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Review Article

Cubosomes: The next generations of drug delivery in nanoparticles form

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ABSTRACT

Self- assembled lipid liquid crystalline nanoparticles, known as cubosomes. Cubosomes are thermodynamically stable and they have a 'honey combed' like appearance. Cubosomes are nanoparticles with proper water-to-microstructure ratios of certain surfactants that have excellent properties. With various drug loading techniques, they show distinct internal cubic structure and composition. They have a greater inner surface area than other carriers, thereby providing the affected cells with more drug molecules and retaining the cubic process, but they have lower viscosity at the same time, thus promoting drug transport. A novel process has been developed for the development of cubic liquid crystalline nanoparticles. Cubosomes have a wide variety of uses in different fields and can be defined by different criteria of assessment. Cubosomes therefore gain more valuable consideration from the pharmaceutical production sector. While no commercial product based on cubosomes is known, most of the research into cubosomes is driven by potential application in drug delivery and material synthesis. Based on the analysis, this study presents cubosomes focusing on their structure, method of preparation, release mechanism, application of cubosomes, advantages and disadvantages.

Keywords: Cubosomes, Cubic phase, Nanoparticles, Lipid, Drugdelivery, Self-assembly.

INTRODUCTION

Recent developments in nanomedicine have resulted in the production of a range of nano particle systems based on hard and soft matter, capable of transporting therapeutic products simultaneously and serving as diagnostic agents[1]. Theranostic nanomedicine is referred to as the latest cross-discipline emerging from these advances. Theranostic nanoparticles are intended for delivery to the site of the disease in order to increase the efficacy of the formulation while

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reducing side effects[1-3]. An effective drug delivery system should also demonstrate a high drug loading capability, a reduction in the quantity of matrix material required, and a controlled drug release to achieve the correct dose at the target. The design of a stimulus-responsive drug carrier is favoured in order to enhance the drug's efficacy. The typical stimuli that are stimulated to deliver the drug to the target site are temperature, pH, light intensity, and magnetic field. It is possible to use pH-responsive drug carriers to treat different kinds of cancer. As the pH of cancer cells is lower than that of healthy cells, they provide the ability to provide selective drug release to targeted tumour cells. As drug carriers for the delivery of therapeutic molecules, new lipid nanostructures with unique properties such as high drug loading capacity and the ability to target a particular location are promising[4-6]. The self-assembly of amphiphilic lipids as a result of the hydrophobic effect among the range of amphiphilic molecules could potentially lead to some well-defined, thermodynamically stable structures such as lamellar (La), hexagonal (HII) and bicontinuous (QII) cubic phases, collectively referred to as lyotropic liquid crystal (LLC) systems, all of which have a sufficient average molecular degree These systems of lyotropic liquid crystal (LLC) all have an acceptable average degree of molecular orientation and structural symmetry[7,8].

This lyotropic liquid crystal (LLC) systems used for drug delivery to cancer cells[4]. The primary commonly obtained nanostructures are: liposomes, cubosomes, hexosomes, by dispersion of these poorly water-soluble structures in aqueous media[9]. These lyotropic liquid crystals are an active research topic particularly in the areas of controlled release and drug delivery. These are biocompatible, digestible, bio-adhesive crystals. Cubosomes have the benefit of increased surface area from these nanostructures and the dispersion of aqueous cubosomes has much lower viscosity than other forms[10]. Three types of cubic phase have traditionally been used as systems for drug delivery: cubic phase gel, precursor cubic phase, and cubosomes. Cubic phase gels have been widely used in the delivery of mucosal, vaginal, periodontal, and transdermal drugs, but the stiffness and viscous nature of cubic phase gels restrict their possible use as a delivery method. The cubic phase precursor was also successfully used on hepatocellular carcinoma for arterial transcatheter chemoembolization. Cubosomes are discrete particles formed from fragmentation and steric stabilisation of inverse bi-continuous cubic phases of lipids that are sub-micron or nanostructured. Cubosomes therefore have a much greater specific surface area and the internal structures and the continuous release property and mechanism of the cubic process as a delivery system remain[11-14]. Cubosomes have traditionally been developed using high-energy input methods and time-consuming procedures. Despite the impressive properties of cubosomes as novel drug carriers[14], the cubosome structure has been well established by cryo-electron microscopy, X-ray, and NMR studies. In this analysis, a thorough examination of cubosomes is briefly outlined with examples of their practical use[15,16].

Cubic phase: The structures that illustrate cubic symmetry are referred to as cubic phases. V. Luzzati F, Husson and later Luzzati et al. first observed the presence of cubic structures, and confirmed the emergence of many liquid crystalline structures during the X-ray scattering analysis of lipid-water systems with concentration and temperature as a feature. Initial cubic phase reports describe them as an optically isotropic 4.5 Å diffuse band usually consisting of a liquid, two sharp and small angles representing the spacing ratio of Braggs of √3: √4. Luzzati suggested the first cubic structure consisting of close-packed spheres filled with fluid spaces[17].

Typically, three forms of cubic phase have been used as drug delivery system: -cubic phase gel, cubic phase precursor, and cubosomes[14]. Biological processes, including plant membranes and models of human digestion, were among the earliest observations of cubosomes and associated structures. The idea came to integrate proteins into cubic phases based on liposome use as model “cells ". The development of cubic-biological interfaces highlights the peculiar bio-adhesive existence of cubosomes, although the mechanism is not yet understood, imaging analysis of tissue bond adhesion, deformation and failure could provide a complex insight into the phenomenon of adhesion and its origin[18,19].

For a number of applications, such as membrane protein crystallisation, drug delivery and biosensor preparation, the cubic step is therefore interesting. Due mainly to its bioadhesion properties, the cubic liquid crystalline form has been assessed for mucosal, periodontal, transdermal and local drug delivery[9,20].

STRUCTURE OF CUBOSOMES:

There are particles called cubosomes when the cubic stage is distributed into small particles. Adjustment of the lipid composition may regulate the internal and structural changes of cubosomes[21]. Honeycombed structures whose size ranges from 10-500 nm in diameter are part of the fundamental structure of Cubosomes. They look like dots, which are structurally slightly spherical. The presence of pore containing aqueous cubic step

in the lipid water system corresponds to each dot[22,23]. In general, the framework preserves the potency of active ingredients such as vitamins and proteins. Water soluble, lipid soluble, and amphiphilic molecules are housed in the structure[24]. The interconnectedness of the structure results in a clear viscous gel similar in appearance and rheology to cross-linked polymer hydrogels[25].

ADVANTAGES[21,43]

- It is economic.
- It is non-toxic and biocompatible.
- Method of preparation is simple.
- It has excellent bio adhesive properties.
- It has skin permeation enhancement.
- For longer time they are thermodynamically stable.
- Capability of encapsulating hydrophilic, hydrophobic and amphiphilic substances.
- Targeted release and controlled release of bioactive agents.
- Due to high internal surface area & cubic crystalline structures there is high drug loading.
- Cubosomes remain stable almost at any dilution level because of the relative insolubility of cubic phase forming lipid in water. So, cubosomes can easily be incorporated into product formulations.
- Increased convenience and compliance (orally, topically and intravenously).
- Decreased health care costs due to simplified handling and less frequent administration.

DISADVANTAGES[37,43]

- Due to presence of large amounts of water inside cubosomes there is low entrapment of water soluble drugs.
- Large scale production is difficult for sometimes because of high viscosity.
- Cubosomes may lead to low drug loading efficiency and Drug leakage in preparation, preservation and transport. In vivo, thus the major problem of their stability acts as a Barrier and thus limiting their use.

STRUCTURAL CHARACTERISTICS OF CUBOSOMES[21,26-28]

- Cubosomal personal care products are prepared by mixing biocompatible lipids and an aqueous process that encourages their use in the development of skin care, hair care and other body care products.
- Due to the potential interaction of stratum corneum and lipids used in cubosomal formulations promoting drug permeation, cubosomal skin care products are becoming important.
- Biocompatible and bioadhesive cubosomes are self-assembled cubic crystals, and are thus well suited for oral administration, which has been shown to be hypoglycemic through oral administration of insulin-loaded cubosomes.
- Phase Transition In aqueous settings, amphiphilic lipids is characteristic of forming self-assembled nanostructures and enabling cosmetic application, delivery of drugs and diagnostics. The phase transition and self-assembly in an aqueous medium of ionic surfactant-phytantriol cubosomal dispersion depends not only on the surfactant lipid mixture concentration, but also on the ionic strength.

STRUCTURAL COMPONENTS OF CUBOSOMES:

Amphiphilic lipids- The most commonly used lipids for the preparation of cubosomes as per the literature are glyceryl mono-oleate (GMO) and phytantriol (PHYT).GMO consists of mixture of the glycerides of oleic acid and other fatty acids, containing mostly of monooleate which fits to the category of amphiphilic lipids with capacity to shape various lyotropic liquid crystals[24]. Increasing the content and temperature of water results in the creation of the cubic process through the reversed micellar and lamellar phases[9]. In addition, GMO is a biocompatible and biodegradable substance listed by the FDA as widely accepted as safe (GRAS), primarily used as an emulsifier in the food industry [24]. Due to the presence of hydroxyl groups in the head area that can form H-bonds with water in an aqueous medium and the hydrocarbon chains in the tail, GMO has hydrophilic and hydrophobic characteristics at the same time. Monoglycerides with hydrocarbon chain lengths between 12 and 22 are extremely likely to form cubic phases, based on Lutton's findings[9]. Phytantriol (PHYT), a molecule containing phytanyl chain, is another known product that is a strong alternative to GMO used to prepare cubosomes[17]. PHYT has an advantage that it shows greater structural stability. The GMO are more prone to ester hydrolysis [24].Phytantriol (PHYT), a molecule that contains phytanyl chain. Phytantriol, 3, 7, 11, 15-tetramethyl-1,2,3-hexadecane thiol ($C_{20}H_{42}O_3$) is a key component used in the cosmetic industry [39]. PHYT is a fatty acid-based substance susceptible to esterase-catalyzed hydrolysis and offers higher structural stability[17]. Although PHYT and GMO have distinct molecular structures, with increasing water content and temperature, these two materials show very similar phase transition behaviours. The PHYT-water system's phase activity was calculated by X-ray diffraction . Micellar, lamellar, Q230 and Q224 at room temperature are reversed in the phase series when the water concentration is increased.

The cubic liquid crystals transition into a reversed hexagonal phase at 44 ºC. The lower purity PHYT showed a phase-transition temperature suppression of up to 15ºC from the cubic to reverse-hexagonal phase[9]. Rizwan et al., showed the PHYT made dispersion are stable which incorporating hydrophilic additives and preserve the internal Pn3m nanostructure, while GMO colloidal dispersions show hexosomes that co-exist with Pn3m cubic structure. The purity of the compounds also affects the phase transition[17].

Stabilizer- With the exception of amphiphilic lipids, a surfactant is necessary to provide the cubosomes with colloidal stability against re-coalescence to the bulk cubic phase[29]. The ideal cubosome stabiliser prevents unfavourable interactions between hydrophobic domains but particle encounters without causing the cubic structure to be disrupted. This happens due to the barrier between the incoming particles that is electrostatic- repulsive. Therefore, the basic components of cubosome formation are known to be these stabilisers [30]. Poloxamer 407 (P407), a tri-block copolymer of PEO-PPO-PEO, is often studied in the preparation of cubosomes with its PPO parts located either on the cubosome surface or inside the bilayer structure, while the PEO chains are exposed to the surrounding water process. Depending on the amount of dispersed process, P407 is typically applied up to a concentration of 20% w/w [31]. Poloxamer 407 (P407), a tri-block copolymer of PEO-PPO-PEO, is often studied in the preparation of cubosomes with its PPO parts located either on the cubosome surface or inside the bilayer structure, while the PEO chains are exposed to the surrounding water process. Depending on the amount of dispersed process, P407 is typically applied up to a concentration of 20% w/w [32]. The stabiliser for cubosomes participates in the structure of the scattered particles and manipulates their phase behaviour [33].

TYPES OF CUBOSOMES[21,22]

Liquid cubosome precursors- The manufacture of cubosomes from liquid phase precursors requires a powerful driving force. Upon liquid precursor dilution, it is possible to create more stable cubosomes of the desired size. The nucleation process allows the creation of particles whose development is seen under the processes of crystallisation and precipitation. This is accomplished by dissolving the monoolein in a hydrotrope that prevents liquid crystalline formation, such as ethanol .Subsequent dilution of this mixture "crystallises" the cubosomes spontaneously or precipitates them. The Quid precursor method allows for faster scale-up of cubosome preparations and prevents the processing of bulk solids and potentially hazardous processes of high energy. In mouth washes, hand washes, where cubosomes can be produced during rinsing, washing, and so on, liquid phase precursors are commonly used.

Powdered Cubosome Precursor- Powdered cubosome precursors are made of polymer-coated dehydrated surfactant. For liquid phase hydrotropic cubosome precursors, such powders give advantages. Cubosomes with an average particle size of 600 nm are formed after reconstitution of powdered precursors with water, in accordance with characterization studies such as light scattering techniques and cryo-transmission electron microscopy (cryo-TEM). To formulate cubosomal powdered precursors, spray drying is an excellent technique. It requires the manufacture of encapsulated particles in emulsion from liquid droplets as well as from dispersed solid particles in aqueous concentrated polymer solution. Waxy, sticky solids are the lipids used to shape cubosomes. The water-soluble coating of non-cohesive starch on the waxy lipid prevents agglomeration and enables particle size regulation.

MATERIAL USED IN CUBOSOMAL PREPARATION:

Bicontinuos cubic phase are found in-

1. Natural lipids
2. Cationic and non-ionic surfactant
3. Polymer systems

Natural lipid: **-** Lipids most widely used to construct bicontinuous cubic phases are

A] Monoglyceride

B] Monoolein

A] Monoglycerides **-** Upon the addition of water, monoglycerides spontaneously form bicontinuous cubic phases, are relatively insoluble (allowing colloidal dispersion of cubosomes) and are resistant to changes in temperature [21].

B] Monoolein **-**Monoolein is the primary precursor of the formation of cubosomes. Monoolein or glyceryl monooleate, which consists primarily of monooleate, is a mixture of oleic acid glycerides and other fatty acids. Monoolein can be obtained in two ways, either in the form of mixed glycerides or as distilled monoolein; due to its high purity, distilled monoolein is favoured for pharmaceutical applications. Monoolein is rendered as a waxy yellow paste with a distinctive odour. In water, it swells, giving rise to many crystalline structures of lyotropic liquid. Monoolein is a GRAS (generally accepted as safe) non-toxic, biodegradable and biocompatible material and is included in the FDA Guide on inactive ingredients and in non-parental medicines approved in the United Kingdom [25].

Monoolein shows the mesomorphic process, which is essential in making the potential pharmaceutical application of the lipid more comprehensible. The presence of a temperature-dependent phase change is a common characteristic of lipids. Below the transition temperature, lipids remain in a gel state. Similar to the fusion of a crystalline solid, an increase in temperature results in the transition to a fluid like state (liquid crystalline state). When the lipid molecule is heated, it transforms directly into an isotropic liquid instead of melting [34].

Surfactant- The surfactants used in the manufacture of cubosomes are poloxamer 407 at concentrations ranging from 0 % to 20 % w/w relative to the dispersion process. In general, the monoglyceride/surfactant mixture concentration varies from 2.5 % to 10 % w/w in relation to the total dispersion weight [21].

Polymer system- In addition to poloxamer, polyvinyl alcohol (PVA) was used as a stabilising agent for the dispersion [34].

METHOD OF PREPARATION OF CUBOSOMES:

Top Down Technique:- It is the most common technique initially recorded by Ljusberg-Wahren in 1996 [35]. In two phases, it is carried out. The first stage is the creation of the viscous bulk cubic process that is accomplished by mixing lipid(s) with stabilizer(s) to circumvent aggregation; the second step is to disperse the resulting from the first step into aqueous medium by applying high energy such as high-pressure homogenization or sonication to eventually shape the cubosomes/nanoparticles [36]. The most widely used technique in the preparation of LLC nanoparticles is homogenization. It is often observed that the cubosomes prepared by top-down approach coexist with vesicles or vesicle structures [37].Worle et al., studied the influence of temperature on the particle size distribution of the cubic phases during homogenization. According to the analysis, it is found that colloidal dispersions can be achieved between 40-60ºC, at a higher temperature at 60ºC it is observed that particle size is lower and the quality of cubic dispersions was weak at a much higher temperature at 80ºC, but at this temporary temperature formation of D kind, cubic structure is observed [38].

Bottom up technique: - With the high energy requirements for the dispersion of cubosomes from the viscous bulk cubic form, the scale-up of the top-down method is found to be very difficult. To solve these problems, Patric T. Spicer et al., in the presence of a hydro trope, studied cubic phase formation. Hydro trope is a molecule that is hydrophilic or hydrophobic but unable to show the action of surfactants (Micelle formation)[17]. This approach involves the creation and then assembly of nanostructure building blocks into the final material. More recently, the cubosome formation technique has been developed to allow cubosomes to form and crystallise from precursors on the scale of molecular length. The formation of cubosomes by dispersion in water at 80 °C of inverse micellar phase droplets, then by slow cooling to allow the droplets to gradually crystallise into cubosomes[39]. By dissolving lipids and preventing the development of a viscous liquid crystal phase at high concentration, the key function of hydrotrope is to build liquid precursors. The dilution-based approach has some excellent advantages over the top-down approach in contrast to the two primary methods used for generating cubosomes. 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[9].

Heat treatment approach :- This method is not an integrated cubosome manufacturing process since it only promotes the transformation from non-cubic vesicles to well-ordered cubic particles consisting of a stage of homogenization and heat treatment as a result of decreasing the small fraction of particle size corresponding to vesicles and forming more cubic phases with narrow particle distribution and strong colloidal stab distribution[37].

Spray drying:- Spray drying approach the dry powder precursor for the preparation of cubosomes was developed due to less flexibility of the liquid precursor for the formation of cubosomes (Spicer et al). Spray drying techniques were used to prepare the monoolein precursor encapsulated with starch and the monoolein precursor encapsulated with dextran. The high proportion of polymer for encapsulation (75 % w/w for starch and 60 % w/w for dextran) reduced the amount of active material loading so that the device was limited to potent drugs, vitamins, flavours or scents. General method of cuboid preparation. Typically, cubosomes are formed at 40 °C by combining monoolein with water. Through the application of mechanical or ultrasonic energy, the resulting cubic liquid crystalline gel is dispersed into particles.

Cubosomes are often formed by high-pressure homogenizers. Finally, the cubosomes are stabilised against flocculation. High energy input aqueousphase [37].

DRUG RELEASE FROM CUBOSOMES:

The drug release mechanism from cubosomes is commonly believed to be based on the drug diffusion theory, and the drug concentration gradient through the cubosomes is the driving force of the diffusion equation[14]. To elucidate the in vitro drug release mechanisms, the pressure ultrafiltration approach and equilibrium dialysis were used to explain that pressure ultrafiltration may have advantages over the colloidal particle-based drug delivery system[21].There are definitely several variables affecting the rate of drug release, such as (1) drug solubility, diffusion coefficient, partition coefficient, etc. (2) cubic crystalline liquid geometry, pore size and distribution, and interface curvature; (3) release medium temperature, pH, and ionic strength[17].

METHOD OF CHARACTERIZATION FOR CUBOSOMES

Visual inspection: For optical appearance, the cubosomes are visually evaluated (e.g. colour, turbidity, homogeneity, presence of macroscopic particles)[25].

Cubosome shape: It is possible to use transmission electron microscopy to view the shape of the cubosome[25].

Particle size analysis: The distribution of particle size (Z-average) and cubosomal dispersion polydispersity index (PDI) was calculated by dynamic light dispersion using the Zeta Sizer Nano-series (Nano ZS, Malvern, Worcestershire, UK). Samples were diluted (100 times) with deionized water and weighed in triplicates at 2570.5 1C[40].

Efficacy of Entrapment: Entrapment preparation and drug loading of cubosomes can be calculated using chromatography of gel permeation or ultra-filtration methods. Unentrapped drug concentration was measured in the later technique, which is subtracted from the total amount of drug added. Using a UV spectrophotometer or HPLC analysis, the volume of drug is measured[40].

Ultrafiltration Pressure: System Drug release calculation of cubosomes can be conducted using the ultrafiltration method of pressure. It is based closely on that suggested by Magenheim et al. using an ultrafiltration cell of Amicon pressure fitted at ambient temperature (22±2) °C with a Millipore membrane[22].

Stability studies: The analysis of organoleptic and morphological aspects as a function of time can study physical stability. The distribution of particle size and drug content can also be measured at various time intervals to determine potential time variations[41].

Viscosity: The viscosity of the prepared formulations was measured using a rotary viscometer at various angular velocities at 25ºC (Brookfield). The speed of rotation was 20 rpm, with spin # 18. The viscosity of the samples was measured using an average of three readings[41].

X-ray dispersion: Small angle X-ray dispersion (SAXS) can be used to evaluate the spatial arrangements in the sample for various types. The diffraction patterns obtained are converted to intensity versus q value plots, which allow peak positions to be defined and converted to Miller Indices. In order to classify the dominant internal nanostructure of the sample, the Miller Indices could then be associated with known values for various liquid crystalline structures and space groups[21].

Infrared spectroscopy: IR spectra for REB loaded cubosomes, blank cubosomes, REB powder, and GMO were acquired using Fourier Transformer Infra-Red (Shimadzu, Japan). Samples have been prepared on KBr discs (about 10 mg sample for 100 mg of dry KBr). In the spectral region 450-4000 cm-11 the IR spectra were acquired[42].

Differential calorimetry scanning: The purpose of this test is to detect any potential change in the physical state of the REB when the cubosomes are trapped. DSC was conducted using a thermal analysis method for REB filled cubosomes, blank cubosomes, REB powder, and GMO (DSC-60, Shimadzu, Japan). The samples (5mg) were heated in an aluminium pan under a nitrogen atmosphere over a temperature range of 30 ºC-350 ºC at a constant rate of 10ºC/min. As a guide, a similar empty pan was used as the reference[42].

APPLICATION OF CUBOSOMES:

In cancer therapy: - Several anticancer drugs have recently been successfully encapsulated in cubosomes and physicochemical properties have been characterised. In melanoma treatment, the peculiar structure of this promising nano carrier suggests its application. Different methods have been envisaged, with passive and active targeting of cancer cells having been shown to be valid approaches in preclinical and clinical trials in order to precisely target nano drugs to tumours[43]. Passive targeting takes advantage of the tumour vasculature's pathophysiological properties, which

are typically highly disorganised with expanded gap junctions between endothelial cells and impaired lymphatic drainage, allowing nanocarriers with sizes of up to several hundred nanometers to be extravasated. Objects of this scale will not move through the close junctions of the vessels of healthy tissues within the endothelial cell lining. Passive targeting is largely based on a drug nanocarrier's ability to display an improved lifetime of circulation resulting in increased accumulation at the target site. The physicochemical properties of the nanoparticle (size, charge, biodegradability, solubility, shape, rigidity) determine circulation time, which can be easily manipulated in most of the delivery systems mentioned[21].

Controlled release or continuous release behaviour: The most common use of cubosomes is to regulate the release of solubilized substances. Due to its small pore size (5-10 nm), ability to solubilize hydrophilic, hydrophobic, amphiphilic molecules and its biodegradability by simple enzymes, the cubic phase is more applicable for control release.

Vaccines: Another key use of cubosomes as agents in vaccines is in addition to cancer therapeutics. One of the earliest examples suggests that cubosomes may be used for protein-based vaccines. Using the solvent precursor dilution process, monoolein and phytantriol cubosomes were prepared and filled with fluorescently labelled ovalbumin, a model protein routinely used in vaccine research. The study showed that ovalbumin's sustained-release profiles act as proof of concept for cubosomes as systems of antigen delivery. In a later research, this was subsequently established where the cubosomes were changed to include adjuvants (Monophosphoryl lipid A, Imiquimod) and tested in vitro and in vivo kinetics of release. Cubosomes allowed greater trapping efficiency compared to liposomes, and were more effective in inducing an antigen-specific cellular response in a mouse model[32].

In treatment of viral diseases: It may be used to design intravaginal treatment of sexually transmitted diseases caused by viruses (e.g. HSV, HIV) or bacteria (e.g. Chlamydia trachomatis and Neisseria genorrticae) due to the microbicidal properties of monoglycerides. It is rational to expect the formation of a mixture of cubosomal monolein with stratum corneum lipids because of the similarities between the cubic phase structure and the stratum corneum structure. In this layer, this type of interaction could lead to the creation of a cubosome depot from which drugs can be released in a regulated manner[21].

Oral drug delivery: Cubosomes resolve the various difficulties of multiple compounds in oral delivery, including low aqueous solubility, poor absorption, and large molecular size. Large proteins for local action in the gastrointestinal tract have been encapsulated in an application. Technology for liquid crystalline nanoparticles (LCNP). Large proteins were encapsulated for local involvement in the gastrointestinal track in an alternative application. The particles are engineered to form in situ at a controlled rate, which allows the drug to be efficiently delivered in vivo. Carriers of liquid crystalline nanoparticles technology can also be released at various absorption sites, such as in the upper or lower intestine, which is critical for drugs with a small regional absorption window[25].

Intravenous drug delivery systems: Lipid nanoparticles composed of internal liquid crystal structures of curved lipid membranes are used to encapsulate solubilization and deliver drugs to areas of disease within the body. Although emulsions and liposomes have been used in drug products as intravenous carriers, liquid crystal nanoparticle structures have increased the payload of peptides, proteins and many insoluble small molecules and are ideal carriers of many active ingredients for injection or infusion[25].

Topical drug delivery systems: In nature, cubic phases are more bioadhesive, so they can be used easily in topical and mucosal depositions and in the delivery of various drugs. Topical delivery systems are focused on the exploitation of liquid crystal (LC) and liquid crystal nanoparticle (LCNP) technologies with their special properties. Topical drug delivery systems allow bioadhesive LC systems unique in situ to enable managed and efficient delivery of drugs to mucosal surfaces (buccal, ophthalmic, vaginal and others). This fascinating device forms a thin surface film consisting of a liquid crystal matrix on mucosal surfaces that can be managed by nanostructure to achieve an optimum distribution profile and offers excellent temporary protection for sore and sensitive skin[22].

Nanoreactors/Biosensors: To the best of our knowledge, there are only two cases of cubosomes used as biosensors or nanoreactors. By synthesising proline-based lipidated organocatalysts that could be integrated into cubosomes without modification of the cubic structure, cubosomes have been demonstrated as nanoreactors. This allows for a hybrid cubosome that includes monoolein and lipid modified by the catalyst that can freely diffuse within the bilayer of the lipid. An organocatalyzed aldol reaction between water-soluble aldehydes and cyclohexanone showed that the rate of catalysis depended on the catalyst's water channel size and

lipid structure, indicating that the properties of the cubosome can be configured to determine the rate of catalysis.

This is the first presentation of cubosomes as new catalysis scaffolds for catalysis. Phytantriol cubosomes stabilised with F127 were attached to a quartz crystal microbalance by the incorporation of a PEG-biotinylated lipid bound to a neutravidin surface on the microbalance to demonstrate the use of cubosomes as a biosensing platform. Specific protein binding glycolipid monosialoganglioside GM1 was introduced into the cubosomes to demonstrate that it is the normal cell surface receptor for cholera toxin B, allowing for specific binding of cholera toxin B. Significantly low levels of non-specific binding has been observed, suggesting that cubosome systems could be designed for biosensing applications. Nanoreactor and biosensor applications are still in their infancy, but have exciting potential for a completely new approach to cubosome device applications[32].

CONCLUSION

Drugs contained in cubosomes can be administered to patients through transdermal, oral, or intravenous routes. Biotechnology companies are designing peptide and protein-related drugs based on the human genome sequence. Cubosomes containing protein and peptide-based drugs are expected to account for more than half of new drugs introduced to the market in the next 10 to 20 years, with antibodies accounting for more than 80% of these protein drugs due to control release activity.

Traditional routes of delivery would be much more difficult for such molecules, and injections may be the only option (at least as of today). The drug, disease state, and desired site of action will all influence the route of administration. Some areas, such as the nose, mouth, and vagina, are relatively easy to access. Some areas, such as the brain, are more difficult to reach. LLC nanoparticles (melted lipid).

LIST OF DRUGS INCORPORATED IN CUBOSOME FOR SUSTAINED DRUG DELIVERY SYSTEM[24]

Sr.No.	Researcher	Drug	Category	Associated Disease
01	Engstrom et al,	2-amino-1-phenylpropanol HCl	Antidepressant	Mania, Depression
		Nitroglycerin	Anti-anginal	Angina pectoris
		Oestriol	Hormonal therapy	Atrophic vaginitis, Pruritus
02	Sadhale et al.	Cefazolin	Antibiotics	Genito-urinary, respiratory track infection
		Cefuroxime	Antibiotics	Meningitis bone and soft tissue infection
		Prilocaine	Local anesthetic	In Destistry
03	Damani	Clindamycin phosphate	Antibiotics	Pertonitis, Staphylococcal bone and joint infection
04	Engstrom et al.	Clomethiazole	Psychotropic	Insomnia
05	Engstrom et al.	Clotrimazole	Antifungal	Vagina, mouth and skin infection
06	Engstrom et al.	Gramicidin	Topical steriod	Corticosteroid sensitive dermatoses
		Insulin	Hypo/Hyper glycaemics	Diabetes mellitus
07	Neilsen et al.	Indomethacin	NSAIDS	Gout, rheumatoid arthritis
		Isosorbidemononitrate	Anti-anginal	Angina pectoris
		Lidocaine hydrochloride	Oral prepration	Fungal infection of external ear
08	Boyd	Diazepam	Sedative-hypnotic	Anxiety, insomnia, seizures
		Rifampicin	Bactericidal antibiotic	Tuberculosis
		Griseofulvin	Antifungal	Fungal infection of skin

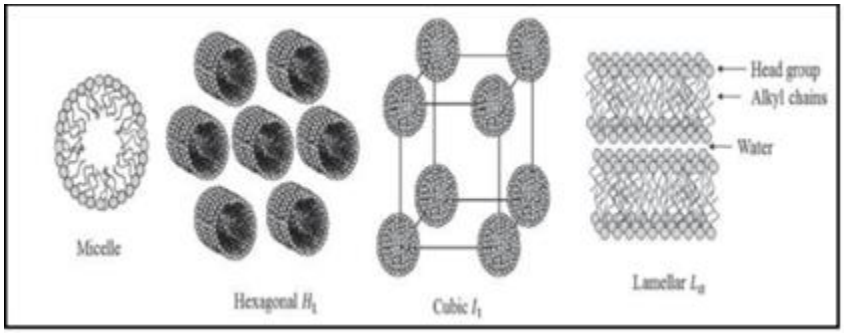

Figure 1: Structure representing aggregation of amphiphiles into the micelle and LLC phase such as Hexagonal, Cubic, and Lamellar phase.

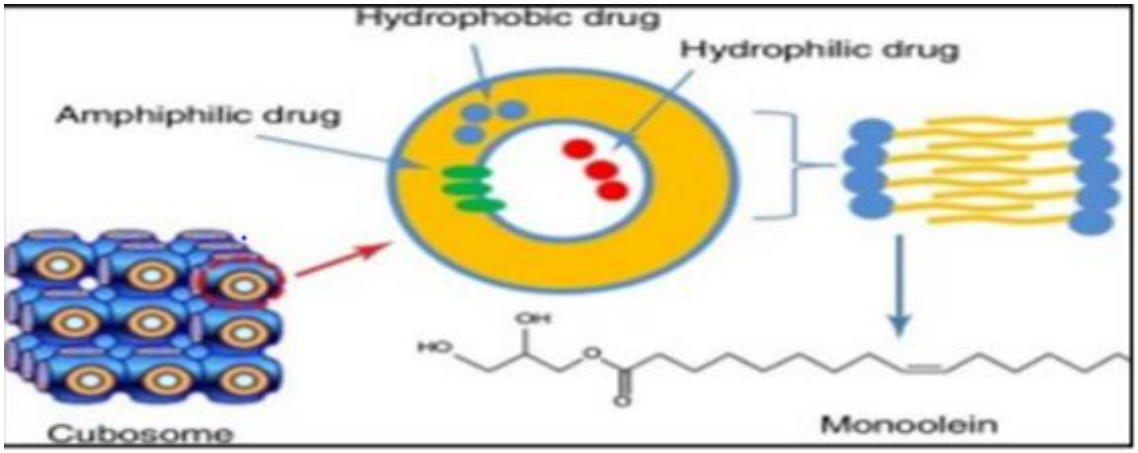

Figure 2: Structure of cubosome separating two internal aqueous channels along with large interfacial area[25].

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