INTERNATIONAL JOURNAL OF
PHARMACEUTICAL AND HEALTHCARE INNOVATION
journal homepage: www.ijphi.com

## Review Article

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# Advances in Lyotropic Liquid Crystals: Structure, Preparation, and Drug Delivery Potential

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**Article Info**

Article history:

Manuscript ID:

**IJPHI1004190421042026**
**Received:** 10-APR-2025
**Revised** : 19-APR-2026
**Accepted**: 21-APR-2026
**Available online**: APR-2025
**DOI:**
***doi:10.62752/ ijphi.v3i2.244***

***Keywords:***
Lyotropic liquid crystals, drug delivery, nanotechnology, controlled release, stimuli-responsive systems.

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**Abstract**

*Nanostructured self-assembling materials known as lyotropic liquid crystals (LLCs) consist of amphiphilic molecules in a solvent and having a number of mesophases such as cubic, hexagonal, and lamellar phases. Since LLCs are concentration-dependent and not temperature-dependent as it is the case with thermotropic liquid crystals, they are heavily applied in drug delivery, nanotechnology, and the biological sciences. Their ability to entrap hydrophilic and hydrophobic molecules supports controlled and site-specific drug release, promoting therapeutic efficacy and bioavailability. Stimuli-sensitive LLC systems have been found promising as devices for transdermal delivery, ocular delivery of drugs, and cancer therapy due to their sensitivity towards pH changes, temperature changes, or mechanical stress. Characterization techniques such as polarized light microscopy (PLM) and small-angle X-ray scattering (SAXS) are often employed to determine phase structures in order to understand their structural properties and enhance their formulations. Dynamic light scattering (DLS) helps in assessing colloidal stability. The fundamental concepts, types, compositions, and preparation methods—such as top-down and bottom-up strategies—of LLCs are all discussed elaborately in this article. It also addresses new advances in biomedical applications, control release strategies, targeted drug delivery systems, and their application to drug delivery. In addition, several case studies related to LLC formulations laden with anti-tumor drugs and their therapeutic capability are discussed. Formulation developments in LLC form are capable of reshaping present day drug delivery procedures and enhance therapeutic outcomes in biomedical applications.*

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## Introduction

The existence of lyotropic liquid crystals (LLCs) predates the discovery of thermotropic by Reinitzer in 1888(1), which is generally considered to mark the start of liquid crystal research. Previous publications by Virchow(2), Mettenheimer(3), Planer(4), Losbisch(5), or Rayman(6) mentioned the liquid crystalline properties, but they did not explicitly state that this was a new kind of matter. In 1889, Lehmann(7), who was studying thermotropic phases, coined the term "liquid crystal." Reinitzer had contributed very significantly to the latter in 1888. Aside from its less immediately tangible practical potential, lyotropic liquid crystal work has been carried out, though quantitatively less successful than for the thermotropic systems. Lyotropics are appearing more and more frequently in liquid crystal laboratories(8). **L**yotropic liquid crystals are a special kind of material that, when a particular kind of substance—typically an amphiphilic chemical like soap lipid—is dissolved in a solvent like water, it forms orderly, fluid phases as shown in table 1. Lyotropic liquid crystals are created by changes in concentration as opposed to thermotropic ones, which react to temperature changes(9). When dissolved in a solvent, amphiphilic molecules self-assemble into a range of structures, such as micelles, bilayers, and other intricate configurations, due to their hydrophilic (which attracts water) and hydrophobic (which repels water) components(10). The organization of lyotropic liquid crystals depends on the concentration of these molecules in the solvent. At certain concentrations, these substances display ordered structures and long-range molecular alignment, producing phases that have properties of both liquids and solids. These phases come in lamellar, hexagonal, and cubic shapes and vary in their level of organization and fluidity(11). Lyotropic liquid crystals have a wide range of uses, including biological systems like lipid bilayer-based cell membranes and industrial applications in detergents, cosmetics, and drug delivery systems. Nanotechnology, biology, and materials science all profit from their unique ability to form ordered structures in a solvent (12). Lyotropic mesophases consist of two chemical components: the organic molecule and the solvent. Upon dissolution of the organic component through the solvent's simple dissolution with no chemical complication, a molecular solution that is dispersed and non-structured yet not liquid crystalline will form (figure 1). The simplest examples are molecules that are amphiphilic. A molecule can be made to selectively hydrate its hydrophilic moiety while avoiding its hydrophobic regions by adding a solvent, such as water. This "schizophrenic" interaction between the solvent and solute causes the molecules to self-assemble, which lowers the water exposure of hydrophobic moieties (10,13).

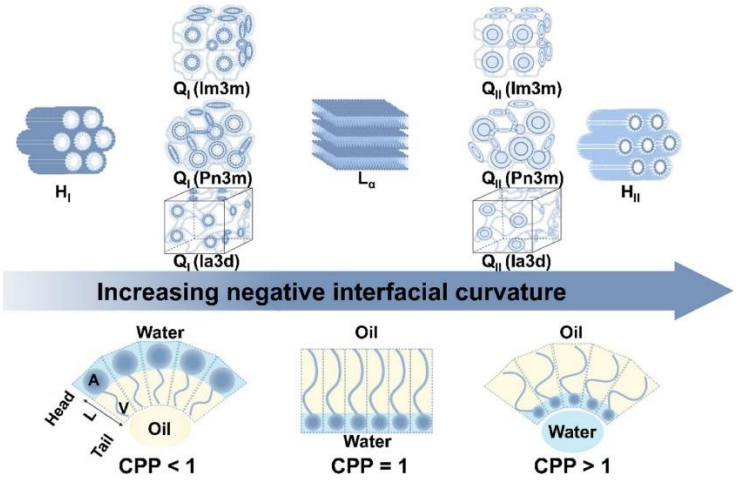


**Figure 1. The mesophases of lyotropic liquid crystals. Reproduced from Liu et al., 2025, under a Creative Commons (CC BY) license. Created with BioRender.com.The essential phenomenon that all liquid**

crystalline phases share is the existence of orientational order, at the very least (11). One important aspect of lyotropes is that they preserve the self-assembly of chemical moieties into multi-molecular domains, which decreases the miscibility of one species in the other from the mono molecular miscibility characteristic of a pure melt phase. This self-assembled mesostructure is often used to idealize the geometry and topology of the interface or interfaces separating immiscible domains. Despite the possibility that the interfaces themselves lack translational or orientational order, this perspective suggests that lyotropic liquid crystals are closely associated with micro emulsions and sponge mesophases (14).

**Phases of LLC**

LLCs are formulated using amphiphilic lipids (figure 2). These lipids play an important role in the formation of phases which depend on the interaction in aqueous media. There is total 3 phases of LLC in which they are divided. The hexagonal phase, as opposed to the micellar phase, is often produced at higher surfactant concentrations (15). Among the specific conditions that must be fulfilled are temperature and the presence of salts or other substances. The molecules arrange themselves into long, cylindrical aggregates and cluster in a hexagonal lattice. This arrangement maximizes hydrophilic interactions with water while reducing the amount of contact between hydrophobic tails and the aqueous environment. Some amphiphilic substances form a hexagonal phase of lyotropic liquid crystals when they react with water or another polar solvent(16). Because the amphiphile molecules group together to form cylindrical structures of unknown length, which are then organized on a hexagonal lattice, this phase displays long-range orientational order. In the cubic phase, surfactant molecules self-organize into a repeating cubic lattice. The usefulness of this arrangement depends on its capacity to encapsulate a significant volume of water or solvent within its structure. The structure of the cubic phase as a thermodynamically stable equilibrium system depends on an understanding of the equilibrium (17). For a very long time, a cubic phase may emerge and stay pseudo-stable at non-equilibrium temperatures. Additionally, the cubic phase is thought to be related to a variety of so-called "gel" materials that serve as the basis for various cream formulations, transdermal treatment systems, and topical medicines. Gyroid phase; characterized by an intricate web of interconnected surfactant molecules, is one of the most studied cubic phases. Its bicontinuous structure has two interpenetrating systems of hydrophilic and hydrophobic areas. The gyroid phase is an attractive material for photonic applications due to its high degree of structural order and periodicity at the visible light scale (18). This configuration can affect the material's diffusion, conductivity, and mechanical strength. The lamellar phase is often constituted of alternating layers of hydrophilic and hydrophobic regions and is typically composed of amphiphilic molecules. The presence of water or other solvents affects the lamellar phase's stability and properties. The balance between hydrophilic and hydrophobic surfaces drives the process of self-assembly. Lamellar structures may change in response to variations in hydration levels (figure 4). Dehydration-induced phase transitions can alter the stability and behavior of the lamellar phase(20). While polar head groups of lipids align together at the water contact, hydrophobic fatty acid acyl chains align parallel to one another in lamellar lipid bilayers, "hiding away" from the water. The lipid head groups are somewhat more "tightly" packed than the somewhat "fluid" hydrocarbon fatty acyl long chains. The lamellar lipid bilayer arrangement therefore exhibits a 'flexibility gradient' of increasing freedom of movements from near the head-groups towards the terminal fatty-acyl chain methyl groups(21). The existence of such a dynamic structure of the lamellar phase in both biological membranes and liposomes may be confirmed by investigations employing spin label electron paramagnetic resonance and high resolution nuclear magnetic resonance spectroscopy (15).

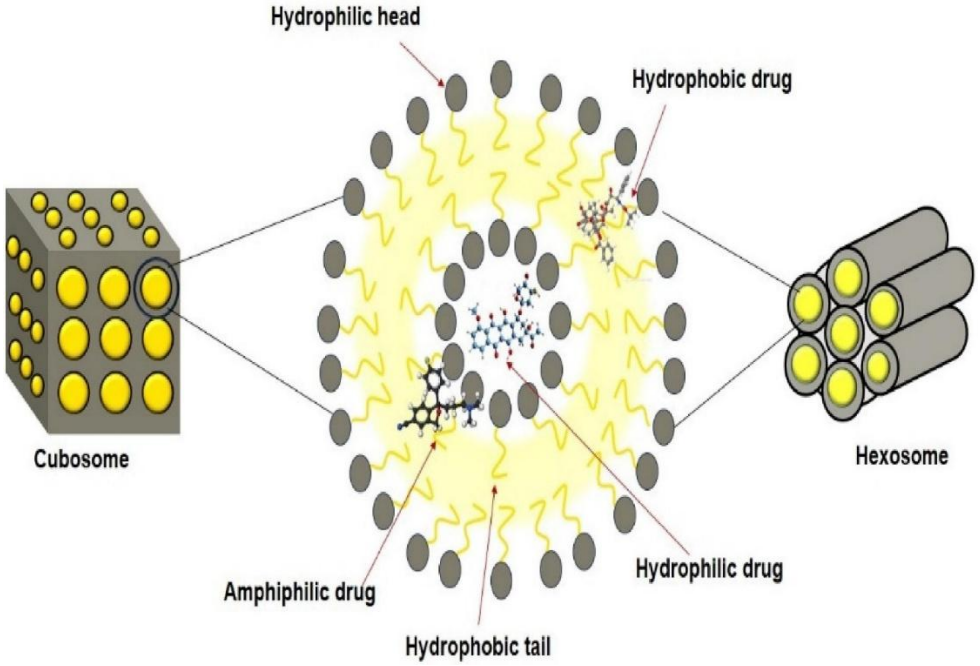


**Figure 2. Structural representation of cubosomes and hexosomes as potential carriers of hydrophobic, hydrophilic, and amphiphilic drug molecules. Adapted from Likhitha U., Nayak U.Y., Advances in tailored drug delivery systems: Amphiphilic lyotropic mesomorphs for targeted therapeutic intervention, Journal of Molecular Liquids (2024), under a Creative Commons CC BY-NC license**

**Table 1: Compositions of LLC**

| **Category** | **Subcategory** | **Description** | **Examples** |
|---|---|---|---|
| 1. Surfactants | (A) Ionic Surfactants | Surfactants with electrical charge. | |
| | (i) Cationic | Positively charged, interact with negatively charged species (proteins, cell membranes). | Benzalkonium chloride |
| | (ii) Anionic | Negatively charged, form micelles by reducing surface tension, encapsulate hydrophobic materials. | Sodium lauryl sulfonate |
| | (B) Nonionic Surfactant | No charge, stable in various pH and electrolyte concentrations. | Cocamide DEA, Triton X-100 |
| | (C) Zwitterionic Surfactants | Both positive and negative charges, stabilize liquid crystals without strong ionic interactions. | Cocoamido propyl betaine, Lauryl dimethylamine oxide |
| 2. Solvent | (i) Water | Primary solvent, essential for surfactant interaction, hydrogen bonding. | |

| | | | |
|---|---|---|---|
| | (ii) Organic Solvents | Modify hydrophilicity, viscosity, lower surface tension, and affect phase behavior and stability. | Ethanol, Isopropanol, Glycerol |
| 3. Co-surfactant | | Fine-tunes liquid crystal properties, helps stabilize phases by adjusting surfactant packing. | Butanol, Propanol, Glycerol monooleate |
| 4. Stabilizers & Thickeners | Stabilizers | Maintain LLC phase integrity, improve thermal and mechanical stability. | Polyvinyl alcohol (PVA), Gelatin |
| | Thickeners | Increase viscosity, affecting drug release rates. | Xanthan gum, Carrageenan |
| 5. pH Modifier | | Influence LLC phase behavior, stabilizing specific mesophases and improving solubility of active substances. | |
| | Acids | Lower pH, can stabilize specific phases. | Citric acid, Acetic acid |
| | Bases | Raise pH, can stabilize specific phases. | Sodium hydroxide, Triethanolamine |
| | Buffers | Maintain pH, prevent destabilization or phase separation. | Phosphate buffers, Citrate buffers |

**Method of preparation**

Mainly, there are two approaches which is used for the preparation of LLC. The first on is “Top-down approach” and the second one is “Bottom-up approach” (figure 3).

**Top-down approach**

The most popular method for establishing LLCNPs is this one. High-energy inputs like sonication or high-pressure homogenization (HPH) are used to create LLCNPs. Lipids and stabilizer are combined in the first step to produce the bulk viscous cubic phase. Dispersing a viscous bulk cubic phase into an aqueous phase requires a large energy input in the second step. Sonication and HPH are examples of high-energy input techniques. Temperature-sensitive medications cannot be used with this method because of its high energy consumption. Moreover, the intermediate phase of viscous bulk cubic phase gel makes the process challenging for scale-up (22).

**Bottom-up approach**

This method mixes amphiphilic lipids with hydrotrope. The energy input for this process is minimal. The 'hydrotrope' inclusion approach was created by Spicer et al. (2). According to the method, LLCs are created by mixing hydro trope with a liquid precursor that forms lipids and then adding it to water. Although hydrotrope is hydrophilic and hydrophobic, it does not function as a surfactant. As a hydrotrope, ethanol prevents the formation of a bulk viscous gel phase. Temperature-sensitive medications can be included while maintaining a stable formulation thanks to the use of low energy input techniques like vortex mixing.

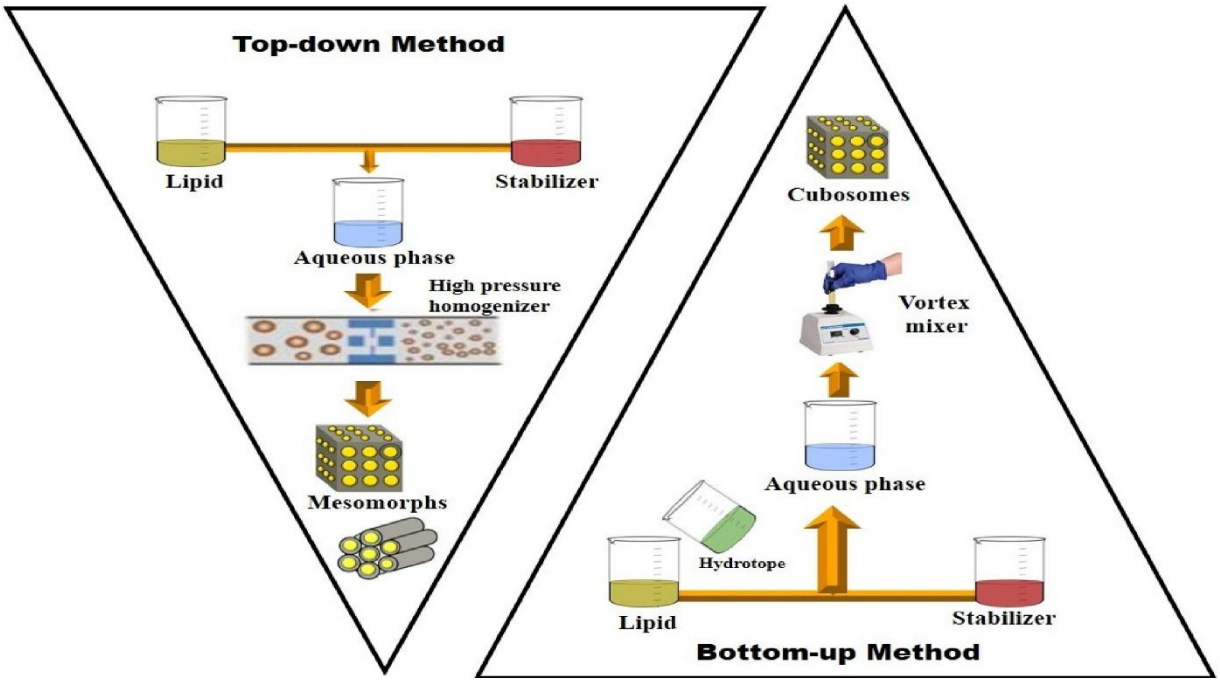


**Figure 3. Lyotropic mesomorph preparation, including top-down and bottom-up methodologies, is visually outlined. Reproduced from Likhitha U., Nayak U.Y., Advances in tailored drug delivery systems: Amphiphilic lyotropic mesomorphs for targeted therapeutic intervention, Journal of Molecular Liquids (2024), under a Creative Commons CC BY-NC license.**

**Shearing Technique**

Shearing is employed to avoid sample heating in addition to top-down and bottom-up methods (Table 2). The method produces quick and concentrated nano-dispersions by dispersing the bulk mesophase using a shearing mechanism based on Couette cells (23).

**Table 2: Methods used to prepare LLCs under various approaches**

| Method | Key Features | Advantages | Limitations | Approach Used |
|---|---|---|---|---|
| Hydration Method (24) | Simple mixing with water | Cost-effective, no organic solvent required | Slow, requires long hydration time | Bottom-Up |
| Solvent Evaporation (25) | Thin lipid film rehydrated | Stable LLC phases, good for hydrophobic drugs | Requires organic solvents, time-consuming | |
| High-Pressure Homogenization (HPH) (14) | High-pressure forces reduce particle size | Scalable, produces uniform LLC nanoparticles | High energy input, expensive equipment | Top-Down |
| Sonication Method (26) | Ultrasonic waves break down particles | Reduces particle size, improves stability | Potential drug degradation, not ideal for large-scale production | |

**Application of LLC**

**Enhanced Drug Delivery by encapsulation**

LLCs can be used to encapsulate hydrophobic drugs, greatly increasing their stability and solubility before to distribution (27). This encapsulation enables higher local concentrations of the medication at the tumor location, perhaps increasing therapy efficacy. Drugs that are hydrophobic or weakly soluble in water can be effectively captured by the LLC structure's hydrophobic regions. This interaction stabilizes the medication and prevents it from deteriorating or precipitating (27,28). Between the lipid bilayers of lamellar LLCs, drugs may intercalate. This arrangement allows for controlled release as the drug slowly permeates out of the layers. One of the main advantages of LLCs is the capacity to encapsulate hydrophobic and weakly soluble in water drugs, limiting their bioavailability and therapeutic potential (29). Integration into Hydrophobic Core: Hydrophobic drugs are incorporated into the hydrophobic core of the LLC, especially in the micellar or lipid bilayer structures. The drug molecules are physically trapped or dissolved by the hydrophobic tails of the amphiphilic surfactants, creating a stable system that improves the drug's solubility in water. In lamellar LLCs (layered structures), hydrophobic drugs can intercalate between the lipid bilayers. This means that the drug molecules are protected from degradation and may be delivered gradually between the layers of phospholipid or surfactant (27).

**Controlled release of drugs in lyotropic liquid crystals**

Maintaining therapeutic drug concentrations over an extended period of time with controlled release can improve efficacy and reduce peak-trough fluctuations associated with conventional dosing. Patients may benefit from less frequent dose schedules, which would increase compliance and therapeutic outcomes. Controlled release formulations may mitigate the negative effects associated with increased blood drug concentrations by localizing medicine release and minimizing systemic exposure (30,31). Below is further information on LLCs' controlled release mechanisms, with a focus on the key factors influencing drug release and how they may be built for optimal outcomes:

**Diffusion controlled release**

Diffusion is the most fundamental and common process behind the controlled release of drugs from LLCs. The drug travels from the LLC structure to the surrounding media, which is frequently biological fluids like blood, lymph, or tumor tissue, due to concentration gradients. Medication that is hydrophobic: In LLCs, the amphiphilic surfactant molecules encapsulate the hydrophobic medicine, which is mostly located within the LLC's hydrophobic core. When drugs come into contact with an aqueous environment, they begin to disperse via LLCs. This can occur via the surfactant layers in lamellar systems or the micelle core in micellar systems(32). Medication that is hydrophilic: Hydrophilic medicines can diffuse through aqueous channels or hydrophilic mesophase zones when encapsulated in LLCs, allowing for a gradual release of the drug (33). The rate of diffusion will depend on the drug's hydrophilicity and affinity for the surfactant's hydrophilic head groups.

**Temperature-Sensitive Release**

Temperature-sensitive release takes use of some LLCs' thermal reactivity. Because tumors have poor vascularization and elevated metabolic activity, their temperatures may be slightly higher than those of normal tissues (usually between 37 and 42°C). Drug release can also be triggered by hyperthermia, which is the deliberate raising of the tumor's temperature(34). Block copolymers that experience a phase transition at particular temperatures or temperature-sensitive surfactants can be used to create LLCs. For instance: When subjected to temperatures higher than the lower critical solution temperature (LCST), lipids or polymers with an LCST will change from a gel-like to a liquid state, resulting in the release of the medication. Temperature-dependent aggregation or disaggregation of thermosensitive hydrogels or

polymer chains can alter the structure of the LLC and speed up the release of the medication (35).

**Mechanical Stress/Shear-Stress Triggered Release**

Additionally, when mechanical factors like tumor compression or shear stress from blood flow occur, LLCs may release medications. LLCs may be subjected to mechanical forces from abnormal blood vessels and tissue stiffness, which are commonly observed in malignancies. If physical deformation or shear stress disturbs the LLC structure, especially if the LLC is in a soft or flexible phase, the encapsulated medication may be released(36). This is particularly crucial for LLCs in the cubic or hexagonal phases, where the fluid character of the mesophase may allow for deformation under stress. The mechanical properties of the tumor, such as increased stiffness and high interstitial fluid pressure, can be utilized to control the drug's release once the LLC has undergone such stress (37).

**Characterization Techniques**

**Visualization**

Visualization of lyotropic liquid crystals (LLCs) is critical for understanding their self-assembled nanostructures, phase behavior, and functional features. LLCs create highly organized mesophases such as lamellar, hexagonal, and cubic phases, which need sophisticated imaging methods for precise characterisation(43). Various approaches, including as polarized light microscopy (PLM), small-angle X-ray scattering (SAXS), cryogenic transmission electron microscopy (Cryo-TEM)**(38)** are routinely employed to examine the morphology, phase transitions, and molecular structure of LLC.

**Cryo-TEM**

A high-resolution imaging method called cryo-TEM is used to examine lyotropic liquid crystals (LLCs) in their naturally occurring hydrated condition. It retains LLC nanostructures without artifacts by quickly freezing materials, enabling the direct viewing of mesophases such as lamellar, hexagonal, and cubic(39). In pharmaceutical applications, this method is crucial for examining LLC shape, stability, and drug encapsulation.

**Small-Angle X-Ray Scattering (SAXS)**

SAXS is a powerful technique for examining the phase behavior and nanostructure of lyotropic liquid crystals (LLCs). It offers comprehensive information on lattice characteristics, molecular architecture, and mesophase symmetry(40). SAXS is crucial for describing LLC-based drug delivery systems and nanomaterials because it aids in the differentiation of lamellar, hexagonal, and cubic phases.

**Particle size and zeta potential**

Measuring the particle size of lyotropic liquid crystals is important to understand the stability, drug loading efficiency and biological interaction. The most common techniques for size measurement are Dynamic light Scattering (DLS) and to measure the zeta potential Zeta Sizer is used. It will give the information about the average size of LLCs and how they are distributed in the solution. It also measures the hydrodynamic radius (how big the particle appears in solution(41). If lyotropic liquid crystals are irregular or have a complex shape, DLS may show a broader size distribution or higher polydispersity index (PDI), meaning there's a range of sizes. The PDI gives an idea of how uniform the LLCs are in size. A low PDI means the LLCs are in similar in size, while a high PDI suggest more variation, possibly due to irregular shapes & The zeta potential of LLcs reflects the charge particle on their surface, which is critical for their stability, aggregation behaviour and interaction with surrounding media. A high (>30 mV) zeta potential (positive and negative) generally indicates that the particle is well dispersed and stable, preventing them from aggregating and moderate (10 – 30 mV) zeta potential that indicate slightly stable of LLCs. If the zeta potential (<10mv) indicates low stability and possible aggregation(42).

**Ex-Vivo Studies**

Drug release from the LLC formulation can be studied by using Franz diffusion cell(43-44)

**Entrapment efficiency and drug loading:**

Entrapment efficiency of LLCs means the percentage of drug or bioactive compound successfully encapsulated within the LLCs structure relative to the amount of drug initially added. It is an important

factor to determine the effectiveness of drug loaded LLCs drug delivery(45-54). Entrapment efficiency of LLCs is generally calculated using the following formula:

$$EE\% = \left(\frac{\text{Encapsulated Drug}}{\text{Total Drug Added}}\right) \times 100$$

The quantity of drugs that are successfully introduced into LLCs is referred to as drug loading. Depending on how the medication interacts with the LLC's structure, the lipid layers and water channels in LLCs aid in drug transportation and enable regulated release. The kind of molecules employed, the characteristics of the medicine, and the manufacturing process of the LLCs all affect how much drug may be loaded. Choosing the appropriate solvent system and balancing the drug-to-carrier ratio are crucial for achieving the optimal drug loading(55). The following formula is used to determine drug loading:

$$DL\% = \left(\frac{\text{Encapsulated Drug}}{\text{Total Carrier Weight} + \text{Encapsulated Drug}}\right) \times 1000$$

**Application**

Their unique structural properties enable them to function as excellent drug delivery vehicles, encapsulating and releasing therapeutic chemicals in a controlled way, hence improving bioavailability and targeting (10) (table 3 to table 8)

**Table 3: List of different application of LLCs**

| Application | Details |
|---|---|
| Drug delivery systems | (i) LLCs encapsulate both hydrophilic and hydrophobic drugs, improving stability, bioavailability, and controlled release.(28,29)<br>(ii) Functionalized LLCs enhance chemotherapeutic agent delivery (e.g., paclitaxel, doxorubicin) to tumor sites, reducing systemic side effects.(31)<br>(iii) Drug release can be controlled through structural modifications in LLCs, responding to environmental stimuli like pH or temperature.(30) |
| Cancer imaging | (i) LLCs carry imaging agents (e.g., fluorescent dyes, contrast agents) for enhanced tumor visualization in MRI, CT scans, and fluorescence imaging.(56)<br>(ii) Enables early tumor detection and monitoring of treatment response.(57) |
| Photodynamic therapy (PDT) | (i) LLCs encapsulate photosensitizers that generate reactive oxygen species (ROS) upon light activation, destroying cancer cells.(58)<br>(ii) Targeted delivery of photosensitizers minimizes damage to healthy tissues and improves PDT efficacy.(34,39) |
| Immunotherapy | (i) LLCs deliver immune-modulating agents (e.g., cancer vaccines, checkpoint inhibitors) to stimulate immune responses against tumors.(38,42)<br>(ii) Enhances immune therapy effectiveness while reducing systemic toxicity. |
| Gene therapy | (i) LLCs deliver nucleic acids (e.g., DNA, siRNA) for gene-editing technologies, correcting genetic mutations in tumors.(38)<br>(ii) Can activate tumor-suppressing genes or suppress oncogenes.(59) |

| | |
|---|---|
| Combination therapy | (i) LLCs enable the integration of multiple therapies (e.g., chemotherapy, PDT, immunotherapy) in a single platform, offering a synergistic effect for better cancer treatment.(29) |
| Biocompatibility and safety | (i) LLCs are made from biocompatible and biodegradable materials, reducing toxicity and minimizing side effects associated with conventional cancer treatments.(60) |

**Table 4: List of anti-cancer drugs loaded in LLCs**

| Sr no | Active ingredient | Type | Amphiphile | Cell line | Application |
|---|---|---|---|---|---|
| 1 | Doxorubicin hydrochloride (DOX), brucea javanica (BJO) | Cubic (pn3m) | Glycerol monooleate (MO) | MCF-7 | Dual-drug loaded novel ph-responsive llcs for human breast cancer.(61) |
| 2 | Doxorubicin (DOX) | Hexagonal to cubic | Pyridin-4-ylmethyl linoleate (PML), monolinolein (MLO) | HT29 | 3-fold increased tumor targeting delivery systems in human colon cancer.(62) |
| 3 | Apigenin (API) | LLC NPs | Glycerol monooleate GMO | B16F10 | Sustained release and better permeation profile in skin cancer.(63) |
| 4 | Seriniquinone (SQ) | Lamellar phase (PLP1) | Soy phosphatidylcholine (PC) | SKMEL28, SKMEL147 & SC5314. | Safe topical formulation for skin cancer and fungal infections.(64) |
| 5 | Gemcitabine and thymoquinone (gem-tq) | Hexosome | Glycerol monostearate (MYVR) | MCF10A | Multifunctional nanodelivery approach for breast cancer.(65) |
| 6 | Fluoxetine Hydrochloride | Hexosome | Glyceryl monooleate (GMO) | HepG2 | Twofold activity in hepatocellular carcinoma.(66) |
| 7 | Chlorin e6 and coenzyme QH | Cubosome and hexosome | 1-Monooleoylglycerol | Me45 | Co-encapsulation & strong photodynamic cytotoxicity against melanoma cells.(67) |
| 8 | 5-FCPal | Lamellar | Prodrug 5-FCPal | 4T1 | Sustained release of self-assembly amphiphile for breast cancer.(68) |
| 9 | Gefitinib | Cubosome | Glycerol monooleate GMO | RCN-9 | Orally Administered Gefitinib-Loaded |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | Cubosomes against Colon Cancer.(69) |
| 10 | Curcumin | Cubosome | 1-Monooleoyl-sn-glycerol & Dioleoyltrimethyl ammonium Propane (DOTAP) | HeLa | Topical mucoadhesive cubosomes for cervical cancer(70) |

**Table 5:Topical application of LLCs**

| Sr.no | Active ingredient | Formulation | Therapeutic use |
|---|---|---|---|
| 1 | Azelaic acid (AZA) | Gel | Antimicrobial activity on acne vulgaris.(71) |
| 2 | Amoxicillin trihydrate | Gel | Impetigo, folliculities infected wounds.(72) |
| 3 | Itraconazole | Cream | Superficial fungal infection of the skin.(73) |
| 4 | Cyclosporin-A | Gel | In Psoriasis treatment used.(74) |
| 5 | Alkaloidal extract from Tabernamontana divaricata | Coarse emulsion | Acetylcholine levels in Alzheimer's patient.(75) |
| 6 | Ascorbyl palmitate (Asc16) | Gel | Increase skin and mucosa permeability of drugs.(76) |
| 7 | Protoporphyrin | Nano-dispersion | Improve the skin penetration of photosensitizer & long-term stability.(58) |
| 8 | Triptolide | Gel | Used in treatment of psoriasis.(77) |
| 9 | Diclofenac | Gel | Used in treatment of pain and inflammation.(78) |
| 10 | Vitamin C | Emulsions of liquid crystalline structures | Protect against the degradation.(79) |

**Table 6: Application of LLCs to deliver biomolecules**

| Sr no | Material | Type | Route of administration | Delivery site |
|---|---|---|---|---|
| 1 | siRNA | Inverse hexagonal phase (HII) | Intramuscular | Cytoplasm.(80) |
| 2 | siRNA | Hexagonal phase (HII) | Topical | Epidermis.(81) |

| | | | | |
|---|---|---|---|---|
| 3 | siRNA | Bicontinuous cubic phase (pn3m and pm3n) | Intratumoral injection | Tumor tissue.(82) |
| 4 | Triptolide and siRNA | Reverse hexagonal mesostructure | Topical | Epidermis.(83) |
| 5 | mRNA | Inverse micellar to hexagonal to cubic mesophase | Intranasal | Lung alveolar macrophages.(84) |

**Table 7: Application of LLCs as ocular drug delivery system**

| Sr no | Active ingredient | Type | Material | Therapeutic use | Application |
|---|---|---|---|---|---|
| 1 | Pilocarpine nitrate (PN) | Bicontinuous cubic phase (pn3m) | Phytantriol (PHYT) | Glaucoma | Sustained drug release and enhanced bioavailability.(85) |
| 2 | Loteprednol etabonate (LE) | Bicontinuous cubic phase ($Q_2$) and hexagonal phase ($H_2$) | Glycerol monooleate (GMO) | Ocular inflammation | Prolongs precorneal residence time.(86) |
| 3 | Coumarin C6 | Lamellar phase (lα) & hexagonal phase (H1) | Sodium dodecyl sulfate (SDS) | Ophthalmic drug delivery | Photodynamic therapy.(87) |
| 4 | Vancomycin hydrochloride (VCHL) | Reversed hexagonal ($H_2$) and reversed cubic ($Q_2$) | Glycerol monooleate (GMO) | Endophthalmitis | Sustained drug release and enhanced bioavailability.(88) |
| 5 | Brinzolamide (BLZ) | Reverse hexagonal phase ($H_2$) | Glycerol monooleate (GMO) | Glaucoma | Reduces ocular irritation and improved corneal permeability.(89) |
| 6 | Tropicamide | Cubosomes | Glycerol monooleate (GMO) | Mydriasis | Reducing dosing frequency & enhanced bioavailability.(90) |
| 7 | Gemifloxacin mesylate | Nanocubosome | Glycerol monooleate (GMO) | Keratitis | Improved its bioavailability and residence time.(91) |

**Table 8: Application of LLCs for oral drug delivery**

| Sr no | Active ingredient | Type | Material | Designed for | Outcome |
|---|---|---|---|---|---|
| 1 | Cromolyn sodium | Cubosomes | Monoolein | Asthma, allergic rhinitis | Reducing dosing frequency & enhanced bioavailability.(92) |
| 2 | Triamcinolone acetonide (TA) | Reverse hexagonal | Mono-o-(5,9,13-trimethyl-4-tetradecenyl)glycerol ester (MGE) | Aphthous stomatitis | A spray formulation for direct application enhancing drug release and mucosal permeability.(93) |
| 4 | P-amino benzoic acid (PABA), methyl-PABA, ethyl-PABA, sodium fluorescein | Inverted hexagonal phase ($H_2$) | C17-monoglycerol ester (MGE) | Oral drug delivery | Improve oral absorption and transdermal penetration of drugs.(94) |
| 5 | Coenzyme Q10 (CoQ10) | Hexagonal phase ($H_{II}$) | Glyceryl monooleate (GMO), Phytantriol (PHY) | Target oxidative stress in cardiovascular diseases. | Enhanced bioavailability and therapeutic efficacy.(95) |
| 6 | Piperine | Cubosomes | Glycerol monooleate (GMO) | Alzheimer | Sustained release, restored cognitive function.(96) |
| 7 | Cefpodoxime proxetil (CFP) | Cubosomes | Phytantriol | Bacterial infections | Improved encapsulation, sustained release, taste masking and colloidal stability.(97) |

## Conclusion

Lyotropic liquid crystals (LLCs) are a diverse group of self-assembled nanostructured materials with great promise in drug delivery, biomedical fields, and nanotechnology. Their capacity to self-assemble into highly ordered mesophases—lamellar, hexagonal, and cubic structures—allows for precise control of drug encapsulation, release, and targeting. The distinctive physicochemical characteristics of LLCs enable enhanced solubility, long-term drug release, and sensitivity to environmental stimuli like pH, temperature, and mechanical stress, making them excellent candidates for next-generation therapeutic uses. Multiple preparation techniques, such as top-down and bottom-up strategies, enable the formulation of stable and effective LLC formulations designed for targeted medical requirements. Recent developments in LLC studies have made way for the creation of novel drug delivery systems for cancer

treatment, ophthalmic therapy, and transdermal formulations that exhibit promise for improving bioavailability and therapeutic effects. Incorporation of LLCs into contemporary pharmaceutical and biomedical platforms continues to propel advancements in targeted and controlled drug delivery. Future work must aim to streamline formulation stability, scalability, and biocompatibility to facilitate clinical translation and realize new horizons in personalized medicine.

## Future Outlook

The future for lyotropic liquid crystals (LLCs) in biomedical and pharmaceutical applications is very promising, with research continuing to address improving their stability, scalability, and biocompatibility for clinical usage. Nanotechnology and materials science are anticipated to further improve LLC formulations by adding stimuli-responsive materials for targeted drug release based on pH, temperature, or biological enzymes. Advancements in multifunctional LLC systems that can co-deliver various therapeutic agents, including chemotherapeutics, gene therapy molecules, and immunomodulators, will further extend their use in personalized medicine. Moreover, combination of LLCs with new technologies such as AI-based drug formulation design and 3D bioprinting may speed their translation into commercially available pharmaceuticals. Future studies should also tackle issues of large-scale production, long-term stability, and in vivo biocompatibility to facilitate regulatory approval and broad clinical acceptance. With ongoing progress, LLCs can potentially transform targeted drug delivery, regenerative medicine, and biomedical imaging, providing novel solutions for challenging therapeutic problems.

## ACKNOWLEDGEMENT

The author's expresses his gratitude toward Parul Institute of Pharmacy & Research, Parul University, Waghodia, Vadodara, Gujarat for providing research environment and all necessary facility for conducting research.

## Informed Consent

Not Applicable.

## FUNDING

No funding was received for conducting this study.

## Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. The authors declare no conflict of interest among themselves. The authors alone are responsible for the content and writing of this article.

## Financial Interests

The authors declare they have no financial interests.

## Human and Animal Rights

NA

## Ethics approval and consent to participate

Not applicable.

## Authors Contributions

JS has written the manuscript, PG made the paper according to journal instruction and MS and AS has prepared table and SM figure, and AS has formatted and removed typological error from manuscript.

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