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CUBOSOMES IN THE TREATMENT OF HERPES SIMPLEX VIRAL INFECTION

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ABSTRACT
Cubosomes are lipid cubic phase nanoparticles that are extremely stable and supported by a polymer-based outer corona. A single lipid bilayer is the basis of lipid cubic phases, which consist of a continuous periodic membrane lattice structure with pores made of two interlaced water channels. Cubosomes often have "honey combed" structures and are thermodynamically stable. The polymer outer corona of cubosomes can be employed for targeting, and they are extremely stable under physiological settings. Cubosome composition can be adjusted to alter pore diameters or add bioactive lipids. Because the cubosome form offers a substantially greater membrane surface area than liposomes, tiny membrane proteins and small medicinal molecules can be put into them. The cubosome can enclose hydrophobic, hydrophilic, and amphiphilic molecules. Herpes simplex virus (HSV) is a viral infection causes a variety of infections including cutaneous and oro-facial herpes, varicella zoster infections, genital herpes, chicken pox, and herpes keratitis. Antiviral medication prescriptions are the current HSV infection treatment. Many medications, including acyclovir, valacyclovir, and famciclovir, are prescribed.

KEYWORDS: Cubosomes, Nano particles, bioactive lipids, Herpes simplex virus.

INTRODUCTION
Cubosomes are discrete, submicron, self-assembled liquid crystalline particles of a specific surfactant that have specific properties that are useful in practical uses. They have an acceptable water to microstructure ratio. The term "Cubosome" was first used by Larsson to describe the cubic molecular crystallography and its resemblance to liposomes. The discovery of cubosomes is a singular event that touches on the study of biological membranes, differential geometry, food science, and digestive processes.[1] Cubosomes are bicontinuous cubic liquid crystalline phase's nanostructured cuboid particles. One of its key advantages is the bicontinuous cubic phase's ability to regulate membrane curvature.[2]

They are created by using an amphiphilic lipid that can self-assemble into cubosomes in water, such as glycerol monooleate (GMO). The cubosomes, which range in size from 100 to 500 nm.[3] The cubosomes are thought to be amphiphilic because they are made up of polar and non-polar polymers, lipids, and surfactants. The hydrophobic effect causes amphiphilic molecules in polar solvents to spontaneously recognise and group into nanometre-sized liquid crystals. Cubosomes' active chemical components are joined to the polar head of the phospholipids through chemical bonds.[4]

ADVANTAGE
- Cubosomes are economic
- Cubosome preparation is simple.
- These are non-irritating, biocompatible, and biodegradable.[5]
- They have a high drug-loading capacity due to their vast inner surface area. They are thermodynamically stable for a longer time.[6]
- They are capable of encasing both hydrophilic and hydrophobic/lipophilic molecules.[7]
- The use of a particular polymer enables the controlled and targeted release of bioactives.
- As a result of less frequent administration, medical expenses are lower overall.
- They reduce the injections adverse effects, which are caused on by the burst release.
- In comparison to liposomes, particle volume and bilayer area have a larger ratio.[8]
- When compared to other common carriers, cubosomes are effective solubilizers (lipid-based). They proved that they could encapsulate drugs that are just barely water soluble. They act as a vehicle for the sensitive drug moiety that has been enzymatically degraded (proteins, peptides). They about 20–100% improve the bioavailability of water-soluble peptides.

- It has enhanced skin permeability and great bioadhesive qualities.[9]

DISADVANTAGE

- There is little trapping of water-soluble medicines in cubosomes because they contain high amounts of water.
- Due to the product's high viscosity, large-scale production may sometimes be challenging.[10]
- Regulated drug delivery is not feasible without the use of a certain polymer. They could leak while being transported or while being stored.
- Particles may increase if they are left alone for a long time. Cubosomes can cause a phase change if the environment changes (dynamics).[11]

Structure Of Cubosome[12]

The cubosomes which has honeycombed structure that separates the two internal aqueous channels and the large interfacial area. Cubosomes are nanostructured particles, which are formed by the self-assembly of amphiphilic or surfactant like molecule with cubic crystallographic symmetry. The cubic phases has a unique property as it possesses a very high solid like viscosity because of their interesting bicontinuous architectures, which encompass two distinct areas of water separated by a controlled bilayer of surfactant. Bicontinuous water and oil channels are formed by amphiphilic molecules, in which bicontinuous refers to the two distinct hydrophilic regions separated by the bilayer (continuous but non intersecting). The interconnectivity of the structure produces a clear viscous gel which has rheology and appearance similar to that of cross-linked polymer hydrogel.

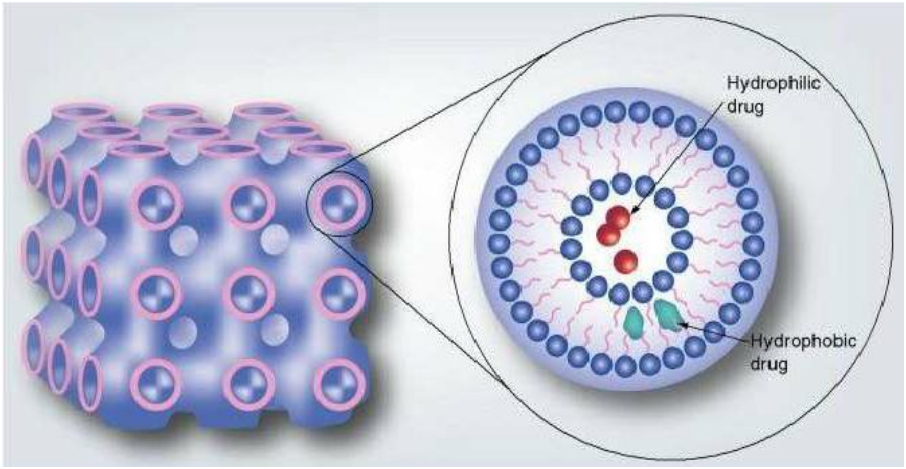

Figure 1: Cubosomes exhibiting its cavernous internal and cubic structure and its membrane compostion with different drug loading modalities.

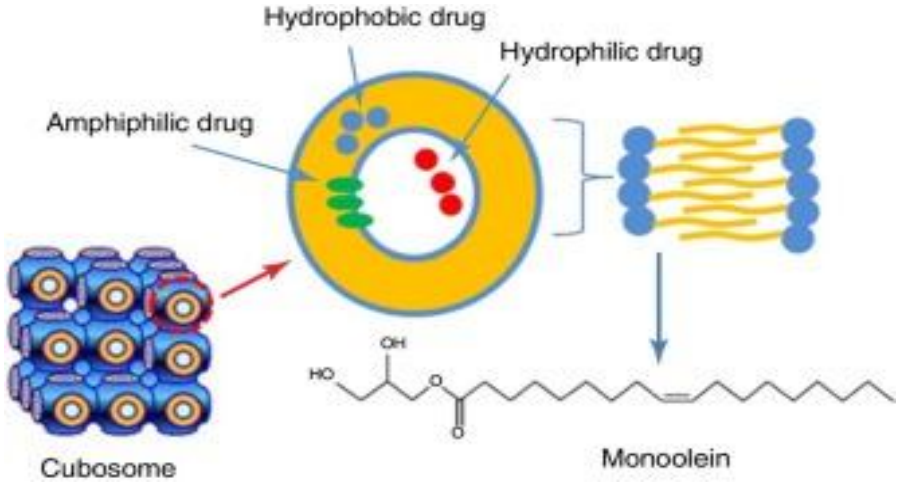

Figure 2: Structure of cubosome separating two internal aqueous channels along with large interfacial area.

Structural Characteristics of Cubosomes

Importance Of Structure[13,14]

Whether in bulk or cubic form, liquid bicontinuous cubic crystals have special qualities that are desirable to the cosmetics industrial sector. Cubosomal personal care products can be used in skin, hair, and other body care products since they are created by mixing biocompatible lipids with an aqueous phase. Cubosomal skin care

solutions are becoming more popular due to the potential interaction between the stratum corneum and the lipids used in cubosomal formulations, which facilitate drug absorption.

As self-assembled cubic crystals, cubosomes are biocompatible and bio adhesive, which makes them perfect for oral administration as shown by the oral administration of insulin-loaded cubosomes for hyperglycemic effect.

Components Of Cubosmes

Glyceryl Mono-Oleate (GMO)[15]

A class of amphiphilic lipids that can be produced from glycerides of oleic acid and other fatty acids primarily consists of GMO. Its head is hydrophilic and its tail is hydrophobic. Additionally, GMOs are used in the food industry to produce cubic lipid phases and as a food emulsifier. GMO is a transparent, colourless, polar unsaturated monoglyceride with a melting point of 35–37 °C and a storage temperature of -20°C. It has an HLB value of 3.

Phytantriol (PHTY)

Phytantriol is a chemical with phytanyl chains that is a good substitute for GMO since they have comparable phase behaviour Both have diverse structures as well as physical and chemical characteristics. A crucial ingredient in the cosmetics industry is phytonatriol. Its chemical name is 3, 7, 11, 15-tetra-methyl-1, 2, 3-hexadecane thiol.[16] Under physiological conditions and temperature, it can form a bicontinuous cubic structure in aqueous environments. Due to its higher chemical stability than monoglycerides due to the absence of an ester group, it has recently attracted greater interest compared to monoglycerides in the biomedical sector.[17] It was found that PHYT-based liquid crystalline matrices could maintain the release of various drug molecules, especially those with hydrophilic qualities; as a result, it is regarded as an excellent sustained drug delivery system.[18]

Stabilizers

Surfactants can provide colloidal stability, which is essential for cubosome formation. The bulk cubic phase is being formed by the clumping of cubosomes. The electrostatic-repulsive barrier that the stabilizer can create between the incoming particles and the cubosomes allows it to prevent undesirable interactions between the hydrophobic domains of the cubosomes as it interacts with particles without harming the cubic structure. The stabilizer is therefore a crucial part of cubosome formation.[19] The most commonly used stabilizing agents are Pluronics, particularly F127 (Poloxamer 407), which is regarded as the "gold standard". Pluronics are self-assembled triblock copolymers made of polypropylene (PPO) and polyethylene oxide (PEO), which are organized in a PEO-PPO-PEO configuration and have the hydrophobic and hydrophilic properties, respectively. Pluronics are water-soluble.[20]

METHOD OF PREPARATION OF CUBOSOMES

1. Top-down approach
2. Bottom-up approach
3. Heat treatment

Top-down approach

It is the most frequently used in research the bulk cubic phase is first generated and then dispersed into Cubosomes nanoparticles by high energy processing. Bulk cubic phases resemble a liquid crystalline structure, whereas cubic phases resemble a transparent stiff gel made of water-swollen crossed linked polymer chains. As there are more oils and surfactants that produce bilayers, the yield stress in the cubic phases rises.[21]

Lipids and stabilisers are combined to create the viscous bulk cubic phase, which is subsequently dispersed into aqueous solution by the application of high energy (such as High-Pressure Homogenization [HPH], sonication, or shearing) to create Lyotropic Liquid Crystal (LLC) nanoparticles. This HPH method most frequently utilized to create LLC nanoparticles. When cubosomes are created by top-down approach, vesicles (distributed nanoparticles of lamellar liquid crystalline phase) or entities that resemble vesicles are always coexist alongside them.[22]

Bottom-up approach

In this procedure, cubosomes are let to form or crystallise from their predecessors. The bottom-up approach first produces the fundamental parts of the nanostructure before assembling them to produce the finished item. Cubosomes can develop and crystallise from molecular-scale progenitors due to this more modern way of cubosome manufacturing. The key element of this process is the hydrotrope, which may convert water-insoluble lipids into liquid precursors. This dilution-based approach produces cubosomes with less energy than the top-down approach. [23] The cubosomes are spontaneously formed by emulsification. Through cryo-TEM, it was discovered that many vesicles and vesicle-like structures coexist with cubosomes, demonstrating that this bottom-up strategy is ineffective at preventing the formation of vesicles.[24]

Heat treatment[25]

Heat treatment just facilitates the transition from noncubic vesicles to well-ordered cubic particles, hence it cannot be considered a complete process for the synthesis of cubosomes in the strictest sense. As a result, a fundamental processing method that incorporates a homogenization and heat-treatment step can be used to create dispersed particles. The experiments reveal that heat treatment results in the production of bigger cubic phases with narrow particle distribution and good colloidal stability while decreasing the small particle size fraction that corresponds to vesicles. It is obvious that the changeover takes place during the heat treatment operation when the full preparation process is taken into account. The transition might have occurred as a result of

a decrease in solubility and stability brought on by a rise in temperature. Because of the surfactant's high solubility at temperatures below cloud point, the particles could exist in a stable form with little fusion. The vesicles quickly fused when the surfactant solubility dropped below a certain threshold.

Cubosomes As Transdermal and Topical Drug Delivery System

Due to their greater bioadhesiveness, cubic phases are excellent for medication delivery as well as topical and mucosal depositions. Topical delivery systems are made possible by the special qualities of liquid crystal (LC) and liquid crystal nanoparticle (LCNP) technologies. Because they create bioadhesive LC systems in situ, topical drug delivery systems are unique in that they provide regulated and efficient drug delivery to mucosal surfaces (buccal, ophthalmic, vaginal, and others). This intriguing method effectively protects irritated and sensitive skin temporarily by forming a thin surface coating at mucosal surfaces made of a liquid crystal matrix, whose nanostructure may be adjusted to create an ideal delivery profile.[26]

Cubosomes have a high potential as mucosal and transdermal drug delivery systems due to their well-defined shape, particle size, and compatibility with human tissues and cells. The medicine contained in cubosomes can easily permeate the epidermis of mucosal and skin because of the similarities between the inner structure of cubosomes and the epithelial cells and the high permeability of cubosomes. This increases drug bioavailability.[27]

Due to its huge body surface area and ability to provide excellent and numerous drug administration sites, administration of drugs through the skin is a promising alternative to traditional drug administration routes. Additionally, the first-pass metabolism is avoided when medications are administered through the skin, increasing their bioavailability and lowering their negative effects. Due to its structure, content, and physicochemical characteristics, the stratum corneum (SC) serves as the body's primary barrier of defence against external agents and serves as the primary impediment to the administration of drugs through the skin. Hence the cubosome based drug delivery system which can able to overcome the limitation.

The application of treatments directly to the skin's surface is referred to as topical medication delivery. The topical distribution of numerous medicinal compounds, including peptides, vitamins, and vaccine components, has found use for lipid-based crystalline nanoparticles.[28]

Drug permeation through stratum corneum

The process by which molecules cross the layers of skin is known as percutaneous or dermal absorption. Three stages make up this process: (1) penetration, which is the access of a substance to one of the skin's layers; (2) permeation, which is the penetration of one layer into another; and (3) reabsorption, which refers to uptake by the circulatory system. The drug enters the SC through passive diffusion after being released from the vehicle through three different pathways: (1) transcellular, (2) intercellular, also known as paracellular, and (3) the appendage, which consists of the eccrine glands, which include the sweat and/or hair follicles.[29]

The medication diffuses through the SC's keratinized dead cells when administered transcellularly. The poor diffusion coefficient of this layer of cells serves as the primary barrier. Drug penetration is thought to be mostly accomplished via the intercellular pathway. The intercellular distances along this path are estimated to be between 19 and 75 nm, and the diffusion path's maximum length is 900 m. The molecular weight and Log P 1-4 of the nonpolar molecules required to permeate the SC must be less than 500 Da. Drugs are displaced through this pathway by successive diffusion with polar group and intercellular lipid alkyl chain partitioning. The appendage pathway is also not thought to be a significant channel for medication penetration.[30]

Herpes Simplex Virus (HSV)

Herpes simplex virus (HSV) commonly causes human infections in the genital area (HSV-1) and orofacial region (HSV-2). A latent viral infection in sensory neurons occurs after a productive viral infection in mucosal epithelial cells, which may cause clinical symptoms. While few or no viral proteins are produced during latent infection, a significant number of viral gene products are expressed during productive infection. However, serious pathology can result from infections of the cornea (keratitis) or central nervous system (encephalitis), and infection of newborns or immunocompromised people can result in severe disseminated disease. Although the common cold sores caused by HSV-1 and the genital herpes lesions caused by HSV-2 are not life-threatening conditions, these infections can cause serious pathology.[31]

There are three antiviral medications that are frequently used to treat symptomatic herpes simplex virus (HSV) infections are acyclovir, valacyclovir hydrochloride, and famciclovir. Immunocompetent patients can typically diagnose HSV infections easily, and all of the medications on the market have a high degree of safety because they are exclusively activated by viral thymidine kinase in virally infected cells.[32] Acyclovir (ACV), in a number of formulations and delivery methods, has been shown to be effective in the management of herpes simplex infection. In immunocompromised patients, ACV (5%) ointment (Zovirax ointment) expedited the healing of herpes simplex viral infection.[33]

Cubosomes In Herpes Simplex Viral Infection Treatment

The topical preparations currently on the market have poor water solubility and restricted skin permeability,

resulting in low bioavailability of the administered drug. In order to create an effective topical formulation, several studies have tried to enhance absorption of the medication. Majority of the HSV infections are treated using oral route however there are various topical preparations are also available which are effective.

CONCLUSION

Cubosomes are nanoparticles, but rather than being solid particles, they are self-assembled liquid crystalline particles that can contain a variety of hydrophilic and lipophilic medications and deliver them in a concentrated and consistent way. It is simple to use top-down and bottom-up methods, as well as ultrasonication method or high-pressure homogenization, to produce cubosomes. Transdermal and topical cubosomes can be developed in order to enhance the permeation and bioavailability of medication. By improving the permeation, the bioavailability of the drug can be increased, thereby can be able to treat various disease condition including the HSV infection. Certain studies have found that transdermal or topical route of cubosomal formulation can be able to overcome the side effects of oral administration. Their use as delivery vehicles primarily offers two key advantages, namely the regulated or prolonged release of loaded actives and the solubilization of medicines with limited water solubility. Numerous drug candidates, proteins, immunological substances, and cosmetics can all make use of cubosomes. The cubosome technology is relatively new, has a high output, and offers numerous research opportunities for creating novel formulations that are both industrially and commercially viable.

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