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A REVIEW ON LIQUID CRYSTALS AS AN INNOVATIVE DRUG DELIVERY MECHANISM AND THEIR RECENT ADVANCES

[1]P. Shailaja,[2]N. Anjali,[3]B. Neerajakshi,[4]K. Satya Ashok,
[1]Associate professor,[2,3]Student,[4]Research scholar
[1]Department of pharmaceutical technology
[1]A.U. College of Pharmaceutical Sciences
Andhra University, Visakhapatnam, India

ABSTRACT: Recently, liquid crystals have been researched as an innovative drug delivery mechanism. Their resemblance to colloidal systems found in living beings is the reason behind this. They have distinguished as superior to conventional, dermal, parenteral, and oral dosage forms. Liquid crystals(LC) have a long shelf life and are thermodynamically stable. Liquid crystal-based drug delivery is a vast area of study. The use of liquid crystals, particularly lyotropic liquid crystals, as nanoparticles (cubosomes and hexosomes) for drug delivery applications has seen a significant increase in interest in recent years. Liquid crystals have prolonged release effects which serves as its main characteristics. In recent years, research has concentrated on strengthening the synthesis and characterization of loaded therapeutic molecules, controlling drug release, and increasing their efficacy. The purpose of this review was to present data on various liquid crystal systems, mesophase characterization, applications, researches undergone and future perspectives of liquid crystals in drug delivery.

Keywords: Liquid crystals, mesophases, nematics, smectics, thermotropic liquid crystals, lyotropic liquid crystals, cubosomes, hexosomes.

1. INTRODUCTION:

Between conventional solids and liquids, there exists an intermediate state of matter known as liquid crystals. They are necessary for life since many essential elements of living organisms, such as cell walls and metabolic fluids, are liquid or crystalline in form. The Organic molecules that are typically elongated and have an unequal distribution of electrical charges along their axes are called liquid crystals. Anisotropy is exhibited by liquid crystalline structures, (have optical direction and both solid and liquid-like characteristics) [1]. Due to their anisotropy, liquid crystals are found to be birefringent. Hence, they show double refraction (having two indices of refraction). The fundamental prerequisite for the development of liquid crystalline phases is anisometric molecule shape coupled with polarizability [2]. They are distinguished from crystalline solids by having lost partial or all of their positional order while maintaining the orientational order of its constituent molecules [3]. Such orientational order can last in the solid state, and as a result, liquid crystals may exhibit mechanical stability. Birefringence, response to magnetic and electric fields, optical activity in twisted (chiral) nematic phases, and temperature sensitivity are some of the general characteristics of Liquid crystals [4]. DNA and lipids of cellular Proteins and membranes are two well-known examples of liquid crystals.

2. CLASSIFICATION:

Liquid crystals can be further classified as thermotropic or lyotropic.

2.1. Thermotropic liquid crystals:

Thermotropic liquid crystals are largely solvent-free and are induced by a change in temperature. Many thermotropic LC are referred to as polymorphic if they can exist in more than one mesomorphic phase. Thermotropic liquid crystals are categorized as discotic (made up of flat or disc shaped molecules) or calamitic (composed of rod-shaped molecules). Calamitic are again classified as Nematic, smectic and discotic are classified into nematic discotic or columnar or smectic discotic phases according to their degree of anisotropy. They are formed by either chilling an isotropic liquid or heating a crystalline solid.

2.1.1. Nematic phase

The simplest liquid crystalline phase, known as the nematic phase (thread-like), is one in which the molecules maintain their long-range orientation. There is no positional hierarchy. Nematic liquid crystals are the most common type of liquid crystal used in electronic displays. The defective patches connecting these domains appear as dark threads under a polarising microscope [5,6]. Nematic crystals only have one structural restriction and that is the molecules' long axes maintain a largely parallel configuration.

2.1.2. Smectic phase

Friedel termed "smectic phase" (soap-like) from a Greek word that means "grease or slime"[7]. As the molecules are stacked in layers, the smectic structure is layered. The tilt angle that a director vector creates with the molecular layers and the configuration of molecules within each layer allow for the distinction between structured and unstructured thermotropic smectic phases. The simplest smectic is the smectic A phase, which is characterised by random positional order within layers and an overall orientation of molecules parallel to molecular layers. At a lower temperature, substances that exhibit the smectic A phase frequently also display the smectic C phase. In this stage, the molecules tilt in relation to the molecular layers but still have the same random order within the layer. Typically, when temperature drops, the tilt angle rises. Other smectic phases, such as those that display hexagonal packing of the molecules, are even more crystalline in that they also have some positional order within the layers.

2.1.3. Cholesteric phase

Cholesteric phase is also called as chiral nematic liquid crystal. The cholesteric phase's arrangement can be characterised as a hybrid of the nematic and smectic [8,9]. The molecules are arranged in a helical pattern in the chiral nematic phase, which imparts a directional rather than a positional periodicity. The orientation of the molecules is the same for each half-turn of the helix. When the entire helical turn is of the same order of magnitude as the wavelength of visible light, cholesteric nematic can exhibit colour. The size of the helical turn will fluctuate depending on temperature, which leads to temperature-dependent colour variations.

2.2. Lyotropic liquid crystals:

Amphiphilic molecule mixes in a solvent at specific temperatures and relative concentrations are known as lyotropic liquid crystals, also known as lyotropics [6]. Solvent induces the formation of lyotropic LC, which are often composed of amphiphilic molecules. The factors like temperature, organic molecule structure, and the water/amphiphile ratio plays a role in the production of lyotropic mesophases [11,12]. Lamellar, hexagonal, and cubic phases are further classifications for lyotropic liquid crystals. Surfactant molecules can be used in lyotropic liquid crystal systems to capture water from the surroundings. Lamellar, hexagonal, and cubic phases are produced as a result of spontaneous phase transitions that are triggered by the environment's water concentration. The degree of contact between the water and the alkyl chain, the strength of the repulsive forces between neighbouring head groups, and conformational aberrations in the alkyl chains are all discovered to play a role in the development of the lyotropic liquid crystalline phase.

2.2.1. Lamellar phase

Lamellar phase or clean phase has multiple layers of surfactant molecules with protruding polar head groups. The hydrocarbon chains are disordered, like surfactant bilayers and liquid paraffin are separated by water [13,14]. The neat phase is fluid despite its high surfactant content, allowing lamellae to glide smoothly [15,16].

2.2.2. Hexagonal phase

Water layers that are hexagonally tightly packed and covered in a surfactant monolayer make up the hexagonal phase. Long-range order has a two-dimensional structure. In aqueous and anhydrous organic fluids, respectively, normal and reverse mesophase, two different types of hexagonal mesophase, can be seen. The hydrophilic polar groups form the inner core of anhydrous organic solvents (solvents with little or no water), which are surrounded by hydrocarbon chains known as reverse hexagonal or reverse middle phase. A hexagonal structure and inverted micelles may also form in the system when non-ionic surfactant concentrations are high. Lamellar phase is softer than hexagonal phase. [17,18].

2.2.3. Cubic phase

Cubic phase structure has continuous curved bilayers and interpenetrating non-intersecting aqueous channels. Cubic phase molecules are packed spherically, with the ionic component on the surface and the non-polar (water-insoluble) portion in the centre [15]. The interfacial area of cubic phase is considerably greater than other phases. Cubic phase microstructure allows regulated drug release. Close micelle packing accounts for the phase's stiffer flow-resistance than the mesophase [18]. In excess water, cubic phases are formed. Due to its dual polar-nonpolar nature, the structure shows slow-release of drugs of different polarity and size. The cubic phase is bio adhesive. The structure is suitable for GI, pulmonary, nasal, oral, buccal, rectal, and vaginal drug delivery. Cubic mesophase is in vitro stable [19].

3. PREPARATION OF LIQUID CRYSTAL PHASE AND ITS DISPERSION:

Liquid crystal preparation is easier than dispersion. Vortexing lipid with aqueous phase creates liquid crystal [8,9]. Repeated vortexing achieves homogeneity. To synthesize liquid crystal, equilibrate the mixture at room temperature for 48 hours. Depending on the lipid, further additives may be added to the mixture or the procedure may be adjusted. For example, if more than one lipid is

employed, both lipids are combined and melted, if necessary, before vortexing with aqueous phase [18,20,21]. Liquid crystal dispersion preparation is challenging. Their dispersal uses two methods. First, lipid and stabiliser are hydrated to form a viscous bulk, which is then disseminated into an aqueous solution using high-pressure homogenization and ultrasonication. The 'Bottom-Up' technique uses hydrotrope to create a liquid precursor and avoid liquid crystal formation at high concentrations. The combination disperses when aqueous medium is added carefully. It uses dilution method and not require fragmentation [9,14,21].

4. CHARACTERIZATION OF LIQUID CRYSTALLINE PHASES

4.1. X-ray diffraction:

X-ray diffraction is the most used method for studying surfactant and block copolymer liquid crystalline phases. Ordered microstructures generate X-ray scattering interferences. Position-sensitive detectors/scintillation counters can detect interferences using X-ray counts or film. Due to liquid crystals' long-range structural order, electromagnetic light of an appropriate wavelength can generate diffraction patterns. Small angle X-ray diffraction (SAXD) and wide-angle X-ray diffraction can be used to detect long and short-range orders (WAXD). SAXD is used to determine diffraction patterns in liquid crystals [22].

4.2. Nuclear magnetic resonance (NMR) spectroscopy:

Crystallizations in liquids can be studied using NMR spectroscopy. Since it correctly identifies the occurrence of various phases, deuterium (2 H) NMR spectroscopy is a potent method for analysing phase equilibrium. Anisotropic phases cause quadrupolar splitting and provide a doublet resonance signal instead of the narrow singlet resonance signal that is produced by isotropic phases for quadrupolar nuclei like 2 H. Also, splitting magnitude separates anisotropic phases. This can determine the phase in a single-phase system and the composition in a multiphase system.

4.3. Polarizing light microscopy (PLM):

It's simple and clear method. Anisotropic liquid crystalline phases such as lamellar, hexagonal and reversed hexagonal are birefringent as a result of molecular ordering. Using polarised light microscopes, phases can be studied. With one polarizer above and one below the objective in this microscope's cross position, plane polarised light is provided at a straight angle and the transit of polarised light from below to above the objective is constrained. Small wavelength aberrations can cause yellow textures and torquoise in liquid crystalline materials. Lamellar phases reveal mosaic patterns under a polarising microscope, while hexagonal phases show nongeometric textures. This approach can detect crystals. Because micellar, cubic phase and reversed micellar solutions are non-birefringent, dark backdrop is seen. The thermotropic smectic mesophases have a range of textures but resemble the lyotropic hexagonal mesophase's fan-shaped texture [23,24]. Polarized optical microscopy is a potent tool for identifying liquid crystal phases, although submicron-scale mesophases may make it ineffective. Other imaging techniques may potentially degrade samples [25].

4.4. Transmission electron microscopy (TEM):

The electron microscope's high magnification allows viewing of liquid crystal microstructure. Aqueous samples require special pre-treatment because the intense vacuum of an electron microscope causes microstructure abnormalities. Freeze-fracture has been effective. For this, an electron microscope replica of the sample is produced. First, shock-freeze the sample to maintain its microstructure throughout replication. Sandwich the sample between two gold plates and shock freeze using nitrogen-cooled liquid propane at -196° or slush nitrogen at -210° for high freezing rates up to 105-106 K/s [26]. Applying pressure prevents sample water from crystallising, preserving its structure.

4.5. Differential scanning calorimetry (DSC):

Energy changes cause phase transitions. Depending on the transition type, endothermic or exothermic signals are observed. Crystalline to amorphous transitions consume less energy than liquid crystalline transitions [25]. To the measurement device's sensitivity and detection limit, care should be taken. Change in baseline slope with specific heat capacity indicates phase transition entropy. Entropic phase transitions of liquid crystalline polymers are second order [27]. Glass transitions. Their detection may be confounded by an enthalpic effect.

4.6. Rheology:

Diverse liquid crystal structures exhibit rheological qualities to varying degrees [28]. With an increase in the liquid crystal's microstructural organisation, the consistency of the crystal thickens and the flow behaviour becomes more viscous. The coefficient of dynamic viscosity Z shows that hexagonal and cubic liquid crystals have relatively higher viscosities than lamellar phase, while being a measure of optimum viscous flow behaviour (Newtonian systems). The major difference between these two types is that the lamellar phase exhibits pseudoplastic flow behaviour (non-Newtonian), whereas cubic and hexagonal crystals exhibit plastic flow behaviour (non-Newtonian)[29]. The order of the viscosity rise for thermotropic liquid crystals is as follows: Nematic< smectic A< smectic C.

4.7. Vesicle size determination:

The physical stability of vesicle dispersion is largely determined by the particle size distribution and particle size, making vesicle size a crucial parameter in both quality assurance and in-process control[30]. Laser light diffraction or scattering (for particle size) is a suitable and very rapid technique (for particle size distribution). According to Fraunhofer's diffraction theory, laser light diffraction is applicable to particles larger than one millimetre in size. This is a reference to the relationship between the particle diameter squared and the diffraction strength. According to Mie's theory, the absorption, scattering angle, refractive indices and size, as well as the dispersion medium, are the main parameters impacting the scattering intensity [20]. With particles ranging in size from 200 nm to 1 mm, photon correlation spectroscopy can be an effective method for determining mesophase.

Table: 1; Characterization of LCNs

Characterization	Observations	Parameters measured
PLM	1.Cubic phase - dark background with no birefringence 2.Hexagonal phase - fan like structure 3.Lamellar phase - shows birefringence	Macroscopic structure; preliminary phase identification
SAXS	Bragg's peak	Molecular dimensions; phase identification; impact of guest molecules on liquid crystalline structure
DSC	increase in enthalpy; transition of endothermic peak; impact of temperature on system	Evaluation of phase transition; guest molecules effect on liquid crystalline structure
NMR	Interactions between loaded molecules and mesophase components	Diffusion pattern of molecule components; Inner structure
TEM and SEM	Visualization of inner structures	Morphological features

5. APPLICATIONS AS DRUG DELIVERY SYSTEMS

5.1. Enhancing oral delivery

Amphiphilic lipids self-assemble in excess water to form thermodynamically stable bicontinuous hexagonal, cubic and lamellar phases. Dispersing lyotropic LC phases in water with a surfactant creates Liquid crystalline nanoparticles (LCNs). Due to their unique structure, these nanostructures can load hydrophobic, hydrophilic and amphiphilic bioactive compounds. LCNs are also used to make poorly soluble drugs more soluble.

Freag et al. loaded rapamycin onto surface-modified LCNs to improve its water solubility and antitumor efficacy. The study showed improved encapsulation efficiency, sustained drug release, and enhanced cytotoxicity against MCF-7 and MDA-MB-231 breast cancer cell lines. In vivo, rapamycin bioavailability was 3.35-fold higher than free drug. Also, free rapamycin had less nephrotoxic and hyperglycemic effects on an Ehrlich ascites tumour model [31]. Synthetic anticancer medications aren't the only ones with poor bioavailability and solubility. Curcumin, a curcuminoid from turmeric (Curcuma longa), inhibits cancer cells. Curcumin's solubility limits its therapeutic use. Baskaran et al. integrated curcumin into LCNs and showed its improved stability and cellular absorption in cancer cells of human colon [32].

5.2. Topical and/or transdermal delivery

Topical carriers have been investigated to improve bioactive molecule penetration through the skin and maintain drug release. These carriers are MO- and PHY-based LC mesophases [33,34,35]. LC mesophases successfully transfer bioactive compounds through the skin due to their structural similarities to skin microstructures, which encourages facile diffusion across the stratum corneum. Mesophases' cubic form resembles the skin's epidermal barrier in vivo [36], which improves the partitioning of liquid crystalline phases and lipid lamellae. A chemo preventative and anti-inflammatory drug taken orally is celecoxib. Propylene glycol and oleic acid were used in the development of a topical carrier to reduce the systemic toxicity of oral LCN. Oleic acid was added to maintain the anti-inflammatory properties of celecoxib, whereas oleic acid-propylene glycol increased the amount of medication released [37]. Excipients changed drastically the LC phase structure, which had an impact on the release of lipophilic medicines [38,39].

Esposito et al. created (mono olein) MO-based LC bulk phases to increase crocetin's cutaneous penetration. Healthy human volunteers participated in an in vivo tape-stripping investigation to evaluate drug in the superficial layer. The stratum corneum had a higher quantity of crocetin than deeper skin layers. For a lipophilic medication, the LC phase permits targeting of the higher skin layers, prolonging skin action and decreasing systemic exposure [40]. 5a-reductase inhibitors with lipophilic characteristics retained more in the higher layers of skin with LCN-based formulations. Lipophilic skin membranes make hydrophilic molecules impermeable [41]. Hydrophilic molecule loading and delivery can be prevented by the 3D bicontinuous structure of mesophases, which features two crossing water channels.

Yu et al. investigated the transdermal delivery of cubic MO-based metformin hydrochloride phases. Drug penetration through mouse skin was studied using in vitro research and molecular docking. The researchers found that MO increased skin lipid fluidity, which in turn increased drug absorption [42].

5.3. Cancer targeting

Thapa et al. produced a layer-by-layer polymer-assembled LCN based on MO and stabilised by P407 to administer sorafenib, a poorly soluble hepatocellular cancer medication. LCN loaded with sorafenib was wrapped in six layers of poly-L-lysine and polyethylene glycol-b-polyaspartic acid. Bio adhesivity, fast clearance from the blood circulation, and LCN-induced haemolysis were overcome by coating nano particles (NPs). It controlled drug release, focused distribution, and increased anticancer therapeutic indices. This study found that multi-layered LCNs boost cellular uptake and apoptosis. Additional to single anticancer drug delivery, experts have highlighted the feasibility of combination chemotherapy employing LCN. Studies conducted in vivo showed better apoptotic marker expression and increased cytotoxicity with few negative side effects. LCNs as dual drug delivery systems for metastatic breast cancer are investigated in this work [43].

Aleandri et al. stabilised paclitaxel cubosomes with modified phenolic matrix resin (PF108). PF108 was coupled with biotin to target HeLa biotin receptors. Biotin receptor-mediated endocytosis improved paclitaxel absorption in HeLa cells [44]. He and colleagues created LCN nano transformers with high siRNA-loading efficiency and low intracellular cytotoxicity for cancer treatment. LCN nano transformers' safety and great gene transfection efficiency make them a promising cancer treatment [45].

Agrawal et al. developed LCN for diabetes. In this study, insulin's oral stability and efficacy were improved. LCNs doubled cumulative hypoglycaemia compared to subcutaneously delivered conventional insulin [46].

Swarnakar and colleagues investigated the effects of lipase digestibility on the oral bioavailability of coenzyme Q10, their in vivo antioxidant potentials, and the interaction between coenzyme Q10-loaded LCNs made using mono-olein and phytantriol in vitro and in vivo. The authors showed that this formulation method could boost coenzyme Q10's oral bioavailability [47].

Hong and his team employed an enzymatic technique to understand cubosome formation and apply it to lipids other than phytantriol. Selachyl alcohol, a nondigestible alternative to phytantriol, was used to produce LCNs enzymatically. Longer chain triglycerides disturb phase structure more effectively. The majority of fatty acids produced during digestion stayed in the particles and didn't need to diffuse into the aqueous bulk[48].

5.4. Theranostic applications

Theranostics aims to enhance the prognoses of diseases like cancer by developing a clinically viable agent or carrier for therapies and diagnostics. LCNs offer a variety of distinctive characteristics, including a simple surface that can be modified with imaging and targeting moieties. Additionally, the viscosity of dispersion of cubosomes and hexosomes is similar to that of water, which is a significant attribute for intravenous administration and the potential for dual loading with drugs and imaging agents, with surface decoration of cancer-specific targeting moieties. For instance, by preserving the internal structure of the LC phase, docetaxel, a weakly soluble anticancer drug stabilised by Pluronic paired with rhodamine and folate, was loaded into monoolein-based hexosomes[49].

Table: 2; Examples of LC drug delivery systems for different applications

Therapeutic molecule	Type of LC phase	Advantages	Applications
Celecoxib[50]	Cubosomes and hexosomes	Improved skin permeation	Topical
Crocetin[51]	Cubic and lamellar	increased skin retention for cutaneous application	Topical
Metformin[31]	Cubic	Transdermal delivery of hydrophilic drugs	Transdermal
Sorafenib[32]	Cubosomes	Greater cellular uptake and increased apoptotic effects in HepG2 cells	Hepato cellular carcinoma
Insulin[36]	Hexosomes	Sustained glucose - lowering and stability of nanoparticles with higher Caco-2 cellular uptake	Oral delivery
Tetraphenylethene and phytoestrogen[45]	Hexosomes	Enhancement in targeted oncotherapy and noninvasive detection of tumor	Theranostics
Docetaxel[43]	Hexosomes	Enhancement in cytotoxic effect against HeLa cells and sustained release of drug	Theranostics

6. Conclusion and future outlook

LCNs are garnering attention in clinical studies due to their favorable features for effective drug delivery. Before LCNs may be used in the clinic, various problems and impediments must be overcome. Key developments include adjusting lipid cubic phase pore diameters, a library of stabilizers to target specific cancer cells, structural investigations to understand internal lipid membrane access, and controlled release systems. A deeper understanding of the interaction between the stabiliser membrane and the LCN, proof of pore size tuning, additional cytotoxicity studies, including interactions with cancer cells and intracellular trafficking, and therapeutics release are still major obstacles that need to be overcome in order to advance the applications of LCNs. LCNs with cell-derived lipids (CDLs) may evolve in the future[52,53]. CDL-coated NPs show promise in preclinical research due to their biocompatibility and tissue targeting [54].

LCNs are still used because of their many benefits, including their ability to incorporate all types of drugs, protect drug stability for longer periods of time than other dosage forms, be handled more easily than other lipid-based dosage forms, have lower toxicity due to their constituent parts, and have improved permeation [55].

References:

1. Martin AN, Sinko PJ. Martin's Physical Pharmacy and Pharmaceutical Sciences. Physical Chemical and Biopharmaceutical Principles in the Pharmaceutical Sciences. 6th ed. Baltimore, Philadelphia: Lippincott Williams & Wilkins; 2011. p. 112-43.

2. Lancelot A, Sierra T, Serrano JL. Nanostructured liquid crystalline particles for drug delivery. Expert Opin Drug Deliv 2014;11(4):547-64.

3. Wu¨nderlich B. 1999. A classification of molecules, phases and transitions as recognized by thermal analysis. Thermochimica Acta 340:37–52.

4. Brown GH. 1972. Liquid crystals and their roles in inanimate and animate systems. Am Scientist 60:64–73.

5. Hussain A, Pina AS, Roque ACA. Bio-recognition and detection using liquid crystals. Biosens Bioelectron 2009;25:1-8.

6. Kawamoto H. The history of liquid crystal display. Proc IEEE 2002;90(4):460-99

7. Oswald P, Pieranski P. Nematic and cholesteric liquid crystals: concepts and physical properties. Boca Raton, Florida, United States: CRC Press; 2005. p. 17-20.

8. Kelker H, Hatz R. Handbook of Liquid Crystals. Weinheim, Germany: Verlag Chemie; 1980. p. 121-34.

9. Stevenson CL, Bennett DB, Lechuga-Ballesteros D. Pharmaceutical liquid crystals: the relevance of partially ordered systems. J Pharm Sci 2005;94:1861-80.

10. Jakli A, Saupe A. One- and Two-Dimensional Fluids: Physical Properties of Smectic, Lamellar and Columnar Liquid Crystals. Boca Raton, Florida, United States: CRC Press; 2006. p. 256-70

11. Attwood D. Surfactant Systems: Their Chemistry, Pharmacy and Biology. Netherlands: Springer; 1983. p. 121-45.

12. Siddig MA, Radiman S. Structure of cubic phases in ternary systems glucopone/water/hydrocarbon. Colloids Surf A Physicochem Eng Asp 2004;236(1-3):57-67.

13. Carvalho FC, Barbi MS, Sarmento VH, Chiavacci LA, Netto FM, Gremião MP. Surfactant systems for nasal zidovudine delivery: structural, rheological and mucoadhesive properties. J Pharm Pharmacol 2010;62(4):430-9.

14. Rosevear FB. Liquid crystals: the mesomorphic phases of surfactant compositions. J Soc Cosmet Chem 1968;19:581-94

15. Shah MH, Biradar SV, Paradkar AR. Spray dried glyceryl monooleate-magnesium trisilicate dry powder as cubic phase precursor. Int J Pharm 2006;323:18-26.

16. Mohammady SZ, Pouzot M, Mezzenga R. Oleoyl ethanolamide based Lyotropic Liquid Crystals as Vehicles for Drug Delivery of Amino Acids in Aqueous environment. Biophys J 2009;96:1537-46.

17. Boyd BJ, Whittaker DV, Khoo SM, Davey G. Lyotropic liquid crystalline phases formed from glycerate surfactants as sustained release drug delivery systems. Int J Pharm 2006;309:218-26.

18. Fraser S, Separovic F, Polyzos A. Cubic phases of ternary amphiphile-water systems. Eur Biophys J 2009;39(1):83-90

19. Clogston J, Caffrey M. Controlling release from the lipidic cubic phase. Amino acids, peptides, proteins and nucleic acids. J Control Release 2005;107(1):97-111.

20. Muller-Goymann CC. Physicochemical characterization of colloidal drug delivery systems such as reverse micelles, vesicles, liquid crystals and nanoparticles for topical administration. Eur J Pharm Biopharm 2004;58:343-56.

21. Guo C, Wang J, Cao F, Lee RJ, Zhai G. Lyotropic liquid crystal systems in drug delivery. Drug Discovery Today 2010;15(23-24):1032-40.

22. Fontell K. Liquid crystals and plastic crystals. In: Gray GW, Winsor PA, editors. Liquid crystals and plastic crystals: physico-chemical properties and methods of investigation. Chichester: Ellis Horwood Publishers; 1974. p. 80-109.

23. Khoo IC. Liquid Crystals: Physical Properties and Nonlinear Optical Phenomena. New York: Wiley-Interscience; 1987. p. 214-85.

24. de Gennes PG, Prost J. The Physics of Liquid Crystals. Oxford, United Kingdom: Oxford University Press; 1993. p. 25-6, 175-9.

25. Gao M, Kim YK, Zhang C, Borshch V, Zhou S, Park HS, et al. Direct observation of liquid crystals using cryo-TEM: specimen preparation and low-dose imaging. Microsc Res Tech 2014;77(10):754-72.

26. Burylov, S. V., & Raikher, Y. L. (1994). Orientation of a solid particle embedded in a monodomain nematic liquid crystal. *Physical Review E*, *50*(1), 358.

27. Murgia S, Bonacchi S, Falchi AM, Lampis S, Lippolis V, Meli V, et al. Drug-loaded fluorescent cubosomes: versatile nanoparticles for potential theranostic applications. Langmuir 2013;29(22):6673-9.

28. Monteiro N, Martins A, Reis RL, Neves NM. Liposomes in tissue engineering and regenerative medicine. J R Soc Interface 2014;11(101):1-24.

29. Roux D, Nallet F, Diat O. Rheology of lyotropic lamellar phases. Europhys Lett 1993;15:53-8.

30. Bertelsen BM, Korsholm KS, Rose F, Nordly P, Franzyk H, Andersen P, et al. The supramolecular structure is decisive for the immunostimulatory properties of synthetic analogues of a mycobacterial lipid in vitro. RSC Adv 2013;3:20673-83.

31. Freag, M.S. et al. (2016) Layer-by-layer-coated lyotropic liquid crystalline nanoparticles for active tumor targeting of rapamycin. Nanomedicine 11, 2975–2996

32. Baskaran, R. et al. (2014) Entrapment of curcumin into monoolein-based liquid crystalline nanoparticle dispersion for enhancement of stability and anticancer activity. Int. J. Nanomedicine 9, 3119–3130

33. Madheswaran, T. et al. (2014) Enhanced topical delivery of finasteride using glyceryl monooleate-based liquid crystalline nanoparticles stabilized by Cremophor surfactants. AAPS PharmSciTech 15, 44–51

34. Liang, X. et al. (2017) HII mesophase as a drug delivery system for topical application of methyl salicylate. Eur. J. Pharm. Sci. 100, 155–162

35. Madheswaran, T. et al. (2017) In vitro and in vivo skin distribution of 5a-reductase inhibitors loaded into liquid crystalline nanoparticles. J. Pharm. Sci. 106, 3385–3394

36. Hoath, S. and Norle´n, L. (2005) Cubic phases and human skin: theory and practice. In Biocontinuous Liquid Crystals (Lynch, M.L. and Spicer, P.T., eds), pp. 41–57, Taylor & Francis

37. Dante, M. and de, C.L. et al. (2018) Liquid crystalline systems based on glyceryl monooleate and penetration enhancers for skin delivery of celecoxib: characterization, in vitro drug release, and in vivo studies. J. Pharm. Sci. 107, 870–878

38. Madheswaran, T. et al. (2013) Design and in vitro evaluation of finasteride-loaded liquid crystalline nanoparticles for topical delivery. AAPS PharmSciTech 14, 45–52

39. Merclin, N. et al. (2004) Transdermal delivery from a lipid sponge phase iontophoretic and passive transport in vitro of 5-aminolevulinic acid and its methyl ester. J. Control. Release 100, 191–198

40. Esposito, E. et al. (2018) Monoolein liquid crystalline phases for topical delivery of crocetin. Colloids Surf. B. Biointerfaces 171, 67–74

41. Chen, L. et al. (2013) Recent advances in predicting skin permeability of hydrophilic solutes. Adv. Drug Deliv. Rev 65, 295–305

42. Yu, X. et al. (2018) Transdermal cubic phases of metformin hydrochloride: in silico and in vitro studies of delivery mechanisms. Mol. Pharm. 15, 3121–3132

43. Thapa, R.K. et al. (2015) Multilayer-coated liquid crystalline nanoparticles for effective sorafenib delivery to hepatocellular carcinoma. ACS Appl. Mater. Interfaces 7, 20360–20368

44. Aleandri, S. et al. (2015) Biotinylated cubosomes: a versatile tool for active targeting and codelivery of paclitaxel and a fluorescein-based lipid dye. Langmuir 31, 12770–12776

45. He, S. et al. (2018) Lipid-based liquid crystalline nanoparticles facilitate cytosolic delivery of siRNA via structural transformation. Nano Lett. 18, 2411–2419

46. Agrawal, A.K. et al. (2017) Liquid crystalline nanoparticles': rationally designed vehicle to improve stability and therapeutic efficacy of insulin following oral administration. Mol. Pharm. 14, 1874–1882

47. Swarnakar, N.K. et al. (2014) Lyotropic liquid crystalline nanoparticles of CoQ10, implication of lipase digestibility on oral bioavailability, in vivo antioxidant activity, and in vitro–in vivo relationships. Mol. Pharm. 11, 1435–1449

48. Hong, L. et al. (2015) Understanding the mechanism of enzyme-induced formation of lyotropic liquid crystalline nanoparticles. Langmuir 31, 6933–6941

49. Meli, V. et al. (2017) Theranostic hexosomes for cancer treatments: an in vitro study. New J. Chem. 41, 1558–1565

50. Tajik-Ahmadabad, B. et al. (2017) A QCM-D and SAXS study of the interaction of functionalised lyotropic liquid crystalline lipid nanoparticles with siRNA. ChemBioChem 18, 921–930

51. Azmi, I.D.M. et al. (2016) A structurally diverse library of safe-by-design citremphospholipid lamellar and non-lamellar liquid crystalline nano-assemblies. J. Control. Release 239, 1–9

52. Bose, R.J. et al. (2018) Cell membrane-coated nanocarriers: the emerging targeted delivery system for cancer theranostics. Drug Discov Today 23, 891–899

53. Bose, R.J. et al. (2018) Bioengineered stem cell membrane functionalized nanocarriers for therapeutic targeting of severe hindlimb ischemia. Biomaterials XX, YYY–ZZZ

54. Bose, R.J. et al. (2018) Tumor cell-derived extracellular vesicle-coated nanocarriers: an efficient theranostic platform for the cancer-specific delivery of anti-miR-21 and imaging agents. ACS Nano XX, YYY–ZZZ

55. Madheswaran, T., Kandasamy, M., Bose, R. J., & Karuppagounder, V. (2019). Current potential and challenges in the advances of liquid crystalline nanoparticles as drug delivery systems. *Drug Discovery Today*, *24*(7), 1405-1412.