INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA):IJPS00]
Journal Homepage: https://www.ijpsjournal.com

Review Article

A Comprehensive Review On Cubosomes

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ARTICLE INFO

Received: 16 May 2024
Accepted: 20 May 2024
Published: 29 May 2024
Keywords:
Nanoparticle, Cubosomes, Nanostructural lipid Carriers, Drug Delivery, Nanotechnology, Pharmaceutical Application
DOI:
10.5281/zenodo.11388371

ABSTRACT

The novel shape and adaptability of cubosomes, which are nanostructured lipid-based particles, have made them an attractive candidate for use as drug delivery vehicles. This abstract provides a concise overview of cubosomes, highlighting their structural features, formation mechanisms, and applications in the biomedical and pharmaceutical fields.Cubosomes are self-assembled lipid nanoparticles characterized by a bicontinuous cubic liquid crystalline structure. Formation of these structures involves the hydration of lipid mixtures, resulting in the creation of a three-dimensional network with water channels. The distinct cubic symmetry of cubosomes imparts them with advantageous properties, like high surface area, stability, and controlled release capabilities. In the context of drug delivery, cubosomes offer an ideal platform for encapsulating hydrophobic and hydrophilic drugs, allowing for improved solubility and bioavailability. Their nanoscale size enables efficient transport through biological barriers, leading to enhanced therapeutic outcomes.

INTRODUCTION

A drug delivery system is a mechanism that transports a therapeutic substance to a specific area of the body at a predetermined rate. This ensures that the medicine reaches the target region at the ideal concentration for its effects. The goal of controlled drug release (CR) is to maximize therapeutic benefits while reducing undesired side effects by systematically releasing the drug over time. Prolonged release over an extended timeframe has the potential to diminish the necessity for frequent dosing, offering advantages in terms of lowered expenses and improved adherence by patients. A vesicular drug delivery system entails enclosing the drug within vesicular structures to provide precise drug delivery targeting. By using the vesicles as carriers, the method enables the delivery of medications with large molecular weights. The vesicles may also function as penetration enhancers, hastening the drug's passage through the skin. There is a plethora of vesicular drug delivery systems

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

available to help with drug targeting and the controlled or prolonged release of conventional pharmaceuticals. Cubosomes play a significant role in these types of systems. The vesicular drug delivery method makes use of cubosomes, a sort of colloidal structure based on lipids. The initial finding of its type was made by them in 1980. Their similarity to liposomes and cubic molecular crystallography led Larsson to coin the name "Cubosomes" to characterize them. Nanoparticles known as cubosomes are one-of-a-kind because of their submicron size and bicontinuous cubic liquid crystal phase structure. Cubosomes are a type of nanoparticle that can form crystalline forms in liquid by itself. A microstructure is created by combining certain surfactants with water in the right proportions. Furthermore, cubosomes display solid-like rheological characteristics. At the Very Top. Cubosomes have a bigger specific surface area than the original cubic phase but keep the same microstructure. Compared to the bulk cubic phase, these dispersions likewise have a much lower viscosity. Cubosomal dispersions are less viscous than bulk cubic phases. Concentrated surfactants that crystallize into cubic liquid usually undergo micelle formation at very low concentrations due to their perfect insolubility in water. Their cubic phases can be dispersed to create cubosomes when there is an excess of water. One of the traditional ways to make cubosomes is to first use high-energy to disperse the bulk cubic phases, and then use polymeric surfactants to stabilize the colloidal particles. One of the many fascinating uses for cubic phase liquid crystals is the controlled release of specific chemicals soluble in oils or water. Cubosomes are formed when cubic lipid phases are emulsified in water. These systems, which contain nanoparticles, are highly biocompatible and bioadhesive. Cubosomes are amphiphilic because they contain polar and non-polar components within their lipid, surfactant, and polymer molecular compositions. Because they don't like water, these amphiphilic molecules in polar solvents suddenly self-assemble into a number of thermodynamically stable liquid crystalline phases that are only a few nanometers long. Within cubosomes, which exhibit a bicontinuous cubic liquid phase, two autonomous water zones are separated by surfactant control. Bicontinuous cubic phases are a good approximation for liquid crystalline solids with cubic crystallographic symmetry due to their solid-like properties and high viscosity. [1-16].

STRUCTURAL COMPONENTS OF CUBOSOMES

Amphiphilic lipids

A couple of amphiphilic lipids that are frequently used to make cubosomes are phytantriol (PHYT) and glyceryl monooleate (GMO), which is also called monoolein. Oleic acid and other fatty acids are part of glyceride mixture known as GMO. Primarily composed of monooleate, an amphiphilic lipid with the ability to create various lyotropic liquid crystals. The tendency for GMO to form cubic phases is higher when hydrocarbon chain lengths are between 12 and 22, according to the research. In addition to its reputation for cubic phase formation GMO is a biocompatible and biodegradable substance that the Food and Drug Administration has classified as GRAS. The food sector mostly uses it as an emulsifier. The phytanyl-chained compound PHYT similarly shows signs of cubic phase development as the water content increases. A potential substitute for genetically modified organisms (GMOs) in cubosome production is PHYT, which is chemically 3,7,11,15-tetramethyl-1,2,3-hexadecanetriol and is widely used in cosmetics. Because GMO is more easily broken down by ester hydrolysis, PHYT has the added benefit of being structurally more stable than GMO. PHYT and GMO are structurally distinct, but they show very similar phase transition characteristics when

heated and exposed to increasing amounts of water. [17-22]

Stabilizers

Cubosomes are stabilized by surfactants, which prevent them from merging into the bulk cubic phase, according to scientists. The PEO-PPO-PEO tri-block copolymer known as Poloxamer 407 (P407) has been the subject of much research as a surfactant for cubosome production. The PPO components are located on the cubosomes' surfaces or in the bilayer structure, whereas the PEO chains are encased in water. Depending on the amount of dispersion phase, P407 is often utilized at concentrations up to 20%w/w. On a phytantriol-based cubosomal system, Wadsten-Hindrichsen et al. investigated three water-miscible solvents: propylene glycol (PG), polyethylene glycol 400 (PEG400), and 2-methyl-2,4-pentanediol (MPD). According to their findings, MPD solely generated sponge phases, while PG and PEG400 solely generated cubic, lamellar, and non-ordered liquid phases. Hydrophobicity and reduced flexibility caused by PHYT's branched hydrocarbon chain were the primary reasons for the phase behavior differences between GMO and PHYT. The form and internal structure of GMO and PHYT-based cubosomes were established by substituting P407 for β-casein as the stabilizer. When β-casein was substituted with P407 as the stabilizer, the phase forms and behaviors of GMO and PHYT-based cubosomes were distinct. At 60˚C, the GMO-b-casein cubosomes displace a Pn3m phase structure, causing a phase transition from QII to HII. Conversely, at temperatures greater than 70˚C, the HII phase became visible in the P407-GMO dispersion, which exhibited an Im3m phase structure. The concentration of the stabilizer had an effect on the phase structure of the PHYT systems. Hotting the b-casein-PHYT system caused a QII to HII to La transition, but the P407-PHYT dispersion went straight from QII to La. The Im3m structure in nanoparticles and the steric stability provided by β-casein inhibited the occurrence of specific phase transitions. It was found that cubosomes worked better with steric stabilizers consisting of poly(ethylene oxide) stearate, which are sold under the brand name Myrj. Even at a concentration five times lower, Myrj 59 (which included an average of 100 poly(ethylene oxide) units) outperformed P407 for PHYT cubosomes. [23-26]

STRUCTURE OF CUBOSOMES

Cubic nanoparticles have a honeycomb-like structure with lipid and water sections arranged hierarchically in three dimensions. In the 1960s, Luzzati and Husson were the first to study the structural behavior of cubic nanoparticles; Scriven subsequently offered a geometric model. Changing the lipid composition of cubosomes controls their internal and structural alterations. The dimension of these individual sub-micron nanostructures usually ranges from 100 to 500 nm. The initial method for identifying cubosomes was X-ray scattering. In lipid-water systems, cubicosomes show up as square or round dots, which represent the presence of pores with aqueous cubic phases. High viscosity is a result of cubic phases, which have fascinating bicontinuous structures. Two independent water areas are contained within these devices, with a controlled bilayer of surfactant separating them. Cubosomes are considered by their cubic crystalline structures and large interior surface areas. Monoolein and water are main components of cubosomes. [27-28]

FORMS OF CUBOSOMES

Macroscopic cubic phase can have three forms: precursor, bulk gel, and particle dispersions. In response to an external stimulus, the precursor phase, which can be a solid or a liquid, changes into a cubic phase when it comes into touch with a liquid. It is common for the bulk phase to resemble cross-linked polymer hydrogels rheologically and visually, and to have a viscous, semi-solid gel

texture. Contact with biological epithelia may cause irritation reactions, and its high viscosity limits its application. Particulate dispersions include dispersing the bulk phase into water as small particles, namely cubosomes, which are cubic particles. Within this distribution, cubosomes can maintain a stable equilibrium.[29]

Liquid Cubosome Precursors

It would be beneficial to investigate less aggressive production methods in light of the difficulties and expenses connected with high shear dispersion of viscous bulk cubic phases to create cubosomes. A technique that can be used to make cubosomes that are smaller and more stable is the hydrotrope dilution process. This technique avoids the creation of liquid crystalline formations by dissolving monoolein in a hydrotrope, like ethanol. Cubosomes crystallize or precipitate upon further dilution of this combination. Like crystallization and precipitation, this process uses a nucleation and growth mechanism to generate particles. When working with thermo-sensitive components like proteins, liquid precursor method makes cubosome preparations easier to scale up. [30]

Powdered Cubosome Precursors

Compared to hydrotropic cubosome precursors in liquid phase, powdered cubosome precursors have several benefits. Dehydrated surfactants covered with polymer make up these powders. Light scattering and cryo-TEM demonstrated that these precursors, when hydrated, generate 600 nm cubosomes. When working with lipids—solids that are waxy and sticky but not well suited to the formation of small, distinct particles—spray drying is an effective method for creating cubosomes. To make cubosomes, the spray drying method involves dispersing solid particles or emulsifying liquid droplets in a highly concentrated water-based polymer solution. The suspension droplets are created using a nozzle and then mixed with a dry, hot air stream that is moving in the opposite direction [31,32]

TYPES OF CUBOSOMES

1. Liquid Cubosome Precursors

Researchers discovered that smaller and more stable cubosomes were produced by the hydrotrope dilution method. Particles are able to take shape in this method because to nucleation, and they expand as a result of crystallization and precipitation. The production of liquid crystals is prevented by effectively dissolving monoolein in a hydrotrope, like ethanol. When this combination is diluted further, cubosomes will naturally "crystallize" or precipitate. Faster cubosome preparation on a larger scale is possible with the liquid precursor method, also called the "quid precursor" method, because it avoids the hazards of handling bulk solids and harmful high-energy procedures. This approach shows great promise as a viable substitute for the scalable and efficient cubosome production process. [33]

2. Powdered Cubosome Precursor

The building blocks of cubosomes, in powdered form, are dehydrated surfactants coated with polymer. Powdered hydrotropic cubosome precursors offer a number of benefits over their liquid phase counterparts. Precursor powders, when hydrated, produce 600 nm cubosomes, as shown by light scattering and cryo-TEM. Cubosomes are solids that are waxy and sticky and are made of lipids. They can produce agglomeration. However, a non-cohesive starch that dissolves in water can be applied over the waxy lipid as a coating to regulate particle size and prevent agglomeration. An ideal method for this application is spray drying, which helps to produce cubosomes with regulated particle size and avoids unwanted agglomeration. [33]

MANUFACTURE OF CUBOSOMES:

There are five different ways to make cubosomes.

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

3. Making ALA-loaded cubosome dispersions,
4. Cubosomes in Hydrotrope
5. Production process
6. Emulsification technique

1. Top-Down Approach

Ljusberg-Wahren initially brought up the method for making cubosome nanoparticles in 1996, and since then, it has been widely used. The procedure is carried out by first creating a large cubic phase, and then using high-energy methods, such as high-pressure homogenization, to further refine it. In bulk, cubic phases resemble water-extended cross-linked polymer chains; they are translucent and inflexible, much like a gel. The periodic liquid crystalline structure and thermodynamic relatedness of these phases make them distinctive. Cubic phase breaking energy grows in a shear-parallel direction with increasing broken branch counts in the tubular network. The procedure begins with the production of bulk cubic phase and continues with the separation of cubosomes by means of high-energy processing. Researchers frequently use this method to create cubosome nanoparticles.

2. Bottom-Up Approach

Permitting precursors to crystallize or evolve into the target structures is an essential step in cubosome development. Droplets of L2 or inverse micellar phase can be sprayed into water at 80°C, allowed to cool slowly, and then crystallized. This is one approach. On a bigger scale, this method produces cubosomes more efficiently. Making cubosomes at room temperature is another option; all you need is a mixture of monoolein ethanol and aqueous poloxamer 407. Emulsification causes cubosomes to form in this combination without any human intervention. [34]

3 Making ALA-loaded cubosome dispersions

Two techniques were employed to create cubosome dispersions:

Breaking up Bulk Cubic Gel (GMO/P407):

- A hot water bath set at 60°C was used to dissolve the P407 and genetically modified organisms (GMOs).
- Continuous stirring was used to dissolve ALA in doses of 25, 50, or 100 mg.
- Little by little, deionized water was added and blended again to ensure that everything was mixed equally.
- During the 48-hour equilibration period at room temperature, a cubic gel phase that is optically isotropic was created.
- To break up the cubic gel, 10 ml of deionized water was added and mechanically stirred.

Traditional Method of Energetic Dispersion in a Pseudo-Binary System (Monoolein-Water with Polymer):

- To make a consistent solution, 92% w/w monoolein and 8% w/w Poloxamer 407 were melted and combined.
- By adding deionized water to the monoolein-polymer solution, it was changed. This made a 1.8% monoolein mix with 98.6% water and 0.2% Poloxamer 407.
- In order to disperse cubic liquid crystalline gel, mixture was subjected to ultrasonication for 60 minutes at a constant temperature of 25°C.
- Both techniques helped create cubosome dispersions, but they used different ways to break up the bulk cubic gel and distribute the cubic liquid crystalline gel.

4 Cubosomes in Hydrotrope

- In presence of substantial amounts of hydrotrope, cubosomes were created using sonication-based techniques. The process involved the following steps:
- An isotropic liquid with low viscosity was made by combining molten monoolein with ethanol, resulting in the formation of a bulk cubic gel.

- For five minutes, the mixture was subjected to sonication.
- This sonication-based technique, coupled with the presence of a hydrotrope, was employed to produce cubosomes, showcasing the adaptability of the method in different formulations.[35]

5 Production process

The process involved in creating cubosomes using GMO/P407 cubic gel at 60°C in a hot water bath is as follows:

- Melted in a hot water bath at 60°C were GMO (5% concentration) and P407 (1.0%).
- The melted mixture was then supplemented with the necessary quantity of medication, which was stirred continuously until dissolved.
- A vortex was used to ensure that the mixture was evenly distributed after deionized water was introduced drop by drop.
- Mechanical stirring disrupted the cubic gel.
- Using a 200W sonicator probe in a water bath set at a chilly 20°C for 20 minutes further disrupted the gel.
- This series of steps resulted in the creation of cubosomes from the initial GMO/P407 cubic gel, involving dissolution, homogenization, gel formation, disturbance, and sonication.[36]

6 Emulsification technique

Following this procedure, 5% GMO, 1% P407, and 5% ethanol are added to 89% water after the GMO and P407 have been added to the water. An ethanolic solution is added to the melting pot after the GMO and P407 have been melted together at 60°C. The mixture is then added dropwise to deionized water that has been heated to 70°C. Then, using a maximum power of 130 kW, it is subjected to 50 minutes of ultrasonic processing at the same temperature. The next step is to store the dispersion solution in a dark, room-temperature place. [37] 38 51

EVALUATION OF CUBOSOMES

Thermal analysis

Assessing the drug's physical state within the cubosomes is the purpose of the method outlined. Glycerylmonooleate may plasticize because the cubosome components seem to melt together at temperatures between 37 and 56 degrees Celsius. No significant drug melting peak at approximately 200°C is detected, and thermal events associated with drug's melting point differ from those of original drug. The breakdown of glycerylmonooleate may also be associated with the thermal events seen between 200 and 300 degrees Celsius. Differential scanning calorimetry (DSC) and other forms of thermal analysis are useful for studying the interactions between formulation components and defining cubosome thermal behavior. [38]

Polarized light microscopy

Cubosomes' optically birefringent surface coating is revealed via polarized light microscopy. Additionally, this method may differentiate between substances that are anisotropic and those that are isotropic. Using a Zeiss III light microscope equipped with crossed polarizers and a λ-sheet, materials are examined throughout the procedure.

This can provide insights into the structural features and optical characteristics of the cubosomes, helping in their characterization and understanding their behavior under polarized light.[39]

Cryo-transmission electron microscopy

The process you described outlines the preparation and imaging steps for Transmission Electron Microscopy (TEM) of cubosomes:

Sample Preparation:

The prepared sample is placed on a pure thin bar 600-mesh TEM grid in a tiny amount at ambient circumstances.

A thin film is formed by blotting the solution with filter paper, which spans hexagonal pores of TEM grid.

Vitrification:

Immersing TEM grid sample in liquid ethane approaching freezing vitrifies it. Vitrification is a process of rapidly cooling a liquid to form an amorphous (non-crystalline) solid without the formation of ice crystals. This is important for preserving the structure of biological samples and soft materials during TEM imaging.

Transmission Electron Microscopy (TEM):

- A transmission electron microscope is used to examine the vitrified material that is mounted on a TEM grid.
- In order to keep the temperature at 175°C while imaging, a cryoholder is utilized.
- Cameras that use charge-coupled devices (CCDs) capture images digitally.
- In order to improve and analyze the captured images, an image processing system is employed.
- Thanks to this technique, the cubosomes' internal structure and morphology may be observed with high resolution using transmission electron microscopy (TEM). The vitrification step is particularly crucial for preserving the sample's structural integrity and preventing artifacts that can arise from traditional sample preparation methods.[40] 55- 61

APPLICATIONS OF CUBOSOMES

1. Melanoma (cancer) therapy

Physicochemical studies of cubosome-encased anticancer drugs have yielded promising results in recent years. These prospective nanocarriers have a unique shape that makes them promising candidates for melanoma treatment. When it comes to delivering nanomedicines to tumors, both active and passive targeting of cancer cells have demonstrated effectiveness in preclinical and clinical trials. It is possible to passively target and extravasate nanocarriers within a range of several hundred nanometers because tumor vasculature exhibits pathological traits such as disarray, increased gap junctions between endothelial cells, and poor lymphatic drainage. Because of the presence of tight junctions, these objects are unable to penetrate the endothelial cell lining of the arteries in healthy tissues. [41]

2. Oral drug delivery

Cubosomes provide an answer to the many problems that arise when trying to provide several potential substances orally. These problems include enormous molecular size, poor absorption, and poor aqueous solubility. Our capsule products incorporate our proprietary technology, which involves self-emulsifying liquid crystalline nanoparticles (LCNP), and these entities are available in powder and liquid forms. Another use case involves the localized action of large proteins within the gastrointestinal tract through encapsulation. You can incorporate controlled release and targeting capabilities into carriers that are based on liquid crystalline nanoparticles technology. These particles allow for an efficient drug distribution in living organisms since they are engineered to develop on site at a controlled rate. Importantly for medications having a small window of opportunity for regional absorption, these carriers can be delivered at different absorption locations, including the small or large intestine. [42]

3. Intravenous drug delivery systems

Lipid nanoparticles, housed in the internal liquid crystal structures of curved lipid membranes, encapsulate and deliver drugs to targeted organs and tissues for treatment. Proteins, peptides, and other small molecules with low solubility can be more effectively delivered when formed into Liquid Crystalline Nanoparticles (LCNPs). LCNPs are perfect vehicles for administering a wide variety of medicinal substances either injection or infusion. Various therapeutic items, on

the other hand, have used emulsions and liposomes as intravenous carriers. [43]

4. Topical drug delivery systems

Due to their enhanced bioadhesiveness, cubic phases are ideal for the administration of medicines, topical and mucosal depositions, and other similar applications. The special properties of liquid crystals (LC) and liquid crystal nanoparticles (LCNPs) are taken advantage of in topical delivery methods. These techniques create in situ bioadhesive LC structures to effectively and precisely deliver medications to various mucosal surfaces, such as the buccal, ophthalmic, vaginal, and others. This technique allows for the formation of an intriguing thin surface coating at mucosal interfaces, which is composed of a controlled nanostructured liquid crystal matrix. An ideal delivery profile can be achieved and sensitive or painful skin can be temporarily protected by this controlled structure. [44]

6. Dermatological applications

The stratum corneum forms an impermeable barrier when medications are administered topically to the skin. In any case, its unique shape and characteristics make it a promising pathway for transdermal medication delivery. For transdermal drug delivery, cubosomes attach effectively to the stratum corneum, which makes them excellent for topical and mucosal medication administration due to their bioadhesive qualities. One important dermatological usage of GMO-cubosomes is transcutaneous immunization (TCI), but they have other dermatological uses as well. Microneedles (MNs) and cubosomes, when used together, have shown to be an effective and synergistic method of skin vaccination delivery in the field of dermatology. Cubosomes, when combined with the peptide, help to extend skin retention, and microneedles help to increase aqueous peptide mixture's penetration through skin's layers. Researchers have demonstrated that the combined use of MNs and cubosomes is an effective system for transferring antigens to specific cells in the skin. [45]

7. Cubosomes in Nasal route

One effective and non-invasive method for treating problems with the central nervous system (CNS) is to directly inject drugs into the brain through the nasal passages, therefore avoiding the blood-brain barrier (BBB). Wu et al. investigated odorranalectin molecules in designed PEGylated cubosomes with coumarin as a marker. The results showed that relative absorption in the brain was around 3.46 times higher than in untreated cubosomes. Mayuri Ahirrao et al. looked explored cubosomes as a potential nasal delivery system for resveratrol to treat Alzheimer's disease. By employing the probe sonication technique, GMO P407 cubosomes were synthesized. For almost 24 hours, the in-vitro drug release followed a regular pattern. Furthermore, research showing the insertion of Gly14-human (S14G-HN) into cubosomes showed that the therapeutic effects of S14G-HN in Alzheimer's disease were enhanced by cubosomes that contained odorranalectin molecules. The results show that cubosomes could be a great way to transport drugs to CNS through nose. [46]**8. Brain targeting**

When it comes to treating disorders affecting CNS, BBB is a hurdle since it prevents drugs, both big and small, from reaching the brain. To improve medication loading into the brain, researchers have looked into cubosomes, a sort of nanoparticle made of lipids. To better transfer resveratrol to brain via transnasal route, for example, cubosomes have been utilized. Glycerol monooleate lipid and Lutrol® F 127 were used in a probe sonication approach to generate these cubosomes. An in situ nasal gel was created by combining the cubosomal dispersion with a Poloxamer 407 polymer after optimization. This formulation exhibited superior transnasal penetration and distribution compared to the medication solution alone, showcasing the potential of cubosomes in overcoming the

challenges posed by the BBB for enhanced drug delivery to the brain.[47]

9. Cosmetics

The cosmetics industry has discovered cubosomes to be useful in the creation of antiperspirants, hair care products, and skin care products. One mitochondrial fatty acid with strong antioxidant capabilities, alpha-lipoic acid (ALA), has been distributed in cubosomes. This formulation has demonstrated excellent outcomes in reducing facial wrinkles and enhancing skin texture and color. The use of cubosomes in cosmetic formulations provides a promising avenue for delivering active ingredients like ALA, contributing to their effectiveness in skincare applications.[47]

10. Controlled or sustained release behaviour

Cubosomes have been loaded with a wide variety of drugs with different physicochemical properties, and their extended drug release patterns have been studied extensively. The prolonged drug release behavior of cubosomes is attributed to residual particles within the cubosomal structure. This extended activity makes cubosomes suitable for topical applications, including percutaneous or mucosal administration, particularly when based on monoglycerides. [48]

11. In treatment of viral diseases

The microbicidal capabilities of monoglycerides could be harnessed to create intravaginal therapies for STDs caused by bacteria (e.g., Chlamydia trachomatis and Neisseria gonorrhoeae) or viruses (e.g., HSV, HIV). [48]

ADVANTAGES AND DISADVANTAGES

ADVANTAGES

1. Cubosomes can be easily prepared using a simple method.
2. Amphiphilic, hydrophobic, and hydrophilic substances can all be encapsulated by them.
3. The biocompatibility and bioadhesivity features of cubosomes are demonstrated.
4. cubosomes are far better at solubilizing compounds than either traditional lipids or non-lipid carriers.
5. In spite of their huge molecular size, poor absorption, and lack of water solubility, cubosomes are able to effectively handle a wide variety of interesting substances. [49]

DISADVANTAGES

1. There are certain disadvantages to using cubosomes, such as the possibility of drug leakage during in vivo transit, preservation, and manufacturing, and limited drug loading efficiency. Their broad use is limited by the stability issue, which continues to be a significant barrier.
2. Cubosomes have a high viscosity, which makes their large-scale manufacture difficult.
3. The channels of cubosomes may be difficult for bigger medications to penetrate, and there is a chance that pharmaceuticals will damage the bicontinuous liquid crystalline phase's lattice structure.[50]

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HOW TO CITE: Sahil N. Kamble, Radhika Subhedar, Nilesh B. Chougule, A Comprehensive Review On Cubosomes, Int. J. of Pharm. Sci., 2024, Vol 2, Issue 5, 1728-1739. https://doi.org/10.5281/zenodo.11388371