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LYOTROPIC LIQUID CRYSTALS IN A DRUG DELIVERY AND ITS APPLICATIONS: A REVIEW

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Abstract:
Lamellar, cubic and hexagonal mesophases are some of the most common lyotropic liquid crystal systems, and have attracted much research attention because of their distinctive structures and physicochemical properties. Polar lipids and surfactants exhibit a range of phase behavior in an aqueous environment, depending on the composition of the lipids and surfactants. These characteristics have been investigated for a variety of applications in drug delivery, and lyotropic liquid crystal systems have potential as drug carriers for small molecules, peptides, and proteins. In this article we provide an overview of recent advances in the state of the art, including methods of preparation and applications in drug delivery. The scope and limitations of lyotropic liquid crystals for drug delivery are discussed, and future research perspectives are identified.

Keywords:
Lyotropic liquid crystal, Drug delivery, Cubosome , Hexosome

Introduction:

Controlled drug delivery systems are advanced methods for the transport of pharmaceutical compounds within the body, and can be used to overcome many of the limitations of conventional drug formulations. The aim of this approach is to create a higher concentration of the drug at a specific site relative to that in the rest of the body, as well as to develop controlled release formulations. Various types of drug delivery system (DDS) have been developed, including hydrogels, nanoparticulate delivery systems, drug-loaded biodegradable microspheres, and drug polymer conjugates. One of the more recent advancements in DDS are liquid crystals (LCs), which have emerged as injectable formulationsbecause of their sustained drug release properties [1]. Lyotropic mesophases form a long-range order with the addition of a solvent, and have historically been used to describe materials composed of amphiphilic molecules. Lyotropic LC phases are formed when dissolving amphiphilic molecules in a solvent, and are influenced by the amphiphilic structure of the molecule, the presence of additives and conditions of the solution. Lyotropic liquid crystal systems (LLCSs) can be classified into lamellar (La), hexagonal and cubic phases. The La phase is a linear arrangement of lipid bilayers, in which the hydrophilic head groups are in contact with water and the hydrophobic tail groups are pointing toward the center of the sheet. The hexagonal phase is the most common nonlamellar phase formed by amphiphilic molecules mixed with water [2]. The normal hexagonal (H1) and inverse hexagonal (H2) phases are cylindrical structures that form a hexagonal lattice. A cubic phase (Q2) may exist between the H2 and lamellar La phases, creating a dense cubic lattice. The H2 and Q2 phases have been

extensively investigated, and have much potential for use as delivery vehicles for a wide range of materials, from low-molecularweight drugs to proteins, peptides and nucleic acids [3]. The H2 phase consists of rod-like water channels arranged in a two-dimensional lattice, separated by lipid bilayers; and the Q2 phase comprises a curved water channel and a bicontinuous lipid bilayer that extends in three dimensions. The inverse hexagonal and cubic mesophases are spontaneously formed from the liquid crystal-forming system (LCFS) in an aqueous fluid. The resulting tortuous networks of aqueous nano-channels in these mesophase particles can form passageways for sustained release of drugs from liquid crystals [4]. A number of amphiphilic materials have been investigated as LCFSs, including glycerol monooleate (GMO), phytantriol (PT), glycerol dioleate (GDO), oleyl glycerate (OG), and phytanyl glycerate (PG) [1]. These polar lipids are not water-soluble; however, they often form Q2 and H2 mesophases in an aqueous environment, which are reconstructed in such a way as to minimize the free energy when in contact with water, so that they can bedispersed in equilibrium with an excess of water to form thermodynamically stable colloidal dispersions.

Cubic and Hexagonal Phase Structure

The structure of the cubic phase comprises lipid bilayers arranged in periodic threedimensional structures by contorting the bilayers into the shape of infinite periodic minimal surfaces. This reverse bicontinuous structural arrangement minimizes stress and free energy, resulting in water and oil domains with a surface area on the order of 400 m2/g [5] The bicontinuous cubic phases can be classified into either the double-diamond lattice (Pn3m, Q224), the body-centered cubic phase (Im3m, Q229), or the gyroid lattice (Ia3d, Q230) (Table 3 [6]. As a bulk phase, it is typically a clear, viscous, semi-solid gel similar in appearance and rheology to cross-linked polymer hydrogels [7]. In addition to the bicontinuous cubic structure, reverse micellar cubic phases exist, consisting of reversed micelles packed on a cubic lattice. This is a discontinuous structure and composed of two populations of reversed micelles, one larger than the other [8]. The two sizes of micelles allow for more efficient packing. Due to the discrete, small water domains associated with this structure, it is expected to exhibit the most extended release profiles of the various liquid crystalline phases [9]. The reverse hexagonal phase (HII) is a closed, extended micellar columnar structure, where there is no direct contact between water inside and outside the hexagonal phase [10]. The bulk and particle structure can be envisioned to be a large micelle with a “core” composed of the extended micellar structures. While the long circular water-filled rods are often illustrated and considered as if they are open to the aqueous environment, it has been reported that these water channels are in fact closed to outside environment [11]. Therefore, the release of hydrophilic drugs from the mesophase has been described as a series of dynamic events involving diffusion through water channels and permeation across the lipid bilayers [12]. However, for release of large hydrophilic molecules such as the peptide drug leuprolide acetate, random perturbation/ dynamic deconstruction reconstruction events of the reverse micelles may be required [13]. The amphiphilicity of the drug molecule will determine the location in the liquid crystalline matrix; hydrophilic drugs will be located close to the polar head of the lipid or in the aqueous channel, lipophilic drugs will be located in the lipid bilayer, and amphiphilic drugs at the interface. Multiple reviews have focused on the self assembly, structure-packing relationships, drug release mechanisms, and how to control molecular transport in LC systems and the reader is directed to these cited review for more detailed information on these aspects [14].

LLC Nanoparticle Production

The formation and structure of cubosomes was first described in 1989 by Larsson [15]. Since then, a number of reports have been published on the use of the various LC phases, particularly the cubic or “cubosomes” and hexagonal or “hexosomes” for the use in drug delivery. Cubosomes have been proposed as a delivery system which may provide both a solubilization effect and a means for controlling or sustaining release [16]. LLC particles are typically sterically stabilized by a secondary emulsifier [17], such as polyethylene oxide polypropylene oxide-polyethylene oxide block copolymers (e.g. Pluronic F127) [18], due to the high external surface area of the submicron particles. As Spicer eluded to in 2005, from an industrial perspective, cubosomes have intriguing and fascinating properties, but relying on top-down approaches for production may be problematic due to the potential of multiple passes for the desired properties and the high energy required [19]. Still, most emulsification methods for the lyotropic liquid crystalline nanoparticles (LCNP) production rely on high-energy input from the bulk phase: ultrasonication, microfluidization, and/or homogenization. Additional methods of production, still relying on high energy input, are the hot-melt method were the precursor solution is dispersed with a homogenizer in hot water (80 °C) loaded with a stabilizer and a drug followed by high pressure homogenization. Reverse to that method is the

application of microfluidization followed by heat treatment (125 °C) for the formation of dispersions of cubosomes and hexosomes [20]. Other methods not relying on the top down approach have been developed. Cubosomes were shown to be formed by the addition of phosphate buffered saline to phytantriolbased cationic liposomes that contained a charged lipid-dodecyldimethylammonium bromide [21].

LC Safety and Degradation

The digestion of GMO after oral dosing was shown to be responsible for a lack of sustained-release effect for the model drug, cinnarizine. Relative to GMO, both oleyl glycerate and phytantriol were able to sustain the absorption of cinnarizine over approximately 48 hrs after oral dosing. Oleyl glycerate is a less readily digested GMO structural analogue and phytantriol is a non-digestible lipid demonstrating similar phase behavior to GMO. Phytantriol was found to be retained for an extended period of time in the stomach relative to GMO also, establishing a link between digestibility, gastric retention, and a sustained release effect Interestingly, despite this link that was found, very few studies have focused on the digestibility/enzymatic breakdown of these systems, let alone the potential gastric retention of these systems. [22-23].

Method of preparation

Gel-like mesophases can be prepared simply by injecting the LCFS into an aqueous solution. LC gels can be prepared by mixing the LCFS with aqueous phase using a vortex or using ultrasonication, however, preparation of lyotropic LC nanoparticles, cubosomes or hexosomes is more complicated, and thus will be discussed in greater detail in the following sections.

High-temperature dispersion

The procedure described by Gustafsson et al., whereby homogenization at high temperatures produces a coarse dispersion, resulting in well-ordered particles of cubosomes . A homogeneous melt of lipids, surfactants and the drug were added dropwise to water to form the coarse dispersion. Further reductions in size via homogenization were achieved at higher temperatures. The elevated temperature promotes transformation of the noncubic vesicles to cubic vesicles. Wo¨rle et al. reported a method of preparing homogeneous cubic nanoparticles by autoclaving an aqueous coarse dispersion . The heat treatment contributes to a reduction in the particle size, and a narrow size distribution and good colloidal stability were reported. Although temperature is important, the heat treatment duration did not appear to affect the size of the particles, nor the distribution or transformation of the dispersions. Small changes in temperature may alter the visual appearance and structure of the particles; however, temperature-sensitive drugs, such as proteins and peptides, may not be suitable for this method. [24]

Mechanical agitation

To prepare lyotropic liquid crystal (LLC) nanoparticles, high-pressure homogenization, sonication or shearing is typically necessary. The viscous bulk phase can be prepared form lipids, surfactants and stabilizers; the resulting mixture is then injected into an aqueous solution, together with mechanical agitation . Mechanical stirring or homogenization is commonly used, and Wo¨rle et al. have reported GMO-based LLC nanoparticles via stirring and homogenization. They investigated GMO-based cubosomes formed at different temperatures and with varying concentrations of F127 as a stabilizer. Heat treatment is frequently used to prepare LLC nanoparticles combined with mechanical agitation. These methods are well established and easy to use in a laboratory setting; however, they can result in mixed structures, including cubosomes, hexosomes and lamellar liquid crystalline phase. Salentinig et al. used shearing to fabricate LLC nanoparticles, shearing can be used to prepare more stable and homogeneous cubosomes and hexosomes with a large hydrophobic phase content compared with ultrasonication. The temperature and viscosity of the sample during emulsification are also important parameters. [25]

Hydrotropic solvents

Hydrotropic solvents can be used to stabilize LLC phases. LLC nanoparticles prepared using a hydrotrope exhibit long-term stability due to the homo-dispersed stabilizers in the particles . LLC nanoparticles can be prepared simply, and have favorable properties compared with other methods of preparation. Swarnakar et al. used ethanol to prepare isotropic LCs, whereby lipids and oil were solubilized . Ethanol was used as a hydrotropic solvent to create a liquid precursor, and diluted to form a colloidal dispersion of hexosomes. Although hydrotropes have both hydrophilic and hydrophobic parts, they generally do not have the critical micelle concentration, because the hydrophobic part is too small to form self-assembled particles. Hydrotropes also exhibit salting-in, thereby

increasing the solubility of lipids and surfactants in aqueous solution; however, the use of hydrotropic solvents requires an understanding of the phase behavior, and thus lipid-water-hydrotrope charting trajectories on the ternary phase diagram should be investigated to determine the optimal point for the formation of stable LLC nanoparticles[26]

Applications in drug delivery

LLCSs have been considered as a new method of drug delivery, because of the unique physicochemical properties. LLCSs have the following advantages as drug delivery systems (i) effective solubilization compared with traditional carriers; (ii) a high carrying capacity for a range of water-insoluble drugs; (iii) 20 to [100-fold improved bioavailability of water-soluble peptides; and (iv) they are a promising vehicle that can protect the sensitive drugs from enzymatic degradation.Cubic LLCSs generally exhibit great flexibility in terms of their composition. It is possible to upload drugs with a wide range of polarities and sizes. They are also biodegradable and the viscosity facilitates slow and sustained release of the incorporated drug. However, LLCSs have a variety of limitations. One practical limitation is due to their viscosity, especially when the cubic and hexagonal phases are injected. Administration of viscous LLCSs by means of traditional delivery routes is impractical because the viscous substance may induce irritation or other adverse effects wheninjected into the human body. However, alternative strategies for utilizing viscous cubic or hexagonal phase have been reported over the past two decades. One is to formulate the active component within a less viscous lamellar phase gel, which is easier to administer. Another limitation of LLCSs is that the active substances may influence the membrane properties of the LLCS, which can in turn affect the release pattern and delivery properties. Several studies have reported that the addition of drugs or solvents to GMO/water systems leads to a modification of the liquid crystalline structure, and alteration of the release kinetics of the uploaded drugs. In addition, a lack of suitable, scalable manufacturing methods to prepare structurally well-defined and stable dispersions is a considerable barrier to the commercialization of cubic LCs for sustained drug delivery systems. Furthermore, the range of lipids available with suitable phase behavior for the preparation of these systems is limited. Despite these limitations, however, various potential routes of drug delivery using LLCS have been investigated. Many studies of drug delivery using LLCS have been reported and can be categorized according to the route of administration used, as described in the following subsections [27]

Intravenous administration of LLCS drug delivery systems

The high viscosity of inverse bicontinuous cubic and hexagonal phases, together with the mechanical stiffness, is problematic for intravenous injection. Several methods have been proposed to overcome this difficulty, however, including the application of flowable forms (e.g., lamellar phases) and the use of lyotropic liquid crystal nanoparticles. Irinotecan is an anticancer drug that exhibits a pHdependent equilibrium between the active lactone and inactive carboxylate forms, with rapid conversion to the carboxylate form occurring at pH 7, and concurrent cleavage of the side chain to the highly cytotoxic SN-38. Boyd et al. developed glyceratebased hexosomes, which can improve the retention of irinotecan in the non-toxic lactone form at neutral pH. Furthermore, the dimensions of the particle appear to be suitable for intravenous administration . Somatostatin is a peptide hormone that is active in the regulation of the endocrine system, and has much potential in the treatment of diseases including acromegaly, acute pancreatitis and gastroenteropathic endocrine tumors. However, the practical use of this drug is limited because of its short half-life of only a few minutes.Cervin et al. showed that the combination of somatostatin with lipid-based liquid crystalline nanoparticle carriers significantly increased the half-life of thepeptide when injected intravenously into rats [28-29].

Subcutaneous administration of LLCS drug delivery systems

Sustained drug release via subcutaneous (SC) injection has potential to maintain an effective plasma concentration for up to several months, with minimal side effects in comparison with intravenous injection or multiple dosing. A number of studies have shown that LLCS may be applied to achieve improved drug delivery via SC injections. Somatostatin and desmopressin uploaded in a GMO– water system showed a prolonged in vivo release profile, following SC injection. More recently, Fong et al. formulated phytantriol- and glyceryl monooleate-based bicontinuous cubic and inverse hexagonal nanostructures, which were converted in response to changes in temperature. When injected subcutaneously at 40 _C, in vivo absorption studies have shown slow release of the hexagonal phase; however, when the temperature decreased to 30 _C (at which temperature a transition from the hexagonal phase to the cubic phase occurred), a statistically significant increase in the plasma concentration of

drugs was observed. In addition, this system exhibited more sustained release profiles compared with the other control formulations. It has recently been reported that an LLCS prepared by using SMO for SC injection of leuprolide acetate showed a sustained release for up to 1 month in rats and in dogs. LLCSs have also been applied in SC injection for immunization. Cubosomes with the Toll-like receptor agonists monophosphoryl lipid A and imiquimod, exhibited sustained release kinetics and induced a more robust immune response in mice compared with liposome and alum formulations. Moreover, LLCSs may also be combined with microneedle (MN) technology, which could provide improved methods of transcutaneous immunization (TCI). Rattanapak et al. utilized MN and cubosomes as a synergistic approach with TCI. Whereas MN increased the permeation of an aqueous mixture through the skin, a cubosome formulation containing the peptide was retained in the skin. It was thus proposed that this approach using MN and cubosome has potential forTCI applications [30]

Oral administration of LLCS drug delivery systems

To achieve effective oral delivery, three important factors must be considered. First, the formulation must possess the inherent property of sustained release; second, it should exist in a stable form in the gastrointestinal (GI) fluids to provide an enduring matrix from which drugs can be released; and third, it should exhibit bioadhesive properties to extend the retention time of the formulations in the GI tract. It has recently been reported that glycerated monooleate-based mesophase formulation exhibited enhanced bioavailability of co-administered poorly water-soluble drugs, which exhibited the first and third features discussed above, but does not exhibit sustained release due to the sensitivity to the digestive process. It has been reported that LLCSs prepared using phytantriol and oleyl glycerate also exhibit enhanced bioavailability and sustained release of orally administered drugs. Cinnarizine is a poorly water-soluble drug that is used as an antihistamine. The poor water solubility and resulting poor absorption were significantly improved when cinnarizine was entrapped in the oleyl-glycerate-based inverse hexagonal phases. This formulation exhibited a sustained release pattern over several days, accompanied by extended absorption. Chung et al. reported GMO-based cubosomes containing insulin, and described a hypoglycemic effect of the formulation when administered orally. Their results showed that the insulin–cubosome formulation provided a hypoglycemic effect that was comparable to insulin injected intravenously over 6 h Simvastatin uploaded in GMO-based cubosomes administered orally showed an increase in bioavailability of 241 % compared with a control comprising a crystal powder formulation of the drug. In addition to the enhanced bioavailability, the cubosome formulation exhibited sustained release of simvastatin over a period of 12 h in beagles. Cubic nanoparticles loaded with 20(S)-protopanaxadiol (PPD), exhibited a 169 % increase in the relative bioavailability compared with raw PPD [31-32].

Transdermal and topical administration of LLCS drug delivery systems

Transdermal administration is an interesting alternative to oral administration because it avoids a number of the limitations of oral delivery, including the hepatic first-pass effect and low oral bioavailability, as well as several dosedependent side effects and compliance problems. Nielsen et al. reported that the high viscosity of the cubic phase formulation was able to adhere to jejunum and vaginal cavity in an in situ study using rabbits. The bioadhesive nature of the cubic phase may be useful for enhancing the transdermal penetration of drugs; however, transdermal delivery typically exhibits limited absorption of drugs. The stratum corneum is believed to be the major rate-limiting barrier for transdermal delivery. LLCSs can form a thin surface film consisting of a liquid crystal matrix, which can be controlled to achieve an optimal delivery profile, and can provide temporary protection for sore and sensitive skin. A number of studies have shown that LLCSs, including cubic and hexagonal mesophase formulations, can penetrate through the stratum corneum, and are promising candidates as transdermal drug delivery systems. Cyclosporin A is an immunosuppressive undecapeptide. When it was solubilized into inverse hexagonal crystalline structures with three dermal penetration enhancer, the formulation showed enhanced penetration through the stratum corneum with less skin irritation compared with a control oil formulation. LLCSs also have potential applications as topical delivery systems for prophylaxis and in the treatment of post-surgical wound infections, as well as for the treatment of post-surgical pain. Several studies have shown that local anesthetics, including bupivacaine and lidocaine, formulated as a cubic phase gel, exhibited sustained release of the drug when it was applied at the site of the wound. Local antibiotic delivery is also considered to be an effective method of preventing post-surgical wound infections. Sadhale and Shah reported improved stability of cefazolin and cefuroxime in GMO cubic-phase gels [33]

Ophthalmic and nasal administration of LLCS drug delivery systems

Proper ophthalmic drug delivery is becoming increasingly important because even a small overdose can induce irritation to the eyes, particularly with flubiprofen (FB) solution. LLCS drug delivery may contribute to improved ophthalmic applications. Han et al. developed cubosomes containing FB and reported reduced ocular irritancy and improved bioavailability compared with FB solution. Gan et al. also demonstrated LC nanoparticles (cubosomes) containing dexamethasone (DEX) as a novel ophthalmic delivery system, with an enhance bioavailability (eightfold increase of AUC) in the in vivo compared with a DEX suspension. Nasal administration using LLCS has also been investigated, and LC vehicles containing zidovudine (AZT) exhibited increased absorption of AZT in rats. These results demonstrate that the LC formulation administered via the nasal route may represent a promising tool for systemic delivery of drugs[34]

Other administration routes of LLCS drug delivery systems

Vaginal delivery of the antimuscarinic drugs propantheline bromide and oxybutynin hydrochloride for treatment of urinary incontinence using a GMO–water LC system has been demonstrated .The incorporated drug induced the formation of a lamellar phase, and formed a cubic phase when it was retained in the vaginal cavity, due to its bioadhesive characteristics. Both drugs were released via diffusion following square-root time kinetics over a period of 18 h. Periodontal delivery of antibiotics using LLCS has been considered for the effective prevention and treatment of infection. Viscous cubic and inverse hexagonal phases have been shown to transform from lamellar phases containing metronidazole when injected into the periodontal pocket. However, cubic phases did not exhibit the desired release characteristics. In another study, Esposito et al. characterized both poloxamer-based and GMObased cubic phase formulations when injected into the periodontal pocket. The results of these studies support the application of LLCSs as a cubic phase for local and periodontal delivery. Swarnakar et al. prepared a hexosomal dispersion loaded with progesterone, which was tested for oromucosal delivery systems. In vitro release tests showed an increased transmucosal flux and a decreased lag time across the mucosa of albino rabbit [35]

Conclusions

The unique structure and physicochemical properties of LLCSs make them suitable for use as a drug delivery carrier, with numerous potential applications in pharmaceuticals. LLCS formulations have exhibited significant entrapment efficiency, sustained drug release, and improved stability. There have been many promising results of these LLCSs; however, a number of limitations need to be overcome for their clinical application. For example, with the direct administration of liquid crystal gels, problems associated with the viscosity and the frequent occurrence of burst-release must be resolved. Although monoolein has been regarded as being generally safe, little is known about its adverse effects upon parenteral administration. In addition, the number of available lipids that exhibit suitable phase behavior for application in humans is limited. Although some new materials, such as PT, OG, PG and SMO have been shown to exhibit promising properties, questions remain regarding their safety and biological stability in vivo.

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