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Liquid Crystal Nanoparticles (Cubosomes): A Novel Nanoparticulate Drug Delivery System

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ABSTRACT

Cubosomes are nanostructured liquid crystal-like particles, formed from a certain group of amphiphilic lipids in fixed amounts in water and stabilized with a triblock copolymer. Cubosomes are rounded bicontinuous lipid bi-layers, which are structured in three-dimensional structures approaching honeycomb-like structure with different amphiphilic, hydrophilic, and hydrophobic regions. They work as a carrier in drug delivery for a numerous bioactive molecules, for example, synthetics, drugs, peptides, and proteins to protect them from hydrolysis, oxidation, or some other method of degradation. This article gives an impression of introductory work that took developments till drug delivery, cubosomes types, structure, approaches for development, and fundamentally the uses of cubosomes in the formulation from the past in several classes of drugs and pharmaceuticals.

INTRODUCTION

The term Cubosomes was first proposed by Larsson, which reveals the cubic molecular crystallography that is similar to liposomes. Selected lipids, surfactants, and polymer molecules have both polar and non-polar additives, termed as amphiphilic (1, 2). The amphiphilic nature of the molecules unite the hydrophobic nature of the polar solvent that unite into a liquid crystal of nanometer scale. Thus, Cubosomes are bicontinuous cubic liquid segments enclosed with water separated by surfactant-managed bilayers (3-5).

Cubosomes are nanostructured particles of the bicontinuous cubic liquid crystalline phase. Cubosomes are nanoparticles, which are self-assembled liquid crystalline particles of definite surfactants with an appropriate part of water with microstructure and also possess rheology like solid (6, 7). Bulk cubic levels have better viscosity than cubosomal dispersion (8-10). At excessive dilutions, most immersed surfactants that form cubic liquid crystals lose these levels to micelle formation, due to the most efficient water insolubility. Cubosomes are naturally produced employing excessive-electricity dispersion of bulk cubic segment, observed through colloidal stabilization the usage of polymeric surfactants. One application of cubic section liquid crystals is the managed release of decided on water-oil soluble molecules (11-13). The emulsification of cubic lipid phases in water imports in the manufacturing of cubosomes that can be described as nanoparticle disperse systems characterized by excessive biocompatibility and bioadhesivity (14-16).

Cubosomes are composed of lipids, surfactants, and polymer molecules, which have both polar and non-polar additives, termed as amphiphilic. The hydrophobic effect drives amphiphilic molecules in polar solvents to spontaneously self-assembling into a collection of thermodynamically strong liquid crystalline stages with lengths on the nanometer scale (17). Thus, cubosomes are bicontinuous cubic liquid segments surrounding two distinct regions of water separated through surfactant-managed bilayers. Bicontinuous cubic stages are optically isotropic, very viscous, and strong like liquid crystalline substance having cubic crystallographic symmetry. Cubosomes have extraordinary significance in nano-drug formulations (17-21).

Structure of cubosomes

The fundamental structure of cubosomes consists of honeycombed structures isolating the inner aqueous channels alongside the massive interfacial area. Cubosomes are nanoparticles,

greater correctly, nanostructure particles of liquid crystalline levels with cubic crystallographic symmetry formed through the self-meeting of amphiphilic or surfactant like molecules. The cubic levels own a completely excessive strong like viscosity that is a unique property because of their attractive bicontinuous structures, which enclose two wonderful areas of water, separated using a managed bilayer of surfactant application. Amphiphilic molecules from bicontinuous water and oil networks, where bicontinuous refers to two different (continuous, but non-intersecting) hydrophilic regions separated by means of the bilayer. The interconnectedness of the shape consequences in a clear viscous gel similar in appearance and rheology to go-related polymer hydrogels. Structure of cubosomes shown in Figure No. 1. (22)(4, 21, 23, 24).

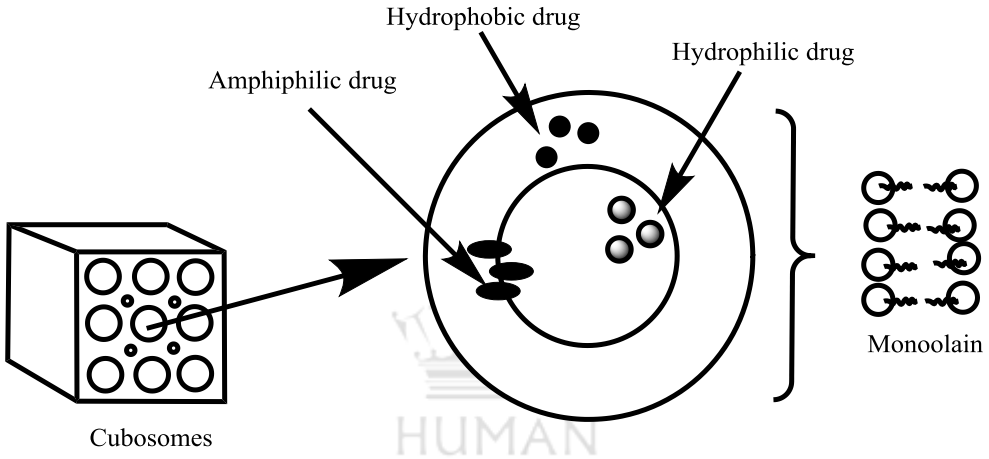

Figure No. 1: Structure of cubosomes

Advantages of cubosomes

1. They may be prepared via an easy approach.

2. High drug payloads because of high inner surface location and cubic crystalline shapes.

3. Cubosomes particles as oil-in-water emulsion stabilizers and pollutant absorbents are applied in cosmetics.

4. Biodegradability of lipids.

5. The controlled release of a solubilized substance is the most popular application of cubosomes. A cubic phase is greater relevant for control release because of its small pore size (five-10nm).

6. The capability of encapsulating hydrophilic, hydrophobic, and amphiphilic materials.

7. Targeted release and controlled release of bioactive agents.

8. Cubosomes deal with the various challenges in oral transport of several promising compounds consisting of poor aqueous solubility, absorption, and massive molecular size(14, 24).

Disadvantages of Cubosomes

1. Due to the presence of huge quantities of water in interior of cubosomes, there's low entrapment of water-soluble drugs.

2. Because of the high viscosity, the big scale production is now and then difficult.

3. Large scale production is hard for now and again because of high viscosity (24, 25).

FORMS OF CUBOSOMES

Three macroscopic types of a cubic segment are typically encountered: precursor, bulk gel, and particulate dispersions (cubosomes). The precursor shape exists as a stable or liquid material that bureaucracy cubic segment in reaction to a stimulus, which includes contact with liquid. Bulk cubic phase gel is an optically isotropic, rigid, solid-like material. The cubic gel in balance through water and can be dispersed into particles called cubosomes, corresponding to the formation of vesicles from a lamellar liquid crystalline material. A current evaluation provides a complete precis of energetic components added via the cubic segment. Despite intense importance in cubosomes applications, it was found no work investigative the practical aspects of large-scale processing and manufacturing of cubosomes (26-30).

Liquid cubosomes precursors

Following the difficulty and cost of high shear dispersion of viscous bulk cubic segment to shape cubosomes, it is ideal to look for much less competitive techniques of manufacture. High-energy tactics being highly-priced and hard to scale-up also proves to be dangerous to thermosensitive elements like proteins. In some product applications, the in situ formation of cubosomes is favoured, along with all through hand washing or mouth rinsing (31, 32). To avoid excessive strength processing and convey them in situ a strong driving pressure exists

ensuing inside the improvement of a liquid phase precursor to cubosomes (33, 34). The Hydrotope dilution method is observed to continuously produce smaller, greater stable cubosomes. In this technique, the particles are designed by using nucleation and growth, as employed in crystallization and precipitation procedures. This is achieved via dissolving the monoolein in a Hydrotope (ethanol) which inhibits liquid crystalline formation. All that is carried out without the requirement for extreme shear, reducing the risk of degrading the cubic liquid crystalline shape (35-37).

Powder cubosomes precursors

Powders composed of dehydrated surfactant coated through polymer are called as powdered cubosomes precursors. Hydration of the precursor powders forms cubosomes with an intermediate particle length of 600 nm, as shown by way of slight scattering and cryo-TEM. A water-soluble non-cohesive starch coating at the waxy lipid inhibits accumulation and allows control of particle size (38). The lipids used to make cubosomes are waxy, sticky solids, rendering them unable to shape small distinct particles. The spray drying method is an inconceivable procedure to provide those particles. Spray drying produces encapsulated particles from an emulsion of liquid droplets or a dispersion of solid particles in a concentrated aqueous polymer solution (27, 39). The nozzle is used for the constant and dispersed phase spraying for the period of making suspension droplets, which can be contacted with a heated, dry air stream flowing inside the different sequences. As a result of this extra water instantly evaporates, leaving dry powder particles composed of the dispersed section encapsulated by a shell of the formerly dissolved polymer (40). Finally, the polymer coating on the powder imparts surface properties to the hydrated cubosomes that can be perfect via a proper selection of the encapsulating polymer. Such powders offer some process and performance benefits to liquid phase hydrotropic cubosomes precursors (3, 26, 27).

MECHANISMS OF DRUG TRANSPORT

Drug transportation throughout the cellular membrane is depending on the character of the activity and composition of the carrier system, the anatomy, and physiology of the skin. Small ions are transported via the hair follicles, pores of skin membranes, the tight junctions without complicated mechanisms. Mechanisms involved in skin membrane transport normally include intra (trans) and inter (para) cellular transports. By employing carriers, drugs may be incorporated either in the center or as a necessary part of the vesicles.

Paracellular diffusion is that the movement of drugs throughout a membrane with the aid of going among, in place of via, cells as shown in Figure No.2. By definition, this technique is solely passive and relies upon pore size, as well as the scale and shape of the xenobiotic. Transcellular diffusion is the movement of a drug across the cellular. When enteric absorption occurs through transcellular diffusion, the drug is exposed to the enzymes in the cell, in addition to any efflux pumps, which might be at the apical area of the membrane. Transcellular diffusion may also be passive, facilitated, or energetic. Transcellular movement, which involves the passage of drugs through cells, is taken into consideration as a maximum common route of drug transport. However, a few drugs are too polar to undergo the lipoid cell wall and they can pass via the paracellular pathway most effectively (41-44).

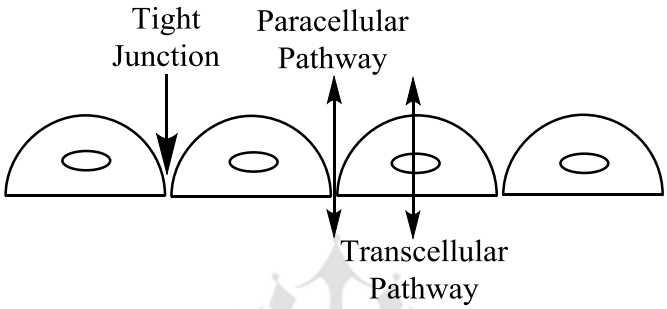

Figure No. 2: Mechanism of drug transport across a biological membrane

COMPONENTS OF CUBOSOMES

Preparation of cubosomes as referred to in the literature is easy that they have been composed of 3 major additives. Amphiphilic lipids, stabilizer, and water. The essential components to discuss amongst are amphiphilic lipids and stabilizers. It is indicated that amphiphilic upon hydration produces cubic liquid crystalline segments. Stabilizers are polymeric materials that protect the reconstruction to the bulk cubic phase. Some of the most studied molecules, which could form lyotropic liquid crystals, are monoglycerides, ethylene oxide amphiphiles, glycolipids, phosphatidylethanolamine amphiphiles, urea amphiphiles, phytantriol, etc (45-47).

Amphiphilic lipids

The most commonly utilized lipids for the preparation of cubosomes as per the literature are glyceryl mono-oleate (GMO) and phytantriol (PHYT) as shown in Figure No.3. GMO is a manufactured compound produced using glycerides of oleic acid and distinctive unsaturated

fats; the primary part is GMO, which goes to the magnificence amphiphilic lipids(48, 49). GMO is a food emulsifier utilized in the food industry is seen to deliver cubic lipid segments in an unusual area. GMO has a hydrophilic head and a hydrophobic tail. Based on Lutton‟s significance monoglycerides with a sequence duration between 12-22. GMOs are biodegradable and biocompatible recognized secure with the aid of GRAS for use within the food industry as an emulsifier (50-53).

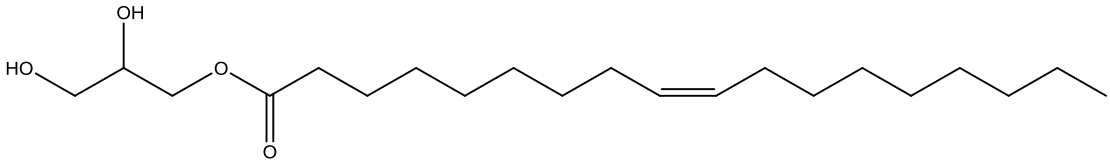

Figure No. 3: Structure of glyceryl mono-oleate

Another known substance that is a great alternative for GMOs that is used to put together cubosomes is phytantriol (PHYT), a molecule that includes phytanyl chain. Phytantriol, 3, 7, 11, 15-tetramethyl-1,2,3-hexadecane thiol ($C_{20}H_{42}O_3$) is a key thing used inside the cosmetic industry. PHYT is a fatty acid-based substance susceptible to esterase-catalyzed hydrolysis and offers a higher structural balance(35). Although the two materials differ in their molecular shape and property, they show similar behaviour with increased water content and temperature (54, 55). The structure of phytantriol is shown in Figure No.4.

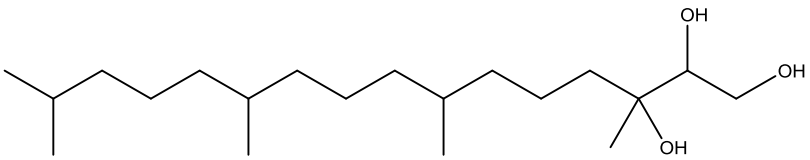

Figure No. 4: Structure of phytantriol

Rizwan et al.,(56) showed the PHYT made dispersion is strong which incorporates hydrophilic additives and keeps the inner Pn3m nanostructure, at the same time as GMO colloidal dispersions display hexosomes that co-exist with Pn3m cubic structure. The purity of the compounds also affects the phase transition(57).

Stabilizers

Surfactants give colloidal stability to formulated cubosomes. Cubosomes with the guide of nature re-mix to the mass cubic phase. Perfect stabilizer for cubosomes prevents ominous

connections between hydrophobic domain however encounters among particles, without inflicting to the cubic structure. This happens due to the electrostatic-repulsive hindrance among the moving toward particles. Consequently, these stabilizers have been viewed as the fundamental added substances of cubosome development. Out of all, the most generally utilized substance to settle cubosomes is the poloxamer 407 (BASF business trademark Pluronic® F127), PEO99-PPO67-PEO99 a tri-square copolymer, with its PPO amounts on both surface or inside the bilayer and PEO chain uncovered to the encompassing water phase were introduced to stabilize the cubosomal dispersion. It stabilizes via taking part in the structure of dispersed particles and manipulates the segment conduct. Usually, poloxamer 407 concentration is carried out at a concentration up to 20% w/w almost about the dispersed segment, while the awareness of the monoglyceride- polymer combination is normally among 2.5 and 10% w/w (58, 59).

Zhai et al. explored the capacity of one, 2-distearoyl-sn-glycerol-3-phosphate-ethanolamine conjugated with PEG (DSPE–PEG) on PHYT-based cubosomes, due to the fact bio-compatibility depends on the selected stabilizers and selected lipid. The cubosomes organized using DSPE–PEG confirmed decreased cytotoxicity (60).

MANUFACTURE OF CUBOSOMES

Methods for manufacture of cubosomes:

Top-down Technique

Bottom-up Technique

Top-down Technique

In the research area, they are the most extensively used methods. It became reported in 1996 through Ljusberg-Wahren. The viscous bulk cubic phase is ready through blending the lipids with stabilizers; through the input of high energy (along with High-Pressure Homogenization (HPH), sonication or shearing) the resultant aggregate is dispersed into an aqueous technique to form Lyotropic Liquid Crystal (LLC) nanoparticles (61, 62). A clean inflexible gel formed via water-swollen cross-linked polymer chains that resembles the bulk cubic phase. In the preparation of LLC nanoparticles, HPH is the most widely used approach. In the top-down technique, cubosomes are prepared and observed to co-exist with vesicles (dispersed

nanoparticles of lamellar liquid crystalline phase) or vesicle-like structures(3, 23, 63, 64). The top down technique is shown in Figure No.5.

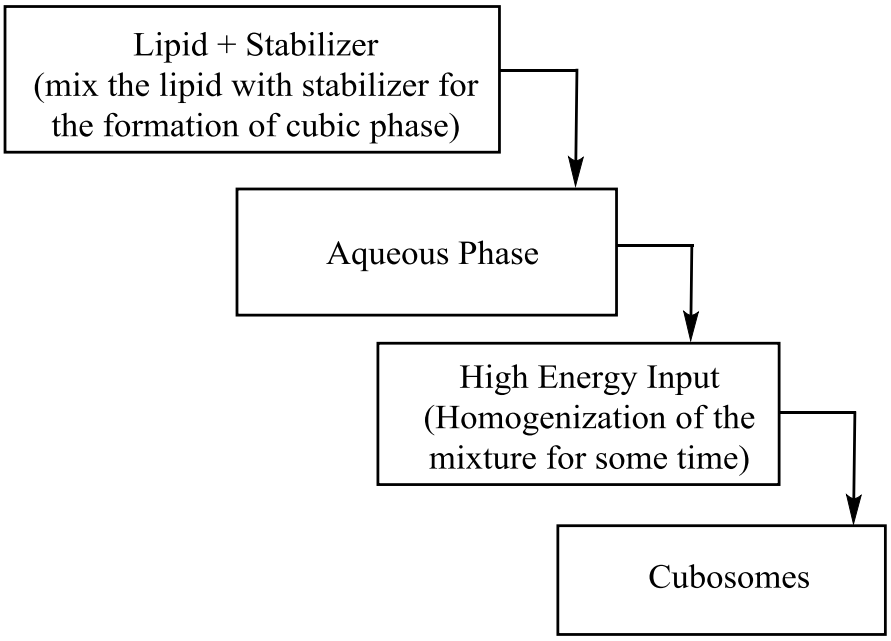

Figure No. 5: Cubosomes by using a top-down technique

Bottom-up technique

In this cubosomes are allowed to form or crystallize from precursors. The arrangement of cubosomes through scattering L2 or inverse micellar phase beads in the water at 80°C, and permit them to gradually cool, slowly drops get takes shape to cubosomes. The cubosomes at room temperature is by means of diluting monoolein ethanol preparation with watery poloxamer 407 solutions. The cubosomes are instantaneously framed with the guide of emulsification. Another strategy is furthermore advanced to give the cubosomes from powdered precursors by spray drying method. Spray dried powders including monoolein coated with starch or dextran results cubosomes on simple hydration. In this cubosomes are permitted to shape or crystallize from precursors(61, 65, 66). The bottom-up method first forms the nanostructure building squares and afterward collects them into the final material. It is a most recent method of cubosomes formation, permitting cubosomes to form and crystalize from precursors at the atomic length scale. The key aspect of this technique is Hydrotope, which could dissolve water-insoluble lipids into liquid precursors. This is a dilution based total technique that produces cubosomes with much less strength input when in comparison to top-down technique as shown in Figure No.6(23, 57, 67).

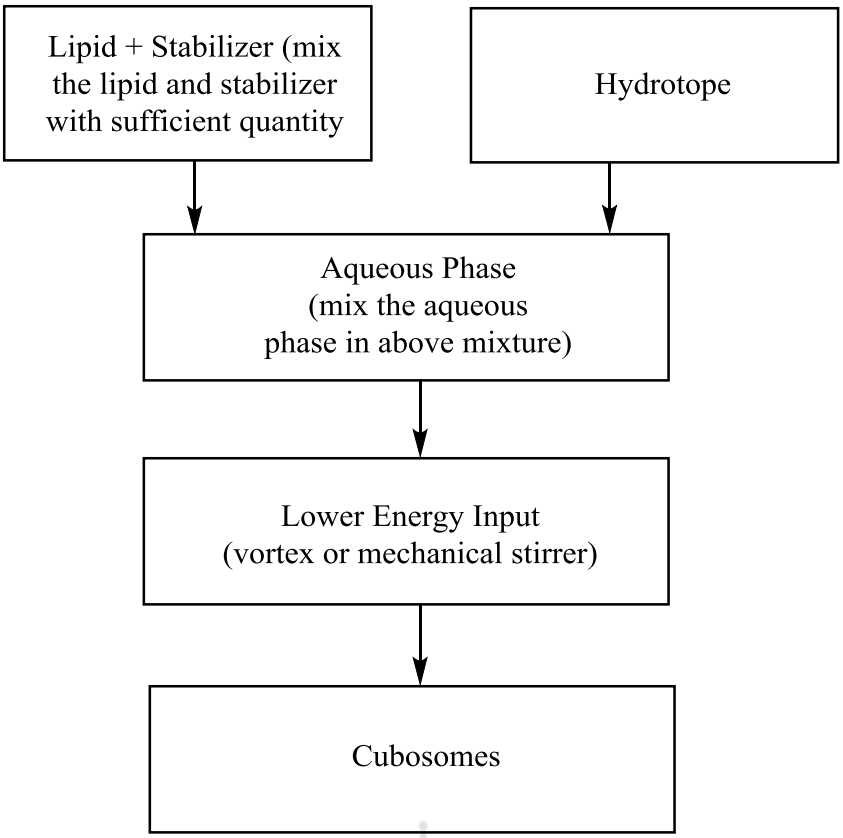

Figure No. 6: Cubosomes by using a bottom-up technique

EVALUATION OF CUBOSOMES

Visual inspection

The cubosomes are visually evaluated for optical appearance (e.g. shade, turbidity, homogeneity, presence of microscopic particles).

The shape of the cubosomes

Transmission electron microscopy may be used to view the form of the cubosomes.

Particle length distribution

Particle length distributions of cubosomes are particularly decided using dynamic laser mild scattering with the use of Zeta sizer (Photon correlation spectroscopy). The sample diluted with an appropriate solvent is adjusted to light scattering depth of approximately 300Hz and measured at 25°C in triplicate. The zeta potential and polydispersity index can be recorded (68-73).

Zeta potential

The degree of zeta potential specifies the degree of electronic repulsion among adjusting, similarly, charged particles. Zeta potential is the main indicator of the stability of the formulation (6, 74).

Entrapment efficiency

The entrapment efficiency of cubosomes could be determined by the use of ultrafiltration methods. In this method, the unentrapped drug concentration is determined, which is subtracted from the total drug added. The amount of drugs is analyzed by using a spectrophotometer (12, 75).

Measurement of drug release

Drug release from cubosomes can be carried out by way of pressure ultrafiltration technique. (22±2)°C (43, 76).

APPLICATION OF CUBOSOMES IN DRUG DELIVERY

Cubosomes for the oral route

Oral drug delivery is one of the conventional routes of administration and most convenient. Cubosomes a novel nano-carrier system with numerous advantages represented the consideration of scientists to plan oral dosage forms (77). Chung et al., (72) prevailing to improve oral ingestion of insulin by GMO-based cubosomes, inadequately water-solvent pills may meet one of an alternate possibility inside the gastrointestinal (GI) tract.YS Tu et al.,(78)detailed cubosomal nano-particles with piperine and curcumin with phytantriol, made into a fluid precursor stabilized out by method of pluronic ® F127 and furthermore Vit. E has seen to have improved bioavailability than the suspension (79, 80).

Cubosomes for the topical route

Drug delivery through the skin is controlled because of the external layer of the pores and skin stratum corneum. Several approaches had been presented to enhance the pores and skin permeation comprehensive of chemical change of the active molecule, applying a skin permeation enhancer and iontophoresis (81, 82). The essential problem in topical formulations is to increase the thermodynamic interest of the active molecule inside the

vehicle at the same time as lowering it inside the skin, which results in increasing the partition of the molecule from vehicle to pores and skin and lowering the barrier function of the pores and skin (2, 83-86).

Sung Kyeong Hong et al.,(87) prepared a warm water extract KIOM-C from plant sources and in comparison to the traditional suspension with cubosomal suspension and concluded that stability and sedimentation price has been improved.

Cubosomes in intravenous route

Intravenous administration has unique consideration to maintain the particle sizes inside the colloidal range, to keep away from problems that would arise from capillary blockage through oversized particles and interaction between the particles and plasma components is significant for the stability of carriers even though the surface modification can probably decrease the interactions of the carrier with blood components, and therefore increase the lifespan inside the blood circulation. Leesajakul et al.,(88) investigated the effects of some plasma components consisting of high-density lipoprotein (HDL), low-density lipoprotein (LDL), and albumin on the integrity and balance of GMO-primarily based cubosomes in addition to the in-vivo behaviour of particles after intravenous injection (35, 89).

Cubosomes in nasal route

Direct nostril-to-mind transport of therapeutics, bypassing the blood-brain barrier (BBB), has provided a non-invasive and effective way in the treatment of central nervous disorder (CNS) problems. Mayuri Ahirrao et al.,(90) studied the delivery of resveratrol focused on the mind in the nasal route with the aid of cubosomes to treat Alzheimer's disease. GMO P407 cubosomes had been made with the help of the probe sonication method. In-vitro drug release showed a controlled release for almost approximately 24 h (42, 91).

Cubosomes for ophthalmic drug delivery

Medications has been directed to the eyes as drops in preferred because of the squinting, tears, nasolacrimal drainage drug removal is normally. PH, the lipophilicity of the medication, and corneal epithelium had been the significant facts that influence the poor bioavailability of the drugs (17, 89, 92). Shun Han et al.,(93)examined cubosomes as an ophthalmic drug transport carrier for flurbiprofen (FB). The cubosomes affirmed low ocular

irritation as assessed by way of the Draize approach and histological assessment. In-vitro corneal penetration demonstrated their capacity of growing the transcorneal saturation of FB. Cubosomes were loaded with the help of dexamethasone (DEX) to expand the pre-ocular retention and ocular bioavailability. The drug incorporated with cubosomes exhibited approximately 3.5 and 1.8 folds increase in assessment with free DEX eye drops (94).

Cubosomes in melanoma (cancer) therapy

Recently few anticancer capsules were effectively encapsulated in cubosomes and characterized physicochemically. The specific shape of this promising nanocarrier suggests it's application in melanoma therapy (6, 92, 95, 96).

FUTURE PROSPECTIVE OF CUBOSOMES

The cubosomes nanoparticles hold promise in the field of drug delivery and sustained drug release, but additional optimization is still necessary, depending on the route of administration, frequency of dosing, and the mode of drug release, before such nanocarriers can truly recognize their therapeutic potential in many diseases (97). They are also attractive nano vehicles for loading and delivery of proteins and peptides but the reported studies are still on a fundamental level. Future development of cubosomes based intravenous nanomedicines should address blood compatibility at the early stages of formulation development. The application of cubosomes for intravenous drug delivery is a determined one; however, these nanocarriers may find faster applications for oral, ocular, and topical delivery of poorly water-soluble drugs, thereby offering an alternative, yet, a cost-effective opportunity in formulation science (98-101).

CONCLUSION

Cubosomes are nanoparticles but instead of the stable particles, cubosomes are self-assembled liquid crystalline particle, they can comprise many hydrophilic and lipophilic drugs and suggests sustained and controlled drug delivery. Two approaches that include top-down and bottom-up procedures may be easily employed to produce cubosomes both via ultrasonication approaches and via excessive stress homogenization. Cubosomes offers increased flexibility for product development and this act as excellent solubilizers, in comparison with conventional lipid or non-lipid carrier. Cubosomes are significant to a vast range of drug candidates, proteins, immune materials, and additionally to cosmetics. Due to

the potential site-specificity, the cubosomal preparations may be widely employed as targeted drug delivery systems for ophthalmic, diabetic, and anticancer therapy. The cubosomes technology is relatively new with high output and would have a wide scope of research in developing new formulations with commercial and industrial viability.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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