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REVIEW ARTICLE

Implication of Solid Lipid Nanoparticles for Topical Drug Delivery

Tayal P*

Department of Pharmaceutical Sciences, I.S.F. College of Pharmacy, Moga- 142001(Punjab) India.

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ABSTRACT

Topical drug delivery system was first came into discussion more than 40 years ago. Transdermal drug delivery has generated great thrill amongst most of the pharmaceutical companies since 1990s. Since then, the tradition of transdermal drug delivery system transferred into large scale industries. The transdermal route can be proved better to bypass the first pass effect and to avoid other side effects related to oral route and can act as a favorite route for systemic or local drug delivery. This can also be proved good for betterment of patients. Solid lipid nanoparticles (SLNs) have shown many permeability enhancing properties and therefore are newly introduced in research area for topical delivery of drugs. Solid lipid nanoparticles (SLNs) are very alluring drug carrier systems to be used for topical purposes because of their different required effects on skin aside from their skin accumulation or distribution raising characteristics. SLNs are attractive systems because of their solid matrix which may be helpful in preventing the explosive release generally seen in conventional delivery systems. SLNs via topical route provide various benefits such as enhanced skin permeation, improved drug delivery etc. This article reviews various aspects of SLNs including their mechanism of penetration, preparation, evaluation parameters, prospective advantages and their applications in topical drug delivery.

KEYWORDS

Solid Lipid Nanoparticles, Transdermal Drug Delivery System, Mechanism of penetration, Skin accumulation, First pass effect

INTRODUCTION

Skin which is the largest human organ mainly comprised of three physiological layers: epidermis, dermis, and sub cutaneous. Skin performs a no. of functions. One of its important functions is to protect the body from water loss and other outside serious shocks. The skin is mainly involved in resistance of entry of unknown fragments and materials. Topical therapeutic and cosmeceutical delivery is a growing field founded on selectively overcoming this barrier[1]. This has the benefit that high concentrations of drugs can be obtained at the required site of action thus minimizing the other associated side effects.

Transdermal drug delivery system is a substituted delivery system to accumulate the drugs into the blood and at local sites[2]. It proposes many gains as compared to conventional drug delivery systems (oral and parenteral drug delivery system). Advantages included are: enhanced patient acceptance, preventing first pass effect, enhanced action duration, side effects reduction and utility of short half- life drugs, improving physiological and therapeutic response, avoiding the variation in drug levels[3]. Introduced at the beginning of the 1990s, SLNs have been intensively investigated for parenteral, peroral and ocular delivery. During the recent times

***Address for Correspondence:**
Priya Tayal
Department of Pharmaceutical Sciences, I.S.F. College of Pharmacy, Moga- 142001(Punjab) India.
E-Mail Id: priyatayal786@gmail.com

several studies have been done and they suggested that novel drug delivery systems based on solid lipid nanoparticles have the capability of increasing topical drug delivery of both hydrophilic and lipophilic, compared to the other conventional and traditional drug delivery systems[4]. So, most of the researchers have focused on solid lipid nanoparticle (SLN) and because of their ability to enhance the penetration of drugs into the skin SLNs are considered as a guarantying drug carrier for topical application**.**

To beat the limitations of current formulations, there is an urgency to develop an innovative formulation which can be able to minimize the adverse-effects and can be proved better in showing the required effects. Thus, SLN can be prepared which would help in increasing skin deposition as well as provide sustained release and become the new generation of nano particulate active-substance vehicles and are drawing major consideration as an innovative particulate vehicles for dermal route delivery of drugs[5]. In SLNs the liquid lipid (as generally used in lipid emulsions) has been replaced by solid lipid. These offer various advantages for topical drug administration.

These are having the size range of 10-1000 nm and are constituted of corporeal accepted lipid materials that generally at room temperature remain in the solid state and are safe, stable and biodegradable in nature[6]. SLNs associate the benefits of and at the same time prevent the drawbacks of polymeric nanoparticles, emulsions and liposomes used for topical drug delivery. SLN are bio adaptable and bio digestible and are adopted for sustained drug delivery. Compared with other delivery systems like creams, tinctures and emulsions, SLN unify the advantages like minimal skin irritation, sustained release and prevention of active ingredient's degradation. Mainly, SLNs assist drug entrance to the skin and hence behave as a ultraviolet (UV) sunscreen system and cut down skin irritation[5] and thus unifying the benefits of micro emulsions, liposomes, polymer based nanoparticles and other carriers for topical use. The solid lipidic matrix can protect incorporated active compounds against chemical degradation and thus helpful in providing the highest opportunities in modifying the drug deliverance profiles[7].

Solid Lipid Nanoparticles Composition

SLNs are mainly consists of solid lipid(s), surfactant(s), co-surfactant (may or may not) and active compounds (mainly drugs) as shown in Figure 1. The lipids used in the production of solid lipid nanoparticles are biocompatible lipids. The lipid which is the main component of lipid nanoparticles, influence the drug loading capacity, stability and the sustained release behavior of the SLN formulations. Surfactants (also known as surface-active agents or emulsifiers) are also the other considerable constituent of the solid lipid nanoparticle system.

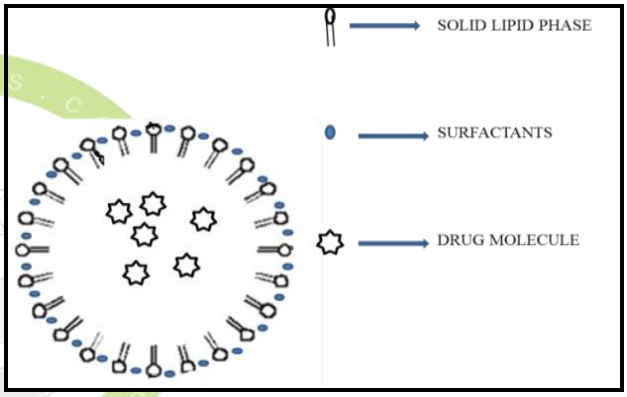

Figure 1: General components of SLNs

The outer solid lipid phase is mainly involved in enhancement of penetration of drug across the skin. Surfactants are added for emulsification and thus the solid core is coated by the surfactants[8]. The smallest particle size is reported using low lipid content (up to 5%). But small lipidic portion and lesser viscosity are disadvantageous for dermal administration. So it becomes necessary to incorporate the SLNs in ointment or gel to make it suitable for dermal delivery that may leads to further decrement of lipid content. On the other hand lipid content increment leads to formation of semisolid and gel like formulation that may be acceptable for direct application to skin[9]. But higher lipid content may result in increased particle size. The various lipids and surfactants incorporated for transdermal application of different drugs summarized in a tabular form:

Table 1: Lipids and surfactants used for incorporation of related drugs in SLNs:

Drug	Lipid	Surfactant	Ref.
Spironolactone	Phosphotidylcholine	Pluronic F68	10
Resveratrol	Glyceryl behenate	Pluronic F68, Polysorbate 80	11
Diclofenac Sodium	Glyceryl monostearate (GMS), Stearic acid, Guggul lipid	Poloxamer188 (polyethylenepolypropylene glycol)	12
Meloxicam	Geleol, Compritol 888 ATO, Precirol ATO5	Poloxamer188	8
Domperidone	Trimyristin, phosphotidylcholine	Tween 80	13
Lidocaine	Compritol 888 ATO, Precirol ATO 5	Tween 80	14
Flurbiprofen	Dynasan 114, Captex 355 EP/NF, Epikuron 200	Tween 80	7

Some other lipids may include Glyceryl palmitostearate, Glyceryl hydroxystearate, Glyceryl dibehenate, Caprylate triglyceride, Caprate triglyceride etc. and surfactants may include Poloxamine 908, Poloxamer 407, Polysorbate 20, Poloxamer 182, Polysorbate 60, Sodium taurocholate, Sodium cholate, Sodium glycocholate, Sodium taurodeoxycholate, etc[15].

Advantages of Topical Delivery Using SLNs[7, 8, 12,14,16]

- Low cell toxicity, low systemic toxicity and thus high tolerability.
- Contains non-toxic and non-irritative raw materials in formulations.
- Improved drug's security as there is less or no entry for water to the inner area core of the lipid particle
- Can be applied for both lipophilic and hydrophilic drugs.
- Avoidance of use of toxic solvents; and easy for application to large scale productivity and no issue with sterilization.
- The encapsulated active ingredients guarded from facing chemical shocks by the solid lipid matrix and provide the best flexibleness in modifying the drug release profiles.
- Applied in a small but sufficient amount may result in less side effects than other drug delivered formulations.
- SLNs may increase drug entrance in cutis, enhance action duration at local parts, and thus avoid intake of drugs in blood hence minimizing adverse effects associated with the drugs like lidocaine.
- Easy to validate the methods and ease of production, capability of dermal targeting and photo stability improvement of active pharmaceutical ingredient.
- The ability to sustain drug delivery for a prolonged period of time than the usual gastrointestinal transit of oral dosage forms.
- SLN exhibit great fondness to the epidermis and leads to enhanced accumulation of the loaded drug to the skin.
- Protection of loaded drug from first pass metabolism and patient compliance.

Mechanism of Penetration of SLNs through Skin

Stratum corneum is the main physical barrier in the percutaneous absorption of topically applied

drugs. Outermost few microns stratum corneum is composed of keratinized corneocytes embedded in the lipophilic matrix. Small particle size and comparatively lower polydispersity index of SLN allow targeted local site delivery of drug to the cutis[17]. These nanometer ranged particles due to their solid lipid matrix may also allow for sustained release of drug (Cevc, 2004; Schafer-Korting et al., 2007). They are used as carriers for topical applications because of their occlusive effect due to which they lead to film formation on the skin surface that lessens the trans-epidermal water loss (TEWL). Due to occlusion they can also add to the entrance of active component to the epidermis by increased water retention. Aside from a nonspecific occlusion effect on permeation, it may also be enhanced through the use of SLNs itself as a vehicle for drug delivery because the nanometeric ranged SLN particles provide large contact area of loaded active component with the cutis. As reported earlier (Müller et al 2002), SLNs stick to the skin surface, forming an adhesive film that may also be responsible for high water retention in skin and promote penetration of drugs or active components. Due to its some physical and chemical properties such as high lipophillicity, solid state at bodily temperature the SLN carrier cannot improve essential oil diffusion through the inner more hydrophilic skin layers and these lipid particles form a depot from which the oil is slowly released and can be used for prolonged release of essential oils on upper layer of skin as in case of Artemisia arborescens[18]. Entrance of SLNs via trans-follicular path of skin can also be a prior mechanism of large concentration of active compound in the skin, which was reported by in vitro dermal distribution study by[19]. Mainly, there can be three main mechanisms for penetration of drug through the skin:

- The penetration of drugs through the skin includes the diffusion through the intact epidermis through the skin appendages. These skin appendages can also be named as hair follicles.
- The intercellular lipid route that is between the corneocytes.

The Trans cellular route includes the crossing through the corneocytes and the interceding lipids.

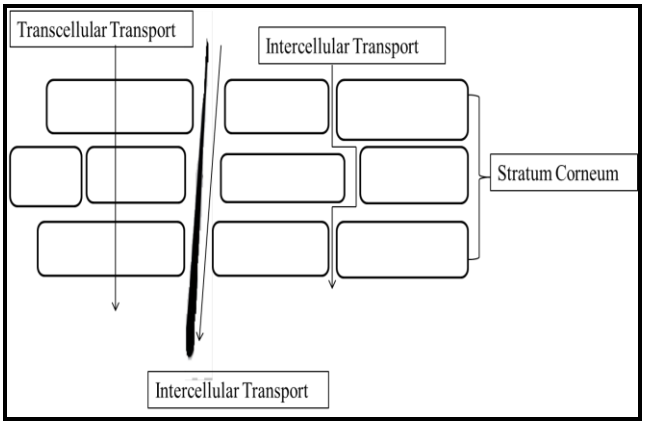

Figure 2: Absorption mechanisms of SLN incorporated drug through skin

Formulation Techniques of SLNs[20-23]

In the 1980's Speiser and coworkers were the first to report the synthesis of solid lipid nanoparticles and after that further research groups modified the synthesis process, mostly the synthesis process involves the variations in two steps: firstly the preparation of o/w nanoemulsion which act as the precursor for the next step and subsequently solidification of solid lipidic phase.

Productivity methods alter from industrial scale to research laboratory level. Various techniques employed for preparation of SLNs for transdermal delivery of different drugs along with their advantages and disadvantages are summarized in table 2.

Two most commonly employed techniques that are very simple and convenient are hot homogenization method and cold homogenization method.

Hot Homogenization

Hot homogenization is done at temperatures higher than that of melting temperature of the lipid and hence regarded as the homogenization of an emulsion. Pre-emulsion of drug in melted lipid and the hydrophilic surfactant at same temperature as that of melting temperature of lipid is formed by homogenization (e.g. using Ultra-Turrax) or obtained by high-shear mixing device[22].

Table 2: Various techniques used for incorporation of related drugs in SLNs with their advantages and drawbacks[15]

S.No.	Techniques	Advantages	Drawbacks
1.	Hot Homogenization	Applicable to lipophilic and insoluble drugs, exposure time to high temperature is short.	Low drug loading efficiency for hydrophilic drugs
2.	High Shear Homogenization (Cold Homogenization)	Exploitation of low surfactant concentration, Scalable, well developed, continuous operation and commercially demonstrated.	Extremely energy consuming process, risk to biomolecule stability.
3.	Solvent Diffusion Technique	Monodisperse distributions.	Remaining portions organic solvents
4.	Microemulsion Technique	Less input of energy and ensured stability.	Very much responsive to change, labor demanding process
5.	Ultrasonication	Reduced shear stress and effective at lab scale	High risk of metal contamination, energy demanding process, controversial scalability and broader particle size distribution.

Table 3: Evaluation Parameters

Sr.No.	Parameters	Importance	Methods
1.	Size and Shape	Determine skin penetration	Photon correlation spectroscopy, Scanning electron microscopy (SEM), Transmission electron microscopy (TEM)
2.	Zeta potential	Stability of particles	Zeta potentiometer, Laser droplet anemometry
3.	Entrapment efficiency	Suitability of method	Ultracentrifugation
4.	Drug content	Important in deciding the amount of nanoparticles preparation to be used	UV, HPLC
5.	In-vitro dissolution	Determine the drug release rate from particles.	Under physiologic and sink conditions.
6.	Skin permeation	Determines rate of drug entrance through skin.	Hairless skin of animals in Franz diffusion cell and by CLSM.
7.	Stability studies	To determine the shelf life of formulation	SEM, TEM, HPLC

This is then further homogenized in controlled pressure and temperature conditions using high pressure homogenizer at 500 bars (or more) and predetermined number of cycles.

Cold Homogenization

Hot homogenization process is linked with various types of limitations. One of them is the deterioration of active constituents due to high temperature. To beat these limitations cold homogenization is introduced as an alternative. In this technique the drug is ground with lipids to get micro particles and these obtained micro particles are spreaded in a cold emulsifier solution. Then this obtained micro-particulate suspension is mixed to obtain a homogenous system at or below room temperature, the shear force is found sufficient to break the lipid micro sized particles directly to nano sized particles[9]. It is considered as a suitable technique for heat labile drugs.

Various Methods of Characterization of SLNs[18,24-26]

Particle Shape

SLNs can be easily visualized by using transmission electronmicroscopy (TEM) and by scanning electron microscopy (SEM).

Particle Size and Zeta Potential

Particle size can be found by using dynamic light scattering (DLS) and photon correlation spectrometry (PCS). Zeta potentiometer can be utilized to determine zeta potential of the formulation.

Drug Entrapment

The entrapment efficiency of SLNs can be determined by the ultracentrifugation technique.

Drug Content

Drug content of the SLNs can be determined using UV spectrometry or can also be quantified by a modified high performance liquid chromatographic method (HPLC).

Stability Studies

The stability of SLNs can be determined by assessing the size and structure of the particles over time. Mean size is measured by DLS and structure changes are observed by TEM.

Skin Permeation Studies

The ability of the SLNs preparation to penetrate into the skin layers can be determined confocal laser scanning microscopy (CLSM) as in case of acyclovir SLNs and *in-vitro* or *ex-vivo* by using hairless skin of some animals like rats in Franz Diffusion Cells as in case of flubiprofen etc.

Applications of SLNs in Transdermal Delivery

A. Delivery of Antiviral Drugs

Acyclovir

HSV (Herpes Simplex Virus) infection mainly affects the dermal or basal epidermal layer of the skin, mucous membranes. Acyclovir (ACV) is frequently used for this infection. All conventionally available ACV-based oral formulations are associated with shortcomings such as low bioavailability, many time dosing, blood toxicity, and some other related side effects. Therefore to overcome the limitations associated with currently available dosage forms some alternative was required. By taking this into consideration Jain and coworkers' developed ACV SLNs that resulted in tenfold higher concentration over the entire epidermis. In vitro skin permeation studies showed that there was 15.17 times increment in accumulation of drug in dermal tissues of rat and 17.65-fold increment in accumulation of ACV in human cadaver skin when compared with the commercial formulation of ACV. CLSM images confirmed that dye-loaded SLNs penetrated and distributed throughout the rat's dermis and they preferentially followed entry via hair appendages. Cutaneous toxicity was almost found negligible by SLN formulation when confirmed by histological examination and scanning electron microscopy[27].

Penciclovir

SLNs of penciclovir were developed and evaluated for their potential in topical delivery of drug. Its skin permeation activity was checked on excised rat skin and drug loaded SLNs were found to possess double penetration capacity than

other commercially available creams. SLNs enhanced the total uptake of penciclovir in cutis. Microscopic pictures revealed that the intercommunication of SLNs and the epidermis leads to change in the morphology of epidermis and destitute the close conjugation of corneocyte layers, which could be the main reason for increased entrance of the penciclovir into epidermis of skin. Thus, SLNs can give a better skin targeting effect and can be proved as a promising carrier for topical delivery of similar antiviral drugs[28].

Artemisia arborescens L

It is an essential oil and was incorporated in SLNs as topical delivery systems against HSV-1 by Lay and coworkers in 2007. In vitro cutis penetration studies were performed on a whole new born pig skin and vertical Franz diffusion cells. Thus, these studies proved that SLNs are good carrier systems for the cutaneous delivery of the antiviral Artemisia arborescens essential oil. Moreover, SLN are proved to integrate the essential oil in high amount and possess a prolonged stability. They also improve remarkably phytocomplex's skin surface accumulation and thus avoiding its permeation through the skin[18].

B. Delivery of Antifungal Drugs

Terbinafine Hydrochloride

Topical application of the drugs at the pathological sites provides a best way of delivering the drug precisely to the site of action. The formulation and characterization of SLNs of terbinafine hydrochloride (TH) was made to sustain the drug release and local topical targeting. These were made by solvent injection method and were optimized on the basis of drug: lipid ratio, surfactant concentration and volume of solvent used. The optimized formulation contains %entrapment efficiency of 73.74% and particle size of 300 nm. The skin accumulation ability of SLNs was studied on rat abdominal skin and was found to exhibit more skin accumulation as compared to commercially available formulations. *In vivo* pharmacodynamics studies were also performed and the SLNs based gel was found to reduce fungal burden of Candida albicans in rats as compared to commercial product in shorter duration of time. SLNs dispersion and gel were found physicochemically stable under refrigeration for 3 months. Thus, it can be resulted that these exhibit cutis drug localization ability and can be used as a assured vehicle in treatment of fungal skin infections[29].

Miconazole nitrate (MN)

Bhalekar and coworkers developed SLN formulation in 2009 by using HPH technique and Compritol-888-ATO lipid, SLN dispersions of miconazole nitrate (MN) having low particle size and long-term physical stability were prepared and were found spherical in shape with smooth surface and possessed mean average size around 207 nm. In vitro drug release of MN-loaded SLN was compared with other marketed formulations and was found to sustain the release of drug over a 24-h period technique and was also found to improve fungal infections. Their anti-fungal activity was checked using candida species infected rats for *in vivo* studies and drug loaded SLNs were found very effective in the treatment of candidiasis and results indicated that they provided a sustained transdermal drug release and also a faster relief from disease[25].

C. Delivery of Anti-Acne vulgaris Drugs

Spironolactone (SP)

Treatment of acne is well possible if drug is delivered to the required site to get accumulation of drug at that site. SLNs of spironolactone were prepared for topical delivery by emulsion solvent evaporation technique. The skin permeation behavior was evaluated based on drug release and drug retention by the skin. After the dissolution study it was found that the drug release from SLNs was found faster than plain SP within the first 30 min. The total amount of SP penetrated through rat skin from SP-SLNs was almost double than that of the plain SP in 24 h after the administration and it was proved that drug's SLN can be a promising vehicle for use in the transdermal diseases.

Thus, SP-SLNs may act as promising vehicles for the topical treatment of skin diseases like acne[10].

Adapalene

Adapalene (ADA) is a primarily used for the treatment of dermal diseases like acne and also shows very less side effects. It is loaded in SLNs for better transdermal drug application. Its skin permeation was checked in rat skin model and is found to increase drug localization in upper layer of skin. Thus, SLNs are proved as a novel carrier for topical delivery of ADA in topical therapeutic approaches and this study opens new ways for drug delivery which better fulfils the requirements of acne treatment[30].

Neem Oil

All components of the Neem oil are strongly antibacterial such as Margolone and Mahmoodin which can be used to kill bacteria P. acne. Salicylic acid is also a main constituent of neem oil that may be responsible for treatment of redness and inflammation. So to get site specific delivery of drug topical application is selected. For that SLNs were selected as novel drug delivery system and study showed that SLN could be a better drug delivery carriers for topical delivery of acne treatment[31].

D. Delivery of Anti-Psoriatic Drug

Mometasone furoate (MF)

It is majorly employed for topical application and hence named as topical glucocorticoid. Due to such pharmacological effects it is advised in deep rooted inflammation and psoriasis. Cream and lotion (0.1%) are the conventional dosage forms of MF found in market, which show slight skin irritation, burning and common side-effects due to steroids. To overcome these side effects and to improve its efficacy, there is a need to develop a novel formulation. Therefore, SLNs of MF are formulated expecting an increase in skin accumulation and to obtain a controlled release of drug. In 2014 Madan and coworkers developed SLNs of MF by solvent - injection method. And skin permeation study showed that the skin permeability of SLN loaded gel was 15.21times more than that of marketed cream. SLN loaded gel showed 83.52% skin accumulation which was 2.67 folds higher as compared to conventional dosage forms and 20 folds higher than plain drug incorporated gel. The stability study showed successful formation of stable SLNs. Therefore SLNs can be a better choice for topical delivery of various MF like glucocorticoid to beat the limitations of other available current dosage forms[5].

Betamethasone dipropionate and Calcipotriol

To get required results it was become urgent to develop a combination drug cure for healing psoriasis like skin diseases. So, Betamethasone dipropionate and calcipotriol were incorporated in SLNs by employing hot melt high shear homogenization method and then were integrated in form of Carbopol gel matrix. *In-vitro* skin penetration and disposition and *in vivo* anti-psoriatic activity studies were performed. Better distribution and permeation of drug and negligible skin irritation and better skin tolerability of SLNs were found and SLNs could be potential strategy for treatment of psoriasis and other topical diseases[19].

E. Transdermal Delivery of Hormones

Testosterone

Orally administer hormones face problems such as high first pass metabolism, low systemic bioavailability and many other side effects related to dose. There is a risk of failure of treatment with every missed pill. A supplement therapy in men suffering from hypogonadism is testosterone[32]. Incorporated testosterone into SLNs for topical delivery because it was associated with extensive first-pass metabolism after oral drug administration and compared it with its recent formulations i.e. topical spray, sublingual tablets, and subcutaneous implants. They observed better cutis absorption of hormones through SLNs than that of currently available ones.

F. Transdermal Delivery of Anticancer Drugs

The main problem associated with the oral drug administration of anticancer drugs is the high risk of damage to normal cell. This can be minimized to some extents by transdermal drug delivery.

Table 4: SLN's Reported Work for Transdermal Drug Delivery

Sr. No	Drugs	Technique	Particle size	Purpose	Applications	References
1.	Spironolactone	Emulsion-solvent evaporation	88.9 nm	To enhance skin permeation of drug.	Treatment for skin disorders such as acne.	10
2.	Safranal	High pressure homogenisation	233 nm	To enhance the efficacy of safranal.	As a sunscreen and moisturizer	34
3	Resveratrol	High shear homogenisation	287 nm	For close contact and increased the amount of drug absorbed into the skin.	As a potent antioxidant	11
4.	Minoxidil and Finasteride	Ultrasonication	200 nm	To penetrate drug through skin in sufficient amounts to achieve the desired therapeutic effect.	Treatment of alopecia	16
5..	Adapalene	Ultrasonication	254 nm	For effective topical delivery.	Treatment of acne vulgaris.	30
6.	Mometasone furoate (MF)	Solvent injection method	248 nm	Greater skin deposition and slow drug release	Treatment of psoriasis	5
7.	Betamethasone dipropionate and calcipotriol	Hot melt high shear homogenization	200 nm	More effective distribution to skin layers	Treatment of psoriasis	19
8.	Retinyl Palmitate	Hot-melt method	100 nm	To enhance the skin distribution properties	As an anti-wrinkle.	35
9.	Dexflurbiprofen	O/W microemulsion	437 nm	To improve drug release into the skin and improve delivery to dermal layers.	For use on local pain relief and for rheumatoid arthritis.	36

10.	Meloxicam	High shear homogenisation	325 nm	Delivering the drug directly to the local site.	Treatment of inflammatory skin disease.	8
11.	Isotretinoin	Ultrasonication	75.3 nm	To overcome the side effects of other available topical formulations	Treatment of acne.	37
12.	Neem oil	Double emulsification	221.6 nm	For topical delivery of drug	Treatment of acne and pimples	31
13.	Terbinafine hydrochloride (TH)	Solvent-injection technique	300 nm	For controlled release and cutaneous targeting.	Anti - fungal	29
14.	Diclofenac	Melt-emulsion sonication	633 nm	Controlled transdermal drug delivery	Treatment of skin inflammation	12
15.	Tretinoin	Hot high pressure homogenization	162.7 nm	To reduce other topical formulation related side effects.	Treatment of acne	38
16.	Idebenone	Phase inversion temperature method	30-49 nm	Targeting IDE into the upper layers of the skin	Treatment of skin oxidative damages	39
17.	Dithranol	Ultrasonication	219 nm	To increase the photo stability of drug	Topical treatment of psoriasis	40
18.	Domperidone	Hot homogenisation	30.45 nm	Reducing dosing frequency	Treatment of motion sickness	13
19.	Cortecosteroid	High pressure homogenization	212.5 nm	To accumulate the more amount of drug on upper layer of skin.	Treatment of skin diseases	41
20.	Minoxidil	O/W microemulsion	125.7nm	To decrease the corrosivity associated with other available topical formulations.	Hair loss treatment.	42
21.	Acyclovir	Double emulsion method	239 nm	To increase the concentration of drug in entire epidermis	Treatment of HSV	27

22.	Penciclovir	Double emulsion	254.9 nm	To evaluate the potential of SLNs as the carrier of penciclovir for topical delivery	Treatment of HSV	28
23.	Flurbiprofen	Hot homogenisation	300 nm	To avoid the gastrointestinal damage associated with oral route.	Treatment of Gout, Rheumatoid arthritis	7
24.	Miconazole nitrate	Hot homogenisation	244 nm	To introduce a novel formulation with skin-targeting effect.	Anti-fungal	25
25.	Tretinoin	Microemulsion	126 nm	To increase skin penetration	Treatment of acne vulgaris, act as first generation topical retinoid	4
26.	Artemisia Arborescens essential oil	Hot pressure homogenisation	242 nm	Cutaneous delivery of the antiviral Artemisia arborescens essential oil	Treatment of HSV-1	18
27.	Podophyllotoxin	High pressure homogenisation	73.4 nm	For epidermal targeting	Anti-Cancer	33
28.	Clobetasol propionate (Cp)	High pressure homogenisation	177 nm	To increase skin uptake of the drug and provide prolonged effect	Eczema Treatment	43
29.	Prednicarbate (PC)	Ultrasonication	145 nm	For selective PC targeting to eczematous viable epidermis	Treatment of acute exacerbations of atopic dermatitis and contact dermatitis.	44
30.	Vitamin A (retinol and retinyl palmitate)	Microemulsion	125 nm	Increase drug penetration	Treatment of Acne vulgaris	45

Chein and coworkers prepared the topical SLNs for epidermal targeting of podophyllotoxin (POD) and SLN provided a good epidermal targeting effect and proved as an assured vehicle for transdermal administration of POD[33].

G. SLNs as Cosmeceuticals

Safranal

It is an herbal UV blocking agent. For getting better results from UV-blocker compounds it is necessary for them not to get very much penetrated to upper skin layer and they must be remained accumulated on top horny layers. It is well established that using a novel carrier offers the ability to modify this feature.SLN could be used as a potential physical sunscreen due to its physicochemical properties. Incorporation of safranal in SLNs improved its efficacy and proved as a promising carrier for transdermal application of drug. The Sun Protection Factor (SPF) of the formulation was determined in vitro using transport tape. Using corneometer SLN's moisturizing affectivity was also checked and found an increase in SPF of SLNs formulations on increasing the concentration of safranal and SLN-safranal formulations were slightly better than free SLN formulations for improving skin hydration SLN-safranal formulations were found to be an adequate carrier for transdermal administration of safranal and was better in providing appropriate sunscreen properties[34].

Reserveratrol

Enormous production of radical oxygen species (ROS) can affect the skin physiology and may result in various skin pathologies. It is incorporated in SLNs to assure better contact and to enhance the drug accumulation into the skin. Cell viability studies showed that it had antioxidant properties at a concentration of 50 μM and found to exhibit better skin penetration and effects on performing *ex-vivo* skin permeation studies[11].

Retinyl Palmitate

Retinyl palmitae is used as an anti-wrinkle agent. So, to get better skin retention effects it was incorporated in SLNs by using hot melt method. To enhance the skin distribution properties of the SLNs dicetyl phosphate (DCP) was incorporated to negatively charge the surface of SLNs and hence resulted in increase in skin penetration. In vitro skin permeation study revealed that surface modification of SLNs by using DCP increases skin distribution of drug than the neutral SLNs. The prepared SLNs were incorporated in a hydrogel and from that hydrogel *in vivo* anti-aging studies were performed and were found better than other formulations. Thus, DCP modified SLN system proved as a good carrier for transdermal drug delivery[35].

H. Delivery of Anti-Arthritis Drugs

Diclofenac Sodium

To get better anti-inflammatory activity and better pain relief the drug is incorporated in SLNs. The SLNs were prepared by melt-emulsion sonication method by using three different lipids that were Glycerol monostearate, stearic acid and guggul lipid. *Ex-vivo* skin permeation study showed that the SLN formulation containing guggul lipid showed 104.68 times higher drug content than other lipids containing SLN formulation and *in-vivo* study revealed that guggul lipid containing formulation was having 8.12 folds better C(max) and 15.28 folds better AUC (area under the curve) than other lipid containing formulations. It also showed a sustained release sketch in addition to a better penetration results[12].

Flurbiprofen

Topical delivery of anti-arthritis drug is a better option for its site-specific delivery and overcomes the problem associated with conventional oral therapy. It is a drug candidate for treating rheumatoid arthritis. Upon oral administration, the most frequently reported side effects of flurbiprofen are abdominal discomfort along with other gastrointestinal side effects. Also, it undergoes frequent dosing because it has a short elimination half-life of 3.9 h and. Therefore, flurbiprofen's long-term percutaneous absorption at a controlled rate is needed. To avoid the gastrointestinal damage and some other problems like low bioavailability, short half-life, and high first pass metabolism associated with

oral route, transdermal delivery would be helpful. So, [7] produced SLNs as a very responsive, skin friendly carrier for dermal preparations. The prepared dermal delivery system is capable of overcoming the limitations of other currently available formulations of flurbiprofen.

I. For Inflammatory Skin Diseases

SLNs of NSAIDS (Nonsteroidal anti-inflammatory drugs) were also prepared for the treatment of inflammatory skin diseases.[8] reported the SLN topical gel preparation of meloxicam to avoid gastric irritation, obtain a considerable minimisation of the various related intrinsic adverse effects, in addition to improve the patient compliance. The sustained release behavior of MLX loaded SLNs with favorable physicochemical characteristics were observed.

CONCLUSION

It can be easily concluded that SLNs can provide better skin applications due to their various desirable effects on skin besides the characteristics of a colloidal carrier system. The main limiting factor of transdermal drug delivery system i.e. epidermal barrier can be overcome by SLNs to some limit. Applications of SLNs provide the benefits like increased penetration via skin and accumulating drug to deeper dermal layers for various skin diseases. Topical applications of solid lipid nanoparticles can be used with promising results for therapeutic or cosmetic purpose. SLNs carrier provides new opportunities for the development of novel improved therapies.

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