REVIEW ARTICLE

# Overview on Solid Lipid Nanoparticle for Topical Delivery and its Inevitable Applications

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***Received: 20th August, 2022; Revised: 02nd January, 2023; Accepted: 29th May, 2023; Available Online: 25th June, 2023***

**ABSTRACT**

Solid lipid nanoparticle is a novel approach for topical drug delivery. As lipids used in preparation of solid lipid nanoparticles (SLN) will also get absorbed in skin layers, enhancing permeation across the biological membranes. For the stability of SLN dispersion, several surfactants were used. Mechanism incorporating for the preparation of SLN also impacts particle size and stability. Since the mechanism of SLN through the biological membrane is still under research as it may follow various skin penetration pathways. This review suggests the various method of preparation, common pathways of skin permeation, lipids and surfactant utilized in the production of SLN.

**Keywords:** Solid lipid nanoparticles, Lipid, Surfactant, Topical Drug Delivery.

International Journal of Drug Delivery Technology (2023); DOI: 10.25258/ijddt.13.2.40

**How to cite this article:** Nandgude TD, Parakhe PS, Mishra RK. Overview on Solid Lipid Nanoparticle for Topical Delivery and its Inevitable Applications. International Journal of Drug Delivery Technology. 2023;13(2):722-730.

**Source of support:** Nil.

**Conflict of interest:** None

## INTRODUCTION

Nowadays, skin-related problems range in severity from benign to lethal, impacting millions around the world.[1] To treat skin-related diseases, topical route is the most effective method of drug delivery, improved patient compliance, self-administration, avoidance of first-pass metabolism, regulated drug release and the capacity to deliver both systemic and local effects via transdermal and dermal drug delivery are all advantages of topical drug delivery.[2] However, overcoming the skin's protective barriers is the most difficult aspect of topical drug delivery. With a thickness of roughly 15 µm, the stratum corneum (SC) is the skin's fundamental membrane and the uppermost non-viable epidermal layer.[3] The basic objective of developing a successful drug delivery system is to deliver drugs to specific to the target region while minimizing drug degradation, maintaining the optimal quantity of drug at the tissue to improve therapeutic outcomes, and avoiding adverse effects. Conventional drug delivery methods have various drawbacks, poor patient compliance, including higher odds of missed doses, drug level fluctuations, unwanted side effects, low bioavailability, drug toxicity and unwanted side effects. Solid lipid nanoparticles (SLNs), pharmacophores, bilosomes, colloidosomes, herbosomes, polymeric nanoparticles, liposomes, transferosomes layerosomes, sphingosomes, ufosomes, ethosomesare examples of target-specific nanocarrier systems that can overcome these limits.[4] SLN's are the fastest growing field in colloidal drug delivery systems. SLN' sare colloidal drug carriers that range in size from 50 to 1000 nm. Biodegradable/biocompatible solid lipids or a mixture of lipids can be used to make SLN delivery vehicles. These SLNs have gained a great deal of interest recently because, as colloidal drug carriers, they combine the benefits of oil emulsions, liposomes, and polymeric nanoparticles while minimizing any of their limitations.[5] Lipids used in SLN preparation have approved status, such as generally recognized as a safe (GRAS). It comprises food additives or excipients that are acceptable for human intake due to their low toxic effects in topical cosmetic or pharmaceutical formulations.[6] Occlusion characteristics are formed by film deposition on the skin, which can aid drug diffusion through the stratum corneum.[7]

### Lipids Used in SLN for the Topical Delivery

Lipid(s) are the fundamental component of solid lipid nanocarriers, and it influences lipid dispersion with a controlled release pattern, stability, drug encapsulation. The primary goal of lipid carrier-based formulations is to deliver lipophilic/hydrophilic drugs to the intended target site. Phospholipids are employed to enhance permeation ability by minimizing the effects of lipophilic moiety solubility Table 1.

### Selection Criteria of Lipid

- The partition coefficient is the most commonly used criterion for selecting lipid carriers.
- The drug and the lipid carrier must be compatible (s).
- To reduce stability issues, the lipid carrier's melting point should be greater than 45°C.
- Core materials should have an HLB value of not more than 2.

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**Table 1:** Lipids used for SLN in topical delivery

| *Lipid* | *Melting Point (°C)* | *Solubility* | *Application* | *References* |
|---|---|---|---|---|
| Saturated fatty acids | | | | |
| Lauric acid (C12) | 43.2–43.8 | Ethanol (95%), ether, methanol- Very soluble (95%). Benzene- Miscible. Chloroform- Slightly soluble. Acetone- Soluble | Cosmetics, Food Products & Pharmaceuticals | 8 |
| Myristic acid (C14) | 54.5 | Chloroform, ethanol (95%), acetone, ether & aromatic and chlorinated solvents, Benzene –Soluble Water- Practically insoluble | As a penetration enhancer in pharmaceutical formulations. | 9 |
| Palmitic Acid (C16) | >110 | Ethanol (95%)- Soluble Water – Practically insoluble | Asa penetration enhancers. For sustained drug release in pharmaceutical formulations. | 10 |
| Stearic acid (C18) | ≥54 | Chloroform & ether, Benzene, carbon tetrachloride, chloroform & ether- Freely soluble Hexane & propylene glycol, Ethanol (95%), - Soluble Water- Practically insoluble. | As a carrier for controlled/ sustained release | 11 |
| Digestible lipids | | | | |
| Glyceryl monostearate | 55–60 | Mineral oil and fixed oils, chloroform, ether, acetone, hot ethanol -Soluble Water- Practically insoluble | Emulsifying agent -α-form Wax matrices- stable β-form | 12 |
| Glyceryl monooleate | 36–40 | Mineral oil, ethanol (95%), ether, vegetable oils, chloroform – Soluble Self–emulsifying grade is dispersible in water. Water-Practically insoluble. | Penetration enhancer in buccal and transdermal preparation. | 13 |
| Glyceryl palmitostearate | 52–55 | Dichloromethane & chloroform-Freely soluble. Mineral oil, ethanol (95%), water, - Practically insoluble. | Pharmaceuticals and biodegradable gels contain this taste masking agent. | 14 |
| Glyceryl behenate | 65–77 | Warm dichloromethane & chloroform- Soluble; Mineral oil, hexane, water, ethanol(95%) - Practically insoluble. | Entraomentof several drug classes (e.g., retinoids) and powder spray coating agent. | 15 |
| Triglycerides | | | | |
| Glyceryl tristearate/ Tristearin | 54 - A-form 65 - β′-form 72 - β -form | Hot alcohol- Soluble. Ether, petroleum ether, cold alcohol- insoluble Acetone & Benzene - Soluble . Water & Ethanol- Insoluble | Food, cosmetics and pharmaceutical formulations. | 16 |
| Glycerol tripalmitate/ Tripalmitin | 61–67 | Chloroform, Diethyl ether, benzene, ethanol – Soluble. Water-Practically insoluble. | Enhance stability and brain targeting. | 16,17 |
| Glycerol trimyristate/ Trimyristin | 55–58 | Dichloromethane & Ether, ethanol, chloroform, Benzene-Soluble Water- Insoluble. | Improved release of the hydrophobic active component and taste masking | 18,19 |
| Glyceryl tricaprate/ Tricaprin | 31–32 | Water- Insoluble Ethanol, chloroform ether- soluble. | Increase p53 gene transfer in lung cancer cells. | 20 |

- They are more lipophilic and have a higher chance of forming solid matrices over hydrophilic materials because they are more lipophilic.
- The lipid carrier should stabilize the incorporated drug (s)
- Drug ejection and degradation are affected by the rate of the crystalline lipid matrix
- Lipidic packing density and thermodynamic stability
- The degree of lipid crystal determines the occlusive characteristics of topical preparations.[7]

**Surfactants Used in SLN**

SLN production methods, lipid selection for greater entrapment efficiency, and lyophilizing and stabilizing agents have all been examined in late by a number of researchers. Stabilizing agents (surfactants) play a vital role in the production of solid lipid colloidal systems among these criteria. They decrease the interfacial tension between the two surfaces. By obtaining colloidal stability, the colloidal dispersion's lipophilic and hydrophilic phases make it easier to produce nanoparticles.

**Table 2:** Surfactants/Co-surfactants used In SLN's[23]

| *Non–ionic surfactant/Cationic surfactants* | *Ionic surfactant /Anionic surfactants* | *Amphoteric surfactant/Zwitterionic surfactants* |
|---|---|---|
| • Poloxamine 908<br>• Span 85<br>• Tween 20<br>• Poloxamer 407<br>• Solutol HS1<br>• Brij78<br>• Span 20<br>• Tego care 450<br>• Tyloxapol<br>• Poloxamer 188<br>• Span 80<br>• Tween 80 | • Sodium dodecyl sulphate<br>• Sodium glycocholate<br>• Sodium taurocholate<br>• Sodium oleate<br>• Sodium cholate<br>• Sodium-Taurodeoxycholate | • Soy Phospholipid (Lipoid S75*)*<br>• Hydrogenated egg phosphatidylcholine (Lipoid E PC–3)<br>• Soy phosphatidylcholine (Lipoid S 100, Lipoid S–PC)<br>• Egg phosphatidylcholine (Lipoid E PCS)<br>• Egg phospholipid (Lipoid E 80, Lipoid E 80 S)<br>• Hydrogenated soy phosphatidylcholine (Lipoid S PC–3, Phospholipon 80 H, Phospholipon 90 H) |

Stability during the preparation of nanoparticles is important.[21] The surfactant deposited on the interface of the colloidal system, lowering the interfacial tension of the colloidal system, lowers the interfacial free energy.[22]

**Method of Preparation of Solid Lipid Nanoparticle**

*High-pressure homogenization [HPH]*

HPH is a technique that involves the production of sub-micrometer particles by forcing a liquid or dispersion through a gap at high pressure ranging from 100 to 2000 bar. This process can be carried out at low or high temperatures, known as cold HPH and high HPH, respectively.[25] During the process, lipids and drugs are heated to about 5 to 10°C above the lipid's melting point to enable the drug to dissolve or diffuse in the molten lipid. Typically, lipid concentrations range from 5 to 20% w/v. In the second step of the HPH process, the aqueous phase containing the amphiphilic molecules is introduced into the lipid phase at the same temperature as the melting point of the lipids. To prepare the hot pre-emulsion, a high-speed stirrer is used. Depending on the formulation and the desired product the lipid is passed through a narrow passage several times, typically 3 to 5 times, at high pressure (100–1000 bar). This process ensures that the drug is solubilized in the lipid matrix before homogenization.[26]

However, certain disadvantages are associated with this technique, including the possibility of introducing impurities into the final product, difficulty scaling up the process, and high energy consumption during production.

- Heat-sensitive drugs shall not be used because they decompose
- An rise in the number of revolutions or inhomogeneity pressure causes a rise in the particle size.[27]

However, preparing SLNs with cold HPH can work around these limitations. As mentioned above, the first stage is to form a residue of melting lipids and drugs, which is then rapidly cooled with liquid nitrogen and dry ice. In the third phase, grinding turns the powder into microparticles. The microparticles are then dispersed in a cold aqueous surfactant solution.

*Ultrasonication/high-speed homogenization*

Ultrasonication and high-speed homogenization are both techniques used for dispersing materials, and they are commonly used in the production of lipid nanoparticle dispersions. In this process, solid lipids are first heated to a temperature that is slightly higher than their melting point, typically around 5–10°C above it. To create an emulsion, the melted lipid is then dispersed into an aqueous surfactant solution heated to the same temperature and stirred at high speed. Ultrasonication is used to further reduce the droplet size of the emulsion, resulting in a more stable lipid nanoparticle dispersion. The heated emulsion is then gradually cooled below the lipid crystallization temperature to produce the lipid nanoparticle dispersion. Concentrated lipid nanoparticle dispersions can be produced using ultracentrifugation.[28]

*Solvent emulsification diffusion method*

The lipophilic molecule was immersed in a water-insoluble organic solvent and subsequently emulsified in an aqueous phase using high-pressure homogenization. The resulting emulsion contained nanoparticles with an average size of 25 nm. The organic solvent was removed from the emulsion through evaporation at low pressure (40–60 mbar), causing the lipid to precipitate in the aqueous media and resulting in a nanoparticle dispersion.[29]

*Solvent emulsification -Evaporation method*

In this process, a lipid substance and a hydrophobic drug are first dissolved in an organic solvent that is insoluble in water, such as dichloromethane, toluene, cyclohexane, or chloroform. Using a high-speed homogenizer, the resulting solution is then emulsified in an aqueous medium. The coarse emulsion is passed through a microfluidizer to further enhance the emulsification. After emulsification, the organic solvent is removed by mechanical stirring at ambient temperature, preferably under low-pressure conditions using a rotary evaporator. This results in the precipitation of the lipid substance as SLN.[30]

*Solvent injection method*

The solvent injection technique is an innovative method for producing SLN that offers numerous benefits over existing methods. This technique employs a pharmacologically acceptable organic solvent, which is dissolved in the lipid to form a solution. Water-soluble solvents such as ethanol, acetone, or isopropanol, or a mixture of water-miscible solvents, can be used for this purpose. The preparation process

involves injecting the lipid-solvent mixture into an agitated aqueous phase, with or without a surfactant. The emulsifier present in the aqueous phase helps reduce the surface tension between the water and the solvent, forming lipid droplets at the injection site. This process stabilizes the SLN until solvent diffusion is complete.[31]

*Supercritical fluid technique*

For the synthesis of SLN's, a highly appealing novel approach based on supercritical fluid (SCF) technology has recently been developed. When the pressure and temperature of a fluid, which is a key component of SCF, exceed their critical values, it is said to be supercritical.

Many gases have been tested as supercritical fluids, including carbon dioxide ($CO_2$), ammonia, ethane, and chloroforms like $CHClF_2$ and $CH_2FCF_3$. Because it is safe and has a readily accessible critical point, $CO_2$ (31.5°C, 75.8 bar), is the best candidate for SCF method. It does not cause drug material oxidation because it is inert, leaves no residue after processing, is low-cost, non-flammable, environmentally friendly, and simple to recycle or dispose of. Organic solvents (e.g., DMSO, DMFA) are commonly used since they are entirely miscible in SCF ($CO_2$).[30]

The method of extracting lipid nanoparticles from emulsions using SCF technology is known as supercritical fluid emulsion extraction (SFEE).[32] The organic solution is produced by dissolving the lipid molecule and medication in an organic solvent like chloroform, then adding a surfactant. The organic solution is dispersed into an aqueous solution (which may contain a cosurfactant) before it is homogenized under high pressure to create an O/W emulsion. The O/W emulsion is injected at a constant flow rate from one end (typically the top) of the extraction column, while the supercritical fluid is delivered counter currently at a constant flow rate. Lipid nanoparticle dispersions are made by repeatedly solvent extraction from O/W emulsions.

**The Following Mechanisms Lead to the Formation of Particles:**

- Supercritical fluid extraction (diffusion) of organic solvents from emulsions and lipid dissolution occur in parallel.
- Organic phase expansion; gives lipid crystallization.[33]

**Membrane Contactor Technique**

With the aim of producing SLN on a large scale, a membrane contactor technology was developed in which the liquid phase is pressed between the pores of the membrane into the moving aqueous phase at a temperature above the melting point of the lipid (e.g. A Kerasep ceramic membrane with active $ZrO_2$ layer on a carrier made of $AlO_2tiO_2$) for the formation of small droplets. In the membrane module, the aqueous phase is continuously stirred and circulates tangentially; this aqueous phase removes the droplets that develop at the outlet of the pores. Cool to room temperature or place in a temperature-controlled bath.[31]

**Microemulsion Technique**

Many research groups have adapted and/or modified the microemulsion approach for SLN synthesis (adding a microemulsion to water causes the lipid phase to precipitate, resulting in small particles), which has since been modified and optimized by Gasco and coworkers. A nanoemulsion is made up of a lipid-soluble component, a surfactant, a co-surfactant (in most cases), and water.[34]

Solid lipids (approximately 10%) are melted at a temperature more than the lipid's melting point (65–70°C) in a basic microemulsion technique. Surfactant, water, and co-surfactant are heated individually to a certain temperature as the lipid and then gently stirred into the melted lipid.[35]

**Double Emulsion (W/O/W) Technique**

The double emulsion approach is used to produce SLNs and involves two steps. Firstly, to form a primary emulsion (w/o), the hydrophilic drug is dissolved in an aqueous solvent (inner aqueous phase) and then dispersed in a lipid-containing stabilizer/emulsifier, such as lecithin-oil phase. Secondly, an aqueous phase of a hydrophilic emulsifier (e.g., poloxamer, PVA) is added and stirred to produce a double emulsion (w/o/w), which is then separated by filtration.[36,37]

**Coacervation Method**

The current study looks at a novel membrane contactor-based approach for preparing SLN in order to enable large-scale manufacturing. The lipid phase is forced through the pores of the membrane at a temperature just above the melting point of the lipid, resulting in the formation of microscopic particles. SLN is generated when the preparation has been cooled to room temperature.[38]

**Incorporation Model of SLN**

There are mainly three drug incorporation model for SLN as shown in Figure 1; this classification is based on the location and structure of the drug in the lipid matrix.

- Homogeneous matrix model
- Drug-enriched shell model
- Drug-enriched core model

**Homogeneous Matrix Model**

A homogeneous matrix with dispersed or amorphous drug can be formed using the cold homogenization technique or by incorporating extremely lipophilic drugs in SLN using the hot homogenization method. Cold homogenization redistributes the dissolved drug in the bulk lipid resulting in nanoparticles with a homogeneous matrix structure. Hot homogenization

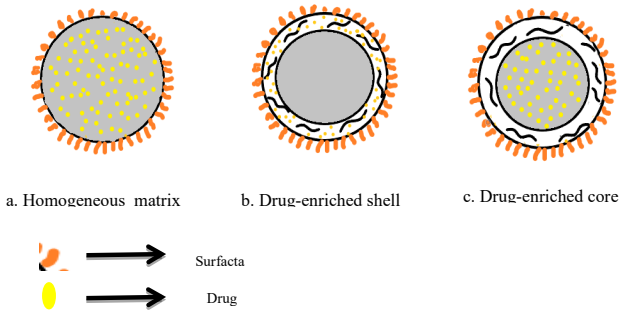


**Figure 1:** Incorporation model of solid lipid nanoparticle

generates oil droplets that crystallize upon cooling, with no phase separation between lipid and drug during the process. This paradigm allows for the time-independent release of drugs such as prednisolone over a range of days to weeks.[39]

### Drug-enriched Shell Model

Drug-enriched shell-based SLN's are generated during the freezing step of phase separation, when there is a very low drug concentration in the melted lipid matrix. A drug-free lipid core forms first when the lipid precipitates. A solid outer shell containing both drug and lipid forms around the drug-free lipid core as the drug's solubility in the remaining melting lipids approaches saturation. Because of the peculiar structural arrangement of SLNs, where the drug largely accumulates on the surface of the SLNs, burst and rapid drug release are prevalent.[40]

### Drug-enriched Core Model

Drug enriched core-based SLNs develop when drug precipitates before lipid recrystallization. This model is the polar opposite of the one explained above. When a drug is dispersed in melted lipid near its saturation solubility, it accumulates in the SLN's core structure. The drug is super-saturated in the melting lipids, which occurs during the cooling phase of the lipid nanoemulsion, resulting in drug precipitation before lipid recrystallization, producing a drug-free lipid shell around the drug core. This type of drug delivery system is similar to a membrane-controlled reservoir in that it allows for regulated drug release, with the lipid shell acting as a rate-limiting membrane.[41,42]

### Mechanism of Topical Delivery of Drug

Topical delivery systems are designed to be applied to the skin, exerting physical effects such as skin protection, lubrication, and hydration. However, the penetration of drugs through the skin's lipid matrix, specifically the stratum corneum, remains a limiting factor for effective delivery. To improve drug permeability, various methods have been explored, including the use of nanoparticulate carrier systems.

Research on the skin permeation of nanocarrier systems has been conducted worldwide, but there is still much debate surrounding the mechanisms of penetration. Differences in experimental settings have led to discrepancies in the proposed theories. Additionally, the ability of nanoparticles to penetrate deeper into the skin's epidermal layers is still not fully understood.[43]

SLN are lipophilic and have the potential to penetrate the skin easily. However, the effectiveness of SLNs is dependent on their physicochemical properties and lipid composition. It has been suggested that SLNs can influence skin barrier properties due to their affinity to physiological lipids. The specific mechanism by which this occurs remains unknown, but several possibilities have been proposed.[44]

### SLN Interaction with Stratum Corneum (Sc)

The lipids and surfactants used to generate SLNs are highly compatible with biological lipids, allowing for greater contact and interaction with skin lipids and retention on the SC surface.[44]

### Lipid-Fluidizing Property

Lipids are utilized to enhance the penetration of medication through the skin by interacting with the membrane properties of the stratum corneum (SC). Egg lecithin, which contains phosphatidylcholine, is a type of lipid that acts as a fluidizer by disrupting the rigid packing structures of the phospholipid bilayer. This disruption allows drugs to move more easily through the SC, thereby improving their skin transport. In a study conducted by Kirjavainen *et al*., it was found that lecithin can enhance the permeability of the SC bilayer and improve the skin transport of bunazosin hydrochloride.[45]

### Occlusive Effect

SLNs are believed to increase skin permeability through the occlusive effect, which involves the creation of a lubricating layer that reduces moisture loss and allows drugs to penetrate more effectively. Due to their small size, SLNs can bind effectively to the stratum corneum (SC) and create an occlusive barrier on the skin, promoting drug absorption into deeper skin layers.[46]

### Skin Transport Pathways

*Transcellular transport*

Active carrier-mediated transport, diffusion, and transcytosis allow transcellular passage across the epidermis.[47] (Figure 2). Surfactant and lipid components of SLNs interact with lipids in the SC to provide an occlusive effect that facilitates nanoparticle transit across the transcellular pathway.[48] Pinaki *et al*., coated SLNs with a cell-penetrating peptide and showed that the transcellular route was the favored mechanism of penetration for the surface-modified SLN's.[49]

*Intercellular transport*

The interstitial regions of the SC have a less organized lipid structure and are favored by small aqueous (hydrophilic) molecules[50] (Figure 2). Escobar *et al*. Recently shown that SLN'smade up of crystalline lipids may permeate the epidermis through the intercellular pathway.[51] The SLN diffusing

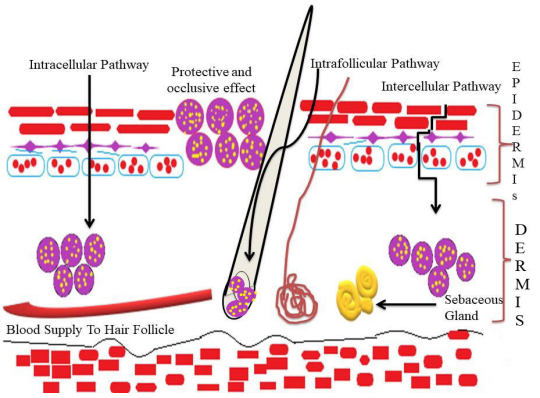


**Figure 2:** Various drug penetration pathways of SLN for topical application

**Table 3:** Recent advances in SLN

| *Author* | *Method* | *Outcome* | *Use* | *Ref.* |
|---|---|---|---|---|
| Deshkar *et al.* | Microemulsion technique which is followed by probe sonication | For the treatment of acne, there is an alternative to traditional topical formulations. | Treatment of acne | 56 |
| Jain *et al.* | Solvent injection method | The drug's location in the epidermis of the skin | Treatment of acne | 57 |
| Gupta *et al.* | Microemulsion method | The AE-SLN gel has the ability to be used as a non-irritant local acne therapy. | Treatment of acne | 58 |
| Pokharkar *et al.* | Solvent evaporation method. | Streptococcus mutans, Escherichia coli and Pseudomonas aeruginosa, antibacterial activities | Treatment of acne | 59 |
| Ridolfi *et al.* | Hot high pressure homogenisation | The antibacterial activity of SLN-chitosan-tretinoin is due to its high encapsulation efficiency. | Treatment of acne | 60 |
| Montenegro *et al.* | Phase Inversion Temperature (PIT) method | In in vitro methods, IDE loading into SLN was able to focus this antioxidant into the higher skin layers, avoiding skin penetration. | Treatment of neurodegenerative diseases and skin disorder | 61 |
| Silva *et al.* | Hot melt homogenization method | Antibacterial activity against P. Acnes,growth inhibitory activity against staphylococcus epidermis | Treatment of Acne Vulgaris | 62 |
| Vijayan *et al.* | W/o/w type double emulsification method | Longer-lasting anti-acne activity of neem oil-loaded SLN with greater lecithin loading in their emulsion | Treatment of acne vulgaris | 63 |
| Kesharwani *et al.* | Low-temperature solidification and melt emulsification | Oral administration of the Non-Steroidal Anti-Inflammatory Drug (NSAID) etoricoxib using a topical gel based on SLN has been linked to gastrointestinal side effects. | Management of arthritis. | 64 |
| Bhalekar *et al.* | High-pressure homogenization | Dermal miconazole nitrate administration is possible with miconazole nitrate loaded SLN (MN-SLN). | Fungal infections | 65 |
| Chen *et al.* | Microemulsion method | As an alternative, an improved SLN formulation with higher penetration, decreased dose rate (thus enhancing compliance), and fewer side effects is available. | Antifungal infections | 66 |
| Butani *et al.* | Solvent diffusion method obtained through homogeni- zation | The use of SLNs to deliver Amphotericin B to the skin proved effective. | Antifungal activity | 67 |
| Tan *et al.* | High-Pressure Homogenization (without solubilizing solvent) | The possibility of administering griseofulvin via topical route has been demonstrated, with GF-LN demonstrating reduced cytotoxicity, similar antifungal efficacy, and greater penetration and skin retention than the control, griseofulvin. | Antifungal activity | 68 |
| Jenning *et al.* | High-Pressure Homogenization Method | The interactions between SLN and porcine skin are investigated in this research. | Antoxidant activity | 69 |
| Khallaf *et al.* | Double emulsion method by homogeni- zation | 5-FU is incorporated into the SLN shell. When compared to the drug alone, the SLN generated showed enhanced dispersion and release. | Anti-cancer activity | 70 |
| Ansari *et al.* | High-Pressure Homogenization | A lipid-based surfactant (Labrasol®) was found to improve the solubility of the lipophilic drug lopinavir. As a result of the increased solubility, drug entrapment inside the SLN increased. | HIV targeting | 71 |
| More *et.al* | Homogenization, etc | Vesicles as a Tool for Enhanced Topical Drug Delivery | Various targeting approaches | 72 |

along this pathway requires a longer, more convoluted route (approximately 450 μm), which is considerably longer than the actual thickness of the skin.[52] The rate of permeation of SLNs is considerably reduced when the diffusion channel gets longer.

*Transappendageal transport*

Molecules can move through hair follicles, sweat ducts, and sebaceous glands through the transappendageal route (Figure 2). This route has received little study in the past since these appendages barely contribute 0.1 to 1% of the entire skin surface area.[53] The average diffusion potential of the appendageal route is too small when compared to other routes, such as the intercellular route, and thus diffusion is poor. Nanoparticle carrier systems can be distributed due to the restricted distribution of appendageal route volume.

Furthermore, the lipid molecules react easily with the lipidic sebum in the follicles, enhancing permeability.[54] As a result, the current study has begun to utilize the follicular pathway by developing colloidal-based drug delivery devices. Penetration through this route is accomplished in two processes. Hair follicles have a varied architectural structure: trans-follicular penetration into the interstitium after penetration into the hair follicle.[55,72]

## CONCLUSION

Several studies have contributed to our understanding of the usage of SLN's for transdermal/topical administration throughout the last several decades. SLNs have been demonstrated to considerably improve medicine permeation through the skin by forming an occlusive layer. More study on the cellular absorption of these carrier systems via the topical route is essential to ensure toxicity, safety, and effectiveness. Improved SLN's topical delivery has been suggested by using an appropriate formulation of semi-solid dosage form/ base, such as gel and hydrogel (Table 3). Few pharmaceutical items are on the market, despite the availability of very well world-class manufacturing technologies and processes for SLN production; this aspect requires additional consideration.

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