ISSN (Online): 2455-3662
EPRA International Journal of Multidisciplinary Research (IJMR) - Peer Reviewed Journal
Volume: 7 | Issue: 5 | May 2021|| Journal DOI: 10.36713/epra2013 || SJIF Impact Factor 2021: 8.047 || ISI Value: 1.188

PHARMACEUTICAL APPLICATIONS OF LIQUID CRYSTAL WITH SPECIAL EMPHASIZED ON ADVANCED DRUG DELIVERY SYSTEM: AN OVERVIEW

[1]Faizan Ahmed Md Israeel , [2]Shivam Patil , [3]Shaikh Ashmeena, [4]Khan Naziya, [5]Charushila Suryawanshi , [6]Rahmani Taskeen
Department of Pharmaceutics, Royal College of Pharmaceutical education and research Malegaon,Savitribai Phule Pune University, Maharashtra , India .

ABSTRACT
Liquid crystals are substances that flow like liquid but maintain some of the ordered structure characteristic of crystalline solid. Liquid crystal can be divided into thermotropic and lyotropic phase. The thermotropic is generated by temperature variation in the liquid state, whereas lyotropic is formed by dissolving the compound in certain solvents. The liquid crystal systems have some advantages such as drug solubilization level, drug degradation, biological and chemical sensing, stability of drug, control drug release, light, thin, sustained and controlled release pharmaceutical properties. Liquid crystal technology has had a major effect in many areas of science pharmacy and engineering, as well as device technology. The drug delivery to site of target can be achieved by using liquid crystal systems. Objective of this review is to provide information in development of targeted drug delivery system, depth information of pharmaceutical liquid crystal technology, its classification and application in the pharmaceutical field.
KEYWORDS: ***Liquid crystalline system, history, display, classification, patent with liquid crystal application***

1. INTRODUCTION

Liquid crystals are the materials that are in many ways intermediate between the liquid and solid states. Liquid crystals exhibit different molecular arrangements than the liquid and solid states [1]. Based on the ways that LCs is 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 [2]. The liquid crystal systems have approach towards physical and chemical properties. Now a day's liquid crystal are becoming a choice for the research and development process in the pharmaceutical field. The liquid crystal systems have some advantages such as drug solubilization level, drug degradation, and control drug release; light, thin, sustained and controlled release pharmaceutical properties [3]. LC'S are influenced by number of factors such as concentration, temperature, pH, and presence of salt. As new properties and types of liquid crystals are investigated and researched, these materials are sure to gain increasing importance in industrial and scientific applications such as optical imaging [4, 5].

Liquid crystals are thermodynamically stable and possess long shelf life. Liquid crystals show bio adhesive properties and sustained release effects [6, 7]. Liquid crystal name was given by Lehmann (1899) to characterize the state of matter. It is also known as mesophase which explains a state of matter that is intermediate between the crystalline solid and the amorphous liquid. They have properties in between liquid and solids, which makes a new form of state [3, 8]. Liquid crystals (LCs) are matter in a state which has properties between those of conventional liquids and those of solid crystals. For example, a liquid crystal may flow like a liquid, but its molecules may be oriented in a crystal-like way [9, 10]. Some liquid crystal may even flow like liquid, but it Atoms or molecules are oriented in a crystal-like way, the liquid crystal state of matter is obtained from orientation-dependent noncovalent interaction between molecules within condensed phases. Because, the balance of intermolecular forces which govern formation of liquid crystals is delicate, this state of matter can, in general, be easily affected by external stimuli [1, 11].

Liquid crystals are anisotropic; which means they have different chemical and physical properties

ISSN (Online): 2455-3662
EPRA International Journal of Multidisciplinary Research (IJMR) - Peer Reviewed Journal
Volume: 7 | Issue: 5 | May 2021|| Journal DOI: 10.36713/epra2013 || SJIF Impact Factor 2021: 8.047 || ISI Value: 1.188

in different axes. It is important to note that [12, 13] not all anisotropic materials are liquid crystals but all liquid crystals are anisotropic compounds. Due to anisotropy of liquid crystals, they also exhibit birefringent i.e. having two refractive indices. Having an anisotropic molecular shape associated with polarizability is the basic requirement for liquid crystals [1, 14]. 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 [2] LCs (mesophases) show structural, mechanical and optical properties intermediate to those of crystalline solids, amorphous and liquid state of matter. LCs, however, are not a mixture of solids and liquids, but indeed a separate state of matter [3, 15]. They have many properties of liquid e.g. formation of droplets, fluidity is high, inability to shear.

It has various properties.

(a) Comparative energy of intermolecular forces in the liquid crystal.
(b) Less intermolecular interaction in liquid crystal. It has properties of cubic and hexagonal phases which make them important to deliver for the scientists through various routes such as buccal, gastrointestinal, rectal, vaginal, lung. The liquid crystal has strong adhesion molecule in liquid crystal and it was weak [8] Now days liquid crystals have played vital role in the transdermal approach to drug delivery, they are useful to enhance both permeability and retention of the drug in skin as stratum corneum is strong barrier and drug with adequate property can cross it. Whether we talk about novel lecithin based liquid crystals or cremophor based cubical cubosomes all have changed and help to make local drug delivery better [16].

A typical LC molecule is represented by two parts:

i) The central rigid part known to be as mesogen and ii) The other flexible side chains known to be as spacer. The liquid crystal molecules for stability make each other align parallel to them because of the strong intermolecular attraction. The energy required for interaction between the liquid crystal and bearing surface can be: (a) comparable with the energy of intermolecular interaction in the liquid crystal; (b) much less than the intermolecular interaction energy in the crystal [1,17]. In this review, we will look about them, their earlier history, their types, will study different phases involved in liquid crystals and application of liquid crystals in pharmaceutical industry.

2. HISTORY

The discovery of an intermediately, liquid crystal, state of matter is credited to Friedrich Reinitzer [7]. In 1888, Austrian botanical physiologist Friedrich Reinitzer, working at the Karl-Ferdinands-Universität, examined the physicochemical properties of various derivatives of cholesterol which now belong to the class of materials known as cholesteric liquid crystals.

Previously, other researchers had observed distinct color effects when cooling cholesterol derivatives just above the freezing point, but had not associated it with a new phenomenon. Reinitzer perceived that color changes in a derivative cholesteryl benzoate were not the most peculiar feature. He found that cholesteryl benzoate does not melt in the same manner as other compounds, but has two melting points. At 145.5 °C (293.9 °F) it melts into a cloudy liquid, and at 178.5 °C (353.3 °F) it melts again and the cloudy liquid becomes clear. The phenomenon is reversible. Seeking help from a physicist, on March 14, 1888, he wrote to Otto Lehmann, at that time a Privatdozent in Aachen. They exchanged letters and samples. Lehmann examined the intermediate cloudy fluid, and reported seeing crystallites. Reinitzer's Viennese colleague von Zepharovich also indicated that the intermediate "fluid" was crystalline. The exchange of letters with Lehmann ended on April 24, with many questions unanswered [5,18]. After this accidental discovery, Reinitzer did not continue studying liquid crystals further. The research was later carried forward by Lehmann, who realized that he had been encountering entirely new phenomenon and was in a position to investigate on it. In his postdoctoral years he had become expert in crystallography and microscopical studies. Lehmann started a systematic study, first of chemical cholesteryl benzoate, and then of its related compounds which exhibits same the double-melting phenomenon. He was then able to make observations in prepolarized light, and his microscope was provided with a hot stage (sample holder equipped with a heater) which enabled high temperature observations. The intermediate cloudy phase may clearly sustained flow, but other features, particularly the signature under a microscope, convinced Lehmann that he was dealing with a solid one. After Lehmann's, his work was continued and scientifically expanded by the German chemist Daniel vorlander, by whom from the beginning of 20th century until his retirement in 1935, had prepared many of the liquid crystals known. However, liquid crystals were not popular among scientists at that time and the material remained as a pure scientific curiosity for more than 80 years [1,19].

1888: Reinitzer observed the two phenomenons, birefringence and the occurrence of iridescent colors between the two melting points in a material that we now were cholesteryl benzole.

ISSN (Online): 2455-3662
EPRA International Journal of Multidisciplinary Research (IJMR) - Peer Reviewed Journal
Volume: 7 | Issue: 5 | May 2021|| Journal DOI: 10.36713/epra2013 || SJIF Impact Factor 2021: 8.047 || ISI Value: 1.188

1889: Lehmann carried out detail tail investigation and reasoned that the birefringent portions of the liquid must be crystals. He previously referred to these materials as liquid crystals.
1890: Gattermann blended the principal fluid precious crystals of azoxy-benzene, with fully known structures. **1908:** D. Vorlaender, the first to integrate a thermotropic smectic compound, related liquid crystallinity to chemical structures, detected polymorphism of liquid crystal state. **1922:** Freidel identified and named the different microscopic textures (nematic, smectic, and cholesteric), observed the impacts of electric and magnetic fields.
1930: Freedericksz studied the transition from a homogeneous structure at some critical value of applied field strength.
1965: the global liquid crystal society by late Glenn Brown at Kent state university. Lehmann and Reinitzer are known as the grandfathers of LCs science [9, 20, 21].

3. DEFINATION AND DISPLAY

A liquid crystal is a thermodynamic stable phase characterized by anisotropy of properties without the existence of a three-dimensional crystal lattice, generally laying in the temperature range between the solid and isotropic liquid phase, hence the term mesophase. Liquid crystals are a class of molecules that, under some conditions, inhabit a phase in which they exhibit isotropic, fluid-like behavior – that is, with little longrange ordering – but which under other conditions inhabit one or more phases with significant anisotropic structure and longrange ordering while still having an ability to flow [4,5,22]. A liquid crystal display (LCD) is a flat –panel display or other electronically regulated optical device that uses the light tweaking properties of liquid crystals. Liquid crystals do not emit light display, instead using a backlight or reflector to produce image in color or monochrome [9, 23, 24].

LCs consists of an array of tiny segments (called pixels) that can be manipulated to present information LCD consist primary of two glass plates with some liquid crystals material between them [9,25].

Plates are usually manufactured with transparent electrodes (ITO) that make it possible to apply an electric field across small areas of the film of liquid crystal LCDs consume much less power cathodes -ray tube (CRT) counterparts Most usually utilized are the twisted nematic (TN) Displays[9,26].

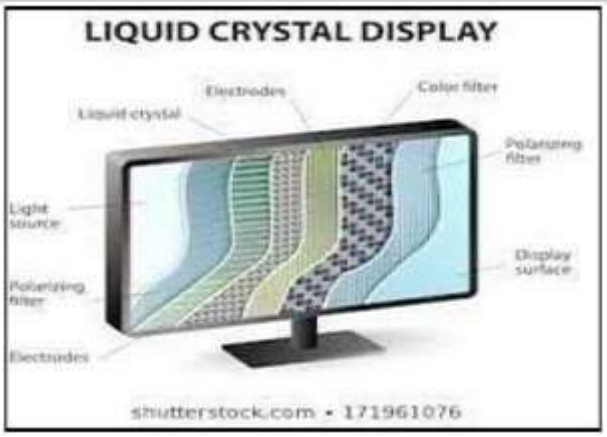

Fig. 1: Liquid crystal display [1]

IDEAL CHARACTERISTICS OF LIQUID CRYSTAL

1. There are two types of liquid crystal such as lyotropic and thermotropic liquid crystal.
2. The liquid crystal can flow similar to liquid due to transition phase.
3. Discotics phases are flat having disc-like molecules which has core adjacent to aromatic rings.
4. A large number of chemical compounds are known which can exhibit one or several liquid crystal phases.
5. Liquid crystal phases are mostly cloudy in appearance that they scatter light in same way as colloids. [3]

4. CLASSIFICATION

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). Moreover order can be either short-range (only between the molecule to each other) or long-range (extending to larger, sometimes macroscopic). LCs mainly classified as Lyotropic (LLCs) and Thermotropic (TLCs), physicochemical parameters responsible for the phase transitions [27, 28, 29].

4.1 Lyotropic Liquid Crystal

It is also called as lyomesophases or lyotropics which is mixture of amphiphilic molecules in solvent at given temperature and concentration. It can be classified as lamellar, cubic and hexagonal. In this solvent molecules will fill space around the compound to have fluidity in system. A compound which has two immiscible hydrophilic and hydrophobic within molecule is called amphiphilic molecule. Those molecules show lyotropic liquid crystalline property which depend on hydrophilic and hydrophobic part. These structures formed through micro-phase segregation of two incompatible components [3].

ISSN (Online): 2455-3662
EPRA International Journal of Multidisciplinary Research (IJMR) - Peer Reviewed Journal
Volume: 7 | Issue: 5 | May 2021|| Journal DOI: 10.36713/epra2013 || SJIF Impact Factor 2021: 8.047 || ISI Value: 1.188

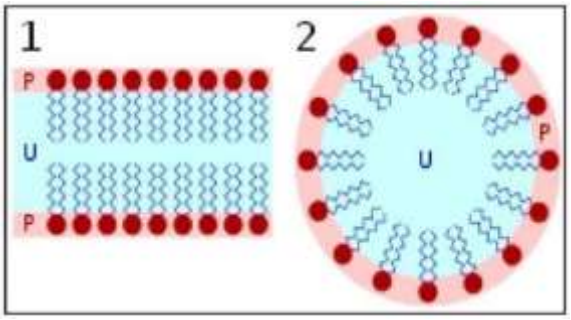

Fig. 2: (1) & (2): Structure of lyotropic liquid crystal [5]

4.1.1Lamellar LCs Lamellar: LCs neat phase is generally having bilayered structure as repetition unit, and which shows long-range positional order in one dimension and long-range orientational order within the layer. They can also be termed as layered packing of indefinitely extended disc like micelles [12, 30, 31].

4.1.2Hexagonal LCs Hexagonal: LCs shows long-range positional order in two dimensions. Both the lamellar and hexagonal LCs can be identified using polarized light microscopy as they exhibit a range of textures that are typical for the corresponding LCs. They are also known as middle phase [12, 32, 33].

4.1.3Cubic LCs:

Cubic LCs shows long-range positional order in three dimensions. Generally these LCs having cubic packing of the micelles and cannot identified using polarized light microscopy. They are highly viscous and have poured flowing property as compare to lamellar and hexagonal LCs [12, 34, 35, 36].

4.2Thermo tropic liquid crystals:

A liquid crystal (LC) is thermotropic in nature if the order of its components is dependent or changed by temperature. Like if temperature is too high, results in rise of energy and therefore motion of the components will show a phase transition. The LCs will become an isotropic liquid. In case, on the contrary, if temperature is too low for supporting a thermotropic phase, the LC will change to glass phase. There is therefore a range of temperatures at which we observe thermotropic LCs; and most of these have several "sub phases" (nematic, smectic. Etc.), which we may observe by modifying the temperature [1,37].

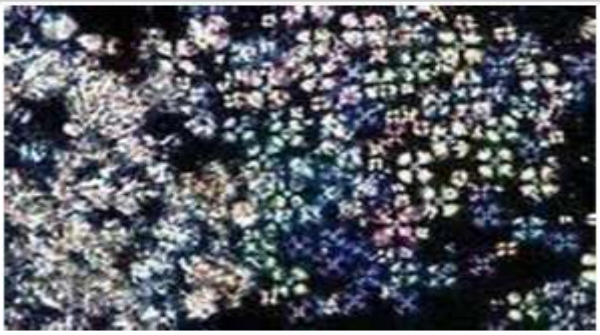

Fig. 3: Phase transition between a nematic (left) and smectic A (right) phases observed between crossed polarizer and the black colour corresponds to isotropic medium [5].

Nematic Phase

One of the most common LC phases is the nematic. The word nematic comes from the Greekνήμα (nema), which means "thread". This term originates from the thread-like topological defects observed in nematics, which are formally called 'disclinations'. Nematics also exhibit so called "hedgehog" topological defects. In a nematic phase, the calamitic or rod-shaped organic molecules have no positional order, but they self-align to have long range directional order with their long axes roughly parallel
[5,38].

Fig. 4: Alignment in a nematic phase [5]

Smectic Phase

These are found at even lower temperatures than nematic phase. The word smetics means cleaning or rather having soap like properties [39, 40]. The long axes of all the molecules in a particular layer are parallel to one another and perpendicular to the plane of layer. True to its name, the layer slides over one another similar to that of soap's. This phase is viscous, fluid and ordered [40,41].

ISSN (Online): 2455-3662
EPRA International Journal of Multidisciplinary Research (IJMR) - Peer Reviewed Journal
Volume: 7 | Issue: 5 | May 2021|| Journal DOI: 10.36713/epra2013 || SJIF Impact Factor 2021: 8.047 || ISI Value: 1.188

Fig. 5: Schematic of alignment in the smectic phases [5] Chiral phases:

The chiral nematic phase expresses chirality (handedness). This phase is popularly known to be as cholesteric phase because it was first found for the cholesterol derivatives. While only chiral molecules (i.e. others which have no internal planes of symmetry) may give rise to such a phase. This phase exhibits a twisting of the molecules perpendicular to its director, with the molecular axis parallel its director [1,42].

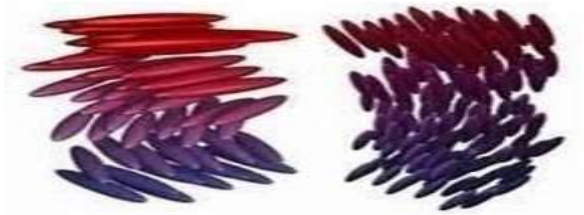

Fig. 6: Schematic of ordering in chiral liquid crystal phases [5]

Blue phases: Blue phases are liquid crystal phases that appear in the temperature range between a chiral nematic phase and an isotropic liquid phase. Blue phases have a regular three-dimensional cubic structure of defects with lattice periods of several hundred nanometers, and thus they exhibit selective Bragg reflections in the wavelength range of visible light corresponding to the cubic lattice. It was theoretically predicted in 1981 that these phases can possess icosahedral symmetry similar to quasi-crystals [5,43,44].

Discotic phase: Discotic phase is having disc-shaped compound of liquid crystal which get involve in fashion which is layer-like. The discotic phase is the disks which is pack into stacks. Discotic columnar is called as chiral a discotic phase which is similar to chiral nematic phase. Rectangular or hexagonal arrays both of them get involved in the column [3].

Bowlic phases: They are Bowl-shaped LCs molecules, like we found in discotics, and can form columnar phases. Other phases, includes polar nematic, nonpolar nematic, string bean, onion and donut phases, have also been found. Bowlic phases, except nonpolar nematic one, are polar phases of LCs [1, 42].

5. APPLICATION OF LIQUID CRYSTALS

5.1 Solubility enhancement of poorly soluble drugs: Many substances are more soluble in lyotropic liquid crystals. One example is hydrocortisone. It is often taken in topical applications, but its uses have been limited because highest concentration possible has been only 1%.When hydrocortisone went up to 4%.In time, liquid crystals may become a primary solvent for topical medications[5,45].

5.2 Biological and Chemical sensing: LCs have been successfully demonstrated to sense and analyze bacteria various and viruses. Additionally, some nontoxic LCs have been figured out and utilized for supporting the growth of mammalian cells and for reporting the interfacial cellprotein interaction [1, 46]. Polyelectrolyte-coated LCs droplets are useful to detect charged macromolecules in a solution. Adsorption of these positively charged dendrimers on negative charged polyelectrolyte-coated droplets results bipolar-to-radial ordering transitions, which were mainly dependent on both the size and number of droplets present in solution [1, 46].

5.3 Drug delivery utilizing liquid crystal structure: Vitamin E TPGS/drug compositions and methods are provided which aviate the need for surfactants or nonevaporated co solvents because the active drug component is dissolved directly onto vitamin E TPGs to form a true molecular solution -not an emulsion or a micro emulsion. The innovation gives a gradually dissolving TPGS/sedate framework that ingests gastrointestinal liquid into the grid at the measurement shape/liquid interface, where a gel like liquid crystal is formed [9, 47]. This gel front structures a liquid crystal limit where tranquilize disintegration is most. At this liquid crystal/GI fluid boundary, synchronization takes place in which the rare of formation of liquid crystal equal the dissolution rate of liquid crystals at the water interface, thereby giving controlled order release of the drug into the GI tract [9,48].

5.4 Stability of drug: Lyotropic liquid crystals have been used to make stable hydrocarbon foam. Hydrocarbon foams have been difficult to produce in the past because surface tension of hydrocarbon is low enough that adsorption to an oil soluble surfactant would have no significant effect. Without adsorption, hydrocarbon simply behaves as liquid. The hydrocarbon and surfactant can dissolve in each other, and surfactant cannot dissolve in water, although water can dissolve in the surfactant and mix into the liquid crystal [5, 49].

5.5 Ophthalmic delivery is also a topic of interest for which LLC NPs are also being considered

ISSN (Online): 2455-3662
EPRA International Journal of Multidisciplinary Research (IJMR) - Peer Reviewed Journal
Volume: 7 | Issue: 5 | May 2021|| Journal DOI: 10.36713/epra2013 || SJIF Impact Factor 2021: 8.047 || ISI Value: 1.188

as effective drug vehicles [50, 51]. Recent studies reported by Gan *et al.* show that aspects such as improved preocular retention, reduction of ocular irritancy and enhanced bioavailability can be attained using cubosomes as nanocarriers for ocular drugs. The trans-corneal permeation of dexamethasone (DEX) [50, 52] and flurbiprofen [49, 52] is enhanced when these drugs are formulated in cubosomes. Indeed, the drugloaded cubosomes are retained in the pre-ocular region much longer than that of the corresponding solutions administered through eye drops, and this enhances their ocular bioavailability. Moreover, the DEX-cubosomes formulation is confirmed not to affect the corneal structure and tissue integrity. For flurbiprofen, cubosomes formulation reduces its inherent irritancy.

5.6 Dermal Application: Drug molecules and pharmaceutical excipients with amphiphilic character can easily form lyotropic mesophases that is particularly for surfactants and are commonly used as emulsifiers in dermal formulations and associate to form micelles after solubilizing in a solvent. Increasing with concentration the probability of interaction between the micelles also increases, hence liquid crystals are formed. Liquid crystal formulations have been used in cosmetics and pharmaceutical controlled release dosage forms. These formulations get enhanced penetration of biologically active materials like vitamin A) through the skin. The delivery systems consist of cholesteric liquid crystals in which the active material is retained inside the lamellar molecular structure (between the molecular sheets) of the cholesteric liquid crystalline phase [1, 53].

5.7 Cancer Therapeutics: Is the most widely reported application of cubosome (liquid crystals) systems. In vitro cubosomes have been loaded with cancer drugs including Doxorubicin,[43,56] Sorafenib [40,54] 5Fluorouracil, [40,55] and Quercetin [40,56] and delivered to cell lines, including human hepatocellular carcinoma (HepG2) cells, glioblastoma T98G cells, and mouse 3T3 fibroblasts [40,57]. Tumor cells have more acidic environments making pH stimuli useful for the payload delivery of chemotherapeutics.

Significantly more in vivo work is needed to establish cubosomes as viable options in cancer therapeutics although early indications are promising.

5.8 Liquid crystals in emulsions: LCs (mesophases) provides the following Advantages to emulsion:

1. Increased stability
2. Prolonged hydration
3. 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 **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 moisturisation / hydrating effect, necessary for drug entry.

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 [57, 58].

5.9 Photo polymerization of lyotropic liquid crystalline systems: A new route to nano structured materials: A novel route to fabricating such materials is through the use of lyotropic liquid crystals (LLCs) that possess highly ordered nano structures. However, LLC phases lack necessary physical robustness. So, templating LLC phase morphology onto other materials such as organic polymers would give a nanostructure retained as part of a robust polymeric matrix. This study focuses on photo polymerization behavior and structure retention of hydroxyethyl acrylate (HEA)/dodecyltrimethyl ammonium bromide (DTAB)/water system in a select liquid crystal phase. [5,59].

5.10 Topical Treatment

In transdermal delivery of active molecules, the skin penetration of the drug is limited as a result of the barrier function of the highly organized structure of the stratum corneum, the most external layer of the skin. Several approaches have been presented to improve the skin permeation such as chemical modification of the active molecule, applying a skin permeation enhancer and iontophoresis. The crucial issue in topical formulations is to increase the thermodynamic activity of the active molecule in the vehicle while decreasing it in skin, which results in increasing the partition of the molecule from vehicle to skin and decreasing the barrier function of the skin [40,60]. Cubosomes(liquid crystals) have been investigated as topical delivery agents in part because of their ability to influence permeability. Silver sulfadiazine is one of the gold standard topical treatments for burns but a delivery agent is needed. Cubosomes formed from monoolein and stabilized with F127 and polyvinyl alcohol were loaded with silver sulfadiazine and incorporated into hydrogels (cubogels) as a potential treatment for burns. In vivo study showed that the cubic nano-structured vehicle was successful in treatment of deep second degree burns, which could result in better patient compliance

ISSN (Online): 2455-3662
EPRA International Journal of Multidisciplinary Research (IJMR) - Peer Reviewed Journal
Volume: 7 | Issue: 5 | May 2021|| Journal DOI: 10.36713/epra2013 || SJIF Impact Factor 2021: 8.047 || ISI Value: 1.188

and excellent healing results with fewer side effects in comparison with the commercially available product [40,61].

5.11 Colloidal Dispersions: The bulk liquid crystalline structure can be found to disperse in water in the presence of additional stabilizer or emulsifier which forms submicrometer soft particles (100-500 nm size) that retains the internal structure of the liquid crystal molecular phase. In the case of lamellar, cubical and hexagonal phases, these soft particles have been termed liposomes, hexosomes, and cubosomes , respectively. They have very good advantages in comparison to the bulk phase as these have very high interfacial area (as compare to their volume) and low viscosities, thus increasing its scope of application [1,62].

5.12 Temperature Modulated drug permeation through liquid crystal embedded cellulose membranes. Stimulisensitive membranes may act as "on-off switches" or "permeability valves", producing patterns of pulsatile release, where the period and rate of mass transfer can be controlled by external or environmental triggers. Cellulose nitrate (CN) and cellulose acetate (CA) monolayer membranes containing thermotropic liquid crystals (LC) were developed as thermo-responsive barriers for drug permeation. A low molecular thermotropic liquid crystal, nheptyl-cyano bi phenyl, with nematic to isotropic phase transition temperature of 41.50C was chosen to modulate drug permeation.

It was found that upon changing temperature, both cellulose membrane without liquid crystal showed no temperature sensitivity to drug permeation, whereas the results for liquid crystal entrapped membranes exhibited a distinct jump in permeability when temperature was raised to above transition temperature of liquid crystal for drug [39,63].

5.13 Vaccines

Apart from cancer therapeutics, another key application of cubosomes is as agents in vaccines. Cubosomes can be loaded with antigens and/or adjuvant and subsequently delivered appropriately by incorporating the immunostimulants such as polysaccharides into the cubosome membrane. In a study, phytantriol cubosomes containing polysaccharides were co delivered with inactivated viruses in a subcutaneous injection. It was found that cubosomes containing polysaccharides were able to potentiate the immune properties of immunostimulants by promoting antigen transport into lymph nodes and enhancing the immune response [40,64].

5.14 Effect of base and salts from different liquid crystalline structures on drug release profile: This study was done for investigate the influence of two types of chlorhexidine species, chlorhexidine base and its salts, on physicochemical features of liquid crystalline systems and on drug transport through liophilic membranes. For this non-ionic surfactant, Synperonic A7(PEG7-C1315)was selected for the liquid crystal formulation. Chlorhexidine species was modified liquid crystalline system. As a result of changes of liquid crystalline structures, drug release of various types of chlorhexidine could be also modified [39,65].

Table 1a : Patents on Liquid Crystal Applications

Sr. No	Title of Patent	Patent No /Date	Abstract
1.	Liquid crystals containing cosmetic and pharmaceutical Compositions and methods for utilizing such compositions	US 4,999,348 / Mar.12, 1991	Cosmetic and pharmaceutical compositions and methods comprising delivery systems for the controlled release and enhanced penetration of biologically active material (e.g. Vitamin A) to the skin. The delivery systems comprise cholesteric liquid crystals wherein the active material is retained within the lamellar molecular structure (i.e. between the molecular sheets) of the cholesteric liquid crystals[57,66]

ISSN (Online): 2455-3662
EPRA International Journal of Multidisciplinary Research (IJMR) - Peer Reviewed Journal
Volume: 7 | Issue: 5 | May 2021|| Journal DOI: 10.36713/epra2013 || SJIF Impact Factor 2021: 8.047 || ISI Value: 1.188

2.	Liquid crystals emulsion type pharmaceutical composition containing cyclosporine and therapeutic method of treating cutaneous disease therewith	US 2010/190695 A1/July 29,2010	A dermal external pharmaceutical composition that excels in feeling at application or after application and that by enhancing of the transdermal absorption of cyclosporine exerts medicinal benefits at low concentration. There is provided a liquid crystals emulsion-type pharmaceutical composition comprising cyclosporine a hydrophilic nonionic surfactant, a lipophilic nonionic surfactant, an oil a fatty acid that is insoluble in the oil at room temperature, a solid fatty alcohol that is insoluble in the oil at room temperature and a water soluble polyhydric alcohol that is immiscible with the oil at room temperature, and a method of testing cutaneous diseases with the use of the pharmaceutical composition [57,67].

Table 1b : Patents on Liquid Crystal Applications

3.	Drug delivery system utilizing liquid crystal structure	US 5,891,845/ April 6,1999	Vitamin E TPGS/drug composition and method are provided which obviate the need for surfactants or non evaporated co solvents because the active drug component is dissolved directly into vitamin E TPGS to form a true molecular solution –not an emulsion or a micro emulsion the invention provides a slowly dissolving TPGS/Drug matrix that absorbs gastrointestinal fluid into the matrix at crystal is formed. This gel front forms a liquid crystals boundary where drug dissolution is highest. At this liquid crystals/GI fluid boundary, synchronization takes place in which the rate of formation of liquid crystals equals the dissolution rate of liquid crystals at the water interface thereby giving controlled order release of the drug into the GI tract. The rate of dissolution is also controlled by the geometry of the dosage form. The solid vitamin E TPGS/ drug matrices of the inventions can be solidified and compressed into tablets or filled into capsules, with other excipients, binder and /or fillers. The solid TPGS/drug solution of the invention also can be made into an immediate release liquid formulation upon addition of water or into a controlled release system solid tablet by the use of impermeable or semi permeable barriers or coating surroundings portions of the tablet.[57,68]

ISSN (Online): 2455-3662
EPRA International Journal of Multidisciplinary Research (IJMR) - Peer Reviewed Journal
Volume: 7 | Issue: 5 | May 2021|| Journal DOI: 10.36713/epra2013 || SJIF Impact Factor 2021: 8.047 || ISI Value: 1.188

4.	Transdermal pharmaceutical composition	10/575,145/June 1, 2010	The invention relates to a liquid crystal gel containing polyoxyethylene- glyceryl- trioleate, propylene-glycol, isopropyl myristate and a hyaluronic acid salt or complex for use in the manufacture of transdermal pharmaceutical compositions and healing cosmetics. The invention also relates to transdermal pharmaceutical composition consists of an estrogen and a progestin component as well as a liquid crystal gel containing polyoxyethylene glyceryl-trioleate, propylene-glycol, isopropyl myristate and a hyaluronic acid salt or complex. The invention can be applied for transdermal hormone replacement therapy and for other transdermal depending on the active principles included.[57,69]
5.	Imine Based Liquid Crystals For The Controlled Release of Bioactive Materials	20090306196	The present invention relates to a delivery system based on a film of an imine forming liquid crystalline phase, mixed with at least with one biologically active substance, to which a constant or variable electric field can be applied. The delivery system can be used as a delivery system for biologically active substances such as flavors, fragrances, bactericides, fungicides, insecticides, insect attractants or repellents, agrochemicals or pharmaceuticals[57]

CONCLUSION

Liquid crystal technology has had a major effect in many areas of science pharmacy and engineering, as well as device technology. The drug delivery to site of target can be achieved by using liquid crystal systems. Objective of this review is to provide information in development of targeted drug delivery system, depth information of pharmaceutical liquid crystal technology, its classification and application in the pharmaceutical field.

REFERENCES

1. *Yogeshvar Tyagi, liquid crystal: An approach to different states of Matter, Pharma innovation journal, 2018, 7(5): 540-545.*
2. *Ashish P. Lodha, Gauri P. Jadhav, Vishal V. Pande, Liquid crystals as a Cubo-Hexagonal Topical Controlled Drug delivery system, Pharmacophore, 2014, 5 (3): 430-441.*
3. *Pallavi Kawara, Vishal Pande, Liquid Crystals: A Novel Approach Drug Delivery System, JETIR June , 2019, Volume-6,402-410.*
4. *Gennes, P.G. and Prost, J. The Physics of Liquid Crystals, Claredon Press ,1993,4(3),7.*
5. *Shaikh Zeba, Liquid Crystalline System: A Novel approach for Drug Delivery, Journal of Biomedical and Pharmaceutical Research 4 (1) 2015, 22-32.*
6. *Bennett, D., Cabot, K., Foster, L., Lechuga-Ballesteros, D., & Tan, T. (1999). Liquid crystal forms of cyclosporin. US Patent Application 990352, WO 99/42124.*
7. *Characterization of Liquid Crystals: A Literature Review. Jiang-Gen an, Saba Hina, Yong Yang, Min Xue and Yongsong Liu. s.l. Rev. Adv. mater. Sci. 2016; 44:398406.*
8. *Chaudhary, H., Gautam, B., & Kumar, V. (2014). Lyotropic liquid crystals. (March). http.//doi.org/10.403/09738398.134102.*
9. *V. Viswanatha, C. Rajaramb, S. R. Fathimac, D. Bhanu Priyad, Brief Review of Liquid Crystals, International Journal of Trend in Scientific Research and Development (IJTSRD), 2018, Volume-2,956-961.*
10. *Collings, P. J. & Hird, M. (1997). Introduction to Liquid Crystals. Bristol, PA: Taylor & Francis. ISBN 074840643-3.*
11. *Structure of the Liquid-Crystal Phases of the Soapwater System: Middle Soap and Neat Soap. Luzzati V, Mustacchi H, Skoulios A. 4586, S. L. Bibcode. 1957; 180:600L. Doi: 10.1038/180600a0, 1957, Vol. 180.*
12. *L. K. Omray, Liquid Crystals as Novel Vesicular Delivery System: A Review, Current trends in Technology and Science, Vol. II, Issue IV,347-349, 2013.*
13. *Kamal Kumar Chaudhary, Pooja Kannojia , Nidhi Mishra, Liquid Crystal Systems in Drug Delivery, Research Gate, 2016, 217-243.*
14. *Lancelot A, Sierra T, Serrano J L. Nanostructured liquid crystalline particles for drug delivery. Expert Opin Drug Deliv2014;11(4):547-64.*

ISSN (Online): 2455-3662
EPRA International Journal of Multidisciplinary Research (IJMR) - Peer Reviewed Journal
Volume: 7 | Issue: 5 | May 2021|| Journal DOI: 10.36713/epra2013 || SJIF Impact Factor 2021: 8.047 || ISI Value: 1.188

15. *Bunjes H, Rades T. Thermotropic liquid crystalline drugs. J Pharm Pharmacol, 57, 807-16, 2005.*
16. *Silicone Liquid Crystals, Vesicles, and gels. Ferritto, Michael Salvatore, Lin, Zuchen a nd Jr, William James Schulz. s.l. Drug. Delivery Rev. 2001; 47:229-250. .*
17. *Liquid-crystalline properties of aqueous suspensions of natural clay nanosheets. Paineau E. 110, S. L. Liquid Crystals Reviews, 2013, 1. doi:10.1080/21680396.2013.842130.*
18. *Reinitzer, Friedrich (1888). "Beiträge zur Kenntniss des Cholesterins".Monatshefte für Chemie (Wien)9 (1): 421–441. doi:10.1007/BF01516710.*
19. *Phase Behavior and Dynamics of the Liquid Crystal 4'butyl-4-(2-methylbutoxy) azoxybenzene. JuszyńskaGałązka E. 21, s.l. The Journal of Physical Chemistry. 2014; 118:14982-14989.*
20. *Sluckin, T. J.; Dunmur, D. A. & Stegemeyer, H. (2004). Crystals That Flow – classic papers from the history of liquid crystals. London: Taylor & Francis. ISBN 041525789-1.*
21. *Hirohisa Kawamoto (2013), The history of liquid crystal display and its industry, ELectro-technology Conference (HISTELCON), 2012 Third IEEE, ,DOI10.1109/HISTELCON.2012.64875 87.*
22. *U. S. Patent 3,834,794: R. Soref, Liquid crystal electric field sensing measurement and display device, filedJune28, 1973.*
23. *U. S. Patent 5,598,285: K. Kondo, H. Terao, H. Abe, M. Ohta, K. Suzuki, T. Sasaki, G. Kawachi, J. Ohwada, Liquid crystal display device filed Sept, 18, 1992 and Jan 20, 1993.*
24. *Competing display technologies for the best image performance; A. J. S. M. de Vaan; Journal of the society*
25. *of information displays, Volume 15, Issue 9 September 2007 Pages 657-666 http://onlinelibrary.wiley.com/doi/10.1889/1.2785 19 9.*
26. *Castellano, Joseph A. (2005). Liquid Gold: The Story of Liquid Crystal Displays and the Creation of an Industry. World Scientific Publishing. ISBN 978-981238-956-5.*
27. *Ola Monika, Bhaskar Rajveer, Patil Gaurav R, Liquid Crystalline Drug Delivery System For Sustained Release Loaded With An Anti-tubercular Drug , Journal of Drug Delivery and Therapeutics,2018, 8(4):93-101.*
28. *Omray L.K. Liquid crystals as novel vesicular delivery system: Review. Curr Trends Technol Sci, 2013; 2:347353.*
29. *[28]Dong-Hwan Kim, Alexander Jahn, SungJoon Cho, Jung Sun Kim, Min-Hyo Ki & Dae-Duk Kim, lyotropic liquid crystal system in drug delivery: a review,Journal of pharmaceutical investigation,2015,45:1-11*
30. *Makai M, Csanyi E, Dekany I, Nemeth Z, Eros I.*
31. *Structural properties of non-ionic surfactant/glycerol/paraffin lyotropic crystals. Colloid Polym Sci, 281, 839-44, 2003.*
32. *Chan HK, Gonda I. Methotrexate: Existence of different types of solid. Int J Pharm 6 8, 179-190, 1991.*
33. *Bunjes H, Rades T. Thermotropic liquid crystalline drugs. J Pharm Pharmacol, 57, 807-16, 2005.*
34. *Farkas E, Zelko R, Nemeth Z, Palinkas J, Marton S, Racz I. The effect of liquid crystalline structure on chlorhexidine diacetate release. Int J Pharm, 193, 239– 45, 2000.*
35. *Lara MG, Bentley MVLB, Collett JH. In vitro drug release mechanism and drug loading studies of cubic phase gels. Int J Pharm, 293, 241-250, 2005.*
36. *Shah J C, Sadhle Y, Chilukuri DM. Cubic phase gels as drug delivery systems. Adv Drug Deliv Rev, 47, 22950, 2001.*
37. *Shah MH, Paradkar A. Cubic liquid crystalline glyceryl monooleate matrices for oral delivery of enzyme. Int J Pharm, 294, 161-171, 2005.*
38. *Liquid Crystals Pharmaceutical Application: A Review. Dr. Sadhana Shahi, Vivek Ramteke, Iftequar Syed. International Journal of Pharmaceutical Research & Allied Sciences. 2012; 1(2):06-12*
39. *Rego, J.A.; Harvey, Jamie A.A.; MacKinnon, Andrew L.; Gatdula, Elysse (January 2010). "Asymmetric synthesis of a highly soluble 'trimeric' analogue of the chiral nematic liquid crystal twist agent Merck S1011". Liquid Crystals37 (1): 37–43. doi:10.1080 /02678290903359291.*
40. *Shaikh Zeba, Naik Nikita, Dusane Prachee, Rane Bhushan, Gujarathi Nayan, Ahirrao Rajesh. Liquid Crystalline System: A Novel Approach for Drug Delivery. Journal of Biomedical and Pharmaceutical Research. Vol. 4, Issue 1, 22-32, 2015.*
41. *Phase Transitions of Liquid Crystal PAA in Confined Geometries. Shao Y, Zerda TW. 18, S.L. Journal of Physical Chemistry. 1998; 102:3387-3394.*
42. *Kleinert H. and Maki K. (1981). Lattice Textures in Cholesteric Liquid Crystals". For tschritte der Physik29 (5): 219–259. Bibcode: 1981 ForPh..29. 219K. doi:10. 1002/prop.19810290503.*
43. *Seideman, T (1990). The liquid-crystalline blue phases.*
44. *Rep. Prog. Phys.53 (6): 659–705. Bibcode: 1990RPPh...53. 659S. doi:10.1088/0034-4885/53/ 6/ 001.*
45. *Savita Mandan, Maitreyee Chavan, Cubosomes: Future of Therapeutics, International journal of pharmacy and pharmaceutical research, March 2020 Vol.:17, Issue: 4, 60-69.*
46. *Kawamoto H. The history of liquid crystal display. Proceedings of the IEEE, 460-99, 2002*
47. *Acciacca A, Spong BR, Fleisher D, Hornedo NR. Mol. Pharmaceutics, 5: 956-967(2008).*
48. *Rebecca J. Carlton, Jacob T. Hunter, Daniel S. Miller, Reza Abbasi, Peter C. Mushenheim, Lie Na Tan, and Nicholas L. Abbott, Chemical and biological sensing using liquid crystals, Liq Cryst Rev, 2013; 1(1): 29–51.*
49. *L. Abbott. 1, s.l. US National Library of Medicine. 2013; 1:29-51.*
50. *P. V. Patel, J. B. Patel, R. D. Dangar, K. S. Patel, K. N. Chauhan," Liquid Crystal Drug Delivery*

ISSN (Online): 2455-3662
EPRA International Journal of Multidisciplinary Research (IJMR) - Peer Reviewed Journal
Volume: 7 | Issue: 5 | May 2021|| Journal DOI: 10.36713/epra2013 || SJIF Impact Factor 2021: 8.047 || ISI Value: 1.188

System",Int. J. Of Pharma. &App. sci./1(1)/2010:118 123.

51. *Garry Myers, Kingsport, Tenn. "Drug delivery system utilizing liquid crystal structure" US 5,891,845/ April 6,1999.*
52. *Paavola A, Kilpelaine I, YliruusiJ, Rosenberg P. Controlled release of vancomycine from poloxamer 407 gels. Int. J Pharm., 288:235-244(2005).*
53. *Alexandre Lancelot, Teresa Sierra & Jose Luis Serrano, Nano-structured liquid-crystalline particles for drug delivery, informa healthcare, 2014, 547-564.*
54. *Gan L, Wang J, Jiang M, et al. Recent advances in topical ophthalmic drug delivery with lipid-based nanocarriers. Drug Discov Today 2013;18(5-6): 290- 7.*
55. *Gan L, Han S, Shen J, et al. Self-assembled liquid crystalline nanoparticles as a novel ophthalmic delivery system for dexamethasone: improving preocular retention and ocular bioavailability. Int J Pharm 2010; 396(1-2):179-87.*
56. *Liquid crystals containing cosmetic and pharmaceutical compositions and methods for utilizing such compositions. Gheorge Cioca, Lake Grove, James Hayward, Port jeffeson, Manuel*
57. *L. Tan, Glen Clove, Morris Herstein scarsdae, N. Y. walter, Stamford, conn. s.l. US 4,999,348, March 12, 1991.*
58. *R. K. Thapa, J. Y. Choi, B. K. Poudel, T. T. Hiep, S. Pathak, B. Gupta, H. Choi, C. S. Yong, J. O. Kim, ACS Appl. Mater. Interfaces 2015, 7, 20360 – 20368.*
59. *M. Nasr, M. K. Ghorab, A. Abdelazem, Acta Pharm. Sin. B2015, 5, 79 – 88.*
60. *S. Murgia, S. Bonacchi, A. M. Falchi, S. Lampis, V. Lippolis, V. Meli, M. Monduzzi, L. Prodi, J. Schmidt, Y. Talmon, et al.,Langmuir 2013, 29, 6673 – 6679.*
61. *Imran Tadwee, Dr.Sadhana Shahi, Vivek Ramteke, Iftequar Syed, Liquid Crystals Pharmaceutical Application: A Review,IJPRAS, Volume 1, issue2 (2012), 06-11.*
62. *Jean-Marie Lehn, Andreas Herrmann Nicolas Giuseppone "Imine Based Liquid Crystals for the Controlled Release of Bioactive Materials" Patent App. No 20090306196.*
63. *Boyd BJ, Whittaker D V, Khoob S, DaveyG. Hexosome formed from glycerate surfactants-Formulation as a colloidal carrier for irinotecan.Internationa Journal of Pharmaceutics, 318: 154-162(2006).*
64. *Zahra Karami and Mehrdad Hamidi, Cubosomes: remarkable drug delivery potential, Drug Discovery Today, Volume 5, Number 5, 790-799, May 2016.*
65. *Rattanapak, T. et al. (2013) transcutaneous immunization using microneedles and cubosomes: mechanistic investigations using optical coherence tomography and two-photon microscopy. J. Control. Release 172, 894– 903.*
66. *Doxorubicin skin penetration from monooleincontaining propylene glycol formulations. Herai H, Gratieri T, Thomazine JA, Bentley MV, Lopez RFV. s. l. Int J Pharm. 2007; 329:88-93.*
67. *Atyabi F, Khodaverdi E, Dinarvand R. Temperature modulated drug permeation through liquid crystal embedded cellulose membranes, International Journal of Pharmaceutics, 339:213-221(2007).*
68. *Z. Liu, L. Luo, S. Zheng, Y. Niu, R. Bo, Y. Huang, J. Xing, Z. Li, D. Wang, Int. J. Nanomed. 2016, 11, 3571 – 3583.*
69. *Farkas E, Kiss D, Zelk'o R. Study on the release of chlorhexidine base and salts from different liquid crystalline structures,International Journal of Pharmaceutics, 340:71-75(2007).*
70. *Gheorge Cioca, Lake Grove, James Hayward, Port jeffeson, Manuel L. Tan, Glen Clove, Morris Herstein Scarsdae, N. Y. Walter, Stamford, Conn "Liquid crystals containing cosmetic and pharmaceutical compositions and methods for utilizing such compositions" US 4,999,348 March 12, 1991.*
71. *Ryo Akamastsu, Masahiro Fujii, Tomoki Sakaguchi, Eijiro Horisawa Japan"Liquid crystals emulsion type pharmaceutical composition containing cyclosporine and therapeutic method of treating cutaneous disease therewith" US 2010/190695 A1/ July 29,2010.*
72. *Garry Myers, Kingsport, Tenn. "Drug delivery system utilizing liquid crystal structure" US 5,891,845/ April 6, 1999. Availablat:https://scholar.google.co.in/scholar?q=%5B68%5D+Garry+Myers,+Kingsport,+Tenn.+%E2%80%9CDrug+delivery+system+utilizing+liquid+crystal&hl=en& as_sdt=0&as_vis=1&oi=scholart .*