REVIEW ARTICLE JPAR 2018

Journal of Pharmaceutical Advanced Research

(An International Multidisciplinary Peer Review Open Access monthly Journal)

Available online at: www.jparonline.com

Liquid Crystalline System: Novel approach in Drug Delivery

Sasmita Nayak[1*], Monika Ola[2]

[1]G D Memorial College of Pharmacy, Jodhpur, Rajasthan - 342005, India.
[2]R.C. Patel Institute of Pharmaceutical Education and Research, Shirpur, Maharashtra-425405, India.

Received: 20.02.2018 Revised: 15.03.2018 Accepted: 20.03.2018 Published: 31.03.2018

ABSTRACT: Crystalline solids are characterized by long-range positional and orientational order in three dimensions, whereas liquids lack long range order in any dimension. Liquid crystal state is a distinct and unique state of matter observed between the crystalline (solid) and isotropic (liquid) state. This is characterized by properties which resemble those of both solids (ordering properties) and liquid (flow properties). There are two main classes of Liquid: Thermotropic Liquid Crystal and Lyotropic Liquid Crystal. Solids are generally characterized as either three dimensional crystals or amorphous solids by X-ray powder diffraction and differential scanning calorimetry. Liquid Crystals are characterized by using polarized light microscope, small angle X-ray scattering, and cryo-Transmission electron microscopy etc. This review presents a general description of the different type of liquid crystal with their methods of characterization and it also includes application of Liquid Crystal in pharmaceutical field.

Corresponding author*
Ms. Sasmita Nayak
G D Memorial College of Pharmacy,
Jodhpur, Rajasthan - 342005, India.
E. Mail ID. sasmita821@gmail.com
Tel. No. +918769844424.

Key words: Liquid crystal, Thermotropic Liquid crystal, Lyotropic Liquid crystal, Characterization, Application.

INTRODUCTIONS:

Matter experiences very different states of aggregation: the most commonly known are solid, liquid and gas, each of them characterized by its own well defined assembling rules. In the solid phase (in the crystalline solid), each atom is located into a definite location in the crystal lattice, realizing a highly ordered and strongly anisotropic structure. Liquid phase, on the contrary, is very disordered: atoms can freely move within the liquid without located into well-defined position and thus liquid is an isotropic phase. Between these two phase matter experience sometimes other states of aggregation, characterized by intermediate properties; one refers to them as Liquid crystal (LC) [1-3].

The first historical evidence of a liquid crystal happened in 1988 by Reinitzer, when an Austraian botanist Friedrich Reinitzer observed that a material known as cholesteryl benzoate had two distinct melting points [4,5]. Reinitzer increased the temperature of a solid sample and watched the crystal change into a hazy liquid. As he increased the temperature further, the material changed again into a clear, transparent liquid (Fig 1). He discovered this new phase of matter as Liquid Crystal phase. Liquid crystals, also named "mesophase", are organic substances that pure, or in aqueous solutions, are capable to reach a special state of aggregation, intermediary between solid state and liquid state. They preserve both the flow proprieties of a liquid and the ordering of a crystal and present multiple anisotropies. Liquid crystals are a condensed state of matter formed by anisotropic organic molecules. While not all anisotropic molecules can form liquid crystals, all liquid crystals are formed by anisotropic molecules [6]. These molecules are termed mesogens and are either of rods-like (prolate) or, less commonly, disc-like (oblate) shape. The existence domain, also named "mesomorphic" is very well defined by two distinct temperatures situated at its limits; the lower one is the melting point (M.P.) at which the solid state ordered i.e. the compound passes from the solid phase into a mesophase and the higher one is the clearing point (C.P.) upon which the isotropic liquid state begins [7].

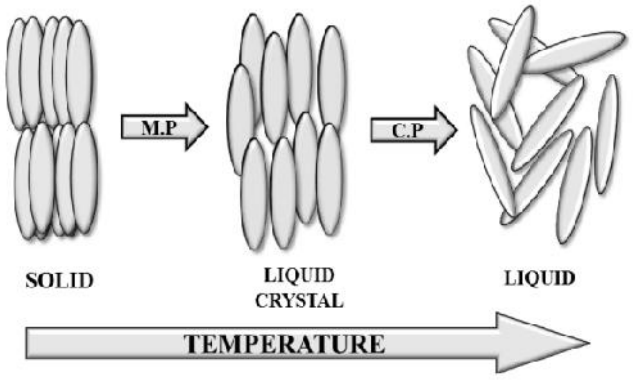

Fig 1. Transitional states of matter.

GENERAL PROPERTIES OF LCS:

The LCs is having following properties like Birefringence, response to magnetic and electric fields, optical activity in twisted (chiral) nematic phases, sensitivity to temperature which results in color changes and serve solid to liquid transitions that are both first (melt-like) or second order (glass transition-like) transitions in the thermodynamic sense [8].

CLASSIFICATION OF LCS:

In 1922 the French scientist G. Friedel produced the first classification scheme of Liquid crystals [9], dividing them into three different types of mesogens, based upon the level of order the molecules possessed in the bulk material: that are Nematic (from the Greek word nematos meaning "thread"), Smectic (from the Greek word smectos meaning "soap") and Cholesteric (better defined as chiral nematic).

The properties of Liquid crystal are very depended on temperature and the presence or absence of solvent [10] and depending upon these properties Liquid crystals fall into two classes [11]: such as Thermotropic liquid crystals (TLCs) and Lyotropic liquid crystals (LLCs). In the thermotropic liquid crystals, the shape of the molecules dictates the orientational order, and the thermal motion gives the mobility. Lytropic liquid crystals that appear in nature in living organisms acquire mobility by addition of a solvent, and their liquid crystalline properties are governed by the relative concentration of the solute. However, the distinction between the thermotropic and lyotropic liquid crystals is not complete and there are materials which exhibit both thermotropic and lyotropic liquid crystalline properties. They are called amphotropic [12]. Depending on of molecular ordering, these two types of liquid crystals may form a number of specific structures [13]. The transition from the solid state to the liquid isotropic state is not a single one, but a succession of transitions passing by several thermodynamic stable phases. The microscopic investigation (texture observation) may be considered one of the most important methods for the identification and ulterior classification of this large number of different liquid crystalline phases.

Thermotropic Liquid Crystals:

Thermotropic mesophases are formed by heating a crystalline solid or by cooling an isotropic melt of a TLC-forming molecule (mesogen). The minimal number of components necessary to form the mesophase is one in case of TLCs i.e. temperature. It has been estimated that 5 % of all organic compounds exhibit thermotropic mesomorphism. As transfer of heat energy to the substances cannot be avoided in many processes in pharmaceutical manufacture, it appears possible that mesophases may be formed upon handling or processing of drugs. It is possible that these mesophases (like a metastable polymorphic form of a drug) do not transform back into the crystalline state once the heat

energy is no longer exerted on to the drug. In that respect the thermotropic liquid crystalline form of a drug may be regarded as special polymorphic form. TLCs are classified into different type of LC structure (Fig 2).

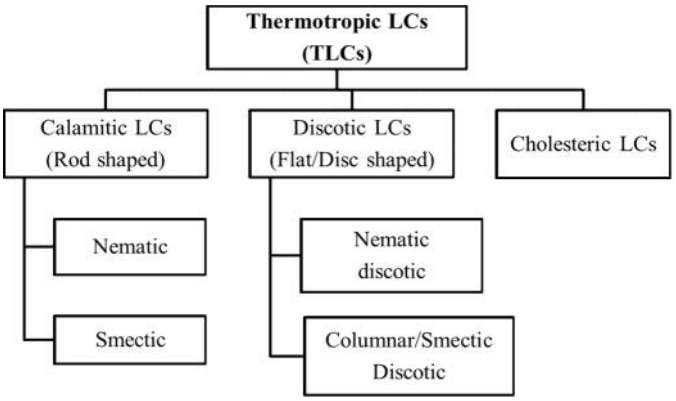

Fig 2. Classification of Thermotropic Liquid Crystal.

Nematic phase:

In the nematic liquid crystal phase, the molecules have no positional order, but they don't have long-range orientational order [14]. Thus, the molecules flow and their centre of mass positions are randomly distributed as in a liquid, but they all point in the same direction (within each domain). Most nematics are uniaxial: they have one axis that is longer and preferred, with the other two being equivalent (can be approximated as cylinders). Some liquid crystals are biaxial nematics, meaning that in addition to orienting their long axis, they also orient along a secondary axis.

Smectic Phases:

The word "Smectic" is derived from the Greek word for soap. In the smectic liquid crystal phase, the molecules show a degree of translational order not present in the nematic. In the state, the molecules maintain the general orientational order of nematics, but also tend to align themselves in layers or planes. The plane may be oriented either perpendicular or tilted to the long axes of the molecules [15]. The increased order means that the smectic state is more "solid-like" than the nematic. Many compounds are observed to form more than one type of smectic phase (Fig 3). In the smectic-A mesophase, the director is perpendicular to the smectic plane, and there is no particular positional order in the layer. Similarly, the smectic-B mesophase orients with the director perpendicular to the smectic plane, but the molecules are arranged into a network of hexagons within the layer. In the smectic-C mesophase, molecules are arranged as in the smectic-A mesophase, but the director is at a constant tilt angle measured normally to the smectic plane. Substances featuring the A phase also often exhibit the smectic C phase at a lower temperature. The tilt angle normally increases with decreasing temperature [16]. Phase transitions occur with increasing temperature, that is, crystalline to smectic C to smectic A to nematic to isotropic, or crystalline to nematic to isotropic. The transition from an isotropic, liquid melts to an anisotropic, liquid crystalline, nematic phase always exhibits a first-order transition according to the Ehrenfest classification, which manifests itself for example as a peak in a differential scanning calorimetry thermogram. Also, transitions from one liquid crystalline phase to another usually are first-order transitions. The transition from a nematic to a smectic. A mesophase, however, can also be second order, which manifests itself for example as step in the baseline in the DSC thermogram i.e. a change in the heat capacity upon transition [17].

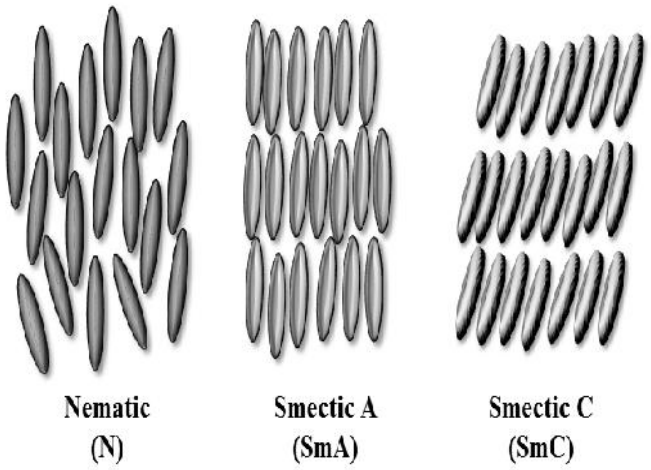

Fig 3. Structures of various Smectic Phase.

Discotic phases:

In 1977, a mesogenic structure, based on discotic (disc-shaped) molecular structures was discovered. Discotic LCs, as well as calametic LCs, can show several types of mesophases, with varying degree of organisation [18-20]. The two principle mesophases are: Nematic discotic and Columnar. Discotic thermotropes (Fig 4) demonstrate two-dimensional order in stacked columns of disc-like molecules, where the molecules lack order along the column length and these are called columnar mesophase. Nematic discotic phases are similar to the calamitic nematic phase, that is, the normals of the discs are oriented parallel.

Cholesteric Phases:

The chiral character of the nematic phase was discovered in 1888 by an Austrian botanist named Friedrich Reinitzer on cholesteryl benzoate (thus the name cholesteric). The cholesteric (or chiral nematic) liquid crystal phase is typically composed of nematic mesogenic molecules containing a chiral center which produces intermolecular forces that favor alignment between molecules at a slight angle to one another [21].

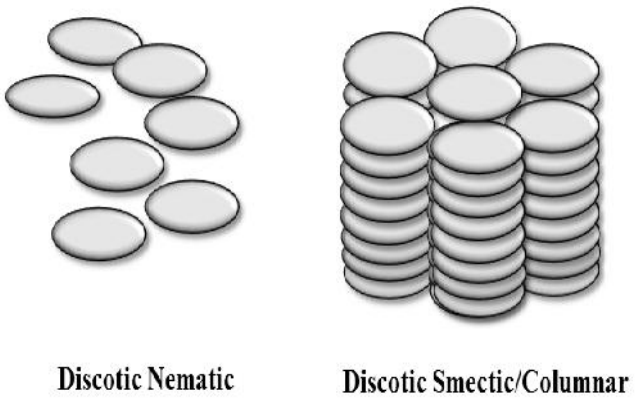

Fig 4. Structures of various Discotic phase.

This leads to the formation of a structure which can be visualized as a stack of very thin 2-D nematic-like layers with the director in each layer twisted with respect to those above and below. In this structure, the directors actually form in continuous helical pattern about the layer. Every half turn of the helix, the molecules present the same orientation. An important characteristic of the cholesteric mesophase is the pitch. The pitch, p, is defined as the distance it takes for the director to rotate one full turn in the helix (Fig 5). A byproduct of the helical structure of the chiral nematic phase is its ability to selectively reflect light of wavelengths equal to the pitch length, so that a color will be reflected when the pitch is equal to the corresponding wavelength of light in the visible spectrum. The effect is based on the temperature dependence of the gradual change in director orientation between successive layers, which modifies the pitch length resulting in an alteration of the wavelength of reflected light according to the temperature. The angle at which the director changes can be made larger, and thus tighten the pitch, by increasing the temperature of the molecules, hence giving them more thermal energy. Similarly, decreasing the temperature of the molecules increases the pitch length of the chiral nematic liquid crystal [22]. TLC are of a great interest as a research topic in physics and have found applications in many other domains such as optical devices, nondestructive testing of materials and medicine (tissues thermography).

Lyotropic Liquid Crystals:

Lyotropic mesophases are formed by dissolving an amphiphilic mesogen in a suitable solvent, under appropriate conditions of concentration and temperature. In the lyotropic phases, solvent molecules fill the space around the compounds to provide fluidity to the system. Lyotropic mesogens are typically amphiphilic, meaning that they are composed of both lyophilic (solvent-attracting) and lyophobic (solvent-repelling) parts.

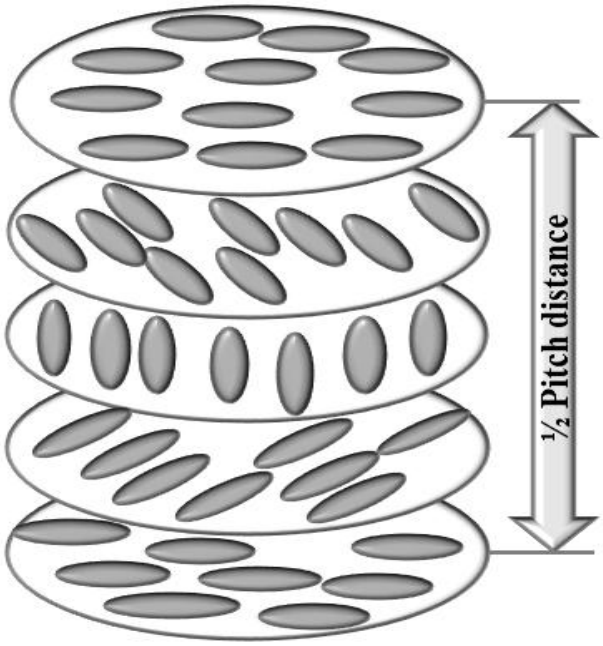

Fig 5. Schematic diagram of Cholesteric phase.

This causes them to form into micellar structures in the presence of a solvent, since the lyophobic ends will stay together as the lyophilic ends extend outward toward the solution. As the concentration of the solution is increased and the solution is cooled, the micelles increase in size and eventually coalesce. This separates the newly formed liquid crystalline state from the solvent [33]. In contrast to thermotropic liquid crystals, these lyotropics have another degree of freedom of concentration that enables them to induce a variety of different phases. Micelles form at low surfactant concentrations. As the degree of orientational order increases with increasing surfactant concentration, the following disorders to order transition are expected. Spherical micelles will be packed into a cubic phase, rod

micelles will be packed into a hexagonal phase, and bilayer micelles will be packed into a lamellar phase [34]. Other phases, including bicontinuous cubic, discontinuous cubic, and the inverse of the above mentioned phases, may be formed at appropriate concentration and surfactant geometry.

A generic progression of phases, going from low to high amphiphile concentration (Fig 6) [23], is

1. Discontinuous cubic phase (micellar phase).
2. Hexagonal columnar phase (middle phase).
3. Bicontinuous cubic phase.
4. Lamellar phase (neat phase).
5. Reverse Bicontinuous cubic phase.
6. Reverse hexagonal columnar phase.
7. Inverse cubic phase (Inverse micellar phase).

The main lyotropic surfactants are of two types: soaps and phospholipids. Lyotropic liquid crystalline materials have been widely used as display devices [24]. LLC have become very important in the biomedical research too [25], because of the great number of living structures implied: cell membrane and vesicles [26], myelin [27], muscles and red cells [28], nucleic acids [29,30].

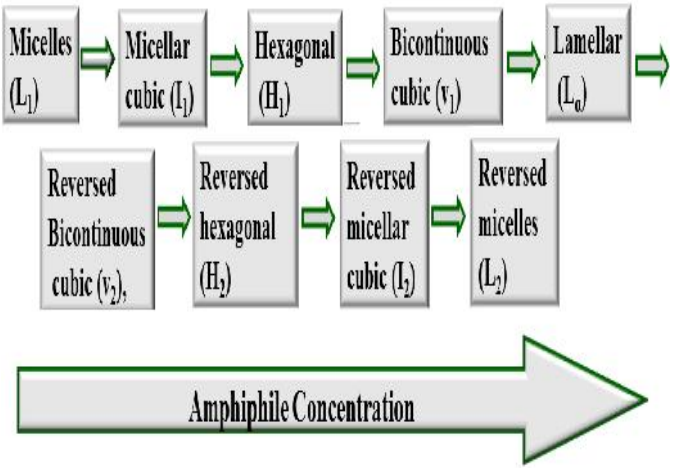

Fig 6. Progression of Liquid crystal phases with increase in Amphiphile concentration.

Middle phase or Hexagonal phase:

Hexagonal phases are formed as the micelles became abundant in solution. The micelles first became elongated and finally form tubes packed in a hexagonal arrangement [31]. If increasing solvent concentration in the cubic phase, the hexagonal phase occurs and forms normal structures H_1, or reversed structures H_2, according to the solvent polarity. Micelles are very long aggregates, rod-like, which can have circular, square, rectangular or hexagonal cross sections. These rod-like aggregates are the structural unit of that structure. With no respect to the continuous medium nature, rods disperse with their long axis in a parallel disposition, creating hexagonal, tetragonal or orthorhomboidal patterns. The amphiphilic molecules arrangement is a radial one, around the rod long axis, with the polar groups exposed to the exterior in the H_1 structure, or with the hydrophobic tails exposed to the exterior in the H_2 structure; the continuous medium is water and hydrocarbon, respectively [32]. Also, when large quantities of nonionic surfactant are added to the system, a reversed hexagonal structure and the solution containing reversed micelles may be formed. Hexagonal mesophases can be recognized by their fan-shaped texture in polarized light microscope. Both type of middle phase give rise to X-ray diffraction lines in the ratio of 1: 1/√3: 1/√4: 1/√7, which corresponds to a two dimensiosnal hexagonal lattice [33]. Using X-ray scattering it has been found that normal rods have a diameter of 1.3 to 2 bigger than the hydrophobic chain length. The dimension of the separation zone between rods is in the 0.8-3 nm ranges for the reversed type, and up to 5 nm for the normal type. Both types show similar optical textures and present a higher viscosity in the hexagonal phase than in the lamellar phase. Hexagonal phases are macroscopically quite stiff and gel like [34].

Neat phase or lamellar phase:

The lamellar phase is a planer structure where the monomers are packed in bilayer sheets with a water region in between. The ideal molecular shape of an amphiphile in this phase is a cylinder. A notable feature of the *neat phase* is its relative fluidity in spite of high surfactant content and thus the lamellae can glide easily over one another [35]. The structural unit for the lamellar phase is the simple and double layers. It has to be mentioned that the bilayer, as a repetitive unit, forms the main matrix of the biological membranes that contain phospholipids as lyotropic compounds and not soaps. The ordered bilayer structure is formed by amphiphilic molecules disposed in bidimensional infinite layers, delimited by water layers, all of them having a parallel disposition. The ionic heads of the molecules are contacting the aqueous medium, while the hydrocarbon chains are interdigitating in order to avoid water. The bilayers are disposed one under another through the third dimension, periodically alternating with water layers [36]. Lamellar mesophases typically show oily streaks with inserted maltese crosses in polarized light microscope. These types of structures give sharp X-ray diffraction

lines in the ratio of 1: 1/2: 1/3 [37]. The width of the double layer is of 30-40 Å, smaller than the double of the amphiphilic molecule length; the width of the intercalated water layers is of about 20 Å. These figures vary with temperature and concentration in the limits of the lamellar phase.

Cubic phase:

Cubic phases can be divided into two main groups; the cubic closely packed aggregates (I) and the bicontinuous cubic phases (V). The cubic packed aggregates consist of micelles or reversed micelles that are packed in a cubic symmetry. The bicontinuous cubic phases are more spectacular since they consist of only one lipid double layer membrane that spans the whole phase, at least when the phase ideally consists of only one crystal. In the reversed bicontinuous cubic phases the membranes circumvent tubes of water with large dimensions. The water tubes are connected into two interconnected three-dimensional networks. The cubic phases I and V can be correctly identified one from another by their precise location among other phases. In the hypothesis of increasing progressively the surfactant concentration, the phase I location is between the isotropic micellar solution and the hexagonal one, while the V phase location is between the hexagonal phase and the lamellar one [53].

These phases give X-ray diffraction lines in the ratio of 1: √3/4: √3/8: √3/4. From an optical point of view, cubic phases present no texture, because they are isotropic and can be distinguished from the isotropic micellar solutions only by their high viscosity [38]. Another phase, which has some similarities with the cubic phase, is the sponge phase, also referred to as the L3-phase. The L3-phase is a liquid but it is believed to be constituted by one lipid double layer membrane. The water channels of this phase are believed to be larger than those of the corresponding cubic phase.

IDENTIFICATION OF THE STRUCTURAL CRYSTALLOGRAPHIC PROPERTIES OF LCS:

The mesomorphism is investigated by multiple experimental techniques such as:

- Small angle X-ray scattering.
- Differential scanning calorimetry.
- Freeze fracture electron microscopy.
- Nuclear magnetic resonance.
- Polarized light microscopy.
- Cryo-Transmission Electron Microscopy.

IMPORTANCE OF LIQUID CRYSTALS IN DRUG DELIVERY:

Liquid crystal has had a major effect in many areas of science and engineering, as well as device technology. The most common applications of LC are as Liquid crystal display, Liquid crystal thermometers. An application of LC is now being explored is optical imaging and recording. These are also used for nondestructive mechanical testing of materials under stress [39]. Recently their biomedical applications such as in controlled drug delivery, protein binding, phospholipid labeling, and in microbe detection have been demonstrated. Apart from material science and bio-science, LCs are now playing significant role in nanoscience and nanotechnology such as synthesis of nanomaterials using LCs as template, the design of LC nanomaterials, alignment and self-assembly of nanomaterials using LC phases and so on. Now-a-days, Liquid-crystalline systems are used as delivery systems in the cosmetic and chemical industries and also in the field of pharmacy because of their stability and special, skin-friendly structure. These lyotropic mesophases are usually formed from water and one or two surfactants and possibly co surfactants at very definite proportions with low energy input or by means of spontaneous structural organization; their production is therefore relatively simple and energy-saving. They are thermodynamically stable, and can be stored unchanged for long periods of time without phase separation [40].

Cubic phases have been proposed as vehicle for various drug delivery systems [41] for example; parenteral [42], vaginal [43] and periodontal drug delivery system [44]. The system can also be used to incorporate proteins and maintain them in their native conformation thus protecting them from denaturation. This property is also used in crystallization of membrane proteins [45]. The cubic phases may provide an environment similar to biomembranes that can be of importance for the activity of many proteins [46]. The role of liquid crystals in protein chemistry is worth mentioning. A number of proteins form liquid crystalline systems. Examples are poly-B-benzyl-L-glutamate, and poly-n-methyl-L-glutamate. Transitions of mesomorphic substances are probably associated with arteriosclerosis. Mixtures of β-lipoprotein complex with several unsaturated esters of cholesterol form liquid crystals near body temperature. Thermotropic and/or lyotropic liquid crystalline mesophases of drug substances interact with

mesomorphous vehicles as well as with liquid crystalline structures in humans. The NSAIDs having the amphiphilic organic acids may form lyotropic mesophases with water at even room or body temperature e.g., diclofenac diethylamine or ibuprofen lysinate. The viscous reverse lyotropic liquid crystalline phases in excess water, such as reverse hexagonal and bicontinuous cubic phase, can provide a slow release matrix for incorporated active molecules. These materials provide a complex matrix consisting of discreate aqueous and lipidic regions. This hetrogenous structure permits incorporation of hydrophilic, lipophilic and amphiphilic materials, or a combination thereof, within the limitation that their presence does not induce a change in lyotropic phase structure [47].

Drug molecules present in the aqueous region of the mesophase in an undissociated form, are the main molecular species that would be able to diffuse out and cross lipophilic barriers. However, solute-solvent interactions play an important role in controlling rate of drug transport from these systems. Therefore, solutes in the LLC systems would be released at rates depending on the mesophase structure and type of dissolved solutes. These properties made it possible to use liquid crystals as drug carriers, solublizing vehicles and to prepare controlled-release formulations [48]. Liquid crystalline excipients are appropriate candidates for controlled drug release because in a liquid crystalline vehicle the drug diffusion is reduced by a factor of 10 to 1000 in comparison with a liquid vehicle such as a solution.

Drug release is controlled by the liquid crystals because diffusion within the liquid crystalline phase is slowest and thus rate-controlling. Amphiphilic excipients in drug formulations form lyotropic liquid crystals. Especially surfactants, which are commonly used as emulsifiers in dermal formulations, associate to micelles after dissolution in a solvent. At high surfactant concentrations, these associates are densely packed and are thus identified as cubic liquid crystals. Ringing gels with cubic liquid crystalline microstructure are used as commercial drug formulations especially for topical NSAID formulations, example Dolgit Mikrogel in German market [49]. Lyotropic liquid crystalline vehicles have generally all the advantages of microemulsions. Unlike microemulsions, some of the liquid crystalline systems may be slightly cloudy, rather than clear. In addition to the advantages of microemulsions, liquid crystals may release drugs over a sustained period either because of slower diffusion from the liquid crystal or because of an increased solubilized residence time for the drug after topical application. Applications of liquid crystals in emulsion stabilization have been studied extensively. To the advantage of a formulation chemist, a stable emulsion can be formed by mixing both the amorphous liquid and an isotropic liquid crystalline solution. The microstructure of both ointments and creams may consist of liquid crystals, as long as a liquid crystalline network or matrix is formed by amphiphilic molecules. To obtain a liquid crystalline matrix, amphiphilic surfactants that form lyotropic liquid crystals at room temperature have to be selected [50].

From among the main types of lyotropic liquid-crystalline compositions, mesophases with a lamellar structure that display the greatest similarity to the intercellular lipid membrane of the skin are primarily recommended for the development of a dermal dosage form [51]. As lamellar liquid crystalline systems contain a major proportion of incorporated water concentrated in the layers between hydrophilic domains, its evaporation is less than in case of traditional o/w creams. Their moisture content is retained for a long time, so that the transepidermal water loss is replaced by long-lasting hydration according to the needs of the skin. Their application elicits a pleasant skin sensation, and they have an ideal consistency and attractive appearance. Nonionic surfactants forming LC affect the permeability of biological membranes as they may intercalate into the structured lipids of the skin, where they can disrupt the packaging, altering membrane permeability without irreversible skin irritation [52].

The LLC systems exhibit good penetration, due to the very low interfacial surface tension arising at the oil/water interface, and they may facilitate the progressive diffusion of biologically active substances into the skin or systemic circulation. They can bring about a considerable increase in the solubility of drugs by means of solubilization, which are either insoluble or slightly soluble in water [53]. As liquid crystalline vehicles with lamellar microstructure have high solubilization capacities, they are recommended as reservoirs for transdermal patches.

In a therapeutic transdermal system (TTS), the vehicle reservoir, the membrane, or the adhesive layer could be made rate determining to control transport of the drug across the skin. It would be of interest to assess the

potential use of LLC as rate determining-vehicle reservoir in transdermal patches [54]. Liquid crystalline gels may be used as a reservoir from which drugs may be released by diffusion through the water channels of the gel matrix. For example poloxamer 407 gels are viscous isotropic liquid crystals and have been used in controlled drug delivery for both the topical and rectal routes [55]. Amhiphiles with glycerate head group form reverse hexagonal phase in excess water and these hexosomes may be benefits for chemically instable drug in maintaining chemical stability and possibly providing sustained release [73]. The liquid crystalline matrices can be used as on-demand stimuli responsive system for hydrophilic drug as it is formed at body temperature on contact with tissue fluid [56,57].

Some mixture of long chain lipids – soy phosphatidyl choline and glycerol dioleate are in-situ self-assembled in controlled manner into one or more reverse liquid crystal phase and encapsulating the drug and restricting diffusive transport to the surrounding tissue [58]. The reverse cubic phase liquid crystal dispersion (Lyocell) technology is a recent technology that meets the criteria of a commercially viable drug delivery technology and offers an excellent choice for high impact for formulation needs [59,60].

CONCLUSION:

We have discussed about Liquid crystal, which is considered as the fourth state of matter after solid, liquid and gas. LCs are important in material science as well as in life science. The unique structure and physiochemical properties of LCs afford them potential utility in the pharmaceutical field as innovative drug carriers. The ability of LC to incorporate and slowly release a variety of drugs with different physiochemical properties by a variety of route of administration can be done. As they allow drug solubilization, therefore, both water soluble and oil-soluble drugs may be incorporated in high concentration.

This also offers possibilities to increase the drug solubility, to decrease drug degradation, and to control and sustained the drug release rate. The similarities of liquid crystalline phase to the intercellular lipid membrane of the skin are recommended for the development of a dermal and transdermal dosage form**.**

ACKNOWLEDGEMENT:

Authors wish to thanks GD Memorial College of Pharmacy and R.C. Patel Institute of Pharmaceutical Education and Research for providing Library facility to carry out this extensive literature survey study to complete this review article.

REFERENCES:

1. Baron M, Stepto RFT. Definition of basic terms relating to polymer liquid crystals. Pure Appl Chem, 2002; 74: 493-509.
2. Berardi R, Orlandi S, Photios DJ, Vanakaras AG, Zannoni C. Dipole effects on the polymorphism in smectic A mesophases. Phys Chem Chem Phys, 2002; 4: 770-777.
3. Bobrovsky AY, Boiko NI, Shibaev VP. Photosensitive cholesteric copolymer with spiropyran-containing side groups – II. Kinetic features of the photo- and thermo- chromic processes. Liq Cryst, 2000; 27: 219-223.
4. Bouligand Y. Liquid crystals and their analogs in biological systems. In: Liébert L, editor. Liquid Crystals, Solid State Physics. Supplement 14. New York: Academic Press; 1978. pp. 259-294.
5. Boyd BJ, Whittaker DV, Khoo S, Davey G. Lyotropic liquid crystalline phases formed from glycerate surfactants as sustained release drug delivery systems. Int J Pharm, 2006; 309: 218-226.
6. Boyd BJ, Whittaker DV, Khoo S, Davey G. Hexosomes formed from glycerate surfactants-Formulation as a colloidal carrier for irinotecan. Int J Pharm, 2006; 318: 154–162.
7. Brown GH. Liquid crystals and their roles in inanimate and animate systems. Am Sci, 1972; 60: 64-73.
8. Burducea G. Lyotropic liquid crystals II. Structural polymorphism. Rom Rep Phys, 2004; 56: 87-100.
9. Burducea G. Lyotropic liquid crystals I. specific structures. Rom Rep Phys, 2004; 56: 66-86.
10. Caffrey M. Membrane protein crystallization. J Struct Bio, 2003; 142: 108-132.
11. Chandrasekhar S, Sadashiva BK, Suresh KA. Liquid crystals of disk like molecules. Pramana J Phy, 1977; 9: 471-480.
12. Chandrasekhar S, Ranganath GS. Discotic liquid crystals. Rep Prog Phys, 1990; 53: 57-84.
13. Chandrasekhar S, editor. Liquid crystals. 2nd ed. Cambridge: Cambridge Universal Press; 1992.
14. Chandrasekhar S, Kumar S. The Liquid State: Its Structure and Dynamics. Sci Spectra, 1997; 8: 66-72.

15. Chandrasekhar S, Krishna Prasad S. Recent development in discotic liquid crystals. Contemp Phys, 1990; 40: 237-245.
16. Cladis PE, Ratna BR, Shashidhar R,Chandrasekhar S. Disscotic Liquid Crystals. Angew Chem Int Ed, 2004; 43: 3360-3375.
17. Collings PJ, Hird M. Introduction to liquid crystals: Chemistry and Physics. Bristol: Taylor & Francis; 1997.
18. Corish J, Carr MG, Corrigan OI. Drug delivery from a liquid crystalline base across Visking and human stratum corneum. Int J Pharm, 1997; 157: 35-42.
19. De Gennes PG. The physics of liquid crystals. Oxford: Oxford University Press; 1993.
20. DePierro MA, Guymon CA. Generation and control of polymer nanostructure through photopolymerization in lyotropic liquid crystalline media. Raditech Report, 2004; 3: 11-21.
21. Drummond CJ, Kaasgaard T. Ordered 2-D and 3-D nanostructured amphiphile self-assembly materials stable in excess solvent. Phys Chem Chem Phys, 2006; 8: 4957-4975.
22. Engstrom S. Drug delivery from cubic and other lipid lipid-water phases. Lipid techn, 1990; 2: 42-45.
23. Ericssion B, Ericssion PO, Lofroth JE, Engstrom S. Cubic phase as delivery systems for peptide drugs. Am Chem Soc Symp Ser, 1991; 469: 251-265.
24. Eros I, Makai M, Csanyi E, Nemeth Z, Palinkas J. Structure and drug release of lamellar liquid crystals containing glycerol. Int J Pharm, 2003; 256: 95-107.
25. Fisch MR, Kumar S. Introduction to liquid crystals. In: Kumar S, editor. Liquid crystals: experimental study of physical properties and phase transitions. Cambridge: Cambridge University Press; 2001. pp. 1-28.
26. Fong W, Hanley T, Boyd BJ. Stimuli responsive liquid crystals provide 'on-demand' drug delivery *in vitro* and *in vivo*. J Control Rel, 2009; 135: 218–226.
27. Geraghty PB, Attwood D, Collett JH, Dandiker Y. The *in vitro* release of some antimuscarinic drugs from monoolein/water lyotropic liquid crystalline gels. Pharma Res, 1996; 13: 1265-1271.
28. Goodby JW. Phase structures of calamitic liquid crystals. In: Demus D, Goodby J, Gray GW, Spiess HW, Vill V, editors. Handbook of Liquid Crystals. Weinheim: Wiley-VCH; 1998. pp. 3-22.
29. Gray GW, Winsor PA. Liquid Crystals and Plastic Crystals. 1st ed. New York: John Wiley & Sons; 1974.
30. Gray GW, Mosley A. A liquid crystal mixture for use in smectic liquid crystal display devices. J Chem Soc Chem Commun, 1976; 4: 147-148.
31. Helfinstinel SL, Lavrentovich OD, Woolverton CJ. Liquid Crystal study and its applications. Lett Appl Microbiol, 2006; 43: 27-32.
32. Brown GH, Wolken JJ. Liquid crystals and biological structures. New York: Academic Press; 1979. pp. 200-222.
33. Hoffmann S, Witkowsky W. Chirality–from weak bosons to α-Helix. Heidelberg: Springer; 1991. pp. 205-218.
34. Hoffmann S, Witkowsky W. Reproduction of supramolecular structure. Kluwer: Dordrecht NATO ASI Ser; 1994. pp. 496-504.
35. Ibrahim HG, Gabboun NH, Najib NM, Assaf S. Release of salicylic acid, diclofenac acid and diclofenac acid salts from isotropic and anisotropic nonionic surfactant systems across rat skin. Int J Pharm, 2001; 212: 73-80.
36. Jakli A, Saupe A. One- and Two- dimentional Fluids: Properties of smectic, lamellar and columnar liquid crystals. London: Taylor & Francies; 2006.
37. Lechuga-Ballesteros D, Stevenson CL, Bennett DB. Pharmaceutical liquid crystals: The relevance of partially ordered systems. J Pharm Sci, 2005; 94: 1861-1880.
38. Lipowsky R, Sackman E. Structure and dynamic of membranes, I: From cells to vesicles. 1st ed. Netherlands: Elsevier Science; 1995.
39. Mani NS. Applied Physics I: For University of Mumbai. India: Dorling Kindersled; 2001. pp. 1-33.
40. McBride C. Computer simulation of liquid crystals. Dissertation, University of Durham: Durham, 1999.
41. Mingos DMP. Liquid crystal I. Verlag Berlin: Springer; 1999.
42. Minghetti P, Cilurzo F, Casiraghi A. Development of patches for the controlled release of dehydroepiandrosterone. Drug Dev Ind Pharm, 2001; 27: 711-717.
43. Moldoveanu E, Marta D, Burducea G. Apoptosis. Int Symp Myelodisplasic Syndrome. Proc: Paris; 2003. pp. 51-56.
44. Muller-Goymann CC, Friedrich I, Reichl S. Drug release and permeation studies of nanosuspensions

based on solidified reverse micellar solutions (SRMS). Int J Pharm, 2005; 305: 167-175.
45. Nalwa HS. Handbook of Advanced Electronic and Photonic Materials and Devices. Vol 7. Liquid Crystals, Display and Laser Materials. London: Academic Press; 2000. pp. 1-37.
46. Norling T, Lading P, Engstrom S, Larsson K, Krog N, Nissen SS. Formulation of drug delivery system based on a mixture of monoglycerides and triglycerides for use in the treatment of periodontal disease. J Clin Periodontol, 1992; 19: 687-692.
47. Palleos GM, Michas J. Membrane-Nucleic Acids systems. Liq Cryst, 1992; 11: 773-780.
48. Rades T, Muller-Goymann CC. Melting behavior and thermotropic mesomorphism of fenoprofen salts. Eur J Pharm Biopharm, 1994; 40: 277-282.
49. Rades T, Bunjes H. Thermotropic liquid crystalline drugs. J Pharm Pharmacol, 2005; 57: 807-816.
50. Razumas V, Kanapieniene J, Nylander T, Engstrom S, Larsson K. Electrochemical biosensors for glucose, lactate, urea, and creatinine based on enzymes entrapped in a cubic liquid crystalline phase. Analy Chimica Acta, 1994; 289: 155-162.
51. Reinitzer F. Progress in Liquid Crystal Chemistry. Chem, 1988; 9: 421-441.
52. Reinitzer F. cholesteric liquid crystals. Liq Cryst, 1989; 5: 7-18.
53. Ridell A. Characterisation of Aqueous solutions, Liquid Crystals and Solid state of non-ionic polymers in association with amphiphiles and drugs. Dissertation, Acta Universitatis Upsaliensis: Uppsala.Sackmann, 2003.
54. Saeva FD. Liquid Crystals: The Fourth State of Matter. New York: Marcel Dekka Inc; 1979.
55. Saez IM, Goodby JW. Chiral nematic octasilsesquioxanes. J Mater Chem, 2001; 11: 2845-2851.
56. Seddon JM, Templer RH. CH_3 in Structure and dynamics of membranes: From cells to vesicles. Netherlands: Elsevier Science; 1995.
57. Stannarius R, Aksenov V, Blasing J, Krost A, Rossle M, Zentel R. Mechanical manipulation of molecular lattice parameters in ascetic elastomers. Phys Chem Chem Phys, 2006; 8: 2293-2298.
58. Tiberg F, Joabsson F. Lipid liquid crystals for parenteral Sustained-release applications: Combining ease of use and Manufacturing with consistent drug Release control. Injectable drug delivery, 2010; 9-12.
59. Wyatt D, Dorschel D. A cubic phase delivery system composed of glycerol monooleate and water for sustained release of water-soluble drugs. Pharma Techn, 1992; 16: 116-130.
60. Ya Zyryanov V, Barannik AV, Presnyakov VV. Introduction and historical overview what are liquid crystals. Liq Cryst, 2005; 32: 345.

Conflict of Interest: None
Source of Funding: Nil
Paper Citation: Nayak S, Ola M. Liquid Crystalline Syatem: Novel approach in Drug Delivery. J Pharm Adv Res, 2018; 1(2): 66-75.