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Review Article

Cubosome As Novel Drug Delivery System

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ABSTRACT

Cubosomes, a unique class of lipid-based vesicles, have emerged as promising candidates for drug delivery applications. Similar to liposomes, cubosomes self-assemble from amphiphilic lipids in the presence of stabilizers. Since their discovery, researchers have shown significant interest in their potential to transport therapeutic agents. Cubosomes offer versatility in terms of administration routes, including oral, ocular, transdermal, and even chemotherapy. Their well-defined cubic structure provides several advantages for drug nano formulations, particularly in cancer treatment. The most common preparation method involves a straightforward emulsification process, followed by techniques like sonication and homogenization. Two primary approaches for cubosome production exist: top-down and bottom-up methods. These advantages include :High drug loading capacity, Large surface area for enhanced interaction, relatively simple and cost-effective fabrication, biodegradable components for minimal environmental impact .

INTRODUCTION

Introduced by Larsson and resembling liposomes in structure, cubosomes are a unique class of lipid-based vesicles with immense potential for drug delivery applications. These self-assembled structures form from amphiphilic lipids in the presence of stabilizers. Since their discovery, researchers have shown significant interest in their ability to transport therapeutic agents via various routes, including oral, ocular, transdermal, and even chemotherapy.(1). Cubosomes exhibit properties characteristic of liquid crystalline materials, including high viscosity, optical isotropy, and a solid-like consistency. They also possess a unique cubic arrangement of their molecules.(2). Cubosomes have emerged as a

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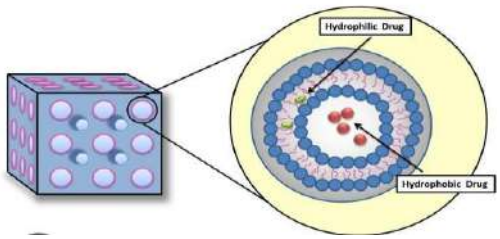
significant area of interest within nanotechnology-based drug delivery systems. Their ability to encapsulate a wide range of therapeutic agents within their 100-500 nanometer sized structures has attracted considerable attention from the pharmaceutical industry.(3) . Cubosomes inherit the unique cubic microstructure of their parent phase, but in a dispersed form with significantly lower viscosity. This difference allows for easier handling and administration. Additionally, cubosomes boast a larger surface area compared to the bulk cubic phase, enhancing their potential for drug interaction and delivery.(4). Cubosomes are typically produced by a high-energy dispersion method that breaks down the bulk cubic phase into nanoparticles. These nanoparticles are then stabilized with polymeric surfactants to prevent aggregation and facilitate their administration. Once delivered, the encapsulated drugs can either diffuse out of the cubosome structure or be actively absorbed by the target cells.(5). Polymeric stabilizers, including block copolymers and those containing PEG moieties, play a crucial role in cubosome development. These polymers not only enhance stability but also influence the drug release profile, allowing for controlled delivery. Notably, the ability to modify these polymers with protein molecules opens doors for further targeted applications(6). While companies like Nivea, L'Oréal, and Procter & Gamble explore cubosomes for cosmetic applications, recent research has delved into their potential for cancer therapy, topical drug delivery, and various other therapeutic areas. The low concentration of anti-cancer drugs traditionally used in formulations makes cubosomes a particularly attractive option due to their ability to effectively encapsulate and deliver these potent agents.(7).



ADVANTAGES

Cubosomes offer a compelling set of advantages for drug delivery applications. Their biocompatible, biodegradable nature minimizes potential side effects and promotes safe absorption into the body. Additionally, the simple preparation method makes them cost-effective to produce.(8) A key strength of cubosomes is their high drug loading capacity due to their extensive internal surface area(9). This, combined with their exceptional thermodynamic and physicochemical stability, ensures they can effectively encapsulate a wide range of drugs – from hydrophobic to hydrophilic – for extended periods. Notably, specific polymers can be incorporated to achieve controlled and targeted release of these encapsulated bioactives(10). The small particle size of cubosomes further enhances their bioavailability, potentially reducing the frequency of administration and lowering overall healthcare costs. Furthermore, compared to liposomes, cubosomes boast a larger ratio of particle volume to bilayer area, potentially leading to more efficient drug encapsulation(11).

DISADVANTAGES

cubosomes also present some challenges. The high water content within cubosomes can limit the encapsulation efficiency of water-soluble drugs. Additionally, their high viscosity makes large-scale production difficult(12). While some inherent controlled release is possible, achieving a truly targeted delivery profile often requires the use of specific polymers. Furthermore, leakage of the encapsulated drug can occur during storage or

transport within the body(13). Long-term storage may also lead to particle growth and potential instability. Finally, changes in the external environment can trigger phase transitions within cubosomes, potentially affecting their drug delivery properties.

METHODS OF PREPARATION OF CUBOSOMES:

1. High-Pressure Homogenization
2. Automated Cubosome Preparation
3. Probe Ultrasonication
4. Other Methods:

- Emulsification
- High Shear Homogenization Technique
- Spray-Drying Technique

5. Special Techniques:

- Top-Down Technique
- Bottom-Up Technique(14)

EVALUATION

This section outlines various methods used to assess the properties and performance of cubosomes, a type of nanoparticle carrier for drug delivery.

Visual Inspection:

The initial assessment involves inspecting the cubosomes for physical characteristics like clarity, color, uniformity, and the presence of any visible aggregates.

Transmission Electron Microscopy (TEM):

TEM offers high-resolution imaging to visualize the cubosome morphology. It provides detailed information about the particle shape and size distribution. Compared to traditional electron microscopy, TEM avoids limitations like vacuum environments and potential structural alterations during analysis.

Zeta Potential Measurement:

Zeta potential is a crucial indicator of cubosome stability. A high zeta potential signifies a strong electrostatic repulsion between particles, preventing aggregation and enhancing dispersion.

Viscosity Analysis:

A rotational viscometer, such as a Brookfield viscometer, is used to measure the viscosity of the cubosome suspension. Viscosity influences factors like drug release and ease of administration.

Particle Size Analysis (Dynamic Light Scattering):

This technique utilizes a Zeta sizer to determine the average size and size distribution (polydispersity index) of cubosomes. Samples are diluted and exposed to a specific light source. The scattered light intensity is analyzed to obtain particle size data.

Polarized Light Microscopy:

This method helps identify the cubosomal surface characteristics. It differentiates between optically isotropic (uniform) and anisotropic (double refractive) structures. Additionally, it can detect changes in the cubic phase, indicating potential instability.

Differential Scanning Calorimetry (DSC):

DSC analysis provides information on thermal transitions within the cubosomes. As liquid crystals, cubosomes exhibit phase transitions due to endothermic and exothermic processes. DSC helps determine if these transitions occur and at what temperatures.

Small-Angle X-ray Scattering (SAXS):

SAXS is a powerful tool for analyzing the internal structure of cubosomes. It reveals information about the spatial arrangement of different components within the particle, including pore sizes and inter-particle distances. SAXS is particularly useful for studying structures at the nanoscale (5-25 nm).

Entrapment Efficiency:

Ultrafiltration techniques are employed to evaluate how effectively drugs are incorporated within the

cubosomes. This method measures the concentration of unencapsulated drug, allowing for the calculation of drug entrapment efficiency using a spectrophotometer.

Drug Loading Determination:

Similar to entrapment efficiency, drug loading can be determined using ultrafiltration or gel permeation chromatography. High-performance liquid chromatography (HPLC) can be employed for analysis.

Drug Release Measurement:

The in vitro release profile of a drug from cubosomes can be studied using pressure ultrafiltration methods. This typically involves an Amicon pressure ultrafiltration cell equipped with a Millipore membrane.

Stability Studies:

Stability assessment involves monitoring various parameters over time, including visual appearance, morphology, drug content, and particle size distribution. This helps identify potential degradation or changes in cubosome properties during storage(15).

APPLICATION

Controlled and Sustained Drug Release:

- The cubic phase's small pore size (5-10 nm) allows for controlled release of encapsulated drugs.
- Cubosomes can encapsulate a variety of drugs with different properties.
- The biodegradability of cubosomes by enzymes facilitates sustained release and prevents drug build-up in the body.

Drug Delivery Vehicle:

- Companies like L'Oréal and Nivea are exploring cubosomes in cosmetics as stabilizers for oil-in-water emulsions and to absorb pollutants.
- Cubosomes offer a versatile platform for various drug delivery applications.

Topical Drug Delivery Systems:

- Cubosomes' bioadhesive nature makes them suitable for topical and mucosal drug delivery applications.
- They can protect sensitive skin and enhance drug permeability due to the ethanol content, which disrupts the skin barrier to a certain extent, facilitating drug absorption.

Treatment of Viral Diseases:

- Certain lipids used in cubosome formulations, like monoglycerides, exhibit antiviral properties.
- This makes cubosomes potentially applicable for treating viral sexually transmitted diseases (HIV) and bacterial infections (genitourinary infections).

Cancer Therapy:

- Cubosomes can effectively encapsulate anticancer drugs, serving as a beneficial carrier system.
- The small size of cubosomes is crucial for enhanced drug delivery, localization, and therapeutic effect in cancer treatment.

Intravenous Drug Delivery:

- Cubosomes' high drug loading capacity compared to liposomes makes them a promising option for intravenous drug delivery.
- They can act as carriers for injectable drugs, particularly poorly soluble small molecules.
- Cubosomes formulated with lamellar phases can be injected subcutaneously. Initially flowable, they absorb surrounding water and transform into a cubic phase, forming an in situ depot for sustained drug release.

Oral Drug Delivery:

- Cubosomes can address challenges associated with oral drug delivery, including:
- Large molecule size
- Poor aqueous solubility

- Limited absorption
- Cubosomes can potentially overcome these hurdles and enable targeted drug release at specific locations in the gastrointestinal tract, which is particularly beneficial for drugs with a narrow absorption window.
- They also offer the possibility of localized effects within the gastrointestinal tract.(16)

FUTURE PROSPECTS:

Cubosomes have great capability in the application of drug delivery, both sustained and direct. Previous studies on cubosomes need to be broadened because they are still at the very basic level, and further investigation is needed. The exact studies are required for the drug loading capacities as well as their release behavior. Further optimization and development in the future are necessary to understand the suitability of cubosomes with body tissues and blood. In order to develop, it is necessary to take into account the stability requirements of cubosomes in biological fluids. To gain knowledge about the factors that affect drug release from cubosomes, studies are necessary.(17)

CONCLUSION

Cubosomes possess the capability to encapsulate many drugs, both hydrophilic and hydrophobic; they are also able to reach targeted sites, such as the brain or central nervous system. Cubosomes are advantageous for a range of drug moieties, immunogenic substances, proteins, and cosmetic preparations. Although they are small, they have a wide drug loading area. The cubosomes have been widely applied for ophthalmic, oral, intravenous, topical, melanoma therapy, and diabetes. Personal care products also possess a unique property. The internal structure of body tissues and cubosomes is similar. They are suitable for treating the skin and various tissues of the body. This is because they are able to target specific areas. This cubosome technology is relatively novel, and it has a lot of scope in the research area for the formulation and development of new products with high output. This leads to industrial and commercial progress in the pharmaceutical sector. Cubosome formulations are made by combining lipids with water and offer flexibility in product development. They are suitable for body. To conclude, there is a need for more research on cubosomes to better understand the safety testing and role of cubosome vesicles in drug delivery systems.

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