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REVIEW ARTICLE

Potential Role of Nanostructured Lipid Carrier as Cutting-Edge Approach for Drug Delivery of Nonsteroidal Anti-Inflammatory Drugs

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Abstract

The majority of nonsteroidal anti-inflammatory drugs (NSAIDs) are categorised as Biopharmaceutics Classification System (BCS) class II or IV drugs, indicating their limited solubility and permeability. The nanostructured lipid carriers (NLCs) can be utilised in drug delivery of NSAIDs to decrease adverse effects and create controlled-release oral formulations. The utilisation of NLCs in transdermal and topical formulations of NSAIDs has demonstrated better efficacy in alleviating inflammation and pain, both at the site of application and throughout the body. This review offers concise insights into the characteristics and mode of action of NSAIDs in the inflammatory cascade. The current review provides a complete overview of the advanced functions of NLCs in delivering NSAIDs through various routes of administrations, including buccal, cutaneous, transdermal, ocular, oral controlled, parenteral and pulmonary routes. To accomplish this objective, an extensive literature search was conducted utilising the *ScienceDirect*, *PubMed* and *Google Scholar* databases. A systematic review was undertaken using scholarly publications published in peer-reviewed journals from 2000 to 2024. Research has established that NLCs possess considerable potential in offering diverse benefits in the delivery of NSAIDs. These benefits include improved skin penetration and precise targeting when applied topically, enhanced drug retention on the corneal surface and effective transport across ocular barriers when administered to the eyes, extended drug residence period in the lungs and increased diffusion mobility when administered through the pulmonary route, as well as prolonged and sustained duration of action when administered buccally, parenterally, or orally. This analysis emphasises the considerable capacity of NLCs to efficiently transport NSAIDs while reducing their negative impacts in the management of inflammatory diseases.

Key words: Drug administration, buccal; Drug delivery systems; Inflammation; Anti-inflammatory agents, non-steroidal; Nanostructured lipid carriers; Administration, ophthalmic; Administration, cutaneous.

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Graphical abstract is presented in Figure 1.

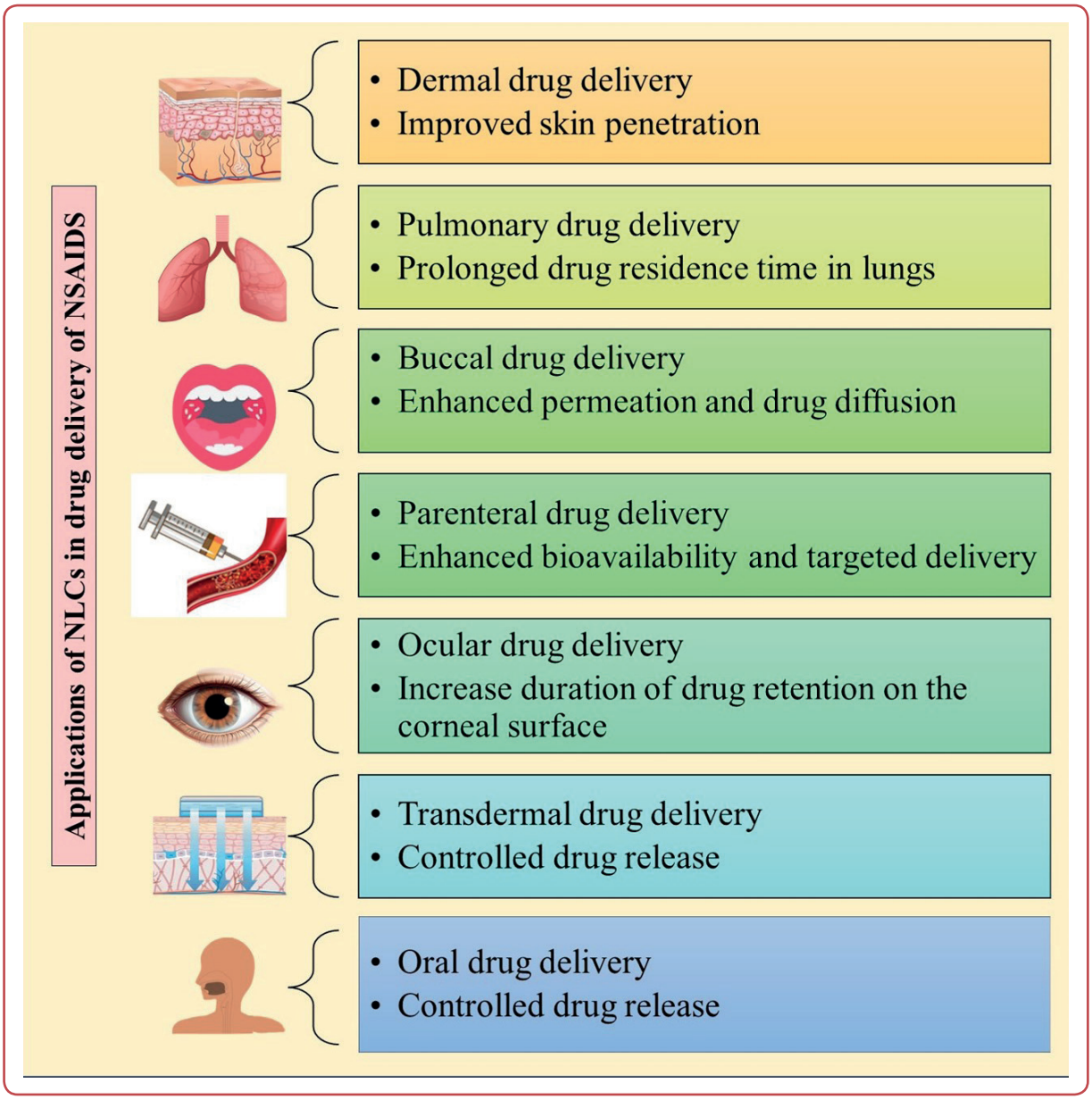

Figure 1: *Graphical abstract*

Introduction

Due to their high efficacy in alleviating inflammation and pain, doctors commonly recommend nonsteroidal anti-inflammatory drugs (NSAIDs). Nevertheless, they are frequently associated with potentially fatal gastrointestinal adverse effects like profound haemorrhaging or gastroduodenal ulcer rupture. Biopharmaceutics Classification System (BCS) class II or IV lists the majority of NSAIDs, indicating their minimal solubility and permeability.[1] Nanocarriers have demonstrated significant importance as delivery systems because of their small size and unique properties and have shown numerous benefits, such as safeguarding the drug from environmental factors like moisture, physiological pH and enzymes. They also reduce dosage, prolong circulation time, improve intracellular permeation and enable targeted delivery by modifying the nano-

carrier's surface.[2, 3] The various types of nanocarriers, such as nanostructured lipid carriers, nanocrystals, nanowires, nanotubes, liposomes, dendrimers and polymeric nanoparticles, have been synthesised for the delivery of drugs and diagnostics. Nanostructured lipid carriers (NLCs) are well acknowledged as a highly esteemed nanocarrier for conveying various medicinal compounds within lipid nanoparticles.[4] NLCs are a novel form of solid lipid nanoparticles that were specifically engineered to address their inherent constraints. NLCs often have dimensions that fall within the region of approximately 200 to 400 nm. However, rather than exclusively utilising a solid lipid, a fraction of it is substituted with an oil. Consequently, this causes a less structured arrangement of lipids, facilitating enhanced encapsulation of drugs and avoiding drug seepage throughout storage.[5, 6] Researchers are assessing NLCs as promising nanocarriers for drug delivery due to their biocompatibility and superior formulation characteristics compared to solid lipid nanoparticles. Currently, researchers are focusing on investigating the development, analysis and verification of drug-loaded NLCs for the goal of delivering and targeting drugs.[7]

This current review aims to provide a detailed overview of the following features: (a) an overview of NLCs and their various forms and (b) the distinctive features and mechanism of action of NSAIDs. (c) The current advanced status of NLCs, as emerging lipid-based nanocarriers in drug administration, is being discussed. (d) The diverse capabilities of NLCs in delivering NSAIDs through various routes of administration, such as oral-controlled, buccal, cutaneous, transdermal, ophthalmic, parenteral and pulmonary.

Types of nanostructured lipid carrier

The production of NLCs typically entails combining solid lipids and liquid lipids in a ratio from 70:30 to 99.9:0.1, while the surfactant concentration utilised generally falls between 1.5 % and 5 % (w/v). The manufacturing process and the composition of the lipid mixture can generate three categories of NLCs. These types include the amorphous or structureless type, the imperfect type and the multiple type.[8] Figure 2 illustrates the three categories of NLCs, categorised according to the composition of their lipids.

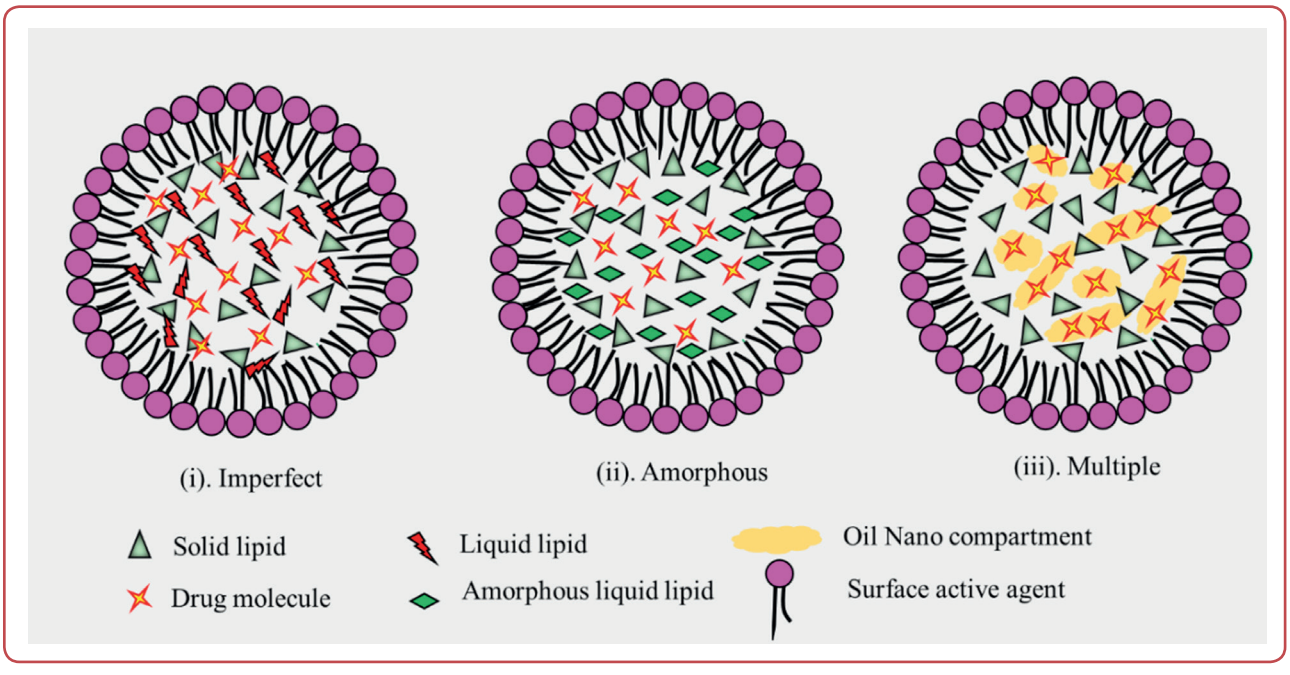

Figure 2: Different types of nanostructured lipid carriers (NLCs): (i) imperfect (ii) amorphous and (iii) multiple type

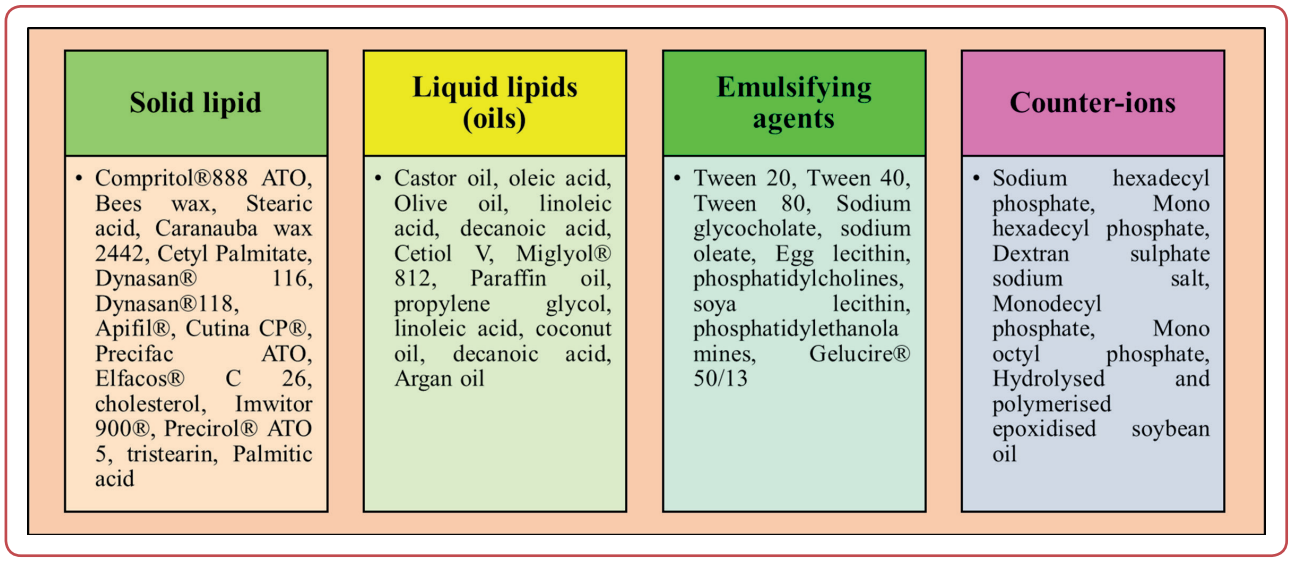

Figure 3: Excipients used in formulating nanostructured lipid carriers (NLCs)

Imperfect type (Type I NLC)

They are characterised by a highly disorganised matrix that contains a substantial number of empty spaces and voids. These empty areas may accommodate a sufficient quantity of drug molecules organised in non-crystalline clusters. The introduction of liquid lipids (oils) in appropriate ratios can result in the formation of these structural imperfections in the crystal lattice of lipids.[9]

Amorphous or structure-less type (Type II NLC)

The absence of a crystalline structure can entirely inhibit or markedly decrease the quantity of medicine lost due to leakage. The presence of a lipid mixture hinders the formation of crystals because crystals are typically formed when the substance is cooled.[10]

Multiple type (Type III NLC)

NLC is primarily a fat-in-water or oil-in-solid form and the exclusive means of its production is through the phase separation process. This method can be employed in the construction of NLCs to improve drug load potential and stability, particularly when the molecule has higher solubility in oil.[11]

Excipients used in formulating NLCs

NLCs typically consist of lipids (both solid and liquid), surfactants, organic solvents and other components, such as counterions and surface modifiers. Figure 3 depicts the excipients utilised in the formulation of NLCs.

Preparation methods

The development of nano-lipid carriers can utilise several different formulation strategies. The preparation techniques for lipid nanoparticles like solid lipid nanoparticles (SLNs) and NLC are quite similar. The only difference between the two formulations is the absence or presence of liquid lipids. In general, NLCs are formulated by nanoemulsifying a lipophilic phase consisting of a combination of solid lipid and liquid lipid in an aqueous solution containing water-soluble emulsifiers.[2, 12] The various techniques employed for the development of NLCs are summarised in the Table 1, along with advantages and limitations of these techniques.

Table 1: Summary of different preparation techniques utilised for development of nanostructured lipid carriers (NLCs) and their advantages and limitations

Description of methodology	Advantages	Limitations
High-pressure hot homogenisation technique Liquid lipid and drug are added to pre-melted solid lipid with subsequent mixing into aqueous surfactant solution to produce pre-emulsion. The processing of pre-emulsion in high pressure homogeniser produces nano-emulsion which on cooling at room temperature recrystallises to form NLC.	Free from organic solvents	Not used for heat sensitive drugs[13-15]

High-pressure cold homogenisation technique Melted lipid comprising drug is solidified quickly by dry ice or liquid nitrogen followed by milling and grinding. These nanoparticles are dispersed into cold surfactant solution and then homogenised at room temperature to produce NLC.	Increased and unform drug entrapment	Size-range variation is larger[16-19]
Solvent-emulsification evaporation technique The lipids and drug are solubilised in water-miscible organic solvent. This lipid solution is emulsified with continuously stirring in aqueous surfactant solution. The evaporation of organic solvent, causing the lipids to precipitate in aqueous phase, resulting in development of NLCs.	Suitable for thermos-sensitive drugs	Involves use of organic solvent, lyophilisation required[20-23]
Solvent-emulsification diffusion method The drug is solubilised in water miscible organic solvent till thermodynamic equilibrium to produce saturated solution. The lipid is dissolved and emulsified with solvent-saturated aqueous emulsifier to produce oil-in-water emulsion. After dilution of o/w emulsion, nanoparticles get precipitate out.	Suitable for thermos-sensitive drugs	Use of organic solvent[24-30]
Microemulsion method Solid lipid is melted followed by mixing of liquid lipid. The drug is dissolved in lipid melt. Aqueous mixture comprised of emulsifier, water and co-emulsifier is heated to achieve the same temperature. This aqueous phase is mixed with the lipid phase with continuous stirring to get stable oil-in-water microemulsion. The hot microemulsion is then added to the chilled water which leads to breakdown of microemulsion into nano-emulsion.	Least particle aggregation, no special equipment required	Not used for heat sensitive drugs, emulsifier required [31, 32-30]
Double emulsion method Drug is dissolved in water and subsequently aqueous phase is dispersed in lipid phase to produce primary emulsion. This emulsion is dispersed in aqueous solution of surfactant and sonicated to produce double emulsion. Solvent is evaporated for purification of lipid nanoparticles.	Suitable for hydrophilic agents	Two-step process[33, 34]
Phase inversion technique Ingredients are heated while continuously stirring and this mixture is then subjected to three cooling and heating cycles (85-60-85 °C). This mixture is diluted with chilled water to create NLC via phase inversion.	Organic solvent free method	Tedious process[35-37]
Solvent injection method The process involves dissolving of drug and lipids in water-miscible solvent, followed by their dispersion into aqueous surfactant solution using injection needle.	Easy and rapid method	Residual solvent[38-43]

Mechanism of action of NSAIDs in inflammatory cascade

Figure 4 illustrates the chemical structures of NSAIDs, which have led to the development of NLCs in previous years.[12, 44-47] NSAIDs function as both pain relievers and anti-inflammatory medicines by blocking the enzyme activity of cyclooxygenase, primarily COX-1 and COX-2.[48] Inhibiting COX-2 results in the anti-inflammatory effects of NSAIDs, while excessive inhibition of COX-1 produces the ulcerogenic effects. The local mechanism of action of NSAIDs may contribute to the unpleasant effects they induce on the gastrointestinal system. Research demonstrates that NSAIDs maintain their crystalline form in the stomach's extremely acidic conditions.[49, 50] Figure 5 schematically depicts the COX inflammatory pathway and the mechanisms of action of NSAIDs in the inflammatory cascade.

In addition, NSAIDs are associated with numerous severe and sometimes fatal adverse effects, particularly with prolonged use, which can increase mortality and morbidity rates. Extended use of

NSAIDs has been associated with an increased risk of gastrointestinal bleeding.[51, 52] Challenges such as limited bioavailability, non-specific biodistribution and/or a short half-life inside the body can hinder drug efficacy. Furthermore, it is essential to deliver substantial amounts of drug to patients, which can result in unintended side effects and a relatively restricted effectiveness in relieving the symptoms of inflammatory disorders.[53, 54] The oral route is the predominant method of administering NSAIDs. Orally administered NSAIDs provide the potential for many side effects, with the most prevalent being irritation of the gastrointestinal tract.[55] Pharmaceutical nanotechnology has progressed, allowing for the use of carriers to transport drugs to specific tissues and release them at ideal concentrations, hence enhancing drug delivery options. This method has the potential to increase the accumulation of substances that reduce inflammation and enhance their effectiveness. The quest for a drug delivery system based on nanotechnology has gained popularity due to its capacity to reduce negative effects and overcome limitations in pharmacology. At the same time, it enhances safety, effectiveness and cost-efficiency in treating inflammation.[12, 56-59]

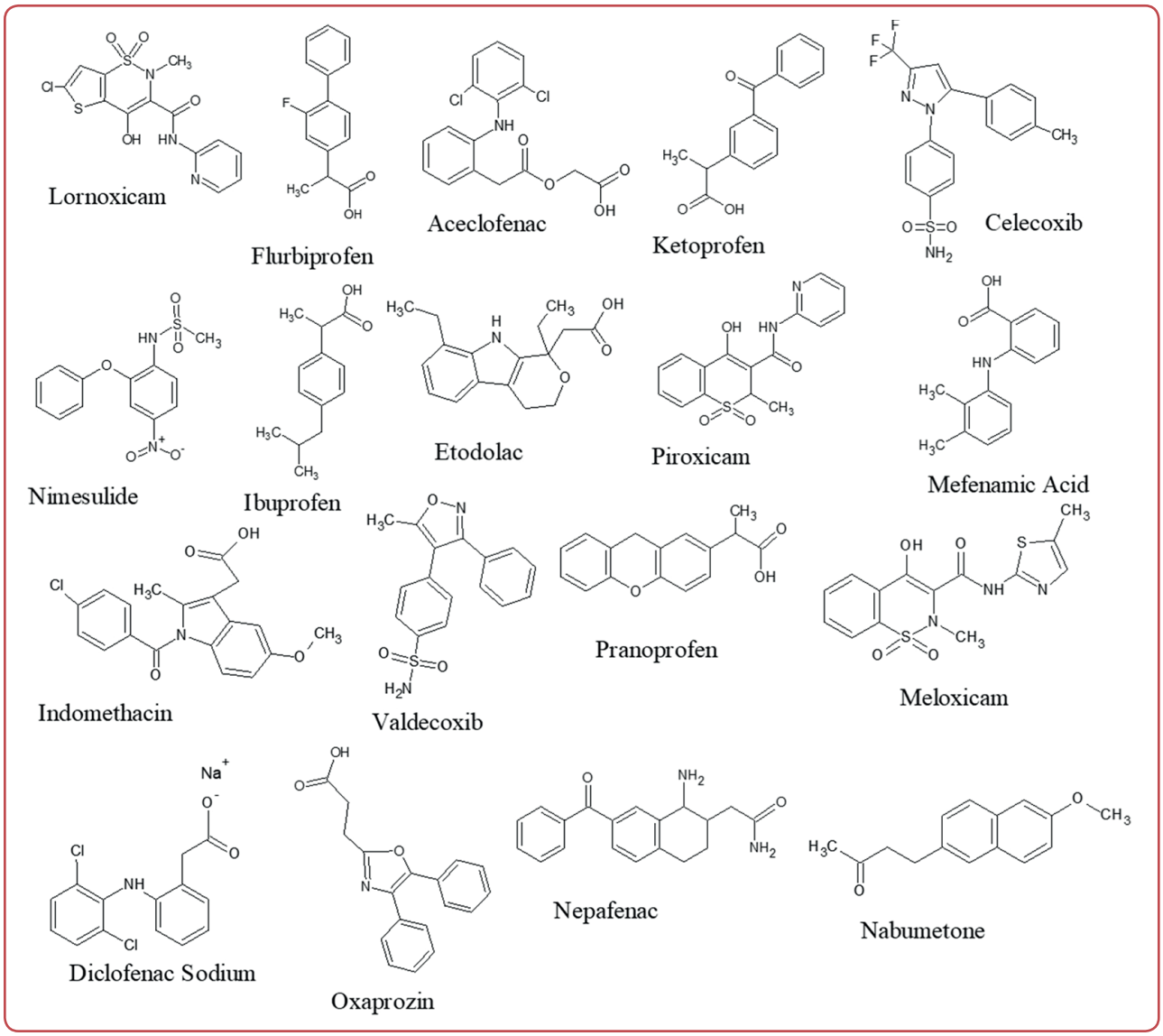

Figure 4: Chemical structures of nonsteroidal anti-inflammatory drugs (NSAIDs)

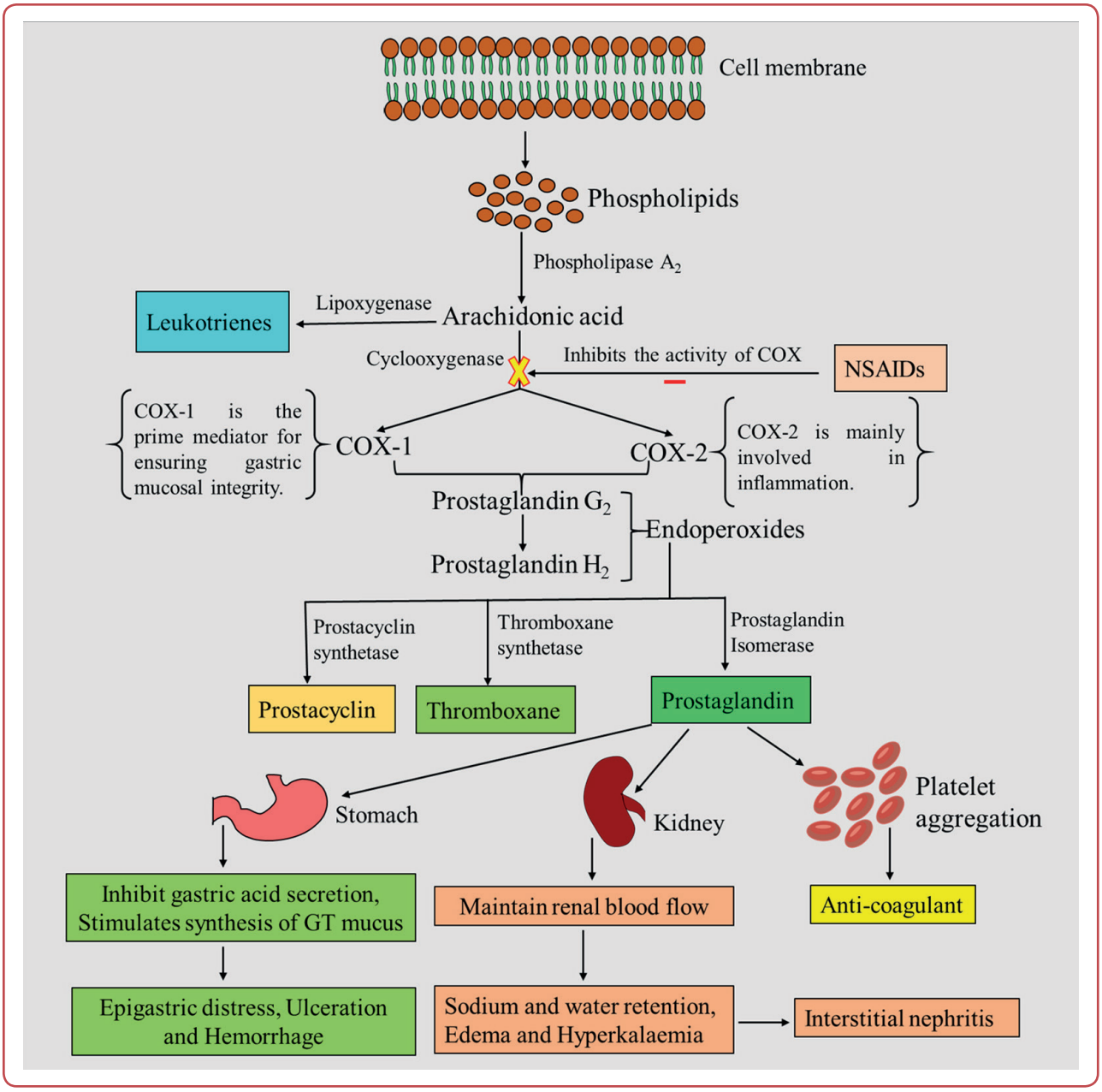

Figure 5: Mode of action of nonsteroidal anti-inflammatory drugs (NSAIDs) through cyclooxygenase (COX) pathway in inflammatory cascade

GT: gastrointestinal;

Nanostructured lipid carriers: emerging nanocarrier in drug delivery

The advancements in understanding the cellular and molecular mechanisms that initiate inflammation and pain have provided opportunities for novel treatments, particularly through the manufacture of well-crafted nanomedicine. Over the past decade, nanotechnology has experienced significant growth and now includes a wide range of scientific fields. The goal of this field of study at the nanoscale level is to develop innovative materials that possess unique and effective properties. Additionally, we can specifically engineer nanoparticles to reach the desired tissue from the delivery site, thereby addressing significant issues associated with conventional

medicines, such as systemic toxicity and unintended harmful effects on other organs, exacerbated by repeated and prolonged doses.[60] The ability to create nanoparticles that are similar in size to proteins has greatly advanced the field of biomedicine, leading to multiple potential applications. These nanoparticles possess the capacity to activate, react to and have a substantial impact on the tissues and cells that are the main focus of the treatment. The aim is to elicit the required physiological responses while concurrently mitigating the unfavourable effects of the treatment. Furthermore, nanotechnology possesses the capability to facilitate a more accurate and optimal control of intricate natural systems compared to conventional pharmaceutical methods, like the blood-brain barrier.[61, 62] The current purpose for creating nanoparticles has been to design a technique for addressing, identifying and averting pain and inflammatory ailments. Several types of nanoparticles, including liposomes, microcapsules, dendrimers, quantum dots, niosomes, NLCs, nanocrystals, nanosuspensions, SLNs, ethosomes, nanoemulsions and pharmacosomes, are commonly used as carriers for different NSAID drugs to enhance specific properties of this drug class.[28-30] NLCs are highly desirable nanocarriers for delivering different NSAIDs due to their capacity to hold a larger quantity of drug molecules.[31] In recent years, numerous studies have addressed NLCs as advanced nano-based systems for diverse drug delivery methods to effectively control inflammatory diseases (Figure 6).

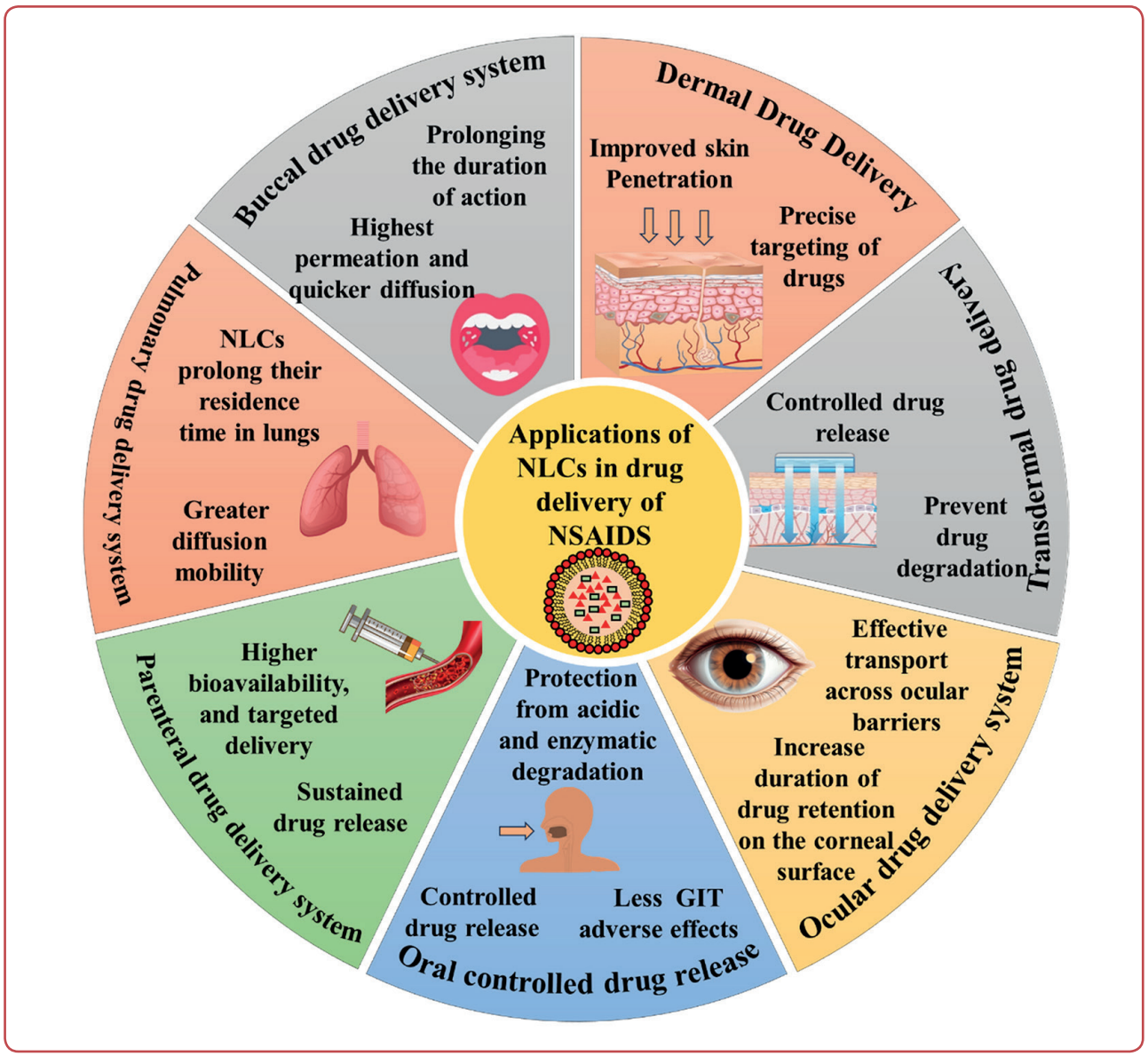

Figure 6: Pictorial depiction of applications of nanostructured lipid carriers (NLCs) in versatile drug delivery systems

NSAIDS: non-steroidal anti-inflammatory drugs; GIT: gastrointestinal tract;

Intricate role of nanostructured lipid carrier in drug delivery of NSAIDs

Nanostructured lipid carrier in dermal drug delivery of NSAIDs

Dermal drug application is a commonly used method for treating skin problems. The *stratum corneum*, which is the uppermost protective skin layer, functions as a potent physical barrier, effectively keeping chemicals from penetrating the innermost layers of the skin. The physicochemical features of the active components and transporters greatly limit the ability of drugs to enter the skin. To ensure effective therapy, the drug particles need to permeate the specific skin layers that treatment requires, at an appropriate concentration and persist there for a specified duration.[63, 64] The topical administration of drugs using traditional dose forms, such as creams and ointments, often lacks precision and may result in restricted drug absorption into the skin, which can vary considerably. In order to address these complexities, innovative drug delivery methods are thoroughly assessed. Nanoparticulate drug delivery techniques, namely NLCs, have garnered considerable interest in recent times owing to their capacity to improve skin permeation and deliver drugs specifically to specific skin regions. Lipids that exhibit both biocompatibility and biodegradability form the basis of NLCs. These lipids are great for applying drugs topically because they help control the release of active ingredients, make drugs more stable chemically, allow more active ingredients to penetrate deeper into the skin and target specific layers of the skin with drugs.[65, 66] Kharwade and Mahajan prepared the lornoxicam-loaded NLCs and then incorporated these NLCs in the topical gel and the outcome of the *in-vitro* release study demonstrated that the prepared gels exhibited the extended release property for 24 h and also the percentage drug release exhibited by the gel was 90.92 % ± 1.96 % at the end of 24 h.[67] Table 2 outlines the use of different NLCs as a means of delivering NSAIDs topically. The goal is to maximise the amount of the drug in the local soft tissues and joints, while minimising its distribution throughout the body to prevent side effects.

Table 2: Exploration of nonsteroidal anti-inflammatory drugs (NSAIDs) loaded nanostructured lipid carriers (NLCs) for the dermal drug delivery used in management of the pain and inflammatory conditions

Drug (technique)	**Excipients**	**Outcome and significance**
Fenoprofen calcium (Emulsion evaporation-solidification at low temperature)	Compritol 888, Tween 80, Oleic acid, Brij 30	Desirability function of optimised fenoprofen calcium NLCs was found to be 0.874. The EE %, flux and percentage yield of fenoprofen calcium NLCs was found to be 72.98 %, 136.19 µg/cm^2/h and 92.89 %.[68]
Aceclofenac (Microemulsion method)	Transcutol® P, Cetyl alcohol, Tween 80, phospholipid	*In-vitro* drug release result indicated that the formulated preparation exhibited biphasic drug release, consisting of an early burst release and then a sustained release for 48 h.[69]
Aceclofenac (Ultra sonication technique or high-speed homogenisation process)	Phospholipon 90 H, stearic acid, tween 80, oleic acid	The prepared NLCs exhibits the spherical uniform particles with size below 500 nm, EE % in the range of 75-85 %. The drug release profile of all the NLCs was found to be between 40 %-78 % after 8 h study and also the optimised NLCs exhibited biphasic drug release pattern, consisting of an early burst release and then a sustained release.[70]
Lornoxicam (High-pressure homogenisation method)	Oleic acid, Poloxamer188, Precirol ATO-5	*In-vitro* release investigation of formed gels demonstrated extended release of drug for 24 h and showed 90.92 % ± 1.96 % of percentage drug release at the end of 24 h.[67]
Aceclofenac (Melt ultrasonication and high-speed homogenisation)	Compritol 888 ATO, Polysorbate 80, PEG-8, Miglyol® 812	*In-vitro* drug diffusion/release investigation exhibited excellent release of drug from the NLCs and in contrast, to the control and standard group, the optimised NLCs gel exhibited a significant reduction in paw volume, markedly decreased inflammation as well as exhibited sustained action.[71]

Flurbiprofen (Hot high-pressure homogenisation technique)	Compritol® ATO 888, Lecithin, Poloxamer 188, Sodium deoxycholate, Miglyol® 812	Flurbiprofen NLC-gel exhibited a more prominent permeation behaviour than Flurbiprofen loaded common gel and no oedema and erythema observed on topical application flurbiprofen NLC-gel as well as the quantity of drug deposited in skin is more on topical application than oral administration.[72]
Flurbiprofen (High-pressure homogenisation technique)	Compritol® ATO 888, stearic acid, miglyol1 812, castor oil, tween 80	The results of *ex-vivo* studies revealed that the NLCs provides delayed and sustained permeation.[73]
Celecoxib (Microemulsion template technique)	Glyceryl dilaurate, cremophor RH 40, capmul MCM, transcutol	The NLCs exhibited quicker onset and induced prolonged action up to 24 h.[74]
Ketoprofen (Ultrasonication)	Glycerol, Compritol® 888 ATO, β-cyclodextrin, Lutrol® F68	The formulation containing the ketoprofen-β-Cd-epichlorohydrin polymer co-ground product loaded into NLCs, showed 50 % and 23 % enhancement in drug permeation rate in contrast to simple drug suspension gel or the plain drug-loaded NLCs gel respectively.[75]
Nimesulide (Melt emulsification ultrasound dispersion method)	Stearic acid, oleic acid, lecithin, poloxamer 188	The optimised NLCs exhibited particle size of 214.4 ± 11 nm, mean flux of 2.66 ± 0.09 μg/cm^2/h and EE % of 89.4 ± 3.40 %. The outcomes of in-vitro drug release investigation revealed that NLCs exhibited prolonged drug release behaviour and followed Higuchi release kinetics.[76]
Lornoxicam (Emulsification-solvent evaporation)	Precirol ATO5, oleic acid	The results of *ex-vivo* permeation studies indicated reduced systemic uptake of drug from NLCs in comparison to lornoxicam gel which signifies the minimum systemic side effects and also the formulated drug loaded NLCs exhibited more anti-inflammatory effectiveness compared to marketed formulation and lornoxicam gel in carrageenan induced rat paw oedema.[77]
Ibuprofen (Hot high-pressure homogenisation method)	Witepsol E85, Lutrol F68, Miglyol 812	Ibuprofen loaded NLCs exhibited EE % of 98.51 and drug loading of 9.85 %. The outcomes of in-vitro diffusion investigation revealed that Ibuprofen loaded NLCs possess higher permeation than Ibuprofen solution.[78]
Etodolac (Melt-emulsification and ultrasonication method)	GMS, Tween 20, Capryol 90	Etodolac loaded NLCs of optimised formulation shows the EE %, particle size, PDI and zeta potential 86 %, 275 nm, 0.55, -33 mV respectively. Optimised NLCs exhibited bi-phasic release profile characterised by a burst action followed by prolonged release.[79]
Indomethacin (Ultrasonication)	Compritol 888 ATO, Miglyol 812	Indomethacin loaded NLCs gel shows prolonged anti-inflammatory effects upon topical application.[80]
Mefenamic acid (Microemulsion method)	Tween 80, Isopropyl myristate, Caprylic acid, Cetyl palmitate	In comparison to nano-emulsion which possess constant sustained release, solid lipid nanoparticles (SLN) and NLCs displayed biphasic release profile- rapid initial release then by a sustained release. NLCs exhibited better stability as compared to SLN and nanoemulsion.[81]
Piroxicam (Microemulsion method)	Soy lecithin, Ethyl oleate, Tween 80, n-butanol	The drug loaded NLCs showed EE % of 100 % and also showed a prolonged release pattern, releasing up to 60 % of encapsulated drug within 120 h. Moreover, no skin irritation is shown on topical application.[82]
Valdecoxib (Microemulsion template technique)	Caproyl 90, GMS, Glyceryl Dilaurate, Labrasol, Tween 80	NLCs exhibited a quicker onset and sustained action for up to 24 h.[83]
Pranoprofen (High pressure homogenisation technique)	LAS (PEG-8 Caprylic/Capric Glycerides), precirol® ATO 5, castor oil, tween 80	The controlled release enhances drug-skin contact, enhancing dermal retention.[84]

Celecoxib (Hot high -pressure homogenisation method)	Compritol, tween 80, miglyol	The cumulative permeation of the drug in micro dialysis dialysate was considerably higher ($p < 0.001$) than that of the drug-encapsulated NLCs and drug solution after 24 h. Surface modification of NLC with cell-penetrating peptides may improve the permeation of the drug in skin.[85]

Nanostructured lipid carrier in transdermal drug delivery of NSAIDs

Numerous inflammatory illnesses localise near the skin's outer layer, making the transdermal drug administration method an advantageous and efficient way to administer pharmaceuticals. Transdermal delivery of NSAIDs at the site of inflammation has the benefit of bringing the drug directly to the inflamed area, which improves its systemic effects and avoids the side effects that come with taking the drug by mouth. Studies have demonstrated that transdermal drug administration aids in the elimination of first-pass metabolism and safeguards the gastrointestinal tract from damage. This leads to an additional enhancement of the safety profile and patient adherence.[86] Because it is a better barrier, the *stratum corneum* helps transdermal drug delivery systems work by limiting the amount of active drug particles that can be absorbed by the different layers of skin. It is crucial to implement measures to guarantee optimal absorption and retention of sufficient active medicinal substances in the skin. Moreover, the presence of substantial quantities of the active drug in targeted areas of the skin confers benefits by enhancing the clinical efficacy of inflammatory treatment.[87] Thus, in order to reduce the effectiveness of the barrier function of the skin and increase the absorption of drugs *via* it, numerous strategies have been designed over the last few years. These methods encompass chemical and physical procedures for improvement, such as magnetophoresis, electroporation, iontophoresis and microneedles. However, the limited usefulness and security of these methods constrain their utilisation. An effective technique to enhance drug absorption *via* the skin is by employing nanoparticles, such as NLCs. The NLCs have demonstrated improved stability, a controlled drug release mechanism and exceptional biocompatibility. Furthermore, NLCs have the capability to reduce the barrier function of the skin and enhance the lipid solubility of drugs, hence improving their effective distribution through the skin and providing protection against drug degradation.[88] Bawazeer et al formulated tenoxicam-loaded NLCs for effective transdermal drug delivery at the target site. The *ex-vivo* skin permeation study showed that the drug was able to pass through the skin more easily because of the lipid content inside the applied hydrogel. This made it easier for the drug to reach the *stratum corneum*.[53] Table 3 outlines the NLCs used as vehicles for transdermal administration of NSAIDs.

Table 3: Exploration of anti-inflammatory drugs (NSAIDs) loaded nanostructured lipid carriers (NLCs) for the transdermal drug delivery used in management of the pain and inflammatory conditions

Drug (technique)	**Excipients**	**Outcome and significance**
Meloxicam (Microemulsion method)	Tween 80, Isopropyl myristate, Caprylic acid, Cetyl palmitate	In comparison to meloxicam gel, meloxicam loaded NLCs gel exhibited sustained release, improved the permeation of drug in skin and deposition of drug molecules mainly into the dermis. The meloxicam loaded NLCs gel showed biocompatibility, excellent skin tolerability and excellent anti-inflammatory effectiveness without toxicity.[89]
Diclofenac sodium (Hot homogenisation followed by ultra-sonication)	GMS, Phospholipon® 90G, Lanolin PEG-75, Glyceryl palmito-stearate, Tween 80	Controlled release pattern and excellent drug penetration as well as greater *in vivo* efficacy.[90]
Flurbiprofen (Emulsification homogenisation-sonication technique)	Coconut oil, tween 80, soya lecithin and stearic acid	The NLCs penetrate the layers of skin and accumulate in the dermis, there was 1.7-fold increase in bioavailability of drug, drug loaded NLCs exhibited early onset and prolonged anti-inflammatory activity over period of 24 h in comparison with the commercial gel for carrageenan-induced rat paw oedema.[91]

Lornoxicam (Emulsion evaporation and low temperature solidification technique)	Soy lecithin, GMS, tween 80	The results of *in-vitro* skin permeation study indicated greater permeation-increasing capacity of R11 (Six histidine-tagged polyarginine containing 11 arginine peptides) (0.02 %, w/w) in comparison to other content (0.01 % or 0.04 %). Also, lornoxicam loaded-NLC-R11 gels showed higher inhibitory actions on rat paw oedema and the secretion of inflammatory cytokines than drug loaded-NLC gels and lornoxicam gels ($p < 0.01$).[92]
Pranoprofen (High pressure homogenisation technique)	Precirol® ATO 5, castor oil, tween 80	The outcome of the *in vivo* investigation indicated that the NLCs showed considerable decrease in dermal oedema and increasing dermal retention as well as exhibited controlled release.[93]
Aceclofenac (Microemulsion method)	GMS, stearic acid, cetyl alcohol, transcutol, tween 80, labrafac, labrasol	The outcomes of *ex-vivo* skin permeation exhibited that the cetyl alcohol containing NLCs exhibited highest cumulative drug permeation (> 3200 µg) as well as the in vivo study indicates that cetyl alcohol containing NLCs-gel formulation showed highly significant ($p < 0.001$) drug release in comparison to marketed gel formulation after 24 h.[94]
Tenoxicam (High shear homogenisation and ultrasonication technique)	Compritol 888 ATO, isopropyl myristate, Pluronic F68, Pluronic F127	The optimised formulation possesses the EE % of 92.36 % and the *in-vivo* study outcome indicates that the optimised formulation is equal to oral tenoxicam in decreasing the excessive inflammatory response caused by carrageenan after irradiation.[53]
Meloxicam (Melt emulsification followed by ultra-sonication)	Compritol, oleic acid, Pluronic F-68	Meloxicam loaded NLCs gel exhibited more sustained inhibitory action in comparison to free meloxicam gel.[95]
Flurbiprofen (Hot homogenisation followed by sonication technique)	Captex 355 EP/NF, Dynasan 114, polysorbate 80, phosphatidylcholine	The NLCs indicated superior entrapment efficiency and quicker release than SLNs. Both the dispersions and gels of NLCs and SLNs possessed sustained release of drug over period of 24 h, with a greater impact observed in the gels of NLCs and SLNs.[96]
Lornoxicam (High pressure Homogenisation method)	Compritol® 888 ATO, Oleic acid, Lanette® O	In comparison to conventional lornoxicam formulation gel, these possess 3-4 times higher drug penetration rate via skin and the nanoemulsion exhibited greatest penetration rate followed by NLCs, SLNs and a lornoxicam gel.[56]

Nanostructured lipid carrier in ocular drug delivery of NSAIDs

Drug delivery devices encounter substantial obstacles when specifically targeting the eye. The drug's ability to reach the eye is hindered by various physical barriers, including the corneal epithelium, iris blood vessels lacking fenestrations, the muco-aqueous barrier, the non-pigmented layer of the ciliary epithelium and the retinal pigment epithelium, as well as the epithelium of the retinal vessels.[97] Moreover, physiological factors such as the act of blinking and the process of tear drainage might diminish the duration during which ocular drug delivery systems stay in the eye. The tiny size of nanocarriers in nanotechnology has facilitated their extensive use in numerous ophthalmic applications, allowing for efficient transport across ocular barriers.[3, 98] The toxicity and elimination of the nanocarrier are expected to differ based on the precise mode of administration to the eye, such as topical, intravenous, intravitreal, transscleral, suprachoroidal, or subretinal. Hence, it is imperative to tailor the nanocarriers according to the precise site of delivery, the encapsulated drugs and the targeted ailment for therapeutic purposes. Lipid-based nanocarriers, namely NLCs, have emerged as a key approach in the area of nanotechnology for the targeted delivery of drugs to the eyes. The nanocarriers have been altered to increase the length of time that drugs are held on the ocular surface, all while enclosing different types of drugs. NLCs formulated for ocular delivery demonstrated extended duration and improved ocular bioavailability of the enclosed drug within the eye.[99-101] Gonzalez-Mira et al developed the flurbiprofen loaded NLCs and the outcomes of *in-vitro* release study revealed that that NLCs exhibited the sustained release pattern as well as the NLCs does not show any toxicity on ocular tissues.[102] Table 4 outlines the use of NLCs as vehicles

for NSAIDs in ocular drug delivery. NLCs are explored because they can help overcome physical obstacles that prevent drugs from reaching the eye when administered.

Table 4: Exploration of anti-inflammatory drugs (NSAIDs) loaded nanostructured lipid carriers (NLCs) for ocular drug delivery used in management of the pain and inflammatory conditions

Drug (technique)	**Excipients**	**Outcome and significance**
Oxaprozin (Modified organic solvent-free emulsification/sonication method combining high shear homogenisation in an ultra-turrax, followed by an ultra-sonication)	Miglyol 182, Tween 60, Precirol ATO 5	Exhibited polydispersity index, particle sise, zeta potential, EE % and loading capacity of approximately 0.2, 200 nm, −40 mV, 95 % and 9 % respectively. The formulations-maintained the release of drug in simulated gastric fluid and enhancing its release in simulated intestinal fluid. The results reveal that formulation have a significant potential for oral administration of oxaprozin with much less gastro-intestinal adverse effects.[54]
Flurbiprofen (Ultrasound method)	Stearic acid, castor oil, tween 80	The NLCs developed possessed the diameter, PI and Zeta potential of 288 nm, 0.245 and −29 mV. The optimised NLCs dispersions showed low irritation or toxicity to the external ocular tissues.[103]
Ibuprofen (Melted-ultrasonic technique)	Compritol ATO,Gelucire 44/14, Miglyol 812, Cremphor EL 40, Transcutol P	The NLCs containing stearylamine exhibited a prolonged pre-ocular retention duration. This may be due to the positive charge present on the surface of the cationic NLC particles, which enhances their affinity for the negatively charged corneal surface, hence leading to an extended retention period.[104]
Ibuprofen (Melt-emulsification and ultrasonication method)	Precirol® ATO 5, Gelucire® 44/14, miglyol® 812, cetyl-trimethylammonium bromide, tween 80	The obtained NLCs possessed the EE% of ~ 87% and the results of HET-CAM assay study revealed that these NLCs does not cause any irritation as well as the results of *in-vitro* release studies demonstrated ibuprofen release over several hours.[105]
Flurbiprofen (High pressure homogenisation)	Tween 80, stearic acid, miglyol 812, castor oil	The NLCs possessed high encapsulation efficiency (~90 %) and the results of *in-vitro* study revealed that the NLCs exhibited sustained release behaviour.[102]
Ibuprofen (Melt-emulsification and ultra-sonication method)	Precirol® ATO 5, miglyol® 812, cetyltrimethylammonium bromide, tween 80, gelucire® 44/14	The results revealed that the addition of pluronic F-127and chitosan to NLCs dispersions increases ophthalmic formulation's bioavail-ability and enhances pre-corneal residence time as well as promot-ing the sustained release of the drug.[106]
Nepafenac (Melt-emulsification and ultra-sonication)	Miglyol 812N, GMS, cremophor EL, soy lecithin	The *in-vitro* drug release indicated that drug loaded NLCs exhibited sustained release for 24 h in a biphasic pattern and the outcomes of preliminary cellular uptake study of NLCs revealed increased pene-tration of nepafenac into human corneal epithelial cells.[107]
Ibuprofen (Melt-emulsification and ultra-sonication method)	Compritol 888 ATO, tween 80, miglyol 812	The inclusion of thermo-responsive polymers into NLC dispersions with ibuprofen for ocular delivery resulted in an elevation in viscosi-ty as a consequence of temperature rise. The formulated optimised formulation exhibited excellent stability and showed a sustained re-lease profile of ibuprofen.[108]
Flurbiprofen (Melt- ultrasonic method)	Compritol ATO 888, solutol HS 15, glycerol, tween 80, gelucire 44/14, miglyol 812	Flurbiprofen-NLCs exhibited slightly greater apparent permeability coefficients in comparison to FP-phosphate eye drops. However, when NLCs were coated with chitosan oligosaccharides, they had a considerably greater apparent permeability coefficient, showing a 2.4-fold higher than non-coated NLCs.[109]

Nanostructured lipid carrier in oral controlled drug delivery of NSAIDs

The convenience of taking drug orally and the willingness of patients to comply with this method are two important factors that contribute to the improved therapeutic effectiveness of orally delivered medicines, emphasising their importance and popularity. Oral formulations are expected to face several obstacles because the gastrointestinal system's main function is to break down and remove chemicals.[110] The gastrointestinal tract (GIT) exhibits a broad spectrum of pH levels, ranging from very acidic in the stomach to almost neutral in the large intestine. Furthermore, the GIT generates and releases many enzymes. The GIT harbours numerous proteolytic enzymes with the capacity to degrade a diverse array of chemical compounds.[111] Pharmaceutical drugs can be enclosed within several types of nanoparticles, such as NLCs, to shield them from the acidic and enzyme-filled conditions of the GIT. Moreover, it has the potential to augment the adhesion and retention of drugs in GIT, leading to increased drug absorption. The NLCs, which are encapsulated with NSAIDs, efficiently alleviate the detrimental gastrointestinal side effects linked to these drugs when taken orally. This delivery mechanism enables a controlled and specific release of NSAIDs.[112] NLCs have been investigated as carriers for NSAIDs to mitigate the negative effects associated with their oral use. Additionally, NLCs have been employed as vehicles for controlled release of NSAIDs when administered orally. Lopes-de-Araújo et al developed lipid nanoparticles containing oxaprozin to prevent the occurrence of oral side effects. The prepared nanocarrier had a polydispersity index of approximately 0.2, a particle size of 200 nm, a zeta potential of -40 mV, an EE of 95 % and a loading capacity of 9 %. The formulations ensured controlled drug release in simulated gastric fluid while enhancing its release in simulated intestinal fluid. The findings demonstrate that the developed nanocarrier has considerable potential for the oral delivery of oxaprozin, while significantly reducing gastrointestinal side effects.[54] Kawish et al created drug-loaded NLCs to enhance the efficacy of nabumetone. The *in-vitro* drug release investigation utilising nabumetone-loaded NLCs demonstrated fast release initially and then continuous release throughout time. NLCs shown a twofold increase in their anti-inflammatory properties compared to a pure drug suspension.[113]

Nanostructured lipid carrier in parenteral drug delivery of NSAIDs

The parenteral route of administration is a highly efficient and common way to administer active drug compounds that have low bioavailability and pharmaceuticals with a limited therapeutic index.[114] This includes intravenous, intramuscular, subcutaneous, intradermal and intraarterial approaches, has efficient absorption properties and guarantees a high level of bioavailability for medicinal compounds. The technique has numerous advantages for patients who are incapable of ingesting drug through the mouth and require a rapid initiation of effects, as is the case with individuals who are asleep.[115] The delivery of lipidic substances achieved success with the market introduction of submicron emulsion-based drugs, like as *Diazemuls* (diazepam) and *Diprivan* (propofol), in the pharmaceutical sector market. Liposomes are lipidic carriers that have greatly transformed the field of parenteral medicine administration. The extensive marketing of many injectable liposomal drugs, like as AmBisome®, Doxil® and DaunoXome®, serves as a clear indication of the advantageous potential of liposomes as advanced lipid carriers. Nevertheless, the successful commercialisation of liposomal formulation faces substantial barriers due to difficulties in liposome synthesis, limited physical stability and exorbitant expenses. Research has been carried out to determine the capabilities of lipid-based carriers, namely nanoparticles known as NLCs, for delivering drugs through the parenteral route. Parenteral use of NLCs has demonstrated increased bioavailability and targeted delivery.[116] Guilherme et al created naproxen loaded NLCs using the emulsification-sonication method. The study found that the optimised NLCs exhibited an encapsulation efficiency of 99.85 % and showed sustained release behaviour. This sustained release behaviour increases the anti-inflammatory activity of the NLCs by significantly reducing the levels of pro-inflammatory mediators (TNF-α and IL-1β) and leukocyte migration.[117]

Nanostructured lipid carrier in pulmonary drug delivery of NSAIDs

Pulmonary drug delivery is an innovative approach for administering pharmaceuticals that provides numerous advantages. Non-invasive medicine delivery is a method that does not require any intrusive procedures and can be utilised for both systemic and local administration. Through the utilisation of this very effective

delivery mechanism, the dosage of drugs can be decreased, leading in a proportional drop in the occurrence of drug-related side effects. Directly inhaling drugs can potentially accelerate the beginning of their effects. Another advantage of this mode of administration is the substantial concentration of medicines at the intended location. The extensive surface area of the pulmonary system and the thin alveolar epithelium enable substantial drug permeability.[118] Regarding pulmonary administration, NLCs can offer several advantages. Due to their ability to dissolve in fats and their small size, NLCs have sticky qualities that make them stay in the pulmonary system for a prolonged period. Because their particle size is less than 500 nm, the increased diffusion mobility may lead to a more rapid deposition in the lung epithelium. Moreover, the behaviour of controlled-release drug can prolong therapeutic advantages and intervals between inhalations.[6] Patlolla et al formulated NLCs containing celecoxib and subsequently assessed the deposition of these carriers in the lungs of mice after nebulisation. The drug-loaded NLCs had a particle size of 217 ± 20 nm, an encapsulation efficiency better than 90 % and demonstrated controlled release characteristics. Nebulising NLCs leads to a fourfold rise in the area under the curve in lung tissues than the solution containing celecoxib.[119]

Nanostructured lipid carrier in buccal drug delivery of NSAIDs

Delivering active chemicals directly to the mucosa in the oral cavity for systemic and/or local effects, by being absorbed across the mucosal membrane barrier, is very beneficial in the buccal region. The buccal region's mucosal membrane offers several clear benefits over oral drug administration. The mucosal membrane is richly vascularised, exhibits reduced enzymatic activity, decreased sensitivity and facilitates the efficient administration and elimination of the drug in case of adverse reactions. This prevents the degradation of the drug by stomach acid and avoids the initial metabolism by the liver. It enhances the bioavailability of the drug, resulting in a reduced dosage requirement and decreased incidence of side effects compared to alternative drug administration methods. The delivery of medicine *via* the buccal route has various drawbacks, the most notable being the restricted surface area (50 cm^2) and the drug the dilution caused by the continuous production of saliva (0.5–2 L per day).[120-122] The inadvertent eating of saliva can affect the absorption of drugs, while the unintended consumption of this mode of delivery can result in asphyxiation, particularly in youngsters, elderly individuals and patients with dysphagia. The primary obstacles encountered by scientists in the development of buccal drug-delivery systems for systemic effects are the restricted absorption area, the cyclic process of salivary regeneration, the influence of chewing while eating and the existence of membrane barrier layers in the mucosa.[123, 124] Nanocarriers such as NLCs are ideal vehicles for drug delivery owing to their smaller size and distinctive physicochemical characteristics, enabling them to efficiently target and transport medicines to specific tissues. NLCs are highly adaptable particles capable of transporting a diverse range of compounds. They can be synthesised utilising various lipids and manufacturing techniques. These carriers offer a solution to overcome specific obstacles commonly connected with the delivery of drug via buccal route.[125] Marques et al synthesised ibuprofen-loaded NLCs using two distinct methods. These dispersions were subsequently integrated into mucoadhesive buccal hydrogels. The NLCs created by the sonication process had a particle size of 96.18 % and a loading capacity of 2.35 %. On the other hand, the NLCs obtained using the high-pressure homogeniser had a particle size of 96.18 % and a loading capacity of 2.37 %. The incorporation of NLCs into made from mucoadhesive polymers resulted in the creation of formulations that exhibit desirable rheological properties, texture (adhesiveness and hardness) and mucoadhesive qualities. These qualities can improve the therapeutic efficacy by extending the duration of action and making it easier to apply the preparation on the buccal mucosa. In addition, the created formulations exhibited the intended extended drug release for these systems.[126] HV and Bhattacharyya synthesised celecoxib loaded NLCs and subsequently integrated them into a nanogel for buccal administration. The study findings showed that the NLCs produced had a particle size between 100 to 300 nm, which is optimal for absorption through the buccal route. *In-vitro* permeation studies demonstrated that the G3 formulation had the highest permeation rate and fastest diffusion compared to other formulations.[127]

Stability considerations of nanostructured lipid carriers

NLCs can incorporate supplementary colloidal structures like as mixed micelles, liposomes, micelles and nanoemulsions, which improve the stability of medicinal formulations. In addition, storage of the dispersion might lead to several notable stability issues, such as particle size enlargement, gelation of the dispersion and release of the drug from the lipid matrix.[8] During storage, the NLCs may experience physical instability, resulting in the formation of aggregates or gels. This is a significant concern. Gelation arises from the formation of a network and the establishment of lipid bridges that link the particles together. It is important to maintain the nanoparticle properties of all NLCs formulations, like as particle size, during the storage procedure. Additionally, it is important to protect the formulations from bacterial growth that may arise in the aqueous phase.[128] There are two methods that can be employed to guarantee the physical stability of NLCs throughout storage: (a) adding preservatives to NLCs dispersions and (b) freeze drying, which involves removing water from nanoparticle dispersions. A freeze-dried product must preserve its visual characteristics and readily dissolve in water, with little reconstitution time. Moreover, it should not alter the dimensions of nanoparticles and must preserve the efficacy of the enclosed drugs. Nevertheless, the occurrence of agglomeration has been seen in freeze-dried formulations, even when cryoprotectants are not present. Various additional polymeric and carbohydrate cryoprotectants have been investigated and employed for preserving NLCs. Examples of cryoprotectants include trehalose, sorbitol, mannitol, sucrose, lactose and dextrose.[129-131]

Preservatives are utilised to preserve the physical stability of dermal products, particularly those that are mostly liquid or semi-solid formulations with water as the dispersing agent. Understanding the impact of various preservatives on the structural integrity of NLCs is crucial, as they have the potential to induce instability.[132] Different preservatives have been employed to modify the characteristics of NLCs by manipulating their impact on stability. Propylene glycol, as an example, is a preservative that has no impact on stability. Caprylyl glycol is a preservative that can lead to slight stability problems. Ethanol is a preservative that significantly compromises stability. The destabilising impact of preservatives is influenced by various factors, like as the hydrophobicity of particles, the binding of preservatives to the particle surface, the capacity to diminish zeta potential, the characteristics of the particle stabiliser and its interaction with the preservative. To ensure the stability and preservation of NLCs, it is crucial for the preservative to have a strong affinity for water and be free of electric charge. This method guarantees limited interaction with the surface of the particles and prevents any significant impact on the zeta potential.[133, 134]

Toxicity and biocompatibility of NLCs

The encapsulation of pharmaceuticals in nanostructured lipid carriers (NLCs) facilitates targeted delivery to specific cells, hence mitigating toxicity concerns.[135] However, this necessitates modification of the surface characteristics of NLC by including targeted moieties or by circumventing drug efflux transporters. The lipids employed in the manufacture of NLCs are biocompatible; however, the surfactants utilised may induce cytotoxicity.[108, 136, 137] Although the lipids and excipients employed in the manufacturing of NLCs are classified as generally recognised as safe (GRAS), a cytotoxicity investigation is essential to confirm their non-harmful effects on cells. The parenteral injection of NLCs may activate the immune system because to the presence of surfactants.[135] The possible negative consequence associated with the application of NLCs to the skin is their propensity to increase the phototoxicity of UV light in dermal fibroblasts. The association between lipid nanoparticles and the generation of reactive oxygen species at the mitochondrial level has been established. This phenomenon has been ascribed to irregularities in the respiratory cycle within the mitochondria.[138] Compared to the cell lines exposed to ultraviolet light, the cytotoxicity of NLCs was markedly elevated, with a 468 % increase in the number of deceased cells.[139] Consequently, further cytotoxic studies should be performed on the generation of reactive oxygen species, particularly with regard respect to topical therapy.

Conclusion

The use of NLCs has revolutionised the production of lipid-based nanoparticles, offering numerous benefits compared to widely utilised lipophilic formulations. Utilising NLCs as drug delivery carriers offers a platform with increased capacity to transport diverse drugs through numerous pathways of application, such as parenteral, oral, ocular, topical and pulmonary routes. Furthermore, the utilisation of NLCs enhanced the chemical and physical durability of the drugs, provided a greater level of regulation over their release, shielded the pharmaceuticals from deterioration and enhanced the pharmacokinetic characteristics. NLCs are highly sought-after for their suitability as carriers for NSAIDs due to their advantageous properties. These qualities encompass their diminutive particle size and the capacity to selectively impact certain areas, hence augmenting the administration of NSAIDs and alleviating the patient from the detrimental effects induced by NSAIDs.

Despite notable advancements in lipid nanoparticle research, there remains a substantial gap to bridge before lipid nanoparticle formulations can attain therapeutic success. Despite extensive research and investigations on the creation, storage and toxicity of NLCs, there are unresolved difficulties. Regarding the development of NLCs, the key issues that require attention include toxicity, challenges in scaling up manufacturing and ensuring long-term stability throughout storage of the NLCs. The investigation of NLCs is currently one of the most captivating areas in which scientists can engage in research. Nanotechnology has anticipated to facilitate new avenues of research in biomedical science by using its tiny size advantages.

Ethics

This study was a secondary analysis based on the currently existing data and did not directly involve with human participants or experimental animals. Therefore, the ethics approval was not required in this paper

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