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LIQUID CRYSTALS AS NOVEL VESICULAR DELIVERY SYSTEM: A REVIEW

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Abstract - Recently, liquid crystals (LCs) studied as novel drug delivery system. The reason for this interest is due to the extensive similarity of these colloidal systems to those in living organism and their superior advantageous properties over traditional dermal, parenteral and oral dosage forms. LCs show structural, mechanical, and optical properties intermediate to those of crystalline solids and isotropic liquids. There are two principal types of LCs. Lyotropic liquid crystals (LLCs) and thermotropic liquid crystals (TLCs). LLCs are prepared by heating the anisotropic substances in presence of solvent while TLCs are prepared by heating the anisotropic substances or cooling an isotropic melt of TLCs forming substances. LCs are thermodynamically stable and they possess longer shelf life. The utility of this novel system is further increased owing to its very low skin irritation potential. This review covers introduction, classification, characterization and applications of LCs.

Keyword - Drug Delivery; Vesicles; Thermotropic; Lyotropic; Liquid crystalline gel.

1. INTRODUCTION

LCs are defined as the state of matter existing between the liquid and the crystalline solid, characterized by the partial or complete loss of positional order in crystalline solids, while retaining the orientational order of the constituent molecules. Such orientational order can persist in the solid state and thus LCs may show mechanical stability like solids as well as flow like liquids. Molecular orientation in LCs is the origin of the birefringence that is not present in the glassy state, as it does not have the molecular orientational order. LCs shows general properties like birefringence, response to magnetic and electric fields, optical activity in twisted nematic phases and sensitivity to temperature resulting in color changes. LCs are condensed state of matter formed by anisotropic organic molecules. While not all the anisotropic molecules can form LCs, all LCs are formed by anisotropic molecules. These molecules are termed mesogens and are either of rod shape or less commonly disc shape. Liquid crystalline systems (mesophases) have been investigated as modern formulations by many authors [1]-[5]. Summary of various categories of drugs studied for liquid crystals as drug delivery system given in Table 1.

Crystalline solids are characterized by long-range positional and orientational order in three dimensions. Whereas amorphous liquids lack long-range order in any dimensions. LCs (mesophases) show structural, mechanical and optical properties intermediate to those of crystalline solids, amorphous and liquid state of matter as shown in Figure 1. LCs, however, are not a mixture of solids and liquids, but indeed a separate state of matter [28].

2. CLASSIFICATION OF LIQUID CRYSTALS

LCs are differentiated on the basis of positional order (i.e. molecules are arranged in randomly structured lattice) and orientational order (i.e. molecules are mostly pointing in the same direction). Moreover order can be either short-range (only between molecules close to each other) or long-range (extending to larger, sometimes macroscopic). LCs are classified by their method of preparation into the lyotropic and thermotropic LCs [29]-[31].

2.1. Lyotropic liquid crystals

Lyotropic liquid crystalline systems are composed of rod like micelles, and which shows a long-range orientational order with respect to symmetry axis of the micelle, but no long-range positional order. The three main types of LLCs are characterized as being lamellar, hexagonal and cubic [28].

2.1.1. Lamellar LCs

Lamellar LCs neat phase is generally having bilayered structure as repetition unit, and which shows long-range positional order in one dimension and long-range orientational order within the layer. They can also be termed as layered packing of indefinitely extended disc-like micelles [32]- [34].

2.1.2 Hexagonal LCs

Hexagonal LCs shows long-range positional order in two dimensions. Both the lamellar and hexagonal LCs can be identified using polarized light microscopy as they exhibit a range of textures that are typical for the corresponding LCs. They are also known as middle phase [35], [28].

2.1.3. Cubic LCs

Cubic LCs shows long-range positional order in three dimensions. Generally these LCs having cubic packing of the micelles and can not identified using polarized light microscopy. They are highly viscous and have pour flowing property as compare to lamellar and hexagonal LCs [36], [37], [2].

2.2. Thermotropic Liquid Crystals

Thermotropic mesophases are formed upon heating of crystalline substance alone (with one component) and unlike lyotropic mesophases, do not require the presence of a solvent for their formation. The thermotropic liquid crystalline form of a drug may be regarded as special polymorphic form [28], [9], [38]. The three types of thermotropic liquid crystalline phases are characterized as being nematic, smectic, and cholesteric. These are based on a system proposed by G. Friedel in 1922.

2.2.1. Smectic LCs

Smectic is derived from Greek meaning grease or clay. The long axes of all molecules in a given layer are parallel to one another and perpendicular to the plane of layers. The layers are free to slip and travel over each other. The smectic state is viscous, yet fluid and ordered [29].

2.2.2. Nematic LCs

Nematic is derived from Greek meaning thread-like. Under a microscope using polarized light, nematic LCs emerge as thread-like structures. In the nematic state, the molecules are not as extremely ordered as in the smectic state, but they maintain their parallel order. LCs used in electronic display is primarily of the nematic type. Owing to its specific molecular alignment, nematic LCs show anisotropic physical characteristics; their refractive index, dielectric constant, permeability, electrical conductivity and viscosity when measured in the direction of the long axis are different from those measured in the plane normal to the long axis [29], [39].

2.2.3. Cholesteric LCs

Cholesteric arrangement is to some extent a combination of the nematic and smectic wherein the layers are nematic but in addition, certain layer formations which resemble the smectic phase are incorporated [9], [40]. The molecules in cholesteric LCs are arranged in layers. Within each layer, molecules are aligned in parallel, similar to those in nematic LCs. The molecular layers in a cholesteric LCs are very thin, with the long axes of the molecules analogous to the plane of the layers [29].

3. Characterization of Liquid Crystals

Appropriate methods for the characterization of lyotropic liquid crystals are frequently used in drug development and may thus be employed in pharmaceutical laboratories. These methods are based on both macroscopic and microscopic determinations.

3.1. Polarized light microscopy

LLCs can be characterized easily with the help of polarized light microscope except cubical mesophases. They show birefringence in presence of polarized light just like real crystals do. Birefringence can be observed in a polarized microscope. Two polarizers in cross position are mounted below and above the birefringent object being examined. The cross position of the polarizers provides plane polarized waves at right angles to each other. Thus, the light passing the polarizer below an isotropic object cannot pass the polarizer in across position above the object. In an anisotropic material, some parts of the light are able to pass the second polarizer because the plane polarized beam has been rotated by an angle relative to the plane of the incoming beam. Each LCs shows typical black and white textures [6], [32], [33].

Hexagonal LCs can be recognized by their characteristic fan-shaped texture. Lamellar LCs typically show oily streaks with inserted maltese crosses. The latter result from defects, so called confocal domains, that arises from concentric rearrangement of plane layers. These defects exist in some lamellar LCs. Hence, no oily streaks occur but maltese crosses are the dominant texture. The smectic mesophases of the thermotropic LCs show a variety of textures but look like the fan shaped texture of the lyotropic hexagonal mesophase [6].

The authors prepared lyotropic liquid crystalline transdermal system using Brij-35, cetosteryl alcohol, propranolol and water. We observed the presence of birefringence (basic property of LCs) in LCs and their distribution in the system was found to be uniform [41].

3.2. Electron microscopy

Transmission electron microscopy offers high magnification power and the microstructure of LCs can be visualized. However, aqueous samples do not survive the high vacuum of an electron microscope without loss of water and thus their microstructure changes. Therefore, special techniques of sample preparation are necessary prior to electron microscopy. The freeze fracture technique has proven to be successful in this regard. In this method, a replica of the sample is produced and viewed in the electron microscope. To preserve the original microstructure of the sample during the replication, the first step is shock freeze the sample. For high freezing rates to (10^5 – 10^6 K/s), the sample is sandwiched as a thin layer between two gold plates and then shock frozen with either nitrogen-cooled liquid propane at –196^{o} or slush nitrogen at –210^{o}. If the temperature of the cooling medium is far below its boiling temperature, an efficient freezing rate can be obtained [6], [32], [33].

The frozen sample within the sample holder is transduced into the recipient of a freeze fracture apparatus, in which the fracture is performed at a temperature of –100^{o} and a vacuum between 10^{-6} and 5 x 10^{-7} bar. Within a homogeneous material, the fracture occurs by randomly because all structural elements have equal probabilities for fracturization. However, even a homogeneous material often consists of more or less polar areas. Within polar areas, stronger interactions via hydrogen bonds prevent the fracture; thus, fracture within polar areas is less probable than is fracture within apolar areas. As a result, the sample profile obtained after fracturization represents the microstructure of the sample just qualitatively and not quantitatively [6], [32], [33].

3.3. X-ray scattering pattern

X-ray scattering technique used to characterize liquid crystalline systems. The characteristic interferences are generated from an ordered microstructure. A typical interference pattern arises due to specific repeat distances of the associated interlayer spacing, *d*. By Bragg's equation, *d* can be calculated as $d = n(\lambda/2)\sin\theta$ where λ is the wavelength of the X-ray (e.g., 0.145nm by using a copper anode or 0.229 nm by using a chromium anode), *n* is an integer and denotes the order of the interference and, λ is the angle under which interference occurs. Bragg's equation points at the inverse proportionality between *d* and θ [6].

Large terms for *d* in the region of long-range order are registered by the small-angle X-ray diffraction (SAXD) technique, while small terms for *d* in the region of short-range order are registered by the wide-angle X-ray diffraction (WAXD) technique. SAXD is important for the exact determination of the distances of *d* of liquid crystalline systems. With WAXD, the loss of short-range order of liquid crystalline systems can be recognized in terms of the absence of interferences, which are characteristic of the crystalline state. Interferences can be detected in two ways: (a) the film detection; and (b) the registration of X-ray counts with scintillation counters or position-sensitive detectors. Though, SAXD does not only detect interferences from which the interlayer spacings can be calculated, but also enables to decide from the sequence of the interferences the type of LCs domain. The sequence of the interferences for Lamellar, Hexagonal, Cubic I and II, LCs gives 1; 1/2; 1/3; 1/4….., 1; $1/\sqrt{3}$; $1\sqrt{4}$; $1\sqrt{7}$ …., 1; $1/\sqrt{2}$; $1/\sqrt{3}$; $1/\sqrt{4}$ …..and 1; $1/\sqrt{4}$; $1/\sqrt{5}$; $1/\sqrt{6}$ ….. X-ray diffraction technique respectively [6], [28].

3.4. Differential scanning calorimetry

Phase transitions occur with changes in energy content of the respective system. This phenomenon is caused by changing either the enthalpy ΔH or the entropy ΔS. Enthalpy changes cause endothermic or exothermic signals depending on whether the transition is due to consumption of energy by melting of a solid or release of energy by recrystallization of an isotropic melt. It should be mentioned that the transition from crystalline to amorphous requires much energy, whereas the transition from crystalline to liquid crystalline, from liquid crystalline to amorphous and particularly the transition between different LCs consume low amounts of energy [6], [34].

3.5. Rheological measurements

Rheological property is another important parameter to characterize LCs. Different LCs have different viscosity. On an increase in the microstructural organization of the LCs, its consistency increases and the flow behavior becomes more viscous. The coefficient of dynamic viscosity η, although a criterion for the viscosity of just ideal viscous flow behavior (Newtonian systems), is rather high for cubic and hexagonal LCs but quite low for lamellar ones; though, the flow characteristics are not Newtonian but plastic for cubic and hexagonal LCs or pseudoplastic for lamellar ones. In thermotropic LCs, the viscosity increases in the following sequence: nematic < smectic < cholesteric [6], [34].

3.6. Determination of vesicle size and their distributions

Liquid crystalline vesicular size is an important parameter for in-process quality control and particularly for quality assurance because the physical stability of the vesicle dispersion depends on particle size and particle size distribution. An appropriate and particularly quick method is the laser light scattering (for particle size) or diffraction (for particle size distribution). Laser light diffraction can be applied for particles >1 μm and according to the diffraction theory of Fraunhofer, refers to the proportionality between intensity of diffraction and the square of particle diameter [6], [42].

4. Applications of Liquid Crystals

LCs have generated considerable alertness over the years as a potential drug delivery vehicle. The coexistence of organic and aqueous phase by means of a structurally well-defined micellar network of surfactants, a large interfacial area, and the possibility to entrap solutes within the gel matrix, along with long-term stability, makes them valuable for a variety of applications. Therapeutic compounds of diverse physicochemical properties such as analgesics, antibiotics, antifungal, anticancer, vitamins, antiasthmatic, immunosuppressive etc. have been either incorporated or itself used for the formation of the LCs with some very encouraging results [9], [43].

5. Conclusion

Liquid crystalline structures provide a wide varied of structural and functional features. They keep ability to encapsulate hydrophobic and hydrophilic drug(s). It appears that these attributes can be advantageously utilized in drug delivery challenges, making surfactant based drug delivery system a successful approach. Challenges related to manufacturing, stability, and reproducibility has been overcome.

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TABLE 1
Drugs studied for liquid crystals as drug delivery system

Drug substances forming LCs	Catagory	Type of liquid crystals	References
Arsphenamine	Antimicrobial agents	Nematic thermotropic LCs	[6]
Nafcillin	Antimicrobial agents	Lamellar, lyotropic LCs	[7], [8]
Tobramycin	Antimicrobial agents	Nematic thermotropic LCs	[9]
Itraconazol	Antimicrobial agents	Nematic thermotropic LCs	[10]-[12]
Methotrexate	Anticancer	Nematic thermotropic LCs	[13]-[15]
Leuprolide	Anticancer	Smectic thermotropic LCs	[16]- [18]
Nafarelin	Anticancer	Smectic thermotropic LCs	[16]- [18]
Detirelix	Anticancer	Smectic thermotropic LCs	[16]- [18]
Fenoprofen and its salts	NSAID	Lamellar, lyotropic LCs or smectic thermotropic LCs	[19]- [21]
Ibuprofen	NSAID	Lamellar lyotropic LCs	[6]
Diclofenac	NSAID	Lamellar, lyotropic LCs	[6]
Leukotriene	Anti-inflammatory	Thermotropic LCs	[22]
Cromolyn	Antiasthmatic	Cholesteric lyotropic LCs or smectic thermotropic LCs	[23]- [25]
Cyclosporine	Immuno-suppresive	Smectic thermotropic LCs	[4], [13], [26], [27]

LCs, liquid crystals; NSAID, non steroidal anti-inflammatory drug.

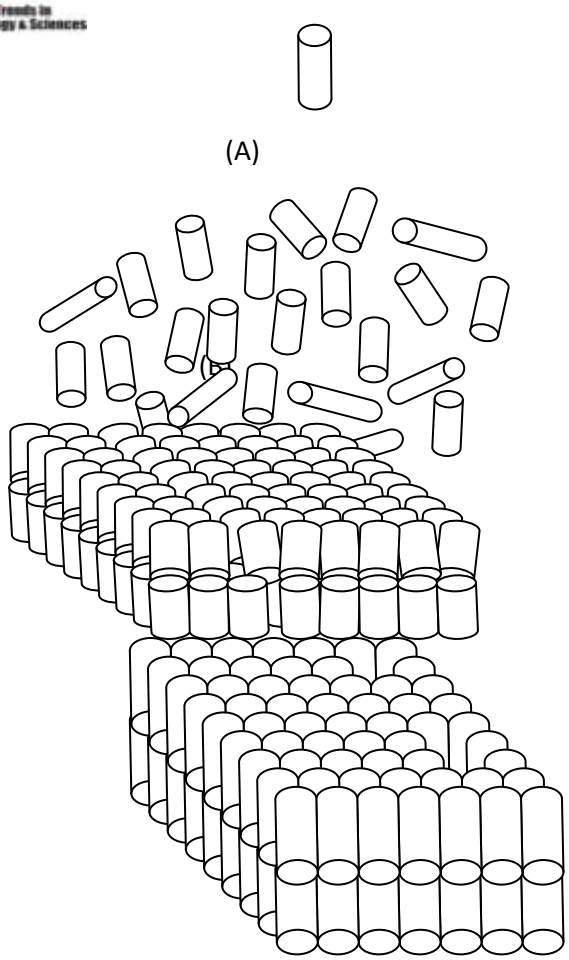

Figure 1. Showing schematic diagram of (A); single surfactant, (B); liquid, (C); liquid crystal, (D); solid crystal