OPEN ACCESS

Saudi Journal of Medical and Pharmaceutical Sciences
Abbreviated Key Title: Saudi J Med Pharm Sci
ISSN 2413-4929 (Print) | ISSN 2413-4910 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://saudijournals.com

Review Article **Pharmaceutics**

Cubosomes in Drug Delivery: A Comprehensive Overview of Mechanisms, Applications, and Future Direction

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DOI: https://doi.org/10.36348/sjmps.2025.v11i06.001 | **Received:** 24.04.2025 | **Accepted:** 03.06.2025 | **Published:** 05.06.2025

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Abstract

Cubosomes, lipid-based nanoparticles characterized by a bicontinuous cubic phase structure, show significant promise as drug delivery systems (DDS) due to their stability, enhanced bioavailability, and targeted delivery capabilities. This review examines the development, structural features, and drug release mechanisms of cubosomes, including diffusion-controlled, stimuli-responsive, and targeted release strategies. Applications in oncology, infectious diseases, and anti-inflammatory therapies highlight their improved therapeutic efficacy and minimized systemic side effects. Challenges related to large-scale manufacturing, particle stability, and regulatory compliance are addressed, along with potential solutions and emerging trends. The review emphasizes the potential of cubosomes in precision medicine and personalizing treatment plans, encouraging further research to meet unmet clinical needs.

Keywords: Cubosomes, Drug Delivery Systems, Nanotechnology, Cancer Therapy, Controlled Release, Targeted Delivery, Biocompatibility, Lipid-Based Nanoparticles, Precision Medicine.

INTRODUCTION

The field of pharmaceutical sciences has seen a growing demand for novel drug delivery systems (DDS) to address the limitations of traditional methods such as oral, intravenous, or topical delivery, particularly in managing chronic diseases, cancers, and infectious diseases. These conventional approaches often struggle with issues of drug stability, bioavailability, targeted delivery, and prolonged release. In this context, cubosomes, lipid-based nanoparticles that self-assemble into a bicontinuous cubic phase, have emerged as a promising alternative for overcoming these challenges.

This review aims to provide a comprehensive analysis of cubosomes as an innovative platform for drug delivery. It explores their structural characteristics, methods of preparation, drug release mechanisms, and therapeutic applications, particularly in oncology, infectious diseases, and anti-inflammatory treatments. Furthermore, the review identifies the key challenges in cubosome development, including production scalability, regulatory hurdles, and stability concerns, while offering potential solutions and future directions for optimizing cubosomes in precision medicine and personalized therapies. By synthesizing existing literature, this study serves as a valuable resource for researchers and clinicians, shedding light on the transformative potential of cubosomes in enhancing drug efficacy and advancing nanomedicine.

Overview of Lipid-Based Nanoparticles

Lipid-based nanoparticles (LNPs) are among the most researched and widely used materials for drug delivery systems because of their biocompatibility, biodegradability, and ability to encase a range of therapeutic agents, such as small molecules, proteins, and nucleic acids. LNPs offer several benefits compared to traditional drug delivery methods, such as improved stability, controlled release, targeted delivery, and the capability to encapsulate hydrophobic, hydrophilic, and amphiphilic drugs [1].

Nanoparticles, in general, are characterized by their nano size, usually starting from 1 nm to 1000 nm, which allows to overcome physiological barriers such as cell membranes, blood-brain barriers, and tumor tissues. Among lipid-based nanoparticles, cubosomes stand out due to their unique structural properties and capabilities for controlled and targeted drug delivery.

Cubosomes belong to a class of lipid nanoparticles that self-assemble into a bicontinuous cubic phase. This phase is a thermodynamically stable structure formed by the organization of amphiphilic lipids into a 3D network that includes two interwoven continuous water channels. These structures can encapsulate both hydrophilic and hydrophobic drugs, making them versatile platforms for drug loading and release. Thanks to their distinctive properties, cubosomes present several benefits over other nanocarriers like liposomes, solid lipid nanoparticles (SLNs), and nanoemulsions.

Cubosomes

Cubosomes are nanoparticulate systems composed of self-assembled lipids that form a bicontinuous cubic liquid crystalline structure. This cubic phase is characterized by the arrangement of the lipid molecules in such a way that interlocking water channels are interpenetrated by a lipid layers [2]. This unique, highly ordered structure enables cubosomes to accommodate both hydrophilic and hydrophobic substances, which are essential for their role as delivery systems.

The lipid bilayers that form the backbone of the cubosome structure are generally made of amphiphilic lipids [3], such as monoolein (MO), phytantriol, and diglycerides, often in combination with surfactants. These lipids spontaneously assemble into the cubic phase when mixed with water, forming stable nanoparticles with a high surface area and the capacity for drug encapsulation. The intercalation of both aqueous and lipid phases within the cubosome structure allows them to load a variety of therapeutic agents, including hydrophobic molecules within the lipid layers and hydrophilic molecules within the water channels.

Cubosomes offer several advantages that distinguish them from other lipid nanoparticles [4].

- ***High surface area***: The cubic phase offers a vast internal surface area for drug encapsulation.
- ***Dual drug encapsulation***: They can encapsulate both hydrophilic and hydrophobic drugs simultaneously.
- ***Stability***: Cubosomes are exceptionally stable and resistant to aggregation, making them suitable for long-term storage and use.
- ***Biocompatibility and biodegradability***: The lipid components used in cubosome formulation are generally biocompatible and biodegradable, ensuring minimal toxicity upon administration.

The ability of cubosomes to encapsulate both hydrophilic and hydrophobic drugs simultaneously is of particular interest in the context of personalized medicine. This is because patients often require a combination of different types of drugs to treat complex diseases, such as cancer, metabolic disorders, or infections.

Need For Cubosomes in Drug Delivery

Conventional drug delivery methods face significant challenges in achieving optimal therapeutic outcomes, especially in complex diseases that require targeted drug release at specific sites in the body. Some of the key limitations of traditional drug delivery systems include:

- ***Poor Solubility and Bioavailability***: Many therapeutic drugs, especially those with hydrophobic properties, exhibit poor solubility in water, which limits their bioavailability when administered orally or intravenously. This results in lower therapeutic efficacy and the need for higher drug doses.
- ***Lack of Specificity***: Numerous traditional drug delivery systems are unable to efficiently target specific tissues or organs which can lead to the distribution of drugs in non-targeted areas and an increase in systemic side effects.
- ***Short Half-Life***: Many drugs are rapidly cleared from the body, necessitating frequent administration to maintain therapeutic drug concentrations.
- ***Toxicity and Side Effects***: Traditional drug administration methods often result in the distribution of drugs to healthy tissues, leading to unwanted side effects, such as cytotoxicity and damage to non-target cells.

Cubosomes, with their highly ordered cubic phase structure, provide a solution to many of these challenges. The amphiphilic nature of the lipids in cubosomes allows them to encapsulate a wide range of both hydrophilic and hydrophobic drugs. By forming nanoparticles with sizes typically ranging from 50 nm to 500 nm, cubosomes can enhance the solubility and bioavailability of poorly soluble drugs, ensuring more effective drug delivery.

Furthermore, cubosomes can be designed to enable targeted drug delivery, either by modifying their surface with specific ligands or by utilizing their capacity to accumulate in particular tissues through the enhanced permeability and retention (EPR) effect which is commonly observed in tumors. The biocompatibility and biodegradability of cubosomes ensure that they are less likely to induce adverse immune responses, making them a safer alternative to traditional drug delivery systems.

Along with their stability and biocompatibility, cubosomes can also facilitate controlled and sustained drug release. The cubic phase structure creates a well-organized matrix in which drugs are gradually released over time through diffusion, resulting in a sustained release profile. This capability is particularly beneficial for the treatment of chronic conditions, where prolonged drug action is necessary to achieve therapeutic efficacy.

Structure of Cubosomes

Cubosomes are lipid-based nanoparticles that adopt a unique, highly ordered, and self-assembled three-dimensional structure [4], which is typically referred to as the bicontinuous cubic phase. This structure is crucial to their function as drug delivery systems, influencing their ability to encapsulate drugs, their stability, and their controlled drug release characteristics.

Lipid Composition and the Bicontinuous Cubic Phase

The structure of cubosomes is primarily formed from amphiphilic lipids, which contain both hydrophilic (water-loving) and hydrophobic (water-repellent) regions. The hydrophilic parts of the lipid molecules interact with water, while the hydrophobic parts avoid water and interact with each other. The ability of these amphiphilic lipids to self-assemble into a variety of mesophases, including the cubic phase, is central to the formation of cubosomes.

The bicontinuous cubic phase refers to a structure in which two continuous, interpenetrating water channels are separated by a lipid bilayer. These water channels are interconnected throughout the structure, allowing both hydrophilic and hydrophobic drugs to be encapsulated. The lipid bilayers within the cubic phase are organized into a regular, repeating lattice, giving cubosomes a highly ordered, stable structure.

The key lipids typically used for cubosome formation include:

- **Monoolein (MO)**: A common surfactant that forms a stable cubic phase in combination with water.
- **Phytantriol**: A fatty alcohol that is particularly well known for its ability to form the cubic phase in aqueous solutions.
- **Other lipids**: Various other lipids, such as phospholipids or diglycerides, can be incorporated into the formulation to modulate the properties of the cubosomes, such as stability, drug loading, and release kinetics.

In addition to the primary lipid, surfactants and co-surfactants are often added to enhance the self-assembly process or to control the size and morphology of the resulting cubosomes.

Structural Characteristics and Drug Encapsulation

The bicontinuous cubic phase structure of cubosomes provides an extensive interface for drug encapsulation. This structure has both aqueous channels and hydrophobic bilayers, which can accommodate a wide range of both hydrophilic and hydrophobic drugs:

- **Hydrophilic drugs**: These drugs can be incorporated into the aqueous channels of the cubosome structure, where they are stabilized within the matrix.
- **Hydrophobic drugs**: These can be incorporated into the lipid bilayers that form the continuous network. The amphiphilic property of lipids enables the incorporation of hydrophobic drugs within the hydrophobic cores of the bilayers.

The encapsulation capacity of cubosomes is enhanced by their high surface area and internal volume due to the bicontinuous cubic phase, making them capable of loading a larger quantity of drug relative to their size. This results in the possibility of achieving high drug loading and long-lasting release profiles, making cubosomes excellent candidates for controlled or sustained drug delivery systems.

Benefits of the Bicontinuous Structure

The bicontinuous cubic phase structure not only facilitates the encapsulation of diverse drug types but also provides several additional benefits:

- **Stability***:* The well-ordered structure confers stability to the cubosome particles, minimizing the risk of drug leakage and aggregation over time.
- **Controlled Releas*e***: The geometry of the bicontinuous cubic phase enables diffusion-controlled drug release, which can be further adjusted by modifying the lipid composition and other variables.
- **High Surface Area**: The interpenetrating water channels and lipid bilayers provide an extensive surface area for interaction with biological membranes, enhancing the bioavailability and cellular uptake of the encapsulated drug.

Mechanism of Drug Release from Cubosomes

One of the major advantages of cubosomes as carriers for drug delivery is their capability to release drugs in a regulated and prolonged manner. The release mechanism primarily influenced by physicochemical properties of the lipids used, the type of drug encapsulated, and the environmental conditions [5]. The key mechanisms that drive drug release from cubosomes include:

Diffusion-Controlled Release

The most common mechanism for drug release from cubosomes occurs through diffusion. Due to the intercalated aqueous channels in the bicontinuous cubic phase, drugs encapsulated within the aqueous phase can diffuse out into the surrounding medium over time. Similarly, hydrophobic drugs incorporated into the lipid bilayer can diffuse out into the surrounding environment. Diffusion is a relatively slow process, making cubosomes suitable for sustained drug release over long periods. The rate of diffusion depends on several factors:

- **Particle size**: Smaller cubosomes possess a higher surface area-to-volume ratio, which can accelerate the rate of diffusion.

- **Lipid composition**: The types of lipids used in the formulation can affect the fluidity of the lipid bilayer and thus the rate of drug diffusion.
- **Drug properties**: Hydrophilic drugs typically diffuse more easily through the aqueous channels, while hydrophobic drugs may require longer release times as they diffuse out of the lipid bilayers.

Stimuli-Responsive Release

Cubosomes can be designed to react to specific external stimuli, such as variations in pH, temperature, or the presence of enzymes or other biological markers. This stimuli-responsive release mechanism is especially beneficial in creating targeted drug delivery systems, where the drug is released solely at the intended site of action, reducing systemic side effects. For example:

- **pH-responsive release**: The pH of certain body tissues, such as tumors, can be more acidic than normal tissues. Cubosomes can be engineered with pH-sensitive lipids that trigger the cubic structure to destabilize and release the drug in reaction to acidic environments.
- **Enzyme-triggered release**: Certain enzymes present in the body can break down specific components of the cubosome, leading to drug release at the site of action.
- **Temperature-sensitive release**: The phase transition temperature of the lipids in cubosomes can be adjusted to initiate drug release in response to temperature variations, making it especially beneficial for localized drug delivery.

Targeted Release

Cubosomes can also be modified to attain targeted drug delivery to particular tissues or cells. This is achieved by attaching targeting ligands or antibodies to the surface of the cubosomes, allowing them to identify and attach to specific receptors on the target cells. Once the cubosomes bind to the target, they can be internalized by the cells, releasing the encapsulated drug directly at the site of action.

Uses of Cubosomes in Drug Delivery

Cubosomes are gaining increasing attention in drug delivery for their versatility and potential to improve therapeutic outcomes. Some of the key applications of cubosomes include:

- **Cancer Therapy**: Cubosomes have been shown to be effective carriers for anticancer drugs, allowing for sustained release at tumor sites. The capability to encapsulate both hydrophilic and hydrophobic drugs simultaneously is particularly useful for the combination therapy of cancer [6].
- **Infectious Disease Treatment**: The controlled release properties of cubosomes make them ideal for delivering antimicrobial agents, including antibiotics and antiviral drugs, with more efficacy and less side effects.
- **Anti-Inflammatory Therapy**: Due to their biocompatibility and ability to release drugs over extended periods, cubosomes are suitable for the delivery of anti-inflammatory agents, such as corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs).
- **Gene Therapy**: Cubosomes can be used as carriers for gene therapy, where they encapsulate nucleic acids (such as plasmids or siRNA) for targeted delivery to specific tissues.

Method of Preparation

Cubosomes are typically prepared using one of two methods: the **top-down** approach or the **bottom-up** approach. Each of these methods has distinct advantages depending on the desired properties of the cubosomes, such as size, drug encapsulation efficiency, and scalability for industrial production [7].

Top-Down Approaches

In the top-down approach, large lipid aggregates or bulk lipid systems are broken down into smaller particles using mechanical forces. The primary goal of this method is to obtain well-dispersed cubosomes with controlled size and morphology [9]. Common top-down techniques include:

High-Shear Homogenization

High-shear homogenization is one of the most widely used methods for producing cubosomes. In this technique, a lipid phase is mixed with an aqueous phase (containing surfactants) and subjected to high-shear forces using a high-pressure homogenizer. This process forces the lipid mixture through small orifices at high pressures, which breaks down the bulk lipid structures into smaller nanoparticles. These nanoparticles can then spontaneously self-assemble into cubosomes as the system cools [8].

- **Advantages**: High-shear homogenization is relatively simple, scalable, and effective for producing a wide range of lipid nanoparticles, including cubosomes.
- **Limitations**: The size distribution can be broad, and repeated homogenization steps may be needed to achieve the desired particle size and distribution.

Sonication

Sonication involves the use of ultrasonic waves to create shear forces in the lipid–water mixture, resulting in the formation of smaller lipid particles. The energy from the ultrasonic waves promotes the self-assembly of lipids into cubic structures.

- **Advantages**: Sonication is a relatively simple and fast method.
- **Limitations**: The method requires careful control of sonication parameters (e.g., duration, power) to prevent excessive heat generation,

which could destabilize the cubic phase structure.

Bottom-Up Approaches

The bottom-up approach involves the self-assembly of lipids from a molecular level into cubosome structures. This process typically occurs in the presence of an aqueous phase under controlled conditions [10].

Solvent Evaporation

The solvent evaporation method is a widely used technique for preparing cubosomes. In this approach, lipids are dissolved in an organic solvent (chloroform or ethanol) to form a lipid solution. This lipid solution is emulsified in an aqueous phase containing surfactants. The solvent is then removed through evaporation under reduced pressure, causing the lipid molecules to self-assemble into the cubic phase, resulting in the formation of cubosomes.

- **Advantages**: This method is well-suited for encapsulating hydrophobic drugs and is relatively simple to perform.
- **Limitations**: The evaporation process can be time-consuming, and the use of organic solvents may be problematic for certain drugs, particularly if they are sensitive to solvent exposure.

Emulsification

Emulsification is another bottom-up method used to prepare cubosomes. This process involves the emulsification of a lipid–surfactant solution in water. Under controlled conditions, the lipid molecules self-assemble into the bicontinuous cubic phase structure [11]. The emulsification process can be performed using high-speed stirring, homogenization, or microfluidic techniques.

- **Advantages**: Emulsification can be a relatively gentle process, which is advantageous for encapsulating sensitive drugs or biologics.
- **Limitations**: The method may not be suitable for large-scale production unless optimized conditions are used.

Microfluidic Methods

Microfluidic devices provide precise control over the flow of fluids, making them ideal for the reproducible production of cubosomes with uniform size and morphology. In microfluidic approaches, lipid and aqueous phases are pumped through microchannels, where they rapidly mix and self-assemble into nanoparticles. This method allows for excellent control over particle size, dispersity, and drug encapsulation efficiency [12].

- **Advantages**: Microfluidics offers high reproducibility, scalability, and precise control over particle properties.
- **Limitations**: Microfluidic methods require specialized equipment and may not be as widely accessible for all laboratories or industrial settings.

Selection of Preparation Method

The choice of preparation method for cubosomes depends on several factors, including:

- **Desired Size**: Smaller cubosomes (typically less than 200 nm) are often preferred for intravenous drug delivery due to better circulation times and cellular uptake.
- **Drug Type**: Hydrophilic drugs may require different preparation conditions compared to hydrophobic drugs, as these drugs must be incorporated into the aqueous channels or lipid bilayers. [13]
- **Scalability**: Top-down methods like high-shear homogenization and sonication are suitable for small-scale laboratory production, while microfluidic and solvent evaporation methods may be more appropriate for larger-scale production.

Evaluation of Cubosomes

Evaluation involves testing cubosomes in laboratory settings to assess key properties such as drug loading, release behavior, cytotoxicity, and cellular uptake. These tests provide a controlled environment to evaluate cubosome formulations before progressing to more complex animal studies [14].

Drug Loading and Encapsulation Efficiency

- **Method***:* The loading capacity and encapsulation efficiency of cubosomes can be assessed by determining the amount of drug successfully incorporated into the cubosome structure. Typically, high-performance liquid chromatography (HPLC) or ultraviolet (UV) spectrophotometry are used to measure the concentration of the drug in the supernatant (unencapsulated) and in the cubosome nanoparticle fraction.

Parameters:

- **Drug Loading Capacity (DLC)**: The mass of drug encapsulated per unit mass of cubosomes.
- **Encapsulation Efficiency (EE)**: The percentage of the total drug loaded into the cubosomes relative to the total drug used in the formulation.

- **Significance**: A high loading capacity and encapsulation efficiency are crucial for ensuring that an adequate therapeutic dose of the drug is delivered to the target site.

Particle Size, Zeta Potential, and Morphology

- **Method**: Dynamic light scattering (DLS) is commonly used to measure the particle size and polydispersity index (PDI) of cubosomes. Zeta potential, which indicates the surface charge of cubosomes, is measured using electrophoretic

light scattering (ELS). The morphological characteristics of cubosomes can be evaluated using electron microscopy techniques, such as transmission electron microscopy (TEM) or scanning electron microscopy (SEM) [15].

Parameters:

- **Particle size***:* Determines the uniformity and stability of cubosomes. Smaller sizes (typically in the range of 50–500 nm) are generally preferred for enhanced tissue penetration and controlled release.
- **Zeta potential**: Provides information on the surface charge and stability of cubosomes. High zeta potential values (either positive or negative) generally indicate good stability due to electrostatic repulsion between particles.
- **Morphology**: Visualizes the cubic structure of cubosomes, which is essential for understanding their stability and ability to encapsulate and release drugs.
- **Significance***:* These characteristics impact the overall drug delivery efficiency, stability, and release rate of cubosomes.

In Vitro Drug Release Profile

- **Method**: The release kinetics of the encapsulated drug from cubosomes are typically evaluated using dialysis or Franz diffusion cell techniques. In the dialysis method, cubosomes are placed in a semi-permeable membrane, which is placed in a release medium, and the amount of drug released into the medium is monitored over time using HPLC or UV spectrophotometry [16].

Parameters:

- **Release rate**: The amount of drug released over a specific period.
- **Release pattern**: The release can be classified into different types such as burst release (rapid release), sustained release, or controlled release.
- **Mechanism of release**: Diffusion-controlled release is the most common mechanism for cubosomes, but other factors like pH or temperature may also influence the release rate.
- ***Significance***: The release profile is essential for ensuring that the drug is released in a controlled manner, minimizing burst release, and achieving the desired therapeutic effect over an extended period.

Cellular Uptake and Cytotoxicity Studies

- **Method***:* The ability of cubosomes to enter cells and their impact on cell viability can be assessed using in vitro cell culture studies. Fluorescently labeled cubosomes (using dyes such as coumarin or rhodamine) can be used to visualize cellular uptake through fluorescence microscopy or flow cytometry. Cytotoxicity is measured using standard assays such as MTT, MTS, or CellTiter-Glo, which evaluate cell viability after exposure to cubosomes [17].

Parameters:

- **Cellular uptake**: The amount of cubosomes internalized by cells, which provides insight into the ability of cubosomes to deliver drugs to target cells.
- **Cytotoxicity**: The effect of cubosome formulations on cell viability. Low cytotoxicity is desired to ensure the safety of cubosomes in biological systems.
- **Significance***:* Cellular uptake is crucial for drug delivery, as it determines how effectively the drug can be transported into the target cells. Low cytotoxicity ensures the safety of the formulation for potential therapeutic use.

In Vitro Stability Studies

- **Method***:* In vitro stability studies evaluate the physical and chemical stability of cubosomes over time under different conditions (e.g., changes in temperature, pH, or ionic strength). The formulation is stored under specified conditions, and parameters like particle size, zeta potential, and drug release profile are periodically measured.

Parameters*:*

- **Particle size**: Stability is often indicated by the maintenance of a consistent particle size.
- **Zeta potential**: A stable zeta potential over time indicates minimal aggregation or flocculation of cubosomes.
- **Significance**: Stability is a critical factor for ensuring that cubosomes remain effective and safe during storage and before administration.

In-Vivo Evaluation of Cubosomes

In vivo evaluation tests are conducted using animal models to evaluate the biodistribution, pharmacokinetics, therapeutic efficacy, and potential toxicity of cubosome formulations in a whole organism. These tests provide a more realistic picture of how cubosomes behave in biological systems and their potential for clinical translation.

Biodistribution Studies [18]

- **Method***:* Biodistribution studies involve administering radiolabeled or fluorescently labeled cubosomes to animal models and tracking the distribution of the nanoparticles in various organs over time. Imaging techniques such as single-photon emission computed tomography (SPECT), positron emission tomography (PET), or fluorescence imaging are

commonly used to visualize and quantify the accumulation of cubosomes in specific tissues.

Parameters:

- **Tissue distribution**: Identifying where cubosomes accumulate (e.g., liver, spleen, tumor tissue) helps evaluate their potential for targeted delivery.
- **Targeting efficiency**: The ability of cubosomes to preferentially accumulate in the target tissue (e.g., tumors, inflammatory sites).

- **Significance**: Understanding the biodistribution of cubosomes is crucial for assessing their ability to deliver drugs to the specific site of action and to minimize off-target effects.

Pharmacokinetic Studies

- **Method**: Pharmacokinetic studies are designed to evaluate the absorption, distribution, metabolism, and excretion (ADME) of cubosome-encapsulated drugs. These studies often involve blood sampling at different time points after administration to determine drug concentrations using techniques such as HPLC or mass spectrometry. Key pharmacokinetic parameters include half-life, maximum plasma concentration (C_max), time to peak concentration (T_max), and area under the curve (AUC).

Parameters:

- **Half-life (t½)**: The time required for the drug concentration in the bloodstream to reduce by half, indicating the duration of the drug's therapeutic effect.
- ***AUC***: The total exposure of the organism to the drug over time.

- **Significance**: Pharmacokinetic data help determine the drug release and circulation times in vivo, which are critical for assessing the suitability of cubosomes for sustained or controlled drug release.

Therapeutic Efficacy Studies

- **Method**: In vivo therapeutic efficacy studies evaluate the ability of cubosomes to produce a therapeutic effect in animal models of disease. For example, in cancer models, cubosomes can be loaded with chemotherapeutic agents, and their efficacy can be tested by monitoring tumor size over time. In inflammatory disease models, cubosomes can be loaded with anti-inflammatory drugs and their ability to reduce inflammation can be assessed.

Parameters:

- **Tumor inhibition**: Reduction in tumor volume or mass following treatment.
- **Reduction in inflammation**: Monitoring the levels of inflammatory markers or assessing histopathological changes in tissues.

- **Significance**: Efficacy studies are vital for determining whether cubosome formulations are effective in treating the targeted disease and whether they provide an advantage over conventional treatments.

Toxicity and Biocompatibility Studies

- **Method**: Toxicity studies assess the safety profile of cubosomes in vivo. These studies typically involve monitoring animal health parameters, including weight, food intake, and behavior, following the administration of cubosome formulations. Organ histology is also performed to check for any damage caused by cubosome administration [19].

***P*arameters**:

- **Acute toxicity**: Observing immediate toxic effects such as lethality, organ damage, or changes in behavior after administration.
- **Chronic toxicity**: Long-term monitoring of toxicity after repeated administration.

- **Significance**: Ensuring that cubosomes are biocompatible and do not cause harm to the animals is essential for their future clinical use [20].

Acknowledgement

I am grateful to the researchers whose work has been cited throughout this review. Without their foundational contributions, this work would not have been as comprehensive. Their pioneering studies on cubosomes, nanomedicine, and drug delivery have significantly influenced the direction of my own research.

CONCLUSION

As self-assembled nanosized lipid structures, Cubosomes, have emerged as a promising carrier system for drug delivery, providing unique advantages over conventional drug delivery systems. Their unique cubic phase structure provides high encapsulation efficiency, stability, and controlled release, making them suitable for a wide range of therapeutic applications, including anticancer drugs, antiviral agents, and vaccines. Furthermore, the biocompatibility and biodegradability of cubosomes enhance their potential for targeted drug delivery, reducing side effects and improving therapeutic outcomes. The mechanisms underlying their effectiveness, such as controlled release kinetics, stability in physiological conditions, and the capability to encapsulate both hydrophilic and lipophilic drugs, make cubosomes versatile nanocarriers. They also offer flexibility in modification for surface functionalization, allowing for enhanced targeting capabilities through ligand-receptor interactions. Looking ahead, the future direction of cubosome research should focus on

optimizing formulation parameters, improving manufacturing processes, and exploring the use of smart materials that can respond to specific stimuli. Collaborative efforts across disciplines, involving material scientists, pharmacologists, and clinicians, will be crucial to connect laboratory discoveries with practical clinical applications.

In conclusion, cubosomes hold great promise in revolutionizing drug delivery systems but future research and development are required to fully harness its potential for safe and effective clinical use.

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