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Review on Liquid Crystals

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A B S T R A C T

Liquid crystalline systems (mesophases) have been investigated as modern formulations. Various categories of drugs are studied for liquid crystals as drug delivery systems. Crystalline solids are characterized by long-range positional and orientational order in three dimensions. LCs are classified by their method of preparation into the Lyotropic and thermo tropic LCs. 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.

Keywords: Liquid crystals, Lytrotropic crystals, Lcs, Differential scanning calorimetry

A R T I C L E I N F O

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1. Introduction

Liquid Crystals (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 orientation 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. These molecules are termed mesogens and are either of rod shape or less commonly disc shape. Solids are characterized by long-range positional and orientational order in three dimensions. Amorphous liquid lacks long-range order in all dimensions. Lyotropic liquid crystal (LLC)[1] systems that commonly consist of amphiphilic molecules and solvents can be classified into lamellar (La), cubic, hexagonal mesophases, and so on. In recent years, LLC systems have received considerable attention because of their excellent

potential as drug vehicles. Among these systems, reversed cubic (Q2)[2] and hexagonal mesophases (H2) are the most important and have been extensively investigated for their ability to sustain the release of a wide range of bioactives [3]from low molecular weight drugs to proteins, peptides and nucleic acids.

2. Classification

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) [4] .Moreover order can be either short- range (only between molecules close to each other) or long-range (extending to larger, sometimes macroscopic).[5] LCs are classified by their method of preparation into the Lyotropic and thermo tropic LCs.[6]

Lyotropic liquid crystals

- Lamellar liquid crystals
- Hexagonal liquid crystals
- Cubic liquid crystals

Thermo tropic liquid crystals

- Smectic liquid crystals
- Nematic liquid crystals
- Cholesteric liquid crystals

Discotic liquid crystals

I. Lyotropic Liquid Crystals

Lyotropic liquid crystalline systems are composed of rod like micelles, and which shows a long-range orientation 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 liquidcrystals[7]

Lamellar LCs

Lamellar LCs neat phase is generally having bilayered 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[8]

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[9]

Cubic LCs

Cubic LCs shows long-range positional order in three dimensions. Generally these LCs having cubic packing of the micelles and cannot identified using polarized light microscopy. They are highly viscous and have pour flowing property as compare to lamellar and hexagonal LCs[10]

Thermotropic Liquid Crystals

Thermo tropic 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 thermo tropic liquid crystalline form of a drug may be regarded as special polymorphic form[9, 11, 13] .The three types of Thermo tropic liquid crystalline phases are characterized as being Nematic, Smectic, and Cholesteric. These are based on a system proposed by G. Friedel in 1922.

Smectic LCs:

The word Smectic is derived from Greek language 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[12]

Nematic LCs

The word Nematic is derived from Greek language meaning thread-like. Under a microscope using polarized light, Nematic LCs emerges 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[15]

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. 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[16]

Discotic Liquid Crystals

The investigation of the liquid crystal (LC) properties of compounds containing disc-shaped molecules has been of considerable interest ever since the discovery of Discotic LCs by Chandrasekhar in 1977. The mesophases of Discotic LCs usually exhibit either Nematic or columnar organizations of their disc-shaped molecules. These unique properties of Discotic LCs have led to predictions of commercial applications in areas as disparate as environmental gas sensing and fast high-resolution light scanning to the building of hybrid computer chips.

Preparation of Liquid Crystals: Liquid crystal gels could be prepared by simply blending aqueous phase with lipid phase using vortex or ultra sonication. The manufacture of Cubosomes or Hexosomes is more complicated, however; therefore, we mainly concentrate on the preparation methods of LLC nanoparticles. The schematic diagrams are represented below

Lyotropic liquid crystals

Lyotropic mesophases are formed from the solid crystalline or liquid association colloids or swelling amphiphiles by the addition of water and in some cases, too, by the addition of a liquid organic solvent. From the aqueous solutions of association colloids mesophases form by three processes

- By the separation of micellar substance in the liquid crystalline state when the water content of solutions is reduced

- By the separation of micellar substance at lower concentrations, from the CMC upward, as a result of the changes that the micelles undergo on solubilization of added amphiphiles or lipophiles
- By the formation of aggregates between a solubilizate and the molecules or ions of association colloids, below the CMC.
- From solutions of swelling amphiphiles in organic solvents Lyotropic mesophases can be formed through an increase in the amphiphile or amphiphile and water content of the solution, and through solubilization of water in the initially anhydrous solution. Just as there are two types of micelles, the normal (type 1) and the reversed (type 2), a number of Lyotropic liquid crystalline structures also can occur as two complementary types. One of them is composed of amphiphilic aggregates with a hydrocarbon core and a layer of polar groups in the boundary against the surrounding water, that is aggregates in a water continuum—normal type (type 1)—while the other consists of aggregates with a core of unhydrated or hydrated polar groups and water, surrounded by layers of hydrocarbon chains, that is aggregates in a hydrocarbon continuum—the reversed type (type 2). Intermediate between these two types are the lamellar mesophases, composed of coherent layers of amphiphile molecules with the hydrocarbon inner most and the polar groups in the boundary with the intervening layers of water molecules.

Thermotropic Liquid Crystals:

Thermo tropic phases are those that occur in a certain temperature range. If the temperature rise is too high, thermal motion will destroy the delicate cooperative ordering of the LC phase, pushing the material into a conventional isotropic liquid phase. At too low temperature, most LC materials will form a conventional crystal[1, 18]. Many thermo tropic LCs exhibit a variety of phases as temperature is changed. For instance, a particular type of LC molecule (called mesogens) may exhibit various Smectic and Nematic (and finally isotropic) phases as temperature is increased. An example of a compound displaying thermo tropic LC behavior is para-azoxyanisole

3. Characterization of Liquid Crystals

1. Particle size determination by laser light scattering

The particle size is an important parameter in in-process control and particularly in quality assurance, because the physical stability of vesicle dispersions depends on particle size and particle size distribution. An appropriate and particularly quick method is laser light scattering or diffraction. Laser light diffraction can be applied for particles ranging in mm and refers to the proportionality between the intensity of diffraction and the square of the particle diameter according to the diffraction theory of Fraunhofer[21]. For particles below 200 nm Rayleigh's theory holds, which considers that scattering intensity is proportional to the sixth potency of the particle diameter? Both, Fraunhofer's and Rayleigh's theories[25], are only approximations of Mie's theory which claims that the scattering intensity depends on the scattering angle, the absorption and the size of the particles as well as[27].

Microscopy

Polarized light microscopy (PLM) is suitable for detection of Lyotropic liquid crystals (except cubic mesophases) because liquid crystals show birefringence just like real crystals. Each liquid crystal shows typical black and white textures. In the case of an additional l-plate with strong birefringent properties, color effects of the textures can also be observed. Hexagonal mesophases can be recognized by their typical fan shape texture. Lamellar mesophases typically show oily streaks with inserted maltese crosses. The latter result from defect structures, called confocal domains that arise from concentric rearrangement of plain layers. In some lamellar mesophases these defects prevail. Hence no oily streaks occur but maltese crosses are the dominant texture. A drawback of PLM is that it is restricted to particle dimensions in the micron or submicron range whereas colloidal dimensions of liquid crystals are only resolved by transmission electron microscopy (TEM).

X-ray scattering

With X-ray scattering experiments characteristic interferences are generated from an ordered microstructure. A typical interference pattern arises due to specific repeat distance of the associated interlayer spacing 'd'. According to Bragg's equation can be calculated. Where l is the wavelength of the X-ray being used, n is an integer and nominates the order of the interference, and g is the angle under which the interference occurs (reflection conditions are fulfilled). From Bragg's equation it can be seen that the interlayer spacing d is inversely proportional to the angle of reflection g: Large terms for d in the region of long-range order can be measured by small-angle X-ray diffraction (SAXD), while small terms for d in the region of short-range order can be investigated by wide-angle X-ray diffraction (WAXD). SAXD is the most appropriate technique for the exact determination of the distances of interlayer spacings of liquid crystalline systems. The short-range order of crystalline nanosuspensions can be detected by WAXD. Interferences can be detected by using either film detection, or scintillation counters or position-sensitive detectors. However, in addition to interference detection, and subsequent calculation of interlayer spacings of the crystalline material, the SAXD method enables the sequence of the interferences and thus the type of ordering to be detected. A further option involving X-ray scattering is the diffuse SAXS technique, which is especially useful for colloidal dispersions because information about size and shape of the particles can be obtained at the same time.

Differential scanning calorimetry (DSC)

Phase transitions are accompanied by free energy changes, and are due to either an alteration in the enthalpy or entropy of the system. Enthalpy changes result in either endothermic or exothermic signals, depending on whether the transition is due to consumption of energy, e.g. melting of a solid, or a release of energy, e.g. recrystallization of an isotropic melt. It should be mentioned that the transition from the crystalline to amorphous phase requires a high energy input. This is in contrast to crystalline to liquid crystalline and liquid crystalline to amorphous transitions as

well as changes between different liquid crystalline phases, which all consume low amounts of energy. Therefore care has to be taken to ensure that the measuring device is sensitive enough to give a sufficiently low detection limit. Entropically caused phase transitions may be recognized by a change in baseline slope due to a change in the specific heat capacity. Liquid crystalline polymer phase transitions are entropically related and are thus considered second order transitions such as those from glass to rubber. These are usually called glass transitions.

Rheology

Different types of colloidal carriers exhibit different rheological properties. With increased organization of the liquid crystal microstructure, viscosity increases. The coefficient of dynamic viscosity h describes the viscosity of ideal flow behavior (Newtonian systems), and is rather high for cubic and hexagonal liquid crystals but fairly low for lamellar systems. However, it should be kept in mind that these systems exhibit flow characteristics that are not Newtonian but plastic and pseudoplastic, respectively. The high viscosity of lyotropic liquid crystals such as cubic and hexagonal mesophases is due to their three-dimensional and two-dimensional order, respectively. Lamellar mesophases with one-dimensional long-range order have a fairly low viscosity. Due to their gel character, cubic and hexagonal mesophases exhibit a yield value after which flow occurs. Unlike the corresponding inverse liquid crystals, the gel character is much more pronounced, resulting from interactions between polar functional groups located at the surface of the associates. The associates may form strong networks with each other through polar interactions such as hydrogen bonds. In contrast, the surface of inverse mesophase associates consists of nonpolar groups. This results in interactions that are weaker and the gel deforms more easily.

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

4. Applications of Liquid Crystals

LCs has 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.

Ability to Sustain or Control Drug Release

As drug carriers, cubic phase liquid crystals have the ability to provide sustained drug release. Drugs with a wide range of molecular weights and water solubilities have demonstrated sustained release in a cubic phase, such as aspirin and vitamin E, propantheline bromide and oxybutynin hydrochloride, metronidazole, tetracycline, timolol maleate, chlorpheniramine maleate, propranolol hydrochloride, melatonin, pindolol, propranolol and and diclofenac salts. Lee et al. studied the in vitro sustained release behavior of a number of model hydrophilic drugs with various molecular weights (14C-glucose, Allura Red, and fluorescein isothiocyanate dextrans FD-4, FD-20, and FD-70) in two types of liquid crystalline matrixes, namely, V2GMO (a cubic phase prepared from GMO) and V2PT (a cubic phase prepared from PT). The release samples were constrained in microbeakers with a fixed surface area to ensure a constant release area between the liquid crystals and the release media. The results showed that in all cases the cumulative amount of drug diffusion through the matrix followed a linear relationship with the square root of time, which represented a Higuchi diffusion controlled release profile.

Ability to Improve Drug Bioavailability and Reduce Drug Toxicity: Cubic phases are used to improve the drug bioavailability and reduce drug toxicity. Yang et al. prepared PT-based Cubosomes containing Amphotericin B (AmB) to improve its bioavailability and reduce nephrotoxicity. After oral administration of an AmB-loaded Cubosomes formulation in rats, nephrotoxicity was not observed and the relative bioavailability of AmB was approximately 285% compared to the control group.

Ability to Enhance the Stability of Drugs.

The results showed that the native conformation of agitated insulin in cubic phase gels was almost unaffected for 2 months at 37^{o} C, while the majority of insulin in solution appeared to aggregate and precipitate only after 8 days. Therefore, the cubic phase gel was able to protect insulin from agitation-induced aggregation and subsequent precipitation.

Ability to Increase the Penetration of Drugs: Cubic phases and Cubosomes also have the ability to improve the transdermal /topical delivery of small molecules such as acyclovir, paeonol, δ-aminolevulinic acid, sulphorhodamine B, calcein, and diclofenac salts, as well as macromolecules such as cyclosporin A.

Application in Stimuli Responsive Drug Delivery System: Because of the possibility to switch between the cubic phase (fast release) and hexagonal phase (slow release) by adjusting temperature and/or pH, researchers have designed a series of stimuli responsive drug delivery systems. Fong et al developed an externally regulated thermo responsive liquid crystalline system for subcutaneous injection of hydrophilic drugs (glucose). In in vivo absorption studies, the drug was released slowly from hexagonal phase when subcutaneously injected at physiological temperature. After application of a cool pack at the injection site, the plasma concentration was significantly increased due to the structure transformed into cubic phase

LC Formulations For Dermal Applications

Since drug molecules with amphiphilic character may form Lyotropic mesophases, amphiphilic excipients in drug formulations also form Lyotropic liquid crystals. This is particularly so for surfactants, which are commonly used as emulsifiers in dermal formulations, and associate to form micelles after dissolving in a solvent. With increasing concentration the probability of interaction between the micelles increases and thus liquid crystals form.

Surfactant gels

The use of monophasic systems of Lyotropic liquid crystals is relatively seldom and is limited to gels. A variety of polar surfactants (e.g. ethoxylated fatty alcohols) hydrate in the presence of water and form spherical or ellipsoidal micelles. At high surfactant concentrations these associates are densely packed and are identified as cubic liquid crystals.

Vesicle dispersions for parenteral administration yielding local effect:

Depending on their size and surface charge, parenterally administered liposome's interact with the reticulo-endothelial system (RES) and provoke an immunological response. After adsorption of certain serum proteins, so called opsonines, the liposomes are identified as a foreign invader and are then destroyed by specific immune cells, mainly in the liver, spleen and bone marrow. This passive drug targeting enables an efficient therapy of diseases of these organs or their affected cells. Clinical tests in the therapy of parasitic diseases, especially concerning the liver and spleen, have proven most efficient with liposomal encapsulation of the drug substance.

Vesicle dispersions for administration to the lung

A liposomal formulation consisting of surfactant, which usually coats the mucosa of the bronchi and prevents collapse of the alveolar vesicles of the lung, has been developed for patients who suffer either from Infant respiratory distress syndrome (IRDS) or adult/acquired respiratory distress syndrome (ARDS). IRDS often affects premature babies who have not developed a functional lung surfactant and therefore develop a failure in pulmonal gas exchange. ARDS is also a life-threatening failure/loss of the lung function and is usually acquired by illness or accident. Clinical trials with liposomal surfactant have proven to be effective in prophylactic treatment of IRDS and ARDS. Alveofact TM contains all relevant components of the lung surfactant for pulmonal gas exchange.

Ointments and creams

Ointments are non aqueous preparations, whereas creams result from adding water to ointment bases. If a liquid crystalline network or matrix is formed by amphiphilic molecules, the microstructure of ointments or creams may be liquid crystalline. In this situation, the system is more easily deformed by shear stress. Such formulations show plastic and thixotropic flow behavior. Systems with a liquid crystalline matrix exhibit a short regeneration time after shearing. In comparison, a crystalline matrix is usually destroyed irreversibly by shear. To obtain liquid crystalline matrix amphiphilic surfactants that form lyotropic liquid crystals at room temperature must be selected

Vesicle dispersions for topical application

Although liposomes have been studied intensely since 1970, only a few commercial drug formulations contain liposomes as drug carriers. The first commercial drug formulation with liposomes for topical administration was registered in Italy. The anti-mycotic econazole was encapsulated in liposomes dispersed in a hydrogel (Ecosom Liposomengel, formerly Pevaryl Lipogel). A highly hydrated gel network of the hydrophilic polymers forms and liposomes are immobilized within the gel network and thus mechanically stabilized. This stabilization via gelation of the continuous aqueous phase can also be applied to other disperse systems, e.g. suspensions or emulsions. An example of such an emulsion/hydrogel combination that contains heparin sodium as the active ingredient and, since 1995, liposomes as an additional dispersed phase is Hepaplus Liposom.

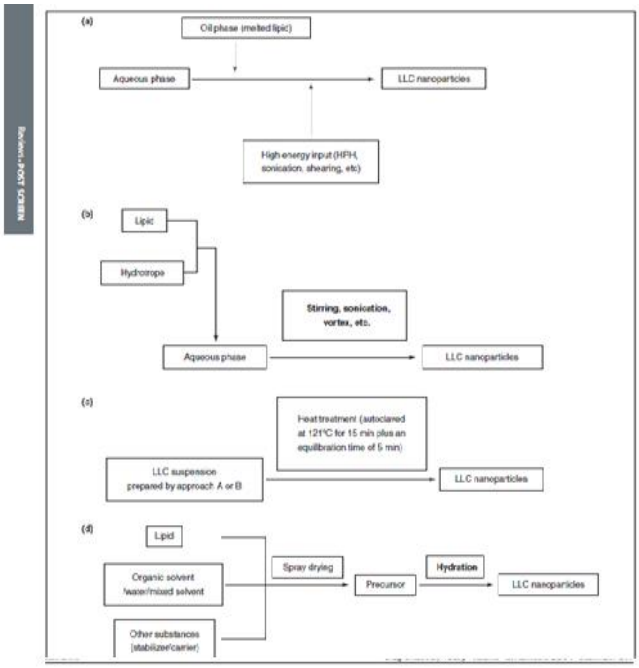

Figure 1: Schematic diagram of preparation for cubosomes (a) Top –down approach (b) Bottom-up approach (c) heat treatment (d) Spray drying

5. Conclusion

Liquid Crystals (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 orientation order of the constituent molecules. LCs, however are not a mixture of solids and liquids, but indeed a separate state of matter. [5] LCs are classified by their method of preparation into the Lyotropic and thermo tropic LCs.[6]lyotropic liquid crystals, lamellar liquid crystals, hexagonal liquid crystals, cubic liquid crystals, thermo tropic liquid crystals, smectic liquid crystals, nematic liquid crystals, cholesteric liquid crystals, discotic liquid crystals.lcs can be prepare by using following methods. top–down approach ,bottom-up approach ,heat treatment ,spray drying. Characterizations of liquid crystals are particle size determination by laser light scattering.

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