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EDITED BY
Alejandro D. Rey,
McGill University, Canada

REVIEWED BY
Linda Reven,
McGill University, Canada
Dana Grecov,
University of British Columbia, Canada

*CORRESPONDENCE
Sulekha Khute,
sulekhakhunte@gmail.com

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Recent advances in lyotropic liquid crystal nanoparticle formulations for drug delivery systems

Paranthaman Subash and Sulekha Khute *

Department of Pharmacy, Sri Shanmugha College of Pharmacy, Sankari, Salem, Tamil Nadu, India

Lyotropic liquid crystalline (LLC) nanoparticles have gained significant attention as drug delivery systems owing to their unique self-assembly properties, biocompatibility, and ability to encapsulate both hydrophilic and hydrophobic drugs. This chapter explores recent advances in LLC formulations, focusing on their structural classification, physicochemical properties, and applications in controlled-drug delivery. Various mesophases, including lamellar, cubic, and hexagonal structures, have been discussed, highlighting their roles in controlled release. A comparative analysis reveals that cubic phases offer superior structural stability for sustained release, while hexagonal phases excel in high-viscosity applications, though their complex preparation limits scalability. In addition, key characterization techniques such as small-angle X-ray scattering, differential scanning calorimetry, and rheology are examined to offer insights into their stability and performance. Furthermore, the development of *in situ* gelling precursor systems and their applications in oral, transdermal, ocular, nasal, injectable, and periodontal drug delivery have been explored. The incorporation of stimuli-responsive materials into LLC systems enhances their adaptability to personalized medicine and advanced therapeutic strategies. Despite these advancements, challenges such as scalability, long-term stability, and clinical translation remain unresolved. This chapter highlights the potential of LLC nanoparticles to revolutionize modern drug delivery by improving bioavailability, therapeutic efficacy and patient compliance. Future research should focus on optimizing formulation strategies and exploring novel biomaterials to expand the clinical utility of LLC-based drug delivery systems.

KEYWORDS

bioavailability, drug delivery system, lyotropic liquid crystals, liquid crystalline phase, nanoparticle

1 Introduction

LLCs, or lyotropic liquid crystals, exhibit highly ordered internal structures and self-assemble into lamellar, hexagonal, and cubic phases. These structures are ideal for drug delivery because they can encapsulate and release substances of various sizes and polarities. The specific LLC phase influences the properties of the encapsulated drug, allowing for customized release profiles, such as sustained or targeted delivery (Baldha et al., 2025). Lyotropic liquid crystals are increasingly being recognized for their potential in advanced drug delivery systems. These materials are excellent carriers due to their unique properties, which include stimuli-responsive drug delivery and sustained release patterns. They can respond to environmental changes such as temperature or pH, ensuring that drugs are

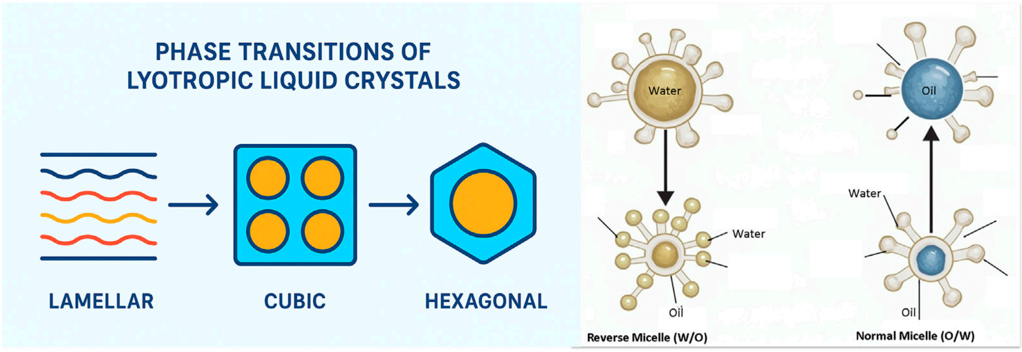

FIGURE 1
Schematic showing phase transitions of lyotropic liquid crystals from lamellar to cubic and hexagonal structures.

delivered precisely where and when they are needed. This adaptability not only improves the efficiency of drug delivery but also enhances patient outcomes by reducing side effects and improving the therapeutic index of drugs. As research progresses, lyotropic liquid crystals are poised to revolutionize how medications are administered, offering a promising future in personalized medicine (Baldha et al., 2025; Govindan et al., 2024). LLC structures, abundant in biological systems like cellular membranes, enable innovative drug delivery applications due to their biocompatibility and structural versatility (Behera et al., 2024).

These systems respond to environmental stimuli (e.g., pH, temperature, light, ultrasound, electromagnetic fields, concentration gradients), enabling controlled drug release tailored to specific conditions (Zhao et al., 2022). For instance, cubic phases provide a tortuous diffusion pathway, enabling prolonged release compared to lamellar phases, which are less viscous and facilitate faster drug release. This method opens new possibilities for modifying the pharmacokinetic profiles of drugs and potentially improving their efficacy and safety. The ability to control drug release is particularly beneficial in treating diseases for which controlled dosing is crucial. The durability of active ingredients when encapsulated forms a strong foundation for drug delivery systems (Rahman et al., 2020). The sol-gel strategy allows precise control over the microstructure of LLC systems, enabling the design of tailored carriers that respond dynamically to environmental changes. This adaptability is critical for the development of smart delivery systems that can release drugs in a controlled manner, improve their therapeutic efficacy, and minimize side effects. However, the high viscosity of cubic and hexagonal phases can complicate administration, posing challenges for patient-friendly delivery methods. Ongoing research in this field is promising for the advancement of personalized medicine, in which treatments can be fine-tuned to individual patient needs, optimizing outcomes, and enhancing patient compliance (AbuAlrob et al., 2025; Shukla and Kumar, 2025).

The amphiphilic nature of polar lipids plays a crucial role in their ability to self-assemble into unique structures that exhibit polymorphism owing to their interactions with water molecules. Amphiphilic molecules have both hydrophilic (water-attracting) and hydrophobic (water-repelling) components, allowing them to arrange themselves in ways that minimize energy, usually by forming distinct phases (Manna et al., 2024). When exposed to water, these lipids can be organized into various liquid crystalline phases, each with distinct structural characteristics. The main types of lipid polymorphisms include the lamellar phase, where lipids form bilayer sheets; the cubic phase, characterized by a complex three-dimensional network; and the hexagonal phase, where lipids are arranged into cylindrical structures. These phases are significant in fields such as drug delivery and nanotechnology because they offer diverse properties and functionalities based on their structure (Sahu et al., 2021). Different phase types offer unique advantages: lamellar phases are simple to produce but lack durability, cubic phases provide excellent encapsulation but require complex characterization, and hexagonal phases have high viscosity but are challenging to scale up. Figure 1 illustrates the phase transitions of lyotropic liquid crystalline systems, depicting the structural evolution from lamellar to unorganized and bicontinuous phases as a function of surfactant concentration and solvent conditions. This schematic highlights the dynamic interplay between molecular organization and environmental factors, supporting the design of tailored drug delivery systems.

1.1 Classification of liquid crystalline phases

LLCs are categorized based on the specific arrangement and behavior of amphiphilic molecules within a solvent. Figure 2 provides a schematic representation of lyotropic liquid crystalline phases, including nematic, smectic, and columnar arrangements, illustrating their molecular orientations and structural order. This figure aids in understanding the structural diversity of LLCs for drug delivery applications (Blanco-Fernández et al., 2023). The primary categories include nematic, smectic, and columnar phases. Nematic LLCs are characterized by molecules oriented parallel to each other, allowing fluidity similar to that of conventional liquids (Blanco-Fernández et al., 2023). Smectic LLCs, on the other hand, exhibit a more ordered structure in which molecules form distinct layers, each maintaining a degree of fluidity. Columnar LLCs arrange amphiphilic molecules into cylindrical structures often forming hexagonal lattices. These

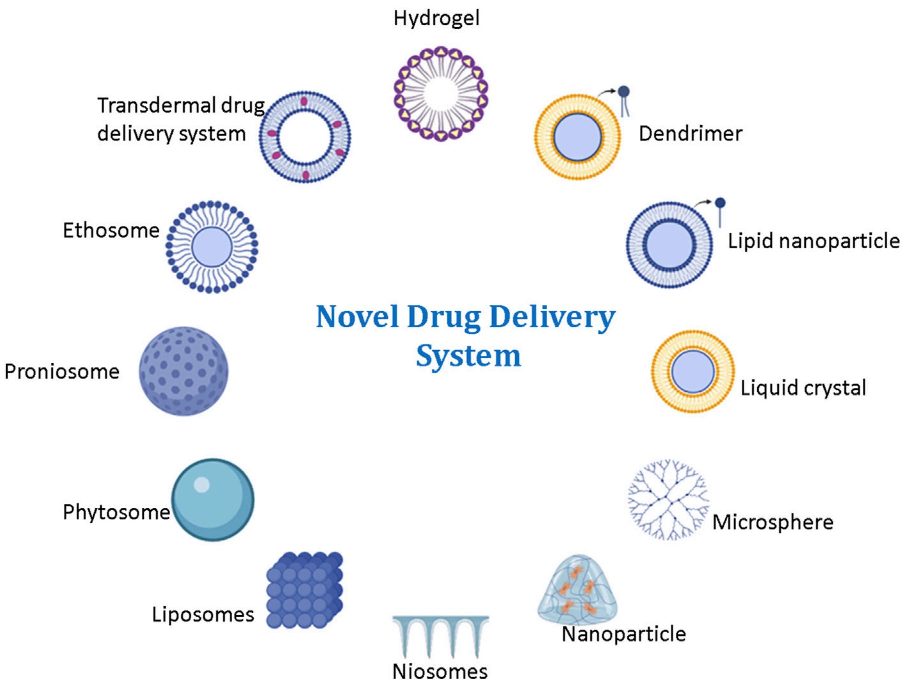

FIGURE 2
Illustration of nematic, smectic, and columnar lyotropic phases based on molecular orientation and order.

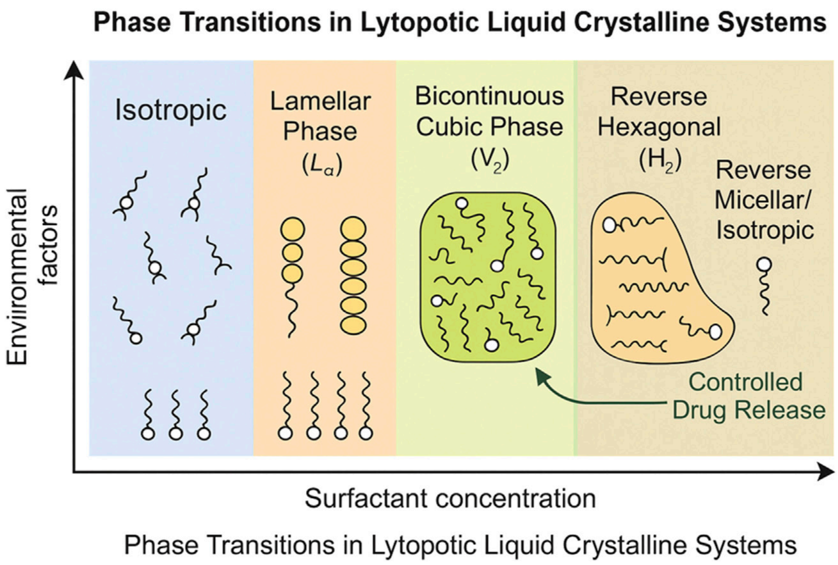

FIGURE 3
Comparison of nanoscale drug delivery systems including liposomes, niosomes, nanocapsules, and cubosomes.

phases are influenced by the concentration of amphiphilic molecules and nature of the solvent, which can lead to diverse applications in fields such as drug delivery, biosensors, and advanced materials. Compared to nematic phases, smectic and columnar phases (Figure 3) illustrates the structural differences between smectic and columnar phases, highlighting their layered and cylindrical organizations, respectively, which contribute to their suitability for controlled drug release offer greater structural order, making them more suitable for controlled drug release, though their higher viscosity can limit injectability.

Emerging advanced techniques in drug delivery include surface modification with various ligands to enhance targeting, stimuli-responsive LLCs for on-demand drug release, and combination therapies using multifunctional LLCs for synergistic effects. These innovations aim to improve targeted and site-specific drug delivery, increasing therapeutic efficacy and minimizing side effects (Priya

TABLE 1 Overview of various lyotropic liquid crystal nanoparticle formulations used in drug delivery.

Lyotropic liquid crystal nanoparticle formulation	Components	Uses	Reference
Cubosomes	Glyceryl monooleate, phytantriol	Delivery of poorly soluble therapeutics, controlled drug release	Nath et al. (2024)
Hexosomes	Glycerol dioleate, oleyl glycerate	Drug encapsulation and targeted delivery	Tan et al. (2022)
Micellar cubosomes	Various surfactants	Aqueous dispersions for effective drug delivery	Yap et al. (2024)
Emulsified microemulsions	Lipid-based components	Delivery systems with enhanced bioavailability	Lin et al. (2024)
Lyotropic liquid crystalline Gels	Surfactants and oils	Injectable drug delivery systems, *in-situ* gel formation upon hydration	Vitek et al. (2025)
Liquid crystalline nanoparticulate systems (LCNP)	Amphiphilic lipids	Long-lasting release profiles for therapeutic agents (e.g., CAM 2029)	Leu et al. (2023)

TABLE 2 Comparison of lamellar, cubic, and hexagonal lyotropic liquid crystalline phases for drug delivery applications.

Phase type	Structural features & suitability	Drug types/ Routes	Performance characteristics	Selection rationale & citations
Lamellar	Layered, membrane-like; mimics skin lipids	Transdermal, topical	Low viscosity, fast release, easy processing	Enhances skin hydration and compatibility with stratum corneum; suitable for topical hydration therapies Chavda et al. (2023), Rajabalaya et al. (2017), Kim et al. (2023)
Cubic	3D bicontinuous structure with large water channels	Injectable, ocular, oral	High viscosity, high drug loading, sustained release	Suitable for hydrophilic and amphiphilic drugs; excellent encapsulation and prolonged release Chavda et al. (2023), Leu et al. (2023) (Nazaruk et al., 2015; Shah et al., 2001; Phan et al., 2015)
Hexagonal (HII)	Cylindrical water channels, densely packed	Depot, injectable	Very high viscosity, slow release	Ideal for lipophilic drugs requiring prolonged retention; used in depot formulations Chavda et al. (2023); Boyd et al. (2006) (Phan et al., 2015; Otte et al., 2017)

et al., 2024). Table 1 presents the different types of lyotropic liquid crystalline nanoparticles, along with their key components and primary applications in drug delivery. Each formulation was categorized based on its structural composition, including cubosomes, hexosomes, micellar cubosomes, emulsified microemulsions, LLC gels, and liquid crystalline nanoparticles (LCNPs). The components listed for each formulation included lipids, surfactants, and other amphiphilic molecules, which facilitated the self-assembly of these nanostructures. These applications highlight their role in encapsulating poorly soluble therapeutics, enhancing bioavailability, enabling controlled drug release, and providing targeted delivery. Cubosomes, for instance, excel in encapsulating hydrophobic drugs due to their bicontinuous structure, but their complex preparation limits large-scale production compared to simpler micellar systems.

The choice of the LLC phase is determined by a combination of the physicochemical properties of the drug (e.g., solubility, stability, and molecular size) and its therapeutic application. For instance, lamellar phases are preferred for transdermal and skin hydration therapies because of their structural resemblance to stratum corneum lipids. Cubic phases, with their large water channels and tortuous paths, are suited for the sustained delivery of hydrophilic drugs via ocular and injectable routes. Hexagonal phases, particularly H2, are ideal for depot formulations or lipophilic drugs in which prolonged retention is desired. Comparison of lamellar, cubic, and hexagonal lyotropic liquid crystalline phases for drug delivery applications illustrated in Table 2. Moreover, the disease condition (e.g., chronic vs acute), desired release kinetics, and administration route should inform the formulation strategy. Employing computational modeling and phase diagrams helps predict phase behavior, thereby improving formulation efficiency and targeting precision.

1.1.1 The lamellar liquid crystalline phase

The lamellar phase is an intriguing structural arrangement of lipid bilayers characterized by one-dimensional layering with interspersed water layers. This unique organization allows the bilayers to slide past each other in a manner restricted to right angles relative to the plane of the layers, contributing to its lower viscosity compared to other mesophases, such as hexagonal and cubic (Gu et al., 2023). Within the lamellar phase, further classification is based on the degree of molecular ordering, resulting in three distinct subclasses: fluid lamellar (Lα), lamellar gel (Lβ), and crystalline lamellar (Lc) phases. The Lα phase is the least ordered, with melted and fluid-like alkyl chains, offering flexibility within the bilayer structure. In contrast, the Lβ phase is more ordered, resembling a gel-like state, whereas the Lc phase is highly structured, akin to a crystalline arrangement. Each phase exhibits unique properties and behaviors that are influenced by molecular interactions and thermal conditions (Kuwabara et al., 2024). The Lα phase's fluidity makes it ideal for transdermal delivery, but its lower stability compared to cubic phases limits

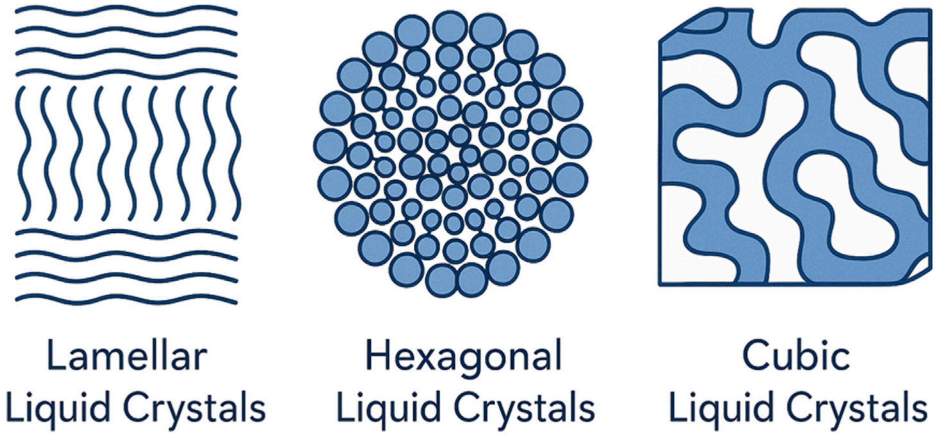

FIGURE 4
Structural arrangement of Lα, Lβ, and Lc lamellar phases highlighting differences in molecular ordering.

its use in sustained-release applications. Figure 4 depicts the structural organization of lamellar liquid crystalline phases, illustrating the bilayer arrangements of Lα, Lβ, and Lc subclasses. This figure emphasizes the varying degrees of molecular ordering and their implications for drug delivery, particularly in transdermal applications.

1.1.2 The cubic liquid crystalline phase

Cubic liquid crystalline phases captivate researchers due to their sophisticated molecular structures, which are classified into bicontinuous and micellar types. These phases are characterized by unique symmetrical space groups such as Ia3d (Q230) and Pn3m (Q224). Cubic phase structures are particularly notable for their curved three-dimensional lipid bilayers interspersed with water channels, which contribute to their distinct properties (Sparavigna, 2023). The elastic energy of the curvature of these bilayers plays a critical role in the stability of cubic phases, which is influenced by the composition of the system. Owing to the absence of shear planes, these structures exhibited sticky and viscous behavior. The cubic phases can be further classified into three mesomorphic structures: Schwartz double diamond lattice (D, Pn3m, Q224), Schwartz primitive cubic phase (P, Im3m, Q229), and Schoen gyroid lattice (G, Ia3d, Q230). The capacity and size of the water channels increase from the G to D to the P phase, with the diameters of these structures ranging from 4 to 20 nm, allowing them to effectively incorporate water-soluble molecules (Rani et al., 2024). The bicontinuous cubic phase's large water channels enable high drug-loading capacity, but its high viscosity complicates processing and administration compared to lamellar phases.

This elaborate configuration serves as a striking example of the detailed geometry commonly seen in liquid crystalline structures. In the Im3m configuration, the orthogonal network of water channels is notable for its symmetry and effectiveness in linking the unit cells, resulting in a strong and stable cubic structure. The P-minimal surface acted as a partition, adding to the structural integrity and unique characteristics of the network. Conversely, the bilayer configuration of the D structure permits the formation of a diamond lattice, which is distinctive for its tetrahedral angle of 109.5°, enhancing its three-dimensional connectivity (Priya et al., 2024). The G-surface, with its left- and right-handed helically positioned channels, adds another layer of complexity, demonstrating the diversity of the possible arrangements within these systems. Such structural intricacies have significant implications in fields such as materials science and biochemistry, where understanding the spatial organization of molecules can lead to advances in technology and medicine (Král et al., 2024).

1.1.3 The hexagonal liquid crystalline phase

The hexagonal mesophase represents a captivating structural pattern that arises from the self-assembly process of surfactant molecules. In this phase, surfactants are organized into a hexagonally packed structure, creating long-range order in two dimensions. This mesophase can manifest in two distinct forms: the normal hexagonal phase (H1) and the reverse or inverted hexagonal phase (H2) (Smaisim et al., 2023). In the H1 phase, the hydrophobic tails of the surfactant molecules form an inner core with the polar head groups oriented outward, thus creating continuous water layers. Conversely, in the H2 phase, the core was composed of hydrophilic polar head groups with alkyl chains forming a continuous network. The viscosity of these hexagonal structures is especially higher than that of the lamellar phase. The H2 phase's high viscosity makes it suitable for depot formulations, but its complex self-assembly process hinders scalability compared to simpler lamellar systems. Recently, a novel lyotropic liquid crystalline phase was discovered, exhibiting a three-dimensional hexagonal close-packed arrangement of inverse micelles, identified with space-group symmetry (P63/mmc). This discovery opens new avenues for exploring the dynamic properties and potential applications of these mesophases (Uranga Wassermann et al., 2024; Pal et al., 2023). Figure 5 illustrates the structural organization of hexagonal liquid crystalline phases, depicting the normal (H1) and reverse (H2) hexagonal arrangements, along with their cross-sectional views. This figure highlights the molecular packing and high viscosity of hexagonal phases, supporting their application in depot drug delivery systems (Pal et al., 2023; Smaisim et al., 2023).

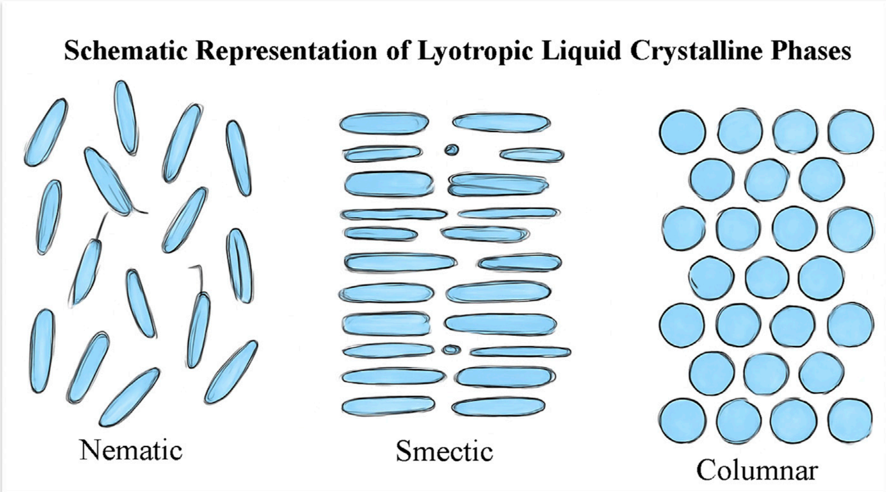

FIGURE 5
Representation of normal (H_1) and reverse (H_2) hexagonal phases showing cylindrical packing of surfactants.

1.2 Composition of lyotropic liquid crystalline gelling system

LLC gels are captivating materials that form through the combination of water, surfactants, and oils, resulting in the self-organization into structured phases. The surfactants in these gels are amphiphilic, indicating that they have both hydrophilic (water-attracting) and lipophilic (oil-attracting) properties (Karakasidis et al., 2025). This dual nature is crucial for the formation of various structures at different concentrations. Initially, at low concentrations, the surfactants formed micelles and spherical aggregates that stabilized the solution. As the concentration increases, these micelles transform into more complex structures, such as cylindrical or plate-like aggregates, leading to the formation of diverse mesophases such as cubic, hexagonal, and lamellar phases. The formation of these phases is significantly influenced by factors such as the surfactant concentration, temperature, and specific molecular structure of the surfactants used (Aguirre-Ramírez et al., 2021). Commonly studied amphiphilic materials include glycerol monooleate and phytantriol, which have shown great potential for the formation of stable and versatile liquid crystalline gels. Glycerol monooleate-based gels offer excellent biocompatibility but are prone to oxidation, whereas phytantriol provides greater chemical stability but is less flexible in phase transitions (Milak and Zimmer, 2015). Phase diagrams are often used to understand and predict the behavior and structure of these systems, offering insights into their practical applications in various fields such as drug delivery and materials science (Kumar et al., 2021).

1.3 Methods for preparation of liquid crystalline gels

Liquid crystalline gels represent an innovative approach to drug delivery systems, leveraging their unique structural properties for enhanced stability and controlled release. The preparation of these gels is straightforward and energy-efficient, involving the combination of aqueous and lipid phases through vortexing or ultrasonication. Their thermodynamic stability ensures longevity without phase separation, making them ideal for long-term storage (Jacob et al., 2024). The process begins with the integration of the drug into the appropriate phase: hydrophobic drugs are mixed with surfactants before dissolving in water, whereas hydrophilic drugs are first dissolved in the aqueous phase. After centrifugation to remove excess water, the mixture was allowed to reach equilibrium by using either a tube roller or standing alone. This careful preparation process creates a strong medium that is ideal for the efficient delivery of various pharmaceutical compounds (Islam et al., 2024). While vortexing is cost-effective, ultrasonication provides more uniform particle sizes, though both methods struggle with scaling up for industrial production.

1.3.1 Characterization of liquid crystalline gels

Characterization of LLC gels is critical for elucidating their structural, thermal, and mechanical properties, which govern their efficacy in drug delivery systems. This section categorizes key characterization techniques into three groups: Microscopic Methods, Spectroscopic Techniques, and Rheological Analyses. These methods offer complementary insights into phase behavior, stability, and functionality, facilitating the optimization of LLC gels for pharmaceutical applications.

1.3.1.1 Microscopic methods

1.3.1.1.1 Small-angle X-Ray scattering (SAXS). Small-angle X-ray scattering (SAXS) is a precise technique for determining the three-dimensional structure and long-range order of LLC phases. By analyzing X-ray diffraction patterns, SAXS reveals the symmetry, lattice parameters, and spatial arrangement of lipid molecules, including hydrocarbon chain spacing and lipid layer thickness. The small-angle region provides data on phase symmetry, while the wide-angle region details molecular packing. Despite its high precision, SAXS requires specialized equipment, limiting accessibility compared to rheology (Masime et al., 2025; Lu et al., 2025).

1.3.1.1.2 Freeze-fracture electron microscopy (FFEM). Freeze-fracture electron microscopy (FFEM) visualizes the nanoscale morphology and self-assembly of LLC gels, capturing high-resolution images of coexisting phases, such as vesicular and micellar structures. Combined with rheological data, FFEM enhances understanding of mechanical properties and phase stability. However, FFEM is labor-intensive and less quantitative than SAXS (Dombrowski et al., 2024).

1.3.1.2 Spectroscopic techniques

1.3.1.2.1 Differential scanning calorimetry (DSC). Differential scanning calorimetry (DSC) measures heat flow during phase transitions, providing insights into the thermal stability and behavior of LLC gels. It identifies transitions between lamellar, cubic, or hexagonal phases and characterizes water molecule interactions within surfactant aggregates. DSC is cost-effective and widely available but less sensitive to microstructural changes than SAXS (Abdulnaby et al., 2024).

1.3.1.2.2 Nuclear magnetic resonance spectroscopy (NMR). Nuclear magnetic resonance (NMR) provides detailed molecular insights into LLC phase structures by analyzing nuclear responses to magnetic fields. NMR diffusion measurements assess polar and apolar domain stability, while Raman spectroscopy probes vibrational modes to study phase transitions. These techniques offer comprehensive data but are time-consuming and costly compared to DSC (Li et al., 2022).

1.3.1.2.3 Low frequency dielectric spectroscopy. Dielectric spectroscopy examines dielectric properties of LLC gels using an oscillating electric field (10^{-3}–10^{6} Hz), identifying mesophases and drug-mesophase interactions. It provides insights into molecular dynamics but requires complex data interpretation compared to DSC [41, 42].

1.3.1.3 Rheological analyses

1.3.1.3.1 Rheology. Rheological measurements characterize the viscoelastic properties of LLC gels, influencing drug diffusion and release. Bicontinuous cubic phases exhibit rigidity, reversed hexagonal phases show moderate viscoelasticity, and lamellar phases display plasticity with a defined yield value. Parameters like storage modulus (G') and loss modulus (G'') reveal structural dynamics under shear stress. Rheology is critical for optimizing injectability, though cubic phases' rigidity may hinder syringeability compared to lamellar phases (Özkaynak et al., 2024).

1.4 Development of an in-situ gelling lyotropic liquid crystalline precursor system

The development of an *in-situ* gelling lyotropic liquid crystalline precursor system represents a significant advancement in drug delivery and biomedical applications. This innovative system is designed to undergo a phase transition from liquid to gel upon contact with physiological fluids, ensuring the localized and controlled release of therapeutic agents. Lyotropic liquid crystals are particularly advantageous because of their ability to form highly ordered structures, such as micellar cubic, hexagonal, or lamellar phases, which can encapsulate and protect active pharmaceutical ingredients (Shete et al., 2021). The precursor system typically comprises biocompatible and biodegradable materials responsive to stimuli. By fine-tuning the composition and properties of these systems, researchers can enhance the drug solubility, stability, and bioavailability, thereby offering a versatile platform for controlled drug delivery. *In-situ* gelling systems excel in site-specific delivery but face challenges in achieving consistent gelation kinetics across diverse physiological conditions. This technology holds promise for applications in areas such as oncology, ophthalmology, and wound healing, where precision and efficiency are paramount (Omenogor and Adeniran, 2024).

1.5 Application of LLC gels and in-situ gelling lyotropic liquid crystalline precursor system

1.5.1 Oral drug delivery

The unique structure of these inverse hexagonal gels allows encapsulation of poorly soluble drugs, improving their dissolution and stability in the gastrointestinal environment. This structure consists of a lipid-based matrix that forms a network of channels, facilitating improved drug dispersion and sustained release. Moreover, the bioadhesive properties of these gels ensure prolonged retention at the absorption site in the gastrointestinal tract, thereby enhancing drug uptake. By utilizing oleyl-glycerate-based gels, researchers aim to overcome the limitations associated with traditional oral drug delivery systems, offering a promising approach to increasing the therapeutic efficacy of drugs with poor solubility and absorption (Vrettos et al., 2021). Hexagonal gels outperform micelles in bioadhesion but are less effective for drugs requiring rapid release due to their slower diffusion rates.

LLCs offer distinct advantages as oral formulations targeting intestinal lymphatic transport. These systems utilize micelle compositions to form structures that enhance drug absorption and transport in the intestines. Key strategies for improving lymphatic transport include the use of lipid-based LLCs to promote chylomicron secretion and the design of LLC nanoparticles with ligands that target M cells. A novel bottom-up fabrication method enables precise control over the LLC bead size, determining the drug release rate by managing the diffusional interfacial surface. The LLC beads, embedded in a gelatin-chitosan coacervate to prevent coalescence, were also formulated to be pH-responsive. This design reduces premature drug release in the acidic gastric environment and enhances drug release at higher pH levels. The effectiveness of this approach was demonstrated using celecoxib, a model drug with low water solubility, which showed increased release rates at elevated pH levels (Dinh and Yan, 2023; Goldmünz et al., 2025).

1.5.2 Skin drug delivery

The innovative formulation of a mixture of TPGS, isopropyl myristate, and propylene glycol in a water-based system is a promising vehicle for delivering quercetin into the skin. This specific combination, formed in a lamellar phase, ensures the preservation of the antioxidant properties of quercetin, making it a valuable candidate for both cosmetic and pharmaceutical applications. The structural similarity of these lamellar systems to the skin enhances drug penetration, allowing gradual release of quercetin and reducing systemic exposure. Additionally, the inclusion of water in these mesophases aids in hydrating the tissues, further improving their penetration capabilities (Brito et al., 2024). Liquid crystalline precursor systems offer strong payload stability and mechanical resilience, making them highly effective for drug delivery, especially in tissue regeneration applications. Lamellar systems are superior for skin hydration but less effective for deep tissue penetration compared to cubosomes.

This study explored the potential of LLCs as temperature-sensitive transdermal drug delivery systems, specifically for doxorubicin (DOX) in the treatment of breast cancer. This highlights how LLC structures transform with temperature, from cubic to hexagonal to micellar, allowing controlled drug release. Incorporating paeonol and adjusting the composition helped fine-tune the phase transition temperatures to near human body levels. *In vitro* tests showed that LLCs were temperature-sensitive, had low toxicity, and improved DOX permeability and deposition in the skin. Confocal laser microscopy and cytotoxicity studies confirmed enhanced drug delivery and significantly increased activity against MCF-7 cell lines compared to DOX solutions, demonstrating the promising potential of LLCs in drug delivery applications (Liu et al., 2021; Shafie et al., 2025).

1.5.3 Ocular drug delivery

Innovations in ocular drug delivery have aimed to improve the effectiveness and safety of treatments for glaucoma. A promising advancement is the development of biofilm-like lipid liquid crystal (LC) gels with cubic and hexagonal matrices. Patel et al. (2022) demonstrated that these gels have been shown to enhance the *in vivo* residence time of drugs such as pilocarpine nitrate when applied topically to the eye (Patel et al., 2022; Adwan et al., 2024). In studies conducted in rabbits, these gels demonstrated superior performance compared with traditional eye drops, maintaining the medication's presence longer in the eye and potentially increasing its therapeutic efficacy. Additionally, drug-loaded liquid crystal gels have been designed to boost drug effectiveness while minimizing systemic absorption, thereby reducing the potential side effects. Cubic gels excel in prolonging residence time but may cause discomfort due to their viscosity compared to lamellar gels. This innovative approach holds promise for more effective and patient-friendly ocular treatment (Malode et al., 2025).

LLCs, particularly those formed from mesogen-like sodium dodecyl sulfate (SDS), display distinct phases that influence their bulk and micro viscosities, which are crucial for applications in energy transfer and drug delivery. LLCs have emerged as promising agents for ocular drug delivery, offering improved targeting and efficacy compared to conventional liposomes. This review explores the photophysical behavior of coumarin 6 (C6), a laser dye and ophthalmic drug, in various LLC phases. The interaction of C6 with LLCs modulates fluorescence, enhancing Förster resonance energy transfer (FRET) with N-doped carbon nanoparticles, which serve as photosensitizers. This dynamic can lead to the generation of reactive oxygen species, which is beneficial in therapeutic contexts. Advanced analytical techniques, including AI-driven modeling, are pivotal in predicting LLC phase behavior and optimizing their use in biosensing and diagnostics. Overall, LLCs have transformative potential in ocular health, providing innovative solutions for drug delivery and diagnostic advancements (Chatterjee et al., 2024; Adwan et al., 2024).

1.5.4 Nasal drug delivery

Nasal drug delivery is an innovative and effective method of administering medications directly through the nasal cavity. This route offers several advantages, such as rapid absorption and onset of action owing to the rich vascularization of the nasal mucosa. It is particularly beneficial for drugs that require rapid systemic effects, such as pain relievers, or treatments for conditions such as migraine and allergic rhinitis. Moreover, nasal delivery bypasses the gastrointestinal tract, reducing the risk of degradation by stomach acids and first-pass metabolism in the liver, which can enhance the bioavailability of certain drugs (Tafazzoli Mehrjardi et al., 2025). Additionally, it is more convenient and less invasive than injections, thereby improving patient compliance. However, challenges remain, including ensuring drug formulation stability and addressing the potential irritation of nasal passages. LLC gels enhance nasal retention but may irritate mucosa compared to simpler aqueous formulations. Overall, nasal drug delivery is a promising area of research and development in pharmaceutical science (Xia et al., 2025).

The development of an Almotriptan malate (ALM)-loaded cubosomal *in situ* gel designed for enhanced permeation through the blood–brain barrier via the intranasal route, promising rapid relief from migraine pain. Cubosomes were crafted with Pluronic F127 and glyceryl monooleate using a Box–Behnken design and optimized using desirability functions. High-resolution transmission electron microscopy confirmed the morphology, while differential scanning calorimetry confirmed drug encapsulation. The optimized formulation, with a particle size of 177.15 nm, exhibited a 90.69% drug release *in vitro* over 5 h and a 2.52-fold enhancement in *ex vivo* permeation compared to plain gels. Histopathology confirmed non-toxicity to the nasal mucosa, and short-term stability was demonstrated at room temperature. This approach highlights the potential for improved migraine treatment with enhanced patient compliance through rapid and effective delivery (Xia et al., 2025; Desai et al., 2023).

1.5.5 Injectable drug delivery

Injectable drug delivery involves the administration of medications directly into the body through a needle and syringe, typically targeting a vein, muscle, or tissue. This approach is especially advantageous for delivering drugs that require rapid absorption and precise dosing, or are ineffective when taken orally because of degradation of the digestive system. Common forms of injectable delivery include intravenous (IV), intramuscular (IM), and subcutaneous (SC) injections, each with varying rates of drug absorption and effects. Injectable delivery is widely used in the clinical settings for vaccines, insulin for diabetes management, pain relief, and antibiotics. Recent advancements in this field have focused on improving patient comfort, reducing pain, and developing smart delivery systems that can provide the controlled release of medication over time. Cubic LLC systems provide sustained release for injectables but require specialized syringes due to high viscosity, unlike lamellar systems. As technology evolves, the future of injectable drug delivery may see innovations such as microneedle patches and minimally invasive techniques, further enhancing patient compliance and therapeutic outcomes (Erstad and Barletta, 2022).

Postoperative analgesia, an *in situ* forming gel (ISFG) based on a lyotropic liquid crystal has been developed to deliver bupivacaine hydrochloride (BUP) for long-acting pain relief. The BUP-ISFG transforms into a gel upon exposure to physiological fluids, undergoing a lamellar-hexagonal-cubic phase transition. This transition facilitates low viscosity for easy injection and sustained drug release owing to the unique nanostructures of the gel phases. *In vivo* studies have shown that BUP-ISFG provides persistent analgesic effects with steadier plasma BUP concentrations than traditional injections, offering a promising solution for reducing the frequency of injections and improving patient compliance while effectively managing postoperative pain (Mei et al., 2018).

1.6 Factor affecting drug delivery systems

The effectiveness of a drug delivery system is influenced by various factors, each of which plays a crucial role in the successful administration and absorption of medication. Physicochemical properties of a drug, such as its solubility and stability, significantly affect its absorption and distribution in the body. Additionally, the route of administration (oral, intravenous, transdermal, or inhalation) affects the speed and efficiency of delivery. The design of the delivery system itself, including the use of carriers such as nanoparticles or liposomes, can enhance targeting and reduce side effects. Patient-specific factors, such as age, weight, and overall health, also play a critical role as they can influence metabolism and the body's response to the drug. Furthermore, environmental conditions and storage can affect drug potency and efficacy. In LLC systems, the complexity of formulation and the stability of phases are crucial. While cubic phases provide strong encapsulation, they present more challenges in scalability compared to liposomes. Understanding and optimizing these factors are essential for developing effective and reliable drug delivery systems (Zhang et al., 2022).

1.7 Translational challenges and clinical readiness of LLC-Based systems

LLC nanocarriers have shown considerable promise in controlled and targeted drug delivery, several critical challenges must be addressed to enable their successful clinical translation. A major concern is toxicity and biocompatibility of the nanomaterials. Although many LLC systems utilize biocompatible lipids, such as glyceryl monooleate and phytantriol, their interactions with biological membranes, long-term accumulation, and degradation byproducts require rigorous evaluation through *in vivo* toxicity and immunogenicity studies (Zhai et al., 2019; Chavda et al., 2023; Waheed and Aqil, 2021; Tiboni et al., 2023). Moreover, scalability and manufacturing consistency are significant obstacles. The production of LLC-based systems, especially high-viscosity cubic and hexagonal phases, often involves complex and energy-intensive techniques, such as high-pressure homogenization or ultrasonication. Ensuring batch-to-batch reproducibility while maintaining structural integrity and drug-loading efficiency is essential for industrial applications.

Another major bottleneck is the regulatory approval process. LLC-based formulations fall under the category of complex drug delivery systems, and the regulatory frameworks for such nanosystems remain underdeveloped. Demonstrating physicochemical stability, pharmacokinetics, biodistribution, and therapeutic efficacy in a reproducible and clinically relevant manner is crucial for regulatory approval (Madheswaran et al., 2019; Chavda et al., 2023). In addition, *in vivo* behavior, including biodistribution, drug release kinetics, metabolism, and clearance, remains insufficiently characterized for many LLC systems. This hinders predictions of therapeutic performance and safety profiles. Therefore, extensive preclinical and clinical studies are needed to bridge the gap between laboratory research and clinical applications (Leu et al., 2023). Future efforts should prioritize the development of standardized manufacturing protocols, toxicity evaluation frameworks, and regulatory guidance tailored to LLC-based drug delivery (Tiboni et al., 2023). Collaboration between academic researchers, industry stakeholders, and regulatory bodies will be vital in overcoming these translational hurdles and realizing the full therapeutic potential of LLC systems.

1.8 Reproducibility and regulatory considerations in LLC systems

The reproducibility of LLC-based formulations remains a major concern because of their sensitivity to preparation conditions, such as lipid composition, temperature, and hydration levels. Minor deviations in processing can lead to phase transitions or instability, thereby affecting the drug release kinetics and bioavailability. Establishing robust standard operating procedures (SOPs) and validated analytical methods is essential for ensuring batch-to-batch consistency. From a regulatory standpoint, LLCs fall under complex nanostructured drug delivery systems, and their evaluation often lacks harmonized guidelines. Agencies such as the FDA and EMA require comprehensive data on physicochemical stability, critical quality attributes (CQA), and performance metrics. Regulatory bottlenecks include classification ambiguity (drug, device, or combination), scalability challenges, and insufficient long-term toxicological data requirements. Collaborative efforts among academia, industry, and regulatory bodies are vital for developing fit-for-purpose evaluation protocols and accelerating the clinical translation of LLC technologies.

2 Conclusion

LLC nanoparticles represent a promising frontier in advanced drug delivery owing to their unique structural versatility, biocompatibility, and ability to encapsulate a wide range of therapeutic agents. The key findings emphasize that cubic phases provide excellent structural stability and sustained drug release, whereas lamellar and hexagonal phases offer advantages in terms of ease of processing and depot formulations, respectively. *In situ* gelling systems have expanded the application potential of LLCs for localized and controlled delivery, particularly in ocular, injectable, and transdermal therapies. However, several challenges remain, including the scalability of high-viscosity formulations, inconsistent gelation under physiological conditions, and limited regulatory clarity for their clinical adoption. To advance the field, future research should focus on developing shear-thinning LLC systems for easier administration, utilizing artificial intelligence to model phase transitions and optimize formulations, exploring novel biodegradable and stimuli-responsive materials, and prioritizing comprehensive *in vivo* and clinical evaluations. By addressing these limitations and leveraging emerging technologies, LLC-based systems can evolve into smart, patient-personalized platforms for precision delivery.

Author contributions

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