IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429
Volume 6, Issue 5, March 2026
Impact Factor: 8.2

Sustained and Controlled Drug Release using Cubosomes

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Abstract: *Traditional drug delivery methods have been replaced by smart drug delivery systems that react to stimuli as a result of the remarkable developments in biomedical nanotechnology over the past few decades. By reacting to particular internal or external stimuli, these well-defined nanoplatforms can increase therapeutic targeting efficacy while lowering payload toxicities and side effects, which are critical factors for improving patient compliance. Cubosomes are lipid vesicles that resemble liposomes and other vesicular structures. When a sufficient stabilizer is present, certain amphiphilic lipids form cubosomes. Self-assembled cubosomes as active drug delivery vehicles have garnered a lot of interest and attention since their discovery and identification. Cubosomes are self-assembling nanoparticles made up of certain liquid crystalline surfactant particles that are balanced between water and microstructure. Unlike regular solid nanoparticles, cubosomes are self-assembled liquid crystalline particles with a solid-like rheology, giving them special qualities of practical importance. Because of their potential benefits, which include high drug dispersal because of the cubic structure, large surface area, a relatively easy manufacturing process, biodegradability, the capacity to encapsulate hydrophobic, hydrophilic, and amphiphilic compounds, targeted and controlled release of bioactive agents, and biodegradability of lipids, cubosomes exhibit great promise in drug nanoformulations for cancer therapeutics. The most common method of preparation involves simply emulsifying a monoglyceride with a polymer, then homogenizing and sonicating the mixture. They are frequently employed in the delivery of chemotherapeutic, oral, ophthalmic, and transdermal medications. The composition, preparation methods, drug encapsulating strategies, drug loading, release mechanism, and applications pertinent to cubosomes will all be thoroughly examined in this paper. Additionally, the difficulties in maximizing certain factors to improve loading capabilities and prospects are also discussed.*

Keywords: drug delivery systems, nanomedicine, cubosomes, and characterization.

I. INTRODUCTION

Larsson first used the word “cubosomes” in 1980 to refer to liposome-like cubic molecular crystallography. Cubosomes are distinct particles of the cubic liquid crystalline phase that are nanostructured and submicron in size. In this application "bicontinuous" refers to the division of the enclosures of two distinct water zones by surfactant bilayers. The capacity to modify the membrane's curvature is a significant advantage [1]. Cubosomes exist in the bicontinuous cubic liquid crystalline phase. Cubosomes are self-assembling nanoparticles composed of certain liquid crystalline surfactant particles with the ideal water-to-microstructure ratio. Cubosomes are self-assembled liquid crystalline particles with a solid-like rheology which sets them apart from conventional solid nanoparticles and offers them unique properties of practical importance [2].

DOI: 10.48175/IJARSCT-31952

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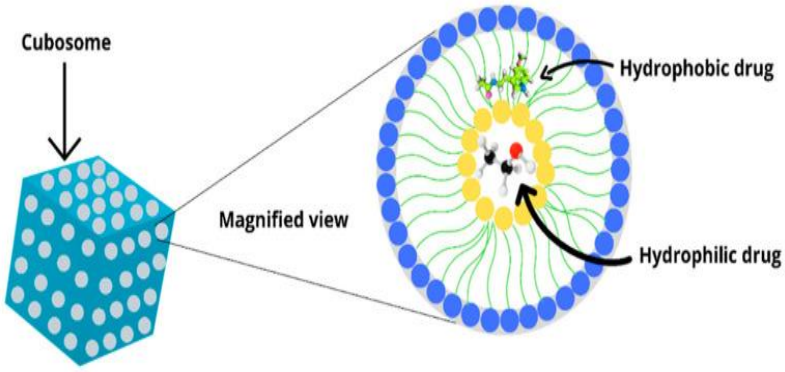

Fig 1: Structure of cubosomes

Cubosomes' structure and physical properties make them an interesting subject for study in fields including materials science, nanotechnology and drug delivery. Amphiphilic substances which contain both polar (hydrophilic) and non-polar (hydrophobic) components include lipids, surfactants and certain polymers. The unique properties that these compounds exhibit at the nanoscale are mainly caused by the hydrophobic effect. One notable structure that arises from these interactions is the bicontinuous cubic liquid crystalline phase, also referred to as cubosomes. Cubosomes high degree of molecular orientation and structural symmetry make them intriguing for a range of applications in medication delivery systems and material research. [3]

Structure of cubosomes:

A cubosome is a type of self-assembled nanostructured lipid carrier that may be identified by its unique three-dimensional cubic phase. Here is a detailed description of how they are organized:

Lipid composition:

Amphiphilic Lipids: The majority of cubosomes are made up of amphiphilic lipids, which have both hydrophilic (which attracts water) and hydrophobic (which repels water) regions. Typical lipids consist of the following:

GMO, or glycerol monooleate

Phospholipids, such as lecithin

Cubic phase structure:

Three-Dimensional Cubic Lattice: Cubosomes are structured as a cubic liquid crystalline phase with a space group of Fm3m. This configuration enables the formation of continuous aqueous channels.

Types of cubic phases: Phase Q229: The most often studied phase, characterized by a highly ordered arrangement of lipid bilayers. [4]

Aqueous Channels:

A variety of drugs, including both hydrophilic and hydrophobic substances, may be stored in the interconnected water channels created by the cubic structure. The loading capacity and delivery efficacy of the drug are enhanced by this feature.

Morphology:

Nanoparticle Size:

Cubosomes can range in size from 100 nm to several micrometers, depending on the environment and formulation method.

Surface Characteristics:

Cubosomes can be made more stable and capable of interacting with biological systems by coating or functionalizing their surfaces.

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Self-Assembly Process:

Hydration:

When lipids are hydrated, they self-assemble into cubosomes, resulting in the formation of the cubic phase. The process is influenced by temperature, the concentration of lipids, and the presence of surfactants.

Stability:

Because of their cubic shape, cubosomes are mechanically stable, allowing them to remain together over time and under a range of environmental conditions. [5]

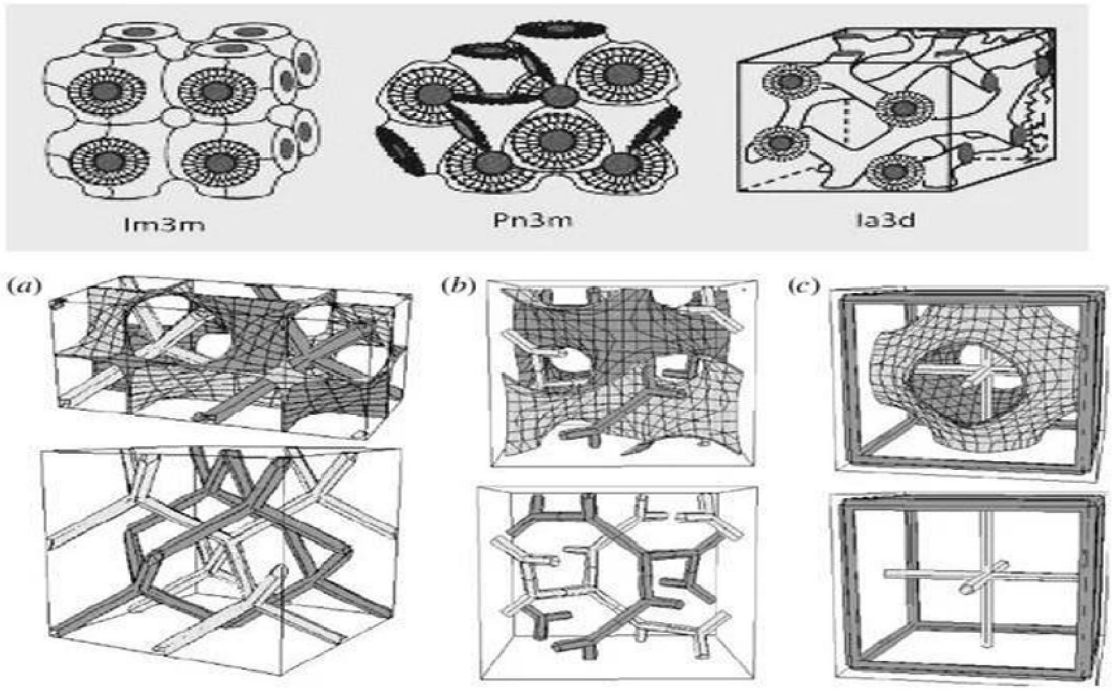

Fig 2: Different Structure of Cubosomes

Methods of Preparation of Cubosomes:

High-Pressure Homogenization

Automated Cubosome Preparation

Probe Ultrasonication

High-Pressure Homogenization:

It is the most effective technique for cubosome preparations that are stable during the high-pressure homogenization process and have a long shelf life [6]. It involves three steps.

Gel Preparation:

During this stage, an organic solvent is used to dissolve the lipid and amphiphilic surfactants, which are then completely combined to create a homogenous mixture. Here, a rotary evaporator is used to evaporate the organic solvent, resulting in a gel phase of formulation.

Shearing

At this point, the produced gel is being sheared. A micro-dispersion is produced by the use of aqueous solvents. It is a critical step in the cubosome process prior to homogenization [7].

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High-Pressure Homogenization:

For big-volume sample systems (30 ml), this method works well; however, it is not suitable for small-volume sample systems. Because this method is temperature sensitive, the temperature is chosen at this stage based on the lipid's properties. This entails using a high-pressure homogenizer to homogenize the generated dispersion. Only one sample may be processed at a time using this method.

2. Automated Cubosome Preparation:

The process could be utilized to generate a lot of cubosomes. This method of preparation makes use of robotic tools and a probe sonicator. The gels With a few modifications, it is fairly comparable to the probe sonication method. This is made using a 96-well plate with a 600-µl solvent capacity. The sonication is then carried out by a robot. This method makes it easy to assess the physicochemical properties [7].

3. Probe Ultrasonication:

Using this procedure, tiny volume samples can be prepared quickly. Even at 600 µl, it is capable of dispersing material. based on the size of the probe. In this process, the gels are prepared using stabilizers. The solvent then equilibrates to create a cubic phase. After that, the cubic phase is moved for ultrasonication. To control the pulse frequency and keep samples from overheating, frequency and amplitude must be properly controlled [7].

Special Techniques:

Top-Down Technique

Among the most popular approaches was first described by Ljusberg-Wahren in 1996 [4]. It is the method most frequently used to produce cubosomes. There are two distinct steps in the process: First, combine the lipids that can form cubosomes with stabilizers to create bulk cubic aggregates. Cubosomes, cube-like structures, are formed in the following step when the generated viscous cubic aggregates are dispersed in aqueous media by applying high energy as a high-pressure homogenizer or by sonication [8].

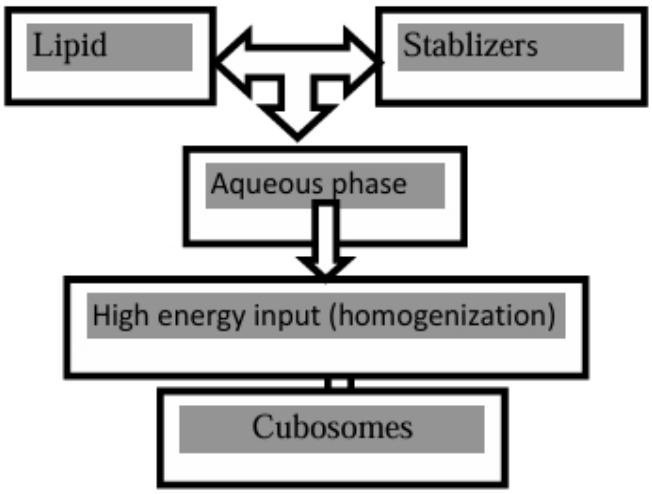

Fig 3: Schematic representation of preparing cubosomes by the top-down approach

Bottom-Up Technique

It is the method most frequently used to produce cubosomes. There are two distinct steps in the process: First, combine stabilizers with lipids that can form cubosomes to create bulk, cubic aggregates. Cubosomes, cube-like structures, are formed in the following step when the generated viscous cubic aggregates are dispersed in aqueous media by applying high energy as a high-pressure homogenizer or by sonication [8].

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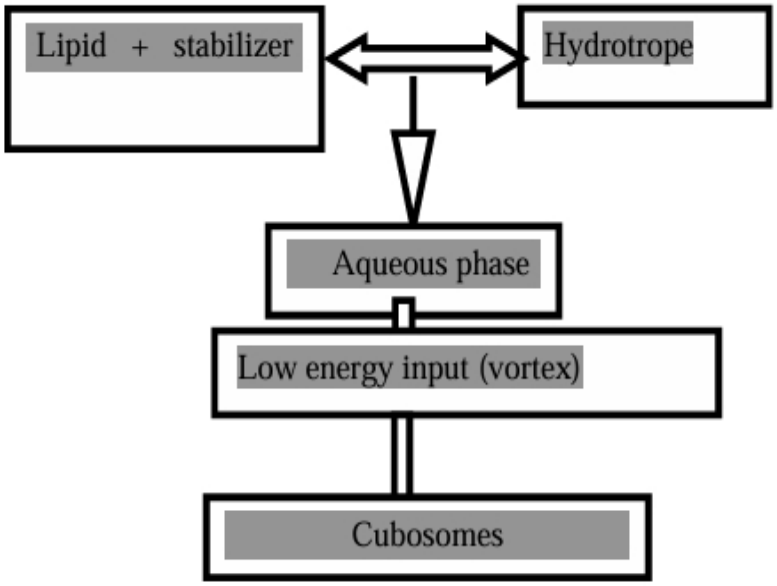

Fig 4: Schematic representation of preparing cubosomes by the Bottom-Up approach

Theories on Cubic Phase Structure:

As a generic drug delivery method, cubosomes, also known as bicontinuous cubic phase liquid crystals, have a number of attractive characteristics. It creates a densely packed structure by forming bilayers inside the surfactant and wrapping them into a three-dimensional, periodic, and minimal surface. The substance has a distinct structure in the nanometer range and is an optically transparent, very viscous bicontinuous cubic liquid-crystalline phase. They can encapsulate hydrophobic, hydrophilic, and amphiphilic molecules while guaranteeing the targeted and regulated release of bioactive substances thanks to the enhanced penetrating power and emulsification qualities of lipids. The precursor, bulk gel, and particle dispersion phases are the three macroscopic stages of the cubic structure that are frequently observed during cubosome synthesis. The precursor state is a solid or semisolid substance that reacts to stimuli, such as coming into contact with a liquid, by producing the cubic phase [9].

Fontell & Drew Theory

Ternary systems of amphiphiles, water and oil, and different monoglycerides all have cubic phases. Monoglycerides are polar lipids that resemble non-ionic surfactants structurally and have limited water solubility and aqueous phase behavior. According to Lutton's findings, monoolein and other monoglycerides with hydrocarbon chain lengths between C-12 and C-22 have larger cubic phase areas. C-18 monoglycerides, another name for monoolein, are unsaturated fatty acids [10].

Gustafson et al. Theory

Cubosomes are single-crystal structures with dispersed lamellar liquid-crystalline phase particles and visible unilamellar vesicles. Increasing the polymer-to-monoolein ratio promotes the production of bigger vesicles. Due to slow transport processes that create extremely viscous crystalline structures and the high energy needed for fragmentation, bulk cubic phases are ultrasonically broken up into vesicles, which eventually form cubosomes through membrane fusion [10].

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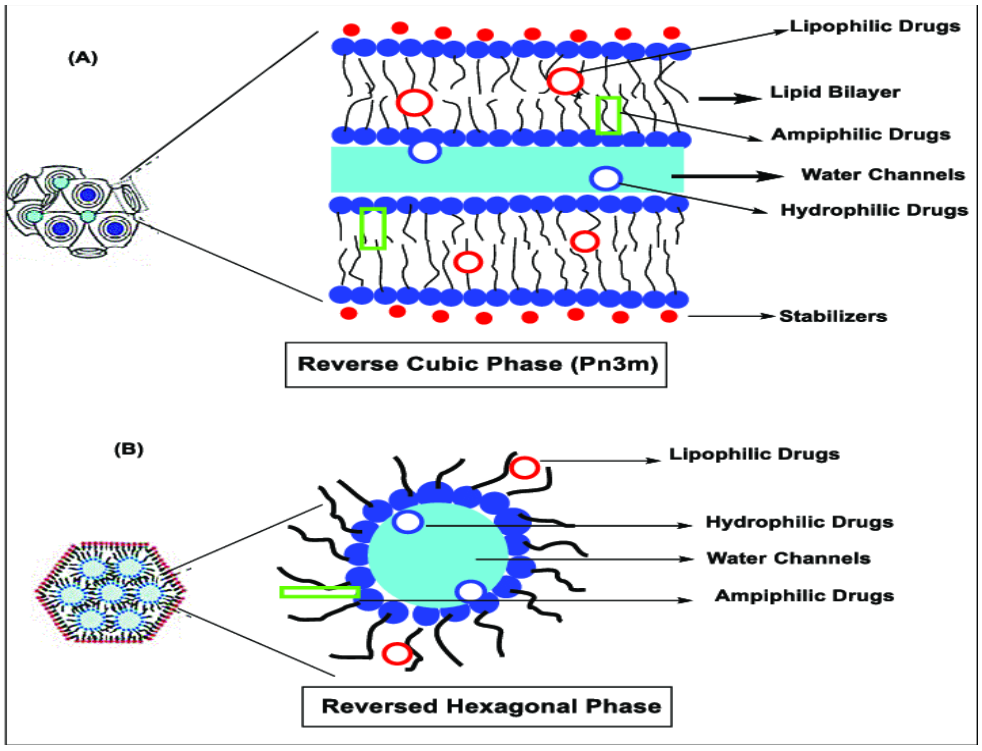

Fig 5: Cubic Phases of Cubosomes

Schwarz, Jacob & Anderson Theory

Cubic phases are often seen wedged between lamellar and hexagonal liquid-crystalline phases in non-ionic surfactant systems. The cubic phase region of the monoolein-water system with a broad range of composition and temperature makes it exceptional. Conversely, concepts for surfactant packing are becoming closer. Monoolein typically exhibits reversed or inversed cubic phases, indicating polar medium phases, due to its hydrophilic head and hydrophobic tail. Periodic minimum surfaces and differential geometry can be used to depict cubic phase structures. Comparing minimal surfaces to soap films is the best approach to describe them. In cubic phases, three kinds of minimum surfaces are studied according to their curvatures. The monoolein-water system produces the G surface at lower water levels and the D-surface at higher water levels. In the monoolein-water system, the p-surface only develops in the presence of a third component, such as caseins or amphiphilic molecules [10].

System Forming Theory

If there is a large miscibility gap between the solvent and the cubic phase, cubosomes can develop in binary and ternary systems. Cubosomes show good colloidal stability when poloxamer 407 is used to stop flocculation and aggregation. They can be covered with lamellar bilayer caps, which provide colloidal stability by keeping hydrocarbon chains away from water and sealing the cubic bilayer opening left by fragmentation. While lamellar liquid-crystalline coatings are stiff, cubosomes coated with a solid crystalline bilayer exhibit superior colloidal stability [11].

Components of Cubosomes:

The primary ingredients of cubosome formulation include polymers, amphiphilic surfactants, and natural lipids with a bicontinuous cubic phase.

In the presence of water, lipids such as monoglycerides, glycolipids, phospholipids, and urea-based lipids can spontaneously self-assemble [12].

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Amphiphilic lipids:

Currently, the most commonly used amphiphilic lipid-phase materials in cubosome synthesis are GMO, also called monoolein, and phytantriol. Monooleate is the most important component of GMO, a synthetic compound composed of oleic acid glycerides and other unsaturated fats. A variety of lyotropic liquid crystals can be formed by the amphiphilic fatty acid monooleate. A cubic crystal that alternates between inverted micellar and lamellar phases emerges as the temperature and water content are raised [13].

GMOs are biocompatible and biodegradable substances that fall under the FDA's generally recognized as safe (GRAS) category. They are mostly utilized in the food sector as emulsifiers. When the water concentration is increased, PHYT, a material having a phytanyl chain, also shows the creation of cubic phases. A common ingredient in cosmetic goods is PHYT, which is chemically 3,7,11,15-tetramethyl-1,2,3-hexadecanetriol. It has been suggested as a suitable substitute for genetically modified organisms in the production of cubosomes [14].

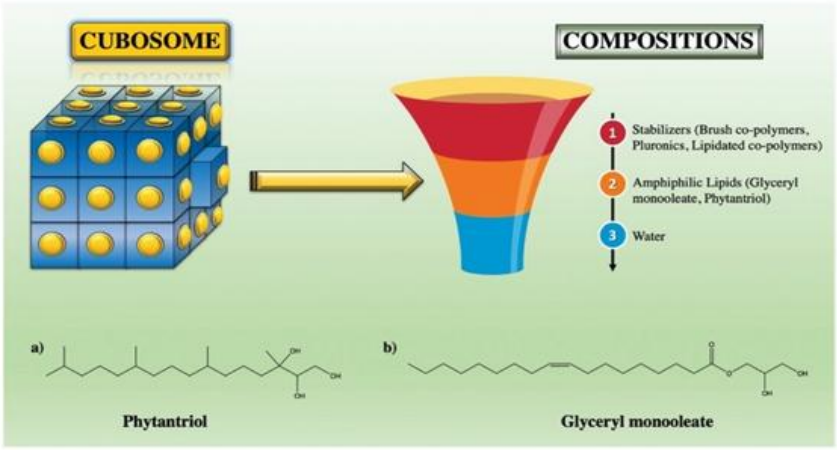

Fig 6: A Graphical representation of the composition of Cubosomes

Stabilizers:

Amphiphilic lipids typically create lyotropic liquid crystal structures by self-assembling in an aqueous solution. Nevertheless, due to their high viscosity, they cannot be administered by nasal, parenteral, or rapid ingestion. These liquid crystals are more likely to assemble in water than a typical emulsion, even though their fundamental structure is thermodynamically stable. A stabilizing agent that provides the liquid-crystalline phase with adequate colloidal stability is used to distribute the lyotropic liquid-crystalline particles into solvent compositions in order to mitigate these problems. [13]

Researchers have proposed that surfactants play a crucial function as stabilizers for enhanced stability of cubosomes against coalescence to the bulk cubic phase.

Poloxamer 407 (P407), a PEO-PPO-PEO tri-block copolymer, is primarily studied as a surfactant in the preparation of cubosomes, where the PEO chains are exposed to the surrounding water phase and the PPO portions are either at the cubosome surface or within the bilayer structure. Depending on the amount of dispersed phase, P407 is typically applied up to a concentration of 20% w/w. [14]

Drug Release Mechanism from Cubosomes:

The ability of cubosomes to release medications in a controlled and extended manner is one of their main benefits as drug delivery vehicles. The type of medicine encapsulated, the environment, and the physicochemical characteristics of the lipids utilized all have a major impact on the release mechanism [5]. Drug release from cubosomes is primarily driven by the following mechanisms:

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Diffusion-Controlled Release

Diffusion is the most popular method of drug release from cubosomes. Drugs contained within the aqueous phase may eventually diffuse out into the surrounding media because of the intercalated aqueous channels in the bicontinuous cubic phase.

In a similar vein, hydrophobic medications integrated into the lipid bilayer may permeate into the surrounding milieu. Cubosomes are ideal for long-term, continuous drug release since diffusion is a comparatively sluggish process. The following variables affect the rate of diffusion:

Particle size: The surface area-to-volume ratio of smaller cubosomes is higher, which can quicken the rate of diffusion.

Lipid composition: The fluidity of the lipid bilayer and, consequently, the rate of drug diffusion can be influenced by the kinds of lipids utilized in the formulation.

Drug characteristics: While hydrophobic medications may need longer release durations as they diffuse out of the lipid bilayers, hydrophilic pharmaceuticals usually diffuse more readily through the aqueous channels.

Stimuli-Responsive Release

Cubosomes can be engineered to respond to particular external stimuli, such as changes in temperature, pH, or the presence of biological markers or enzymes. When developing targeted drug delivery systems, where the medication is only released at the desired site of action, this stimuli-responsive release mechanism is very helpful in minimizing systemic adverse effects. For instance:

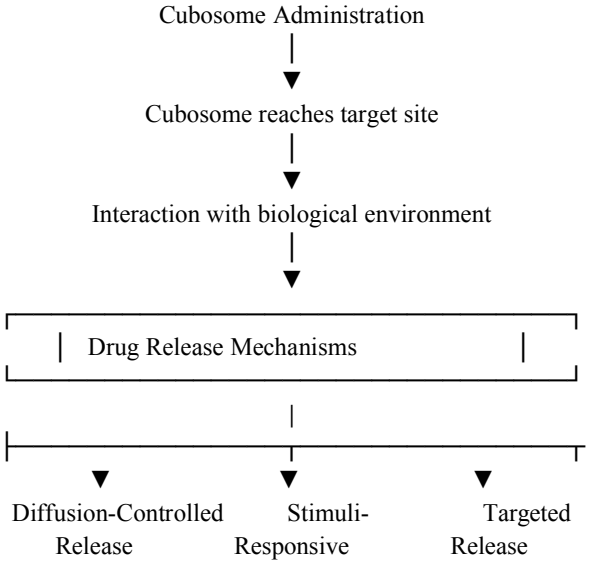
pH-responsive release: Some bodily tissues, such tumors, may have a pH that is higher than that of healthy tissues. It is possible to construct cubosomes with pH-sensitive lipids that, in response to acidic conditions, cause the cubic structure to destabilize and release the medicine.

Enzyme-triggered release: Drug release occurs at the site of action when certain cubosome components are broken down by the body's enzymes.

Temperature-sensitive release: It is particularly useful for localized drug administration since the phase transition temperature of the lipids in cubosomes can be changed to start drug release in response to temperature changes.

Targeted Release

Additionally, cubosomes can be altered to deliver drugs to specific cells or regions. This is accomplished by affixing targeting ligands or antibodies to the cubosomes' surface, which enables them to recognize and bind to particular receptors on the target cells. The encapsulated medication can be released right at the site of action once the cubosomes attach to the target and are internalized by the cells. [15]



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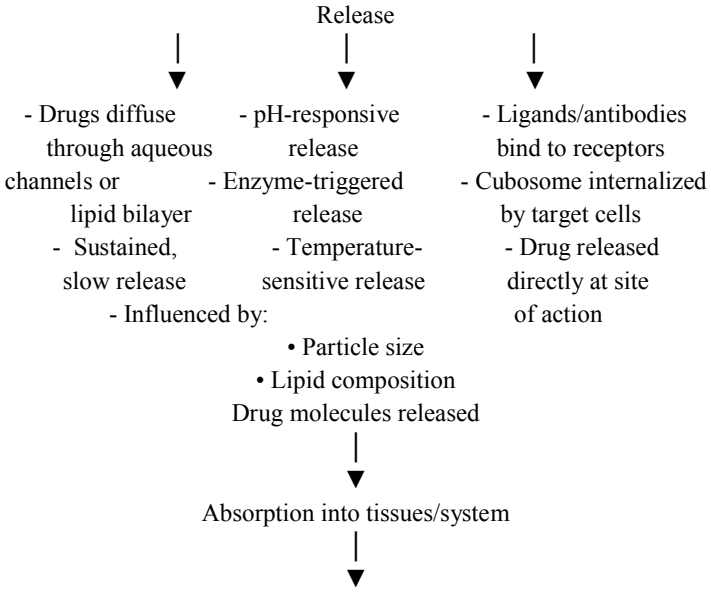

Fig 7: Flowchart of Drug Release Mechanism

Green synthesis of Cubosomes:

Green synthesis of nanoparticles is a sustainable approach that minimizes waste production. Nontoxic precursors and mild reaction conditions are employed in this technique. This technique allows us to create a variety of metallic nanoparticles without the need for costly or dangerous chemicals. Using a variety of biological organisms, including bacteria, algae, yeast, molds, plants, and their products, it can be completed in a single step. Molecules from plants and microbes, such as proteins, alkaloids, amines, and phenolic chemicals, can also be utilized. It is devoid of harmful substances, and various plant sections can be utilized to create nanoparticles.

Fig 8: Green Synthesis of Cubosomes

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The green manufacture of cubosomes using plant extracts has garnered a lot of interest. In order to create metallic nanoparticles, we can also extract stabilizing and reducing substances from plants. Cubosomes can be made from a variety of plant components, including curcuma longa, capsicum, neem plant, tulasi herb, red onion, moringa oleifera, lippia citriodora, allium sepa, eucalyptus, tridax procumbens, etc. [15]

Potential routes of delivery for cubosomes

Cubosomes for oral drug delivery

Cubosomes' distinct shape has sparked particular interest in using them as oral medication carriers. There hasn't been much research done on cubic nanostructures' potential as an oral medication delivery vehicle. Even though Chunet et al. were able to increase insulin oral absorption using GMO-based cubosomes, poorly water-soluble medications would have a different outcome in the gastrointestinal (GI) tract. Cubosomes, however, appear to be potential oral delivery vehicles for weakly water-soluble actives due to a few special benefits. [16]

One of the most challenging aspects of therapeutic development is the low oral bioavailability of poorly water-soluble medications. Cubosomes' highly ordered, segregated internal architecture, high lipid content, and large surface area have recently drawn the attention of formulation scientists for their potential application as drug delivery vehicles. A promising delivery system that can encapsulate both hydrophilic and hydrophobic medications, boost absorption, and protect them against deterioration is the cubosome (CUB). [17]

The confined activity of big proteins through encapsulation within the gastrointestinal tract is another use case. Liquid crystalline nanoparticle-based carriers can have targeted and controlled release features. Because these particles are designed to form on site at a controlled rate, they enable effective drug distribution in living creatures. Crucially, these carriers can be administered at several absorption sites, such as the small or large intestine, for drugs with a limited window of opportunity for regional absorption. [18]

Cubosomes for topical delivery

In transdermal delivery of active molecules, the skin penetration of the drug is limited as a result of the barrier function of the highly organized structure of the stratum corneum, the most external layer of the skin. Several approaches have been presented to improve the skin permeation such as chemical modification of the active molecule, applying a skin permeation enhancer and iontophoresis. [16]

Cubosomes for ophthalmic delivery

Although topical application of drug solutions (eye drops) is usually employed in ocular diseases, the removal mechanisms such as blinking, tears and nasolacrimal drainage are considerable challenges. The cornea is the main route of anterior drug absorption for drugs to reach the ocular tissue. [16]

Cubosomes can encapsulate a variety of amphiphilic, hydrophilic, or hydrophobic medications and are known to have a large surface area and good physical stability. Because of their bilayer structure, which resembles physiological barriers, they are being investigated for use in ocular drug administration. This makes it easier for cubosome amphiphilic nanocarriers to integrate with the corneal epithelium's bilayer lipid membrane. Previous studies on cubosomes revealed improved skin retention ability through transcutaneous administration. Therefore, encapsulation into cubosomes is a viable method for treating ocular disorders such as glaucoma, posterior segment ocular diseases, uveitis, and age-related macular degenerative condition. [13]

Cubosomes for Parenteral Drug Delivery

Cubosomes' distinctive solubilization, efficient encapsulation, sustained release behavior, and in vivo stabilization have made them appealing drug delivery systems. Additionally, cubosomes maintain the controlled release capability while having a lower viscosity than liquid crystalline phase. In comparison to the comparable somatostatin solution, Cervin showed that the terminal half-life of somatostatin cubosomes administered intravenously in rats was significantly prolonged more than six times. Additionally, cubosomes are an attractive alternative to standard microspheres and implants because of their reduced solvent consumption during preparation and good syringe ability. However, some

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research revealed that self-assembled monoglyceride and GMO materials could cause hemolysis in vivo when administered intravenously; as a result, parenteral administration of drug delivery systems based on cubosomes was limited. [18]

Approaches for encapsulating various drugs

Currently, there are three different loading techniques for drug encapsulating in cubosomes.

Pre-loading:

Pre-loading involves first incorporating the drug into a liquid-crystalline gel and then dispersing it into NPs. The medication may fuse with the LC structure, increasing the encapsulation efficiency and adding value to pre-loaded cubosomes. [13]

Post-loading:

During post-loading, drugs are adsorbed onto previously modeled cubosomes. This method creates a sterile cubosome dispersion by heating the post-incorporated particles prior to medication addition. Sonication typically results in a final product with fewer vesicles [17].

Hydrotrope loading:

Putting a drug into cubosomes as they naturally form is known as hydrotrope-loading [17]. In hydrotrope-loading, the medication is loaded while cubosomes form on their own in an ethanol/GMO combination. Because the aforementioned process eliminates the need for high-shear mixing equipment, manufacturing costs are reduced. [13]

Mechanisms for drug loading and quantification:

Examples of cubosomes can be stacked in three different ways: inside the lipid layer, attached to the lipid bilayer, or isolated inside the fluid phases of the cubic phase.

Cubosomes can be consolidated either lately or after scattering by introducing the payload to liquid lipids, co-lyophilizing the dynamic chemicals with the bilayer movies, or stacking the cubosomes after brooding [20]. Up to now, most reports of loaded cubosomes have involved proteins or tiny molecules integrated into the lipid membrane, and they have mostly used single or binary lipid compositions based on phytantriol or monoolein. Cubosome systems loaded with small compounds, such as cancer aspirin antimicrobial peptides, have been reported to function as potentiators for immunostimulant delivery. The anti-cancer medications' reported encapsulation efficiencies range from 71 to 103%, whereas aspirin was reported to be between 61.9 and 71.6% [21]. Cubosomes' bigger hydrophobic area, which enables a greater loading capacity of hydrophobic medications while still allowing the loading of hydrophilic ones, is their main benefit over other particles, such as liposomes. Curcumin in phytantriol cubosomes has a greater loading capacity than curcumin liposomes, according to the study. Additionally, the particle membrane curvature can be adjusted regardless of its size because of the cubosomes' lattice structure [10].

Sr. No.	Drug Loaded Cubosomes	Category of Drug	Results
1.	flurbiprofen	NSAIDs	Increased trans corneal penetration and lowered ocular irritation.
2.	Dexamethasone	Corticosteroids (Glucocorticosteroids)	Improved biocompatibility to the eye and corneal penetration.
3.	Timolol maleate	Beta blocker	Improved biocompatibility to the eye and corneal penetration.
4.	Ketorolac	NSAIDs	Increased corneal retention and trans corneal penetration.

Table1: Summary of administered drugs loaded in cubosomes via ophthalmic route

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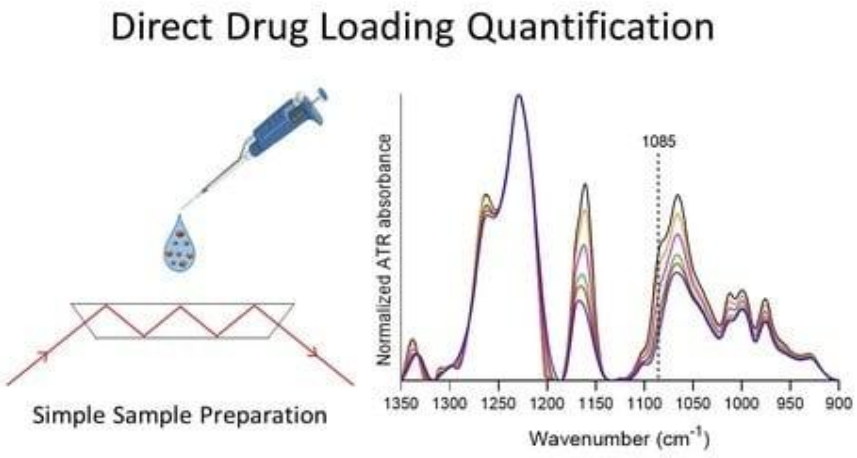

Fig 9: Drug Loading Quantification

Examples of Loading

Cubosomes loaded with bigger molecules and protein cargo are much less common, despite the abundance of examples of small compounds loaded into cubosome systems. Dopamine D2L receptor loading into monoolein and phytantriol cubosomes doped with Ni (II) chelated EDTA amphiphiles, pH-responsive cubosomes with Outer Membrane Protein F (OmpF) reconstituted into the bilayer, beta casein-loaded cubosomes, and cubosomes used to release nerve growth factor in PC12 cells are some important examples.

Application of Cubosomes in Drug Delivery:

Cubosomes have numerous in vitro applications in biomedicine. Cubosomes' primary biomedical use to far is therapeutic delivery, partly because many of their component parts are already approved for use in medicine. Lipid carriers are a desirable alternative for therapeutic administration because to the limited solubility and permeability of many medicines. Antimicrobials are one example. Cubosomes have been studied as antimicrobial peptide carriers to cure pneumonia and infected wounds, as well as for the treatment of fungal diseases [21].

In Oral Drug Delivery System

One of the most challenging aspects of therapeutic development is the low oral bioavailability of poorly water-soluble medications. Cubosomes' highly ordered, segregated internal architecture, high lipid content, and large surface area have recently drawn the attention of formulation scientists for their potential application as drug delivery vehicles. A promising delivery system that can encapsulate both hydrophilic and hydrophobic medications, boost absorption, and protect them against deterioration is the cubosome (CUB). Cubosomes have the potential to greatly enhance oral medication absorption. For instance, oral administration of insulin-loaded cubosomes resulted in a sustained drop in rats' blood glucose levels. Because cubosomes have so many uses, they are essential to oral medication delivery systems [17].

Controlled release of drugs:

The most common use of cubosomes is the control release of solubilized substances. Because of its tiny pore size (5–10 nm), capacity to dissolve hydrophilic, hydrophobic, and amphiphilic compounds, and biodegradability by simple enzymes, cubic phase is more suitable for control release [14].

Melanoma (cancer) treatment:

A few anticancer medications have recently been physicochemically described and successfully encapsulated in cubosomes. This intriguing nanocarrier's distinct shape points to its potential use in melanoma treatment [14].

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International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429
Volume 6, Issue 5, March 2026
Impact Factor: 8.2

For Topical Drug Delivery System:

Cubosomes' strong bio-adhesion makes them useful in topical and mucosal drug delivery systems. They are useful for safeguarding sensitive skin. Cubosomes have a high degree of permeability because they contain ethanol, which causes the skin to tear. Fat fluidity improves as a result, increasing the drug's skin penetration [22].

Controlled or sustained release behavior

Numerous medications with various physicochemical characteristics have been added to cubosomes, and their sustained drug release behavior has also been examined. Cubosome residual particles were responsible for the cubosomes' persistent behavior. Cubosomes based on monoglycerides may be suggested for topical applications, such as mucosal or percutaneous administration [23].

Advantages:

It is economic.
It is non -toxic and biocompatible.
Method of preparation is simple.
It has excellent bio adhesive properties.
It has skin permeation enhancement.
For longer time they are thermodynamically stable.
High drug payloads due to high internal surface area a cubic crystalline shape.
Biodegradability of lipids.
Capability of encapsulating hydrophilic, hydrophobic, and amphiphilic substances.
Targeted release and controlled release of bioactive agents.
Due to high internal surface area & cubic crystalline structures there is high drug loading [24].

Disadvantages:

Large-scale production can often be difficult due to the high viscosity of cubosomes.
Regulated medication distribution is not possible if the drug form inside the cubosome is polymer-based.
Water-soluble medications are not well trapped in cubosomes due to their high-water content.
Cubosomes have a significant stability problem that acts as a barrier and limits their use.
During production, preservation, and in vivo transportation, they could have poor drug loading efficiency and result in drug leakage.
After extended exposure, particle growth may occur.
Cubosomes are capable of the following: In the case that the external environment
changes, cause their dynamics to undergo a phase shift [25].

Future prospect:

Cubosome nanoparticles show promise in the areas of drug delivery and sustained drug release however, before such nanocarriers can fully realize their therapeutic potential in many diseases, additional optimization is still needed depending on the route of administration frequency of dosing and mode of drug release. They are also appealing nanovehicles for loading and delivering proteins and peptides but the studies that have been published are still at a basic level, and it is necessary to address various aspects of the structural and morphological characteristics of these soft nanocarriers the loading capacity of biomolecules and their release. Blood compatibility should be considered early in the formulation development process for future intravenous nanomedicines based on cubosomes. Additionally, there is still a lack of knowledge regarding their stability in biological fluids and biological factors that regulate drug release from cubosomes, including interactions with cell membranes, structural changes upon contact with biological fluids like plasma and reactions related to infusion. Although the use of cubosomes for intravenous drug delivery is an ambitious goal, these nanocarriers may find expedited applications for oral, ocular and topical delivery of drugs that are poorly soluble in water providing an alternative and economic opportunity in formulation science [23].

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II. CONCLUSION

Cubosomes represent a cutting-edge class of nanostructured liquid crystalline particles with immense potential in drug delivery and biomedical applications. Their unique bicontinuous cubic structure provides a high surface area and internal compartmentalization, making them ideal for encapsulating both hydrophilic and hydrophobic agents.

• The methods of preparation, such as top-down and bottom-up approaches, allow for scalable and tunable synthesis, while green synthesis techniques are gaining traction for their eco-friendly and biocompatible advantages.

• Theoretical models, including curvature elasticity and self-assembly thermodynamics, help explain the formation and stability of cubosomes.

• Key components like monoolein, phytantriol, and stabilizers (e.g., Pluronic F127) are critical in maintaining structural integrity and functional performance.

• Their drug release mechanisms—typically diffusion-controlled or triggered by environmental stimuli—enable sustained and targeted delivery.

• Drug loading mechanisms leverage the amphiphilic nature of cubosomes, allowing efficient encapsulation through passive entrapment or active loading strategies.

• With multiple routes of administration—oral, topical, ocular, intravenous—cubosomes offer flexibility in therapeutic design.

• Their applications span across pharmaceuticals, cosmetics, and nutraceuticals, including cancer therapy, vaccine delivery, and transdermal systems.

In essence, cubosomes are a versatile and promising nanocarrier system, merging structural sophistication with functional adaptability. Their continued development, especially through sustainable synthesis and precision targeting, holds great promise for the future of advanced drug delivery.

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