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Review Article

Drug Delivery Via Lyotropic Liquid Crystals: An Innovative Approach

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Abstract

The lyotropic liquid crystal are self-assembled mesophases that exhibit the properties of both crystalline solid and isotropic liquids. They can potentially deliver hydrophilic, lipophilic, amphiphilic molecules including proteins and peptides. The unique structure of liquid crystals facilitates the improved drug loading and controlled release of the drug. Liquid crystals are widely explored for topical delivery of drugs because of their strong bio-adhesive property and resemblance to the structure of the biological membrane when applied topically. The biological membrane like structure of LLC improves the skin retention and permeation of the drugs. Lyotropic liquid crystals are mainly classified into three main categories i.e., lamellar, hexagonal and cubic. The structural difference between various types of liquid crystals can be determined by using a number of characterization techniques such as transmission electron microscopy, small angle x-ray diffraction and polarized light microscopy. In this review, we have discussed the classification, preparation and characterization of liquid crystals along with their various therapeutic applications. We have discussed the potential effect of liquid crystals in brain targeting via intranasal route and its applications in targeting various types of tumour cells.

Keywords: Lyotropic Liquid Crystals; Cubosomes; Hexosomes; Transdermal Delivery; Brain Targeting; Tumour Targeting

Introduction

The research in the field of nanotechnology has continued to emphasize on exploring engineered nanosized particulate systems for the effective delivery of various pharmaceutically active constituents. In recent years, interest has been increased in developing a nanocarrier system that mimics the curvature of the cellular membrane. This is due to the various advantages of nanosized particulate systems such as higher membrane surface area and volume ratio, membrane stress variations and increased loading capacity of hydrophobic and membrane proteins compared with other systems [1,2].

Lyotropic liquid crystals (LLC) or liquid crystalline nanoparticles (LCN) are nano-biomimetic lipid-based systems that exhibit great potential in drug delivery due to their unique structural property. They are self-assembled mesophases that have properties of both crystalline solid and isotropic liquids. Liquid crystals (LC) are multifunctional, versatile carriers that can solubilize oil and water-soluble compounds and therefore can be potentially used to deliver both hydrophilic as well as hydrophobic drugs [3].

Liquid crystals exist as an intermediate form between solid and liquid crystalline matter. Based on their class of order and orienta-

tion they can be structurally classified into nematic, sematic, cholesteric and columnar. All the materials that demonstrate liquid crystal behaviour are either lyotropic or thermotropic. Lyotropic crystals are formed because of the interactions between anisotropic aggregates of amphiphilic molecules and the phase transition is a function of temperature and concentration whereas, thermotropic crystals are formed due to interactions between partially rigid anisotropic molecules in which the phase transition occurs due to change in temperature [1]. At low concentration the basic functional unit of LLC is a micelle which is formed by orientation of polar groups towards the water, this phase is known as the liquid isotropic phase because it has same properties in all directions. Various physicochemical parameters affect the phase behaviour and internal structure of self-assembled LLC like temperature, pressure, lipid/additives, water composition ratio, pH, and shearing [2].

In this review, we have enunciated the classification, preparation, characterization and various therapeutic applications of LCNs.

Classification of lyotropic liquid crystals

Lyotropic liquid crystals are amphiphilic in nature i.e., they consist of both hydrophilic and hydrophobic part on the same molecule. The hydrophilic head and the hydrophobic tail are responsible for maintaining orientation in both polar and non-polar solvents. Lyotropic liquid crystals are subjected to phase transition which depends on the water content of the formulation. LLC are mainly classified into three main categories i.e., lamellar, hexagonal and cubic. The structures of various types of LLC are depicted in figure 1.

Figure 1: Types of lyotropic liquid crystals.

In lamellar liquid crystals irregular disc like micelles are packed in layers. The surfactant molecules in lamellar structures are connected tail to tail and are arranged in alternate flat layers facing water layers. Addition of water and drug molecules in the polar layer increases the thickness of the layers. Even in high concentration of surfactant the phase of lamellar crystals remain fluid in nature and their crystal composition stays intact.

Hexagonal liquid crystals are formed by adding excess of water and stabilizer and then they are dispersed into nanoparticles. The hexagonal crystals contain polar heads towards the aqueous medium and fatty acid chains are pointed inwards. Hexagonal mesophases are further classified into two types: reverse and normal mesophase mainly in case of anhydrous and aqueous solution. They have high drug loading capacity and improve the in-vivo stability of loaded drugs. Hexagonal phase can effectively deliver compounds with larger molecular size like peptides and proteins.

Cubic liquid crystals have unique and typical structure with curved bilayer of lipid. Cubic phase contains separate and non-intersecting aqueous channels that are responsible for the controlled drug release. The compartmentalization in cubic liquid crystals can be used to incorporate drugs of hydrophilic, lipophilic and amphiphilic nature. Hydrophilic drugs are present near the polar head or aqueous channels, whereas the lipophilic drugs are present within the lipid bilayer and amphiphilic drugs are situated in the interface [4,5]. The cubic phase has clear, viscous and gel like consistency having similar appearance and rheology to cross-linked polymer hydrogels. The dispersion of cubic liquid crystals in water and stabilizer forms nanoparticles also known as cubosomes. The phase is classified into three types i.e., the body-centred cubic lattice, the gyroid lattice, and the double diamond lattice. The major disadvantage of cubic phase is that it cannot incorporate highly water-soluble drugs due to the presence of large amount of water.

Among LLC, cubic phase (reverse cubic) and hexagonal phase (hexagonal mesophase) have grabbed the interest of researchers, due to their ability to form highly ordered structures that provide a slow-release matrix for therapeutic agents of varying sizes and polarities [6].

Preparation of liquid crystals

Lyotropic liquid crystals can be prepared by a variety of methods, including size reduction using sonication, homogenization,

and shearing [7]. Lyotropic liquid crystals are mainly fabricated by two approaches: the bottom-up and top-down approaches [8].

The top-down approach

It is the most widely used technique for preparation of lyotropic liquid crystals. It is a two-step process in which firstly, viscous bulk lamellar/nonlamellar phase is formed using lipid and stabilizer. Later, the prepared viscous solution is dispersed in the aqueous phase with the help of high-pressure homogenization or sonication. High energy can result in formation of stable and reproducible liquid crystals that doesn't show aggregation.

The bottom-up approach

This method is also called as solvent dilution method or liquid precursor method. In this method a dispersion of liquid crystal is formed using lipid, a polymer and a hydrotrope in excess water with minimal energy input. The hydrotrope is used to reduce energy input and stabilizes the liquid crystals [9].

The combination approach

Top-down and bottom-up approaches have some disadvantages. The top-down approach uses high energy which makes it non-economical process. In order to eliminate the disadvantages of both processes, the best of both the process are being conjugated to achieve the desired product in a simple and economic way.

Characterization of liquid crystals

Liquid crystals are characterized for appearance, viscosity, pH, particle size, zeta potential, appearance. For identification of lyotropic phases techniques like transmission electron microscope (TEM), small angle X-ray (SAXR) scattering and polarizing optical microscope are used.

Transmission electron microscopy

This technique is used to visualize the morphology of liquid crystals. The major disadvantage of transmission electron microscopy is emission of high energy electrons that can affect the structure of liquid crystals. To triumph over this drawback, sample preparation is modified. Sample can be prepared using cryo-electron microscopy of vitreous section, plunge freezing, and freeze-fracture TEM.

In Cryo-electron microscopy of vitreous section, the sample placed and attached onto an electron microscopy grid and is subjected to extreme pressure followed by freezing in liquid nitrogen. The pressure is used to reduce the crystallization of water while dextran is added for samples with high water content [10].

Plunge freezing preserves the sample in the most native state and is hence the method of choice. In this technique the sample is placed into a thin film across an EM grid and is mixed with a cryogen (usually liquid ethane), but success depends critically on the properties of the grid and sample, the production of a uniformly thin film, the temperature and nature of the cryogen, and the plunging conditions [11].

The freeze fracture TEM is another method that is used to visualize morphology of the liquid crystals. This technique is used to produce high resolution images.

Small angle X-ray diffraction

Small angle X-ray diffraction is a technique which can be used to differentiate structural configurations of liquid crystals as in cubosomes and hexosomes [12]. Temperature also plays a vital role in small angle x-ray diffraction studies in determination of the type of liquid crystal phase dispersion and also the change in its configuration.

Polarized light microscope determination

Polarized light microscopy is used to characterize all types of liquid crystals expect cubic mesophase. It can also detect structure of loaded and unloaded liquid crystals [13]. Moreover, it can be used to study phase transitions in lyotropic liquid crystals.

Applications of lyotropic liquid crystals

LLC have been extensively investigated as a carrier system for their potential applications in oral, topical/transdermal, intranasal and cancer targeting. The several applications of LLC are summarized in table 1.

Oral delivery

The amphiphilic lipids self-assemble themselves in excess water which results in the formation of thermodynamically stable LC phases like bicontinuous cubic, hexagonal, and lamellar phases. For the preparation of LCNs the lyotropic LC phase is dispersed in aqueous media with appropriate surfactant. LLC have several advantages due to their unique structure that can be effectively used

Application	Type of liquid crystals	Therapeutic/ diagnostic agent	Outcome	Reference
Topical	Cubosomes	ketoconazole	Sustained release pattern was observed in cubosomes with a release rate of 92.73 % over a period of 24h.	[24]
Topical	LCNs	Luliconazole	Luliconazole loaded lyotropic liquid crystalline nanoparticles showed extended in vitro drug release up to 54 hours with 2 folds higher flux value in ex vivo skin permeation when compared with the marketed formulation. Higher retention of the drug in stratum corneum (~1.5 folds) and epidermis (~2 folds) was observed as compared to the marketed cream. The drug penetration in case of LCNs was also enhanced by 4.7 folds in epidermis and 6.5 folds in dermis than the marketed cream.	[17]
Topical	Cubosomes	Colchicine	Transdermal delivery of colchicine cubosomal gel significantly improved the drug absorption as compared to the oral colchicine solution. The relative bioavailability was evidently increased by 4.6 times than that of oral colchicine solution.	[16]
Topical	Cubosomes	Resveratrol	The resveratrol loaded cubosomal gel demonstrated better drug permeation and deposition in mice skin layers.	[18]
Topical	Cubosomes	Methotrexate	The topical methotrexate loaded cubosomes showed better in vivo skin permeation as compared to standard diclofenac gel. In vitro anti-inflammatory activity was enhanced in case of cubosomes 11.9% as compared to diclofenac sodium 10.4%.	[19]
Topical	Lamellar and hexagonal	Dexamethasone	Lamellar and hexagonal lyotropic liquid crystals of dexamethasone were prepared. The rheological analysis showed higher storage modulus for hexagonal phases as compared to lamellar phases. These systems exhibited greater bioadhesion property and controlled dexamethasone release in vitro.	[25]
Oral	Cubosomes	Indomethacin	The cubosomes of indomethacin showed reasonable entrapment efficiency (49.30±2.6 to 95.55±3.4 %) with biphasic release profile in which 50 % of the drug released in 2 hours followed by a continuous sustained release over a period of 24 hours.	[14]
Oral	Cubosomes	Norfloxacin	In this study norfloxacin loaded cubosomes were formulated for the management of otitis externa. The in vivo skin deposition studies were carried out using rabbit ear skin that exhibited higher amount of norfloxacin was deposited in the skin throughout the study period (10 hrs) when compared with the drug suspension.	[26]

Oral	Cubosomes	Berberine	In this research work the authors formulated LCNs of berberine to enhance its solubility and bioavailability. The formulation was tested for its anticancer activity against MCF7 human breast cancer cells. The results revealed that the IC_{50} values were 10 folds lower in LCNs and 55 folds lower in LCNs containing transcutol. The cellular uptake by MCF7 and Caco-2 cells was significantly higher in formulation as compared to the free drug solution.	[3]
Oral	LCNs	Rapamycin	This study revealed the fabrication of layer by layer coated liquid crystalline nanoparticles that specifically targeted the CD44 receptor which is overexpressed in cancer cells. The formulation showed higher encapsulation efficiency and sustained release. The study demonstrated enhanced cytotoxic effect against various human breast cancer cell lines like MCF-7 and MDA-MB-231. Moreover, in vivo studies showed 3.35 folds increase in the bioavailability when compared with the free drug.	[15]
Intranasal	Hexagonal	Donepezil	The intranasal delivery of LLC preparation of donepezil reduced gastrointestinal side effects which were observed in case of oral administration. In artificial nasal fluid the microemulsion swelled (12-20%) which resulted in the phase transition from isotropic to anisotropic. A sustained in vitro release was observed with significant levels of the drug in brain after nasal administration.	[27]
Intranasal	Hexosomes	Vinpocetine	In situ hexosomal gel was prepared for the intranasal delivery of vinpocetine to treat vascular dementia. The study was designed to overcome the problems associated with vinpocetine i.e., poor bioavailability and frequent dosing. The optimized in situ gel showed controlled drug release over 24 hrs. The delivery of the drug to the brain was confirmed by high brain targeting efficiency of 370.97 and 480.70 % and drug transport percentage of 73.04 and 79.19 %.	[20]
Intranasal	LLC	Tranilast	In this study the effect of liquid crystal formulation on the pharmacokinetics of tranilast and its distribution in the therapeutic region of the brain in rats was investigated. Formulations were prepared using C_{17}-monoglycerol ester and glyceryl monooleate, both the lipids showed enhanced brain uptake by 10-12 folds and 2-2.4 folds, respectively.	[21]

Table 1: Various application of Lyotropic liquid crystals.

to load hydrophilic, lipophilic and amphiphilic molecules. Moreover, they have been reported to enhance the solubility of poorly soluble drugs. Alfagih., *et al*. prepared a cubosomal dispersion of indomethacin which is a BCS class II drug and has poor solubility. The LC dispersion was prepared to improve the solubility and detect the *in vitro* release of the drug, the formulation showed a sustained release over a period of 24 hours [14]. Furthermore, Freag., *et al*. developed rapamycin loaded surface modified LCNs to improve the aqueous solubility and anticancer activity of the drug. The study demonstrated enhanced cytotoxic effect against human breast cancer cell line with increased encapsulation efficiency and sustained drug release, moreover the *in vivo* studies showed an increase in the bioavailability of the drug when compared with the free drug. Besides synthetic drugs, various natural compounds are clinically effective but are not frequently used due to their poor solubility and low bioavailability [15].

Loo., *et al*. incorporated berberine an isoquinoline alkaloid derived from *Berberis vulgaris* into LCNs to enhance its solubility and anticancer activity. The cell viability assay of berberine loaded LCNs in MCF7 human breast cancer cells revealed significantly lower IC50 values. The cellular uptake by Caco-2 cells was observed to be higher in berberine LCN as compared to the free berberine. The LCNs potentially enhanced the solubility and thus improved the anticancer activity of berberine [3].

Topical/Transdermal delivery

The LC mesophases have been widely explored as carrier systems for topical delivery because of their ability to improve permeation of bioactive molecules through the skin layers due to their nano size and occlusive nature. LLC have strong bio-adhesive property and they resemble the structure of the biological membrane when applied topically. They tend to interact with the lipids of the stratum corneum and form a drug depot on the skin which releases the drug in a controlled manner. The biological membrane like structure of LLC improves the skin retention and permeation.

Colchicine is a natural alkaloid extracted from the *Colchicum autumnale L*. plant. It is highly effective in the treatment of gout, but it is not used frequently due to various side effects associated with its oral and parenteral delivery. Nasr., *et al*. prepared a transdermal cubosomal gel of colchicine and studied the *in vivo* absorption of colchicine cubosomal gel and the oral drug solution in rats. The findings revealed that the cubosomal gel showed better absorption and 4.6 times higher relative bioavailability than the oral solution of colchicine [16].

Furthermore, Mahmood., *et al*. formulated LCNs of luliconazole which is an antifungal drug to improve its aqueous solubility and skin permeation. The LCNs demonstrated extended *in vitro* drug release up to 54 hours with higher values for ex vivo skin permeation when compared with the marketed cream of luliconazole. The results revealed higher retention of the drug in stratum corneum and deeper layers of the skin with improved penetration [17]. Similar results were reported in studies in which the use of LC as drug carrier enhanced the aqueous solubility of various drugs leading to enhanced bioavailability and improved skin permeation and deposition [18,19].

Intranasal delivery

Intranasal administration is a proficient method of delivering drugs to the brain because the nasal route is directly linked to the central nervous system and bypasses the blood brain barrier. The nasal route is non-invasive and can be easily used for self-administration of drug which could lead to improved patient compliance. Vinpocetine is effective in the management of cerebrovascular and cerebral degenerative disorder but its clinical use is limited due to its poor solubility, poor oral bioavailability, slow dissolution rate, extensive first pass hepatic metabolism and extremely short biological half-life which leads to repeated administration. Bakr., *et al*. developed vinpocetine loaded in situ hexosomal gel for the intranasal brain delivery of the drug to treat vascular dementia. The study revealed controlled release of the drug over a period of 24 hours. The maximum serum concentration (C_{max}) and area under the curve (AUC) values were significantly higher in rat brain after the intranasal application of the in-situ gel in comparison to the drug solution given intravenously at same dose [20].

Similarly, see., *et al*. conducted a study to enhance the nose to brain delivery of tranilast by using LC as the carrier system. They formulated C_{17}-monoglycerol ester (MGE) and glyceryl monooleate (GMO) based LC for the intranasal delivery of the drug. Both the formulations significantly enhanced the brain uptake of the drug, the highest concentration and fluorescent signals were observed in the olfactory bulb region which signifies the direct nose to brain delivery of LC formulation [21].

Cancer targeting

David., *et al.* developed a novel curcumin LC vaginal drug delivery system for the treatment of cervical cancer. The formulation was tested using Hela cells depicting an IC_{50} value of 22.5 µg/ml and drug release up to 87.25% over a period of 8 hours. The site-specific application ensured the fast distribution of drug and avoided the first pass metabolism effects associated with the oral delivery. The authors concluded that the treatment of Hela cells with LC formulation showed better results than the pure drug solution [22].

Thapa., *et al.* formulated a layer-by-layer polymer assembled LCNs to deliver sorafenib, a poorly water-soluble drug used in the treatment of hepatocellular carcinoma. The LCNs were formulated by coating them with poly-L-lysine and polyethylene glycol-b-polyaspartic acid six times. The coating was done to overcome the limitations associated with the intravenous administration of LCNs such as bio adhesivity, rapid elimination and LCN-induced haemolysis. The study revealed controlled release of the drug from the LCN preparation with targeted delivery. Higher cellular uptake and superior apoptotic effect of LCNs was observed in HepG2 cells indicating better antitumor effect [23].

Conclusion

The inherent properties of LLC make them suitable carriers for the delivery of active pharmaceutical ingredients to the targeted site. The ease of preparation and characterization make them appropriate delivery systems for oral, topical and intranasal delivery of therapeutic agents. The LLC formulations are composed of biodegradable and biocompatible constituents that provide enhanced drug loading and controlled release of drug. They can be produced by using low shear input which makes them feasible and economical carrier systems for drug delivery.

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