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A Review of Formulation and Evaluation of Cubosome

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Abstract

Cubosome are produced nanoparticles with a soft texture that are used to activate lipids. (for example, phytantriol or monoolein) in water. Cubosomes consist of two distinct aqueous channels that are non-intersecting and three dimensions in size, produced by a lipid bilayer. Cubosomes are special properties that enable medications that are amphiphilic, hydrophilic, and liophillic to be accepted.Here, biocompatible and biodegradable excipients like phytantriol or monoolein are employed. Because of their extremely stable cubic form, cubosomes offer better stability, increased drug retention, and more dissolution. As a result, cubosomes that have these added characteristics have a greater acceptance spectrum. Cubosomes have several uses in various fields. These lyotropic cubic liquid crystalline nanoparticles are becoming more and more well-liked as efficient vehicles for enhancing the solubility of many medications. Water, stabilizer, and amphiphillic lipid make up its key ingredients.

Keywords - Drug delivery systems, nanomedicine, cubosomes

INTRODUCTION

Cubosomes are defined as bicontinuous cubiform nanovesicles with discrete, sub-micron, and nanostructure. Liquid crystalline cuboid aggregates are dispersed in compound media to form them. They are similar to their parent cuboid aggregates in terms of great expanse and microstructure. Their sizes range from 100 to 500 nm, and they exhibit honeycomb (cavernous) architectures that indicate a structural constant. As a cutting-edge drug delivery technique, cubosomes are gaining popularity; they have lately been used in the fields of cancer, specialty medicine, ophthalmology, and oral health. Compound particles, on the other hand, are square measurements created by an Associate in Nursing amphiphilic substance that, at high concentrations of the critical particle concentration (CMC), self-assembles in water into a core-shell structure. After becoming intercalary, hydrophobic drugs are typically integrated intermittently into the hydrophobic particle core, whereas hydrophilic bioactive molecules are incorporated into the micelles' outer hydrophilic shell.Cubosomes form a bilayer of macromolecules at a regulated temperature. Cubosomes are defined as bicontinuous cubiform structures that are nano-structured, discrete, sub-micron unit distinct, and nanovesicles created by dispersing liquid crystalline cuboid aggregates in compound media. They share the same microstructure and high expanse as their parent cuboid aggregates. Their size varies between 100 and 500 nm, and their structure is similar to honeycomb (cavernous) formations. [1,2]

Cubosome

Cubosomes are lipid carriers with a nanostructure that are created by self-assembling lipid cubic phases. Because of their unique cubic structure, they can encapsulate Both water-soluble and water-insoluble molecules, making them valuable for the variety of applications in drug administration and other domains.

Structure of Cubosome

A particular kind of self-assembled nanostructured lipid carrier known as a cubosome is distinguished by its distinct three-dimensional cubic phase. This is a thorough explanation of their organization:

Lipid Composition

Amphiphilic Lipids: Amphiphilic lipids, which have both hydrophilic (which attracts water) and hydrophobic (which repels water) areas, constitute the bulk of cubosomes. Common lipids include:

Glycerol Monooleate (GMO)

Phospholipids (e.g., lecithin)

Cubic Phase Structure

Three-Dimensional Cubic Lattice: Cubosomes have a space group of Fm3m and are arranged as a cubic liquid crystalline phase. The creation of continuous aqueous channels is made possible by this arrangement.

Cubic phase types: Phase Q229: The most often investigated phase, distinguished by a highly organized configuration of lipid bilayers.

Aqueous Channels

The cubic shape creates interconnected aqueous channels that may hold a range of medications, including both hydrophilic and hydrophobic compounds. This characteristic improves the medication's loading capacity and delivery effectiveness.

Morphology

Nanoparticle Size

Depending on the environment and formulation technique, cubosomes can have a size ranging from 100 nm to several micrometers.

Surface Characteristics

Cubosomes' surfaces can be coated or functionalized to improve their stability and ability to interact with biological systems.

Self-Assembly Process

Hydration

The self-assembly into cubosomes happens when lipids are hydrated, leading to the creation of the cubic phase. Temperature, the presence of surfactants, and the concentration of lipids all affect the process.

Stability

Cubosomes are mechanically stable because of their cubic form, which enables them to hold together throughout time and in a variety of environmental circumstances.[3]

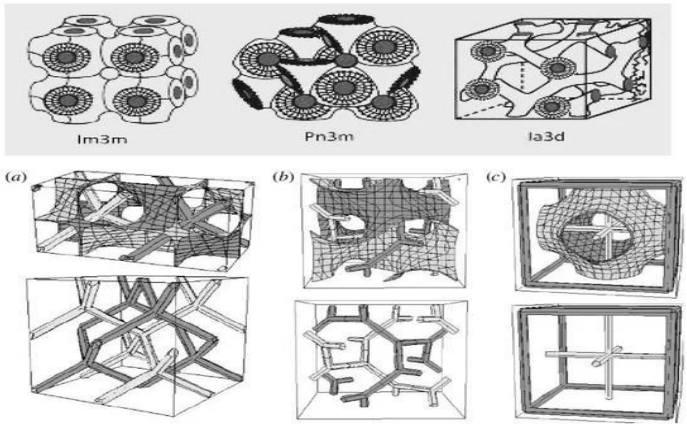

Figure 1: *Different Structure of Cubosome*

Types of Cubosome

Liquid cubosome precursors

A fluid phase that can spontaneously generate cubosomes under the right circumstances—such as dilution or temperature changes—is referred to as a liquid cubosome precursor. Usually composed of a blend of solvents and lipids, this precursor self-assembles into the cubic phase under particular circumstances.

Constructing smaller, more stable cubosomes is the aim of the hydrotropic dilution operation. The nucleation process, which makes it possible to produce particles whose growth is seen during the precipitation and crystallization phases. [4]

Key Components

Lipid Components

Aminoglycoside's: Because they may produce stable cubic phases, monoglycerides like glycerol monostearate (GMS) are frequently employed to form cubosomes.

Phospholipids

Phospholipids that improve drug encapsulation ability and biocompatibility include lecithin.

Surfactants

Non-ionic surfactants, such polymer's, can increase stability and make the cubic structure easier to form.

Solvents

Organic solvents

These are frequently used to dissolve lipids, such as ethanol, methanol, or chloroform, which are then extracted to create a concentrated lipid mixture.

Aqueous Phase

The self-assembly process is often started by adding water

Characterization

The properties of liquid cubosome precursors include:

Particle size

Determined by methods such as DLS, or dynamic light scattering.

Morphology

Examined using techniques from microscopy, including Transmission Electron Microscopy (TEM).

Stability

Tested in various scenarios to see how the precursor develops into stable cubosomes.[5]

Powdered cubosome precursors

Solid lipid formulations known as powdered cubosome precursors can be reconstituted in the right solvent to produce cubosomes. These precursors are usually lipid powders that self-assemble into the cubosome-like cubic phase structure upon hydration.

A polymer-coated, dehydrated surfactant makes up their composition. Cryo-TEM and light scattering show that the precursor powders hydrate to form The average particle size of cubosomes is 600 nm..[6]

Key Components

Lipid Materials

Monoglycerides

Frequently used lipids that, when hydrated, aid in the creation of cubosomes, such as glycerol monostearate (GMS).

Phospholipids

These improve stability and biocompatibility, just as lecithin.

Fatty Acids

These can be added to change characteristics such as encapsulation efficiency and phase behaviour

Excipients

Stabilizers

These include surfactants, which enhance rehydration and preserve the stability of the powder.

Cryoprotectants

During the drying process, they could be added to preserve the lipid structure.

Characterization

Dynamic Light Scattering (DLS): used to measure the size and distribution of particles.

Transmission electron microscopy (TEM)

Demonstrating the organization and structure of cubosomes.

X-ray scattering at small angles (SAXS)

To determine the cubic phase and structural properties.

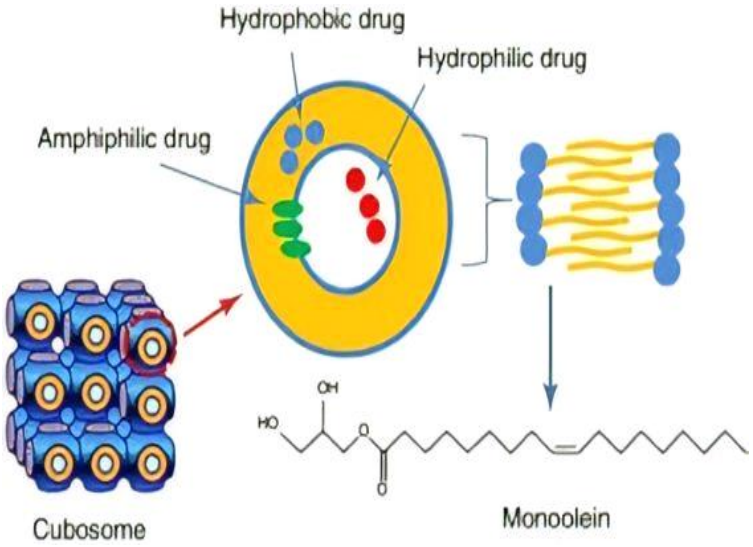

Figure 2: *Structure of cubosome*

Advantage

A rather easy procedure can be used to create cubosomes.

They are capable of encasing molecules that are hydrophilic, hydrophobic, or amphiphilic.

Cubosomes are known to be biocompatible and bio adhesive.

The solubility of cubosomes is superior to that of standard lipids or non-lipid carriers.

Cubosome particles are used as stabilizers of oil-in-water emulsions as pollutants absorbers in cosmetics.

Low cost of raw materials.

For peptides that are soluble in water, the cuboidal method increases the bioavailability range by 20–100 times.

They possess qualities of both biocompatibility and bio adhesivity.

They are non-toxic and economically viable. [7,8]

Disadvantage

Their high viscosity might make large-scale manufacture challenging at times.

Cubosomes are sometimes difficult to create on a big scale due to their high viscosity.

Cubosomes that include medication based on polymers forms do not provide restricted substance distribution.

Uses

Drug Transport

By encasing hydrophilic and hydrophobic medications, cubosomes improve their solubility and stability and enable controlled release.

Vaccine formulation

By optimizing antigen delivery, their structure can boost immunological responses.

Cosmetics

They can be utilized to more efficiently distribute active chemicals in skincare products.

Food Industry

By encapsulating tastes, nutrients, and probiotics, cubosomes can increase their stability and bioavailability.

Diagnostics

In the context of medical diagnostics, they could act as transporters for imaging agents.

Gene Delivery

Because of their characteristics, they can be used in gene therapy applications to transfer nucleic acids.[9]

Method Of Preparation

Depending on the origins of power utilized to break Cubosome preparation techniques for the bulk phases can be separated into top-down and bottom-up approaches categories. Sonication combined with high-pressure homogenization are used in top-down techniques, while hydrotropes are used in bottom-up techniques to lower energy inputs. is used as a triblock polymer, Poloxamer-407 (also known as Pluronic F127 or PF127) maintains the liquid inner structure of lyotropic non-lamellar liquid-crystalline nanoparticles (LCNs) and creates a steric barrier, which aids in stabilizing the particles. Typically seen predecessors include bulk phase gel, particle dispersion, and the three macroscopic forms of cubosomes. Nevertheless, melting under extreme pressure and sonication produce intricate dispersions that comprise. Cubosomes with using every molecule type's time-varying ratio and vesicle-like features [10]

There are two different technologies available for producing cubosomes.

They are as follows:

Top-down method

Bottom-Up Method

Creating cubosome dispersions filled with ALA:

From Pseudo-Binary Systems

In the Presence of Hydrotrope

Top-down method

Among the most popular approach was first described by Ljusberg-Wahren in 1996. The use of this technology is divided into two stages. Lyotropic Liquid Crystal (LLC) nanoparticles, often referred to as cubosome dispersions, are then produced by dispersing the cubic form in volume into a liquid medium using analysing with a lot of energy methods like synthesis at extreme pressure or vibration. A stiff, transparent gel that mimics bulk cubic phases but has a crystallographic structure of cyclic liquids. Including thermo-labile components like proteins and peptides is extremely difficult, and homogenizing the bulk phase on a large scale utilizing the high energy input technique is nearly impossible. By increasing shear during dispersion, cubic phases display lamellar phase behavior. HPH is the technique most frequently used to create LLC nanoparticles. We observe the coexistence of cubosomes with the formation of vesicle-like structures. Cubosomes produced upward and

scattered Lamellar liquid-crystalline phase or vesicle-like nanoparticles are examples of vesicles that always coexist. When vibration frequencies increase, cubic phases turn into extremely flexible.[11,12]

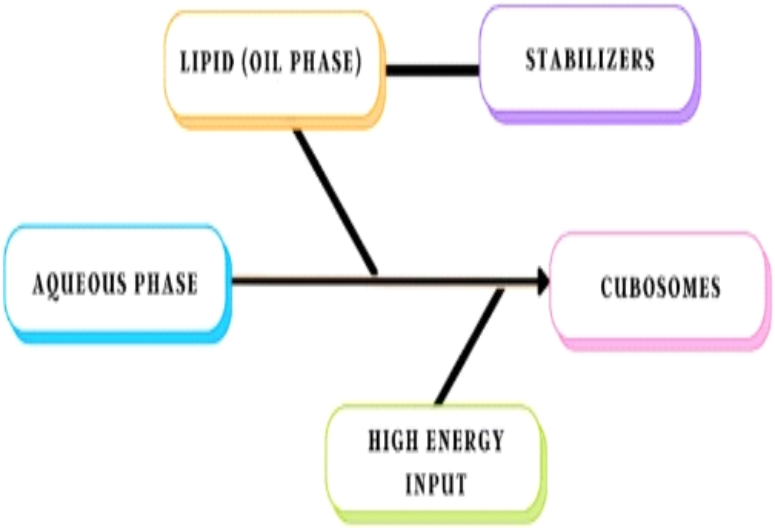

Figure 3: *Top-Down Method*

Bottom-Up Method

This alternative method allows Cubosomes to develop from precursors, crystallization occurs at the molecular scale length while being prepared at room temperature. It is the most modern method for developing cubosomes. Building blocks in a nanostructure are formed first in this type of technique, which subsequently assembles them to produce the final product. The substantial process efficiency required to create particle dispersions from the viscous cubosome. It is quite difficult to scale up this technology in Cubical phases in bulk. Thomas T. In order to prevent these issues, Spicer looked at how the cubic phase developed when a hydrotrope was present. A chemical that can be water-soluble or water-insoluble, but is unable to exhibit the surfactant serves activity (The creation of micelles) is referred to as a hydrotrope in this context. Despite not producing LLC, hydrotropes increase lipid solubility, which leads to a process called "salting out," which can happen in either a liquid or solid precursor. Lipid (monoolein) ethanol is combined with ethanol to form the liquid precursor. Cubosomes are created when the precursor is diluted. A polymer-coated, dried substance that hydrates to form cubosomes makes up powdered precursors. This process dissolves the input factor hydrotrope in lipids that are insoluble in water to produce liquid precursors. Powdered precursors have a few advantages over liquid precursor cubosomes. The tiny particles condense into cubosomes once they have gradually cooled. A room-temperature aqueous solution of poloxamer 407 made from cubosomes, is then added to dilute the monoolein-ethanol mixture. Therefore, vesicles cannot be prevented using cryo-TEM; Cubosomes have also been observed to cohabit with a number of vesicle-sized entities. The process of freeze-drying is used to create drug-containing vesicles.[13]

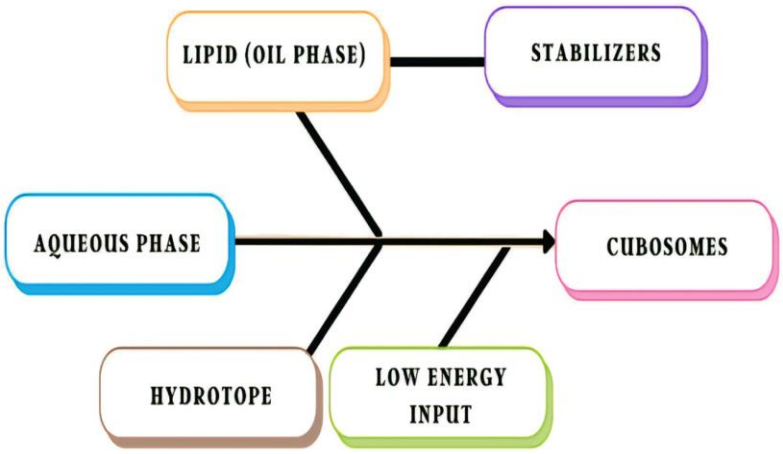

Figure 4: *Bottom-Up Method*

Creating cubosome dispersions filled with ALA

Two distinct techniques were used to create cubosome dispersions. In the first method, GMO/P407 bulk cubic gel was broken up. 5.0 percent GMO and 1.0 percent P407 were melted initially in a hot water bath at 600C.After that, to dissolve it, ALA (25, 50, or 100 mg) was added and constantly stirred. To create a uniform condition, deionized the water had introduced gradually and vortexes. After that, the crude dispersion was chilled in a water bath at 20 °C and subjected to intermittent probe sonication for 20 minutes at 200 W of energy input. The second technique was accomplished by emulsifying P407 and GMO In water, then ultrasonically agitating the mixture. In addition to 1% P407 and 5% ethanol, the dispersion contains 5% GMO in 89% water. Following the careful melting of GMO and P407 at 60 OC, the ethanolic solution of ALA was introduced. The resultant blend was injected drop wise after deionized water was heated to 700C and ultrasonically sonicated for 15 minutes at the same temperature with a 130-kW maximum output. [14]

From Pseudo-Binary Systems

The classic technique of energetically dispersing bulk cubic gel (containing polymer at low levels) in a pseudo-binary system of monoolein-water was used to make cubosomes in the beginning. Melted polyloxamer Monoolein (92% w/w) and 407 (8% w/w) were mixed to create a uniform mixture. After that, the monoolein-polymer solution was combined with Water that has been deionized to produce a monoolein of 1.8% combination that contained 0.2% Poloxamer 407 and 98% water. By sonicating the blend for sixty minutes at 25°C in an ultrasonic bath at a controlled temperature, the Crystalline gel in a cubic liquid form was scattered. Most of the cubosomes seen by cryo-TEM (Figure 4) were square and measured between 100 and 300 nm along an edge.

In the Availability of Hydrotrope

Using sonication-oriented techniques, cubosomes were also produced when hydrotrope levels were high. A low-viscosity isotropic liquid was created by combining molten monoolein (93% w/w) with ethanol (7% w/w) to create bulk cubic gel. Poloxamer 407 was added to the liquid in a 1.2% solution, and when it was mixed with additional water, it created The final composition of the viscous, cubic liquid crystalline gel is 68% monoolein, 26.7% water, 5% ethanol, and 0.3% Poloxamer 407.They sonicated the concoction for five minutes.[15]

Formulation Of Cubosome

The top-down approach was used to fracture the bulk cubic gel of glyceryl monooleate (GMO)/poloxamer407 to produce cubic nanoparticles. After melting GMO and poloxamer407 (F127) in a water bath at 60 °C, Sim was added and stirred until it completely dissolved.0.25 ml of

deionized water was added progressively using vortex mixing until the mixture was homogenous. The result was an optically isotropic cubic phase gel after equilibration at room temperature for 24 to 48 hours. Ten milliliters of deionized water were added with magnetic swirling to break up the cubic gel. At 20°C for 15 minutes (Pulse 5 on, 2 of), the coarse dispersion was broken up using an intermittent probe sonicator. It was then homogenized by running through a high-pressure homogenizer a predetermined number of times to produce cubosomal nanoparticles. Before being used, the nanoparticles were kept in a refrigerator between 4 and 8 °C. [16]

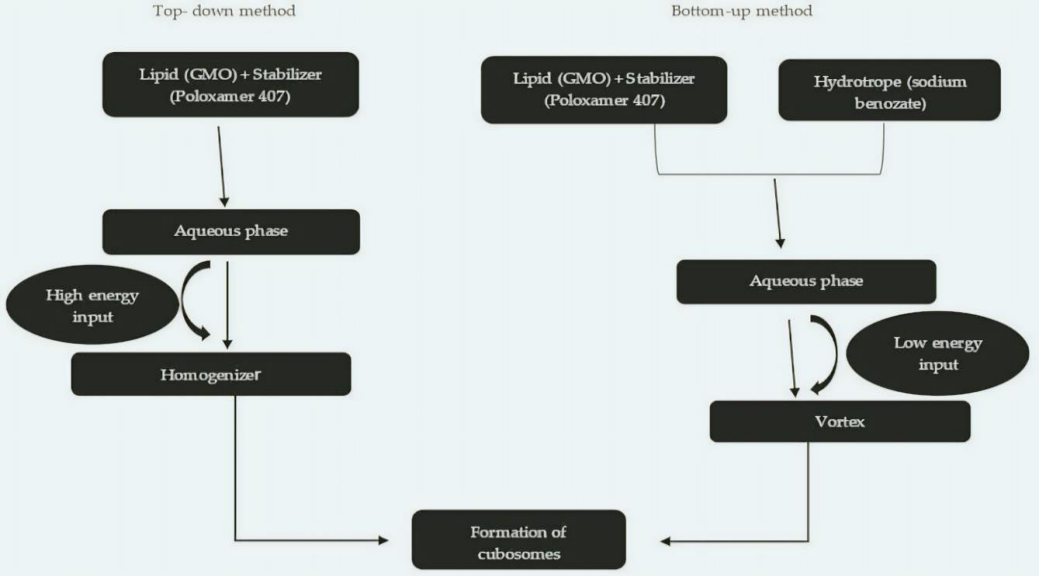

Figure 5: *Formation of Cubosome*

Evaluation of Cubosome

In Vitro Drug Release Studies

An explanation of techniques for evaluating release kinetics, such as dialysis and Franz diffusion cells.

Stability Studies

Stability testing, both fast and long-term, under different circumstances.

In Vivo Studies

Summary of research on biodistribution and pharmacokinetics to assess the effectiveness of treatments.[17]

In Vitro Drug Release Studies

Purpose of In Vitro Drug Release Studies

To evaluate the formulation's medication release rate and extent.

To comprehend the mechanism of release (e.g., erosion, diffusion).

To contrast various distribution methods or formulations.

Common Methodologies

Drug release in vitro can be studied using a variety of approaches:

Dialysis Method

Setup

A dialysis bag submerged in a release medium (such as phosphate-buffered saline) contains the drug-loaded cubosomes.

Procedure

To quantify the quantity of medication released into the medium, samples are collected at prearranged intervals.

Benefits

Easy to use, repeatable, and appropriate for both hydrophilic and hydrophobic medications.

Franz Diffusion Cell

Setup

Consists of a receptor chamber that is filled with release medium and a donor chamber that holds the formulation.

Procedure

A membrane that divides the two chambers is covered with the formulation. Samples are collected throughout time as the medication diffuses into the receptor media through the membrane.

Benefits include simulating physiological circumstances and offering a regulated environment.

Static or Dynamic Release Systems

Static

Passive diffusion is made possible by not stirring the release medium.

Dynamic

The diffusion process is improved by constantly stirring or replacing the releasing media.

Benefits

For sustained-release formulations in particular, dynamic systems can offer more precise release profiles.

Basket Method

Setup

The mesh basket containing the drug formulation is immersed in the release medium.

Procedure

To determine the drug concentration, samples are obtained at regular intervals while the basket is shaken.

Benefits

Makes sample collection simple and is appropriate for solid dose forms.

Factors Influencing Drug Release

Formulation Composition

Drug launching, surfactants, and lipid species.

Physical-chemical characteristics include the drug's solubility, molecular weight, and partition coefficient. [18,19]

Stability Studies

Purpose of Stability Studies

To evaluate the formulation's stability on a physical, chemical, and microbiological level.

To ascertain the proper shelf life and storage circumstances.

To determine probable processes and paths of degradation.[20]

Methodologies for Stability Testing

Storage Conditions

Switching up the humidity and temperature (such as ambient temperature or refrigeration) to replicate various settings.

Sampling

Sample intervals that are regular and frequently specified by recommendations (such as ICH guidelines).

Analytical Techniques

UV-Vis Spectroscopy: To quantify variations in absorption.

In Vivo Studies

Importance of In Vivo Studies in Cubosome Evaluation

Studies conducted in vitro mainly offer preliminary information about cubosome formulations (such as drug release rates, size distribution, and stability), but they are not very good at forecasting behavior in living systems. [21,22]

In vivo research fills this gap by:

Evaluating Safety and Biocompatibility

To ascertain whether cubosomes have negative impacts on living things, such as toxicity, immunogenicity, or irritation, these investigations are essential.

Assessing Biodistribution and Pharmacokinetics (PK)

Absorption, distribution, metabolism, and excretion within the body of cubosomes are all revealed via in vivo research. These investigations aid in the optimization of medication formulations for improved targeted delivery and bioavailability.

Assessing Long-Term Stability

The durability of cubosomes following injection and their capacity to distribute medications reliably over time are evaluated with the aid of long-term in vivo research.

CONCLUSION

With a number of benefits that can help overcome many of the drawbacks of traditional delivery methods, cubosomes have become a flexible and promising nanocarrier platform for drug delivery. Their distinct cubic phase structure makes it easier to encapsulate a variety of hydrophilic and lipophilic medicinal substances, increasing the medications' bioavailability and effectiveness. Cubosomes are very attractive to prolonged drug publication applications due to the fact that large surface area and controlled release properties, which can greatly enhance therapeutic results.

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