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Review on: Liquid crystal (Mesophase) as a sustained drug release matrix.

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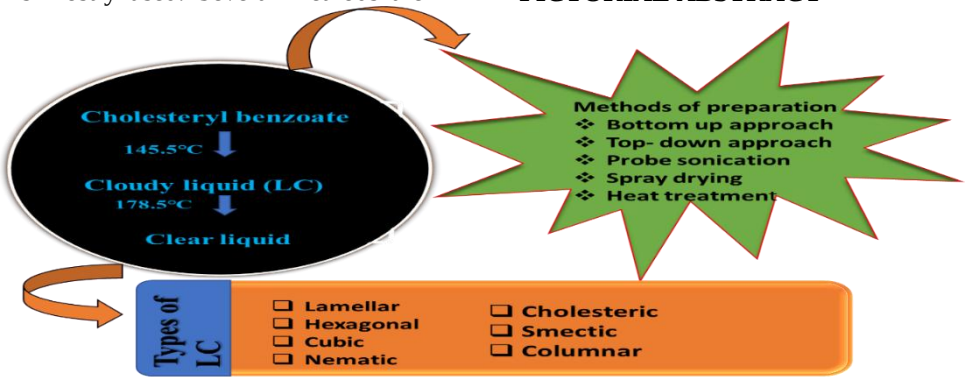
ABSTRACT

Aim: Many drugs shows their side effect or interaction with biological component to reduce this liquid crystal formulation is applicable. Some of the drug are having less or poor oral bioavailability to reduce that liquid crystal formulation used, also liquid crystal formulation reduces the cost which required for formulation because it required very less excipient for preparation. **Material and method:** There are many types of LC available such as lamellar, hexagonal, cubic, nematic, cholesteric, Smectic (A, B, C) and columnar liquid crystal. On the basis of solvent, temperature, molecular structure and concentration of amphiphile in solvent different mesophase observed. The preparation of liquid crystal lipid is mostly used. Several methods are available for preparation of LC such as Bottom-up approach, Top-down approach, Prob sonication, Heat treatment and Spray drying. **Result:** The evaluation and characterization of LC is done by various evaluation parameter such as X-ray diffraction, NMR, Polarizing microscope, TEM, DSC and Rheology. **Conclusion:** Formulation of LC required very less excipient due to that preparation cost reduces. LC are intermediate phase between solid and liquid phase.The LC is intermediate phase between liquid and solid state. Liquid crystal material is unique in their uses and property.

KEYWORDS: Liquid crystal, Mesogen, Thermotropic, lyotropic, sustained release.

PICTORIAL ABSTRACT



I. INTRODUCTION

The liquid crystalline state is combined property of solid and liquid state. The liquid state is ability to flow, whereas the solid state is identified by a crystalline structure and ordered. Crystalline solid exhibit short as well as long order with regard to both orientation of molecule and position. Liquid are amorphous in nature but shows short range order with respect to orientation and position. The characterization of crystalline solid is by long range positional and orientational order in 3D. The amphiphilic molecule is having ability to self-assemble including lipid molecule. The structure of cubic phase is unique. Based on X-ray

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crystallographic studies cubic phase divided into three types: the double-diamond (Pn3m), gyroid (Ia3d), and primitive (Im3m) phases.[1]

LCs system containing high concentration of amphiphilic surfactant, which exhibit three-dimensional arrangement of surfactant molecules capable of being transformed into each other in a definite sequence under certain circumstances, are termed as lyotropic liquid crystals. Different lyotropic liquid crystalline phases include lamellar, cubic and hexagonal phase. Cubic phase contains water channels surrounded by saddle- like curved bilayer of the amphiphile extended in three dimensions. The structure is formed separates two continuous networks of water channels.[2]In various drug delivery systems, such as liposome, solid lipid nanoparticles, nanostructure lipid carriers, and lipid based liquid crystals lipid are widely used as main ingredient. Crystal are highly order, internal nanostructure thermodynamically stable, due to that they act as sustained drug release matrix. [23,27]

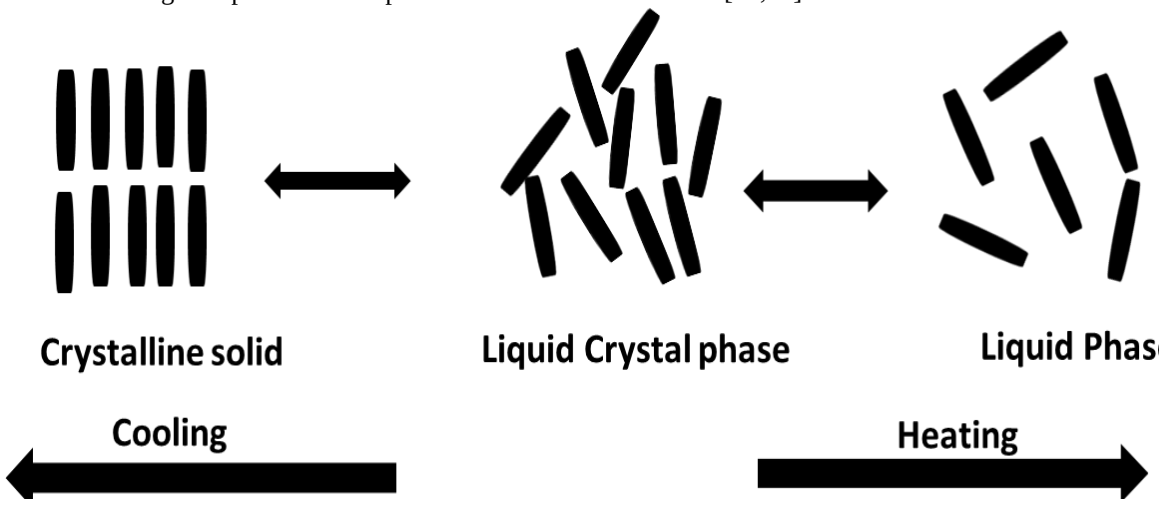

Figure: 1 Liquid crystal phase with solid phase and liquid phase.

The LC is the state of matter which is shows both liquid and crystalline property at same time such as inability to support shear, fluidity, formation and coalescence of droplets. On the basis of arrangement of molecule in mesophase or its symmetry, the liquid crystal is classified as Nematic, cholesteric, Smectic and columnar mesophases.[3] The LC is intermediate phase between liquid and solid state.[4] Liquid crystal material is unique in their uses and property. The research on liquid crystal is continuous and developed several applications. In modern technology LC play an important role. LC have many common characteristics such as rod like molecular structure, rigidness of long axis and strong dipole or easily polarizable substituents. LC shows dipole when two equal magnetic or electric charge of opposite sign separated by a small distance. The molecule in liquid crystal has not proper order.[25,28]

In solid state the molecule is highly order and also have little transdermal freedom. The orientational order of liquid state is occur between liquid and solid phase and this is origin of mesogenic state it is called “liquid crystal phase”. The Mesogen is like as rod like, disc like, molecule which are part of liquid crystalline material. Many times, it is difficult to determine whether material is in a liquid crystal or crystal phase. The crystalline material shows the ling rang periodic order in 3D, but in liquid no orientational order occur. In liquid crystal order are not as solid, but still have some degree of alignment are proper way called as liquid crystal. The synonym of liquid crystal is mesophase. In simply LC shows the property between property of liquid and solid. Certain classes of organic molecule, main and side chain polymer, surfactant micelle solution and large number of biological systems are known to be liquid crystalline. The LC molecule are made up of two part or component such as i) Rigid centre part called as Mesogen. ii) Flexible side chain called Spacer. Following fig shows the rod like structure of LC.[20,24,30]

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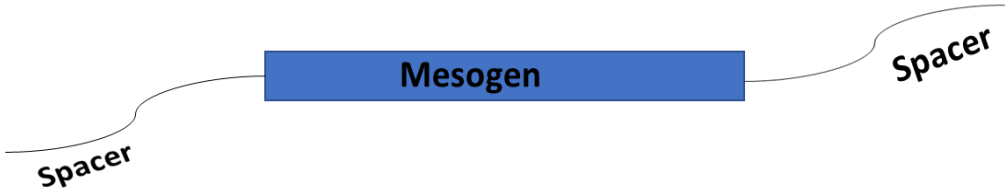

Figure: 2 Rod like structure of LC.

Figure: 3 Component of rod shape structure of LC.

It is made up of two or more ring connected to central linked group. The liquid crystal molecule is aligning parallel to each other because strong π-π interaction between molecule. LC shows variety of phases and they are differing from one another by their physical and structural property.[5] The mesophase obtained by temperature variation called "Thermotropic". The stable mesophase obtained by both cooling and heating are called "Enantiotropic". The mesophase obtained on cooling called "Monotropic". By dissolving the compound in solvent, liquid crystal phase obtained called "Lyotropic". The LC obtained by both heating and solvent called "Amphitropic". Liquid crystal structure exhibit anisotropy. LC are found to be birefringent, due to their anisotropic nature so they show double refraction. When we see liquid crystal under polarizing microscope containing crossed Nicole prism, the intense colour band and birefringence occur. The basic requirement for formation of liquid crystal is anisometric molecular shape, associated with the polarizability. The drug which contains organic acid or basic salt with anisometric molecule shape are fulfil the all requirement for formation of LC. The liquid crystal is having two main types such as i) Thermotropic and ii) Lyotropic mesophase. When change of temperature occur then thermotropic LC form and mixing with aqueous phase forms lyotropic LC. The phase transition of thermotropic LC is temperature dependent and lyotropic LC depends on both concentration and temperature. In drug delivery hexagonal and cubic mesophase are having high interest due to exceptional potential as drug vehicle. They both are mostly used for sustain and controlled release of hydrophilic and hydrophobic drug having different molecular weight. Hexagonal and cubic mesophase containing drug can be administered via different routes such as buccal, intravenous, nasal, oral, rectal, gastro-intestinal and vaginal. When amphophilic molecule (surfactant) added in a polar solvent then true molecule goes toward the low concentration of surfactant. After increasing the concentration of surfactant above critical concentration, then formation of aggregates with finite size are called "micelle". When the concentration of surfactant further increases then spherical micelle can converted into cylindrical, disc like and plate like aggregates and finally then self-arrange into cubic, hexagonal, columnar, Nematic and lamellar lyotropic mesophase.[6,7,26,29]

HISTORY:

The study of liquid crystal starts in 1888, when friedrich Reinitzer (Austrian botanist) is observed that cholesteryl benzoate had two differentiate melting point. In this experiment Reinitzer again increase the temperature of solid sample and he observed that crystal converted into hazy liquid. He further increases temperature and material converted into transparent clear liquid. Due to that experiment Reinitzer discovered a new phase of matter and that is "liquid crystal phase".

$$\text{Cholesteryl Benzoate} \xrightarrow[145.5^{\circ}C]{\text{Heat}} \text{Cloudy liquid (LC)} \xrightarrow[178.5^{\circ}C]{\text{Heat}} \text{Clear liquid}$$

In 1904- Firstly liquid crystal commercialised by marck-AG.

In 1922- Georges friedel classify the liquid crystal into different phases such as nematic, smectic, and cholesteric on the basis of their structure.

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In 1950- F.C. Frank and other further progress done on liquid crystal.
In 1960s end the cholesteric liquid crystal sugested as analytical metrology, cancer diagnostic, temperature indicator and non-destructive testing material.
Today LC have lots of application or uses in display technonogy and other places.[5,33]

CLASSIFICATION OF LC

LCs are differentiated on the basis of positional order (i.e. molecule are arranged in randomly structure lattice) and orientational order (i.e. molecule are mostly pointed in the same direction).LCs mainly classified as Lyotropic (LLCs)and Thermotropic (TLCs), physicochemical parameters responsible for the phase transitions.[8] classification of liquid crystals are as following:

1) Lyotropic liquid crystals
1.1) Lamellar LCs
1.2) Hexagonal LCs
1.3) Cubic LCs
2) Thermotropic liquid crystals
2.1) Smectic liquid crystal
2.2) Nematic liquid crystal
2.3) Cholesteric liquid crystals
2.4) Columnar liquid crystals

1) Lyotropic liquid crystals

LLCs (Lyotropic liquid crystals) systems are composed of rod like micelles, and which shows a long-range orientational order with respect to symmetry axis of the micelle, but no long-rang positional order. The three main types of LCs are characterized as being lamellar, hexagonal and cubic. LLCs (Lyotropic liquid crystals) can be formed by certain amphiphilic molecules in the presence of solvents. The lyotropic mesophase is consist of flexible lipophilic chain (tail) and hydrophilic (ionic or non-ionic) head group.

The tail is consisting of alkyl chain mainly methylene group about 6 to 20.
On the basis of solvent, temperature, molecular structure and concentration of amphiphile in the solvent, different mesophase observed. The example of lyotropic mesophase is formed by dissolution of soap in water, DNA and biological membrane.[9,22,35,31]

1.1) Lamellar LCs

Lamellar mesophase is generally having bilayer structure as repetition unit, and which shows long-range positional order in one dimension and long-range orientational order within the layer. If the concentration of hexagonal phase is increase above certain threshold then decrease in the viscosity of system can be observed. Opening with the crystalline state, the mesophase is reached either by increasing the temperature or by adding a solvent. Accordingly, lyotropic or thermotropic LC form as with thermotropic LC by variation in temperature can be causes transformation between mesophase of lyotropic LC. The Mesogen are not molecule themselves but from that after hydration lyotropic LC obtained.

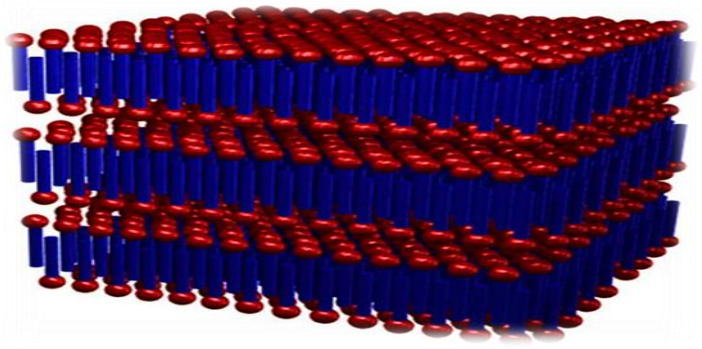

Figure: 4 Arrangement of lamellar liquid crystal

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Water or a mixture of water and organic solvent are the most important solvents for drug molecules, and the degree of hydration or salvation depends on the amphiphilic properties of a drug molecule. Hydration or salvation of a mostly rod-shaped molecule results in different geometries, i.e. cone or cylinder. Cylinders arrange in layers. This result lamellar phase containing alternating polar and non-polar layer. When we adding aqueous drug solution into polar layer then the increase in thickness of layer. Some molecule having proper affinity they can be included in non-polar layer. By adding the layer thickness of lamellar phase increase and increasing the solvent concentration lateral inclusion between molecule is also possible. This leads to phase transformation the rod shape of solvated molecule converted into cone shape.

Lamellar liquid crystals identify by polarize light microscope and optical microscope. This lamellar structure is considered to be one-dimensional as there is only one parameter that can be quantified, that of the repeat distance between the bilayers. The layers can slide over each other readily; their movement is restricted only in perpendicular direction to the plane of the layers.[9,40] This property explains the lower viscosity of lamellar phase compared to the hexagonal arrangement. The fluid lamellar phase (Lα) is not restrained as the alkyl chain are melted and fluid like, in which the least ordered of the lamellar place movement within the bilayer. In recent years lamellar liquid crystal are used mostly because of their excellent potential as drug vehicle. The lipid is use for the formation of structure of LC. This lipid can absorb the water and forms a gel like phase with unique internal structure into that drug can be incorporated. Lamellar phase other than the fluid case arise a gel type (Lβ) and crystalline liquid crystal occur with the lateral appearing at a temperature lower than that of the Lα but higher than that of liquid crystal.[10,37]

1.2) Hexagonal LCs

Hexagonal liquid crystals show long-range positional order in two dimensions. Both the lamellar and hexagonal LCs can be identified using polarized light microscopy as they exhibit a range of textures that are typical for the corresponding LCs. They also have known as middle phase as shown in Figure 5.[8]

Figure 5:Arrangement of hexagonal liquid crystal

The liquid crystalline matrices possess distinct lipidic and aqueous domains and may exhibit a number of well-defined geometric arrangements depending on the chemical structure of the lipid, the aqueous content of the system, the presence of other additives, and solution conditions such as pH, temperature and pressure. Most often this arrangement consists of lamellar bilayer structures, but for a relatively small subset of lipids, the exhibited phase structures may include the viscous reverse hexagonal phase (HII) or bicontinuous cubic phase (Q).[11,36] Figure 5 show on addition of some amphiphilic lipid in aqueous environment then spontaneous formation of liquid crystal occur. When combination of mesophase, excess water and stabilizer such as Pluronic co-polymer dispersed into nanoparticle forms hexasome or cubosome.[1,39]The hexagonal mesophases composed of glycerate-based surfactants such as oleyl glycerate (OG) and phytanyl glycerate (PG) have shown great potential in drug delivery.[11] Hexosomes are colloidally stabilize by using the tri-block co-polymer PluronicF127 and F68. Non-ionic steric stabilizers have been most often employing for the stabilization of the dispersion, as ionic stabilizer

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typically disrupt the internal nanostructure. A number of stabilizers have been used in attempt to create stable liquid crystalline dispersion such as beta casein, polyethylene glycol, hydroxypropyl methyl cellulose acetate succinate etc.

1.3) Cubic LCs

Cubic LCs mainly shows long-range positional order in three dimensions. Generally, these liquid crystals having cubic packing of the micelles and cannot Identified using polarized light microscopy. Cubic LCs highly viscous and have poor flowing property as compare to lamellar and hexagonal LCs.[8] 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.

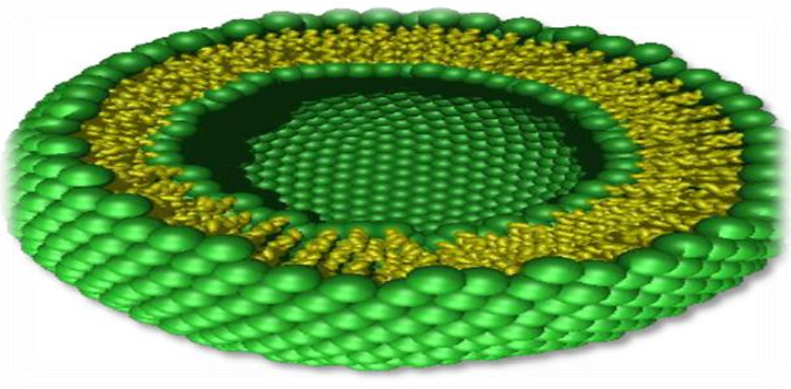

Figure 6: Cubic liquid crystals

The bulk phase is commonly a clear, viscous, semi solid gel that is similar in appearance and rheology to cross- linked polymer hydrogel. Cubic phase have been shown to improve the transdermal or topical delivery of relatively small molecule such as nicotine, acyclovir, salbutamol and aminolaevulinic acid. Cubic liquid crystals a highly viscous but not injectable, cubic phase with sustained release properties form from unsaturated monoglyceride in contact with aqueous phase.[38]

2) Thermotropic liquid crystals

The temperature at which crystal converted into mesophase is called as "melting point" and conversion of mesophase to isotropic state is called "cleaning point". The organic and metal containing organic compound shows the thermotropic liquid crystal property.[7]

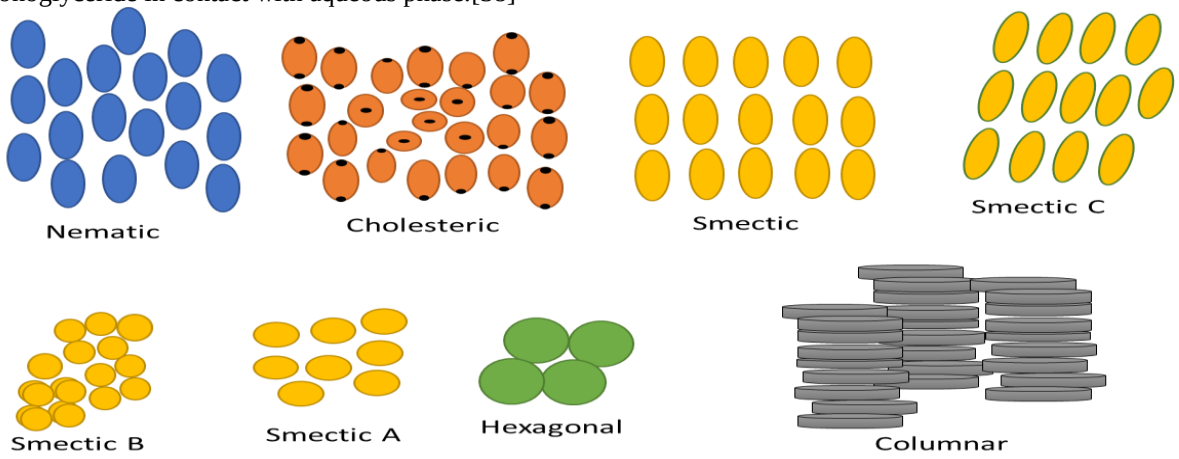

Figure: 7 Types of Thermotropic LC.

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2.1) Smectic liquid crystal

The word "Smectic" is obtained from Greek word "soap, grease or slime". The Smectic phase shows the degree of transitional order but this not occur in nematic mesophase. When Smectic state is more means order increased "solid-like" than the nematic. The most important feature of Smectic mesophase is it differentiate from cholesteric and nematic on the basis of its stratification. Smectic molecule arrange in a layer and shows some correlation in their position. The layer of molecule can be slide freely over one another. On the basis of arrangement/order or position of molecule in layer the smectic classified in several types.

In smectic A- the molecule in the layer which are perpendicular to the layer.

In smectic C- molecule in the layer are not perpendicular to the layer, so that phase has biaxial symmetry.

In smectic B- within the layer hexagonal crystalline order occur.

Many of the compound shows both cholesteric or nematic and smectic mesophase. The lower temperature phase having more degree of crystalline order. At higher temperature nematic mesophase occur than smectic mesophase. The smectic mesophase are occur in following order such as A → CB as the temperature decrease.[2,32]

2.2) Nematic liquid crystal

In a nematic mesophase molecular possess a long range orientational order with molecular long axes aligned along a preferred direction. The centre of mass of molecule have not long-range order in position. The preferred direction may be very through the medium called as director. The orientation of the director is represented by a unit vector, n (r). In nematic mesophase, there is no arrangement of their end, even if they differ and molecule are having ability to reduce around their own long axes.[2]

The LC is an anisotropic material, the physical property of the system differs with average alignment with the director. The material is very anisotropic if alignment is large same as if small alignment is there then material is mostly isotropic. The nematic type of liquid crystal are generally used in electronic display.[21,34,43]

2.3) Cholesteric liquid crystals

The cholesteric phase can be combination of nematic and smectic.[6] The cholesteric molecule is a chiral variant of the nematic mesophase and therefore it is known as chiral nematic phase. The name cholesteric has historical origin that is types of LC organization was observed in ester of cholesterol. The cholesteric is similar to nematic mesophase. The centre of mass of molecule have not long-range positional order but it has long range orientational order. The cholesteric and nematic mesophase is different from each other in that director completely different all over medium in a regular way even in an unstrained state.[2,7]

2.4) Columnar liquid crystals

The columnar mesophase are class of liquid crystal phase. This molecule is arranging in cylindrical structure. The lipid crystal called as discoid liquid crystal because the columnar structure is made up of stacked flat shaped discoid molecule.[2]

METHOD OF PREPERATION OF LIQUID CRYSTAL

i) Spray drying
ii) Probe sonication
iii) Bottom-up-approach
iv) Heat treatment
v) Top-down-approach

i) Spray drying

In pharmaceutical field cubosome have lots of application. By using spray drying dry powder precursor can be fabricated and this output of spray drying use for preparation of inhalant and solid formulation. This approach was originally proposed and investigated by scientist Spicer. In this method the powder precursor can be prepared by drying the pre-dispersed aqueous solution that are consist of or containing hydrophobically modified starch, GMO and water or sometime contain combination of GMO, ethanol, dextran and water. This dispersion finally hydrates with aqueous phase and then colloidally stable dispersion of nano-structured cubosome forms.[12] Afterward prepared GMO based cubosome precursor containing diclofenac sodium through spray drying. 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.[47]

Advantages:

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1) Spray drying technique is useful for powder formulation such as DPI (Dry powder inhaler, dry syrup).
2) Organic solvent can use in this method.
3) This technique used for microencapsulation.

Disadvantages:

1) Spray drying method is complicated as compare to other method.
2) From this method has low yield of formulation as 5-30% out of 100%.[41,37,28]

ii) Probe sonication

Initially were for production of solid lipid nanoparticle the high shear homogenization and ultra sound technique used. However, its quality is compromised by the presence of microparticles. The combination of melted lipid, water and mixture of surfactant are stirred with ultra-Turrex T25 then pre-emulsion was obtained. A sonication probe was placed in this pre-emulsion which lead to droplet breakage by acoustic cavitation's and subsequent formation of oil in water (o/w) nano emulsion which immediately cooled down to room temperature to generate liquid crystals.

Advantages

1. Both methods are widespread and easy to handle.
2. Equipment's whatever use here are very common in every lab.
3. Shear stress Reduced.

Disadvantages

1. Potential metal contamination.
2. Physical instability like particle growth upon storage.[41,37,31]

iii) Bottom-up-approach

This bottom-up-approach can produce the cubosome without fragmentation as compared to top-down approach. The bottom-up-approach required very less energy for production of cubosome. The efficiency of this method is more for production of small particle as compared to top-up-approach. 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. The cubosome which are obtained from dilution shows the long-term stability, which might be attracted to the homo-disperse stabilizer on the surface of cubosome. The hydrotropes use and it can simplify the preparation and produce cubosome and having better property than those fabricated by the top-down-approach. However, that this process via dilution is a pathway by charting trajectories on the ternary phase diagram (lipid and water hydrotrope), which requires knowledge of the full phase behavior; 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 mesophase formulations are administered. Finally, this bottom-up approach cannot effectively avoid forming vesicles.[13,31,37,34,41]

Advantages

1) Lower energy input.
2) Less time-consuming process.
3) At high concentration prevent the formation of LCs.
4) No need the organic solvent.

Disadvantages

1) Milky white formulation formed.
2) Hydrotrope which shows allergic reaction when the mesophase formulation administered orally.

iv) Heat treatment

The coexistence of cubosomes with vesicles is speculated to provide multiphase manipulation of the sustained release of drugs; hence, to better investigate the release behavior of plain mesophases, vesicles should be eliminated as much as possible. The heat treatment can be good approach in this case. 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. By simple processing scheme comprising homogenization and heat treatment steps dispersed particle can be produced. 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. 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

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phenomenon of fusion was hardly observed. The solubility of surfactant decreases and fast fusion among vesicle would occur, once reaching cloud point. Through heat treatment the mass of vesicle can transform to cubic nanoparticle, it does not mean that all lyotropic liquid crystal system are suitable for this procedure, the systems loading drugs that cannot provide sufficient stability under the condition of high temperature (usually above 120°C), such as some proteins and temperature-sensitive drugs are not suitable.[14,28]

Advantages

1) It can reduce particle size.
2) It produced good colloidal dispersion.

Disadvantages

1) Degradation of thermo sensitive substance due to formation of aggregate.
2) Reduction of stability of formulation.

v) Top-down-approach

The extreme viscous bulk phase containing LLC nanoparticle are formed by mixing stabilizer and lipid then this mixed solution adds into aqueous solution by increasing high energy such as high-pressure homogenization, sonication or shearing. At present, HPH is the most extensively used technique in the preparation of LLC nanoparticles.[13] Cubosomes Based on the results observed, the concentration of F127 and temperature during HPH were regarded as crucially important parameters. By using laboratory build shearing apparatus, novel approach of shearing was proposed to fabricated LLC nanoparticle. The top-down approach produces the more stable and homogenous hexasome and cubosome which contain high concentration of hydrotropic phase and this method superior to ultrasonication approach. It seems that the preparation procedure is simple enough to be realized conveniently. 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 resensitive ingredients.[34,31,37]

Advantages

1) Lower impact to overall organization.
2) Visibility of formulation changes is clear.
3) No need of organic solvent.
4) Simple method as compare to other method such as spray drying.

Disadvantages

1) Solution provides limited coverage in the first phase.
2) High energy input required.
3) Time consuming process.

SIGNIFICANCE

1) Liquid Crystal's enhances the solubility as well as permeability of poorly water-soluble drug.
2) Lamellar liquid crystal (LLC) shows good compatibility.
3) Liquid crystal useful for self-emulsifying drug delivery system (SEDDS).
4) It gives nano particle size.
5) For oral administration, liquid crystal is helpful.
6) It helps sustained release for poorly water-soluble drugs.
7) Provides maximum drug loading and entrapment efficiency.

CHARACTERIZATION OF LC

NMR (Nuclear Magnetic Resonance)

For investigation the NMR spectroscopy have more possibility. The identification of phase equilibrium the deuterium (^2H) NMR spectroscopy is most powerful technique. Different phases of liquid crystal are also investigated by this method. In this method isotropic phase shows narrow singlet resonance signal of quadrapolar nuclei such as ^2H but anisotropic phase shows the quadrapolar splitting means yielding of double resonance signal. The composition of phase may also be determined by NMR spectroscopy.[6,42]

X-ray diffraction

The liquid crystal made up of surfactant and block co-polymer system are generally investigated by x-ray diffraction method. From on order microstructure, characteristic interface obtain by using x-ray scattering experiment. There are mainly two method used to detect the interference such as position-sensitive detectors that is registration of x-ray counts and film detectors. The LC having long range order and when electromagnetic radiation (EMR) interact with structure then diffraction pattern is formed. The both small x-ray diffraction (SAXD) and wide-angle x-ray diffraction are used for characterization of liquid crystal.[42]

Polarizing microscope

The polarizing microscope is vivid and very simple method. This method is generally used

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for study of different phases. In this microscope one polarizer is present above and below to objective in a cross position of objective and it provide plane polarized light at right angle and stop the passing of plane polarised light from above and below of objective due to above and below polarizer. In polarizing microscope, the lamellar phase usually yields the mosaic pattern and whereas hexagonal phase shows the non-geometric texture. In this method the occurrence of crystal may be identify. The smectic mesophase of the thermotropic LC shows different texture but lyotropic hexagonal mesophase shows fan-shaped structure. Due to the sub-micron size of liquid crystal for identification of liquid crystal, polarised optical microscope is an important tool.[6,42]

Differential Scanning Calorimetry (DSC)

The transition of phase occurs due to change in energy which present in respective system. On the basis of transition type the consumption and emission of energy are depends. For example- during melting of solid consumption of energy take place and during recrystallization emission of energy occur. During emission and consumption, the exothermic and endothermic reaction take place and this signal can be observed. The consumption of energy decrease during transition of crystalline phase to amorphous phase. Between this crystalline phase to amorphous phase, the liquid crystalline phase occurs and for liquid crystalline phase consumed very less energy. The sensitivity and detection limit of measuring device are must be proper. Many time entropies change during phase transition due to change of baseline slope with a change in specific heat capacity. Therefore, phase transition of liquid crystalline polymer result from entropic reason are considered as transition of the second order.[43,44]

Transmission Electron Microscope (TEM)

The electron microscope having high magnification power due to that micro-structure of liquid crystal can be seen. The aqueous sample required for electron microscope and that are prepared in special condition which are used in high vacuum of an electron microscope. This sample may be responsible for change in micro-structure. This is proven by freeze-fracture technique. To avoid this problem replica of sample prepared and viewed in electron microscope. To maintain the original micro-structure of sample during replication is very important, for this purpose following steps are most important. The first step is sample leave in shock freeze, for high freezing rate are must be 105-106 k/s, then sample is sandwiched between the gold plate and at -196^0c by using nitrogen cooled liquid propane to store for frozen. The sample which are in liquid form, when we store it for frozen then chances of crystallization of liquid which are present in sample to avoid or reduce this, application of pressure required.[42,43]

Rheology

The different form of liquid crystal shows rheological property in various angle. As micro-structure organization of liquid crystal increase, its consistency increase and flow behaviour also more viscous. The newtonian system, cubic and hexagonal LC shows higher viscosity than lamellar phase. Plastic flow behaviour is observed in hexagonal and cubic crystal but the lamellar phase shows the pseudo plastic flow and this is key factor to differentiate between these two types. The viscosity increases in thermotropic LC in following way: Nematic < Smectic A< Smectic C.[6,45]

Particle Size

The particle size is determined by photon correlation spectroscopy using a Zetasizerat 25°C. Samples is diluted with deionize water prior to the measurement. Particle size is analysed by the dispersion technology software provided by instruments. The polydispersity index (PDI), which is dimensionless number indicating the width of the size distribution.[6,45,46]

Entrapment efficiency

For the entrapment efficiency 10mg of liquid crystals powder is weigh and a quantity of powder equivalent to 100 mg of formulation is dissolved in pH 7.4 buffer and the liquid is centrifuge by using ultracentrifuge at 20000rpm and Supernatant is collected. That collected supernatant is determined by measuring the absorbance at λmax using UV spectrophotometer, after appropriate dilution with pH 7.4 buffer.[45,46]

$$EE = \frac{\text{Mass of drug in formulation} - \text{mass of drug in supernatant}}{\text{mass of drug in formulation}} \text{x } 100$$

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TABLE:1 TECHNIQUE USED FOR CHARACTERIZATION OF LIQUID CRYSTAL.

TYPES OF LC	PROPERTIES BEING STUDIED	CHARACTERIZATION TECHNIQUE
Azobenzene-containing liquid crystalline block copolymer films	Realignment process of LC films	GI-SAXS, AFM, Polarized UV-Vis
Water-dispersed LC microdroplets	Optical transitions	POM, Forward light scattering (FSC), SAXS
4-Cyano-42 -pentyl biphenyl	Viscosities and refractive indexes	FWM
Benzeneammonium columnar LCs	Phase transition	XRD, GISAXS
Discotic columnar liquid crystals in nanopores of inorganic template	Orientation behaviour in nanoconfiments	SAXS, AFM, GISAXS
Polyphilic LCs	Composite mesostructured	SAXS, AFM, XRD
T-shaped polyphilic molecules	Thermotropic LC phases	POM, DSC, XRD, GISAXS
Liquid crystalline block co-poly- mer matrix	Faceted grain growth of hexagonal cylinder domains	AFM, GISAXS, DSC
Liquid crystal tri-block co-poly- mer	Structural properties, mechanical strength and photo responsive behaviour	SAXS, TEM, DSC, POM, photo contraction tests
Pyridine based mesogens	mesophase characterization	Solid state NMR, FTIR, POM
Thiophene LCs	Structural aspect and phase transition behaviour	FT-IR, 2D NMR, POM, DSC
Phenyl ring core-based thiophene mesogens	Mesophase transitions molecular shape mesophase characteristics	DSC, 13C NMR
Rod-like mesogens with three and four-ring core	Structural characterizations	XRD and 13C NMR
Biaxial nematic liquid crystal phases	Twist viscosity and the alignment angle	Molecular Dynamics simulation
ABA triblock copolymer	Phase transition, density, molecular weight dependence, structural parameters, microphase behaviour	SAXS, TEM
Wedge-shaped onium salts	Mesomorphic properties	SAXS, DSC
Naturally occurring amphotropic liquid crystals	Physical properties	POM, DSC, Mid- and n e a r - i n f r a r e d photoacoustic spectroscopy
LCP	Photo responsive behaviour, thermal behaviour	POM with in situ UV irradiation, DSC, UV-/Vis
Poly (2,5-bis {[6-(4-methoxy-40-oxyazobenzene) hexyl]- oxycarbonyl} styrene) based LC polymer	Phase structures and transitions	DSC, POM
2,4,6-tris(thiophene-2-yl)-1,3,5- triazines based molecules	Crystal and molecular structure liquid-crystalline properties	X-ray, Molecular Dynamics simulation, Cyclic voltammetry,

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		UV/ Vis, POM
ABA triblock B5 Cin co-poly mer	Morphology and photo-crosslinking, thermal properties	1H NMR, FT IR, DSC, SAXS, TEM
Polylactide-based liquid crystalline brush-like block co-polymers	Morphology and phase behaviour	DSC, TEM, SAXS
Polymer-dispersed liquid crystal/graphene oxide nanocomposites	Photomechanical response of the nanocomposite film	POM
Cross-linked liquid crystal polymer films	Thermodynamic properties, meso-morphic properties	DSC, POM
LC-based sensor	Birefringent properties	POM
poly(methacrylate) with liquid crystal side chains	Aggregation states	DSC, POM
PEO-b-PMA(Az) block co-poly mer	Phase behaviour	SAXS, TEM
Diblock copolymers	Structural features and hierarchical segment self-assembly	DSC, XRD, POM
Liquid-crystalline brush co-polymer	Phase behaviour	SAXS, DSC, TEM
Triphenylene-based side chain liquid crystalline block co-poly- mer	Microphase structures	DSC, POM, Variable SAXS
LC side chain diblock co-poly mer	Structural analysis	SAXS, TEM
T-shaped bola amphiphiles	Influence of spacer length and position of the spacer on the self-assembly in liquid crystalline phases	POM, DSC, XRD
Bola amphiphiles with swallow tail lateral chains	Self-assembly in thermotropic liquid crystalline phases	DSC, POM, XRD
D- (+)-Glucose	Liquid crystal formation	DSC, TGA, POM
p-alkoxybenzoic acids	Phase behaviour	Melting point techniques, DSC, POM
Mesomorphic azo compounds	Phase transitions transition temperatures	POM, DSC
Discotic azo compounds	Thermal and liquid crystalline properties photoisomerization capacity	POM, DSC, XRD, 1H NMR
Discotic liquid crystalline block copolymers	Morphology, molecular structure, thermal analysis	POM, TEM, XRD, DSC
Bent rod shaped molecules	Structural properties in solution, solid and fibre state	DSC, XRD, TEM
Biphenyl acetylene LC	Phase behaviour, morphologies	POM, DSC, XRD
Organo siloxane mesogens	Phase behaviour, morphologies	POM, DSC, SAXS

APPLICATION

Therapeutic compounds of diverse physicochemical properties such as analgesic, antibiotics, antifungal, anticancer, vitamins, anti-asthmatics, immunosuppressive etc. monoglyceride based cubosome can be used for topical, such as for mucosal applications. HIV, HSV (sexually transmitted disease) caused by virus and bacteria for this treatment monoglyceride are use due to their antimicrobial activity. The cubosome technology is used to develop a synthetic vernix the cheesy white substance that coats infants in late gestation to help premature infants who are born without it. E vernix is a complex mixture of lipid (fat), proteins and water. Cubosome can also be used for controlled release application. In cosmetic

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cubosome used as pollutant absorbent and also its stabilised oil-water emulsion. More recent use is about personal cure product areas as varied as skin care, hair care, cosmetics and antiperspirant.[48,49]

Oral administration

Many drugs show the less oral bioavailability due to poor water solubility that types of drug can be incorporate into LLC.Through animal experiments, the OG-based hexagonal formulation showed a considerably higher relative bioavailability that was almost 3.5 times greater than that of the control suspension of cinnarizine and 3 times greater than the GMO-based cubic formulation. The oral administration of drugs incorporated into LLC nanoparticles has also been reported, prepared GMO-based cubosomes containing insulin and investigated the hypoglycaemic effect generated by oral administration of this formulation. The blood glucose concentration–time profile showed that the insulin formulation could provide a hypoglycaemic effect comparable to intravenous administration of insulin over six hours.[50,51]

Topical administration

Topical drug delivery is an attractive alternative to oral administration. Its main drawback is the limited absorption of drugs through the skin barrier, and investigations on topical drug uptake are necessary to facilitate the design of efficient topical drug delivery systems. At present, stratum corneum (SC) is considered to be the rate-limiting barrier in transdermal drug delivery. In transdermal drug delivery stratum cornium is rate limiting step. For topical drug delivery cubic and hexagonal mesophase formulation are having capability to penetrate through stratum cornium. Cyclosporine A incorporated in hexosomes comprising GMO, oleic acid and water was reported to be capable of enhancing drug permeation when applied topically. There are several natural characteristics that reversed the liquid crystal such as hexagonal and cubic phase to make them suitable for topical drug delivery.[49]

Parenteral administration

Injectable in situ thickening formulation are interesting also for parenteral administration, e.g., in the form of intramuscular or subcutaneous depot formulation with the aim of achieving controlled drug release over a prolonged time. Also, in this context, formulation based on liquid crystalline phases offer some possibilities e.g., antitumor treatment using IL-2 has shown positive results for several cancers in both experimental animal models and in humans.

Mucosal drug delivery

Not only the bulk mesophases but also their dispersions could be utilized for mucosal drug delivery.[15]Reported that after application of progesterone loaded hexosomes on the albino rabbit mucosa for 12 h, an obviously enhanced transmucosal flux was observed and that it was fivefold higher than that of progesterone loaded gel and nearly fourfold higher than plain progesterone suspension.

Rectal administration

Another application area for system displaying in situ thickening, such as liquid crystalline phases formed by PEO/PPO block copolymers, is rectal administration. As an example of this, shows results on the rectal administration of indomethacin, the usefulness of which is severely reduced by GIT side effects. Although the bioavailability of the Pluronic F127-based formulation, as determined from the integration of the plasma concentration over time, is comparable to that of suppositories, the Pluronic F127-based formulation offers several advantages.[47,52]

TABLE: 2 FORMULATION OF LIQUID CRYSTAL

DRUG	FORMULATION	LIQUID CRYSTAL TYPE	ROUTES OF ADMINISTRATION	REFERENCE
Vitamin E	Nanostructured lipid-based liquid crystals	Bicontinuous cubic phase	Oral	16

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Cyclosporine A	Topical gel	Hexosomes	Topical	17
Progesterone	Gel	Hexosomes	mucosal delivery	15
Indomethacin	Gel	Cubosomes	Rectal delivery	18
Rapamycin	Nanoparticle	Hexosomes	Parenteral delivery	19

II. RESULT AND DISCUSSION

The liquid crystal is best another formulation for drug delivery. These liquid crystals are having less toxicity and it has wide applicability in several disease treatment. LC increase the bioavailability of several which are show less bioavailability if use for improve the bioavailability of drug. For formulation it required very less excipient so that less incompatibility occur and cost of formulation also reduce. The particle size of liquid crystal is also very small as niosome and liposome, so due to that bioavailability increase of liquid crystal. Many pulmonary formulations of liquid crystal are available in market, such as for treatment of TB. These several methods are available for preparation of liquid crystal such as probe sonication, top-down approach, heat treatment, bottom-up approach and spray drying.

III. CONCLUSION

The liquid crystal is the advance dosage form for drug delivery. The excipient required for formulation of liquid crystal are very less as compared to other formulation. Due to that less excipient the compatibility of drug with excipient is more and reduce the chances of drug interaction. There is various type of liquid crystal present such as cubic, hexagonal and many more and in which various type of drug incorporate. The drug having less oral bioavailability that can be incorporated in liquid crystal formulation. The liquid crystal is novel phase such as liquid and solid phase, this shows the both property of liquid phase and solid phase. Liquid phase is intermediate phase of solid and liquid phase.

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CONFLICT OF INTEREST

No conflict of interest.

ABBREVIATION

3D: 3 Dimension; **LC**: Liquid Crystal; **LLC**: Lyotropic Liquid Crystal; **TLC**: Thermotropic Liquid Crystal; **OG**: Oleyl Glycerate; **CPP**: Critical Packing Parameter; **DIP**: Dry Powder Inhaler; **SEDDS**: Self Emulsifying Drug Delivery System; **NMR**: Nuclear Magnetic Resonance; **EMR**: Electro Magnetic Resonance; **SAXD**: Small X-ray Diffraction; **DSC**: Differential Scanning Calorimetry; **TEM**: Transmission Electron Microscope; **PDI**: Poly Disperse Index; **GI-SAXS**: Grazing Incidence-Small-Angle-X-ray Scattering; **AFM**: Atomic Force Microscopy; **PMO**: Poly Methylene Oxide; **FSC**: Forward Light Scattering; **SAXS**: Small X-ray Scattering; **XRD**: X-Ray Diffraction; **FTIR**: Fourier-Transform Infrared Spectroscopy;**PG**: Phytanyl Glycerate; **GMO**: Glyceryl Mono Oleate.

SUMMARY

Primary objective of liquid crystals drug delivery system is to ensure safety and to improve efficacy of drug as well as patient compliance, which can be achieved by better control of less frequent dosing. Liquid crystalline drug delivery is very important to use minimum number of excipients with minimum processing steps in order to reduce the particle size and drug entrapment variation.

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