INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

Review Article

Comprehensive Review on Nanostructured Lipid Carriers

Limaye Akhilesh, Dr. Shaikh Nasheer*, Humnabade Shital, Anantwal Akshat, Babhulkar Akshay, Joshi Maharudra, Rajput Amrapali

Department of Pharmaceutics, Channabasweshwar Pharmacy College (Degree) Latur, Maharashtra - 413512.

ARTICLE INFO

Published: 20 May 2025
Keywords:
Nanostructured Lipid Carriers, Nanoparticulate System, Solid Lipid Nanoparticles
DOI:
10.5281/zenodo.15474137

ABSTRACT

Nanostructured lipid carriers (NLCs) represent a novel nanoparticulate drug delivery system composed of solid lipids, liquid lipids, emulsifying agents, and an aqueous phase. In recent years, NLCs have garnered considerable scientific and clinical interest due to their superior drug delivery capabilities, offering notable advantages over conventional dosage forms. Nanostructured lipid carriers (NLCs) are second generation lipid-based nanocarriers formulated using biocompatible solid lipids, liquid lipids, surfactants, and co-surfactants. These systems are capable of encapsulating a wide range of pharmacological agents, offering controlled drug release, improved drug stability and scalability for industrial production without the requirement for organic solvents. This article provides a comprehensive overview of nanostructured lipid carriers (NLCs), focusing on their structural composition, preparation techniques, characterization methods, and the advantages they offer over first-generation lipid-based nanoparticles.

INTRODUCTION

NLCs (Nanostructured Lipid Carriers) are a type of colloidal carrier system where the core is composed of a blend of solid lipids and liquid lipids. The solid lipid core provides structural stability, while the liquid lipid adds flexibility to accommodate drug molecules, enhancing the loading capacity and release profile. nanostructured lipid carriers (NLCs) are indeed a fascinating area in pharmaceutical technology, known for their ability to improve the delivery and bioavailability of drugs. These NLCs are composed of solid lipid and liquid lipid, which can provide better stability and sustained drug release compared to other drug delivery system.(1) Nanostructured lipid carriers (NLCs) enhance drug loading by utilizing a blend of solid and liquid lipids with varying fatty acid chain lengths in their crystalline structure, this allows efficient encapsulation of both hydrophilic and lipophilic drugs.(2) Nanostructured lipid carriers (NLCs) are lipid-based colloidal nano drug delivery system,

***Corresponding Author:** Dr. Shaikh Nasheer
Address: *Department of Pharmaceutics, Channabasweshwar Pharmacy College (Degree) Latur, Maharashtra - 413512.*
Email ✉: nasheershaikh@gmail.com

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

NLCs are represent an advanced form of solid lipid nanoparticles (SLNs), designed to enhance drug delivery through improved stability, loading capacity, and controlled release.(3) Biodegradable and biocompatible lipids (both solid and liquid) and emulsifiers are utilized in the formulation of nanostructured lipid carriers (NLCs). Nanostructrured lipid carriers have emerged as a promising drug delivery system for administration via various routes including oral, parentral, ocular, pulmonary, topical and transdermal.(3)

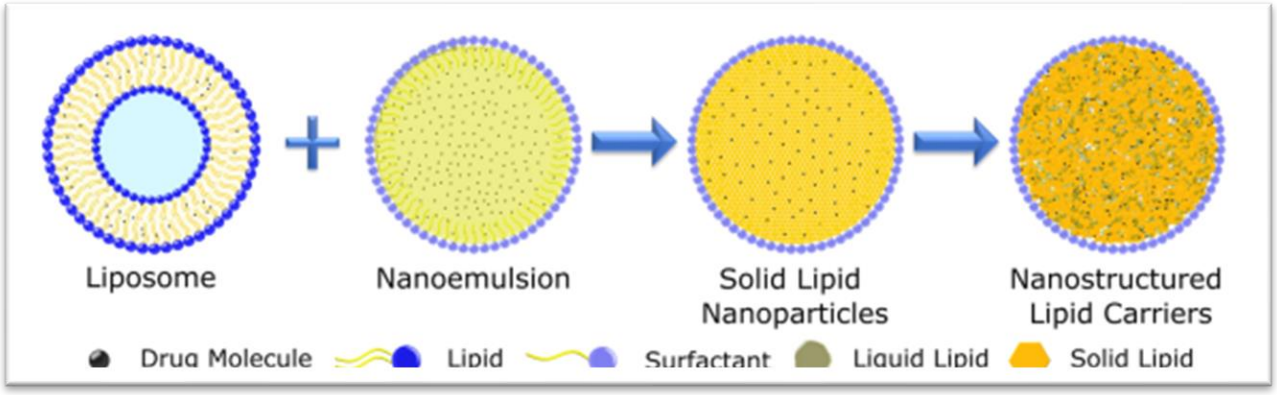


Fig:1 Structure of NLC

Types of NLC:-(4)

NLC type- I (Imperfect crystal model):-

Imperfect crystal-type nanostructured lipid carriers (NLCs) feature a highly a disordered matrix with numerous voids and spaces, allowing for the accommodation of a greater number of drug molecules within amorphous clusters. The imperfections in the crystal structure are induced by blending solid lipids with an appropriate proportion of solid and liquid lipid(oils). The matrix of NLCs fails to form a highly ordered structure due to varying chain lengths of fatty acids and the presence of a mixture of mono-di-and triglycerols. The spatially distinct lipid enhances the drug payload capacity; however, this model typically results in lower entrapment efficiency.

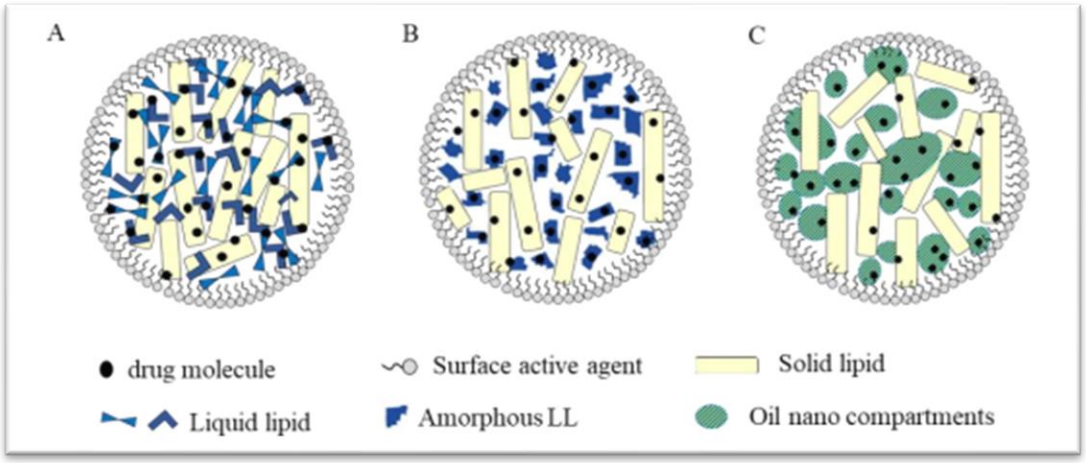


Fig:2 Types of NLCs

NLC type-II (Multiple type):-

The multiple type of NLC includes oil/lipid/water system, lipophilic drugs exhibit higher solubility

in liquid lipids compared to solid lipids, the incorporation of oil nano-compartments enhances the drug loading capacity. Composed of combination of liquid lipids, solid lipids, and surfactants mixed in specific ratios and dispersed in aqeous solution. exceeding the solubility limit of oil induces sepration, resulting in the formation of the small oil nano-compartments encapsulated within the solid lipid matrix. the type II model offers several advantages including high drug entrapment efficiency, controlled drug release and reduced drug leakage.

NLC type-III (Amorphous model): -

Amorphous type nanostructured lipid carriers (NLC) are formulated through precise blending of the lipids to minimize drug leakage, which occurs during the crystallization process. In the amorphous type the drug expulsion due to lipid matrix crystallization is minimized by combining solid lipids with liquid lipids that solidify into an amorphous, non-crystalline matrix (e.g, hydroxyoctacosanyl hydroxystearate or iso-propyl myristate.) the lipid matrix is maintained in a amorphous state.

ADVANTAGES:-(5)

1. The drug is secularly integrated into the storage.
2. Adaptable modulation of the release profile.
3. Enhanced efficacy in the production of the final dosage forms includes creams, tablets, capsules and Injectable.
4. Suspensions with a elevated solid content (e.g.30-50% solids) can be effectively produced.
5. Enhances drug loading capacity.
6. The feasibility concurrently loading both lipophilic and hydrophilic drugs into a single formulation or delivery system is a complex yet promising approach in drug delivery.
7. More affordable (less expensive than polymeric/surfactant based carriers.

DISADVANTAGES:-(5)

1. The cytotoxic effects associated with the characteristics of the lipid matrix and its concentration.
2. The irritant and sensitizing properties of surfactants.
3. The application of protein and peptide drugs, as well as gene delivery systems,still require further exploration and optimization.

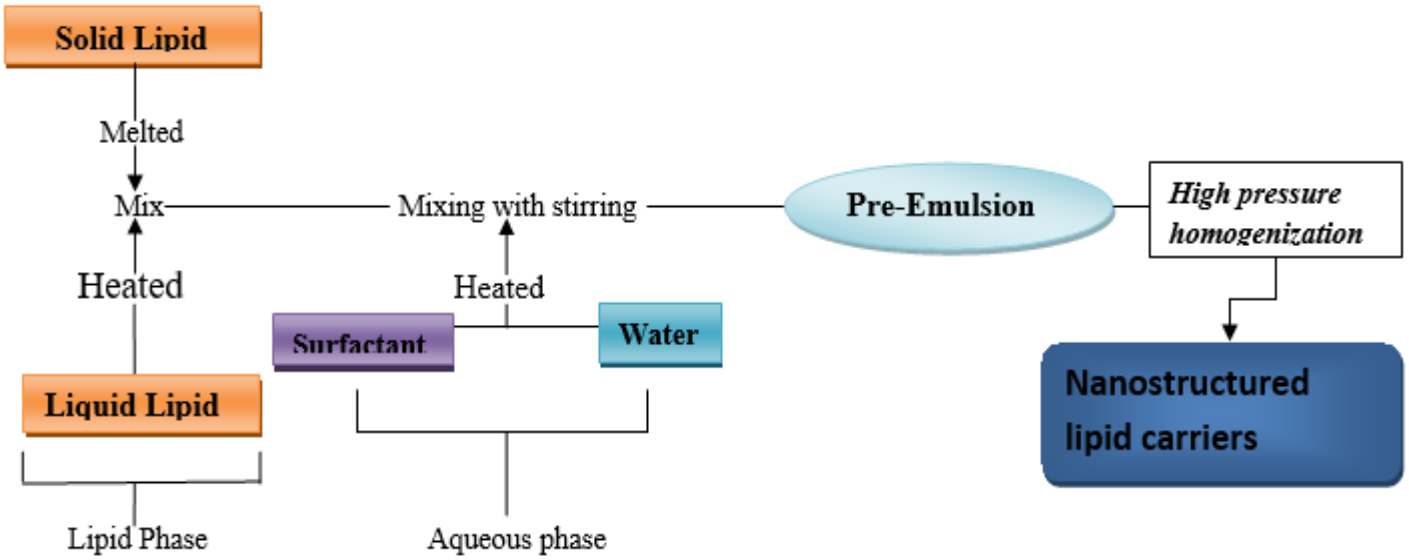
Method of preparation (NLCs):-

1. Hot high- pressure homogenization technique
2. Cold high-pressure homogenization technique
3. Microemulsion technique
4. High shear homogenization technique
5. Solvent diffusion and evaporation technique
6. Hot melt extrusion
7. Solvent injection technique
8. Supercritical fluid method
9. Phase inversion method

1. Hot high-pressure homogenization:-(6)

This technique is a highly effective and dependable for the large- scale commercial production of nanostructured lipid carriers (NLCs). The high pressure applied during the homogenization process eliminates the need for

organic solvents in the formulation, making the process more environmentally friendly. High-pressure homogenization (HPH) is a highly scalable and efficient technique, making it an attractive method for the manufacturing of pharmaceuticals and cosmetics intended for topical application. This process enables the production of stable emulsions and suspensions by reducing particle sizes to the nanometer scale, which is essential for ensuring uniform distribution of active ingredients. In both industries, HPH enhances product consistency, stability and bioavailability, contributing to improved performance and efficacy in formulations such as creams, gels, and serums. Its scalability allows for the production of large quantities without compromising product quality. Hot homogenization is conducted at elevated temperatures, while cold homogenization is performed at temperatures below room temperatures. The active ingredient is dissolved or dispersed in the molten lipid prior to high pressure homogenization in both methodologies. High pressure (ranging from 100 to 2000 bar) forces the fluid through the narrow gap within the homogenizer.



Hot high-pressure homogenization

2. Cold high-pressure homogenization:-(6)

The well-established hot high-pressure homogenization (HPH) method has a limitation in that the elevated temperatures during processing may lead to the decomposition of hydrophilic and thermolabile drugs. To mitigate this issue, a straightforward approach involving the rapid cooling of the nano-emulsion is employed. The liquid and the solid lipids are heated to a temperature above the melting point of the solid lipid to facilitate melting. The drug is dispersed or dissolved in the heated lipid melt and subjected to the high-pressure homogenization (HPH). The resulting emulsion is rapidly cooled by exposure to liquid nitrogen or dry ice. The solid mass obtained is ground to produce microparticles, which are then dispersed in a cold aqueous phase containing an appropriate surfactant. This dispersion is subjected to high-shear homogenization or ultrasonication to yield nano-lipid carriers (NLCs).

3. Microemulsion technique:-(6)

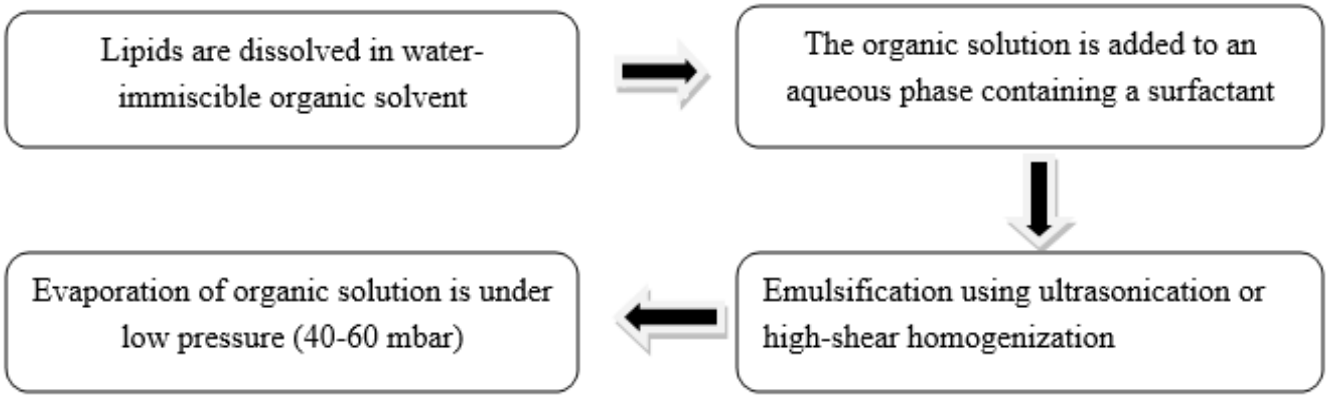
In this approach, solid lipid is the first melted, followed by the addition of the liquid lipid and solubilization of the drug in resulting mixture. Meanwhile, a separate mixture of emulsifier, co-emulsifier and water is heated to the same temperature. The lipid phase is added in aqueous phase under mechanical agitation at a consistent temperature, facilitating the formation of microemulsion. The warm microemulsion is subsequently added to cold water (2-4 c) under continuous stirring. A substantial volume of cold water is required for the dilution process, which induces the precipitation of microemulsion globules, leading to the formation of nanostructured lipid carriers (NLCs). Dilution with a large volume of water results in reduction in the concentration of active ingredients. Therefore, further concentration of the formulation or lyophilization is necessary to achieve the desired formulation strength.

4. High shear homogenization technique:-(7)

In this method, the drug is first incorporated into a molten lipid phase to form a homogeneous mixture. The mixture is then subjected to homogenization using a high-speed stirrer to produce a nanodispersion. Prior to mixing, the surfactant solution, which may contain poloxamers, lecithins, polysorbates, and polyethoxylated monoglycerides, is heated to the melting temperature of the lipid phase. The attainment of a homogeneous mixture with smaller particle sizes depends on the gradual incorporation of the lipid mixture. Increased stirring speed can result in smaller particles. Furthermore, this method is often coupled with ultrasonication techniques, utilizing probe-type ultrasonication to break down agglomerates or large globules. This method has been successfully employed to formulate nanostructured lipid carriers (NLCs) incorporating active compounds such as eucalyptus essential oil (EEO) and rosemary essential oil (REO). This approach, soya lecithin can function both as solid lipid and liquid lipid.

5. Solvent emulsification:-(8)

This technique involves the dissolution of the drug lipid mixture in a water-immiscible organic solvent, followed by emulsification in an aqueous phase through ultrasonication or high shear homogenization. The organic solution is subsequently maintained under the reduced pressure 40-60 mbar until complete evaluation of organic solvent. This method is particularly suitable for the preparation of nanostructured lipid carriers (NLCs) containing heat sensitive drugs, as it utilizes low pressure rather than elevated temperature for the removal of organic solvent and the precipitation of the drug loaded NLCs. However, the process is constrained by the presence of residual traces of the organic solvent in the final product, which may result systemic toxic effects upon administration. Additionally, this method may necessitate an additional filtration step, which may not be economically viable for large-scale manufacturers and typically leads to decrease in the percentage yield.



6. Hot melt extrusion:-(6)

Most of the employed for NLC preparation (as mentioned above) are derived from either the methods used for the preparation of SLN or other nanocarrier systems. These are the multistep processes, and their commercialization is challenging, with the exception of high-pressure homogenization. The extruder was equipped with three feeding ports: the first for the addition of the lipid-drug mixture, second for the addition of liquid lipid, and third for the addition of aqueous phase. The solid lipid and drug mixture were introduced through the first port via a volumetric feeder, while heated liquid lipid was added through second port using a peristaltic pump as the mixture progressed through the extrusion barrel, it underwent melting and mixing. The third port was designated for the addition of the preheated aqueous phase containing the appropriate surfactant, which was introduced via a peristaltic pump and mixed at the desired speed to form a pre-emulsion. The pre-emulsion is extruded into a vessel equipped with a probe sonicator to produce NLCs. The feeding rates were optimized prior to the experiment.

7. Solvent injection:-(9)

The fundamental principle of the solvent injection method is similar to the solvent diffusion method. In the solvent injection method, lipids are dissolved in a water miscible solvent (e,g., acetone, isopropanol or methanol) or a mixture of water-miscible solvents, which is then rapidally injected into an aqueous solution of surfactants via an injection needle. The advantages of this method includes its simplicity in handling and a rapid production process, which does not require the use of technically advanced equipment, such as high-pressure homogenizers. However, a key drawback is the reliance on organic solvents, which may pose environmental and safety concerns. This method provides the advantages of straightforward preparation, while minimizing the need for the high temperatures, shear stress and complex equipment.

8. Supercritical fluid method:-(10)

Supercritical fluids have been employed in a diverse array of applications, including extraction, green chemical reactions, and chromatography. More recently, this technology has been investigated for the production of micro and nanoparticles. The application of supercritical fluid technology in particle production remains in the early stages of development. A supercritical fluid is a substance that exists as both a liquid gas at temperature and pressures exceeding its critical pressure. It exhibits properties that are distinct from those of conventional gases or liquids under standard conditions. Supercritical carbon dioxide (SC-CO2) is one of the most commonly utilized supercritical fluids due to its availability, inertness,

non-flammability, and easily attainable critical conditions. Typically solid lipids are melted and combined with the supercritical fluid, along with the drug and liquid lipids, to facilitate their solubilization. A gas-saturated suspension or solution is created depending on the solubility of the components in the supercritical fluid (SCF) the resulting dispersion is then atomized and sprayed into a confined chamber, where the decompression and evaporation of the gas facilitate the formulation if nanostructured lipid carriers. The supercritical fluid (SCF) method offers several advantages, including the elimination of organic density if SCFs varies with pressure, a straightforward depressurization and recover the solvent.

9. Phase inversion method:-(7)

This method can be considered an innovative approach for the preparation of nanostructured lipid carriers (NLCs). It utilizes the surfactants ability to display varying hydrophilic-lipophilic balance (HLB) values at different temperatures. At elevated temperatures, surfactants exhibit a relatively low HLB. Upon reaching a specific temperature threshold, the surfactant undergoes a change in its HLB value, which subsequently alters the emulsion phase formed. The formation of the NLCs system using this method begins with the active ingredients, lipid phase, and surfactant, followed by thorough stirring. The mixture is then subjected to significant temperature fluctuations across three cycles (85^oC-60^oC-85^oC-60^o-85^o) to generate an oil-in-water (o/w) emulsion phase. Subsequently, the mixture is rapidly transferred to cold water (0^oC) to invert the phase into a stable oil-in-water (o/w) emulsion. This technique is particularly advantageous for thermolabile active substances, effectively addressing challenges associated with high-temperature organic solvent evaporation.

Characterization of NLCs:- (11)

Characterization of nanostructured lipid carriers (NLCs), like other colloidal delivery systems, is a critical aspect for evaluating their quality, stability, and release kinetics. For solid lipid nanoparticles (SLN) and NLC, this process presents unique challenges. In addition to their extremely small size, these systems are inherently dynamic due to the complex behavior of lipids, which can undergo phase transitions, altering their structure and properties over time. This dynamic nature further complicates the characterization, as it requires sophisticated techniques to accurately assess the morphological, physical and release characteristics of the system under various conditions. The characteristics of nanostructured lipid carriers (NLCs) involves several key measurements, including particle size and its distribution, structural properties, surface charge, and the thermal behaviour of the lipids. The following outline the principal characterization techniques used to evaluate these parameters.

1. Polydispersity index, size and zeta potential:- (12)(13)

The particle size, polydispersity index, and zeta potential of nanostructured lipid carriers (NLCs) are assessed using dynamic light scattering (DLS) techniques. The size of NLCs plays a crucial role in the effective delivery of active ingredients across the skin layers, with smaller NLCs facilitating closer interaction with the stratum corneum and enhancing the transdermal penetration of the active compound. Additionally, small-sized nanoparticles are more readily able to penetrate the stratum corneum through intracellular pathways. A polydispersity index (PDI) value of less than 0.3 is typically preferred, as it indicates a unimodel size distribution and minimizes the likelihood aggregation.

The particle size of a formulation is influenced by other factors, including the composition of formulation (such as the properties of lipids and drugs, and the type of surfactant used), as well as the manufacturing process. Key process variables that affect particle size include the choice of process, the equipment utilized, processing temperature and pressure, the number of the cycles during high-pressure homogenization (HPH), sterilization conditions, and lyophilization. Generally, a higher surfactant-to-lipid ratio results in smaller particle sizes, while decrease in surfactant concentration leads to an increase in particle size. Additionally, higher drug concentrations typically results in larger particle sizes compared to formulations with lower drug concentrations.

2. Drug encapsulation efficiency loading capacity:-(14)

The encapsulation efficiency (EE) and loading capacity (LC) of the NLCs were determined indirectly by measuring the amount of nano-encapsulated present in the aqueous phase of the colloidal dispersion. To eliminate the ibuprofen adhered to the surface of the NLCs, the dispersion was diluted with a ph 7.4 phosphate buffer solution. The dilution was carried out at a 1.10 ratio. Following this step, the sample underwent simultaneous filtration and centrifugation using an amicon ultra-4 centrifugal filter unit equipped with an ultracel-10k membrane (with a nominal molecular weight cutoff of 10,000 Da). The filtration process was performed at 3500 rpm for one hour.

3. Surface Charge:-(15)

The surface charge plays a crucial role in the formulation of nanostructured lipid carriers (NLCs), as it significantly influences particle aggregation, dispersion behavior, and overall long-term stability. This surface charge is typically assessed through the measurement of zeta potential (ZP), which can vary depending on factors such as pH, ionic strength, and the specific types of ions present in the surrounding aqueous environment. A higher surface charge is generally associated with increased electrostatic repulsion between particles, thereby reducing the likelihood of aggregation. For optimal colloidal stability, nanostructured lipid carriers (NLCs) typically require a minimum zeta potential of ±20 mV. Cancer cells exhibit a higher negative surface charge compared to normal cells, primarily due to the overexpression of negatively charged phospholipids on their membranes. This characteristic facilitates preferential electrostatic interactions between cationic nanostructured lipid carriers (NLCs) and tumor cells, enhancing targeted delivery. Accordingly, modulation of the surface charge of nanostructured lipid carriers (NLCs) enables passive targeting of tumor cells. How et al. investigated the influence of pH and drug loading on the particle size, zeta potential (ZP), and physical stability of NLCs by incubating tamoxifen-loaded NLCs (TAM-NLC000s) and drug-free NLCs in media with pH values of 2.3, 6.4, 7.4, and 10.9. These pH conditions correspond to the gastric environment, the post-preparation pH within the stomach, physiological blood pH, and the pH representing the deprotonated state of the drug, respectively

REFERENCES

1. Doktorovova S, Souto EB. Nanostructured lipid carrier-based hydrogel formulations for drug delivery: A comprehensive review. Expert Opin Drug Deliv. 2009;6(2):165–76.
2. Karnati V Chandana, N. Vishal Gupta, Sandeep Kanna. Nanostructured Lipid Carriers: the Frontiers in Drug Delivery. Asian J Pharm Clin Res. 2019;12:8–12.

3. Praveen S, Gowda D V., Srivastava A, Osmani RAM. Formulation and evaluation of nanostructured lipid carrier (NLC) for glimepiride. Der Pharm Lett. 2016;8(6):304–9.
4. Chauhan I, Yasir M, Verma M, Singh AP. Nanostructured lipid carriers: A groundbreaking approach for transdermal drug delivery. Adv Pharm Bull [Internet]. 2020;10(2):150–65. Available from: https://doi.org/10.34172/apb.2020.021
5. Shidhaye S, Vaidya R, Sutar S, Patwardhan A, Kadam V. Solid Lipid Nanoparticles and Nanostructured Lipid Carriers – Innovative Generations of Solid Lipid Carriers. Curr Drug Deliv. 2008;5(4):324–31.
6. Salvi VR, Pawar P. Nanostructured lipid carriers (NLC) system: A novel drug targeting carrier. J Drug Deliv Sci Technol [Internet]. 2019;51(990):255–67. Available from: https://doi.org/10.1016/j.jddst.2019.02.017
7. Wathoni N, Suhandi C, Elamin KM, Lesmana R, Hasan N, Mohammed AFA, et al. Advancements and Challenges of Nanostructured Lipid Carriers for Wound Healing Applications. Int J Nanomedicine. 2024;19:8091–113.
8. Haider M, Abdin SM, Kamal L, Orive G. Nanostructured lipid carriers for delivery of chemotherapeutics: A review. Pharmaceutics. 2020;12(3).
9. Jaiswal P, Gidwani B, Vyas A. Nanostructured lipid carriers and their current application in targeted drug delivery. Artif Cells, Nanomedicine Biotechnol. 2016;44(1):27–40.
10. Garg J, Pathania K, Sah SP, Pawar S V. Nanostructured lipid carriers: a promising drug carrier for targeting brain tumours. Futur J Pharm Sci [Internet]. 2022;8(1). Available from: https://doi.org/10.1186/s43094-022-00414-8
11. Khosa A, Reddi S, Saha RN. Nanostructured lipid carriers for site-specific drug delivery. Biomed Pharmacother [Internet]. 2018;103(February):598–613. Available from: https://doi.org/10.1016/j.biopha.2018.04.055
12. Iqbal MA, Md S, Sahni JK, Baboota S, Dang S, Ali J. Nanostructured lipid carriers system: Recent advances in drug delivery. J Drug Target. 2012;20(10):813–30.
13. Arora R, Katiyar SS, Kushwah V, Jain S. Solid lipid nanoparticles and nanostructured lipid carrier-based nanotherapeutics in treatment of psoriasis: a comparative study. Expert Opin Drug Deliv [Internet]. 2017;14(2):165–77. Available from: http://dx.doi.org/10.1080/17425247.2017.1264386
14. Tamjidi F, Shahedi M, Varshosaz J, Nasirpour A. Nanostructured lipid carriers (NLC): A potential delivery system for bioactive food molecules. Innov Food Sci Emerg Technol [Internet]. 2013;19:29–43. Available from: http://dx.doi.org/10.1016/j.ifset.2013.03.002
15. Nagaich U, Gulati N. Nanostructured lipid carriers (NLC) based controlled release topical gel of clobetasol propionate: design and in vivo characterization. Drug Deliv Transl Res [Internet]. 2016;6(3):289–98. Available from: http://dx.doi.org/10.1007/s13346-016-0291-1.

HOW TO CITE: Limaye Akhilesh, Dr. Shaikh Nasheer*, Humnabade Shital, Anantwal Akshat, Babhulkar Akshay, Joshi Maharudra, Rajput Amrapali, Comprehensive Review on Nanostructured Lipid Carriers, Int. J. of Pharm. Sci., 2025, Vol 3, Issue 5, 3423-3431. https://doi.org/10.5281/zenodo.15474137