High-Pressure Homogenization
2) Automated Cubosome Preparation
3) Probe Ultrasonication
4) Other Methods:

4.1) Emulsification

4.2) High Shear Homogenization Technique

4.3) Spray-Drying Technique

5) Special Techniques:

5.1) Top-Down Technique

5.2) Bottom-Up Technique

1. High-Pressure Homogenization:

It is the best technique for cubosome preparations, which have a long shelf life [28, 29] and are very stable during the high-pressure homogenization process [26, 27]. There are three steps involved:

1.1 Gel Preparation:

In order to create a homogenous mixture, the lipid and amphiphilic surfactants are dissolved in an organic solvent and then thoroughly mixed. Here, the organic solvent is evaporated using a rotary evaporator to create a formulation's gel phase

1.2 Shearing:

The created gel is undergoing shearing in this step. The micro-dispersion is created using the aqueous solvents. It is the decisive stage in the production of cubosomes process that comes before homogenization.

1.3 High-Pressure Homogenization:

This approach is not appropriate for small volume sample systems; it is only suitable for high volume sample systems (30 ml). Since this approach is temperature sensitive, the temperature is chosen in this step based on the

characteristics of the lipid. Within in order to homogenize the prepared dispersion, a high-pressure homogenizer is being used. Just this approach could be used to process a single sample.

2. **Automated Cubosome Preparation:**

With a few modifications, it is comparable to the probe sonication approach. Using this technique, a big number of cubosomes may be produced. This protocol for preparing cubosomes makes use of robotic devices and probe sonicators. This technique involves utilizing a 96-well plate with a 600 µl of solvent capacity. After then, a robot does the sonication. Thus, using this technique, the it is simple to evaluate physicochemical characteristics [30].

3. **Probe Ultra Sonication:**

Samples with a small volume are prepared quickly using this method. It has the capacity to disperse samples up to 600 µl in volume. The probe's size determines this. In this procedure, stabilizers are added to the gels to prepare them. Subsequently, a solvent equilibration occurs, creating a cubic stage. Following this, the cubic phase is moved in preparation for ultrasonication [31]. In order to manage the pulse frequency and to prevent samples from overheating, meticulous maintenance of variables, like as amplitude and frequency.

a. **Advantages**:

The equipment used in this procedure is widely available. This approach is popular and simple.

b. **Disadvantages**:

There is a possibility of metal contamination. Particle growth may occur during the storage phase.

4. **Other Methods**:

a. **Emulsification**:

Poloxamer 407, which dilutes the monoolein-ethanol solution, is what creates the cubosomes in this approach [32].

b. **High Shear Homogenization Technique:**

Stabilizers are used in this procedure to prevent particle aggregation during the shelf-life span. (It is a good method, but due of the high shear application, it has certain limits as well [33].

c. **Spray-Dried Technique:**

Cubosome manufacturing is another application for this method. With this technique, polysaccharides (starch/dextran) coat the monoolein upon hydration.Subsequently, the polymers are incorporated into this to preserve stability [34].

Advantages:

This technique can be used with powdered compositions. This technique makes microencapsulation feasible. Organic solvents can also be used in this approach.

Disadvantages

This approach is more intricate than other approaches. This process yields 5 to 30%, which is a relatively low number.

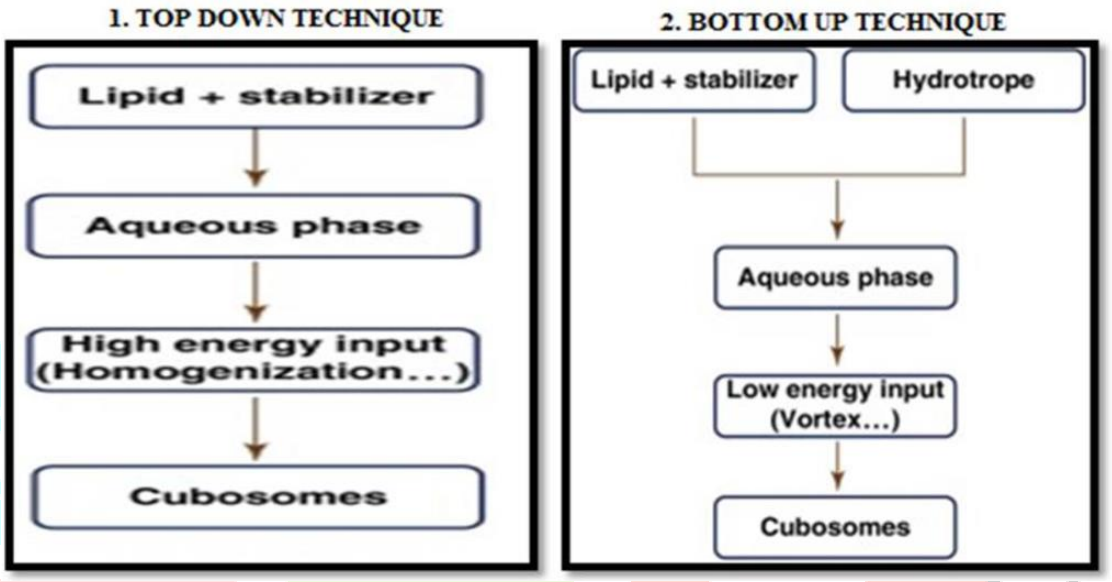

Fig No. 2: Method of Preparation of Cubosomes

❖ SELECTION CRITERIA FOR DRUGS AND EXCIPIENTS:

The basic idea behind the cubosome formulation was to transport lipophilic drugs, like griseofulvin, rifampicin, propofol, and diazepam, to the target area, where the phospholipid layer increases permeability by reducing the solubility issue of the lipophilic moiety. Should the hydrophilic glucose and insulin moieties' permeability Even if the biomembrane is constrained, this can be effectively achieved by incorporating them into lipid components; thus, they can be lessened. Both kinds of medications can therefore be included in cubosomes; nevertheless, lipophilic drug encapsulation has been found to be more common thus far. Peptides were efficiently dispersed using cubosomes, and their stability was increased by limiting their exposure to a range of pH ambient conditions. The disadvantages of other site-specific/targeted drug delivery techniques may therefore be lessened by carefully choosing a cubosome carrier that permits drug moiety distribution to particular tissues/organs. 37] Two physicochemical factors to take into account when choosing excipients are drug dispersion in the solid lipid matrix and drug compatibility with the polymer.

❖ EVALUATION AND CHARACTERIZATION OF CUBOSOMES:

1. **Visual Inspection Studies:** In these, the cubosomes' exterior characteristics—such as their shape, turbidity, color, homogeneity, and particle presence—are examined.

2. **Transmission Electron Microscopy (TEM)**: TEM can be used to evaluate the cubosome morphology. It might offer cubosomal particle forms. It provides a high-resolution image and electron microphotographsTM for observation. Visualization is therefore feasible. When compared to light microscopes, it can provide far higher resolution. It is a great tool for figuring out the soft matter dispersions' characteristics. It was able to overcome every drawback of conventional electron microscopy, including the vacuum environment, low image quality, generating structural changes in the cubic phase, etc.

3. **Zeta Potential**: The zeta potential's magnitude can be used to evaluate the stability of the preparation. It exhibits a strong repulsiveness.

4. **Viscosity**: A rotational Brookfield viscometer, or viscometer, can be used to measure viscosity.

5. **Particle Size Analysis**: This involves dilution of the materials with a suitable solvent and exposure to 300 Hz, the light scattering intensity at 25 ºC[39]. Using a Zeta sizer, dynamic laser light scattering is used to quantify it. Zeta potential and PDI measurements are also possible in this. It provides information about average weight, volume, and size. The samples could be diluted 100 times with water in order to determine the particle size using the Malvern Zeta Sizer.

6. **Polarized Light Microscopy:** This technique may be used to determine the cubosomal surface coatings, which are optically short vesicular or ringent coatings. This approach could also give the anisotropic and isotropic differentiation [40]. It could watch. The transition between cubic phases. It offers details regarding the potential coexistence of layered (hexagonal liquid crystals and a cross or striated pattern) [41].

7. **Differential Scanning Calorimetry (DSC):** Because phase transitions in liquid crystals are caused by endothermic and exothermic processes, DSC can provide information regarding whether or not a phase transition occurs in the system.

8. **Small Angle X-ray Scattering:** This technique can be used to identify the various groups within a sample as well as their spatial layout. In addition, it offers details on particle shapes, pore diameters, and the separations between partially ordered materials. It is capable of measuring molecular structure information at very small

sizes (5 to 25 nm). It can be used to ascertain the three-dimensional configuration of different groups that are included in the formulation.

9. **Entrapment Efficiency**: Cubosomal entrapment efficiency might be evaluated using the ultrafiltration techniques [42]. Using a spectrophotometer, this method measures the concentration of an unentrapped drug and uses that information to determine the concentration of an entrapped drug. This involves centrifugation after the material has been diluted with deionized water. Following this, there is an ultrafiltration procedure where a certain medication concentration is determined using spectrophotometry.

10. **Usage of drugs Determination:** Gel permeation chromatography or ultrafiltration techniques could be used to find out. HPLC analysis might then be performed on it [43].

11. **Measuring Drug Release:** Another technique for doing so is pressure ultrafiltration [44]. An Amicon pressure ultrafiltration cell makes up this system. This has the Millipore membrane attached to it.

12. **Stability Studies:** In these, the organoleptic properties and morphological traits related to the time period could be used to evaluate the stability. Moreover, the drug content and the time-dependent determination of the particle size distribution [45]. This examines assessments of potential time-related changes.

❖ APPLICATIONS OF CUBOSOMES:

- **Melanoma Therapy [46]**

A few anticancer medications have recently been physically and chemically characterized while encapsulated in cubosomes. Because of its unique structure, this promising nanocarrier may find application in melanoma treatment. Various strategies have been put forth to target nanomedicines specifically to tumors; preclinical and clinical research have demonstrated the validity of both passive and active targeting of cancer cells. The pathophysiological features of the tumor vasculature, which are typically disorganized, with lots of gaps between endothelial cells and impaired lymphatic drainage, are advantageous to passive targeting because they allow for the extravasation of nanocarriers, which can range in size from a few hundred to hundreds of micrometers. The endothelial cells that line healthy tissue vessels contain tight junctions that are impenetrable to objects this size.

- **Oral Drug Administration [47]**

  Cubosomes have challenges when it comes to the oral delivery of many promising compounds, including poor absorption, large molecular size, and poor aqueous solubility. An alternative application for local activity in the gastrointestinal tract has been developed that encapsulates large proteins. Liquid crystalline nanoparticle-based carriers with controlled release and targeting capabilities can be combined. The particles work well for drug delivery in vivo because they are made to form in situ at a regulated rate. For medications with a narrow window for regional absorption, cubosome carriers must also be released at various absorption sites, such as the upper or lower intestine.

- **Intravenous Drug Administration Systems [48]**

  To solubilize, encapsulate, and deliver medications to disease sites throughout the body, lipid nanoparticles with interior liquid crystal structures of curved lipid membranes are used. Liquid crystal nanoparticle structures have larger payloads of peptides, proteins, and numerous insoluble small molecules, making them ideal carriers for injection or infusion of numerous active ingredients, although emulsions and liposomes have been used as travenous carriers in drug products.

- **Topical Drug Delivery system [49]**

  Due to their higher bioadhesive qualities, cubic phases are good for drug delivery as well as topical and mucosal depositions. Topical delivery systems are made possible by the special qualities of liquid crystal (LC) and liquid crystal nanoparticle (LCNP) technologies. Topical drug delivery systems are unique in that they enable controlled and efficient drug delivery to mucosal surfaces (buccal, ophthalmic, vaginal, and others) by forming bioadhesive LC systems in situ. This intriguing system effectively protects sensitive and irritated skin for a brief period of time by forming a thin surface film at mucosal surfaces made of a liquid crystal matrix, whose nanostructure can be adjusted to achieve an ideal delivery profile.

- **Vehicle for Drug Delivery**

  Drug delivery vehicles are one commonly used application for these novel materials. It is anticipated that the life sciences sector's explosive expansion will push previously "exotic" delivery methods and ingredients into more mainstream markets like consumer goods and personal hygiene. Self-assembled surfactant phases have therefore undergone extensive testing to determine their compatibility with a variety of medicinal active ingredients and applications. Cubosome particles are being investigated for use in cosmetics as pollutant absorbents and as oil-in-water emulsion stabilisers. These studies are being conducted in partnership with cosmetic companies like L'Oreal and Nivea. Moreover, these investigators found that phytantriol, another amphiphile, possesses an aqueous phase behavior sufficiently akin to that of monoolein to form cubosomes under comparable circumstances.

- **Sustained Drug Release Behaviour**

Recently, there has been a lot of patent activity by. Use of cubosomes in personal care products as skin care, hair care, cosmetics, and so forth. Antiperspirants. Despite recent effort, there is still a lot of work to be done. There is still a dearth of practical features such as material scalability and manufacturing scalability customization that is required to be a leader. Cubosomes should be considered by formulators. Commercially available goods.The cubic phase has been completed. Demonstrated to be a carrier for various in vivo experiments depot, transdermal, and other delivery methods ophthalmic adhesion and mucoadhesion as a result Monoolein's fusogenic property raises the macromolecular penetration. It also improves macromolecule penetration. Drugs with a range of physicochemical features have been integrated into cubosomes, and their sustained release behaviour has been investigated. Cubosome residual particles were responsible for the cubosomes' long-term activity. Topical usage of monoglyceride-based cubosome dispersion, such as for perctuneous or mucosal applications, is possible.

- **Continuous Release of Substances**

A great deal of patent activity has occurred recently. Using cubosomes in cosmetics, skin care, hair care, and other personal hygiene products.counter-perspirants. A lot more work has to be done despite the recent efforts. The necessary practical elements to be a leader are still lacking, such as customization of manufacturing scalability and material scalability. Formulators ought to think about cubosomes. Products that are sold commercially It is the end of the cubic phase. Shown as a transporter for several transdermal, depot, and other administration techniques used in in vivo studies monoolein's fusogenic characteristic increases the macromolecular penetration and, consequently, ocular adhesion and mucoadhesion. Better macromolecule penetration is another benefit. Many physicochemical characteristics have been found In drugs.When Managing Viral Infections Because of their microbicidal properties, monoglycerieds may be used to produce intravaginal therapies for STDs brought on by bacteria (like Chlamydia trachomatis and Neisseria genorrticae) or viruses (like HIV, HSV). Because the cubic phase structure and the stratum corneum structure are comparable, it makes sense to combine cubosomalmonolein with stratum corneum lipids. This interaction may lead to the formation of a cubosome depot in this layer, from which controlled drug delivery could occur. To help premature newborns born without the vernix, a cheesy white fluid that coats children in late pregnancy, a synthetic version is being created using the cubosome technology. Lipids make up the vernix.

- **In Topical and Mucosal Dispositions:**

Because cubic phases are more bioadhesive in these environments, they are more useful for drug administration and topical and mucosal deposition.

- **Controlled-Release Drug Delivery:**

The most common use pursued by cubosome researchers is controlled release of solubilized actives and comprehensive evaluations of attempted delivery applications as well as pharmaceutical actives that have been solubilized in bulk cubic phase and cubosomes exist. Because of its tiny pore size (5–10 nm), capacity to solubilize hydrophobic, hydrophilic, and amphiphilic compounds, and biodegradability by simple enzyme activity, cubic phase is appealing for controlled release. Researchers that study cubosomes most frequently look into the controlled release of solubilized actives, thorough assessments of attempted delivery applications, and pharmaceutical actives that have been dissolved in bulk cubic phase and cubosomes. Cubic phase is attractive for controlled release due to its small pore size (5–10 nm), ability to solubilize hydrophobic, hydrophilic, and amphiphilic chemicals, and biodegradability by simple enzyme activity. Due to its strong bioadhesion and potential role as a skin penetration enhancer, the cubic phase is thought to be very compatible with the delivery of active ingredients and topical and mucosal deposition. Parallels between the bicontinuous structures formed in the layers of human skin and those discovered in cubic phases have been discovered recently, suggesting that skin transport may be better understood and treated. The convoluted geometry of the cubic phase is perfect for delaying the diffusive release of solubilized actives.Theoretically, a solute will have a 33% decrease in diffusivity in free solution. In studies, the small molecule diffusivity in cubic phases is found to be on the order of 10 10 m2/sec. Apart from treating periodontal disease using mixtures of triglycerides and monoolein with the antibiotic metronidazole, there are no known commercial uses for cubic phase delivery vehicles. The medicine is subsequently distributed to the gums by the lipid–drug mixture, which hydrates to form a bulk cubic phase upon contact with saliva after application. The extraordinarily high viscosity of the bulk cubic phase makes cubosomes necessary for a number of applications, even though the phase has the potential to be used as a delivery system.Different controlled-release paths for cubosomes may exist, even though the previously mentioned controlled-release limits apply to small molecule solutes and unmodified cubosomes. Large poly(amidoamine) dendrimer molecules exhibit a 100 reduction in free diffusivity when they are confined in cubic phases.

- **Materials Synthesis:**

From a materials science perspective, the creation of ordered structures at the nanoscale Pore geometries are of great interest to many individuals.Catalysis, photonics, and electronics are only a few examples.in addition to creating strong structures and pharmaceuticals Cubic phases are typically utilized as a model. Polymerization or a procedure that results in solids made from precursors that have been dissolved In or consists of the cubic phase matrix. One of the components developed in the first and most effective The cubic phase template is the aluminosilicate. MCM-48 zeolite for petroleum catalytic processing. Yang et al. succeeded in finishing the project. Inside cubosomes, polymerization occurs,resulting in a cubic solid nanostructured particle symmetry. Photonic and semiconductor applications could benefit from the employment of such particles. Lu et al have created unique aerosol techniques that produce nanometer-scale particles by evaporating solvent from isotropic

phase liquid droplets, pushing them into cubic phase structures, and hardening the particles. As the cubic phase template area becomes more sophisticated, structure optimization will become a major focus. Larson argues that prior to templating, the cubic phases could be aligned by steady or large-amplitude oscillatory shearing, resulting in materials with unique and highly anisotropic characteristics. Polymerization takes place inside cubosomes, producing a solid nanostructured particle symmetry that is cubic in shape. Such particles could find useful uses in photonic and semiconductor fields. By forcing isotropic phase liquid droplets into cubic phase structures, evaporating the solvent, and hardening the resulting particles, Lu et al. have developed novel aerosol procedures that yield nanometer-scale particles. Structure optimization will become a primary concern when the cubic phase template area becomes increasingly complex. According to Larson, materials with distinct and highly anisotropic properties could be produced via continuous or large-amplitude oscillatory shearing in order to align the cubic phases before templating.

- **Biologically Active Substances:**

  At 25 oC, combinations of alcohol and water monoolein generate cubic phase. Propanol and butanol were found to be less suitable than ethanol. A novel translucent, 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 ethanol. By using polarized light microscopy and bright field light microscopy, no structures were discovered, suggesting that OL is an isotropic phase. Large domains of this ordered phase were visible in CryoTEM, and a Fast Fourier Transform allowed for the phase's identification as a cubic phase.[50]

- **Treatment of Skin, Hair, and Body Tissue:**

  Biologically compatible lipids and water can be combined to create cubic phase materials, which is perfect for treating skin, hair, and other body tissues. Mono-olein, or monoglycerides, is found in cubosomes. Monoglyceride characteristics that are microbicidal Ethanol in cubosomes causes skin disruption. More lipid fluidity allows for greater penetration through the skin. Drugs are released into the deep layers of the skin once cubosomes attach to lipids in the skin.[51]

❖ **CONCLUSION:** With emerging growth in review, Cubosome have been proved to be interesting Drug Delivery system for pharmaceuticals products. Cubosomes are more effective for oral, ophthalmic, intravenous, topical drug delivery as it able to achieve better bioavailability.

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