

CHARACTERISTICS: LIQUID CRYSTALLINE NANOPARTICLES

Abstract

Lyotropic non lamellar liquid crystalline nanoparticles (LCNs), such as cubosomes and hexosomes, possess distinctive structural features that make them valuable tools in drug delivery applications. LCNs exhibit versatility as carriers suitable for topical, oral, and intravenous treatments. Recent research efforts have been dedicated to refining the preparation and characterization of LCNs, with a particular focus on controlling drug release and improving the effectiveness of encapsulated bioactive molecules. Despite these advancements, the clinical adoption of LCN-based carriers has been sluggish. This review emphasizes recent progress and challenges in the development and utilization of LCNs, offering examples of their applications in topical, oral, and intravenous drug delivery. Additionally, it discusses the translational hurdles associated with LCNs as a nanoparticle technology.

Keywords: Liquid Crystalline nanoparticles (LCN), Cubosome, Hexosome,

Authors

Nirzari Antani

M.Pharm, PhD*

Assistant Professor

Veerayatan Institute of Pharmacy

Gujarat Technological University, Kutch

Dr. Chintankumar J. Tank

M.Pharm., PhD

Professor,

School of Pharmacy,

Dr. Subhash University, Junagadh

Dhvanirajsinh Jadeja

M.Pharm.

Assistant Professor

Veerayatan Institute of Pharmacy

Gujarat Technological University, Kutch

I. INTRODUCTION

Liquid Crystalline Nanoparticles (LCNs) stand out as a captivating category of nanomaterials that have garnered significant interest within the realm of drug delivery and nanomedicine. These nanoparticles showcase distinctive liquid crystalline phases marked by organized arrangements of amphiphilic molecules, commonly lipids, leading to the creation of thermodynamically stable nanostructures. The self-assembly of these amphiphilic molecules in an excess of water results in the formation of specific liquid crystalline phases, including bicontinuous cubic, hexagonal, and lamellar structures.

The defining characteristic of LCNs lies in their capacity to encapsulate and transport a diverse array of bioactive molecules, encompassing hydrophilic, hydrophobic, and amphiphilic compounds. This adaptability arises from the structural attributes of liquid crystalline phases, which establish a favorable environment for solubilizing and safeguarding various therapeutic agents. Consequently, LCNs have emerged as promising vehicles for drug delivery with potential applications in enhancing drug solubility, bioavailability, and targeted delivery.^[1]

The preparation of LCNs involves the dispersion of lyotropic liquid crystalline phases in aqueous media, often in the presence of suitable surfactants. Diverse techniques, including homogenization, sonication, and shearing, can be utilized to reduce the size of bulk liquid crystalline phases, yielding nanoparticles characterized by distinctive structural features. The resultant LCNs can be customized to encapsulate specific types of drugs, making them suitable for a broad range of therapeutic applications.^[7]

In recent years, considerable research efforts have been directed towards advancing the development and characterization of LCNs. Researchers are dedicated to overcoming challenges related to stability, scalability, and clinical translation, with the aim of fully leveraging the potential of these nanocarriers in delivering therapeutically active molecules. This involves exploring inventive formulations, comprehending the influence of various physicochemical factors on LCN behavior, and determining optimal conditions for drug loading and release.^[16]

This introduction underscores the significance of LCNs in the field of nanomedicine, emphasizing their distinctive properties and the potential they hold for enhancing drug delivery strategies. As ongoing research in this field unfolds, it holds the promise of unveiling new avenues for targeted and efficient therapeutic interventions.^[11]

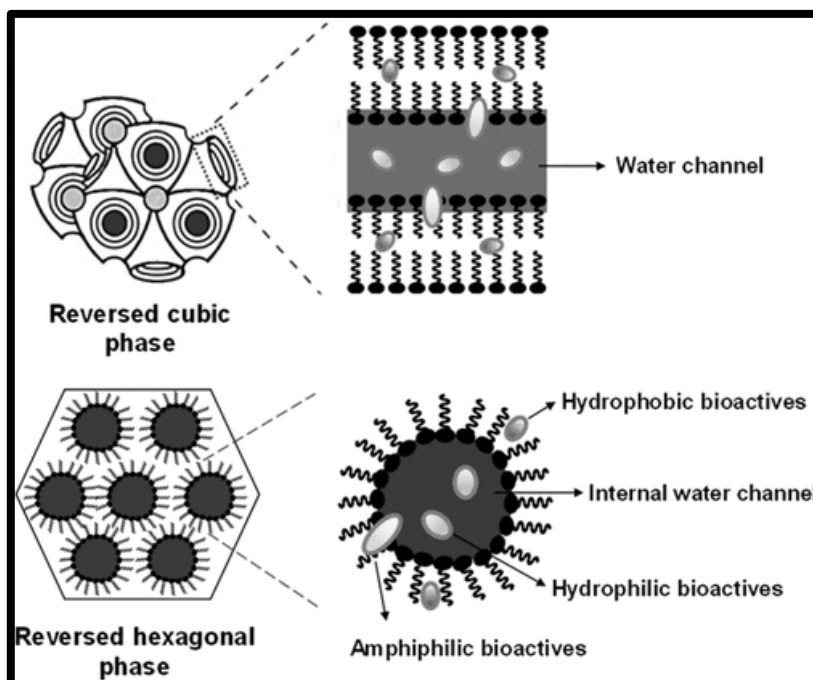


Figure 1: Structural Characteristics of Liquid Crystalline Nanoparticles

II. ADVANTAGES OF LIQUID CRYSTALLINE NANOPARTICLES: ^{[2],[7]}

1. Enhanced Drug Delivery

- LCNs provide an effective platform for drug delivery due to their ability to encapsulate both hydrophilic and hydrophobic drugs.
- The liquid crystalline structure facilitates controlled release, improving drug bioavailability and therapeutic efficacy.

2. Biocompatibility ^{[13],[14]}

- Many LCN formulations are composed of biocompatible materials, making them suitable for biomedical applications.
- The biocompatibility of LCNs is essential for minimizing adverse reactions when used in biological systems.

3. Versatility in Payloads

- LCNs can encapsulate a wide range of payloads, including drugs, imaging agents, and other bioactive compounds.
- This versatility makes them applicable in diverse fields, including medicine, cosmetics, and materials science.

4. Stability and Long Shelf Life

- LCNs often exhibit good stability, maintaining their structural integrity over time.
- This stability contributes to a longer shelf life and ensures the effectiveness of the encapsulated substances during storage.

5. Tailorable Nanostructures

- The lipid or surfactant composition of LCNs can be adjusted to achieve specific nanostructures, such as cubic, hexagonal, or lamellar phases.
- Tailoring the nanostructure allows for optimization based on the desired application.

6. Controlled Release Profiles

- LCNs enable controlled and sustained release of encapsulated substances.
- This controlled release profile can be crucial in drug delivery to achieve therapeutic concentrations over an extended period, minimizing side effects.

7. Improved Solubility^[8]

- LCNs can improve the solubility of poorly water-soluble drugs by encapsulating them within their nanostructures.
- Enhanced solubility contributes to improved bioavailability and efficacy of the drug.

8. Biological Targeting

- The surface properties of LCNs can be modified to achieve targeting capabilities, enabling specific delivery to tissues or cells.
- Targeted drug delivery reduces off-target effects and enhances the therapeutic impact.

9. Ease of Functionalization

- LCNs can be easily functionalized with various ligands or molecules for specific purposes.
- Functionalization allows for customization of LCNs for targeted drug delivery or imaging applications.

10. Compatibility with Various Formulation Techniques

- LCNs can be prepared using a variety of formulation techniques, including high-pressure homogenization, thin-film hydration, and microfluidics.
- This flexibility in preparation methods allows researchers to choose the most suitable technique for their specific application.

III. DISADVANTAGES:^[5]

1. **Complex Formulation:** The preparation of LCNs frequently entails intricate formulation procedures, demanding specialized equipment and expertise.
2. **Instability in Biological Fluids:** LCNs might encounter difficulties regarding stability when introduced into biological fluids like blood or gastrointestinal fluids, potentially influencing their performance over time.
3. **Limited Loading Capacity:** The loading capacity of LCNs might be restricted, particularly for specific drug types or large biomolecules, potentially affecting their efficiency in delivering payloads.
4. **Potential Toxicity of Components:** Certain lipid or surfactant elements employed in LCN formulations may possess inherent toxicity, necessitating careful consideration of their potential impact on biological systems.

5. **Storage and Shelf-Life Concerns:** LCNs may necessitate specific storage conditions to preserve stability, and external factors such as temperature, humidity, or light exposure could potentially affect their shelf life.
6. **Challenges in Scale-Up:** Expanding the production scale of LCNs for industrial or commercial purposes may present difficulties, given the complexity of maintaining desired characteristics at larger scales.
7. **Limited Control Over Drug Release:** Despite offering controlled release profiles, achieving precise control over release kinetics with LCNs can be demanding, leading to potential variations.
8. **Biocompatibility Issues:** While many LCN formulations aim for biocompatibility, certain components or modifications may elicit concerns regarding their interaction with biological systems.
9. **Potential Immune Response:** The introduction of LCNs into the body might instigate an immune response, particularly if the surface properties or components are perceived as foreign by the immune system.
10. **Expense of Formulation and Production:** Formulating and producing LCNs, particularly those incorporating specialized materials, can incur high costs, thereby limiting their widespread use and accessibility.
11. **Limited Applications for Certain Payloads:** Certain types of payloads, particularly large or highly charged molecules, may encounter challenges in effective encapsulation and delivery by LCNs.

IV. FORMULATION ASPECTS OF LIQUID CRYSTALLINE NANOPARTICLES:^{[9],[10]}

1. **Choice of Lipids or Surfactants:^[15]**
Criteria for Selection: Choose lipids or surfactants possessing amphiphilic properties suitable for self-assembling into liquid crystalline structures.
Examples: Common options include monoolein, phospholipids, or block copolymers.
2. **Hydrophilic-Lipophilic Balance (HLB)**
Significance: HLB consideration is crucial to achieving the appropriate balance in the formulation for effective self-assembly.
Adjustment: Modify the HLB to ensure the formation of the desired liquid crystalline nanostructure.
3. **Selection of Solvents**
Objective: Select solvents capable of dissolving lipids or surfactants efficiently, facilitating the formulation process.
Common Solvents: Chloroform, dichloromethane, or a blend of ethanol and water.
Biocompatibility: Ensure the solvent is biocompatible, particularly in biomedical applications.

4. Formulation Design for Liquid Crystalline Phase:^[3]

Customization: Formulate to attain the desired liquid crystalline phase, such as cubic, hexagonal, or lamellar.

Application Influence: The choice of phase is influenced by the intended application and desired characteristics.

5. Adjustment of Lipid-to-Surfactant Ratio

Objective: Modify the ratio to influence the nanostructure of LCNs.

Effect: This adjustment can impact stability, particle size, and overall performance.

6. Incorporation of Payloads:^[12]

Payload Types: Identify the payload type (hydrophilic or hydrophobic drugs, imaging agents, etc.) for encapsulation.

Optimization: Optimize payload loading capacity to ensure efficient delivery and therapeutic efficacy.

7. Preparation Methods

Variety: Choose from various preparation methods, such as high-pressure homogenization, thin-film hydration, sonication, or microfluidics.

Nanostructure Influence: The chosen method influences the resulting nanostructure of LCNs.

8. Purification Techniques

Methods: Utilize purification techniques, including centrifugation or filtration, to remove residual solvents or unincorporated materials.

Purity Assurance: Wash LCNs with a suitable buffer to ensure high purity.

9. Functionalization

Objective: Consider the need for functionalization to modify the surface of LCNs for specific applications like targeted drug delivery.

Customization: Functionalization allows customization based on the intended purpose.

10. Stabilizers and Excipients

Incorporation: Introduce stabilizers or excipients to enhance stability and prolong shelf life.

Role: Stabilizers may contribute to preventing aggregation or degradation.

11. Temperature and Environmental Factors

Consideration: Account for the impact of temperature and environmental factors during formulation and storage.

Stability: Ensure stability under varying conditions to maintain desired characteristics.

12. Characterization of Nanostructures:

Techniques: Employ advanced methods such as Small-Angle X-ray Scattering (SAXS) to analyze the internal nanostructure and confirm liquid crystalline phases.

Insight Gain: Characterization provides insights into the structural properties of LCNs.

13. Controlled Release Mechanisms:

Design Consideration: Design the formulation to achieve controlled release profiles based on the application.

Optimization Factors: Optimize factors like nanostructure and payload characteristics to control release kinetics.

14. Biocompatibility Considerations:

Critical Aspect: Ensure that components and resulting LCNs are biocompatible, particularly for applications involving drug delivery in biological systems.

Safety Assurance: Biocompatibility is critical to minimizing potential adverse effects.

V. EVALUATION PARAMETERS OF LIQUID CRYSTALLINE NANOPARTICLES:^{[4],[6],[17]}

1. Morphological Assessment

Techniques: Utilize Transmission Electron Microscopy (TEM) and Scanning Electron Microscopy (SEM).

Insights: Gain understanding into the dimensions, shape, and surface morphology of LCNs.

2. Size and Distribution Evaluation

Techniques: Apply Dynamic Light Scattering (DLS) and Atomic Force Microscopy (AFM).

Measurements: Evaluate the hydrodynamic diameter, size distribution, and surface topography of LCNs.

3. Structural Characterization

Technique: Employ Small-Angle X-ray Scattering (SAXS).

Objective: Analyze X-ray scattering patterns to ascertain the internal nanostructure and identify phase transitions in LCNs.

4. Thermal Analysis

Techniques: Employ Differential Scanning Calorimetry (DSC) and Thermogravimetric Analysis (TGA).

Information: Observe alterations in heat flow, phase transitions, and the thermal stability of LCNs.

5. Optical Properties Evaluation

Technique: Utilize Polarized Light Microscopy (PLM).

Observation: Evaluate birefringence and liquid crystalline behavior of LCNs under polarized light.

6. Zeta Potential Measurement

Technique: Apply Electrophoretic Light Scattering.

Quantification: Assess the surface charge of LCNs, providing insights into stability and colloidal behavior.

7. Encapsulation Efficiency Assessment

Technique: Employ High-Performance Liquid Chromatography (HPLC).

Quantification: Measure the quantity of encapsulated payload through analysis post-purification of LCNs.

8. In vitro Release Studies

Methods: Monitor the controlled release of encapsulated substances over time using appropriate methodologies.

Objective: Evaluate the release kinetics and sustained release behavior of LCNs.

9. Biocompatibility and Cytotoxicity Evaluation

Assays: Conduct Cell Viability Assays, such as the MTT assay.

Assessment: Evaluate the biocompatibility of LCNs with diverse cell lines and potential cytotoxic effects.

10. Stability Studies

Parameters: Investigate alterations in size, structure, and drug release under various storage conditions over time.

Purpose: Ensure the stability and sustained performance of LCNs during storage.

11. Drug Loading and Release Kinetics Analysis

Methods: Analyze the loading capacity and release kinetics of drugs or payloads from LCNs.

Significance: Assess the efficiency and controllability of drug delivery.

12. Surface Modification and Functionalization Confirmation

Analysis: Verify the success of surface modification and functionalization processes.

Importance: Assess the ability to tailor LCNs for specific applications.

13. Particle Surface Charge Evaluation

Technique: Employ Zeta potential measurement.

Assessment: Provide information on the stability and electrostatic interactions of LCNs.

14. Rheological Properties Assessment

Analysis: Evaluate the viscosity and flow characteristics of LCNs.

Significance: Particularly relevant for applications where rheological behavior is crucial, such as topical formulations.

15. Environmental Impact Consideration

Consideration: Evaluate the potential environmental impact of LCNs, including aspects of toxicity and biodegradability.

16. Scale-Up Feasibility Evaluation

Assessment: Evaluate the scalability of the production process for industrial or commercial purposes.

Importance: Determine the feasibility of large-scale manufacturing for LCNs.

VI. CONCLUSION

Liquid Crystalline Nanoparticles (LCNs) emerge as a notably promising and adaptable category of nanomaterials, offering extensive applicability. The distinctive characteristics of LCNs, such as their capacity to encapsulate substances with differing hydrophilic and hydrophobic natures, controlled release capabilities, and flexibility in diverse formulations, render them appealing for utilization across a broad spectrum of fields.

REFERENCES

- [1] 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.
- [2] Waghule, T., Dabholkar, N., Gorantla, S., Rapalli, V. K., Saha, R. N., & Singhvi, G. (2021). Quality by design (QbD) in the formulation and optimization of liquid crystalline nanoparticles (LCNPs): A risk based industrial approach. *Biomedicine & Pharmacotherapy*, 141, 111940.
- [3] Zhai, J., Fong, C., Tran, N., & Drummond, C. J. (2019). Non-lamellar lyotropic liquid crystalline lipid nanoparticles for the next generation of nanomedicine. *ACS nano*, 13(6), 6178-6206.
- [4] Meli, V., Caltagirone, C., Falchi, A. M., Hyde, S. T., Lippolis, V., Monduzzi, M., ... & Murgia, S. (2015). Docetaxel-loaded fluorescent liquid-crystalline nanoparticles for cancer theranostics. *Langmuir*, 31(35), 9566-9575.
- [5] Guan, S., Zhang, C., Wen, W., Qu, T., Zheng, X., Zhao, Y., & Chen, A. (2018). Formation of anisotropic liquid crystalline nanoparticles via polymerization-induced hierarchical self-assembly. *ACS Macro Letters*, 7(3), 358-363.
- [6] Liu, R., Wang, S., Fang, S., Wang, J., Chen, J., Huang, X., ... & Liu, C. (2016). Liquid crystalline nanoparticles as an ophthalmic delivery system for tetrandrine: development, characterization, and in vitro and in vivo evaluation. *Nanoscale research letters*, 11, 1-12.
- [7] Tran, N., Mulet, X., Hawley, A. M., Hinton, T. M., Mudie, S. T., Muir, B. W., ... & Drummond, C. J. (2015). Nanostructure and cytotoxicity of self-assembled monoolein-capric acid lyotropic liquid crystalline nanoparticles. *RSC Advances*, 5(34), 26785-26795.
- [8] Agrawal, A. K., Kumar, K., Swarnakar, N. K., Kushwah, V., & Jain, S. (2017). "Liquid crystalline nanoparticles": rationally designed vehicle to improve stability and therapeutic efficacy of insulin following oral administration. *Molecular Pharmaceutics*, 14(6), 1874-1882.
- [9] Ferreira, G. A., & Loh, W. (2017). Liquid crystalline nanoparticles formed by oppositely charged surfactant-polyelectrolyte complexes. *Current opinion in colloid & interface science*, 32, 11-22.
- [10] Kim, D. H., Lim, S., Shim, J., Song, J. E., Chang, J. S., Jin, K. S., & Cho, E. C. (2015). A simple evaporation method for large-scale production of liquid crystalline lipid nanoparticles with various internal structures. *ACS applied materials & interfaces*, 7(36), 20438-20446.
- [11] Leu, J. S., Teoh, J. J., Ling, A. L., Chong, J., Loo, Y. S., Mat Azmi, I. D., ... & Madheswaran, T. (2023). Recent Advances in the Development of Liquid Crystalline Nanoparticles as Drug Delivery Systems. *Pharmaceutics*, 15(5), 1421.
- [12] Thapa, R. K., Youn, Y. S., Jeong, J. H., Choi, H. G., Yong, C. S., & Kim, J. O. (2016). Graphene oxide-wrapped PEGylated liquid crystalline nanoparticles for effective chemo-photothermal therapy of metastatic prostate cancer cells. *Colloids and Surfaces B: Biointerfaces*, 143, 271-277.
- [13] LLi, J. C., Zhu, N., Zhu, J. X., Zhang, W. J., Zhang, H. M., Wang, Q. Q., ... & Hao, J. F. (2015). Self-assembled cubic liquid crystalline nanoparticles for transdermal delivery of paeonol. *Medical science monitor: international medical journal of experimental and clinical research*, 21, 3298.
- [14] Jain, S., Heeralal, B., Swami, R., Swarnakar, N. K., & Kushwah, V. (2018). Improved oral bioavailability, therapeutic efficacy, and reduced toxicity of tamoxifen-loaded liquid crystalline nanoparticles. *AAPS PharmSciTech*, 19, 460-469.
- [15] Chountoulesi, M., Perinelli, D. R., Pippa, N., Chrysostomou, V., Forys, A., Otulakowski, L., ... & Demetzos, C. (2020). Physicochemical, morphological and thermal evaluation of lyotropic lipidic liquid crystalline nanoparticles: The effect of stimuli-responsive polymeric stabilizer. *Colloids and Surfaces A: Physicochemical and Engineering Aspects*, 595, 124678.
- [16] de Souza, J. F., da Silva Pontes, K., Alves, T. F. R., de Barros, C. T., Amaral, V. A., de Moura Crescencio, K. M., ... & Chaud, M. V. (2020). Structural comparison, physicochemical properties, and in vitro release

profile of curcumin-loaded lyotropic liquid crystalline nanoparticle: Influence of hydrotrope as interface stabilizers. *Journal of Molecular Liquids*, 306, 112861.

- [17] Butreddy, A., Narala, A., & Dudhipala, N. (2015). Formulation and characterization of Liquid Crystalline Hydrogel of Agomelatin: In vitro and Ex vivo evaluation. *Journal of Applied Pharmaceutical Science*, 5(9), 110-114.