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Review Article

Cubosomes: A Potential Drug Delivery System

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ABSTRACT

The discovery of cubosomes is a classic story and deals with food science, differential geometry, biological membranes and digestive processes. Cubosomes are highly balanced and nanoparticles in design formed primarily from the lipid cubic state and protected by a polymer-based outer circle. Hydrating a surfactant that designates cubic phase and then disperses a solid state into smaller particles, typically forms cubosomes. They behave concretely like rheology with unique properties of practical interest. Cubosome formation can be optimized to engineer pore size or consist of bioactive lipids, polymers can be used for targeting to the outer circle and they are highly secure under physiological conditions. This type of network structure gives them greater drug trapping potential. Related to liposomes, the structure adds a significantly more enhanced membrane surface area to trap membrane proteins and small drug entities. Cubosome may increase the solubility of poorly soluble drugs. Due to modern advances, nanoparticles patterns include drug delivery, membrane bioreactors, artificial cells and biosensors and can be engineered both in vitro. This review, focused on modern advances in cubosome technology, not only facilitates their work but also contributes to standard procedures for the rational design of innovative systems for biomedical applications. Due to the nature of cubosome dispersion being bio-adhesive and biocompatible, as well as having different properties, cubosomes are functional systems, administered in a variety of ways, such as orally and parenterally. Cubosome structure is investigated through electron microscopy, light scattering, X-rays, and NMR, although some researchers are studying the potential of cubosomes as a delivery system.

Keywords: Cubosomes, Cubic Phase, Mono-olein

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INTRODUCTION

Cubosomes are discrete, sub-micron, cubic liquid crystalline phase bicontinuous lipid containing nanoparticles. They are liquid crystalline particles that self-arrange and have a large surface area. Polymers, lipids, and surfactants with polar and non-polar constituents are mostly amphiphilic in cubosomes. Cubosomes are nanoparticles that are self-assembled liquid crystalline particles of certain surfactants with a specific water-to-microstructure ratio. Amphiphilic molecules travel into polar solvent due to the hydrophobic effect, causing them to

impulsively recognise and change into a nanometre scale liquid crystal. The finding of bicontinuous cubic liquid crystals is growing rapidly¹. Surfactant-controlled bilayers separate two separate zones of water. Furthermore, these are optically isotropic, viscous, and solid liquid crystalline solids with cubic crystallographic symmetry. Further cubic phase decomposition may occur, resulting in a thermodynamically stable particle dispersion². They have a structure that is comparable to honeycomb (cavernous) structures and range in size from 100 to 500 nm³. Cubosomes are attracting a lot of attention as a novel drug delivery system, and they've lately been used in ophthalmic, dermatological, oral, and

cancer therapy⁴. Actually, cubosomes and polymeric micelles are structurally identical, and both are widely utilised in drug delivery applications. Polymeric micelles, on the other hand, are synthesized by an amphiphilic polymer that self-assembles into a core-shell structure in water when its concentration exceeds the critical micelle concentration. When a hydrophobic medication is added, it can be incorporated into the micelle's hydrophobic core, while a hydrophilic bioactive molecule can be incorporated into the micelle's outer hydrophilic shell⁵. Cubosomes have an advantage over alternative delivery systems because of its liquid crystalline structure, which consists of well-defined networks of aqueous channels and lipid bilayer membranes structured in periodic 3D topologies. Biocompatible methods for the encapsulation of natural and synthetic lipophilic, hydrophilic, and hydrophobic drug molecules, as well as a variety of macromolecular medicines (peptides, proteins, DNA, m-RNA, and other imaging agents) have been developed. Complex cubic lattice networks with large surface areas preserve the integrated payload from degradation and allow for the release of encapsulated bioactive compounds over a longer period of time⁶.

Properties of cubosomes

The viscosity of cubosome dispersions is substantially lower.

Cubosomes are bicontinuous cubic liquid crystalline particles that are distinct, sub-micron nanostructured particles.

The most intriguing is probably cubosomes⁷.

Cubic liquid crystals are physically stable in excess water because they are transparent and isotropic.

Cubosomes are attractive for controlled release due of their narrow pore size.

It has the ability to solubilize hydrophobic, hydrophilic, and amphiphilic compounds, as well as biodegradability.

Advantages of Cubosomes^{8,9}

- They have ability to encapsulate both hydrophilic and hydrophobic also amphiphilic drugs.
- They have a sustained- release drug delivery characteristics.
- Cubosomes have biocompatibility and bioadhesivity properties.
- Bicontinuous cubic liquid crystalline phase of Cubosomes even stable in excess water.
- Cubosomes are excellent solubilizers, compared with conventional lipid or non-lipid carriers.
- They show high drug carrier capacity for a range of sparingly water-soluble drugs.
- These are an excellent vehicle to protect the sensitive drug from enzymatic degradation and in-vivo degradation, such as peptides and proteins.
- The cuboidal system enhances the bioavailability range twenty to more than one hundred times of water-soluble peptides.
- With respect to liposomes, cubosomes possesses a larger ratio between the bilayer area and the particle volume and a larger breaking resistance.

- Because of their high internal surface area and crystalline cubic structures they have high drug payloads.
- They can be prepared by simple method and possess lipid biodegradability.
- Targeted release and controlled release of bioactive agents.
- Cubosomes are excellent solubilizers, compared with conventional lipid or non-lipid carriers.
- They show high drug carrier capacity for a range of sparingly water-soluble drugs.
- These are an excellent vehicle to protect the sensitive drug from enzymatic degradation and in-vivo degradation, such as peptides and proteins.
- The cuboidal system enhances the bioavailability range twenty to more than one hundred times of water-soluble peptides.
- The cubic phases of cubosomes can be fractured and dispersed to form particulate dispersions that are colloiddally and/or thermodynamically stable for longer time.

Disadvantages of Cubosomes¹⁰

- Challenging in large scale production due to the high viscosity of cubic phase.
- They have low entrapment efficiency for water-soluble drug molecules due to their high water content inside their structure.

Cubic Phase Liquid Crystals

The solubilized active is thought to be the only determinant of the loading and release properties of cubic phase liquid crystals. The allocation of actives between existing phases determines the loading qualities. The partitioning is influenced by thermodynamic restrictions, which require that the chemical potential of the active in each phase be equal at equilibrium. The idea behind functionalization is to change the properties of the cubic phase to influence the loading and release qualities of the active. Amphiphilic molecules are incorporated into the liquid crystal to enable functionalization; the hydrophobic portion of the amphiphile inserts into the cubic phase bilayers, while the hydrophilic portion extends into the water channels. It is feasible to manage the interactions of the hydrophilic sections with the actives by tailoring their unique qualities. A positively charged hydrophilic part, for example, is expected to boost the loading of a negatively charged active⁴. Amphiphilic actives including chlorpheniramine maleate, diltiazem-HCl, and propranolol HCl bind to the monoglyceride in diverse ways, leading to further partition differences. However, when actives like chlorpheniramine maleate and pseudoephedrine hydrochloride interact with the liquid crystal, their release rates follow a different pattern at longer durations. As the concentration in each phase approaches its equilibrium partition value, the release rates slow as well¹¹.

Theory of Cubic Phase Structure

There are basically 4 theories regarding cubic phase structure

Fontell & Drew Theory

Cubic phases can be found in ternary systems of amphiphiles, oil and water, and certain mono glycerides. Monoglycerides are polar lipids with low water solubility and aqueous phase behaviour that structurally resemble non-ionic surfactants. Lutton's results show that monoglycerides with hydrocarbon chain lengths between C-12 and C-22, particularly monoolein, have a bigger cubic phase area. C-18 Monoglycerides are unsaturated monoolein¹².

Table 1: Monoolein Properties

Chemical Name	9-Octadecenoic acid (Z)-monoester with 1,2,3-propanetriol
Synonyms	Glycerol-1-oleate, glycerol oleate, glyceryl monooleate, monoolein, α -monoolein glycerol
Empirical Formula	C ₂₁ H ₄₀ O ₄
Boiling Point	238°C–240°C
Density	0.94 g/cm ³
Melting point	35-37 °C
Flash point	180 °C
Storage temp	-20°C
Solubility	chloroform: 50 mg/ml clear, colorless

Gustafson et al Theory

Cubosomes are single crystal structures with visible unilamellar vesicles and distributed lamellar liquid crystalline phase particles in the liquid crystalline phase. The creation of bigger vesicles is aided by increasing the polymer-to-monoolein ratio. Because of the slow transport processes involved in forming high viscous crystalline structure and the high energy required to fragment them (bulk cubic phase), ultra sonication of bulk cubic phases produces mostly vesicles, which eventually trace form into Cubosomes via membrane fusion. This meta stability is characteristic of Cubosomes systems¹³.

Schwarz, Jacob & Anderson Theory

In non-ionic surfactant systems, cubic phases are frequently encountered wedged between lamellar and hexagonal liquid crystalline phases. The monoolein-water system is remarkable in that it has a cubic phase area with a wide range of composition and temperature. Surfactant packing concepts, on the other hand, are getting closer. Normally, monoolein has a hydrophilic head and a hydrophobic tail, resulting in reversed or inversed cubic phases, indicating polar medium phases. At high water levels, the monoolein water system forms the D surface, and at lower water levels, the G surface¹⁴. The p-surface forms in the monoolein water system, but only when a third component, such as caseins or amphiphilic molecules, is present. The block copolymer is incorporated. The existence of cubic phases can be determined using the X-ray scattering technique.

System Forming Cubosomes

Cubosomes can be formed in binary and ternary systems that have a large enough miscibility gap between the cubic phase and the solvent. When poloxamer 407 is used to prevent cubosome aggregation and coalescence, the colloidal stability of the cubosomes is good. Cubosomes can be coated with lamellar bilayered 'caps,' which cover the cubic bilayer opening generated by fragmentation and offer colloidal stability by preventing hydrocarbon chains from being exposed to water. Cubosomes coated with a solid crystalline bilayer have higher colloidal stability, whereas lamellar liquid crystalline coatings are rigid¹⁵.

Structure of Cubosomes

Cubosomes have a honeycombed structure that separates the two internal aqueous channels, as well as a significant

interfacial surface. Cubosomes are nanoparticles, or more precisely nanostructure particles, generated by the self-assembly of amphiphilic or surfactant-like molecules in liquid crystalline phases with cubic crystallographic symmetry. Because of their interesting Bicontinuous structure, which encompasses two distinct areas of water separated by a controlled bilayer of surfactant application, the cubic phases have a very high solid-like viscosity, which is a unique feature. Bicontinuous water and oil channels are formed by amphiphilic molecules, with Bicontinuous referring to two distinct (but non-intersecting) hydrophilic regions separated by the bilayer. The structure's interconnectivity produces a clear viscous gel with a rheology and looks similar to cross-linked polymer hydrogels¹⁶. Cubosomes resemble small square or slightly round specks. Each dot in the lipid water system relates to the presence of a pore containing aqueous phase cubic phases. Luzzati and Husson were the first to discover them using the x-ray scattering technique. Monoglycerides are polar lipids with low water solubility that behave in the aqueous phase due to their structural resemblance to non-ionic surfactants. Monoolein hydration at 20-40% w/w results in the formation of bulk cubic phase¹⁷.

Mechanism of Drug Transport

The nature of the carrier's activity and composition, as well as the structure and physiology of the skin, all influence drug transport through the biological membrane. Small ions are transferred without much complexity through hair follicles, epidermal membrane pores, and tight junctions. Intra (trans) and inter (para) cellular transports are both involved in skin membrane transport mechanisms. Drugs can be introduced into the core or as an inherent part of the vesicles by altering carriers¹⁸. The passage of a substance across a membrane by travelling between, rather than between, two cells is known as paracellular diffusion. By definition, this is a passive process that is influenced by pore size and the size and form of the xenobiotic. The passage of a drug across a cell is known as transcellular diffusion. The drug is exposed to the enzymes within the cell, as well as any efflux pumps present on the apical area of the membrane, when enteric absorption occurs through transcellular diffusion. As a result, the amount of medication that reaches the systemic circulation may be reduced. Passive, facilitated, or active transcellular diffusion is all possibilities¹⁹. The most prevalent mode of drug transport is transcellular migrations, which involves

drug transit across cells. Some drugs, however, are too polar to pass across the lipoidal cell membrane and for them only the paracellular pathway, between the cells, is generally available.

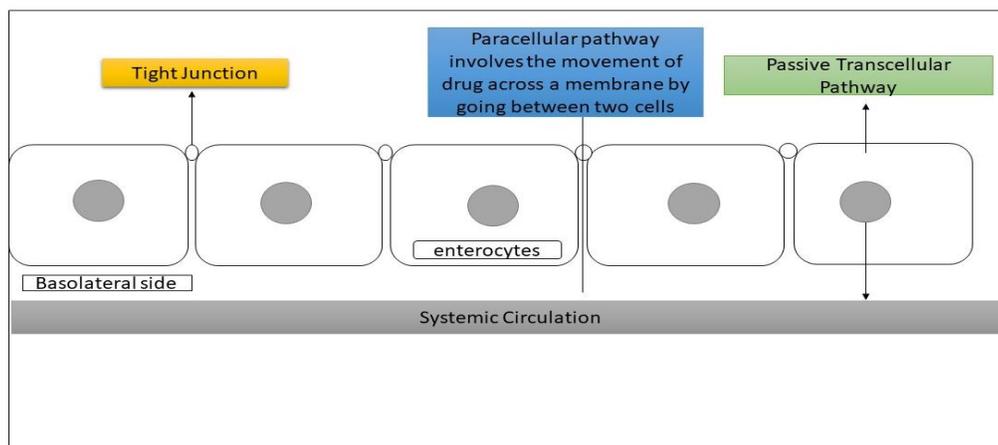


Figure1: Mechanism of Drug Transport via Skin

Types of Cubosomes

Liquid Cubosome Precursors

It has been discovered that the hydrotrope dilution procedure produces more stable and smaller cubosomes. The nucleation process permits particles to form, which then increase through crystallisation and precipitation processes. Monoolein is properly dissolved in a hydrotrope such as ethanol, which prevents it from forming liquid crystals. As a result, diluting this mixture causes the cubosomes to spontaneously “crystallise” or precipitate. Quid precursor technique allows for faster cubosome preparation scale-up while avoiding bulk solids handling and possibly destructive high-energy operations²⁰.

Powdered Cubosome Precursor

Dehydrated surfactant covered with polymer makes up powdered cubosome precursors. Compared to liquid phase hydrotropic cubosome precursors, such powders have advantages. The hydration of the precursor powders produced cubosomes with a mean particle size of 600 nm, as validated by light scattering and cryo-TEM. Cubosomes are waxy, sticky solids that are made up of lipids. The coating of the waxy lipid on water-soluble non-cohesive starch normally prevents from agglomeration and regulates particle size. An excellent process for his purpose is spray drying.

Methods Used in Cubosomes Preparation

There are four main approaches to produce cubosome nanoparticles: ‘top-down’ and ‘bottom-up’. Besides the differences, to prevent cubosome dispersion aggregation, both techniques require a colloidal stabilizer such as P407, as described.

Top down Technique

It is the most extensively utilised approach in the research field, with Ljusberg- Wahren first reporting it in 1996. The viscous bulk cubic phase is created by combining lipids with stabilisers, and then dispersing the resulting mixture into aqueous solution using high energy (such as High-Pressure Homogenization [HPH], sonication, or shearing) to produce Lyotropic Liquid Crystal (LLC) nanoparticles. HPH is the most widely used method for making LLC nanoparticles. Cubic phases vary from other thermodynamic phases in that they are a single thermodynamic phase with a periodic liquid crystalline structure²¹. Wörl et al. looked into the factors that influence the qualities of cubosomes made of glyceryl monooleate (GMO). The concentration of F127 and the temperature during HPH were regarded crucially significant parameters based on the findings²². Vesicles (distributed nanoparticles of lamellar liquid crystalline phase) or vesicle-like structures are always detected coexisting with cubosomes made using a top-down technique.

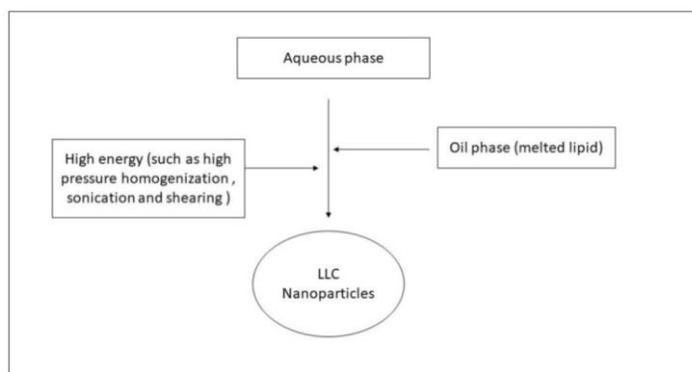


Figure 2: Top down Technique

Bottom Up Technique

Cubosomes are permitted to develop or crystallise from precursors in this method. There are two types of precursors: liquid and powder. Monoolein and ethanol solution make up the liquid precursor. It is made by adding hydrotrope (ethanol) to molten monoolein at room temperature. The monoolein-ethanol solution is then emulsified with a solution of poloxamer 407, resulting in a viscous cubic liquid gel. A Cubosomes nanoparticle are created by diluting the

generated gel with water and sonicating it for five minutes. The powder precursor, on the other hand, is made up of monoolein powder that has been coated with either starch or dextran. This precursor, which is made up of dehydrated surfactant that has been coated with polymer, is then hydrated to produce a liquid droplet emulsion. Using spray drying technique, the nanoparticle cubosomes are formed from these powder precursors²³.

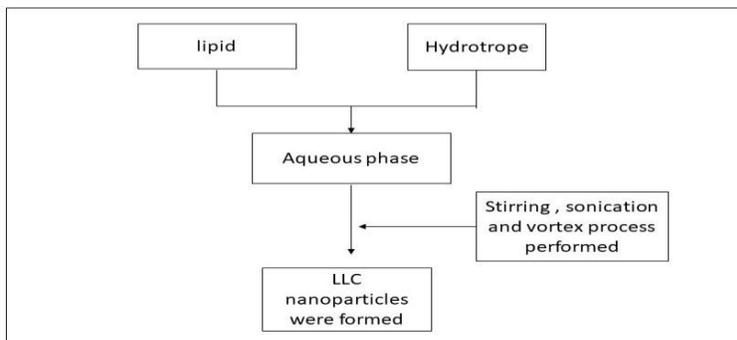


Figure 3: Bottom up Technique

Heat treatment approach

This technique is not an integrated cubosome manufacturing process because it only promotes the transformation from non-cubic vesicles to well-ordered cubic particles via a homogenization and heat-treatment step, resulting in a decrease in the small particle size fraction that corresponds to vesicles and the formation of more cubic phases with narrow particle distribution and good colloidal stability.

Spray drying

Using a spray drying method Due to the limited flexibility of liquid precursors for cubosome production (Spicer et al), a dry powder precursor for cubosome preparation was devised. For the manufacture of starch encapsulated monoolein precursor and dextran encapsulated monoolein precursor, they used a spray drying process. Encapsulation with a high proportion of polymer (75 percent w/w for starch and 60 percent w/w for dextran) reduced the amount of active material loading, hence the method was limited for powerful medicaments, vitamins, flavours, or smells. Cuboidal preparation method in general Monoolein and water are frequently combined around 40° C to make cubosomes. Mechanical or ultrasonic energy is used to disperse the resulting cubic liquid crystalline gel into particles. To make cubosomes, high-pressure homogenizers are frequently used. The cubosomes are finally secured against flocculation. Phase aqueous Input of a lot of energy²⁴.

Materials used in cubosomes

Bicontinuous cubic phases are found in-

- A. Natural lipids
- B. Cationic and non-ionic surfactants
- C. Polymer systems

A. Natural lipids

Although the lipid most widely used to construct bicontinuous cubic phases are-Monoglyceride, Monoolein.

Monoglycerides

Monoglycerides are spontaneously form bicontinuous cubic phases upon the addition of water, are relatively insoluble (allowing the formation of colloidal dispersions of cubosomes), and are resistant to changes in temperature.

Monoolein

Monoolein is the most important precursor for cubosome development. Monoolein, also known as glyceryl monooleate, is a mixture of oleic acid glycerides and other fatty acids, with the monooleate constituting the majority of the mixture. Monoolein is commercially available in two forms: mixed glyceride and distilled monoolein; distilled monoolein is selected for pharmaceutical purposes due to its high purity. Monoolein is a waxy yellow substance that has a distinct odour. Monoolein is a nontoxic, biodegradable, and biocompatible substance that is listed in the FDA's inactive ingredients guide and in non-parenteral medicines registered in the UK. The mesomorphic phase of monoolein is significant for understanding the lipid's possible medicinal applications.

B. Surfactant

Poloxamer 407 is a surfactant that is employed in the manufacture of cubosomes in concentrations ranging from 0% to 20% w/w with regard to the disperse phase. In terms of total weight of the dispersion, the concentration of the monoglyceride/surfactant mixture is usually between 2.5 percent and 10% w/w.

C. Polymer system

Polyvinyl alcohol (PVA) used in addition to poloxamer as a stabilizing agent of the dispersion²⁵.

Superiority of cubosomes over other drug delivery system

Cubosomes have a higher skin permeation rate, making them ideal for medication administration through the skin. It is the most effective method for delivering a large number of

proteins and peptides. According to scientific literature, the lipids utilised in the creation of cubosomes are biocompatible and biodegradable, with a low risk profile. The preparation procedure is relatively easy and does not require the use of specialised equipment. In comparison to other carrier systems, the preparation has a high level of stability. This nano vesicular technology is passive, non-invasive, and ready for rapid commercialization. Due its proprietary technology it gained higher market attractiveness²⁶.

Comparison of Cubosomes with Liposomes

Cubosomes²⁷

- Cubosomes are formed when a hydrating mixture of monoolein and poloxamer 407 forms a bicontinuous cubic liquid crystalline phase.
- Artificial, colloidal, and spherical vesicles with a diameter of 0.05-5.0 μ m.

- Chemical bonds bind active chemical constituent molecules to the polar head of the phospholipids in cubosomes.
- Depending on the substance, the polymer and the specific medicinal ingredient form a 1:1 or 2:1 complex in cubosomes.

Liposomes

- Liposomes are hydrated mixtures of cholesterol and phospholipids that form vesicles.
- They resemble square dots with a diameter of 10-500 nm and a somewhat spherical form.
- In liposomes, the active ingredient is dissolved in the cavity medium or the membrane layers. There are no chemical bonds established.
- In liposomes, hundreds and thousands of phosphatidylcholine molecules surround the water-soluble molecule.

Characterization and Evaluation of cubosomes²⁸

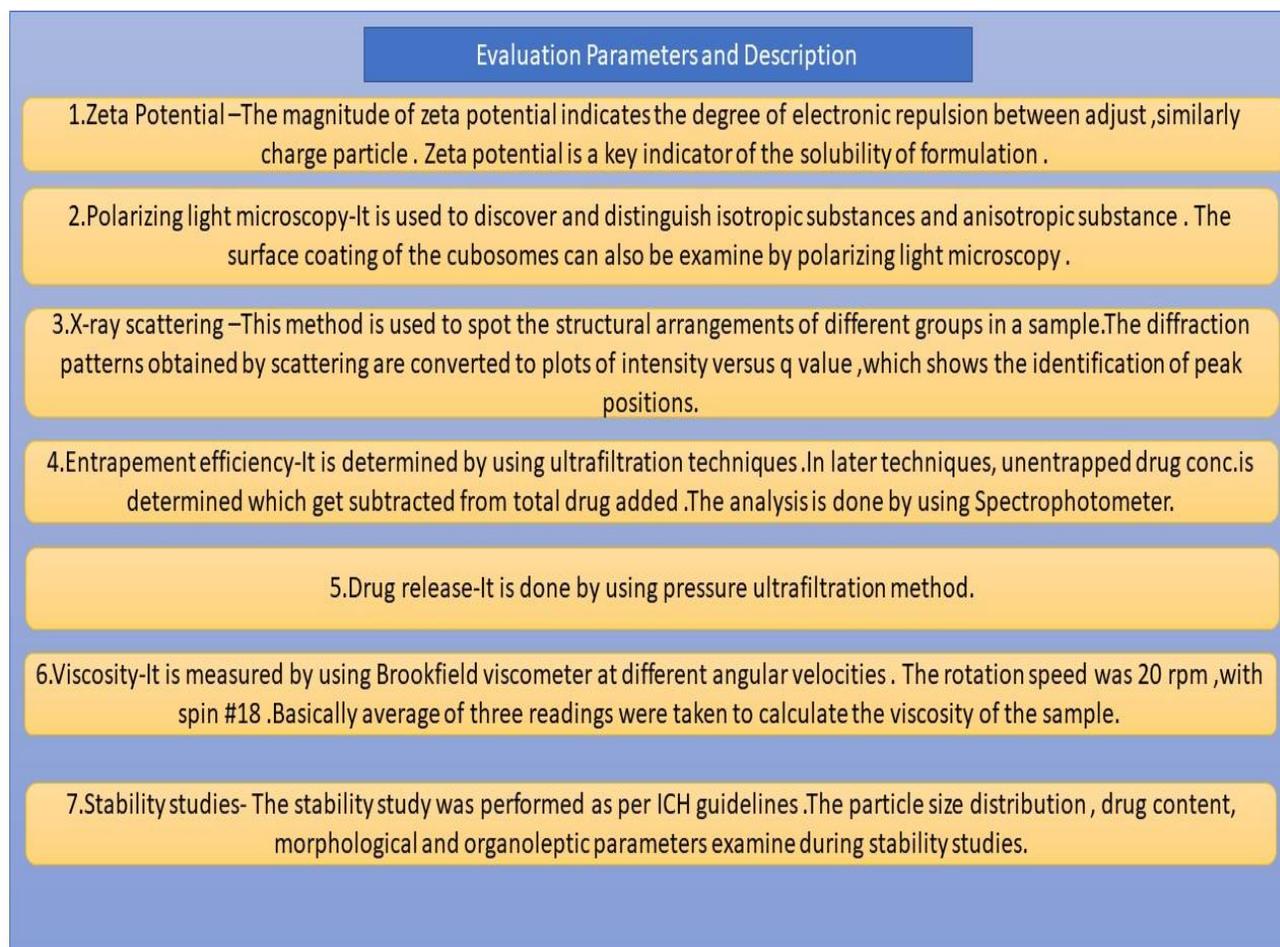


Figure 4: Characterization parameters of Cubosomes

Applications of cubosomes

Dermatological applications

The stratum corneum, which is the highly structured outermost layer of skin, acts as a strong barrier to skin penetration of topically administered medications in transdermal drug delivery. Cubosomes, on the other hand,

offer a promising vehicle for transdermal medication administration due to their unique structure and characteristics. Cubosomes can be employed efficiently in topical and mucosal drug administration due to their bioadhesive qualities to the stratum corneum as a result of GMO. Cubosomes have recently been used in a number of

dermatological applications. Vaccination using transcutaneous (TCI) immunisation is an important dermatological use. Microneedles (MNs) and cubosomes, on the other hand, have been successfully used as a synergistic strategy for delivering vaccinations through the skin. The use of MNs improved the penetration of the aqueous peptide mixture through the skin layers, and the cubosome-formulated peptide had longer skin retention. As a result, researchers discovered that using a combination of MNs and cubosomes to transfer antigen to specified cells in the skin is an effective system²⁹.

Cubosomes in Nasal route

The administration of medicines directly from the nose to the brain, bypassing the blood-brain barrier (BBB), has proven to be a non-invasive and successful method of treating central nervous system (CNS) problems. Engineered PEGylated cubosomes with functional odorranalectin molecules were investigated using coumarin as a marker, and their relative absorption was roughly 3.46-fold in the brain compared to untreated cubosomes, according to Wu *et al*. Gly14-human (S14G–HN) was also inserted into cubosomes and studied for its therapeutic efficacy in Alzheimer's disease. The findings revealed that odorranalectin cubosomes could improve the effects of S14G-HN in Alzheimer's disease. Mayuri Ahirrao *et al.*, investigated the use of cubosomes to transfer resveratrol to the brain via the nasal route in the treatment of Alzheimer's disease. The probe sonication method was used to create GMO P407 cubosomes. In-vitro drug release followed a consistent pattern for nearly 24 hours³⁰.

Brain targeting

The BBB prevents medications from reaching the brain for treatment of CNS illnesses. The administration of both tiny and large medication molecules is made more difficult by this barrier. Cubosomes, a form of lipid-based nanoparticle, have been studied for increasing medication loading into the brain. One example is using cubosomes to improve resveratrol delivery to the brain via the transnasal pathway. These were made utilising a probe sonication method with glycerol monooleate lipid and Lutrol® F 127. After optimising cubosomal dispersion, it was mixed in Poloxamer 407 polymer to generate an in situ nasal gel. It had a greater transnasal penetration and distribution than the medication solution.

Cosmetics

Cubosomes have been used to create hair care, skin care, antiperspirants, and other cosmetics. Alpha-lipoic acid (ALA) is a mitochondrial fatty acid that has powerful antioxidant properties. This ALA dispersion in cubosomes has excellent results in minimising facial wrinkles and improving skin texture and colour³¹.

Controlled or sustained release behaviour

A variety of medicines with various physicochemical features have been integrated into cubosomes, and their long-term drug release behaviour has been investigated. Cubosome residual particles were responsible for the cubosomes' long-term activity. Topical usage of

monoglyceride-based cubosomes, such as for percutaneous or mucosal administration, is possible.

In treatment of viral diseases

Monoglycerides, due to their microbicidal capabilities, could be employed to develop intravaginal treatments for sexually transmitted illnesses caused by viruses (e.g., HSV, HIV) or bacteria (e.g., Chlamydia trachomatis and Neisseria gonorrhoeae)³².

Intravenous Drug Delivery Systems

To solubilize, encapsulate, and distribute drugs to diseased locations within the body, lipid nanoparticles made up of the internal liquid crystal structures of curved lipid membranes are utilised. LCNP structures enhanced the payloads of peptides, proteins, and many insoluble small molecules, and are perfect carriers for injection or infusion of many actives, while emulsions and liposomes have found usage as intravenous carriers in therapeutic products³³.

Brain targeting

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In cancer cell targeting

Cubosomes have been used to encapsulate a variety of cancer medicines with great success. Resveratrol, for example, has low water solubility, undergoes substantial first-pass metabolism, and isomerizes to the inert cis-isomer when exposed to light. Cubosome formulation improved cellular absorption of this anticancer drug³⁴.

Melanoma (cancer) therapy³⁵

Few anticancer medicines have been successfully encapsulated in cubosomes and physicochemically examined in recent years. The unique structure of this potential nanocarrier suggests that it could be used to treat melanoma. Different methodologies have been proposed to specifically target nanomedicines to tumours, with passive and active targeting of cancer cells proving to be viable approaches in preclinical and clinical research. The pathophysiological properties of the tumour vasculature, which are generally highly disorganised with enlarged gap junctions between endothelial cells and compromised lymphatic drainage, allow for the extravasation of nanocarriers with sizes up to several hundred nanometre ranges, are exploited in passive targeting. Objects of this size cannot pass through the tight junctions that exist within the endothelial cell lining of the vessels of healthy tissues.

Drugs Incorporated in Cubosomes

Table 2: Encompasses the list of drugs incorporated in cubosomes for various outcome of study

S. No.	Outcome of the study	Drug used in study	Reference
1	Cubosomes made with doxorubicin had greater drug loading, pH sensitivity, and controlled release at the target site. The carrier system improves cell cytotoxicity while minimising unfavourable side effects.	Doxorubicin	(36)
2	Ketorolac-loaded cubosomes with an optimised formulation produced nano-sized particles with greater ketorolac encapsulation. Trans corneal permeability and retention are other factors.	Ketorolac	(37)
3	AmB could be delivered orally using this formulation. Cubosomes were used to create a controlled release of AmB for oral delivery.	Amphotericin B	(38)
4	The cubic liquid crystalline nanoparticles (cubosomes) Formulation was developed of SSD dispersions to bypass the cytotoxic effects of silver by regulating the release of SSD. When compared to marketed formulations, it helped reduce the dose of SSD to 0.2 percent and showed enhanced and better healing with less side effects.	Silver sulfadiazine	(39)
5	With sustained administration of lipophilic medication through the skin, a homogenised monoolein and poloxamer containing cubosomes formulation was successfully achieved.	Indomethacin	(40)
6	Cubic nanoparticles boosted the transport of flurbiprofen to the cornea and increased its bioavailability.	Flurbiprofen	(41)
7	The rapamycin-carrying particles were subsequently incorporated into a polymeric matrix made up of microneedle pads that dissolve quickly. On a skin-like agarose gel of the filled cubosome-like particles, the designed microneedles displayed efficient penetrating and deposition. The studies illustrate the ability to transport cubosome-like particles into the skin and facilitate the continuous release of drug.	Rapamycin	(42)

CONCLUSION

With the widespread use of cubosomes in various fields, they can be characterized by various evaluation parameters. They are now available for targeting cells of interest using cubosomes and major advances include tailoring of pore size into lipid cubic phases, libraries of stabilizers, structural studies to understand access to the inner lipid membrane, and systems for controlled release and design which is also included. There are still some major outstanding challenges such as further enhancing the applications of cubosomes, including a deeper understanding of stabilizer as well as membrane interactions, demonstration of pore size tuning in line with bulk phase work and cell, and demonstration of smart release in the future and cytotoxicity studies including the mechanism of interaction with cells and further elucidation. The exploitation of cubosomes made of bioactive lipids as therapeutics would also novel an

interesting future development. As development progresses into the next generation of smart lipid nanoparticles, cubosomes are also applicable for a wide range of drug candidates, immunoassays, proteins and cosmetics. Cubosomal preparations can be widely employed as targeted drug delivery systems for ophthalmic, diabetes and anticancer therapy because of its potential site specificity. When developing new formulation, cubosome technology is relatively novel with high efficiency and will have wide scope of research with commercial and industrial feasibility. Not only does the ability to fabricate cubosomes provide a great deal of flexibility for product development efforts either in use, during, or during manufacturing, but the precursor forms extend its further scope into the technological

CONFLICT OF INTEREST

The author declared no conflict of interest.

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