CHAPTER

# 7

# Liquid crystalline drug delivery systems

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## 1. Introduction

The first observation of liquid crystalline systems was attributed to the Austrian botanist-physiologist Friedrich Reinitzer [1] when he described the existence of an intermediate to the crystalline solid and liquid states. At the same time, Otto Lehmann [1a] observed that substances with ammonium oleate and *p*-azoxy-phenetole melted, passing through an intermediate state in which the liquid was birefringent [1]. In 1922, Lehmann coined the phrase liquid crystals (LCs) thinking that the only difference between LCs and solid crystals was the degree of fluidity [1].

LCs are designated as systems that behave like a liquid, but retain some structural characteristics of crystalline solids, such as fluidity and inability to withstand shear, droplet formation, and coalescence, as well as anisotropy of optical, electrical, and magnetic properties, and a periodic arrangement of the molecules, constituting a fluid and orderly phase. Therefore LCs represent intermediate states and are also called mesophases, as shown in Fig. 7.1 [2]. An important feature is to have the structural order of strongly reduced molecules, but maintain both the orientation order, with the characteristic rotational and translational movement characteristic of liquids, and the orientation and interaction between molecules characteristic of crystalline solids [3].

LCs were used predominantly for the topical administration of drug delivery in the early 1980s [4] because they have the ability to enhance both the solubility and control of the drug release rate [5]. LCs are easy to produce, biocompatible, cheap, and stable [6].

The mesophase is reached either by increasing the temperature or by adding a solvent being denominate lyotropic. Thermotropic liquid crystals (TLCs) exhibit phases as


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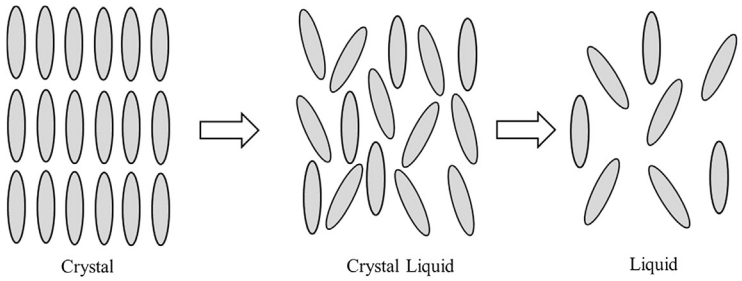


FIGURE 7.1 Formation of the liquid crystal phase between the crystal and liquid state of aggregation.

a function of temperature [7], whereas lyotropic liquid crystalline (LLC) systems are based upon the self-assembly of amphiphilic molecules when mixed with the aqueous phase, in most cases water or an organic polar solvent [8]. With this, the main difference between TLCs and LLC systems is the components used.

TLCs are pure components and may be organic or anisotropic molecules with molecular weights in the range of 250–500 g/mol. These molecules are composed of structural characteristics. Fig. 7.2 shows the salvarsan molecule as a model. In the figure (1) is the central group and shows polar characteristics linked to two ring systems (2), which are linked to two terminal groups one of which is a flexible alkyl chain (3), (4), (5), and (6). Examples of drugs with these characteristics are nafoxidine hydrochloride, palmitoyl propranolol hydrochloride, penbutolol sulfate, itraconazole hydrochloride, fenoprofen sodium, fenoprofen calcium, ciclosporin, and cholesteryl myristate [8].

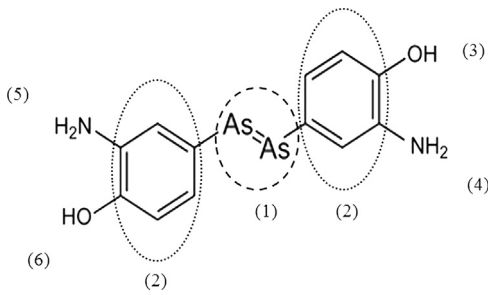


FIGURE 7.2 Salvarsan as a model of structural formulas of thermotropic liquid crystalline drugs.

Generally, TLCs show structures as rod-like molecules, which are classified as nematic, smectic, or cholesteric (Fig. 7.3). In the nematic phase the rod-like molecules maintain the same orientation. However, the order of position is not organized. In the smectic mesophase the molecules maintain the orientation of smectics arranged in layer or plane structures. The cholesteric (and chiral smectic) phase is considered the smectic phase incorporated in the nematic layers [9].

LLC systems are composed of at least two molecules: an amphiphilic molecule (surfactant) and a solvent. A hydrophilic solvent such as water, for example, hydrates the polar portions of the amphiphilic molecule with hydrogen bonds, while the aliphatic tails of the amphiphilic molecule aggregate in fused hydrophobic regions, based on van der Waals interactions. This interaction forms organized structures known as ordered micelles. The hydrophobic and hydrophilic properties of the lyotropic mesophases are important in determining the shape of the crystal [7].

In this way, mesophases can be organized structurally in lamellar, hexagonal, and cubic phases [10]. The lamellar phase is formed by bilayers separated by layers of surfactants and solvents, which form a one-dimensional or two-dimensional network. An important feature of this phase is its fluidity, and thus

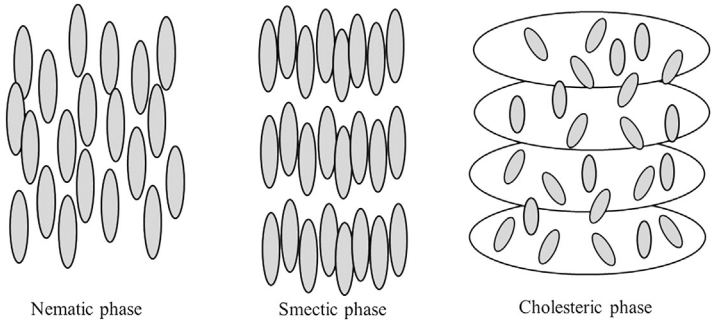


**FIGURE 7.3** Thermotropic liquid crystals: nematic, smectic, and cholesteric mesophases.

the slats can slide easily over one another [11]. The hexagonal phase forms aggregate by long cylindrical that form two-dimensional or three-dimensional structures. Two types of hexagonal mesophase can be found: normal and reverse mesophase depending on the solvent used, in this case aqueous and anhydrous organic solvents, respectively. Due to these characteristics, the hexagonal phase is much more rigid than the lamellar phase [12]. Cubic phases are obtained spontaneously more than water and have more complex and three-dimensional structures, consisting of a bicontinuous and curved lipid bilayer that extends in three dimensions to generate two interpenetrating, but not connected, aqueous channels. This single microstructure of a formed cubic phase offers advantageous properties for controlled drug release [13].

The formation of LLC systems is influenced by the temperature and concentration of the amphiphile molecule and solvent. Due to the amphiphilic nature of the components used to fabricate these systems, hydrophilic, lipophilic, or amphiphilic molecules can be encapsulated into these systems [14]. Table 7.1 shows the main amphiphilic molecules used in LLC systems for drug delivery.

In recent years, LLC systems have received considerable attention because of their excellent potential as drug delivery systems. The LLC system is the most used in drug delivery. The advantages of this carrier are: spontaneous reorganization and thermodynamic stability;

**TABLE 7.1** Main amphiphilic molecules used in lyotropic liquid crystalline systems for drug delivery.

| Material | Drug/pharmacology | References |
|---|---|---|
| Monoolein/glycerol monooleate | Celecoxib/antiinflammatory | [5] |
| Phytantriol | *Trans*-cinnamaldehyde/arthritis | [15] |
| Glycerol dioleate | Peptide BMS-686117/type II diabetes | [16] |
| Phosphatidylcholines | bupivacaine hydrochloride/ postoperative analgesia | [17] |
| Oleyl glycerate | vancomycin hydrochloride'/ocular infection | [18] |
| Polyoxypropylene-(5)-polyoxyethylene-(20)-cetyl alcohol | antimicrobial peptides/dental biofilm | [19] |

*Adapted from Otte A, Soh B-K, Yoon G, Park K. Liquid crystalline drug delivery vehicles for oral and IV/subcutaneous administration of poorly soluble (and soluble) drugs. Int J Pharm 2018;539:175–183.*

solubilized hydrophobic and hydrophilic compounds; promotion of sustained drug release; improved penetration into the skin; protection against physical and chemical degradation of drugs; and reduction in the adverse side effects of therapeutic compounds.

## 2. Preparation of LC systems

LC preparation is simple in comparison to other dispersions. Several methodologies have recently been reviewed in [20]. TLCs are obtained by heating the crystalline solid or cooling the isotropic liquid [7]. LLC system preparation requires homogenization of the aqueous phase and the oil phase [21].

Homogenization may be used with high (top-down) or low (bottom-up) energy. In top-down homogenization the lipid and stabilizer are hydrated to self-aggregate in a viscous volume, and then the volume is dispersed in an aqueous solution using high-pressure homogenization or ultrasonication, i.e., high-pressure homogenization, sonication, or shear. In bottom-up homogenization, the presence of the hydrotrope plays a leading role, creating a liquid precursor and preventing the formation of LCs in high concentration. The controlled addition of aqueous medium to the mixture leads to the formation of its dispersion. It is a dilution-based method and requires no fragmentation procedure [22].

After homogenization, the mixture is allowed to stand at ambient temperature for at least 48 h to obtain the LCs. Depending on the characteristics of the lipid, other additives may be added to the blend or the method may be modified, e.g., if more than one lipid is used, both lipids are mixed and, if necessary, melted before mixing with the aqueous phase. However, small differences can be observed in the preparation technique, depending on the mesophase that is desired to obtain the methods that can be classified [23].

The process is based on dilution, wherein the lipid moiety is dissolved in the surfactant before dilution in an aqueous medium. This is performed through the mapping of trajectories in the pseudoternary phase diagram (aqueous phase, oil phase, and surfactants) that obtains knowledge of the behavior of the complete phase. This method is more efficient in generating small particles, which form large particles by aggregation. These particles are also called cubic phases. This shows long-term stability, which can be attributed to the monodispersible stabilizers on the surface. The preparation procedure is simple and is extensively used in the preparation of LLC systems.

## 3. Characterization of liquid crystalline phases

The main methods available to investigate the structural characteristics of LC mesophases are X-ray diffraction, polarized light microscopy (PLM), and rheology.

A more common method for investigating LC crystalline phases of X-ray diffraction is the small-angle X-ray scattering technique, which is based on the elastic spread of X-rays by electron clouds of atoms present in the sample, as well as on the differences in the electronic density of the dispersion object and the medium. In this way, information is provided about the structure of spreader objects even if they are not organized in an orderly fashion. This evaluates the average size and distance between objects such as droplets, micelles, or crystalline structures, as well as the interactions between them [8,24].

Scattering intensity can be characterized as isotropic, a behavior of dilute solutions dependent on scattering or anisotropic angle for

more concentrated and ordered structures. In this way, the spreading profile provides information on the orientation of its components. Thus according to the position of the diffraction peaks in the axis of the scattering vector $q$ the structure of the liquid lyotropic crystals can be studied. Lamellar structures show the position of the peaks in relation to the first peak, which is more intense with a ratio of 1:2:3, whereas for hexagonal structures the ratio is $1:\sqrt{3}:2:\sqrt{7}$; the ratio of the cubic phase is 1.41:1.73:2.82:3 [25].

PLM is a standard tool for the identification of LC phases and phase transitions, because they exhibit birefringence as real crystals, except in the cubic mesophases where a dark background is observed [13]. They are presented with a white color; strong colors can also be observed. Each LC shows typical black and white textures. Hexagonal mesophases can be recognized by a typical fan form. Lamellar mesophases usually show oily streaks with malt crosses [5,13]. However, this technique only identifies particles in micron or submicron dimensions. For colloidal dimensions the crystalline liquids are solved by transmission electron microscopy. However, for aqueous samples, there may be a change in their microstructure, because they do not survive the high vacuum of an electron microscope without loss of water. Therefore special techniques of sample preparation are necessary, and freezing proved to be successful in this respect.

With the increase in the structural organization of LCs, the consistency increases, and the behavior of the flow becomes more viscous. In this way, LCs have different viscosities, which makes rheological property an important parameter. The high viscosity of the lyotropic liquid crystals such as cubic and hexagonal mesophases is due to their three-dimensional and two-dimensional structures, respectively, thus presenting high dynamic viscosity coefficient $h$. The opposite happens with lamellar systems. Another important feature that these systems exhibit is that they are not Newtonian, but plastic and pseudoplastic, respectively [11,26].

## 4. Applications of liquid crystalline systems

The application of LCs as drug carriers has been growing exponentially, with a great deal of attention focused on biological applicability *in vitro* and *in vivo* [27,28]. This type of system promotes the controlled release of active substances, increased potency, and pharmacological efficacy in the living organism. Given this, there are many studies that have explored the physicochemical characteristics of drugs to make them more effective and bioavailable [2,4,6].

Aida et al. demonstrated that anticaries agents must interfere with the adhesion of *Streptococcus mutans* and its proliferation in dental biofilm, without causing host toxicity and bacterial resistance [19]. Cationic antimicrobial peptides, such as β-defensins, have been introduced as future antimicrobial agents due to their rapid onset killing and broad-spectrum activity against Gram-positive and Gram-negative bacteria, fungi, and viruses, allied with potentially low levels of induced resistance [19]. According to Freires and Rosalen [29], natural compounds with antimicrobial properties have been studied as topical agents for an oral cavity to reduce pathogens without causing bacterial resistance.

Several studies have evaluated the incorporation of peptides in drug delivery systems in the treatment of cardiovascular diseases [30], diabetes [31], and AIDS [3].

Bernegossi et al. explain that LC is a drug delivery system that can be used for incorporating peptides [32]. LCs can promote the controlled release of drugs and protect active ingredients from thermal degradation and photodegradation while improving the effectiveness of these peptides [33,34].

Beside that, LCs can promote the controlled release of drugs and protect active ingredients from thermal degradation and photodegradation while improving the effectiveness of these peptides. The bioadhesive property of these systems can maintain a high concentration of the peptide at the site of action for a long period, while also protecting it from environmental degradation.

A study developed by Calixto et al. [33] evaluated a safe buccal drug delivery system for the treatment of several buccal diseases because buccal mucosa is accessible, shows rapid repair, has an excellent blood supply, and shows the absence of the first-pass effect, which makes it a very attractive drug delivery route.

The results showed that it is possible to develop a precursor of LCs composed of chitosan and polyethyleneimine as the aqueous phase, oleic acid as the oil phase, and ethoxylated and propoxylated cetyl alcohol as the surfactant for use as a drug delivery system for the buccal route. Nanotechnology-based drug delivery systems, such as LCs, can increase drug permeation through the mucosa and thereby improved delivery of drug.

Celecoxib (CXB) is a widely used antiinflammatory drug that also acts as a chemopreventive agent against several types of cancer [5]. The composition of the systems and crystalline structure influence the potency of antiinflammatory activity in a model of aerosol-induced rat paw edema inflammation. Cubic phase systems containing an oleic acid/propylene glycol association reduced edema in a sustained manner, indicating that they modulate CXB release and permeation. Our findings demonstrate that the developed liquid crystalline systems are potential carriers for the skin delivery of CXB.

The topical administration of metronidazole via nanotechnology-based drug delivery systems, such as LCs, can modulate both drug permeation and activity, decreasing side effects and increasing potent drug activity against Gram-positive bacteria [34]. This research is aimed at structurally developing an LC composed of chitosan and polyethyleneimine dispersion as the aqueous phase, oleic acid as the oily phase, and ethoxylated and propoxylated cetyl alcohol as the surfactant for metronidazole incorporation.

Subsequently, *in vitro* release and skin permeation and retention properties of metronidazole-loaded liquid crystalline systems and investigation of *in vitro* antibacterial activity against *Staphylococcus aureus* were investigated. Therefore it can be concluded that the LCs developed in this study can improve the clinical performance of metronidazole in the treatment of Staphylococcal skin infections [35].

Among anticancer drugs, 5-fluorouracil (5-FU) is one of the major agents used clinically, alone or in combinations with other chemotherapy agents, for the treatment of gastric, stomach, colorectal, head and neck, and breast cancers [36]. In this sense, LLC systems have received increasing attention due to their unique microstructural and physicochemical properties as nanocarriers efficient for drug release.

The study carried out by Astolfi et al. [37] analyzed the preparation and characterization of granular phases and dispersions in phytantriol cubosomes loaded with the anticancer drug 5-FU. In addition, the optimized, possibly targeted, delivery of 5-FU to cancer cells via engineered LLC system vectors may represent a major step toward a more effective and safer breast cancer therapy.

According to Fonseca-Santos et al. [38] evidence shows the beneficial effects of resveratrol (RE) on human health, which can be attributed to its antiinflammatory activity. However, the poor aqueous solubility of RE limits its therapeutic efficacy. Therefore the use of nanostructured

delivery systems for RE, such as LCs, may be a solution. In the present study, the *in vivo* effectiveness of RE-loaded LCs was determined. As a result of the study, it was observed that the topical application of the RE-loaded lamellar mesophase LCs resulted in edema inhibition in a carrageenan-induced paw-inflammation mouse model. Moreover, all LCs were as bioadhesive as conceptualized bioadhesive formulations, and in particular these LCs were able to maintain the antiinflammatory activity of RE.

The pharmacological action of tamoxifen-loaded liquid nanoparticles (TMX-LCNPs) was investigated by Jain et al. [39] to improve oral bioavailability and safety of existing chemotherapy treatment. TMX-LCNPs were found to be considerably more highly cytotoxic to MCF-7 cells compared to free TMX. From extensive optimization *in vitro* and *in vivo* evaluations, it can be concluded that the TMX-LCNP formulations used in this study showed a significantly higher relative bioavailability, subsequently leading to better tumor regression with less hepatotoxicity.

Musa et al. also investigated the efficacy of exemestane, an antiestrogen and aromatase inhibitor, on the anticancer activity of estrogen [40]. It is used to treat breast cancer in high-risk postmenopausal women [39]. In this context, the purpose of this study was to develop and evaluate LC gel formulations to deliver the anticancer drug exemestane through the transdermal route. Results have also demonstrated that the formulations developed in this study were able to produce a sustained release and permeate a full-thickness skin without any visible adverse reactions. Besides that, the in vitro effectiveness study indicated that even at low exemestane concentrations (12.5 and 25 μg/mL) the formulations were able to induce cancer cell death. Histopathological analysis of the epidermis shows that the formulations penetrate the intercellular regions of squamous cells.

Another well-known disease is diabetes mellitus, a metabolic disease, typically characterized by a high level of glucose in the blood, either because of an insufficient amount of insulin produced in the body or because of the lack of response of cells against insulin. The present report investigated the feasibility of liquid crystalline nanoparticles (LCNPs) to improve the stability and therapeutic efficacy of insulin following oral administration [41]. Given the observed results, it was possible to verify that the developed LCNPs showed excellent stability, absorption, and sustained glucose reduction profile. Also, there was a facility in the production technique and low cost of components of the formulation that made this approach easy and scalable.

## 5. Conclusion

In this chapter we concluded that using LCs as a drug delivery system is useful in various routes of administration. The method of production and scale-up is easy. The structure of these systems consists of a complex matrix that retards diffusion and provides sustained release of drugs; for this reason, these systems have been studied as sustained drug delivery devices for several drugs and routes of administration, including skin delivery of drugs. Thereby, the use of LC formulations for drug delivery has considerably improved the current delivery methods in terms of bioavailability and efficacy.

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