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Review Article

LIQUID CRYSTALS AS A CUBO-HEXAGONAL TOPICAL CONTROLLED DRUG DELIVERY SYSTEM

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ABSTRACT

Liquid crystals (LCs) are substances that flow like liquids but maintain some of the structure characteristics of crystalline solids. Based on the ways that LCs are generated, they can be classified as thermotropic LCs and lyotropic LCs. The thermotropic is generated by temperature variation in the liquid state, while the lyotropic is formed by dissolving the compound in certain solvents. Either way offers the systems sufficient large amplitude molecular mobility so that molecules can change positions and reorient themselves forming LC phases. The thermotropic LCs usually are one-compound systems, while Lyotropic LCs are always solutions consisting of multiple compounds containing solute and solvent. Lyotropic liquid crystal systems, such as reversed bicontinuous cubic and hexagonal mesophase, are attracting more and more attention because of their unique microstructures and physicochemical properties. And mainly it shows an application such as increase the penetrability, compatibility, bioadhesive properties and sustained release effect due to different phases. The aim of this review article is to scientifically highlight pharmaceutical liquid crystals, its importance in current development of targeted drug delivery system. Objective of this review is also to provide in depth information of pharmaceutical liquid crystal technology which include its latest & advanced technology development.

Keywords: Pharmaceutical liquid crystals, Mesophase, Topical formulation, Percutaneous absorption, Phases, Controlled drug delivery system.

INTRODUCTION

The design of new dosage form increase effectiveness of exiting drug is one of new trend observed in pharmaceutical technology. In this context liquid crystal novel dosage forms because of their considerable capacity to be solubilise both oil and water soluble compounds. Liquid crystalline phase was formed towards oil phase were spontaneous emulsion was formed and liquid Crystals are intermediate state, show combines properties related to both liquids and crystals. Molecules in a crystal are highly ordered, while molecules in a liquid are free to diffuse in a random way. A generally used synonym for liquid crystal is the mesophase, indicating the unique structure intermediate between that of a true liquid and a solid crystal phase. The liquid state is associated with the ability to flow whereas the solid state characterized by an ordered, crystalline structure (Guo, C *et al.*, 2010; Makai, M *et al.*, 2003). The liquid crystals are of thermotropic and lyotropic types, lyotropic liquid crystals are prepared by the presence of solvent, and have been extensively described in the context of emulsion technology; however, other pharmaceutical examples are developing. Thermotropic liquid crystals are induced by a change in temperature and are free of solvent, where more pharmaceutical applications appear in the context

(Stevenson, CL *et al.*, 2005). Liquid crystals (LC) are liquids featuring a certain level of orientational order. Molecules in LCs tend to point to a certain direction, while they still haven translational (positional) freedom. Although they are best known for their application in liquid crystals is also an essential part of all life. Lyotropic liquid crystals are essential organic substances, DNA, lipids of cellular membranes and proteins are some examples of well-known liquid crystals. In liquid crystals drug delivery crystalline solids exhibit short as well as long-range order with regard to both position and orientation in the molecules. Whereas liquids are amorphous in general but may show short-range order with regard to position and/or orientation. Liquid crystals show at least orientational long-range and may show short-range order, whereas positional long range order disappears due, liquid crystalline phases and it represent intermediate states and are also called mesophase (Christel, C *et al.*, 2010). Lyotropic liquid crystal (LLC) systems that Mainly consist of an amphiphillic molecule is characterized by the possession of both a non-polar, hydrophobic tail and a polar, hydrophilic head on the same molecule which allows this molecule to form ordered structures in polar and non-polar solvents. At low concentration the basic unit of an amphiphillic is the micelle, a cluster of molecules with their polar groups oriented in the water. This phase is indicated as liquid isotropic phase, isotropic means that the structure shows identical properties in all directions. It fulfils the requirements making drug loading and drug absorption faster from the site of application of topical formulation. They attain controlled release for both hydrophilic and hydrophobic drugs, increase solubility of drugs and provide long-term hydration of skin (Jain, A *et al.*, 2010). Lyotropic liquid crystal systems formed from aqueous surfactants can absorb water from the environment inducing spontaneously phase-transitions, forming lamellar, hexagonal and cubic phases, depending on the water content. A lamellar phase can be considered as alternate double flat layers of surfactant molecule tail-to-tail with the polar groups facing the intervening layers of water molecules. Noticeable is that this phase is relative fluid despite the high surfactant concentration. The structure responsible for the fluidity of the lamellar phase is indicated as sematic. The layers can glide easily over one another, but at the same time their crystal-like composition among these systems, shows reversed cubic (Q2) and hexagonal mesophase (H2) are the most important and have been extensively investigated for their ability to sustain the release of a wide range of bioactive from low molecular weight drugs to proteins, peptides and nucleic acids (Clogston, J *et al.*, 2005; Drummond, CJ *et al.*, 1999; Mezzenga, R *et al.* , 2005; Mohammady, SZ *et al.* , 2009; Ubbink, J *et al.* , 2008). Reversed cubic and hexagonal mesophase are often formed by polar lipids in an aqueous environment. The structure-forming lipids can absorb a certain amount of water and then spontaneously form gel-like phases with unique internal structures, into which drugs can be incorporated. Moreover, non-toxic, biodegradable and bioadhesive properties also contribute to their applications for drug delivery (Shah, JC *et al.*, 2001). Owing to infinite swelling capability, reversed cubic and hexagonal mesophase can also be dispersed in equilibrium with excess water and form colloidal dispersions with superior stability (Spicer, PT *et al.*, 2005; Yaghmur, A *et al.* , 2009). At present, reversed cubic and hexagonal mesophase are being investigated as candidates for, buccal, gastrointestinal, intravenous, lung, nasal, oral, rectal and vaginal administration of drug with considerable progress (Drummond, CJ *et al.*, 1999). In the following study, we briefly introduce the cubic and hexagonal mesophases based on recent literature survey, including their textures, preparation methods, phase behaviours and applications in drug delivery. In particular, we discuss the current status of investigations with respect to the applications of cubic and hexagonal mesophase as drug vehicle.

Structures of Reversed Cubic and Hexagonal Mesophases

For reversed bicontinuous cubic and hexagonal mesophases, three macroscopic forms are typically encountered precursor, bulk gel and particulate dispersions.

Structure of Cubic Mesophase

The structure of cubic mesophases is unique and comprises a curved bicontinuous lipid bilayer (with an estimated thickness of 3.5 nm) extending in three dimensions and two interpenetrating, but non-contacting, aqueous Nano-channels (with a fully swollen diameter of approximately 5 nm), with a high interfacial area of 400 m^2/g (Drummond, CJ *et al.*,1999; Spicer, PT *et al.*, 2005; Yaghmur, A *et al.*, 2009). These mainly shows cubic mesophases prepared by unsaturated monoglycerides or phytantriol (PT) are the most frequently investigated liquid crystal structures for drug delivery (Amar-Yuli, I *et al.*, 2009; Dong, YD *et al.*, 2006; Dong, YD *et al.*, 2008). The compartmentalization in cubic mesophases can be used to introduce guest drugs of hydrophilic, lipophilic or amphiphillic nature shown in figure 1. Hydrophilic drugs will be located close to the emulsifier polar head or in the water channels, whereas lipophilic drugs will be localized within the lipid bilayer and amphiphillic drugs in the interface (Sagalowicz, L *et al.*, 2006). The bulk phase is commonly a clear, viscous, semi-solid gel in appearance and rheology to cross-linked polymer hydrogels (Spicer, PT *et al.*, 2006). Its high viscosity makes it difficult to handle and limits its application and, furthermore, the bulk phase can cause the irritation reaction when in contact with the biological epithelia (Rosen, MR *et al.*, 2006). To overcome these issues, an innovative strategy has been formulated to disperse the bulk phase into water in the form of small particles. The dispersed cubic particles are denoted as 'cubosomes, which can stably exist in equilibrium with aqueous solution with the internal bicontinuous structure unchanged (Gustafsson, J *et al.*,1996). On the basis of polarized light microscopy and X-ray crystallographic studies, three distinct reversed bicontinuous cubic phases can be identified the double-diamond lattice, the body-centred cubic phase and the gyroid lattice (Larsson, K *et al.*, 2000; Shah, JC *et al.*, 2001).

Structure of Hexagonal Mesophase

Hexagonal mesophases are closed and extended micellar columnar structures (Laughlin, RG *et al.*, 2006), and the long-range order is two-dimensional. It has been reported that there is no direct contact between water inside and outside the hexagonal phases (Sagalowicz, L *et al.*, 2006). Likewise, the dispersed reversed hexagonal particles denoted as 'hexosomes' can also be obtained by dispersing the hexagonal gel into aqueous solution (Gustafsson, J *et al.*, 1996). To date, the hexagonal mesophases composed of glycerate-based surfactants such as oleylglycerate (OG) and phytanylglycerate (PG) have shown great potential in drug delivery (Boyd, BJ *et al.*, 2006), hydrophilic drugs will be entrapped in the internal water domain, whereas lipophilic drugs will be located within the lipid domain and amphiphillic drugs in the interface.

Preparation Methods for Lyotropic Liquid Crystals Mesophase

Liquid crystal gels could be prepared by simply blending aqueous phase with lipid phase using vortex or ultra-sonication. The production of liquid crystals is relatively simple and energy saving. They are thermodynamically stable and can be stored for long periods of time without phase separation (Bentley, VB *et al.*, 2005). The manufacture of cubosomes or Hexosomes is more complicated, however; therefore, we mainly concentrate on the preparation methods.

- **Top-down approach**

  This approach was primarily reported to formation mechanism (Ljusberg-wahren, H *et al.*, 1996]). The extreme viscous bulk phase is prepared by mixing structure-forming lipids with stabilizers, then the resultant is dispersed into aqueous solution through the input of high energy (such as high-pressure homogenization (HPH), sonication or shearing) to form LLC nanoparticles. At present, HPH is the most extensively used technique in the preparation of LLC nanoparticles (Spicer, PT *et al.*, 2005) investigated the parameters influencing the properties of glyceryl monooleate (GMO)-based cubosomes. Based on the results observed, the concentration of F127 and temperature during HPH were regarded as important

parameters. Recently, a novel approach of shearing was proposed to fabricate LLC nanoparticles using a laboratory-built shearing apparatus (Mezzenga, R *et al.*, 2005). Compared with the well-established ultrasonication approach, the shearing treatment could effectively prepare more stable and homogeneous cubosomes or hexosomes with high content of the hydrophobic phase (oil + lipophilic additives) within a short time (< 1 min). In fact, the operation units in this procedure require several cycles to achieve the desired nanoparticles with appropriate characteristics, and the high-energy input is also regarded as a barrier to the temperature sensitive ingredients (Spicer, PT *et al.*, 2005). In addition, the cubosomes prepared through top-down approach are always observed to coexist with vesicles (dispersed nanoparticles of lamellar liquid crystalline phase) or vesicle-like structures, which will hamper the investigations on plain cubic mesophases.

- **Bottom-up approach**

The key factor in the bottom-up approach is hydrotrope, which can dissolve water-insoluble lipids to create liquid precursors and prevent the formation of liquid crystals at high concentration (Mezzenga, R *et al.* , 2005). Compared with the top-down approach, this dilution-based approach can produce cubosomes without laborious fragmentation. In other words, it needs less energy input. Moreover, this approach is far more efficient at generating small particles. The reason for this might relate to the forming mechanism of cubosomes. The dilution-based approach can be regarded as a process of small particles forming big particles through aggregation, which is analogous to the use of precipitation processes to produce nanoparticles, whereas the top-down approach is more analogous to the attrition of big particles. In addition, cubosomes prepared through dilution show long-term stability, which might be attributed to the homodisperse stabilizers onto the surface of cubosomes (Spicer, PT *et al.*, 2005). Indeed, the use of hydrotrope can simplify the preparation process and produce cubosomes possessing similar or even better properties than those fabricated by the top-down approach. It should be noted, however, that this process via dilution is an Oil phase (melted lipid) pathway by charting on the ternary phase diagram (lipid–water–hydrotrope), which requires knowledge of the full phase behaviour hence, the extent of dilution is difficult to control precisely. Owing to the addition of hydrotrope, many issues arise, such as the effects exerted by varying concentrations of hydrotrope on the physicochemical properties of LLC nanoparticles and the possible occurrence of irritation and allergic response when the mesophases formulations are administered. Finally, this bottom-up approach cannot effectively avoid forming vesicles. Through cryo-TEM, many vesicles and vesicle-like structures were also observed to coexist with cubosomes (Rosen, MR *et al.*, 2006).

- **Heating**

The coexistence of cubosomes with vesicles is speculated to provide multiphasic manipulation of the sustained release of drugs**,** (Jain, A *et al.*, 2010) hence to better investigate the release behaviour of plain mesophases; vesicles should be eliminated as much as possible. In this case, heat treatment can be regarded as a good approach. Note that in the strictest sense, heat treatment is not an integrated process for the manufacture of cubosomes because it only promotes the transformation from non-cubic vesicles to well-ordered cubic particles. The dispersed particles, therefore, can be produced by a simple processing scheme comprising a homogenization and heat-treatment step. From the reported studies, heat treatment

could cause a decrease in the small particle size fraction that corresponded to vesicles and form more cubic phases with narrow particle distribution and good colloidal stability (Barauskas, J *et al.*, 2005; Worle, G *et al.*, 2006). Taking the whole process of preparation into account, it is obvious that the transition takes place during the procedure of heat treatment. The reason for transition could be speculated as an elevated temperature giving rise to a reduction in solubility and stability. When the temperature was below cloud point, the surfactant had a high solubility and thus the particles could exist stably and the phenomenon of fusion was hardly observed. Once reaching cloud point, the solubility of surfactant decreased notably and a notable fast fusion among vesicles would occur (Barauskas, J *et al.*, 2005). Although masses of vesicles can transform to cubic nanoparticles through heat treatment, it does not mean that all the LLC systems are suitable for this procedure in particular, the systems loading drugs that cannot provide sufficient stability under the condition of high temperature (usually above 120^0C), such as some proteins and temperature-sensitive drugs, are not suitable.

- **Spray drying**

  To widen the applications of cubosomes in pharmaceutical field, dry powder precursors can be fabricated by spray drying and used for the preparation of oral solid formulations and inhalants. This approach was originally proposed and investigated to show spray drying for formation of nanoparticles (Worle, G *et al.*, 2006). In his research, the powder precursor could be prepared through drying a pre-dispersed aqueous solution that consisted of GMO, hydrophobically modified starch and water or contained GMO, dextran, ethanol and water, and then the colloidally stable dispersions of Nano-structured cubosomes could be created by hydration of the precursors. Prepare GMO-based cubosomes precursor containing diclofenac sodium through spray drying (Spicer, PT *et al.*, 2002). The precursor was proven to have more effective and prolonged anti-inflammatory and analgesic activity than pure drug when administered per orally; it is noteworthy however, that residual solvent content is still a problem that cannot be ignored (Shah, MH *et al.*, 2006).

Drug Release and Loading

According to the nature of drug, it can be added in both the oil phase as well as aqueous phase. Drug loading depends on solubility of active constituents and their partition between phases (Engstrom, S *et al.*, 1995). Simply if higher affinity of active constituents for liquid crystals it leads to higher loading (Engstrom S *et al.* , 1990). It shows that changing the ionization states of active constituents alter the solubility and its loading in liquid crystal,(Nielsen, LS *et al.*, 1998) at low pH, the active constituents is more hydrophobic and can loaded to higher levels and vice versa. A wide variety of drug with different physiochemical properties (Engstrom, S *et al.*, 1992) have been incorporated in glycerol monooleate base phases and their sustained release were studied (Sadhale, Y *et al.*, 1998). The solubility of the drug determines the concentration present in absorption site, and the water/lipid partition coefficients influence the rate of transport and inverse relationship appear to exist between the absorption rate and molecular rate (Jungiger H *et al.*, 1981). There exists the little correction between size and penetration rate.

Evaluation of Lyotropic Liquid Crystal

- ***Appearance***

  A Lyotropic crystalline gel formulation is observed for appearance, colour and consistency.

- ***pH***

  2.0gm of gel is accurately weighed and dispersed in 20ml of distilled water. The PH of dispersion is measured by using

digital PH meter. This procedure can be carried out in triplicate.

- ***Viscosity***

  A Brookfield digital viscometer, cone and plate type of viscometer is used to determine viscosity of the formulations .The viscosity is measured at 5 RPM after 30 sec, by using spindle no.7

- ***Drug Content***

  0.50gm of formulation Lyotropic liquid crystalline gel is weighed accurately. It is added in 100 ml volumetric flask which contains 100 ml of PBS 6.8.Resultant solution is kept for sonication for 30 mins. For complete solubility of drug, the resultant solution is filtered. Absorbance of solution is checked at 266 nm and compared with pure drug absorbance at same wavelength and concentration. Thus % assay is calculated this procedure can be carried out in triplicate.

- ***Polarized Light Microscopy (PLM)*** *(Muzzalupo, R et al., 2010)*

  It is suitable for the identification of Lyotropic liquid crystal cubic, hexagonal, lamellar phase. Phase characterization of the formulations is performed by using Leica polarizing microscope equipped with f-601 camera. Liquid crystalline phases are identified by image and classified according to the visualized textures of liquid crystalline described by literatures.

- ***Particle Size Analysis***

  Particle size analysis is done for size analysis using particle size analyser (Zetasizer) for determination of particle size of the formulation.

- ***Transmission Electron Microscopy (TEM)***

  Surface morphology of formulated lyotropic liquid crystalline suspension is studied using transmission electron microscopy. TEM analysis is done for TEM analysis, a small drop of sample is placed on a polymer filmed copper grid and allowed to stand for 2 min. The excess sample is removed using filter paper, followed by addition of 10µl of unaryl acetate. The grid is then allowed to stand for another 2 min ,washed in distilled water and air dried, forming a thin film, which is viewed at 70 kv.

- ***Texture Characterization (Muzzalupo, R et al., 2010)***

  ❖ *Texture Profile Analysis (TPA)*

  Texture profile analysis (TPA) was CT3 texture analyser in TPA mode. Sensory properties included measures such as consistency, firmness, cohesiveness (attractive forces within the formulation) and work of adhesion (attraction between the formulation and substrate).A conical shape holder is filled evenly with the z-LLCG care should take that, no air bubble introducedin it and testing surface was as flat as possible to avoid rarely triggering of the test. The probe(TA/3/100) is programmed to descend into the sample at a speed of 0.5 mm/s with target value 20 mm and then ascend back at the same speed to its original position the force encountered by the probes to break away from the gel when starting to ascend(the point of maximum force)was measured.

  ❖ *Spreadability*

  Spreadability test is performed by using CT3 Texture Analyser in compression mode. A cone analytical Probe (60^{o}) was forced down into each sample at defined rate (0.5mm/s) and to a defined depth (12mm).The test is performed and results are observed.

- ***In Vitro Drug Release (Muzzalupo R et al., 2010)***

  The in vitro release study of lyotropic liquid crystalline gel is performed to investigate the amount of drug released from a gel. Dialysis membrane (cellophane) is used as diffusion membrane. Membrane is soaked in phosphate buffer 6.8 for 2hr before subjecting to diffusion study. The

membrane is positioned between the two cell halves of a glass chamber. The two compartments were held together with a clamp. The receiver/receptor compartment contained 25 ml of phosphate buffer. In the upper donor compartment 0.5gm of formulation is spread evenly on the membrane. The receptor phase (phosphate buffer) was continuously stirred with the help of magnetic stirrer at 300 rpm and maintained at 37°C using a circulating water bath. At predetermined time intervals (1,2,3,4,5,6,7,8,9,10,11,12,24,36,48) 1ml samples are collected from the receiver compartment and replace with fresh buffer solution. The samples collected from the receiver compartment are analysed for drug content using UV spectrometric method at suitable wavelength.

- ***Skin Irritation Study***

  Rabbit weight 3 kg is used in this study. The animals were housed in propylene cage, with access to standard laboratory diet and the animals is acclimatized for at least seven days before experimentation, the dorsal abdominal skin of rabbits tagline gel is applied onto the dorsal skin of rabbit area 1x1 squares after a 48 hrs.

APPLICATIONS

Liquid Crystal Emulsion

A large part of cosmetic products are made in the form of emulsions, a form that allows the simultaneous use of lipophilic and hydrophilic ingredients in the required dosages. A product in the form of an emulsion also has the advantage of having the most convenient appearance and texture that also facilitates its application. They can be formulated to be liquid, milk type emulsions of variable consistency, creams, or even super liquid spray able emulsions (Garry, M *et al.*, 1999). Finally, we should also consider the fact that an emulsion is the best carrier for active ingredients and functional substances. The theory of stabilising an emulsion through the formation of a network of liquid crystals is different to the HLB theory or the Schulman couples theory. The gellification of the water phase obtainable with hydrosolvatable polymers or with emulsifiers that are able to form a reticular organised structure in liquid crystal form, eliminates the need to use waxy components in large quantities and consistency. Factors that is no longer in harmony with the modern conception of light and easy to spread Emulsions (Eros, *et al.*, 2010).

Advantage of Liquid Crystals in Emulsions

LCs (mesophases) provides the following advantages to emulsion (Imran, K *et al.*, 2012)

- ❖ Increased stability
- ❖ Prolonged hydration
- ❖ Controlled drug delivery

- ***Stability***

  Emulsion stability of the multilayers around the oil droplets act as a barrier to coalescence. If oil droplets coalesce emulsion breaks. This barrier for coalescence acts as increased stability property of the emulsion. [Garry M et al., 1999]

- ***Prolonged Hydration***

  Lamellar liquid crystalline and gel network contain water layer, which shows that 50% of the water of oil in water (o/w) emulsion can be bound to such structures. Such water is less prone to evaporation when applied to the skin and permits a long lasting miniaturisation /hydrating effect, necessary for drug entry (Imran, K *et al.*, 2012).

- ***Controlled Drug Delivery***

  Liquid crystals prevent the fast release of the drug dissolved in the oil phase of an emulsion. This is attributed to the lamellar liquid crystalline multilayer, which reduces the interfacial transport of a drug dissolved within the oil droplets. Microscopic observations under polarized light show the exceptional thickness of liquid crystalline lamellar layer around the oil droplets (Imran, K *et al.*, 2012).

Function & Properties of the Liquid Crystal System

LCs when present at the oil/water interface, the liquid crystals help give the system rigidity and, by limiting the fluctuation of the components at the interface, give the emulsion great stability. Furthermore, the liquid crystal system enhances the moisturising ability of the emulsion; in this special network. The quantity of inter-lamellar water can be extremely high and become immediately available when the cream is applied to the skin. For these reasons these emulsions have a shiny surface, a fresh and original feel and they leave a light and pleasant sensation on the skin (Lehn, JM *et al.*). In recent years, the moisturising effect of creams and lotions has become increasingly more important and cosmetic chemists are constantly searching for better methods of retaining water in the superior layers of the skin. The evaporation of the bonding water in emulsions containing anisotropic lamellar phases is slower and permits a hydro retentive action that prolongs the moisturising effect. The associations that are formed because of the excess water are particularly interesting; in these cases the ability of the crystalline phase to swell is strictly linked to the stability and the behaviour of the emulsion because, in a liquid crystal system, the quantity of inter-lamellar water and of hydrophilic elements can amount to 70% of the total external phase.

CONCLUSION

Liquid crystals technique for drug delivery can be effective and useful for delivery of drug. Liquid crystals are mainly lyotropic and thermotropic, this approach is widely utilized in topical drug delivery, as it possesses the advantage of smooth feel and drug loading of water soluble and insoluble molecule. Liquid crystal gels could be prepared by simply blending aqueous phase with lipid phase using vortex or ultra-sonication. The production of liquid crystals is relatively simple and energy saving. They are thermodynamically stable and can be stored for long periods of time without phase separation. The glycerate-based surfactants such as oleylglycerate (OG) and phytanylglycerate (PG) have shown great potential in liquid crystalline drug delivery. The liquid crystals can be prepared by simple techniques like top-down, bottom-up, heating, spray drying. The liquid crystals formulations are mainly characterized by Polarized light microscopy, small angle X-ray diffraction, Transmission electron microscopy, confocal microscopy and texture analyzer. LLCs show applications as controlled drug delivery system and mainly increase the stability and permeability.

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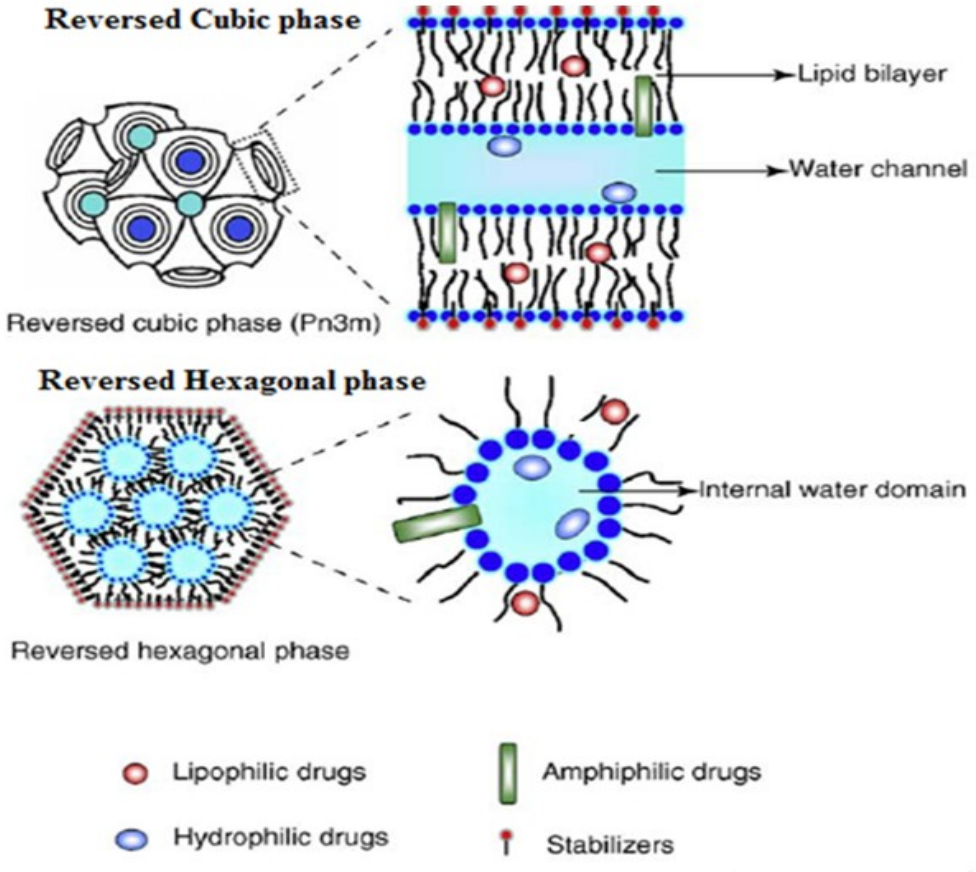

Figure1: Structure of Phases

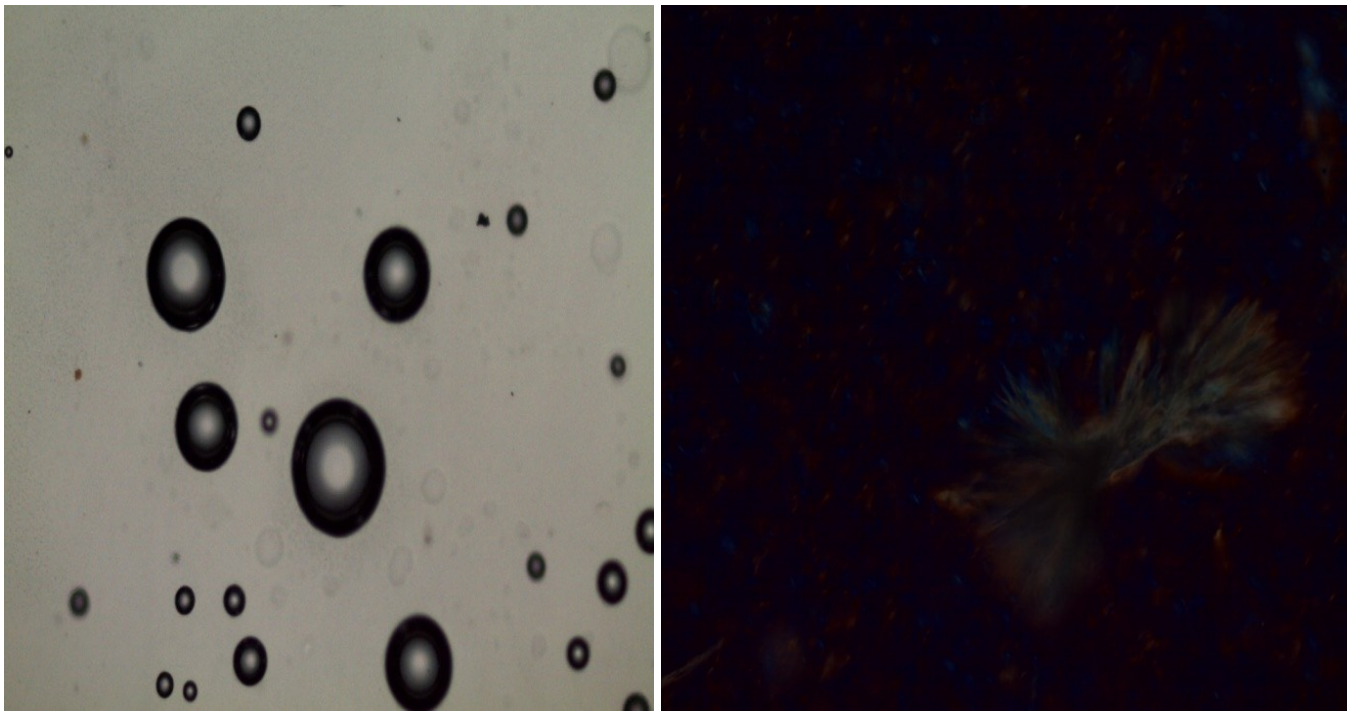

Figure 2: Images of Liquid Crystals (PLM)

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