International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 14, Issue 4, 2022

Review Article

NANOSTRUCTURED LIPID CARRIERS FOR TRANSDERMAL DRUG DELIVERY

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Received: 26 Feb 2021, Revised and Accepted: 11 Apr 2022

ABSTRACT

Transdermal drug delivery offers many advantages over oral delivery, such as avoiding first-pass metabolism, enhancing the bioavailability of poorly soluble drugs, and providing better patient compliance. However, only small lipophilic molecules can be delivered across the stratum corneum, the outermost layer of the skin. Unfortunately, the delivery of larger molecules remains a challenge. Nanostructured lipid carriers (NLCs) are second-generation lipid nanocarriers composed of biocompatible solid lipids, liquid lipids, surfactants, and co-surfactants. NLCs can be loaded with various classes of drugs, provide a controlled drug release profile, enhance drug stability, and be scaled up without needing organic solvents. This review article discusses the features, composition, formulation processes, and characterization of NLCs and their potential use in transdermal drug delivery.

Keywords: Nanostructured lipid carriers, Transdermal drug delivery, Controlled release

DOI: https://dx.doi.org/10.22159/ijap.2022v14i4.44564. Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

The transdermal drug delivery route has significant advantages over the conventional oral route. It can provide more patient compliance, especially in patients with swallowing problems, more stable serum drug levels, pain-free drug administration, avoiding hepatic first-pass metabolism and drug degradation in the gastrointestinal tract, food-drug interaction, and reducing side effects [1]. Moreover, transdermal drug delivery is suitable for long-term administration, especially for insulin and analgesic drugs [2]. However, the low skin permeability, which limits drug penetration and inconsequence affects drug bioavailability, represents the most challenging mission for delivering drugs across the skin layers [3].

The application of lipid nanoparticles offers a suitable carrier for transdermal delivery due to their high biocompatibility with the skin lipids. Nanostructured lipid carrier (NLC) is the second generation of lipid nanoparticles, which was created to overcome the drawbacks of solid lipid nanoparticles (SLNs), such as the low drug loading capacity, gelation, and reduced stability [4]. Unlike SLNs, which are made entirely of solid lipid (at room temperature), NLCs are made up of both solid and liquid lipid. Because liquid lipids lowered the melting point of lipids, the solid lipid matrix became less ordered than SLNs, and the solid lipid matrix became more flexible. Therefore, a higher degree of imperfections is found, and consequently, a higher drug loading capacity, especially for lipophilic drugs, is obtained [5]. Also, oil in the NLCs composition reduces the solid lipid's recrystallization over the storage period, giving a more thermodynamic stable formulation.

Upon application on the skin surface, NLCs create a thin hydrophobic monolayer leading to a marked occlusive effect with a reduction in the transepidermal water loss and thus increasing skin hydration and enlarging the inter-keratinocyte gap, thus enhancing the drug penetration, providing more molecular retention and more drug penetration across the skin layers [6]. Also, NLCs can alter the natural organization of the corneocytes by interacting with the sebum and skin lipids leading to the release of the encapsulated drugs and thus may improve their penetration into the deeper layers of epidermis and dermis, depending on their lipophilicity [7]. In addition, the nano size of NLCs provides a higher specific surface area for drug absorption through the skin, resulting in greater efficacy in delivering the drugs trans-dermally. Furthermore, the presence of surfactants in NLC induces structural changes in the skin and acts as skin permeability enhancers [8].

MATERIALS AND METHODS

This review article was oriented to explore the potentiality of NLC as an effective lipid nanoparticle for enhancing the transdermal delivery of various classes of drugs.

Search strategy

Data were collected from five international databases, including Scopus, PubMed, Web of Science, research gate, and Google Scholar, from 2017 to 2022. The search keywords used were lipid nanoparticles, nanostructured lipid carriers, and transdermal drug delivery.

Composition of NLCs

The composition of the lipid matrix and the preparation process are mainly responsible for the created NLCs' primary features, such as mean particle size, loading capacity, drug release profile, and stability.

As previously stated, NLCs are made up of a mixture of solid and liquid lipids with a ratio ranging from 70:30 to 99.9:0.1 [9]. The overall lipid content of NLCs varies between 5 and 40% [10]. Surfactants in concentrations ranging from 0.5 to 5% w/w stabilize NLCs formulations in the aqueous media [11]. Some parameters must be considered when selecting components for NLCs formulations, such as drug solubility in the lipid, lipid melting temperature, compatibility and miscibility between the selected solid and liquid lipids, surfactant choice and its Hydrophilic-Lipophilic Balance (HLB), and production method.

Lipid

Lipid is the critical component of NLCs that controls drug loading capacity, duration of action, and formulation stability. Physiologically acceptable, biodegradable, non-toxic, and generally recognized as safe (GRAS) status lipids are preferred to prepare NLCs [12]. NLCs consist of solid lipids such as fatty acids, triglycerides, partial glycerides, steroids, and waxes. The liquid lipids (oils) are mainly taken from natural sources such as medium-chain triglycerides, Miglyol 812, oleic acid, and linoleic acid. Also,

oils from botanical sources such as citral [13], linalool [14], and limonene [15] have been investigated in numerous research due to their inherent dermatological benefits. The choice of lipids is critical as it affects the various characteristics of NLCs, such as the drug loading capacity, size and charge, and structural properties of the NLCs. Usually, the selection of lipids depends on the solubility of the active ingredients. As high solubility of the drug in melted lipid is the precondition for achieving high entrapment efficiency [16].

Surfactants

Surfactants such as poloxamers, polysorbates, alkyl aryl polyether alcohol, bile salts, phospholipids, ethylene oxide, and sorbitan esters impact the extent of drug permeability across the skin. As surfactants facilitate active transport of NLCs through the skin via endocytosis, and solubilization of endothelial cell membrane lipids, fluidizing the membrane resulting in enhanced drug permeability. Also, surfactants affect the stability and particle size of NLCs formulation [17]. Surfactants are mainly chosen based on their hydrophilic-lipophilic balance (HLB) value. Therefore, the required HLB (rHLB) plays a vital role while selecting the suitable type and amount of surfactant for NLCs formulation [18].

Surface modifiers and counter ions

Surface modifiers are hydrophilic polymers such as polyethylene glycol, poloxamines, poloxamers, chitosan, and lecithin are usually used to coat NLCs to enhance their transport across the epithelium, drug targeting, stability, and/or increase their circulation systemically, avoiding their uptake by the reticuloendothelial system (RES). Surface modification is beneficial for drug transport through the skin using lipid nanoparticles. [19]. Counter-ions such as organic salts and ionic polymers may be used in the composition of NLCs to overcome the challenge of encapsulating water-soluble drug molecules [6].

Types of NLCs

Type I (imperfect model)

The imperfect type consists of a very disordered matrix with many voids, and this void can accommodate more drug molecules in the amorphous clusters [20]. This type is characterized by low liquid lipid content than the solid phase. In the first step, o/w nanoemulsion is prepared from mixed liquids and solids. Then nanoemulsion is cooled to room temperature, and a very disordered matrix is produced due to the crystallization of solid lipid. Due to lipids with different lengths of fatty acids and mixtures of mono, di, and triacylglycerols, type I NLCs cannot form highly ordered structures [21].

Type II (amorphous model)

Type II is created with the amalgamation of specific lipids such as hydroxyoctacosanyl hydroxy stearate and isopropyl myristate, which do not crystallize after cooling and form a lipid matrix in an amorphous state [22].

Type III (multiple model)

Type III contains a high concentration of liquid lipids and is used when the active ingredient has poor solubility in solid lipids. Adding a high amount of liquid oil improves drug solubility and provides higher drug loading. This type is derived from multiple water-in-oil-water (w/o/w) emulsions and comprises nano compartments of liquid lipid within the lipid matrix [23].

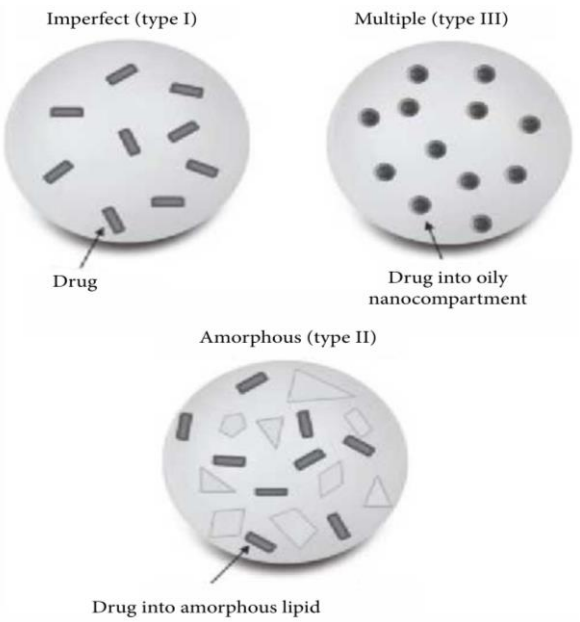

Fig. 1: Scheme of the NLCs types [24]

Method of NLCs production

Several fabrication methods for NLCs include the microemulsion technique, solvent diffusion method, and ultrasonication. However, the most usual method is high-pressure homogenization [25]. This method offers large-scale production, easy scale-up, short production time, and the absence of organic solvents. The high-pressure homogenization method is classified into the hot and the cold method [26].

In the hot method, a hot surfactant solution is added to a mixture of melted lipids (melted around 5–10 °C above their melting point) containing a given drug, using a high-speed stirring. The emulsion is homogenized under high pressure (usually 500 or 800 bar) to make a hot nanoemulsion, subsequently cooled to room temperature to form an NLC [27]. Because the energy required to shear the lipid mass is directly proportional to its concentration in the formulation, the number of homogenization cycles will be determined by the emulsion lipid concentration [28]. Increasing the number of homogenization cycles, on the other hand, frequently results in increased particle size as particle kinetic energy rises, encouraging coalescence [29]. The disadvantages of this method include high temperatures, pressures, and the presence of high concentrations of surfactants. Lipid formulations prepared by this method are often characterized by burst release. Also, another problem that may arise from high temperature is the reduction in the emulsifying capacity of surfactants as surfactants have cloud points lower than 85 °C,

which may induce instability to nanocarriers. Furthermore, the elevated temperature used in the process may cause the partitioning of hydrophilic drugs from the lipid phase to the aqueous phase [30].

The cold homogenization method could achieve prolonged release of NLCs and reduce the burst effect. The melted lipid-containing active substances are cold using liquid nitrogen or ice. The solidified mass is then milled and ground before being dispersed in the cold surfactant phase and subsequently homogenized at room temperature. The pressure used in the cold process is higher, i.e., 5-10 cycles of 1500 bar. This approach minimizes the thermal exposure of drugs and is well suited for thermolabile drugs. Improved drug entrapment efficiency and uniform distribution of drugs within the lipid are other benefits of the method. However, it results in larger and polydisperse nanoparticles than the hot method, and the active substance must be dissolved in the melted lipid phase in the initial step [31]. Also, this fabrication method involves using high energy in the homogenization step.

Evaluation of NLCs

Their composition and production method may affect the primary features of NLCs, such as particle size, stability, drug loading, and drug release profile.

Particle size distribution, polydispersity index, and zeta potential

The particle size, polydispersity index, and zeta potential of NLCs are evaluated using the dynamic light scattering technique. The size of NLCs is of critical importance in delivering the active ingredients across the skin layers, where smaller NLCs ensure nearby contact with the stratum corneum and enhance the skin penetration of the active compound [32]. Also, small-sized nanoparticles easily penetrate the stratum corneum following intracellular pathways. The polydispersity index is usually preferred to be less than 0.3, which indicates a unimodal size distribution and minimal chances of predisposition to the aggregation [33]. The particle size of NLCs is usually affected by the ratio of solid to liquid lipids [1]. There is a strong correlation between lipid concentration and particle size since an increase in lipid concentration leads to increased particle size [34]. The effect of surfactant on particle size is verified across several studies where Kapoor *et al.*, Pandey *et al.*, and Nguyen *et al.* found that by increasing the surfactant concentration, the particle size of NLCs decreases due to the reduction in interfacial tension between the two phases, leading to the formation of smaller size emulsion droplets [35-37].

The preparation method may also affect the size and PDI of NLCs. For example, Garg *et al.* found that NLCs formulation prepared by probe sonication with homogenization had a more uniform size distribution with small size than NLCs prepared by the probe sonication method [38]. At the same time, Ahmed *et al.* found that sonication time had a negative effect on the particle size of NLCs prepared with the emulsification technique followed by ultrasonication [39].

In addition, zeta potential is a crucial factor for evaluating the stability of any nanodispersion system. A higher zeta potential value (above±30 mV) means that the particle aggregation is reduced due to electric repulsion between the dispersed particles. In contrast, dispersions with lower values tend to coagulate or flocculate, leading to a less stable system [40]. The addition of surfactants allows for the electrosteric stabilization of NLCs, where the increase in surfactant concentration usually shifts the zeta potential of NLCs to higher values [7]. The surface charge is vital in transdermal drug delivery as the charge affects the permeation of nanocarriers across the skin layers [41].

Entrapment efficiency and drug loading capacity

Entrapment efficiency (EE%) is the amount of drug encapsulated compared to the total amount of drug initially added to the formula [42]. In contrast, drug loading (DL%) capacity refers to the amount of drug encapsulated compared to the amount of lipids. Both values measure free drug concentration in the external aqueous phase, obtained by centrifugation [43].

$$EE\ (\%) = (\text{total amount of drug} - \text{amount of free drug})/(\text{total amount of drug}) \times 100$$

$$DL\ (\%) = (\text{total amount of drug} - \text{amount of free drug})/(\text{weight of lipids}) \times 100$$

Usually, the higher entrapment efficiency of NLCs suggests higher solubility of the active substance in the selected lipid. Furthermore, the preparation method may also affect the drug entrapment efficiency. Low homogenization speed leads to an imperfect lipid matrix (model I), accommodating greater drug quantity [44].

Morphology

The morphology and structural properties of NLC can be evaluated by scanning electron microscopy (SEM), transmission electron microscopy (TEM), or atomic force microscopy (AFM) [45]. AFM is suitable for measuring the morphological radius that is extremely small. In addition, AFM provides nanometer resolution structural, mechanical, and functional information about NLCs surfaces [46]. The NLCs usually appeared spherical in the TEM or SEM micrographs [47]. However, some studies found that the shape of NLCs was nonspherical, mainly cuboid. Nnamani *et al.* concluded that the shape NLCs is dependent on the purity of the lipids used, and the particles prepared from highly pure lipids are more cuboid in nature [48]. In contrast, those obtained using chemically polydispersed lipids are typically spherical.

Application of NLCs in transdermal drug delivery

Numerous studies have been developed over the last years concerning the ability of NLCs to deliver the drug to the systematic circulation across the skin layers, mainly to avoid first-pass metabolism, thereby enhancing the drug bioavailability or obtaining a more controlled drug release profile than the other conventional routs. Where Solís *et al.* fabricated adhesive film containing NLCs loaded with olanzapine and simvastatin to treat psychiatric disorders. NLCs system was prepared using a hot, high-pressure homogenization technique and comprised 7.50%, 11.25%, and 15.00% w/w tripalmitin and oleic acid as lipid phase (at a ratio of 50:50, w/w) and 3% w/v tween 80 as a surfactant. The results of the *in vitro* release studies revealed that the release of olanzapine was faster than simvastatin, and this may be due to the higher solubility of olanzapine in liquid lipid (oleic acid) than simvastatin, and that enhances the olanzapine diffusion through the lipid matrix and enables a faster partition into the polyvinyl alcohol film network, unlike the simvastatin that has higher solubility in tripalmitin (solid lipid), therefore retained for a more extended period and has a limited release [49].

Another study was performed on simvastatin conducted by Raj *et al.*, where different NLCs formulae were prepared using optimized hot homogenization technique using Compritol 888ATO (solid lipid) and Softigen (liquid lipid), Pluronic F-68, and span 80 as main components of NLCs. The NLC was then loaded into a transdermal patch of polyvinyl alcohol and polyethylene glycol. Compared to the marketed oral dose form, *in vivo* pharmacokinetic studies suggest that simvastatin has higher bioavailability [50].

Chauhan *et al.* studied the incorporation of rivastigmine into NLCs to treat dementia. NLCs were prepared by high-pressure homogenization using glycerol monostearate as solid lipid, castor oil as liquid lipid, tween 80 and span 80, then loaded into a transdermal patch made of Eudragit E-100 and poly-butyl methacrylate-co-methyl methacrylate. The pharmacokinetics studies revealed increased rivastigmine plasma concentration in albino Wistar rats treated with NLCs loaded transdermal patches compared with marketed transdermal Exelon® [51].

Mendes *et al.* developed NLCs based gel loaded with donepezil for treating Alzheimer's disease for better patient compliance. NLCs were made by a microemulsion technique using stearic acid (solid lipid), oleic acid (liquid lipid), lecithin, and sodium taurodeoxycholate. The results of the *in vitro* drug permeation confirmed the enhancement of NLCs formula in increasing drug flux across the skin [52].

Gu *et al.* prepared triptolide-loaded NLCs for treating rheumatoid arthritis to obtain more controlled release and enhance patient

compliance. NLCs were prepared with an emulsification technique using Compritol 888 ATO (solid lipid), Capryol 90 (liquid lipid), soybean oil, tween 80, and Transcutol. The pharmacokinetic results indicated that triptolide-loaded NLCs enhanced the treatment of rheumatoid arthritis by avoiding the first-pass metabolism and gastrointestinal reaction and had a remarkable effect of decreasing knee edema by inhibiting inflammation by regulating the levels of TNF-α, IL-1β, and IL-6 [53].

Raval *et al.* prepared NLCs for enhancing the bioavailability of paliperidone palmitate through transdermal delivery for treating schizophrenia. NLCs were formulated by the nanoprecipitation method followed by incorporation in a transdermal patch. The NLCs system is composed of Dynasan 118 as solid lipid, oleic acid as liquid lipid, and poloxamer 407. The *in vivo* pharmacokinetics study showed enhancement of bioavailability, half-life, and mean residence time of paliperidone palmitate. The authors concluded that the controlled release profile obtained by the NLCs would help maintain the therapeutic concentration in the systemic circulation, which can be used for improved management of schizophrenia compared with conventional oral drug delivery [54].

Moura *et al.* combined NLCs loaded with lopinavir with iontophoresis for enhanced skin permeation. The authors also studied the effect of lipid dynamic behavior of NLCs before and after the electrical current using electronic paramagnetic resonance and differential scanning calorimetry. After applying an electric current, the researchers found that NLCs loaded with lopinavir were chemically and physically stable. Furthermore, the combination of NLCs and iontophoresis significantly enhanced the permeation of lopinavir compared to the passive strategy. Also, electronic paramagnetic resonance showed that the faster release might be related to the decrease of lipid dynamics with the application of an electrical current. Furthermore, the differential scanning calorimetry studies revealed that electrical current could trigger the polymorphic transition of NLCs and drug solubilization in the lipid matrix [55].

Nnaman *et al.* studied the transdermal delivery of artemether characterized by poor water solubility and limited bioavailability. The authors used hot homogenization/ultrasonication methods for NLCs preparation utilizing Gelucire 43/01 and Phospholipon 85G as solid lipid, Transcutol as liquid lipid, and Tween 80 as surfactant. The nanoparticle was lyophilized in order to formulate nanogel. The formulated nanogels had good skin tolerance and occlusivity, leaving a thin film after application on the skin due to good hydration and preventing skin transepidermal water loss. Ex vivo skin permeation tests revealed that a considerable amount of artemether passed through the skin of the rat's abdomen. A two-patch per week concurrent application of the studied nanogels could provide a 100% cure of malaria using a lower dose of artemether (50 mg) to reduce severe side effects [56].

Jiang *et al.* used penetration enhancer and transcriptional transactivator peptide to enhance the performance of NLCs for efficient transdermal delivery of lidocaine hydrochloride, where a novel pyrenebutyrate compound was synthesized by the amide action of the carboxylic acid group of (1-pyrenyl) butyric acid (pyrenebutyrate), which is cell membrane-permeable peptide (PB) with the amido groups of 1, 2-Distearoyl-sn-glycero-3-phosphoethanolamine-polyethylene glycol (DSPE-PEG). The PB-PEG-DSPE has a hydrophobic group, hydrophilic group, and lipid group. Therefore, the lipid group can be inserted into NLCs to form PB functional NLC to improve the permeation of lidocaine hydrochloride. Also, multi-decorated NLCs (TAT/PB NLC) were formulated using TAT-PEG-DSPE instead of DSPE-PEG. The study concluded that the multi-decorated NLCs showed the most prominent anesthetic effect than single ligand decorated or undecorated LID NLC *in vivo*. Furthermore, this result was correlated with enhancement in skin penetration of lidocaine hydrochloride from multi-decorated NLCs (TAT/PB NLC) compared to the other formulae [57].

The previously mentioned studies found that NLCs have improved the delivery of different classes of drugs with various physicochemical properties across the skin layers. This improvement was reflected in the drug's bioavailability and its therapeutic efficacy.

Patent status of NLC

Various patents have been granted for NLC. Table 1 presents a recent brief review of patents about original inventions in the NLCs.

Table 1: Patent status of NLC

Patent name	Patent number	Inventors	Publication date	Reference
A method of preparation of Triamcinolone Acetonide encapsulated nanostructured lipid carriers for psoriasis treatment	AU 2021106678 A4	Singh *et al.*	Dec.16, 2021	58
Nanostructured lipid carriers and stable emulsions and uses thereof	US 2022/0054416 A1	Fox *et al.*	Feb. 24, 2022	59
A lipid-polymer hybrid nanoparticle	US 2021/0369631 A1	Chitkara *et al.*	Dec. 2, 2021	60
Nanostructured lipid carrier delivery system, composition, and methods	WO 2021/168573 A1	Domenico *et al.*	Feb. 25, 2021	61

CONCLUSION

NLCs are nanometric lipid particles with numerous advantages such as chemical and physical stability, enhancement of the drug encapsulation, skin occlusive effect, skin hydration properties, and consequently improvement of drugs permeation across skin layers. Therefore, NLCs are a safe and effective candidate for delivering drugs transdermally.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declare that there is no conflict of interest regarding the publications of this paper

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