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Revolutionizing Drug Delivery: Unraveling the Nanostructural Marvels of Cubosomes and their Comprehensive Evaluation in Pharmaceutical Applications

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A B S T R A C T

Cubosomes, recognized as innovative lipid-based drug delivery systems, share similarities with other nanosystems like liposomes and niosomes [1]. These nanostructures are liquid crystalline particles commonly crafted using specific amphiphilic lipids, such as glyceryl monophosphate and phytantriol, in the presence of an appropriate stabilizer [1]. Characterized by their unique three-dimensional organization, cubosomes manifest as curved bicontinuous lipid bilayers arranged in a honeycomb-like structure.

In the realm of drug delivery, cubosomes offer a promising platform with distinct advantages. Their nanostructure, composed of carefully selected lipids, provides a tailored environment for drug encapsulation and controlled release. The amphiphilic nature of the lipids contributes to the stability and versatility of cubosomes as drug carriers[2].

Keywords: Cubosomes, bicontinuous layer, amphiphilic lipids, honey combed structures.

INTRODUCTION

In the realm of drug delivery systems, the quest for innovative carriers that can efficiently encapsulate and deliver therapeutic agents has led to the emergence of cubosomes. Coined by the pioneering scientist Kare Larsson in the 1980s, cubosomes represent a unique class of lipid-based nanostructures with distinctive characteristics, making them promising candidates for advanced drug delivery applications. The genesis of cubosomes can be traced back to observations made by Patton and Carey in 1979 during their studies on fat digestion, where the combination of stomach contents, lipase, and bile salts resulted in dispersed particles exhibiting a bicontinuous cubic phase. However, it was Larsson who propelled the understanding of cubic phases, revealing their ability to form from bulk non-dispersed phases and exist as submicron particles with identical internal nanostructures upon dispersion [3].

The fundamental architecture of cubosomes is intricately linked to the cubic lipid-water-based systems, showcasing a highly twisted lipid bilayer and two congruent, non-intersecting water channels. This unique internal nanostructure imparts both hydrophobic and hydrophilic domains to the particles, contributing to their versatility in solubilizing actives with diverse physicochemical properties. The distinctive bicontinuous cubic liquid crystalline phase structures of cubosomes are formulated by dispersing liquid crystalline cubic aggregates in aqueous media, resulting in nanovesicles characterized by high surface area and identical microstructure to their parent cubic aggregates [6].

The potential of cubosomes in drug delivery lies not only in their unique nanostructure but also in their ability to offer high solubilization of therapeutic agents. The self-assembly of amphiphilic molecules, a key component of cubosomes, under specific conditions allows the formation of highly organized structures, making them a compelling choice for drug delivery systems [5]. This comprehensive introduction will delve into the intricate details of cubosomes, exploring their formation, nano structural characteristics, and their role in drug delivery, including mechanisms and release patterns.

Formation and Nanostructure of Cubosomes: Unraveling the Intricacies

Cubosomes owe their existence to the meticulous interplay of lipids and water, giving rise to the distinctive bicontinuous cubic liquid crystalline phase structures. Larsson's groundbreaking work unveiled that cubosomes can be formed from bulk non-dispersed phases and, upon dispersion, manifest as submicron particles with an identical internal nanostructure [3]. The highly twisted lipid bilayer and two congruent, non-intersecting water channels define the nanostructure of cubosomes, endowing them with unique hydrophobic and hydrophilic domains.

The formation of cubosomes is a dynamic process that involves the dispersion of liquid crystalline cubic aggregates in aqueous media. This dispersion results in the creation of nanovesicles characterized by a large surface area and a microstructure mirroring that of their parent cubic aggregates [6]. The amphiphilic nature of the lipids used in cubosome formulations plays a pivotal role in the self-assembly process, facilitating the creation of these intricate nanostructures.

Understanding the nano structural intricacies of cubosomes is crucial for appreciating their potential in drug delivery. The bicontinuous cubic phase structures provide an ideal environment for encapsulating a variety of therapeutic agents, from hydrophobic to hydrophilic compounds. This versatility stems from the unique arrangement of the lipid bilayer and water channels, allowing cubosomes to accommodate molecules with diverse physicochemical properties.

Cubosomes in Drug Delivery: Harnessing Nano structural Advantages

The application of cubosomes in drug delivery heralds a new era of precision and efficiency in therapeutic interventions. The distinct advantages of cubosomes lie in their ability to solubilize active pharmaceutical ingredients (APIs) with varying physicochemical properties. The amphiphilic nature of the lipids in cubosomes allows for the creation of well-defined nanostructures through self-assembly, providing an organized and tailored environment for drug encapsulation.

One of the key features that make cubosomes appealing in drug delivery is their potential for sustained release of therapeutics. The nanostructure, akin to the parent phase, comprises a highly twisted lipid bilayer and two congruent, non-intersecting water channels. This intricate arrangement not only facilitates high drug loading due to the large surface area but also contributes to sustained release kinetics. The bicontinuous nature of the cubic phase allows for optimal drug encapsulation, ensuring efficient utilization of the available surface area and promoting improved bioavailability.

Cubosomes, with their unique characteristics, serve as nanocarriers that can navigate the complexities of biological systems. The liquid crystalline nature of cubosomes enhances their adaptability to physiological conditions, making them well-suited for interacting with biological membranes and cellular structures. This attribute is crucial for ensuring targeted drug delivery, where therapeutic agents can be directed to specific tissues or cells, enhancing efficacy while minimizing off-target effects.

Amphiphilic Molecules and Cubosomes: A Symbiotic Relationship in Drug Delivery

Amphiphilic molecules, a cornerstone of cubosome formulation, play a pivotal role in the self-assembly process that gives rise to the unique nanostructures. The ability of these molecules to spontaneously organize under specific conditions is harnessed to create well-defined cubic liquid crystalline phases. This self-assembly phenomenon is particularly advantageous in drug delivery systems, where the organized structures formed by amphiphilic molecules contribute to the stability and functionality of cubosomes.

The amphiphilic nature of the lipids in cubosomes allows for the creation of organized structures through self-assembly, providing an environment conducive to drug encapsulation. This self-assembly ability is driven by the hydrophobic and hydrophilic characteristics of the lipid molecules, which arrange themselves to minimize exposure to water while maximizing interactions with lipid tails or other hydrophobic moieties. The resulting organized structures, such as the bicontinuous cubic phase of cubosomes, offer a tailored and stable environment for drug loading and delivery.

Tailoring Drug Release Patterns for Optimal Therapeutic Outcomes

The release pattern of drugs from delivery systems is a critical factor influencing therapeutic efficacy and patient compliance. Cubosomes, with their unique nanostructure and bicontinuous cubic liquid crystalline phase, offer a platform that allows for precise control over drug release kinetics.

The bicontinuous cubic phase structure of cubosomes, characterized by a highly twisted lipid bilayer and two congruent, non-intersecting water channels, imparts distinct advantages to their drug release capabilities. The three-dimensional honeycombed arrangement provides a large surface area for drug loading, allowing for efficient encapsulation of a variety of therapeutic agents. This high surface area, coupled with the bicontinuous nature of the cubic phase, facilitates sustained and controlled drug release.

The sustained release kinetics of cubosomes can be attributed to the unique properties of their nanostructure. The hydrophobic and hydrophilic domains, along with the non-intersecting water channels, create a complex environment that influences the diffusion and release of drugs. As a result, cubosomes can be tailored to release drugs over extended periods, contributing to prolonged therapeutic effects and potentially reducing the frequency of drug administration.

Advantages

1. High solubilization capacity for diverse physicochemical properties of therapeutic agents.
2. Unique nanostructure with a bicontinuous cubic liquid crystalline phase.
3. Potential for sustained and controlled drug release kinetics.
4. Versatile drug delivery platform due to amphiphilic lipid composition.

5. Large surface area for efficient drug loading.

6. Tailored for targeted drug delivery with adaptability to physiological conditions.

7. Liquid crystalline nature enhances interactions with biological membranes.

8. Self-assembly ability of amphiphilic molecules contributes to stability.

9. Honeycombed architecture allows for optimal drug encapsulation.

10. Offers a promising avenue for precise and efficient therapeutic interventions.

Disadvantages

1. Due to presence of large amounts of water inside cubosomes there is low entrapment of water- soluble drugs.
2. Because of the high viscosity the large-scale production is sometimes difficult.
3. Large scale production is difficult for sometimes because of high viscosity.[2]
4. Complex manufacturing processes may pose challenges for large-scale production.
5. Limited stability over extended storage periods.
6. Potential issues with reproducibility in formulation due to sensitivity to conditions.
7. Variability in drug release patterns can be challenging to control.
8. Limited understanding of long-term safety implications.
9. High dependence on specific lipid compositions for optimal performance.
10. Challenges in achieving uniform particle size distribution.
11. Potential interactions with biological components may affect biocompatibility.
12. Limited commercial availability and higher production costs compared to conventional drug delivery systems.
13. Regulatory approval hurdles due to the relatively recent emergence of cubosomes in pharmaceutical research.

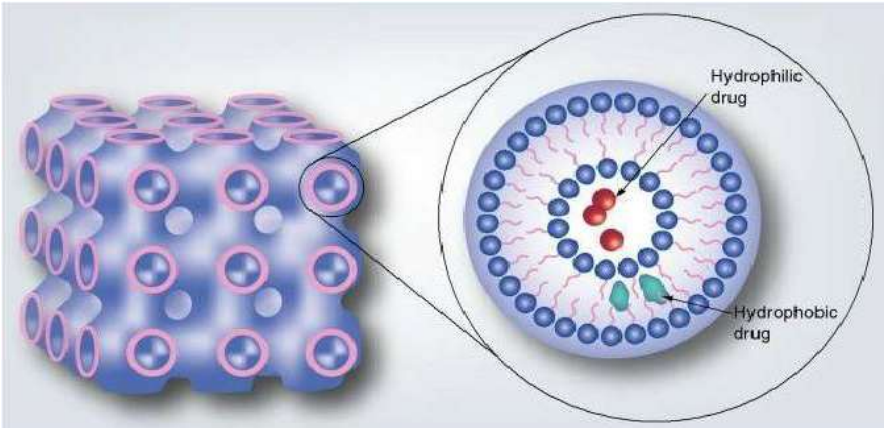

Fig. Cubosomes with bilayer structure

Materials used in cubosomes formation:

Natural lipids, cationic and non-ionic surfactants, and polymer systems all contain bicontinuous cubic phases. The monoglyceride monoolein is the lipid that is most frequently employed to create bicontinuous cubic phases; it spontaneously forms these phases when water is added, is comparatively insoluble, and is resistant to temperature variations. Monoolein is the primary precursor to cubosome development. A mixture of glycerides containing oleic acid and other fatty acids, primarily monooleate, is known as monoolein or glyceryl monooleate. There are two ways to obtain monoolein: as a mixed glyceride form or as distilled monoolein. Due to its high purity, distilled monoolein is favored for pharmaceutical purposes. Monoolein naturally appears as a waxy yellow paste with a distinctive odor.

It expands when submerged in water, forming a number of lyotropic liquid crystalline formations. Monoolein is a substance that is nontoxic, biodegradable, and biocompatible and is categorized as GRAS (generally regarded as safe). It is also present in non-parenteral medications that are approved in the UK and the FDA's list of inactive components. Monoolein exhibits the mesomorphic phase, which is crucial for better understanding the lipid's potential for use in pharmaceuticals.[1][5]

When exposed to water, monoglycerides typically display several phase behaviors. Poloxamer 407 is a surfactant that is used to make cubosomes and is present in concentrations between 0% and 20% w/w with regard to the disperse phase. According to the total weight of the dispersion, the concentration of the monoglyceride/surfactant mixture typically ranges between 2.5% and 10% w/w.

METHOD OF PREPARATION:

The ability to produce nanostructured aqueous dispersions with homogeneous particle size is a desirable and essential goal for many pharmaceutical applications. Cubosomes, nanostructured particles of bicontinuous cubic liquid crystalline phase, are formulated easily by a hydrating mixture of glyceryl-monooleate and poloxamer 407. The cubic phase produces colloidal and thermodynamically stable particulate dispersions. Cubosomes have many benefits, such as high drug encapsulating and loading ability of hydrophilic and hydrophobic active pharmaceutical ingredients (APIs), simple preparation techniques, lipids biodegradability, and both sustained and targeted release of drugs.

Cubosome nanoparticle production can be done in two different ways: top-down and bottom-up.[5]

TOP-DOWN APPROACH:

Introduction to Top-Down Nanofabrication:

Top-down nanofabrication is a cutting-edge approach in the field of nanotechnology that involves the creation of nanostructures by breaking down larger materials into smaller components. In this methodology, the starting material is progressively reduced in size through various mechanical, chemical, or physical processes, ultimately reaching the nanoscale. This approach enables precise control over the dimensions, shapes, and properties of the resulting nanostructures, making it a powerful tool for a wide range of applications in materials science, electronics, medicine, and beyond.

The fundamental principle of top-down nanofabrication lies in the controlled manipulation of bulk materials to obtain nanoscale entities. Unlike bottom-up approaches, where nanostructures are built from individual atoms or molecules, top-down methods leverage existing materials and utilize techniques that impose structure and functionality on a larger scale, subsequently refining them to nanoscale dimensions.

Top-down nanofabrication techniques encompass a variety of methodologies, each with its unique advantages and applications. Examples include high-pressure homogenization, ultrasonication, and microfluidics. These methods are employed in diverse fields, ranging from pharmaceuticals to electronics, enabling the production of nanoparticles, nano sensors, and nanodevices with tailored properties and functionalities.

As technology advances, the demand for smaller, more efficient devices has grown, driving the exploration and development of top-down nanofabrication techniques. The ability to engineer materials at the nanoscale opens up new possibilities for creating novel materials and devices with enhanced properties, leading to breakthroughs in fields such as nanoelectronics, nanomedicine, and nanomaterials research.

In summary, top-down nanofabrication represents a crucial paradigm in nanotechnology, offering a powerful means to engineer materials and devices at the nanoscale by starting from larger structures. The precision and versatility of top-down approaches make them integral to the advancement of nanoscience and the realization of innovative technologies with broad-ranging applications.

1.Top-Down Approaches:

1.1 High-Pressure Homogenization:

High-pressure homogenization is a top-down technique widely used for the fabrication of nanoparticles and nanosuspensions. In this method, a substance is subjected to high pressure and forced through a narrow gap, leading to the reduction of particle size. The process involves two main steps: first, a pre-emulsion is formed, and then it is subjected to high-pressure homogenization. This method is particularly effective for the production of pharmaceuticals, food products, and various nanomaterials.

1.2 Ultrasonication:

Ultrasonication involves the use of ultrasonic waves to break down larger particles into smaller ones. This technique is employed in various fields, including nanotechnology, chemistry, and material science. The ultrasonic waves create high-frequency pressure waves, leading to the formation of cavitation bubbles. When these bubbles collapse, they generate intense local heating and pressure, resulting in the breakup of particles into nanoscale dimensions.

1.3 Microfluidics:

Microfluidics is a top-down approach that involves the manipulation of fluids in microscale channels. In nanoparticle fabrication, microfluidic devices can be designed to precisely control the mixing of reagents and the formation of nanoparticles. This method offers advantages such as uniform particle size distribution, high throughput, and the ability to produce complex structures. Microfluidics is widely used in the synthesis of drug delivery systems, sensors, and imaging agents.

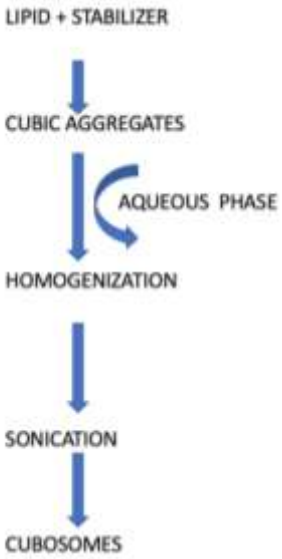

Fig. Flow chart of Top-Down Approach

2. BOTTOM-UP APPROACH

Cubosomes can be produced using an alternative method at room temperature by crystallizing from precursors. This method is known as the liquid precursor or solvent dilution method. It involves the dispersion of a mixture comprising the liquid-crystal-forming lipid, the polymer and a hydrotrope in excess water with minimal energy input to form discrete nanoparticles. The main role of the hydrotrope is creating the liquid precursors by dissolving the lipids and prevention of the formation of a viscous liquid crystal phase at high concentration. In comparison between the two main approaches used for producing cubosomes, the dilution-based approach has some outstanding advantages over the top-down approach.

First, it needs less energy input because of avoiding the laborious fragmentation; second, it allows working with temperature-sensitive materials; third, because of the unique formation mechanism of cubosomes, this approach is much more efficient in generating small particles; fourth, the resulting cubosomes show long-term stability, which might be attributed to the homogenous dispersion of stabilizers onto the surface of nanostructured particles; fifth, the use of hydrotrope simplifies the preparation process while producing cubosomes possessing similar or even better properties than those fabricated by the top-down approach; and, finally, the bottom-up approach is more qualified for scaleup to commercial batches. Nevertheless, it should be noted that this dilution-based method is a pathway by charting trajectories on the ternary phase diagram including lipid, water and hydrotrope, which entails full phase behaviour knowledge. Therefore, the extent of dilution is a crucial factor and must be controlled precisely.[5]

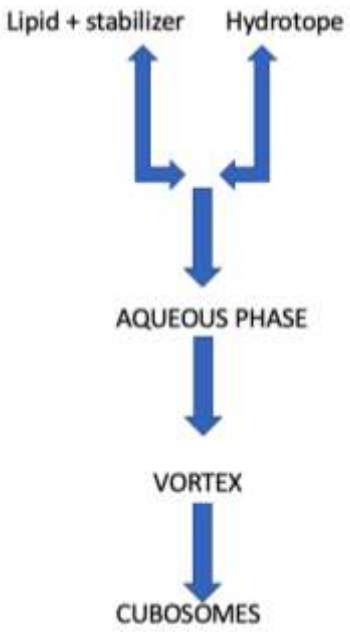

Fig. Flow of Bottom-Up approach

2.1 Spontaneous Emulsification:

Spontaneous emulsification is a bottom-up method that relies on the self-assembly of amphiphilic molecules. These molecules spontaneously organize at the interface between immiscible liquids, leading to the formation of nanoscale droplets. This technique is commonly used in the synthesis of nanocarriers for drug delivery. The advantages include simplicity, scalability, and the ability to control particle size through formulation parameters.

2.2 Liquid Crystal Templating:

Liquid crystal templating is a bottom-up strategy where liquid crystals act as templates for the formation of nanostructured materials. By controlling the alignment and organization of liquid crystals, it is possible to create well-defined nano porous structures. This method is employed in various applications, such as the fabrication of photonic crystals, sensors, and membranes.

2.3 Solvent Injection:

Solvent injection is a bottom-up technique used for the preparation of nanoparticles from a polymer or lipid solution. In this method, a polymer or lipid solution is injected into a non-solvent, leading to the precipitation of nanoparticles. The solvent extraction process results in the formation of nanocarriers with controlled size and morphology. Solvent injection is widely applied in drug delivery systems and the synthesis of nanomaterials for biomedical applications.

3 Hybrid Approaches:

3.1 Combining Top-Down and Bottom-Up Strategies:

Hybrid approaches involve the combination of top-down and bottom-up strategies to achieve precise control over nanoparticle properties. This integration allows for the synthesis of complex nanostructures with improved functionality. For example, combining high-pressure homogenization with self-assembly techniques can result in multifunctional nanoparticles with enhanced drug delivery capabilities.

3.2 Advantages and Limitations of Hybrid Approaches:

The advantages of hybrid approaches include the ability to tailor nanoparticles with specific properties, improved reproducibility, and enhanced control over size and morphology. However, challenges may arise in terms of scalability, process optimization, and potential compatibility issues between different fabrication techniques.

In conclusion, the methods mentioned above showcase the diversity of approaches available for nanoparticle fabrication. Researchers choose these techniques based on the specific requirements of their applications, considering factors such as particle size, morphology, and the intended use of the

nanoparticles. Each method has its unique advantages and limitations, contributing to the broader landscape of nanotechnology and its applications in various industries.

Two different methods for the fabrication of drug-loaded dispersions using a combination of glyceryl monooleate (GMO) and poloxamer 407 (P407). These methods aim to create optically isotropic cubic gels for drug delivery applications.

1. **Fabrication method**

GMO/p407 cubic gel GMO 5% and P407 1.0% were melted at 60°C in hot water bath and add the required amount of drug and stir continuously till dissolve. Deionized water is added drop by drop and vortex is set to the homogenisation. It kept up to 48 hrs at room temperature the optically isotropic cubic gel is formed and disturbed by mechanical stirring crude dispersion was subsequently fragmented by sonicator probe having the energy 200W under cool temperature at the 20°C in water bath for the 20 min.

2. **Emulsification method:**

In this method the GMO and P407 are put in to the water and it followed the ultrasonication the 5% GMO and1% P407and 5% ethanol in 89% water are taken GMO and P407 are melted at the 60°C and mixed the ethanolic solution was added to the melting. The resultant mixture is added drop wise to deionized water preheated at the 70°C, it ultrasonicated at maximum power 130kW for 50min at the same temperature the disperse solution are kept in to the ambient temperature and protected from light.[1][2]

EVALUATION OF CUBOSOMES

SURFACE MORPHOLOGY

The morphology of the prepared cubosomes was analyzed for surface characteristics using a scanning electron microscope (SEM). To visualize the cubosomes, a 10 µl sample was evenly distributed on glass slide then left to dry at temperature which is normal i.e., room. After applying a gold coating with a Polaron E5100 gold sputter coater, the morphology was examined using a Philips 505 electron microscope with an accelerating voltage of 20 kV to confirm the cuboidal structure.

PARTICLE SIZE, POLYDISPERSITY INDEX AND ZETA POTENTIAL

The dynamic light scattering technique with a Malvern zeta sizer was employed to determine the particle size, zeta potential and polydispersity index (PDI) of cubosomes. Samples were appropriately diluted in distilled water and measured at a temperature of 25ºC. Zeta potential serves as an indicator of the repulsion strength between similarly charged particles in a dispersion system, playing a crucial role in dispersion stability. The zeta potential values of cubosomal dispersions were analyzed using the zeta sizer, and these values fell within the standard range. The results indicate that the particles carry a neutral charge, attributed to the use of poloxamer 407 as a stabilizer and glyceryl mono oleate (GMO) in the solution. The zeta potential of the formulation serves as a predictive measure for the stability of cubosomes.

ENTRAPMENT EFFICIENCY

To assess the entrapment efficiency, the cubosomal dispersions underwent centrifugation at 5000 rpm for 20 minutes. The resultant solution was separated, and the supernatant liquid was extracted. After proper dilution, the collected supernatant was quantified using a UV-visible spectrophotometer at 214 nm, referencing it against phosphate buffer (pH 7.4). The percentage of encapsulation efficiency (%EE) was calculated using the following equation.

$$\% \text{ EE} = \frac{\text{Total drug- Free drug}}{\text{Total drug}} \times 100$$

DRUG CONTENT

To determine the drug content in the cubosomal formulation, the formulation was blended with methanol and subjected to sonication for 10 minutes to achieve a clear solution. The resulting solution was then filtered, and the filtrate was examined for drug content using UV analysis at the wavelength maximum of 214 nm.

$$\text{Drug content} = \frac{\text{Actual yield}}{\text{Theoretical yield}} \text{X } 100$$

IN -VITRO RELEASE STUDIES

The release study utilized a dialysis membrane, where the cubosomal formulation was placed within the membrane, and the ends were sealed with clamps. This assembly was then suspended in a beaker containing phosphate buffer at pH 7.4. Samples were withdrawn at predetermined intervals (1, 2, 4, 6, 8, 10, 12, and 24 hours), and an equivalent amount of buffer solution was promptly replenished to maintain sink conditions. UV Spectrophotometer analysis at 214 nm was conducted on the withdrawn samples. The results were used to plot a graph with time on the X-axis and % cumulative drug release on the Y-axis.

DRUG KINETICS

The study analyzed the release of a substance over time and applied various kinetic models to better understand the release process. The models used included the first-order model (equation 1) which presumes constant proportion of the substance is released over time, the zero-order model (equation 2), which assumes a constant amount of the substance is released over time, the Higuchi model (equation 3), which assumes the release rate decreases as the substance diffuses through a matrix, and the Korsemeyer-Peppas model (equation 4), which accounts for both diffusion and erosion of the substance matrix.

$$\ln\left(\frac{M^0}{M_t}\right)_1 = k\,t \quad \text{---- equation 1}$$

$$M_0 - M_t = K_0\,t \quad \text{------equation 2}$$

$$M_t = K\sqrt{t} \quad \text{----------equation 3}$$

$$\frac{M_t}{M_{oe}} = K\,t^n \quad \text{----------equation 4}$$

In this context, W_o and W_T represent the initial and time-dependent weights of the drug, respectively. The variables M_o, M_t, and $M\infty$ denote the drug amount at the start (time zero), dissolved at a specific time (t), and at infinite time, respectively. The symbols k1, k0, k$\sqrt{2}$, and kt n stand for the release kinetic constants derived from the linear plots corresponding to first order, zero order, Higuchi model, and Korsmeyer-Peppas, respectively.

Applications

1. In cancer therapy

Anticancer drugs have been successfully encapsulated in cubosomes and characterized physicochemical properties. The unique structure of this promising nano carrier suggests its application in melanoma therapy. In order to specifically target nano medicines to tumours, different approaches have been predicted, with passive and active targeting of cancer cells having been shown to be valid approaches in preclinical and clinical studies.

2. Oral drug delivery

Cubosomes direct the differing challenges in oral delivery of numerous compounds including poor aqueous solubility, poor absorption, and large molecular size. In an application of large proteins have been encapsulated for local activity in the gastrointestinal tract. Cubosomes technology provides drug release at different absorption sites, for example in the ascending or descending colon, which is important for the drugs that have narrow absorption window.

3. Intravenous drug delivery systems

Lipid nanoparticles comprising interior liquid crystal structures of curved lipid membranes are used to solubilize encapsulate and deliver medications to disease areas within the body. Compare to emulsions and liposomes the cubosomes nanoparticle shows increased payloads of peptides, proteins and many insoluble small molecules, and are perfect carriers for injection.

4. Topical drug delivery systems

Cubosomes are more bio adhesive by nature, making it simple to use them for topical and mucosal medication delivery. Utilizing the special qualities of liquid crystal and liquid crystal nanoparticle technology forms the foundation of topical delivery systems. In situ generating bio adhesive liquid crystal systems that provide controlled and efficient drug administration to mucosal surfaces like buccal, ocular, and vaginal surfaces make topical drug delivery systems unique.

5. Drug delivery vehicle: Drug delivery vehicle is a common application for such new materials. The research in association with cosmetic companies like ponds and Lakme are trying for the use of cubosome particles as oil-in-water emulsion stabilizers and pollutant absorbents in cosmetics.

6. Controlled or sustained release behaviour

Numerous medications with various physicochemical characteristics have been added to cubosomes, and their sustained drug release behaviour has also been investigated. Cubosome residual particles were responsible for the cubosomes' sustained behaviour. It is possible to suggest using monoglyceride-based cubosomes topically, such as through mucosal or percutaneous administration.

7. In treatment of viral diseases

Monoglycerides' microbicidal characteristics could be exploited to develop intravaginal treatments for sexually transmitted diseases brought on by bacteria like Chlamydia trachomatis and Neisseria gonorrhoeae and viruses like HSV and HIV.

8.Ocular applications

The use of cubosomes in the delivery of ocular drugs has been the subject of numerous recent researches. Utilizing their advantages of biodegradability, the ability to encapsulate all three types of therapeutic molecules as hydrophilic, hydrophobic, and amphiphilic, and their ability to produce bioactive agents with targeted release and controlled release. They are discovered to increase the ocular bioavailability of the loaded drugs because they have a prolonged residence time at the corneal surface and are endowed with mucoadhesive qualities as a result of the presence of GMO, which increases corneal permeability and, as a result, increases the ocular bioavailability of the loaded drugs [49]. Cubosomes were investigated as topical ocular medication delivery systems, and interesting findings were discovered. Results of an in vitro experiment demonstrating the penetration of dexamethasone-loaded cubosomes into excised rabbit corneas.

9.Dermatological applications

In transdermal drug delivery, the stratum corneum which is highly organized outer most layer of skin, represents a strong barrier for skin penetration of topically applied drugs. However, cubosomes with their unique structure and properties provide a promising vehicle for transdermal drug delivery. Because of the bio adhesive properties of cubosomes to the stratum corneum as a function of GMO, they can be effectively used in topical and mucosal drug delivery. Recently there are several dermatological applications of cubosomes. An important dermatological application is vaccination through transcutaneous (TCI) immunization. However, microneedles (MNs) and cubosomes have been effectively used as a synergistic approach for the delivery of vaccines through the skin. Results showed that the use of MNs enhances the permeation of the aqueous peptide mixture through the skin layers and cubosomes formulated peptide showed longer retention within the skin. Consequently, the use of combined approaches of both MNs and cubosomes were found to be an efficient system for local delivery of antigen to the targeted cells in the skin.

10.Intranasal applications

injection of cubosomes through the nose is the system of medicinal drug delivery directly from the nose to the brain, avoiding the brain barrier (BBB) has made treating illnesses of the central nervous system (CNS) non-invasive and successful. A methodology for surface engineering PEGylated cubosomes with functional odorranalectin molecules was created by Wu et al. [112]. Using coumarin as a marker, the nose-to-brain delivery characteristic of odorranalectin cubosomes was investigated. Its relative absorption was roughly 3.46 times higher in the brain when compared to untreated cubosomes.

Additionally, Gly14-humanin (S14G-HN) was included in cubosomes and tested for its potential to treat AD. The findings suggested that odorranalectin cubosomes could enhance S14G-effects HN's in AD.

11.INTRA DERMAL

The stratum corneum, the skin's outermost layer, has a highly ordered structure that serves as a barrier, the skin penetration of active molecules delivered transdermally is constrained. Several strategies have been put forth to increase skin permeability, including iontophoresis, chemical modification of the active molecule, and adding a skin permeation enhancer. The key to topical formulations is to raise the thermodynamic activity of the active molecule in the vehicle while lowering it in the skin. This raises the molecule's partition from the vehicle to the skin and lowers the skin's barrier function. Kwon and Kim [104] created GMO-based cubosomes for trapping in an effort to solve the aforementioned issue.[5][4][1]

CONCLUSION

In conclusion, the exploration of cubosomes as a novel drug delivery system reveals a plethora of opportunities and challenges in the realm of pharmaceutical sciences. The distinctive structural characteristics, primarily the bicontinuous cubic phase, set cubosomes apart from conventional drug carriers, offering a versatile platform for encapsulating both hydrophobic and hydrophilic drugs. The variety of fabrication techniques, including top-down, bottom-up, and hybrid approaches, enables researchers to tailor cubosomes to specific drug delivery requirements, providing a level of flexibility crucial for diverse therapeutic applications.

The stability of cubosomes, influenced by lipid composition, temperature, and pH, plays a pivotal role in their performance as drug carriers. Understanding and optimizing these factors are essential for ensuring sustained drug release and prolonged therapeutic effects. The ability to load a wide range of drugs, from chemotherapeutic agents to vaccines, showcases the versatility of cubosomes in addressing various medical needs. The controlled drug release mechanisms, including diffusion-controlled, degradation-controlled, and stimuli-responsive release, further enhance the potential of cubosomes for precision medicine.

Applications of cubosomes in cancer therapy, infectious diseases, and central nervous system disorders illustrate their capacity for targeted drug delivery and imaging. The potential to overcome biological barriers, such as the blood-brain barrier, positions cubosomes as promising candidates for treating

neurodegenerative diseases. The advantages of cubosomes, including enhanced drug stability, improved bioavailability, and targeted delivery, highlight their potential impact on advancing therapeutic outcomes.

However, the journey toward integrating cubosomes into mainstream drug delivery faces significant challenges. Manufacturing complexities, regulatory considerations, and translational hurdles must be addressed to ensure the successful clinical implementation of cubosome-based formulations. Collaboration and interdisciplinary research efforts are crucial for overcoming these challenges and unlocking the full potential of cubosomes in the pharmaceutical landscape.

Looking forward, the future of cubosomes in drug delivery holds great promise. Continued technological advances, such as the integration of nanotechnology and the application of artificial intelligence in formulation design, are expected to address current limitations and propel cubosomes into mainstream pharmaceutical use. Tailoring cubosome properties for specific applications and fostering collaborations between academia, industry, and regulatory bodies will be essential for navigating the complexities of translating cubosome-based formulations from bench to bedside.

In conclusion, cubosomes stand as a beacon of innovation in drug delivery, offering a unique combination of structural versatility, drug-loading capacity, and controlled release mechanisms. As research in this field progresses, cubosomes hold the potential to revolutionize the landscape of drug delivery, providing safer and more effective therapeutic options for a wide range of medical conditions.

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