Expert Opinion on Drug Delivery

ISSN: 1742-5247 (Print) 1744-7593 (Online) Journal homepage: https://www.tandfonline.com/loi/iedd20

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To cite this article: Eliana B. Souto, Iara Baldim, Wanderley P. Oliveira, Rekha Rao, Nitesh Yadav, Francisco M. Gama & Sheefali Mahant (2020): SLN and NLC for topical, dermal, and transdermal drug delivery, Expert Opinion on Drug Delivery, DOI: 10.1080/17425247.2020.1727883

To link to this article: https://doi.org/10.1080/17425247.2020.1727883

Published online: 17 Feb 2020.

EXPERT OPINION ON DRUG DELIVERY
https://doi.org/10.1080/17425247.2020.1727883

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REVIEW

SLN and NLC for topical, dermal, and transdermal drug delivery

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ABSTRACT

Introduction: From a biopharmaceutical standpoint, the skin is recognized as an interesting route for drug delivery. In general, small molecules are able to penetrate the *stratum corneum*, the outermost layer of the skin. In contrast, the delivery of larger molecules, such as peptides and proteins, remains a challenge. Nanoparticles have been exploited not only to enhance skin penetration of drugs but also to expand the range of molecules to be clinically used.

Areas covered: This review focus on Solid lipid nanoparticles (SLN) and Nanostructured lipid carriers (NLC) for skin administration. We discuss the selection criteria for lipids, surfactants, and surface modifiers commonly in use in SLN/NLC, their production techniques, and the range of drugs loaded in these lipid nanoparticles for the treatment of skin disorders.

Expert opinion: Depending on the lipid and surfactant composition, different nanoparticle morphologies can be generated. Both SLN and NLC are composed of lipids that resemble those of the skin and sebum, which contribute to their enhanced biocompatibility, with limited toxicological risk. SLN and NLC can be loaded with very chemically different drugs, may provide a tunable release profile, can be produced in a sterilized environment, and be scaled-up without the need for organic solvents.

ARTICLE HISTORY
Received 10 November 2019
Accepted 6 February 2020

KEYWORDS
Solid lipid nanoparticles; nanostructured lipid carriers; skin administration; lipids; surfactants

1. Introduction

Solid lipid nanoparticles (SLN) were developed in the early 1990s as alternative delivery systems to liposomes, emulsions, and polymeric nanoparticles [1–3]. Owing to the lipid biocompatibility and versatility, SLN show many advantages over polymeric and inorganic nanoparticles for the delivery of a set of drugs [4–7]. Advantages, such as reduced toxicity [3,4], higher loading capacity [8], chemical versatility [9], biodegradability of lipids [9], possibility of large-scale production [8,10,11], and a wide range of applications in various fields [4,10], reason the interest of academia and industry in seeking new applications of lipid nanoparticles as delivery systems. SLN are composed of a solid lipid matrix with a melting point above 40ºC, in which the drug is incorporated and/or attached. As nanoparticles remain solid after administration, they offer controlled release of the loaded drug [10].

The second generation of lipid nanoparticles is known as nanostructured lipid carriers (NLC). Unlike SLN, the lipid matrix of NLC consists of a blend of solid and liquid lipids (oils), which provides a reduction in the melting point of the solid lipid, the matrix yet still remaining solid at room and body temperatures [3]. NLC are also stabilized in aqueous dispersion using a surfactant or a mixture of surfactants. The presence of oil in the composition avoids the recrystallization of the solid lipid over storage, contributing to increase the loading capacity, in particular, for lipophilic compounds [10]. Moreover, as the addition of oil prevents the recrystallization of solid lipids, a more thermodynamically stable system is obtained, less likely to expel the payload from the particle, also improving its release properties [4,10,12]. The mean particle size of SLN and NLC is in the submicron range, ranging from about 40 to 1000 nm, depending on the composition of the lipid matrix (i.e. lipid and surfactant combination) and on the production method [5]. Figure 1 illustrates the differences between SLN and NLC lipid matrix structure.

Literature describes different combinations of lipids and production methods to obtain SLN and NLC. The possibility of using generally recognized as safe (GRAS) materials or even raw materials of natural origin [13] increases the application range and the interest of different market segments in the use of these nanoparticles. In addition, the proper selection of components may allow the control of the morphology, structural and occlusive properties, as well as drug loading. This review focuses on the cutaneous application of SLN and NLC, giving an overview on commonly used materials (and selection criteria), production methods and drugs that have been successfully loaded in these nanoparticles.

2. SLN and NLC ingredients for cutaneous delivery

SLN are composed of solid lipids (at room temperature), usually at a concentration between 0.1% (w/w) and 30% (w/w) [14,15]. In

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Article highlights

- Lipid nanoparticles possess important application for topical, dermal, and transdermal drug delivery.
- Both SLN and NLC can be prepared by different techniques, with the advantage of being an easy scale up production.
- Tailoring their composition in terms of lipids and surfactants it is possible to obtain important therapeutic outcomes with the site-specific targeting.
- Their constituents are biocompatible, which limits the risk of toxicity and irritation when applied onto the skin.
- SNL and NLC can be composed of lipids capable of enhancing the permeation of the drug, which requires less of the drug to exhibit its therapeutic effect and reduces possible side effects.

This box summarizes the key points contained in the article.

contrast, the matrix of NLC is derived from a combination of solid lipid and oil (liquid lipid), and the ratio of this blend may vary from 70:30 to 99.9:0.1 [16–18]. The total lipid content of the NLC may vary from 5-40% [16–19]. In both cases, the nanoparticles are stabilized in aqueous medium using at least one surfactant in a concentration ranging from 0.5-5% w/w [3,5,14]. Proper combination of ingredients can be achieved using factorial design experiments usually setting the mean particle size, polydispersity index (PI), and zeta potential (ZP) the dependent variables [13,20–26].

The selection of excipients is instrumental to ensure biocompatibility and safety [27–31]. When selecting components for SLN and NLC formulations, some parameters have to be considered, namely, drug solubility in the lipid, melting temperature of the lipid, compatibility, and miscibility between the selected solid and liquid lipids, choice of surfactant and its Hydrophilic-Lipophilic Balance (HLB) and also the method of production [5,32]. A summary of components typically used in the formulation of SLN and NLC for topical drug delivery is presented in Table 1.

2.1. Choice of lipids

The solid lipids employed in the formulation of SLN and NLC are biocompatible/physiological and biodegradable lipids, which may either be used independently (in SLN) or as a mixture of two or more lipids in a specified ratio (NLC). The wide variety of lipids used in topical lipid nanoparticulate formulations may be classified as fatty acids, waxes, steroids, partial glycerides, and triglycerides. These lipids are melted during the fabrication of nanoparticles at high temperature, i.e. above 80°C. The liquid lipids (oils), typically found in the lipid matrix of NLC, are usually derived from natural sources and have been granted GRAS (Generally Recognized As Safe) status by regulatory bodies. Medium-chain triglycerides, such as Miglyol® 812, together with oleic acid and linoleic acid, have been most commonly used as penetration enhancers [61]. Some authors have also explored oils from botanical sources, e.g. Mediterranean essential oils [16,62], alpha-pinene [25], citral [26], linalool [22], Siberian pure seed oil [63], sucupira oil [13], *Croton argyrophyllus* Kunth essential oil [64], limonene [65,66], owing to their inherent dermatological benefits. Use of tocols has also been proposed in this regard [67–70].

The choice of lipids is dictated by the solubility properties of the active moiety (i.e. drug) to be loaded [71–73]. This can either be located between the lipid layers (possible only when the size of drug molecules is smaller by 20%, as compared to lipid molecules) or between the fatty acid chains and imperfections of the lipid matrix [3]. The type of lipids used, as well as the ratio of solid and liquid lipids forming the core of NLC was found to influence the drug loading and structural properties of the particles, namely, type I (imperfect model), type II (amorphous model), or type III (multiple model) [71]. For SLN, the classical structures are the type I (homogeneous matrix model), type II (drug-enriched shell model) and type III (drug-enriched core model). Some general rules in this respect may be considered:

(i) Highly ordered matrices, spatially similar lipids or monoacid glycerides of high purity (e.g. tristearin) lead to a decrease of the loading capacity, while accelerating the drug expulsion process [3,74].
(ii) Admixture of dissimilar lipids enhances the loading capacity owing to the creation of imperfections in the lipid matrix. Such mixtures can, however, result in the creation of supercooled melts. For instance, mixing triglycerides (possessing high melting points and high crystallization

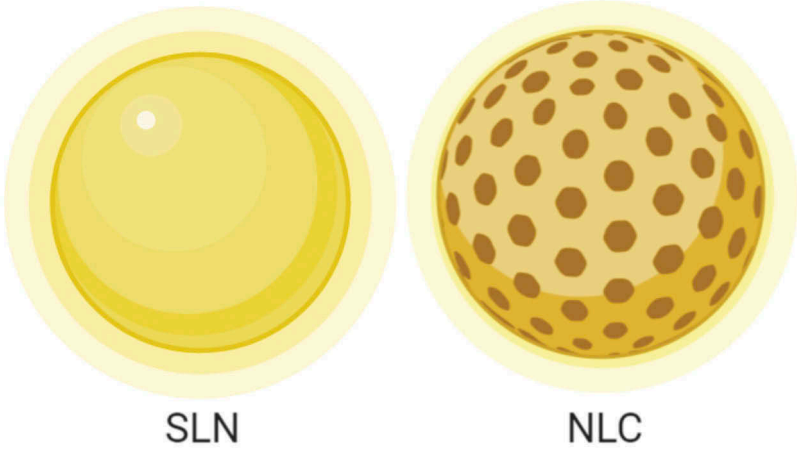

Figure 1. SLN and NLC matrix structure.

Table 1. Frequently used ingredients for SLN and NLC production.

Ingredient	Examples	Properties	References
Solid lipids	Beeswax	Natural wax with GRAS status, composed of a mixture of fatty acids and fatty alcohols esters, with melting point of 62-64°C; it requires HLB of 9 to be emulsified.	[33–35]
	Carnauba wax	Natural wax with GRAS status high melting point of 82-85°C, composed of monoesters; it requires HLB of 12 to be emulsified.	[34–37]
	Cetyl palmitate	Synthetic wax produced by esterification of cetyl alcohol and palmitic acid, with melting point between 40.5-51°C, depending of the composition; it requires HLB of 10 to be emulsified.	[1,33,36,38–40]
	Compritol® 888 ATO	Blend of different esters of behenic acid with glycerol; it holds acceptable safety profile, with a melting point of 69-74°C, and is also stablished as emulsifier, with HLB ≈ 2.	[5,36,41–43,67]
	Dynasan®	Triglycerides series from Sasol; a group of natural and safe lipids, which includes Dynasan 112 (trilaurin; melting point 46°C), Dynasan 114 (trimyristin; melting point 55-58°C), Dynasan 116 (tripalmitin; melting point 61-65°C), and Dynasan 118 (tristearin; melting point 70-73°C).	[33,40,41,44,63]
	Gelucire®	Series of lipid from Gatefossé defined by their melting points between 33-70°C and by the HLB between 1–18. The most frequently used for SLN/NLC is Gelucire 50/13 (stearoyl macrogol-32 glycerides) and is GRAS listed.	[5,45–49]
	Precirol® ATO 5	Glyceryl palmitostearate, is a mixture of mono, di and triglycerides of palmitic and stearic acid, of GRAS status, melting point of 58°C, low HLB of 2.	[33,42,50–52]
	Softisan® 378	Blend of triglycerides with hydrocarbon chain length of C8-C18, low melting point of 35-42°C and GRAS status.	[44,52,53]
	Stearic acid	Endogenous long-chain saturated fatty acid, GRAS listed, with melting point around 70°C and HLB around 15.	[32,54–56]
Liquid lipids	Miglyol® 812	Triglycerides of capric and caprylic acid, are medium chain triglycerides with high stability against oxidation, holds GRAS status and high solubility for many drugs.	[32,36,44,46,53]
	Oleic acid	Pure substance used as emulsifying agent and penetration enhancer, with GRAS status.	[5,50,52,56]
	Squalene	Triterpene produced by human skin cells (as precursor for cholesterol).	[5,42,51]
	Vitamin E/α-tocopherol	Liquid lipid with the advantage of providing protection to oxidation sensitive substances.	[67,68]
Surfactants	Lecithin	Is an essential component of cell membranes, obtained from different sources (egg, vegetables) and used in a wide variety of pharmaceutical application as emollient, emulsifying and solubilizing agent, with HLB between 4–9.	[19,35,52,54,57]
	Plantacare® 810	Caprylyl/capryl glucoside is a highly effective stabilizer for SLN and NLC, with HLB 15–16.	[1,39]
	Poloxamer® 188	Nonionic triblock copolymer with hydrophilic and lipophilic units, used as emulsifier and stabilizing agent in a wide variety of pharmaceutical formulations, it is nontoxic and nonirritant, with HLB > 24.	[5,44,52,55,68]
	Quillaja saponin	Natural saponin-based surfactant, isolated from the tree *Quillaja saponaria*, composed by a complex mixture of amphiphilic constituents. Exhibit antioxidant properties and HLB of 13.5.	[5,58,59]
	Sodium lauryl sulfate	Sodium dodecylsulphate is an anionic surfactant, widely used in cosmetics and pharmaceutical formulations, moderately toxic, but with GRAS status and HLB ≈ 40.	[52,60]
	Tween®80	Polyoxyethylene sorbitan monooleate, or polysorbate 80, is an O/W surfactant widely used in cosmetic, food and pharmaceutical formulations, including intravenous products. Holds GRAS status and HLB around 15.	[5,35,41,44,46,50–52]

temperature) with lipids of small chain length causes an increase in the supercooling effect. Likewise, the addition of long-chain length lipid molecules to lipid with low crystallization temperature reduces supercooling. Differential Scanning Calorimetry (DSC) studies are commonly run for the identification of supercooling [20,67,75–77].

(iii) Lipids, such as tricaprin, trilaurin, trimyristin, and certain Witepsol bases are known for their tendency to yield supercooled melts. Thus, lipid nanoparticles meant for prolonged release and/or enhanced occlusion should not be formulated with these lipids [78,79].

(iv) The structure of NLC varies with the lipid composition of the matrix. When a solid lipid is mixed with a small amount of a liquid one, an 'imperfect crystal' type of NLC arises. The 'amorphous type' is obtained by mixing special lipids, such as hydroxyoctacosanyl hydroxy stearate, isopropyl myristate, which do not crystallize after cooling. The third type of NLC is derived from multiple water-in-oil-water (w/o/w) emulsions, comprising nanocompartments of liquid lipid within the lipid matrix (e.g. oil-fat-water type III NLC). These are obtained when the liquid lipid is present in a concentration that exceeds its solubility in solid lipid. In this case, the drug exhibits greater solubility in the liquid lipid than in the solid one, getting entrapped in the oily nanocompartments [80–84].

Yang et al. evaluated the effect of the liquid lipid in the crystallization and aggregation stability of tristearin NLC dispersions [85]. The amount of oil present in the NLC formulation significantly influenced the crystallization of NLC, their melting temperature and degree of polymorphism observed. An effective liquid lipid, such as triolein and tricaprylin, enhanced the ability of the surfactant to stabilize NLC dispersion. Additionally, oils (such as olive oil) offer higher mobility at the interface, enabling the surfactant to completely cover hydrophobic surface during polymorphic transitions. The use of liquid lipids, which produce less ordered crystal lattice (e.g. pentadecane), results in more stable NLC formulations.

2.2. Role of surfactant

Surfactants act by reducing the interfacial tension between the lipid and the aqueous phase, thereby contributing to the

stability of the resulting formulation. Surfactants are amphiphilic in nature and their molecules get preferentially located at the interface. The surfactants of ionic nature (e.g. sodium deoxycholate) increase the nanoparticles surface charge, causing electrostatic repulsion and, thus, improving the physical stability [32,76]. Nonionic surfactants (e.g. Poloxamer 188, Sorbitan monoesters, and polysorbates) circumvent nanoparticle aggregation by virtue of steric stabilization effect. Addition of co-emulsifying surfactants possessing high mobility also retards the gelation of colloidal nanoparticle dispersions [86].

Radomska-Soukharev carried out an in-depth investigation to study the stability of lipids in SLN formulations using different lipids and varying amounts of surfactants [87]. It was found that triglycerides yield more stable products as compared to mono and diglycerides. It was postulated that a binary mixture of surfactants imparts more stability than a single surfactant. It was further stated that the nature of surfactant and its concentration have an impact in its solubilizing capacity for water in the lipid phase, and also brings about variations in the incorporation of the surfactant in the outer shell of SLN and its distribution in the molten lipid phase. SLN dispersion can cause distortion in crystallization behavior, thereby, lowering the melting enthalpy. Moreover, the effects of electrostatic and steric stabilization were found to be additive.

In practice, the selection of surfactant mix is realized in view of the HLB of the lipids constituting the nanoparticle matrix and their concentration in the lipid phase of the dispersion [32]. Surfactants belonging to the following categories have found application in the formulation of SLN/NLC: Phospholipids, ethylene oxide/propylene oxide, copolymers, and sorbitan esters, polysorbates, alkylaryl polyether alcohol polymers, and bile salts [74]. Table 2 lists the commonly used excipients in lipid nanoparticle formulations.

2.3. Use of surface modifiers

Surface modification of SLN/NLC has been attempted by many formulators with the view to enhance their stability and/or increase their circulation systemically, avoiding their uptake by reticuloendothelial system (RES) [74]. This strategy involves the use of hydrophilic substances such as PEG [88–90], chitosan [91,92], lecithin [93–95] and dicetyl phosphate [96], which coat the hydrophobic surface of the nanoparticles. As a result, not only their stability and dispersibility are improved but also their interaction with mucosal membranes can be customized for drug targeting. Additional advantages include reduced thrombogenicity of nanoparticles and the feasibility of providing a depot effect for the release of hydrophobic drugs from drug carriers bound by a hydrophilic coating [74]. Surface modification is particularly useful for drug transport through the skin using lipid nanoparticles if the drug reaches systemic circulation via the transdermal route [88]. Gao et al. reported an increased penetration and skin deposition of lornoxicam NLC, whose surface had been modified with polyarginine peptide [97]. On the other side, Silva et al. reported that the surface coating of clobetasol-loaded NLC increased the retention of the drug in the *stratum corneum* [98].

The perspectives presented above substantiate the influence of SLN/NLC components on their structure, stability, and drug release. In the broader outlook of formulation development, certainly other aspects also draw our attention. These include the disease-specific parameters and route of the drug administration, propensity of skin irritation and delivery mode/vehicle [99]. The following points must be taken into account:

(i) The nature of the disease and the desired site of action dictate the route of drug administration. For transdermal drug delivery, lipid nanoparticles should have a mean size below 100 nm. Such small-sized particles can be tailored by the appropriate choice of lipids, surfactant, and their ratio.
(ii) Although lipid nanoparticles have been crowned as 'nanosafe carriers' [18], the surfactants employed in their formulation could be a cause of skin irritation [100], particularly when using new surfactants with less known toxicity profile [28,29,101].
(iii) Depending upon the therapeutic requirements, the developed NLC/SLN could be embedded in a suitable semi-solid, such as hydrogel, cream, ointment [102]. This not only facilitates application at the desired site but the properties and ingredients of the semi-solid could act in a synergistic fashion with the SLN/NLC to yield a therapeutic response or dermatological effect.

Besides the nature of the disease, the therapeutic effect of SLN/NLC upon skin application differs significantly whether they are intended for topical, dermal, or transdermal action. If topical, this means that the drug is retained onto the upper layers of the skin, not reaching the dermis. If dermal, the drug reaches this layer; if transdermal, the drug reaches systemic circulation. The degree of particles penetration onto the skin is

Table 2. Commonly used excipients in lipid nanoparticle formulations for cutaneous applications.

Solid lipids	Liquid lipids	Surfactants
Glyceryl behenate (Compritol® 888 ATO)	Oleic acid	Polysorbates
Glyceryl palmitostearate (Precirol® ATO5)	Castor oil	Sodium cholate
Cetyl palmitate	Caprylic/capric triglycerides (Miglyol® 812)	Soybean lecithin
Beeswax	Olive oil	Tyloxapol
Carnauba wax	α-Tocopherol	Poloxamer 188 (Pluronic® F68)
Glyceryl monostearate	Squalene	Sorbitan esters
Glyceryl tristearate	Labrafac	Phosphatidylcholine
Glyceryl tripalmitate	Isopropyl myristate	Egg lecithin
Glyceryl trimyristate	Transculol HP	Gelucire 50/13
Hydrogenated palm oil (Softisan® 154)	Linoleic acid	Sodium oleate
Stearic acid	Soybean oil	Solulol H515

governed by their composition in lipids, surfactants, as well as their size and surface properties. These latter are intimately dependent on the type of lipids, surfactants, and production method (discussed below). The interplay of various components forming a lipid nanoparticulate system determines their characteristics and performance specifications. Therefore, the selection of ingredients of the lipid matrix and other excipients should be based on vigorous pre-formulation studies and sound literature review. These often-overlooked elements of formulation design and development hold much significance in determining the final outcome.

3. Methods for SLN and NLC production

3.1. High-pressure homogenization (HPH)

High-pressure homogenization is the main method stablished for SLN and NLC production [4,103]. The advantages of this technique go beyond the short production time. This method also allows laboratory-scale production to be easily transposed to large-scale production [104]. Besides, the avoidance of organic solvents, yielding average particle size in the submicron region [9], and the variety of homogenizers brands and models at a reasonable price [105], make this a widely used technique in many industries. However, being a process that requires high-energy intensity, it increases the temperature of the samples, which is not suitable for heat-sensitive compounds [103]. This technique involves pushing the high-pressure sample into a very narrow gap (a few microns wide). High shear stress and cavitation forces reduce particles to submicron range [105]. High-pressure homogenization of SLN and NLC can be performed at both high and low temperatures (hot and cold homogenization, respectively). However, it is important to keep in mind that for both techniques it is necessary to dissolve or disperse the drug at a temperature about 5°C above its melting point [103,105].

3.1.1. Hot HPH

In hot homogenization, the entire process is carried out at temperatures above the melting point of the lipid. First, a pre-emulsion of the drug-loaded lipid melt and the aqueous emulsifier phase (5-10°C above lipid melting point) are obtained by high speed stirring (e.g. Ultra-Turrax). The hot pre-emulsion is then homogenized at high pressure at controlled temperature. For SLN and NLC production, a single homogenization cycle is sufficient to produce a hot emulsion with particle size in the range of 250–300 nm [106], when the pre-emulsion lipid concentration is in the range of 5-10%. Finally, the nanoemulsion obtained is cooled to room temperature and recrystallizes, forming SLN and NLC [14]. It is also possible to homogenize emulsions whose concentration reaches 40% [105,107]. However, lipid concentrations above 30% cannot be used to form NLC, but rather highly concentrated SLN formulations [108]. Nonetheless, the number of cycles will depend on the emulsion lipid concentration, since the energy required to shear the lipid mass is directly proportional to its concentration in the formulation [108]. On the other hand, increasing the number of homogenization cycles often results in increased particle size, since particle kinetic energy increases, favoring coalescence [105,109]. The literature usually reports the use of three homogenization cycles at 500 bar [106]. Literature reports that, in general, hot homogenization can be used even for temperature-sensitive compounds, since the time of exposure to elevated temperature is relatively short [108]. The temperature employed in the process is nevertheless a limitation of this technique, especially for extremely temperature sensitive compounds and hydrophilic compounds, which, with the high temperature, can partition from the lipid phase to the aqueous phase [9,108].

3.1.2. Cold HPH

Cold homogenization has been developed to overcome the problems related to the hot homogenization [105]. This process is recommended for extremely temperature sensitive and hydrophilic compounds [108]. Although it minimizes thermal exposure, this technique does not fully prevent it, since the active substance must be dissolved in the melted lipid phase in the initial step [105]. Then, the melted mixture is rapidly cooled down to a solid-state with dry ice or liquid nitrogen. This rapid cooling favors the homogeneous distribution of the active compound in the lipid phase. The formed solid is then ground to powder microparticles, and a pre-emulsion is formed by high-speed stirring of the powder in a cold aqueous surfactant solution. The dispersion is subjected to the homogenizer at or below room temperature, usually for five cycles at 500 bar, to form the lipid nanoparticles [14,103]. The disadvantage of this technique lies on the need for high energy in the severe homogenization step. In other words, this is not an energy-efficient process [103]. Moreover, compared to hot HPH, larger and more polydisperse particles are observed in cold HPH [105].

3.2. Microemulsion technique

This method consists of melting the lipid (or lipid blend) and heating the aqueous phase (containing surfactant) at the same temperature. The microemulsion is prepared by adding the aqueous solution to the lipid phase under mild stirring. Lipid nanoparticles are obtained by dispersing the microemulsion in cold water (2-10°C) under stirring. Finally, the system is washed with distilled water, filtered (to remove larger particles) and can be lyophilized to remove the excess of water [8,110]. This technique allows the formation of nanoparticles at mild temperature conditions. Nevertheless, the disadvantages include the need for relatively high concentrations of surfactants, the strong dilution of the particle suspension by pouring the microemulsion into water, and obtaining a suspension with a very low particle concentration [8,106].

3.3. Emulsification-solvent diffusion

This method involves the formation of an oil-in-water emulsion with a partially water-miscible solvent with low toxicity. The process is based on the water miscibility in these solvents, which contains the drug. Once formed, this transient oil-in-water emulsion is transferred to water, under continuous stirring, which causes the solvent to diffuse into the outer phase, resulting in the solidification of dispersed phase and formation

of nanoparticles. Depending on the boiling point, the solvent may be further removed by evaporation under reduced pressure [111,112]. As advantages, this approach is versatile, reproducible, and easy to implement; does not require high-energy sources; does not expose the drug to conditions of temperature stress and agitation; and results in narrow size distribution. On the other hand, it is necessary to clean up and concentrate the lipid nanoparticle dispersion [112].

3.4. Emulsification-solvent evaporation

In this technique, the lipid matrix is dissolved in a water-immiscible organic solvent and emulsified by the aqueous phase. The solvent is evaporated under reduced pressure, favoring the formation of nanoparticle dispersion by lipid precipitation in the aqueous medium. This is a totally heat-free technique that can result in very small nanoparticles up to 100 nm, depending on the components used. However, one drawback is the use of organic solvent, which can leave toxic residues in the sample [111].

3.5. Solvent injection (or solvent displacement)

This approach consists of dissolving the lipid matrix in a water-miscible solvent and rapidly injecting the mixture through an injection needle into a stirred surfactant-containing aqueous phase [113]. The technique is easy to implement, is versatile and efficient for obtaining lipid nanoparticles. Nonetheless, the use of organic solvent is a disadvantage [113].

3.6. Phase inversion

This is a solvent-free technique that consists of mixing the formulation components (lipid matrix, drug, water, and surfactant) under magnetic stirring and applying three temperature cycles (85-60-85-60-85°C) to reach the inversion process. Thereafter, a thermal shock is applied by diluting the mixture in cold distilled water resulting in lipid nanoparticle formation [114]. This technique does not use organic solvents and the heating is only for a short period. However, it is a time-consuming process, requiring several steps.

3.7. Sonication or ultra-sonication

Like high shear homogenization, this is a dispersion technique. The method involves melting the lipid matrix (with the drug) 5–10°C above its melting point, followed by the dispersion in an aqueous phase containing surfactant at the same temperature, under high-speed stirring, to form an emulsion. This is then sonicated to reduce droplet size and gradually cooled to form the nanoparticle dispersion [103]. The use of a very common equipment in laboratories is an advantage [14]. However, obtaining lipid nanoparticles requires long sonication times, which improves the risk of metal contamination from the probe. Moreover, as the energy distribution in the sample is not completely homogeneous, the resulting particles are highly polydisperse [115].

3.8. Membrane contactor technique

This method was developed for large-scale production of lipid nanoparticles. The molten lipid matrix containing the drug is pressurized through a porous membrane (usually with a pore diameter of 0.05 μm) to the aqueous phase containing a surfactant, maintained at lipid melting temperature. When passing through the pores, the lipid forms small droplets that precipitate as lipid nanoparticles, when the preparation is cooled to room temperature [12]. The method is scalable, simple, and the particle size can be controlled by using membranes with a different pore size [8].

4. Skin applications of SLN and NLC

4.1. Topical and dermal drug delivery by SLN/NLC

When considering the skin as a route of drug delivery, one has to consider the topical, dermal, and transdermal administration. While all are applied onto the skin, only the transdermal formulations are aimed to penetrate and reach systemic circulation. Topical drug delivery stands for the drug action at the superficial layers (e.g. epidermis), whereas dermal drug delivery happens when the drug reaches the skin dermis. Hair follicles also provide a versatile penetration route, both for dermal and transdermal drug delivery, with special application for lipid nanoparticles, since SLN and NLC are formed by lipids, which also appear in the composition of sebum in hair follicles [116]. In order to provide an insight into the recent research undertaken in this domain, the relevant literature is summarized in Tables 3 and 4.

Navigating through the scientific reports, it is apparent that NLC have been widely appreciated for their merits as compared to SLN. However, it must be noted that SLN have the same benefits as NLC, in the context of cutaneous application. It is perhaps for this reason that SLN have also engaged the attention of formulation scientists till date. The few drawbacks associated with these latter can be meticulously dealt with, keeping in view the pharmaceutical considerations in light of their composition and design.

The available scientific data advocate lipid nanoparticles as the most promising drug delivery alternatives for cutaneous administration, owing to their inherent attributes. Moreover, incorporation of these particles in a suitable base (i.e. cream, gel, ointment, emulgel, or lotion) enhances their benefits.

Topical delivery of drugs constitutes an important part of the therapeutic regimen for the management of skin disorders in which no systemic absorption is recommended. The preference for the topical route can be ascribed to its advantages over the parenteral and oral parenteral route. It not only circumvents the systemic side effects but also avoids fluctuations in plasma drug levels. Further, it enables a greater drug concentration to be delivered at the affected site and the first-pass metabolism is bypassed. However, traversing the *stratum corneum* constitutes a major challenge in the topical delivery of hydrophobic moieties (since most of the drugs used in the treatment of skin disorders are hydrophobic in nature). The tight packing of corneocytes in the stratum corneum imposes a barrier for xenobiotics [206]. In order to meet this challenge,

Table 3. Examples of drugs incorporated in SLN (since 2010).

Drugs	Category	Excipients Used	Purpose	References
Aceclofenac	NSAID	Glyceryl monostearate, Carbopol 934, soya lecithin, Tween 80	Development of SLN loaded hydrogel for topical administration of aceclofenac	[117]
N-Acetyl-D-Glucosamine	Anti-hyperpigmentation	Cetyl palmitate, phosphatidylcholine, PEG-25 hydrogenated Castor oil, Sasol, Areosil 200, hydrogenated Gliceryl palmate, Arlacel P-135	Formulation of N-acetyl-D-Glucosamine SLN for topical delivery in order to improve dermal properties in skin disorders	[118]
Aconitine	Analgesic	Transcotol P, Compritol® 888 ATO, polyethylene glycol- 35, castor oil, ethyl oleate	Improvement in safety and skin permeability of aconitine SLN via transdermal route	[119]
Acyclovir	Antiviral	Compritol® 888 ATO, soya lecithin	Development of acyclovir SLN for enhanced dermal delivery	[120]
Adapalene	Anti-acne	Tristearin, hydrogenated soya phosphatidylcholine, Triton X-100	For effective topical delivery of adapalene in acne	[121]
		Stearic acid, cetyl palmitate, tristearin, Brij 78, Pluronic F68, Tween 80, Span 20, Sodium dodecyl sulfate, glyceryl monostearate, Compritol® 888 ATO, Precirol ATO 5, glyceryl monooleate, Carbopol 980 NF, Carbopol Ultrez 10 NF, Pemulen TR-1	Enhancement of efficacy and improve skin tolerability of topical adapalene embedded gel	[208]
Amphotericin B	Antifungal	Compritol® 888 ATO, Precirol ATO 5, Poloxamer F-127, Poloxamer F-68, stearic acid, glycerol, Tween 80, sodium carboxymethyl cellulose	Design of amphotericin B SLN for improvement of therapeutic antifungal activity	[122]
Articaine	Local anesthetic	Poly(ε-caprolactone), capric/caprylic triglycerides, glyceryl tripalmitate, propylene glycol, polyvinyl alcohol, methylparaben	Enhancement of chemical stability of articaine in topical nanocarrier loaded hydrogel	[123]
Avanafil	For erectile dysfunction	Cholesterol, Compritol® 888 ATO, Tween 80, castor oil	Formulation and optimization avanafil SLN and SLN-loaded hydrogel film for transdermal delivery	[124]
Benzoyl peroxide	Anti-acne	Precirol ATO 5, Tween 80, Carbopol 934 NF	Benzoyl peroxide SLN to reduce side effects associated with drug for acne treatment	[125]
Betamethasone 17-valerate	Corticosteroid	Cetyl palmitate, glycerol distearate, glycerol tripalmitate, liquid paraffin	Elucidation of the effect of corticosteroid on skin barrier and drug penetration	[126]
Caffeine	Anticancer	Xanthan gum, Softisan 100, Pluronic® F-68	Development of SLN of hydrophilic drug caffeine for topical administration	[127]
Capsaicin	Diabetic neuropathy	Tripalmitin, caprylic/capric/myristic/stearic triglyceride, Miglyol® 812, Poloxamer 188,Tween 80, xanthan gum	Evaluation of the influence of crystallinity and lipid matrix on physicochemical characteristics and skin permeation of capsaicin SLN	[44]
Coenzyme Q10	Antioxidant	Compritol® 888 ATO, Precifac ATO, Labrasol, stearyl alcohol, stearic acid, Span 60, Tween 80, Tween 20, beeswax, cetyl alcohol	Investigation of the dermal penetration of Coenzyme Q10 SLN cream for hydration and anti-wrinkle property	[128]
		Compritol® 888 ATO, Lebrasol®, Poloxamer® 188, Tween 80, carbopol 974P	Development of coenzyme Q10 SLN loaded gels for enhanced dermal delivery	[129]
Colchicine	Anti-gout	Glyceryl monostearate, Tween 20, Sodium lauryl sulfate	Formulation and evaluation of colchicine SLN based transdermal patch for management of gout	[130]
Curcumin	Anti–inflammatory	Ceramide 2, Glyceryl monostearate, stearic acid, palmitic acid, Tween 80	Formulation and evaluation of curcumin SLN (ceramide-palmitic acid complex) for physical features and *ex vivo* permeation	[224]
	Anti–inflammatory, antioxidant, antimicrobial, antitumor	Pluronic F68, xanthan gum, Tween 80, soy bean lecithin	Development and investigation of curcumin thermoresponsive SLN gel for transdermal delivery	[131,132]
Cyclosporin A	Immunosuppressant	Lipocire™ DM, Pluronic® F-127, oleic acid	Production of stable, safe and improved Cyclosporin A nanocarrier for topical delivery	[133,134]
Diclofenac	NSAID	Epikuron 200, polyethylene glycol 400, Pluronic F68, Pluronic F127, Precirol ATO 5, Precirol ATO 888, Dynasan 114, Dynasan 118, Glycerol monostearate, stearic acid, Tween 80, Tween 60, Tween 20, glycerol, sorbitol	Preparation, characterization and *in vitro* evaluation of diclofenac sodium SLN for transdermal delivery	[135]
Doxorubicin	Anti-cancer	Stearic acid, lecithin, taurodeoxycholate sodium	Investigation of influence of iontophoresis on skin penetration from doxorubicin SLN	[136]
		Poloxamer 407, Precirol ATO 5, triethylamine, phosphoric acid	Investigation of potential of doxorubicin SLN for topical administration against skin cancer	[137]
Eugenol	Antifungal	Poloxamer 188, Compritol® 888 ATO, stearic acid	Formulation of eugenol SLN loaded hydrogels for epidermal targeting in skin fungal infections.	[138]

(*Continued*)

Table 3. (Continued).

Drugs	Category	Excipients Used	Purpose	References
Flucinolone acetonide	Corticosteroid anti–inflammatory	Compritol® 888 ATO, soya lecithin, Poloxamer 188	Fabrication, optimization and evaluation of potential of flucinolone acetonide SLN for prolonged release and targeted delivery via topical route	[139]
Fluconazole	Antifungal	Compritol® 888 ATO, phosphatidylcholine, Pluronic F-68, Sephadex G-50	Design of fluconazole SLN for its topical delivery against candidiasis	[140]
		Poloxamer 407, carbopol 934, Compritol® 888 ATO, Pricerol ATO5	Improvement in efficacy of Fluconazole SLN topical gel for Pityriasis Versicolor	[141]
		Compritol® 888 ATO, oleic acid, phosphatidylcholine, pluronic F-68, sephadex G-50	Improvement of dermal delivery of fluconazole via SLN and their evaluation for cutaneous candidiasis	[142]
Genistein	Anticancer and antiproliferative	Tween 80, Span 85, glyceryl behenate, Miglyol® 812 N	Preparation of genistein SLN for its delivery to deeper skin layers	[143]
Griseofulvin	Antifungal	Tween 80, Rhodamine 123, Compritol® 888 ATO, Carbopol 980 NF, Phospholipon 90G	Fabrication of griseofulvin SLN for dermal application	[144]
Halobetasol propionate	Corticosteroid anti–inflammatory	Glycerol monostearate, Tween 80, methyl and propyl paraben	Development of halobetasol propionate SLN for skin targeting via topical route	[206]
Hydroquinone	Anti-hyperpigmentation agent	Precirol® ATO 5, Poloxamer 407, Span 20, Carbopol 934	Encapsulation of hydroquinone in SLN in order to improve its stability, skin penetration and reduce systemic absorption	[145]
Idebenone	Ubiquinone derivative having antioxidant activity	Brij 58, Brij 98, cetyl palmitate, Poloxamer 188, glyceryl oleate	For targeting idebenone to the upper layers of skin via topical delivery	[146]
		Glyceryl oleate, cetyl palmitate, methylisothiazolinone, Brij 98, methylchloroisothiazolinone, triethanolamine	Formulation of idebenone ester with pyroglutamic acid SLN to improve topical efficacy	[147]
Isotretinoin	Anti-acne	Phosphatidylcholine, Compritol® 888 ATO, butylated hydroxy toluene, tocopherol	Development of optimized SLN for isotretinoin to reduce dermal irritation and enhance therapeutic performance of drug	[148]
Ivermection	Antiparasitic	Palmitic acid, polyvinyl alcohol, polyglycerol fatty acid ester	Ivermection SLN were proposed for transdermal delivery to avoid systemic toxicity	[149]
Lornoxicam	NSAID	Compritol® 888 ATO, Lanette O, Pluronic F68, oleic acid, xanthan gum	Preparation of SLN and NLC gels for inflammatory and painful conditions of skin	[150]
Meloxicam	NSAID	Cetyl palmitate, propylene glycol, Tween 80, polyethylene glycol 400, Carbopol 940	Investigation of potential of meloxicam SLN gel for dermal application	[151]
Metformin	Anti-diabetic	Tween 60, cholesterol, Span 60, beeswax	For enhancement of skin delivery of metformin via SLN topical gel	[152]
Miconazole nitrate	Antifungal	Soya lecithin, carbopol 934, tristearin, Tween 80	Investigation of miconazole nitrate SLN hydrogel for topical delivery in fungal infections	[153]
Mometasone furoate	Glucocorticosteroid Anti-psoriasis	Glycerol monostearate, Compritol® 888 ATO, cetyl palmitate, Syncrowax-HRC and HGL, stearic acid, Tween 80, Carbopol 974p	Fabrication of mometasone furoate SLN for topical delivery to address the short coming conventional formulation of this corticosteroid	[154]
Naproxen	NSAID	Tween 80, Span 80, glyceryl mono stearate	Preparation of naproxen SLN to improve skin permeation and to explore influence of hydrophilic-lipophilic balance modifications on nanolipidic carriers	[155]
Piroxicam	NSAID	Brij 35, Brij 72, triethanolamine, chloroform, acetic acid, cholesterol and stearic acid, Carbopol	Preparation and assessment of piroxicam SLN gel to enhance its skin permeation for topical application	[156]
Resveratrol	Anti- inflammatory and antiproliferative	Precirol ATO 5, carbopol 940, Compritol® 888 ATO, Tween 20, Lebrasol	Resveratrol SLN engrossed gel for skin targeting in contact dermatitis	[157]
	Anti-tyrosinase activity	Stearic acid, soy phosphatidylcholine, poloxamer 407, polysorbate 80	Preparation of trans-resveratrol SLN for skin delivery and their *in vitro* evaluation for hyperpigmentation	[158]
Retinoic Acid	Anti-acne	Cholesterol, Brij 58, stearylamine, butylated hydroxytoluene (BHT), methyl-paraben, Compritol® 888 ATO, Vitanol A, hydroxyethyl cellulose	Evaluation of application of retinoic acid loaded SLN for topical treatment of acne	[159]
Retinoic acid and Lauric acid	Retinoids, Anti-microbial	Propylene glycol, Compritol® 888 ATO, Brij 58, cholesterol, stearylamine, Butylated hydroxy toluene	Development of SLN for retinoic acid and lauric acid and evaluation of their antibacterial potential	[160]

(*Continued*)

Table 3. (Continued).

Drugs	Category	Excipients Used	Purpose	References
Retinyl palmitate	Anti-wrinkle	Precirol® ATO5, Gelucire® 50/13, dicetyl phosphate, Carbomer® 940	Improvement of surface modified SLN loaded gel for enhancement of skin distribution of retinyl palmitate for skin aging	[96,161]
Safranal	Sunscreen and moisturing agent	Glyceryl monostearate, Tween 80	Loading of safranal in SLN and their evaluatation for sunscreen potential for topical delivery	[162]
Sesamol	Antioxidant and anticancer	Glyceryl monostearate, sodium deoxycholate, phosphatidylcholine	Fabrication of sesamol SLN for skin cancer	[163]
Silybin	Antioxidant and anti–inflammatory	Tween 20, Tween 80, Span 20, Span 80, Triton X-100, cetyl palmitate, stearic acid, Compritol® 888 ATO, Glyceryl monostearate, Precirol ATO5, Carbopol 940	Preparation and evaluation of silybin SLN gel for irritant contact dermatitis	[164]
Spironolactone	Anti-acne potential	Tween 80, Span 80, Span 60, stearic acid, dichloromethane, Highly Ordered Pyrolytic Graphite (HOPG)	Formulation of spironolactone SLN and their exploration for dermal delivery	[165]
Tacrolimus	Immunosuppressive macrolide	Cocoglyceride, Poloxamer 188, stearic acid, soybean lecithin, Brij® 93, Brij® 58	Improvement in penetration and retention of tacrolimus thermosensitive SLN in skin layers	[166]
Terbinafine	Antifungal	Glyceryl behenate, glyceryl palmitostearate, Pluronic F-127	Development of terbinafine hydrochloride SLN for controlled release via topical application	[167]
		Cremophor® EL, RH40, and RH60, Gelucire® 39/01, Gelucire® 44/14, glyceryl behenate (Compritol® 888 ATO), and glyceryl palmitostearate, Tween 80, Tween 60, Tween 40, Tween 20, propylenglycol	Terbinafine SLN as topical delivery system to resolve issues of longer treatment time and frequent delivery	[168]
Tretinoin	Metabolite of vitamin A having antiacne potential	Myristyl myristate, chitosan	Preparation and evaluation of tretinoin SLN with and without chitosan for acne	[169]
Triamcinolone acetonide	Glucocorticosteroid	Compritol® 888 ATO, precirol ATO 5, soya lecithin, poloxamer, glycerol monostearate, stearic acid	Entrapment of triamcinolone acetonide in SLN for topical application in order to alleviate its systemic side effects	[170]

two strategies are being currently employed: the use of penetration enhancers and the design of nanoparticle-based formulations. Second approach has proved to be more promising, in view of the skin irritation potential of penetration enhancers. Nanoparticles, in general, act as a drug reservoir, which maintains relatively higher drug concentration in the skin layers. In this respect, lipid-based nanoparticles are a better alternative as compared to polymer-based nanoparticles, as the epidermis is chiefly composed of lipids [86]. Some examples are described ahead.

El-Housiny et al. formulated a well-known antifungal drug, fluconazole (FLZ) in SLN topical gel in order to enhance its efficacy in Pityriasis Versicolor (PV). FLZ-loaded SLN were crafted employing ultrasonication technique and modified high shear homogenization, followed by their incorporation into Carbopol 934 gel. FLZ-loaded SLN exhibited reasonable colloidal size, no aggregation, and were of spherical shape. The encapsulation efficiency ranged from 55.49% to 83.04%. Particles showed electrostatic stability (high ZP) and prolonged release profile *in vitro*. Further, clinical evaluation of FLZ-loaded SLN gel was carried out on PV patients comparing with commercial cream Candistan. FLZ-SLN gel showed remarkable enhancement ($p < 0.05$) in therapeutic response, in comparison to commercial cream. The findings of this study advocated a superior therapeutic index of the prepared FLZ-loaded SLN gel over the marketed Candistan cream.

Montenegro et al. developed SLN for topical delivery of idebenone (IDE) to enhance its effectiveness [207]. For this purpose, IDE ester (IDEPCA) with pyroglutamic acid was synthesized. Then, IDEPCA was encapsulated in SLN. The prepared SLN were evaluated for *in vitro* antioxidant, antiglycation and *in vivo* hydrating effect, after topical application (in human volunteers) of IDEPCA-SLN gel and compared with IDE-SLN. All SLN displayed satisfactory technological characteristics (mean particle size, polydispersity index, and stability). Results of antioxidant activity showed similar oxygen radical absorption capacity of IDEPCA and IDE-SLN, while for *in vitro* nitric oxide scavenging activity IDEPCA-SLN were found more effective. For antiglycation activity, both IDE and IDEPCA SLN depicted similar effectiveness in the inhibition of the formation of advanced glycation products. *In vivo* findings established this as a better strategy to prepare topical nanoformulation with enhanced hydrating action.

Harde et al. developed a topical adapalene (Ada) SLN gel for ameliorating skin irritation behavior of the drug commonly used in acne [208]. Ada-SLN were produced via hot homogenization method and optimized using a Box-Behnken design. The optimized formulation showed mean particle size of 102 ± 5 nm, with encapsulation efficiency above 85%. Ada-SLN were embedded in a Carbopol gel. The obtained semi-solid exhibited an optimal viscosity of 24.57 ± 0.27 Pa.S, with spreadability of 12.39 ± 2.62 cm^2 appropriate for skin application. *In vitro* dermatokinetic results revealed enhanced dermal bioavailability for 0.1% w/w Ada-SLN gel (4.69 fold, ~0.48 μg/cm^2) and 0.1% w/w Ada-SLN gel (3.19 fold, ~0.37 μg/cm^2), in comparison to a gel containing 0.1% free Ada (non-loaded into SLN) (~0.12 μg/cm^2). Confocal microscopy illustrated significant follicular localization of lipid nanoparticles, followed

Table 4. Examples of drugs incorporated in NLC (since 2010).

Drugs	Category	Excipients Used	Purpose	References
Acitretin	Anti-psoriatic agent	Oleic acid, Tween 80, Precirol ATO 5	Fabrication and evaluation of acitretin NLC for topical treatment of psoriasis	[50]
Adapalene and Vitamin C	Retinoid, Antioxidant	Phospholipid, tristearin, Triton X-100	Preparation and evaluation of topical gel of adapalene and vitamin C	[211]
Artemether	Antimalarial	Gelucire® 43/01, Compritol® 888 ATO, Transcutol® P, Phospholipon® 85 G, polysorbate 80 and 20, Macrogol 4000, sorbitol, Pluronic F68, Span 60	Fabrication of artemether NLC for topical delivery	[171,172]
Betamethasone dipropionate	Glucocorticoid	Oleic acid, Tween 80, Span 80, liquid paraffin, stearyl alcohol, iso-propyl alcohol, isopropyl palmitate, Precirol ATO 5, Carbopol 971	Investigation of betamethasone dipropionate NLC ointment for atopic dermatitis	[173]
Bupivacaine	Anesthetic	Polysorbate 80, dimethylaminopyridine, fetal bovine serum, soya lecithin, Compritol® 888 ATO, Precirol® ATO 5	Design of Hyaluronic acid modified bupivacaine NLC for effective transdermal local anesthetic delivery	[174]
Calcipotriol and Methotrexate	Anti-psoriatic, Anticancer	Precirol ATO5, Myverol™ 18-04K, Pluronic F68	Evaluation of combination of calcipotriol and methotrexate in NLC for topical management of psoriasis	[175]
Clobetasol propionate	Corticosteroid	Oleic acid, sodium taurodeoxycholate, low molecular weight chitosan, stearic acid, propylene glycol	Clobetasol propionate NLC for epidermal targeting	[98]
Coenzyme Q10	Antioxidant	Cetyl palmitate, Labrasol, carbomer	Coenzyme Q10 NLC for epidermal targeting	[176]
Diclofenac sodium	NSAID	Glyceryl monostearate, lanolin PEG-75, Phospholipon 90G, Precirol ATO 5, Tween 80, Cremophor RH 40, polyvinyl alcohol, carboxymethyl cellulose sodium, cetyl alcohol, cetosteryl alcohol, propylene glycol	Fabrication and evaluation of diclofenac sodium NLC gel for transdermal drug delivery	[177]
Difluctolone valerate	Corticosteroid	Precirol® ATO5, Labrasol®, Labrafil® M1944CS, Capryol™ 90, tristearin, Poloxamer® 407, isopropyl myristate, stearic acid	NLC work as reservoir for difluctolone valerate targeting via topical delivery	[178]
Diphencyprone	For alopecia areata	Cetyl palmitate, Pluronic F68, hydrogenated soybean phosphatidylcholine	For improving skin absorption of diphencyprone and its follicular targeting	[179]
Docetaxel and nicotinamide	Anti-cancer, penetration enhancer	Egg lecithin, glycerin monostearate, capric glyceride	Development and evaluation of docetaxel-nicotinamide complex NLC to enhance skin permeation	[180]
Donepezil	Cholinesterase inhibitor	Oleic acid, stearic acid, sodium taurodeoxycholate hydrate, soy lecithin, glycerol monooleate	NLC gel for transdermal application of donepezil	[181]
Enoxaparin	Anticoagulant	Tristearin, oleic acid, tween 80, Carbopol 934	Investigation of NLC as a vehicle for topical delivery of enoxaparin	[182]
Flucinolone	Corticosteroid	Compritol® 888 ATO, polysorbate 80, Miglyol® 812	Design and evaluation of topical flucinolone acetonide NLC for psoriasis	[139]
Flurbiprofen	Anti-arthritic drug/ NSAID	Soya lecithin, coconut oil, soybean oil, olive oil, castor oil	Evaluation of potential for transdermal delivery of flurbiprofen NLC	[54]
		Compritol® 888 ATO, Miglyol® 812, lecithin, Poloxamer 188, sodium deoxycholate, Tween 80, carbopol 940	Design of flurbiprofen NLC gel for topical application	[183]
Ketoprofen	NSAID	Glycerol, β-cyclodextrin, Compritol® 888 ATO, Lutrol® F68	Ketoprofen cyclodextrin complex loaded NLC improved therapeutic efficacy via topical delivery	[184]
Lansoprazole	For stomach infection	Glyceryl monostearate, stearylamine, Pluronic F68, Sodium dodecyl sulfate	Fabrication of lansoprazole NLC for transdermal application	[185]
Lidocaine	Anesthetic	Cetyl ester wax, propylene glycol USP, Carbomer 940 NF, Tween 80	Lidocaine incorporated in NLC aiming to localization of drug and its controlled delivery	[186]
Lycopene	Antioxidant	Orange wax, rice bran oil, Eumuglin SG, mineral oil	Characterization of lycopene NLC for topical application	[187]
Meloxicam	NSAID	Cetyl palmitate, Caprylic acid, propylene glycol (PG), Tween 80, polyethylene glycol 400 (PEG 400), triethanolamine, Carbopol 940	Meloxicam NLC gel for improving transdermal delivery	[188]
Miconazole	Antifungal	Glyceryl monostearate, olive oil, coconut oil, mustard oil, lavender oil	Development of miconazole nitrate ultra-small NLC for topical delivery against athlete's foot	[189]
Minoxidil	For alopecia	Tristearin, oleic acid, cholesterol, Tween 80, soya lecithin, Pluronic F-68, Triton X-100, carbopol 934	Minoxidil NLC gel for alopecia	[190]
Nimesulide	NSAID	Poloxamer 188, isopropyl alcohol, methanol, ethanol, soya lecithin, oleic acid, stearic acid	Fabrication, optimization of topically applied nimesulide NLC	[210]
Phenylethyl resorcinol	Tyrosinase inhibitor	Glycerol monostearate, olive oil, behenic acid, palmitic acid, stearic acid, Dynasan, Compritol® 888 ATO, Precirol ATO 5, Labrasol, Miglyol® 812, mineral oil, oleic acid, olive oil, polyvinyl alcohol, lecithin, Tween 80	Enhancement of skin whitening property of phenylethyl resorcinol by loading in NLC	[191]

(*Continued*)

Table 4. (Continued).

Drugs	Category	Excipients Used	Purpose	References
Pioglitazone	Anti-hyperglycemic agent	Apifil, Labrasol, Carbopol, Tween 80	Design of pioglitazone NLC for its bioavailability enhancement via transdermal route for diabetes	[192]
Podophyllotoxin	Antimitotic Agent	Cremophor RH 40, Compritol® 888 ATO, Labrasol, soybean phosphatidylcholine	Fabrication of podophyllotoxin NLC for skin targeting	[193]
Quercetin	Flavonoid having anti-cancer, anti-oxidant activity	Soya lecithin, glyceryl monostearate, stearic acid	NLC encapsulating quercetin for topical administration	[194]
Retinyl retinoate	Anti-aging	Canola oil, Compritol® 888 ATO, Precirol® 5 ATO, Labrafil M 1944 CS, Miglyol® 840, oleic acid, soybean oil, Tween 80	NLC topical formulation entrapping retinyl retinoate for antiaging and anti-wrinkle effects	[195]
Rivastigmine	Cholinesterase inhibitor	Castor oil, Capmul MCM, soya oil, olive oil, palm oil, peanut oil, Tween 80, Span 80, Eudragit E-100, glyceryl monostearate, polyvinyl pyrrolidone, diethyl phthalate	Development of rivastigmine NLC loaded transdermal formulation for bioavailability enhancement	[196]
Ropivacaine	Anesthetic	Soya lecithin, glyceryl monostearate, stearic acid	Evaluation of ropivacaine NLC for transdermal application	[197]
Salicylic acid	NSAID with antifungal activity	Compritol® 888 ATO, Miglyol® 812, Cremophor RH 60	Development and optimization of salicylic acid NLC for dermal use	[198]
Sildenafil citrate	Phosphodiesterase type 5 inhibitor	Cetyl palmitate, glycerol monolinoleate, hydrogenated castor oil, Span 85, propylene glycol, Tween 80	Transdermal permeation of NLC and SLN loaded with sildenafil citrate	[199]
Spironolactone	Diuretic having antiandrogenic properties	Tween 80, Transcutol® P, Compritol® 888 ATO	Follicular targeting of spironolactone NLC in alopecia	[200]
Tacrolimus	Immunosuppressive macrolide	Soybean lecithin, propylene glycol monocaprylate, glyceryl palmitostearate, Butylated hydroxytoluene, polysorbate 80	NLC lotion for improving dermal application of tacrolimus	[201]
Terbinafine	Antifungal	Precirol ATO 5, Compritol® 888 ATO, glyceryl monostearate, Tween 20, Tween 80, castor oil, oleic acid, Span 80	Investigation of terbinafine hydrochloride NLC for fungal infection via topical application	[202]
Tripterine	Anti–inflammatory/ anticancer	Glyceryl behenate, isopropyl myristate (IPM), Pluronic F68, Precirol ATO-5, soybean lecithin	Evaluation of surface charge of tripterine NLC on permeation and *in vivo* performance	[203]
Voriconazole	Antifungal	Compritol® 888 ATO, Miglyol® 812 N, Tween® 80, Span® 85	*In vitro* evaluation of the impact of the follicular pathway on epidermal deposition	[204]
		Oleic acid, Tween 80, polyethylene glycol	Fabrication of voriconazole NLC gel for skin targeting and alleviating adverse effects of drug	[209]
		Precirol® ATO 5, Labrafil M 1944 CS, Tween 80, Carbopol 940 NF	NLC hydrogel of voriconazole for mycotic infection via topical administration	[205]

by their diffusion into the dermis. Transepidermal water loss studies and skin irritation evaluation in Episkin (reconstituted human epidermis) supported higher skin tolerance of fabricated nanogel. Histological and visual findings further reinforced the enhanced anti-acne potential of the novel Ada-SLN gel, when compared to the gel containing non-loaded Ada.

Waghule *et al.* proposed NLC embedded in a topical gel for the delivery of anti-fungal voriconazole (VCZ) to minimize the intensity and frequency of its adverse effects [209]. A Box-Behnken design was again used for the optimization of process and formulation parameters. The optimized formulation exhibited suitable mean particle size, and high encapsulation efficiency and drug loading. VCZ-loaded NLC depicted prolonged release of drug up to 10 h. The chosen formulation was embedded in a Carbopol gel and *ex vivo* permeation studies were performed. Results revealed enhanced permeation 66.45% and sustained release up to 11 h in comparison to a gel containing free drug. The results reported the NLC embedded gel retained more drug in skin strata, preventing its systemic permeation and, as a result, minimizing the adverse effects associated with the free VCZ. *In vitro* evaluation of antifungal activity (*Aspergillus flavus*) showed significantly higher zone of inhibition (22.5 ± 0.5 mm) of NLC formulation than the free drug counterpart (14.5 ± 0.5 mm). This study aids an understanding regarding the interaction between formulation and process variables. Further, it was reported that VCZ-loaded NLC gel, capable of targeting the skin, could be a promising alternative for the management of topical fungal infections.

Moghddam et al. developed a nimesulide NLC for topical delivery [210], optimized through Box-Behnken design. Selecting the ratio of stearic to oleic acids and the concentrations of Poloxamer 188 and lecithin as independent variables, the particle size, and encapsulation efficiency (the dependent variables) were optimized. Additionally, skin permeation assay, *in vitro* release, confocal laser scanning microscopy (CLSM) and stability evaluation were performed. The optimized nimesulide NLC demonstrated reasonable encapsulation efficiency, particle size, and skin permeation. The results of preliminary studies displayed delayed drug release for the optimized batch, following a Higuchi release kinetics. CLSM revealed an improved penetration of Rhodamine loaded NLC to deeper skin layers. The findings of this study revealed NLC as a potential carrier for the topical application of nimesulide.

Jain et al. produced and characterized a topical NLC gel, co-loading adapalene (Ada) and vitamin C (AP-Ascorbyl-6 palmitate) [211]. NLC were produced by HPH and then dispersed into a gel. Drug-loaded NLC gels were tested for skin permeation and biodistribution, and anti-acne therapeutic efficacy against testosterone-induced acne (male Wistar rat). NLC gel enhanced epidermal targeting and retarded systemic absorption. The findings of this research suggested not only the potentiality of NLC for the dermal application of Ada, but also synergistic effect of vitamin C in topical acne therapeutics.

The therapeutic outcome in cutaneous disorders can be increased by means of drug targeting approach. The targeting benefits of lipid nanoparticles have been realized in the last decade. By virtue of the small particle size and controlled release property, a low concentration gradient is attained in the epidermal layer, which results in drug accumulation, preventing its further penetration into deeper layers [212]. Occlusive property of the SLN/NLC is a further advantage in this regard, which is complimented by the lipids and surfactants composing the nanoparticles [92,213].

Shrotriya et al. prepared resveratrol (RES) loaded SLN, as an alternative to topical corticosteroids in irritant contact dermatitis [214]. The challenges encountered in formulating RES, like poor solubility and bioavailability, were overcome. RES-loaded SLN were produced by ultrasonication technique, employing Precirol ATO 5 (lipid) and Tween 20 (surfactant) and further embedded into a Carbopol gel. RES-loaded SLN gels were studied for their *ex vivo* permeation, skin deposition (using human cadaver skin) and skin irritation (using New Zealand white rabbits). In addition, the effect of the prepared nanogel was checked in BALB/c mice. RES-loaded NLC showed a mean particle size below 100 nm and encapsulation efficiency of 68-89%. Particles exhibited a controlled release of RES up to 24 h. Further, skin deposition and irritation studies validated skin targeting potential, with no irritation. Finally, RES nanogel exhibited a decrease in skin water content and competent suppression of ear swelling in BALB/c mouse model, in contact dermatitis, in comparison to commercial gel. The findings of this work confirm the added value of lipid nanoparticles in the management of skin contact dermatitis, as suggested by expert opinion [215].

Raj et al. developed aceclofenac (ACF) SLN containing hydrogel for improved topical delivery of the non-steroidal anti–inflammatory drug (NSAID) [216]. SLN were prepared using ultrasonic emulsification and optimized for lipid content and stirring speed. Besides routine characterization for particle size, zeta potential, polydispersity index, encapsulation efficiency, and surface morphology, *in vivo* anti–inflammatory studies were also performed. The *in vivo* data illustrated a prolonged inhibition of edema from ACF-loaded SLN hydrogel, in comparison to plain ACF gel (after 24 h). Results of skin retention from CLSM validated skin targeting by ACF-loaded SLN gel, which can serve as a potential carrier for ACF in topical application.

Akbari et al. loaded naproxen (NAP) in SLN by ultrasonication to enhance skin permeation [217]. The performance of NAP-loaded SLN was evaluated in terms of *ex vivo* skin permeation and retention of the NSAID in skin layers. SLN contributed to increase the amount of NAP in skin strata, with low systemic absorption, and reduced side effects.

Bikkad et al. produced halobetasol propionate (HP) SLN to minimize the side effects associated with the corticosteroid, and to provide controlled release [218]. HP-loaded SLN were fabricated employing solvent injection technique and optimized using 3^2 factorial design experiment. The optimized HP-loaded SLN was dispersed in Carbopol gel for skin application. The nanogels were compared with a commercial formulation, in terms of *in vitro* skin permeation, drug disposition (using human cadaver skin) and skin irritation. HP-loaded SLN displayed an average size of 200 nm and an encapsulation efficiency of 84-94%. A prolonged drug release up to 12 h was obtained, while drug disposition and skin irritation studies confirmed that HP-loaded SLN gel was capable of avoiding systemic uptake, with a better accumulation of drug in upper

skin layers with limited skin irritation, as compared to the commercial formulation.

Silva et al. studied the epidermal targeting of clobetasol propionate (CP) NLC and chitosan-coated clobetasol propionate NLC [98]. After physicochemical characterization, epidermal targeting was validated with extensive *in vitro* skin permeation experiments and drug quantification, in various skin layers. Results showed increased drug concentration in the epidermal layer, higher than 80-fold, with chitosan-coated and uncoated NLC, in comparison to marketed formulation. Further, the uncoated NLC did not display dermal retention.

Zhao et al. loaded podophyllotoxin (POD) into NLC, in order to enhance its skin distribution [219]. For this, two types of POD-loaded NLC were produced. Their targeting efficacy in skin was compared via *in vitro* and *in vivo* experiments. Remarkably higher deposits of POD were detected in skin layers from *in vitro* and *in vivo* activity in rat skin. Additionally, to analyze the skin distribution of POD, Nile red loaded NLC formulations were prepared and checked via CLSM, suggesting higher skin targeting through NLC. Skin irritation of POD-loaded NLC was also investigated in damaged and intact rabbit skin. No irritation was observed, which suggested its safety for topical use.

Chen et al. prepared Coenzyme Q10 (Q10) NLC for epidermal targeting [220]. Formulation and process parameters were optimized using Box-Behnken design. The prepared Q10-loaded NLC were tested in rat skin. Results of skin permeation assay showed 10.11 times more accumulation of Q10 in the epidermal layer from Q10-loaded NLC, when compared with Q10-loaded emulsion. After 24-h exposure to daylight, the amount of Q10 available in Q10-loaded loaded NLC was diminished only by 5.59%, whereas a decrease of 24.61% was seen in the emulsion. These results suggest the protective effect of the lipid matrix against light degradation also contributing to a significant epidermal targeting potential of Q10.

Rocha et al. demonstrate the potential of NLC to enhance topical nail drug delivery by producing NLC as a delivery system for the antifungal drug voriconazole (VOR) [221]. VOR-containing NLCs were produced by the microemulsion technique and the *in vitro* drug penetration was evaluated in porcine hooves for NLC, NLC containing urea as a penetration enhancer and unloaded VOR. Results showed similar penetration for NLC and NLC added by urea, with a significantly higher amount of drug in deeper regions of hooves, when compared with the unloaded VOR, which indicates a very promising strategy for the onychomycosis management.

4.2. Transdermal drug delivery by SLN/NLC: a road less traveled

Other cutaneous application of lipid nanoparticles is the transdermal delivery of drugs, in which the skin is used as a route of administration of drugs for systemic distribution. In this case, lipid nanoparticles are used as carriers of drugs meant to treat disorders other than those affecting the skin, owing to the advantages of transdermal over oral and parenteral routes. Digging into the literature, it is perceivable that lipid nanoparticles have been exploited to a much greater extent for topical and dermal drug delivery, in comparison to transdermal application. Further search reveals that SLN have been better explored as carriers than NLC for systemic drug delivery via skin, in the present decade. To this end, the investigations have been limited to *in vitro* evaluation of drug permeation and retention through skin, while *in vivo* pharmacokinetic studies have been overlooked. It must be emphasized that *in vivo* evaluations of transdermal delivery systems are imperative to arrive at any conclusion, regarding their efficacy and clinical utility.

Guo et al. formulated ivermectin (IVM) SLN employing hot homogenization technique, which was followed by ultrasonication, in order to reduce their size [222]. The obtained SLN were almost spherical in shape and displayed good stability. Delayed release was demonstrated from IVM-SLN and there was no burst release, owing to effective entrapment of the drug. Cumulative drug permeation across rat skin from SLN was found remarkably enhanced when compared with IVM suspension. This study demonstrated that IVM-SLN is an efficient carrier for transdermal application to avoid extended systemic distribution, thereby reducing the drug toxicity.

Lee et al. developed and investigated a thermo-responsive hydrogel embedding curcumin (Cur) loaded SLN for transdermal application [223]. Ultrasonication-homogenization was utilized for encapsulation of Cur with SLN, which were further introduced into Pluronic F68 and F127 (10:90 ratio) and xanthan gum thermo-responsive hydrogel. The prepared hydrogels gel in contact with the skin (at 29.3°C). Xanthan gum played an important role, providing skin adhesiveness. Physicochemical evaluation of prepared nanogels was carried out for polydispersity index, particle size, and morphological properties. The cumulative amount of curcumin that penetrated the skin was remarkably higher than its ethanolic solution.

Gaur et al. crafted curcumin SLN using emulsion solvent evaporation. Besides physicochemical evaluation, the prepared formulation was evaluated for *in vitro* drug release, pharmacokinetic parameters, and anti–inflammatory effect [224]. Selected SLN were also assessed for stability. The prepared SLN were spherical in shape, with mean particle size ranging from 102 to 156 nm (with negative zeta potential). Among the three types of curcumin SLN fabricated, ceramide-2: palmitic acid showed the highest encapsulation efficiency. The drug release presented the following order: stearic acid-SLN > glyceryl monostearate-SLN > ceramide-2: palmitic acid-SLN. The selected optimized formulation displayed good stability and drug permeation (through human skin). Bioavailability enhancement for the optimized nanoformulation was enhanced up to 68.12%. Further, C_{max} of the chosen formulation showed the highest value. Lastly, this formulation afforded high edema inhibition (90.75%) in 6 h. This study showed that the nature of lipid plays a key role in designing an improved SLN-based delivery system, having optimum transdermal permeation.

Very recently Mendes et al. developed and characterized donepezil (DPB) NLC gel for transdermal application [181]. Drug-loaded NLC were produced using the microemulsion technique. Excipients were chosen on the basis of their *in vitro* skin permeation potential. Stearic acid was chosen as

a solid lipid, oleic acid as a liquid lipid, whereas lecithin and sodium taurodeoxycholate as surfactant and co-surfactant, respectively. Skin permeation of DPB was enhanced, as revealed from *in vitro* permeation assays, which was attributed to excipients used, as well as lipid nanocarriers. DPB-NLC gel was presented as an interesting formulation for improving Alzheimer's disease treatment.

Chauhan and Sharma developed NLC-based transdermal carrier of rivastigmine for improvement of bioavailability [225]. For the optimization of NLC, Box-Behnken design was employed. The optimized NLC formulations were engineered using castor oil (4% w/w), Span 80 (1.8% w/w/) and Tween 80 (3% w/w), and subsequently characterized. In this attempt, after routine characterization of NLC, these were loaded in transdermal patches. Results of *in vitro* release behavior showed drug release in a sustained fashion, in comparison to commercial Exelen® patch. The results of pharmacokinetic studies presented higher C_{max} and $AUC_{0\text{-}72}$ values in plasma treated with NLC transdermal patches, in comparison to conventional patches. The findings of this work validated the potential of the NLC transdermal patch for bioavailability enhancement of rivastigmine in dementia.

Yue et al. produced hyaluronic acid (HA) modified NLC for transdermal delivery of bupivacaine (BPV) and assessed their *in vitro* and *in vivo* performance [226]. Firstly, HA and linoleic acid conjugated PEG (propylene glycol) was prepared (HA-PEG -LOA) and the complex was then added to NLC during the course of production. Besides physicochemical characterization, *in vitro* skin permeation, drug release, and *in vivo* therapeutic activity were also carried out. The prepared NLC were of small size (150 nm), with zeta potential −40 mV. BPV-NLC showed very high encapsulation efficiency, i.e. 90%. *In vitro* release assay reported sustained profile for 72 h. BPV-NLC and HA-BPV-NLC exhibited 1.6 and 2.5-fold enhancement in percutaneous penetration when compared to free BPV. Results demonstrated the efficacy of HA modified BPV-NLC for prolonging and improving anestheticthe action of the drug.

Although being an attractive and fascinating approach, the use of lipid nanoparticles is still restricted to the cosmetic market.

5. Expert opinion

Looking at the landscape of SLN and NLC, a few aspects standout. Being lipoidal systems, lipid nanoparticles have been most preferentially exploited for lipophilic and poorly water-soluble drugs. Nevertheless, some studies have successfully demonstrated their suitability for the delivery of hydrophilic moieties. On the other hand, studies have been undertaken to compare the inherent characteristics of SLN and NLC, using the same drug. The exploitation of SLN and NLC for co-delivery of drug moieties for better therapeutic outcomes, with recognized synergistic effects. Although hydrogels represent a vehicle of choice for loading SLN and NLC, a few reports have described the use of ointments, lotions, emulgels, patches, and other films as semi-solids most suitable for skin application. SLN and NLC can be used for topical, dermal, and transdermal drug delivery. Tailoring their composition in terms of lipids and surfactants, optimized by factorial design approaches, site-specific targeting can be achieved with important therapeutic outcomes. Besides, the carriers are by definition biocompatible while their composition limits the risk of toxicity and irritation when applied onto the skin. Several skin lipids are used as raw materials in the composition of SLN and NLC thereby acting as penetration enhancers. Improving skin permeation and penetration of drugs, less drug may be needed to exhibit its therapeutic effect, further reducing eventual adverse side effects. With the expansion of knowledge and technical competences in the field, lipid nanoparticles have won the cosmetic market. However, the clinical application remains a challenge of its own, which comes up against issues such as the complexity of regulatory requirements. In addition, there is still little *in vivo* knowledge about the ability of these nanosystems to permeate biological membranes, distribute the drug in the skin strata, and deposit themselves in the body's tissues. Many companies are working with these nanoparticles, and it is only a matter of time before they reach the pharmaceutical market.

Funding

The authors acknowledge CAPES (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior) for the financial support and for the fellowship of the second author (88887.368385/2019-00). Authors also acknowledge the support received from the Portuguese Science and Technology Foundation, Ministry of Science and Education (FCT/MEC) through national funds, and co-financed by FEDER, under the Partnership Agreement PT2020, for the projects M-ERA-NET-0004/2015-PAIRED and UIDB/04469/2020 (strategic fund).

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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