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Liquid crystals: An approach to different state of matter

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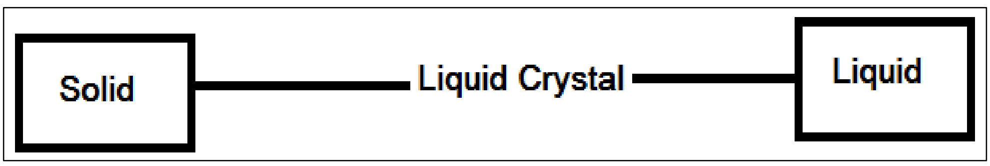
Abstract
Liquid crystals are the materials that are in many ways intermediate between the liquid and solid states. Liquid crystals exhibit different molecular arrangements than the liquid and solid states. The liquid crystalline state may result either from the heating of solids (thermotropic liquid crystals) or from the action of certain solvents or solids (lyotropic liquid crystals).The two main types of liquid crystals are: smectic (soap like or grease like) or nematic (threadlike). LC based systems can provide specific advantages of thermodynamic stability, high solubilisation levels, improved bioavailability, protection against oxidation and controlled release properties to the pharmaceuticals. Thus material characterization and understanding of the liquid crystalline states of active pharmaceuticals can yield wide range of options to enhance formulation performance for drug delivery. Liquid crystal materials are unique in their properties and uses. This review will provide basic information about liquid crystals, their types, phases involved, and uses in pharmaceutical and non-pharmaceutical industry. LCs based delivery systems such as creams, ointments, gels, liposomes, colloidal dispersions and transdermal patches have been used in pharmaceuticals and cosmetics. Liquid crystals have many applications in fields of science, engineering and device technology.

Keywords: Liquid crystals (LCs), mesophase, phases involved, pharmaceutical uses, recent approach

1. Introduction

The word “liquid crystal” (also known as LC or mesophase) explains a state of matter that is intermediate between the crystalline solid and the amorphous liquid. They have properties in between Liquids and solids, which makes them new form of state.

Some liquid crystal may even flow like liquid, but it Atoms or molecules are oriented in a crystal-like way, the liquid crystal state of matter is obtained from orientation-dependent non-covalent interaction between molecules within condensed phases. Because the balance of intermolecular forces which govern formation of liquid crystals is delicate, this state of matter can, in general, be easily effected by external stimuli. Many different types of liquid crystals with different respective are there, which can be differentiated by their specific optical properties like birefringence).



When viewed under the microscope by using a polarized light source, different liquid crystal phases will show to have different textures. LCs materials possible may not always be in a liquid-crystal phase (just as water can turn into ice or steam). Examples of liquid crystals are found both in the natural world and in technological applications. In general most famous electronic displays (LCD) use liquid crystals. Lyotropic liquid-crystalline phases are enough in counting in living systems but are also be found in the mineral world. For example, many polypeptides and plasma membranes are liquid crystals. Other much known examples of liquid crystals are solutions of soap [1] and different related detergents, as well as the tobacco mosaic virus, and some clays. [2] A typical LC molecule is represented by two parts: i) the central rigid part known to be as mesogen and ii) the other flexible side chains known to be as spacer. The liquid crystal molecules for stability make each other align parallel to themselves because of the strong intermolecular attraction. The energy required for interaction between the liquid crystal and bearing surface can be: (a) comparable with the energy of intermolecular interaction in the liquid crystal; (b) much less than the intermolecular interaction energy in the crystal. In the prior case the strong adhesion of liquid crystal (LCs) molecules to the bearing surface occurs; in the former case the adhesion force is weak. The characteristic features of LCs are the presence of long-range orientational order in the arrangement of constitutional molecules, and sometimes one- or two- and even three dimensional long-range translational or positional order. LCs expresses a great variety of phases, which differ one from another by their structures and physical properties. Although LCs combines the properties of a crystalline solid and an isotropic liquid, they express very specific electro optical phenomena, which have no equivalent analogues in solids or in liquids. Due to the anisotropic nature of the electrical and magnetic properties, the orientation of the LC molecules could be effectively monitored by weak electric or magnetic fields. Changing the LC molecules orientation, it is possible to change resultant optical and mechanical properties of the medium. All of these factors are important for the functioning of devices based on LCs, called LC displays, such as digital watches, calculators, panel TVs and thermometers LCs whose pitch changes strongly with temperature can be used inform of crude liquid crystal thermometers, since the color of the material will going to change as the pitch is changed. Liquid crystal color transitions are being used on many aquarium and pool thermometers as well as on thermometers for infants or baths. Other liquid crystal materials change their color when stretched or stressed. Therefore, liquid crystal sheets are often used in industry to look for hot spots, map heat flow, measure stress distribution patterns. It took more than two decades to recognize the existence of the liquid-crystal state of the matter. This is not surprising since, according to the understanding of many physicists and chemists of the beginning of the 20th century, the phrase “liquid crystals” was nonsensical. This is Leman’s blame. It was he who proposed the expression “liquid crystal” unfortunate at that time. Now days liquid crystals have played vital role in the transdermal approach to drug delivery, they are useful to enhance both permeability [3] and retention of the drug in skin as corneum stratum is strong barrier and drug with adequate property can cross it. Whether we talk about novel lecithin based liquid crystals or cremophor based cubical cubosomes all have changed and help to make local drug delivery better. In this review, we will look about them, their earlier history, their types, orientation, will study different phases involved in liquid crystals and approach of liquid crystals in pharmaceutical industry. We will try to cover all the aspects involved with liquid crystals.

2. History

The discovery of an intermediately, liquid crystal, state of matter is credited to Friedrich Reinitzer. [4] He in his study found that cholesteryl benzoate did not melt in the same manner as like other compounds, but has two different melting points. At 145.5 °C or (293.9 °F) it meltdown into a cloudy liquid, and at 178.5 °C (353.3 °F) it again melt down and the cloudy liquid convert into clear. The phenomenon is reversible in nature and examined as the intermediate cloudy fluid, and reportedly shows crystallites.

After this accidental discovery, Reinitzer did not continue studying liquid crystals further. The research was later carried forward by Lehmann, who realized that he had been encountering entirely new phenomenon and was in a position to investigate on it. In his postdoctoral years he had become expert in crystallography and microscopical studies. Lehmann started a systematic study, first of chemical cholesteryl benzoate, and then of its related compounds which exhibits same the double-melting phenomenon. He was then able to make observations in pre-polarized light, and his microscope was provided with a hot stage (sample holder equipped with a heater) which enabled high temperature observations. The intermediate cloudy phase may clearly sustained flow, but other features, particularly the signature under a microscope, convinced Lehmann that he was dealing with a solid one.

After Lehmann's, his work was continued and scientifically expanded by the German chemist Daniel vorlander, by whom from the beginning of 20th century until his retirement in 1935, had prepared many of the liquid crystals known. However, liquid crystals were not popular among scientists at that time and the material remained as a pure scientific curiosity for more than 80 years.

After end of World War II work, on the synthesis of liquid crystals was again started in premises of university research laboratories in Europe. George William grey, a known researcher of liquid crystals at that time, start investigating these materials in England in the year 1940s. His group prepared many new materials that express the liquid crystalline state of matter and produced a better understanding of how to design molecules that express this state.

Liquid crystal (LCs) materials became a key of research in the production of flat panel electronic displays in beginning of 1962 at RCA Laboratories, when physical chemist Richard Williams provided an electric field to a very thin layer of a nematic liquid crystal at 125 °C. In 1966, Joel E. Goldmacher and Joseph A. Castellano, research chemists in Heilmeier group at RCA, founds that mixtures made only of nematic compounds that differed only in the number of carbon atoms in the terminal side chains could give room-temperature nematic liquid crystals. A ternary mixture of Schiff Base compounds provides a material that had a nematic range of 22-105 °C. Processes at room temperature provide the first practical display device possible to made. The team then proceeded to synthesize large number of mixtures of nematic compounds, many of which had much low melting points. The technique of blending nematic compounds to get wide Operating temperature range eventually became the industry standard and is still used to this very day to tailor materials to meet specific applications.

In 1969, Hans Kelker succeeded in preparing a material which had a nematic phase at room temperature that is MBBA which is one of the popular kind subjects of liquid crystal research. In 1991, when liquid crystal displays were well established, Pierre-Gilles de Gennes working in the University Paris-Sud was honored with the Nobel Prize in physics "for discovering the methods for studying the order phenomena in simple systems which can be generalized to more complicated forms of matter, in particular to liquid crystals and few polymers".

3. Classification of Liquid crystals

The liquid crystals are classified in two major types i.e. thermotropic and lyotropic. These types are further distinguished into different phases depending on the changes in their orientational or positional order under influence of external factors such as temperature.

3.1 Thermotropic liquid crystals

A liquid crystal (LC) is thermotropic in nature if the order of its components is dependent or changed by temperature. Like if temperature is too high, results in rise of energy and therefore motion of the components will show a phase transition. The LCs will become an isotropic liquid. In case, on the contrary, if temperature is too low for supporting a thermotropic phase, the LC will change to glass phase. There is therefore a range of temperatures at which we observe thermotropic LCs; and most of these have several "sub phases" (nematic, smectic. Etc.), which we may observe by modifying the temperature [5].

3.1.1 Nematic phase [6]

In a nematic phase, the calamitic or rod-shaped organic molecules have no more positional order, but they make them align to give long-range directional order with their long axes roughly parallel. Thus, the molecules are mostly free to flow and their positions of center of mass are randomly distributed as like in a liquid, but still have their long-range directional order. Mostly nematics are uniaxial in naturel. They have only one axis which is longer and preferred, and the other two being equivalent (can be approximated as cylinders or rods). However, some liquid crystals are also biaxial nematics, meaning that in addition to make orienting their long axis, they also orient with a secondary axis. Nematics also have fluidity similar to that of normal (isotropic) liquids but they can be simply aligned by an external magnetic or electric field. Aligned nematics have their optical properties of uniaxial crystals and this makes them more useful in liquid-crystal displays (LCD).

3.1.2 Smectic phases

In the A phase of smectic crystals, the molecules are oriented along with the normal layer, while in the C phase of smectic crystals they are tilted away from it. These phases are liquid-which means within the layers. There are more different smectic phases, each of them characterized by respective types and degrees of positional and orientational order.

3.1.3 Discotic phases

Disk-shaped LC molecules can change their orientation and align themselves in a layer-like known as discotic columnar. The columns their selves may be organized into shape of rectangular or hexagonal arrays.

3.1.4 Bowlic phases

They are Bowl-shaped LCs molecules, like we found in discotics, and can form columnar phases. Other phases, includes polar nematic, nonpolar nematic, string bean, onion and donut phases, have also been found. Bowlic phases, except nonpolar nematic one, are polar phases of LCs.

3.1.5 Chiral phases

The chiral nematic phase expresses chirality (handedness). This phase is popularly known to be as cholesteric phase because it was first found for the cholesterol derivatives. While only chiral molecules (i.e. others which have no internal planes of symmetry) may give rise to such a phase. This phase exhibits a twisting of the molecules perpendicular to its director, with the molecular axis parallel its director.

3.1.6 Blue phases

Blue phases are liquid crystal phases that are produced in the temperature range between an isotropic liquid phase and chiral nematic phase. Blue phases mainly have a general three-dimensional cubic structure of some defects with lattice periods of few hundred nanometers.

3.2 Lyotropic liquid crystals

A lyotropic liquid crystal mainly consists of two or more than two components which express liquid-crystal properties in certain concentration ranges only. In the lyotropic phases, solvent molecules will fill the space mostly around the compounds to provide fluidity to the whole system. In case to thermotropic liquid crystals, these lipotropic crystals have some another degree of freedom in the concentration that provide them to initiate a variety of different phases. A compound which has two immiscible hydrophilic and hydrophobic parts inside within the same molecule is known as an amphiphilic molecule. Most of amphiphilic molecules show lyotropic liquid-crystal phase sequences depends on the volume balances between the hydrophobic part and hydrophilic part. These structures are formed by the micro-phase segregation of two incompatible components on a nanometer scale. Soap is one of everyday example of a lyotropic liquid crystal.

A general progression of phases, going from low to high amphiphile concentration, [7] is:

- Discontinuous cubic phase (micellar cubic phase)
- Hexagonal phase (hexagonal columnar phase) (middle phase)
- Lamellar phase
- Bicontinuous cubic phase
- Reverse hexagonal columnar phase
- Inverse cubic phase (Inverse micellar phase)

3.3 Biological liquid crystals

Lyotropic liquid-crystal phases are abundant in our surrounding, the study of which is known to be as lipid polymorphism. Accordingly, lyotropic liquid crystals attract significant attention in the area of biomimetic chemistry. In general, biological membranes and plasma membranes are a form of liquid crystal. Their constituent molecules (like phospholipids) are perpendicular to the surface of membrane, although the membrane is flexible. These lipids vary in shape. The constituent molecules can mingle internally easily, but never tends to leave the membrane due to the high energy requirement of the process. Lipid molecules can actually flip from one side of the membrane to the other one, this process mainly being catalyzed by flippases and floppases (hichever depending on the direction of specific movement). These liquid crystal phases of membrane can also direct important proteins like that of receptors freely "floating" inside or partly outside the membrane.

3.4 Mineral liquid crystals

Liquid crystals can also be found in the mineral forms, mostly these minerals being lyotropics. The first one discovered was Vanadium (V) oxide, by Zocher in 1925. From then, many others have been clays family was raised by Langmuir in year 1938, but mostly remained open for a very long interval and was only solved in recent years. Because of the rapid development of Nano sciences, and synthesis of many new anisotropic nanoparticles, numbers of such minerals liquid crystals are quickly increasing, for example, graphene and carbon nanotubes. A lamellar phase was also discovered, $H_3Sb_3P_2O_{14}$, which express hyper swelling up to ~250 nm range for the interlamellar distance.

4. Application in pharmaceutical industry
It has been found that approximately 5 per cent of all the organic molecules have ability to exist as thermotropic LCs. Pharmaceutical compounds have been increasingly authenticated by their lyotropic liquid crystalline states with mostly fewer examples of thermotropic LC states. LCs based pharmaceutical delivery systems such as creams, gels, ointment, liposomes, transdermal patches and colloidal dispersions have been used in pharmaceuticals and cosmetics [8].

4.1 Pharma drugs as LCs
Most of the small molecular pharmaceutical active compounds have been derived to form LC mesophases. Nafoxidine hydrochloride is one of such example, this cationic drug also has amphiphilic properties and which give rise to thermotropic (smectic type) and lyotropic liquid crystal structures. Palmitolyl propranolol hydrochloride is an amphiphilic derivative of the beta-blocker propranolol hydrochloride that forms smectic type liquid crystal phase. It has been mostly administered as a liquid crystal dispersion for cardiac problems. Other includes Itraconazole hydrochloride, which is an antifungal drug forms chiral nematic phases. Few of the other examples of small molecular pharmaceuticals which can form LCs are arsphenamine, fenoprofen calcium, fenoprofen sodium, methotrexate, penbutolol sulphate, nafcillin, folic acid and tobramycin.Big molecular pharmaceutical active compounds are also available to form LCs; some common examples of these are calcitonin, cyclosporine, nafarelin, amylin, detirelix and leuprolide [9]. Recent research has provided a new investigational LC based anti-cancer drug called Tolecine, this is a compound which also has antiviral and antibacterial therapy. Some of the other pharmaceutical excipients such as ethyl cellulose, hydroxypropylcellulose and cellulose acetate have also shows LC phases. Apart from this, other examples of naturally occurring LCs are DNA, biological membranes and cholesterol.

4.2 LCs for solubility enhancement
Thermotropic liquid crystal state of fenoprofen calcium (class II drug from biopharmaceutical group of system) has shown higher solubility as compare to its crystalline state. Liquid crystal state of lipids has been used as a model of mimic the biological systems [10]. In various foods, biotechnical and pharmaceutical applications, the liquid crystal phases obtained from surfactants in aqueous medium shows useful host systems for amino acids, drugs, proteins, peptides and vitamins. Various biologically active food additives are not soluble in aqueous neither in oil phase and require environmental protection from hydrolysis or oxidation. Many lyotropic liquid crystals meet these requirements mainly because of their high solubilization capacities for lipophilic, hydrophilic and amphiphilic nature of molecules. Moreover, current studies demonstrated sustained and controlled release of solubilized molecules form various liquid crystal matrices

4.3 LCs in Biological and Chemical sensing
LCs have been successfully demonstrated to sense and analyze bacteria various and viruses. Additionally, some non-toxic LCs have been figured out and utilized for supporting the growth of mammalian cells and for reporting the interfacial cell-protein interaction [11]. Polyelectrolyte-coated LCs droplets are useful to detect charged macromolecules in a solution. Adsorption of these positively charged dendrimers on negative charged polyelectrolyte-coated droplets results bipolar-to-radial ordering transitions, which were mainly dependent on both the size and number of droplets present in solution [12].

4.4 Colloidal dispersions
The bulk liquid crystalline structure can be found to dispersed in water in the presence of additional stabilizer or emulsifier which forms sub-micrometer soft particles (100-500 nm size) that retains the internal structure of the liquid crystal molecular phase. In the case of lamellar, cubical and hexagonal phases, these soft particles have been termed liposomes, hexosomes, and cubosomes [13], respectively. They have very good advantages in comparison to the bulk phase as these have very high interfacial area (as compare to their volume) and low viscosities, thus increasing its scope of application.

4.5 Smectic nanoparticles
Colloidal smectic nanoparticles are increasing popularly as a carrier system for lipophilic or oil based drugs due to their liquid crystalline nature. One of such example includes this smectic Nano particulate carrier that is cholesteryl myristate. Colloidal smectic nanoparticles are highly suitable models for studying the crystallization behavior of pharmaceuticals and determining the effect of various parameters in the development of smectic nanoparticles that are resistant to crystallization upon storage.

4.6 Dermal application
Drug molecules and pharmaceutical excipients with amphiphilic character can easily form lyotropic mesophases that is particularly for surfactants and are commonly used as emulsifiers in dermal formulations and associate to form micelles after solubilizing in a solvent. Increasing with concentration the probability of interaction between the micelles also increases, hence liquid crystals are formed. Liquid crystal formulations have been used in cosmetics and pharmaceutical controlled release dosage forms. These formulations get enhanced penetration of biologically active materials like vitamin A) through the skin. The delivery systems consist of cholesteric liquid crystals in which the active material is retained inside the lamellar molecular structure (between the molecular sheets) of the cholesteric liquid crystalline phase.

Some of the recent approaches of liquid crystals in pharmaceutical industry are:-

1. Liquid crystals containing cosmetic and pharmaceutical compositions and methods for utilizing such compositions. Patent No. US 4,999,348 [14].
2. Liquid crystals emulsion type pharmaceutical composition containing cyclosporine and therapeutic method of treating cutaneous disease therewith. Patent No. 2010/190695 [15].
3. Silicone Liquid Crystals, Vesicles, and Gels. Patent no. US 6608126 [16].
4. Imine Based Liquid Crystals For The Controlled Release Of Bioactive Materials. Patent No. 20090306196 [17].
5. Enhanced Topical Delivery of Finasteride Using Glyceryl Monooleate-Based Liquid Crystalline Nanoparticles Stabilized by Cremophor Surfactants [18].
6. Novel lecithin based liquid crystal nanogel for enhanced

targeted delivery of Terconazole [19].

5. Non-Pharmaceutical use of Liquid crystal

Its principle is useful to make liquid crystal based optical devices.

Liquid crystal tunable filters are useful as electro optical [20] devices, like in hyper spectral imaging.

Thermotropic chiral LCs where pitch varies strongly with temperature is useful as crude liquid crystal thermometers, as the color of the material can easily change with the change in pitch. Liquid crystal color transitions are useful in many aquarium and pool thermometers as well as in thermometers useful for infants or baths. Other liquid crystal materials that change color when are being stretched or stressed. Therefore liquid crystal sheets are mostly used in industry to look forward for hot spots, measure stress distribution patterns, map heat flow and so on. Liquid crystals (LCs) in fluid form are used to detect electrically generated hot spots to analyze failure in the semiconductor industry.

Liquid crystal lasers have used a liquid crystal in form of the lasing medium as a distributed feedback process instead of any external mirrors. Emission at a photonic band gap produced by the periodic dielectric nature of the liquid crystal provides a very low-threshold high-output device that stabilize monochromatic emission.

Polymer dispersed liquid crystal or (PDLC) sheets and rolls are also available as adhesive backed Smart film that can be applied in windows and electrically switched between transparent and opaque to provide privacy.

Many common used fluids, like soapy water, are mainly in fact liquid crystals. Soap can form a variety of LC phases depending on its concentration and strength in water.

Bowlic columns can also be used for fast switches.

6. Conclusion

There are mainly three states of matter that is gas, liquid and solid. A fourth state of matter is the liquid crystale state or mesophase. The term liquid crystal is although an apparent contradiction, but it is useful in a descriptive sense just because materials in this state are in many ways intermediate between the liquid and solid states. The two main types of liquid crystals are known to be as smectic (soap like or grease like) and nematic (threadlike). Generally, molecules that form mesophases involves (a) organic, (b) elongated and rectilinear in shape, (c) rigid and (d) possess strong dipoles and easily polarizable groups. The liquid crystalline state may result either from the heating of solids (thermotropic liquid crystals) or from the action of certain solvents or solids (lyotropic liquid crystals). LCs based delivery systems such as gels, cream, ointment, liposomes, colloidal dispersions and transdermal patches have been used in pharmaceuticals and cosmetics. Non-pharma applications of liquid crystals involves-liquid crystal displays, liquid crystal thermometers and optical imaging. As research into this field continues and a new applications can be developed, liquid crystals will play a vital role in modern technology.

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