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Role of Surfactants as Penetration Enhancer in Transdermal Drug Delivery System

Anushree Pandey, Ashu Mittal, Nitesh Chauhan and Sanjar Alam*

Department of Pharmaceutics, KIET School of Pharmacy, Ghaziabad, India

Abstract

Human skin is a remarkably efficient barrier, designed to keep "our insides in and the outsides out". This barrier property causes difficulties for transdermal delivery of therapeutic agents. One long-standing approach to increase the range of drugs that can be effectively delivered via this route has been to use penetration enhancers, chemicals that interact with skin constituents to promote drug flux.

To-date, a vast array of chemicals has been evaluated as penetration enhancers (or absorption promoters), yet their inclusion into topical or transdermal formulations is limited since the underlying mechanisms of action of these agents are seldom clearly defined. In this article we review some uses of the more widely investigated chemical penetration enhancers and discuss possible mechanisms of action.

Keywords: Transdermal; Surfactant; Penetration enhancer; Skin

Introduction

Transdermal drug delivery is the topical application of drugs to the skin in the treatment of skin diseases, wherein high concentrations of drugs can be localized at the site of action, thereby reducing the systemic drug levels and side effects [1-3]. 'U.S. Emerging Transdermal Drug Delivery Technologies Markets', reveals that this market generated revenues worth $1.57 billion in 2002 and reached a staggering $5.67 billion in 2009 [4]. In 1924, Rein proposed that a layer of cells joining the STRATUM CORNEUM-the thin, outermost layer of the skin-to the EPIDERMIS posed the major resistance to transdermal transport [5]. The corneocytes, which comprise cross linked keratin fibres, are about 0.2-0.4 μm thick and about 40 μm wide [6]. Penetration enhancers are used to promote the drug transport across the skin barrier. The interaction of the enhancers with the polar head groups of the lipids is the possible way to increase the penetration [7]. Surfactants have the potential for the solubilization of the stratum corneum lipids and thus act as penetration enhancers. Keratin interactions are also thought to explain the penetration-enhancing effects of surfactants [8].

Target Site for Transdermal Drug Delivery System: Skin

The outermost layer of the epidermis, the stratum corneum, provides a formidable barrier to dermal absorption that determines the rate of dermal penetration [9-14]. The stratum corneum differs from the rest of the epidermis in being a two-compartment tissue consisting of dead cornified cells (corneocytes) with a matrix of intercellular lipids [15]. The hydrophilic properties of the skin increase as the depth increases from the surface, such that the viable epidermis represented by the stratum granulosum, the stratum spinosum and the stratum basale, respectively is significantly hydrophilic. The dermis layer is also hydrophilic, hence favoring the uptake of hydrophilic chemicals [16]. The viable epidermis contains corneocytes at varying stages of differentiation, as well as melanocytes, Langerhans cells (important for antigen presentation and immune response), and Merkel cells (involved in sensory perception). This layer facilitates the diffusion of, for example, xenobiotics and decreases in surface area with age [17] (Figure 1).

Barriers Posed by Skin Against Percutaneous Absorption

Corneocytes are the 'bricks' embedded in an intercellular lipid matrix of mainly fatty acids, ceramides, cholesterol and cholesterol sulfate [18]. The corneocytes are held together by corneodesmosomes, which confer structural stability to the stratum corneum. The stratum corneum lipids are composed primarily of ceramides, cholesterol and fatty acids that are assembled into multi-lamellar bilayers. This unusual extracellular matrix of lipid bilayers serves the primary barrier function of the stratum corneum [19]. The cells are joined together by desmosomes, maintaining the cohesiveness of this layer [20]. The heterogeneous structure of the stratum corneum is composed of approximately 75-80% protein, 5-15% lipid and 5-10% unidentified on a dry weight basis [21]. There are two general options for drug substances to permeate the stratum corneum: the transepidermal route and the route via pores [22].

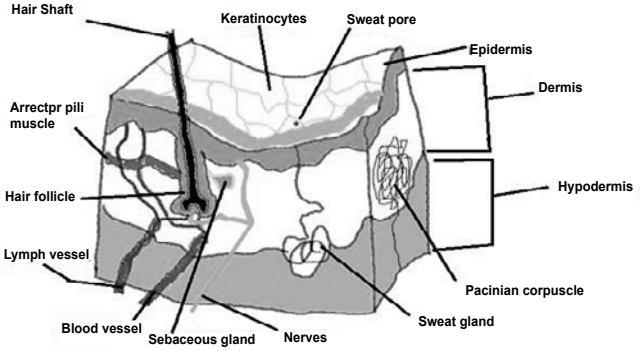

Figure 1: Diagrammatic representation of skin.

***Corresponding author:** Sanjar Alam, Department of Pharmaceutics, KIET School of Pharmacy, Ghaziabad, U.P-201206, India, Tel: +91- 9891674226: E-mail: sanjaralam10@gmail.com

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Factors Affecting Skin Penetration

- Thickness of horny layer
- Skin condition

Factors Associated With Medicament

- Solubility
- Dissociation constant
- Particle size

Factors associated with vehicle:

- Contact with skin
- Penetration into epidermis
- Alteration of skin permeability

Routes of Drug Permeation through the Skin

Intercellular route

Transcellular route

Follicular route

Intercellular route: The more common pathway through the skin is via the intercellular route. Drugs crossing the skin by this route must pass through the small spaces between the cells of the skin (Figure 2).

Transcellular route: Drug crossing the skin via this route must pass through the cells (Keratinocytes).

Transappendagal route: Passage of molecules via sweat glands, hair follicles and sebaceous glands.

Penetration Enhancers

Currently, the most widely used approach to drug permeation-enhancement across the stratum corneum barrier is the use of chemical penetration enhancers (sorption promoters and accelerants). One of the most recent comprehensive reviews on the classes of enhancers used was written by Ghosh et al. [23]. According to Shah, enhancers:

- increase the diffusivity of the drug in the skin;
- cause stratum corneum lipid-fluidization, which leads to decreased barrier function (a reversible action);
- increase and optimize the thermodynamic activity of the drug in the vehicle and the skin;
- result in a reservoir of drug within the skin;
- Affect the partition coefficient of the drug, increasing its release from the formulation into the upper layers of the skin [24].
- disrupt the order within and between the corneocyte upon binding to the keratin filament [25].

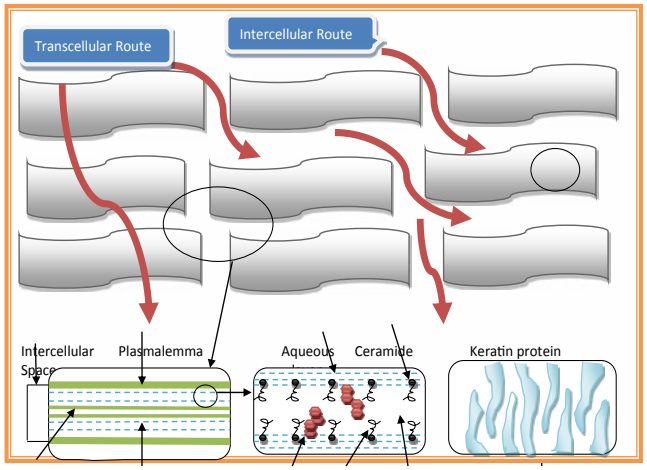

Figure 2: Diagrammatic representation of the stratum corneum and the intercellular and transcellular routes of penetration.

The following classes of compounds have been tested for their enhancer action: water, hydrocarbons (alkanes and alkenes); alkanols and alkenols; acids; esters; alkyl amino esters; amides; ureas; amines and bases; sulfoxides; terpenes [26], steroids; dioxolanes; pyrrolidone and imidazole derivatives; laurocapram (Azone) and its derivatives. Other approaches to enhancement include the use of enzymes, natural oils, phospholipid micelles, liposomes, niosomes, polymers [27-30]. isopropyl myristate [31], nicotinic acid esters [32], ethanol, hydrogenated Soya phospholipid [33], essential oils [34], n-octanol and decanol [35], surfactants [36-43] have been reported to enhance the permeability of drugs.

Surfactants

Surfactants are frequently used as emulsifiers in formulations for dermal application. A substance which is positively adsorbed at the liquid/vapour and/or at other interfaces is called surfactants [44]. Surfactants are usually organic compounds that are amphiphilic, meaning they contain both hydrophobic groups (their tails) and hydrophilic groups (their heads). Therefore, a surfactant molecule contains both a water insoluble (and oil soluble) component and a water soluble component. Surfactant molecules will diffuse in water and adsorb at interfaces between air and water or at the interface between oil and water, in the case where water is mixed with oil [45].

Classification of surfactants

Surfactants can be classified into four main categories according to the presence of formally charged groups in the head;

anionic (e.g. sodium laurylsulfate),

cationic (e.g. cetyltrimethyl ammonium bromide),

nonionic (e.g. polyoxyethylene sorbitan monopalmitate) and

amphoteric (e.g. N-dodecyl-N, N-dimethylbetaine).

The investigation of enhancing abilities of nonionic surfactants has been focused on five principal series of surfactants, which are polysorbates, sorbitan esters, polyoxyethylene alkylethers, polyoxyethylene alkylphenols and poloxamers [46]. It is generally recognized that nonionic surfactants possess the least toxicity and skin irritation potential [47], and therefore they have been widely investigated as skin penetration enhancers (Figures 3 and 4a-4g).

a. Mechanism of action of surfactants as penetration enhancers

Anionic surfactants: In general, anionic surfactants are more effective than cationic and nonionic surfactants in enhancing skin penetration of target molecules. Some anionic surfactants interact strongly with both keratin and lipids. alter the permeability of the skin by acting on the helical filaments of the stratum corneum, thereby resulting in the uncoiling and extension of keratin filaments

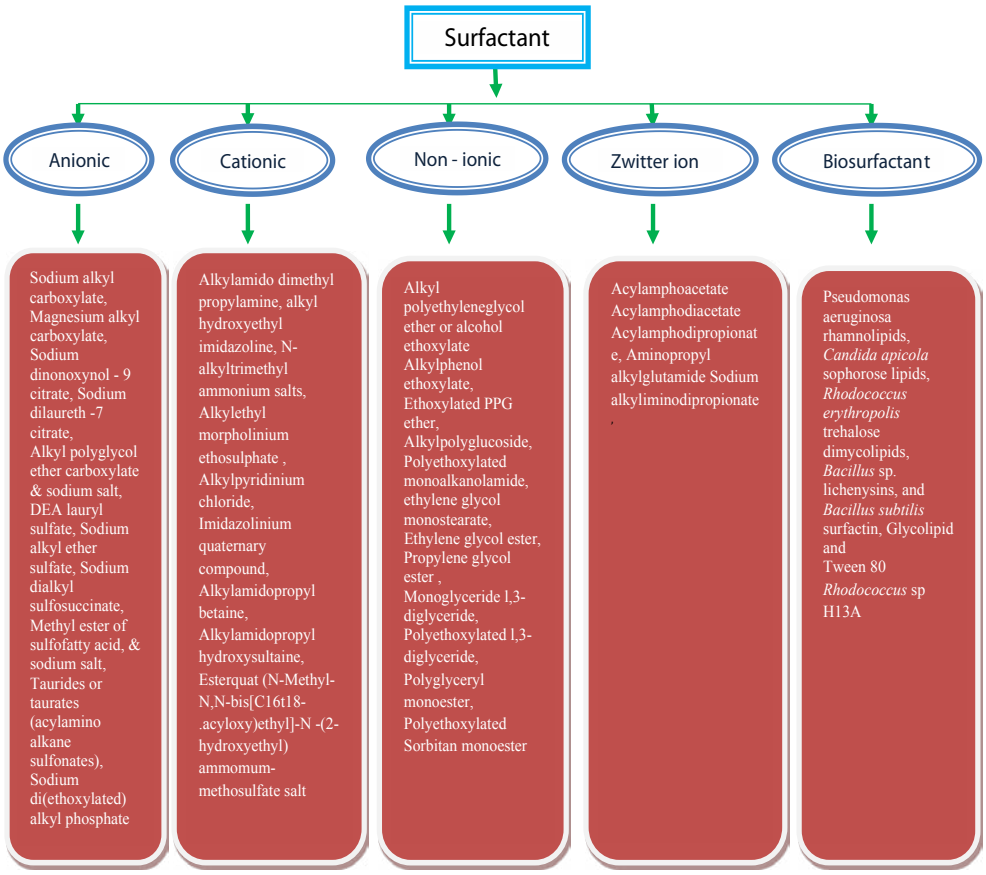

Figure 3: Classification of Surfactants.

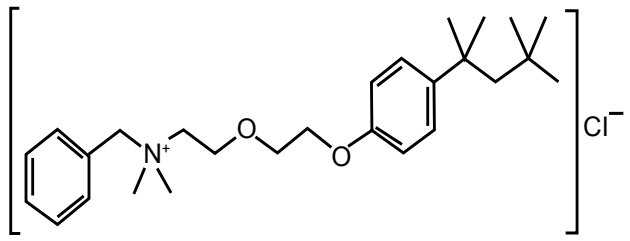

Figure 4a: Benzethonium chloride.

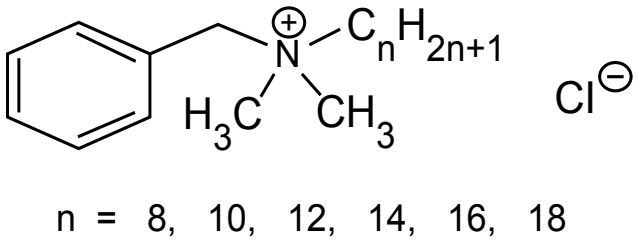

Figure 4b: Benzalkonium chloride.

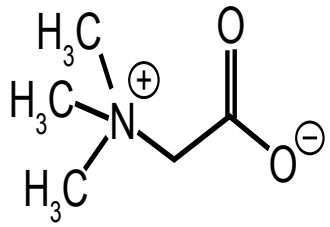

Figure 4c: Phosphatidylcholine.

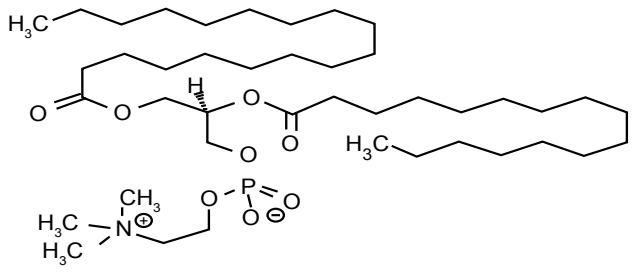

Figure 4d: Glycine betaine.

to produce keratin. Then they cause an expansion of the membrane, which increases permeability [48].

Sodium lauryl sulfate (SLS), an anionic surfactant, possesses skin penetration enhancer properties and enhances penetration into the skin by increasing the fluidity of epidermal lipids [49-52]. An additional mechanism for the skin penetration enhancement by SLS could involve the hydrophobic interaction of the SLS alkyl chain with

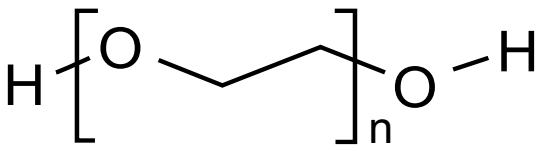

Figure 4e: Polyethylene glycol.

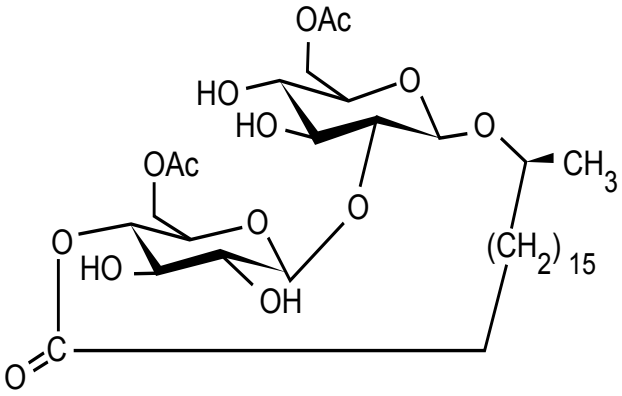

Figure 4f: Lactonic Sophorolipid.

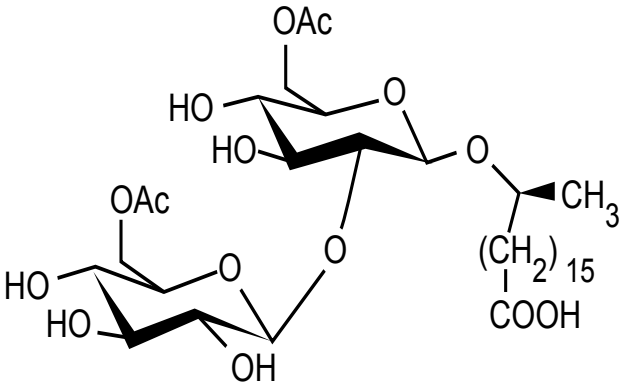

Figure 4g: Acid Sophorolipid.

the skin structure which leaves the end sulphate group of the surfactant exposed, creating additional sites in the membrane which leads to permit an increase in skin hydration [53,54].

Cationic surfactants: The cationic surfactants interact with the keratin fibrils of the cornified cells and result in a disrupted cell-lipid matrix. The cationic surfactants may interact with anionic components of the stratum corneum, change the electonic property there, and stimulate the transfer of the anionic drug into the skin [55].

Nonionic surfactants: The nonionic surfactants enhance absorption by inducing fluidization of the stratum corneum lipids [48]. They are two possible mechanisms by which the rate of transport is enhanced using nonionic surfactants. Initially, the surfactants may penetrate into the intercellular regions of SC, increase fluidity and eventually solubilize and extract lipid components. Secondly, penetration of the surfactant into the intercellular matrix followed by interaction and binding with keratin filaments may results in a disruption within the corneocyte [47,56].

Zwitter ion: Zwitterionic (amphoteric) surfactants have both cationic and anionic centers attached to the same molecule. The cationic part is based on primary, secondary, or tertiary amines or quaternary ammonium cations. The anionic part can be more variable and include sulfonates, as in CHAPS (3-[(3-Cholamidopropyl)dimethylammonio]-1-propanesulfonate). Other anionic groups are sultaines illustrated by cocamidopropyl hydroxysultaine. Betaines, e.g., cocamidopropyl betaine, lecithin [55,56].

Biosurfactants: Biosurfactants are surface-active substances synthesized by living cells. Interest in microbial surfactants has been steadily increasing in recent years due to their diversity, environmentally friendly nature, possibility of large-scale production, selectivity, performance under extreme conditions, and potential applications in environmental protection. Few of the popular examples of microbial biosurfactants includes Emulsan produced by Acinetobacter calcoaceticus, phorolipids produced by several yeasts belonging to candida and starmerella clade, and Rhamnolipid produced by *Pseudomonas aeruginosa* etc. [57].

Biosurfactants enhance the emulsification of hydrocarbons, have the potential to solubilize hydrocarbon contaminants and increase their availability for microbial degradation. The use of chemicals for the treatment of a hydrocarbon polluted site may contaminate the environment with their by-products, whereas biological treatment may efficiently destroy pollutants, while being biodegradable themselves. Hence, biosurfactant-producing microorganisms may play an important role in the accelerated bioremediation of hydrocarbon-contaminated sites. These compounds can also be used in enhanced oil recovery and may be considered for other potential applications in environmental protection. Other applications include herbicides and pesticides formulations, detergents, healthcare and cosmetics, pulp and paper, coal, textiles, ceramic processing and food industries, uranium ore-processing, and mechanical dewatering of peat [58].

Factors Governing the Activity of Surfactant as Penetration Enhancer

Critical micelle concentration

In biological systems the effects of surfactants are complex, particularly their effect on cell membranes, which can lead to alterations in permeability [46]. The effect of surfactants on membrane permeability describe an apparent concentration-dependent biphasic action, such that an increase in membrane permeability occurs at low surfactant concentrations, but this decreases at higher concentrations, generally above the critical micelle concentration (CMC) of the surfactant. Above the CMC, the added surfactant exists as micelles in the solution and micelles are too large to penetrate the skin [48]. The CMC represents a narrow range of concentrations above which surfactants form dynamic aggregates known as micelles. The structure of micelles is such that in aqueous solution the monomers are aligned with their hydrophobic regions towards the centre and their hydrophilic sections outwards towards the aqueous bulk [59].

Chain length of carbon atoms

Enhancement depends on the carbon chain structure of the enhancer [60]. Maximal enhancement is generally attained for enhancers with a carbon chain length in the range of 10–14. This optimal range was found for anionic, cationic and neutral enhancers [61-65].

Transdermal gradient

The driving force for penetration into the skin is the "transdermal gradient" caused by the difference in water content between the relatively dehydrated skin surface (approx 20% water) and the aqueous viable epidermis (close to 100%) [66].

Hydrophilicity of surfactant head (Laughlin's hypothesis)

Surfactants with hydrophilic head groups should more effectively enhance the percutaneous penetration of polar molecules, while those of lesser hydrophilicity should be less effective The results obtained in the present work in agreement with Laughlin's hypothesis because Cetyltrimethylammonium bromide (log P_{oct} < 1) which is more hydrophillic than benzalkonium chloride (log P_{oct}=1.9) is less effective in enhancing lorazepam skin penetration. This could be attributed to the lipophilicity of lorazepam [67].

Steric forces

Steric repulsive forces are caused by the reduced conformational freedom of adsorbed molecules and changes in molecule/solvent interactions as two surfaces are approached. They are present in both surfactant and polymer systems and increases in magnitude and range with the size of the adsorbed molecules [68] (Table 1).

Various Surfactants Used to Enhance Penetration across the Skin in Current Scenario

Tween 80

Permeant	Surfactant	Description	References
Chloramphenicol	Sodium Lauryl Sulphate	significant enhancement of surfactant facilitated permeation through hairless mouse skin	[36,37]
Hydrocortisone, lidocaine	Tween 80	Acceleration of permeating across hairless mouse skin	[36,37]
5-fluorouracil, antipyrine and 2-phenyl ethanol	Span 20 (1 and 5% w/v in ethanolic solution)	increased the penetration through Wistar rat epidermis in- vitro	[40]
Naproxen, naloxone	sodium decyl and dodecyl sulfates	increased the in vitro permeation rates	[69,61]
Lorazepam	Sodium lauryl sulfate 5%, Cetyltrimethyl-ammonim bromide	enhancing activity on the skin permeation across rat skin in vitro	[70]
Lidocaine (from saturated systems in propylene glycol-water mixtures)	Cationic surfactants	promote the permeation through excised human skin	[71]
5-flourouracil	0.1% Tween		
20 in normal saline	permeation across hairless mouse skin 6-fold	72	
Chloramphenicol	0.5 and 1% Tween 80	increased the skin penetration	[73]
Laurocapram	SLS	produce variations in the structural organisation of lipids when it is used above the critical micellar concentration [73]	[75,76]
Fluoxetine	Labrasol (caprylo-capryloyl macrogol-8-glyceride)	Permeation significantly enhanced from a vehicle system consisting of 65% v/v ethanol	[77]
Nitrendipine	Benzalkonium chloride, SLS, Tween 80	Enhance the permeation of nitrendipine across rat skin.	[78]
Piroxicam	polyoxyethylene-2-oleyl ether	Enhancing effects with an enhancement factor of 2.84.	[42]
Diazepam	sodium lauryl sulfate	increase the permeation of diazepam across rat skin	[43]
Foscarnet	sodium lauryl sulfate (SLS)	Increase the penetration thereby, its efficacy against HSV-1 cutaneous lesions in hairless mice.	[79]
Hydrocortisone	Span 20: Span 80	An increase in diffusion through the skin (58.29%)	[80]
Mepivacaine	polyoxyethylene 2-oleyl ether	enhancement of permeation through skin	[81]
Diltiazem			
hydrochloride	Tween80	improve the in vitro	
permeation through pig ear skin	82		
Hydrocortisone Acetate	2-(2-ethoxy-ethoxy) ethanol (Trans-Cutol)	Functions as solubilizer and permeation enhancer.	[83]
Acyclovir	Transcutol	enhancing ability to pass through	
the skin	84-86		
Progesterone	medium-chain mono- and diglycerides	ability to interact with membrane lipids and proteins, increasing membrane permeability enhanced the topical and transdermal delivery of PGT by 2.5- and 7-fold	[87-90]
Adenosine	polysorbate 80, medium-chain glycerides, and propylene glycol	increases in the skin penetration and transdermal delivery	[90-93]
Fluconazole	Labrasol (Lab) /EtOH (1:1, w/w) mixture	showed the highest permeation profile among other formulations 9.12 times higher	[94,95]
Ropinirole	Tween 20	the skin permeation increased from 20% to 35%	[96,97]
Flurbiprofen	span 20, span 80	showed a larger amount of flurbiprofen penetration through rabbit skin	[98]
5-fluorouracil	lecithin/ethanol/decyl glucoside (14.67:12.15:18.18% w/w,)	significant increase in permeability coefficient in newly born mice skin	[99]
Interferon	nonoxynol-9	indications such as ending of new-lesion formation, scabbing, and healing of lesions in patients with recurrent genital herpes	[100]
Piroxicam	Tween 80:Span 20	enhance permeation through various skin models by reversible disturbance of the stratum corneum layer	[40,42,101,102]

Paclitaxel	Cremophor EL	intracellular penetration enhancer for liposomal drugs to improve their anticancer efficiency	[103]
Ibuprofen	Tween 80	Higher penetration through the skin	[104]
2,3,5,6-tetramethylpyrazine	Labrasol®	the skin penetration were 0.9- to 4.7-fold higher	[105]
Ketorolac	Span 60, Tween 20	provided a higher ketorolac flux across the skin (7-and 4-fold the control, respectively)	[106]
Amlodipine besilate	SLS, tween 20, sodium tauroglycolate and hyaluronidase	hyaluronidase enzyme show higher permeability and steady state flux increased linearly with increasing donor concentration	[107,108]
Lacidipine	Tween 80 and Labrasol	enhances the drug permeation through the skin	[109]
Nicardipine Hydrochloride	Tween 80 / Span 20 mixture	enhances the drug permeation through the skin	[110]
Ramipril	Cremophor EL	enhances the drug permeation through the skin	[111]
Tamoxifen citrate	Cremophore EL, Tween 80	excellent skin penetration rate of drug	[112]
Diclofenac diethylamine	Span 20	enhancement of skin permeation of the drug of up to 30% in rat skin	[113]
Atenolol	Polyoxyethylene-2-oleyl ether	best enhancement for the atenolol transdermal drug delivery	[114]
Propranolol, metaproterenol sulfate	Lauric acid	enhancement on the percutaneous absorption	[115,116]
Methyl nicotinate	polyoxyethylene (10) lauryl ether, poly-oxyethylene (10) stearyl ether	permeability rate of methyl nicotinate from aqueous solution is increased two-fold	[117]

Table 1: Enlist the description of permeant i.e drug which shows excellent skin permeation enhancement with the use of the surfactant.

Acceleration of hydrocortisone and lidocaine permeating across hairless mouse skin by the nonionic surfactant Tween 80 [36,37]. It has been shown that at concentrations of 0.5 and 1% Tween 80 increased the skin penetration of chloramphenicol [73]. It is apparent that propylene glycol and Tween 80 interact to affect the skin barrier so as to promote the penetration of lorazepam. It was evident from surface tension studies that the addition of propylene glycol raises the CMC of the nonionic surfactants by approximately a factor of 10. The increase in monomer concentration might be an explanation for observed synergistic effect of propylene glycol and Tween 80. Highest permeation rate was observed with the solution containing 1% w/w of Tween 80 in diazepam permeation [43]. Initially, the surfactants may penetrate into the intercellular regions of stratum corneum, increase fluidity and eventually solubilize and extract lipid components. Secondly, penetration of the surfactant into the intercellular matrix followed by interaction and binding with keratin filaments may results in a disruption within the corneocyte. Tween 80 is thought to enhance the penetration of lorazepam via both the lipophilic and the hydrophilic molecular mechanisms, and to disrupt the lipid arrangements in the stratum corneum and to increase the water content of the proteins in the barrier [56,57]. The structure of Tween 80 is relevant to this role. It contains the ethylene oxide and a long hydrocarbon chain. This structure imparts both lipophilic and hydrophilic characteristics to the enhancer, allowing it to partition between lipophilic mortar substance and the hydrophilic protein domains. Tween 80 may interact with the polar head groups of the lipids and the modification of H-bonding and ionic forces may occur. The other possible mechanism related to our studies involves the protein domains (keratinocytes). In this case, targets of the enhancer are the keratin fibrils and their associated water molecules. The disruption caused by the enhancer makes this area more aqueous. With high enough volumes an increase in the solubilising ability of the aqueous layer could result and actually change the operational partition coefficient of this region of the skin [72]. This would then allow for drug transport through the corneocytes.

Sodium lauryl sulfate

Surfactant facilitated permeation of many materials through skin membranes has been researched, with reports of significant enhancement of materials such as chloramphenicol through hairless mouse skin by sodium lauryl sulfate [36,37]. Sodium lauryl sulfate at 5% showed a remarkable enhancing activity on the skin permeation of lorazepam across rat skin in vitro. A marked increase in the drug flux was attributed to the skin damage caused by this anionic surfactant at 5% concentration, the highest concentration used in the study [70]. Sodium lauryl sulfate is able to produce variations in the structural organisation of lipids when it is used above the critical micellar concentration [73], and similar effects on organisation of skin lipids have been described for other permeation enhancers such as Laurocapram [74,75], reported that SLS was able to increase the penetration rates of compounds that have values of lipophilicity lower than an optimum lipophilicity. An additional mechanism for the skin penetration enhancement by SLS could involve the hydrophobic interaction of the SLS alkyl chain with the skin structure which leaves the end sulphate group of the surfactant exposed, creating additional sites in the membrane which leads to permit an increase in skin hydration [53,54].

Dodecyl trimethyl ammonium bromide

Dodecyl trimethyl ammonium bromide (DTAB) as to the pretreatment with cationic surfactant DTAB, opposing effects on the flux are found compared to LA. During all three experimental intervals (passive before iontophoresis, iontophoresis, passive after iontophoresis) an inhibition. This is most likely related to the positive charge of surfactant DTAB. During the passive period, the partitioning of the positively charged R-apomorphine into the membrane is hindered by the repulsion of absorbed positively charged DTAB. After turning on the current, DTAB is driven into the skin and compensates for the native negative charge of human stratum corneum, thereby reducing the electro-osmotic flow [118].

Laureth-3 oxyethylene ether

Laureth-3 oxyethylene ether ($C_{12}EO_3$) the nonionic surfactant $C_{12}EO_3$ substantially increased iontophoretic transport rate of R-apomorphine by 2.3-fold, whereas passive delivery was basically unchanged or slightly affected. The magnitude of enhancing effect of C EO was dependent on the surfactant concentration and the pretreatment duration [119].

Span 20

Pretreatment of skin with Span 20 (1 and 5% w/v in ethanolic solution) significantly increased the penetration of 5-fluorouracil, antipyrine and 2-phenyl ethanol through Wistar rat epidermis *in vitro* [40].

Tween 20

Tween 20 has been shown to increase the permeation of hydrocortisone and lidocaine across hairless mouse skin *in vitro* [36,37].

Sodium lauroyl sarcosinate and sorbitan monolaurate

Sodium lauroylsarcosinate, and a nonionic surfactant, sorbitan monolaurate, more markedly increased the transdermal flux of drugs than the individual components used alone. Moreover, the formulation exhibited a reduction in skin irritation [120].

Sodium decyl & dodecyl sulfates

Sodium decyl and dodecyl sulfates increased the in vitro permeation rates of several drugs including naproxen [121] and naloxone [48,60] reported that the capacity of the stratum corneum to retain significant quantities of membrane-bound water is reduced in the presence of sodium dodecanoate and sodium dodecyl sulfate. This effect is readily reversible upon removal of the agents. These investigations proposed that anionic surfactants alter the permeability of the skin by acting on the helical filaments of the stratum corneum, thereby resulting in the uncoiling and extension of β-keratin filaments to produce α-keratin. Then they cause an expansion of the membrane, which increases permeability.

Cetyltrimethyl ammonium bromide

The permeation profile of lorazepam in presence of the other cationic surfactant, CTAB, reveals that an increase in the concentration of CTAB cetyltrimethylammonium bromide results in an increase in the flux of lorazepam Similar results were reported on the effect of other cationic surfactant cetrimide which is a cationic surfactant which contains higher percentages of CTAB on haloperidol permeation through rat skin [122].

n-Dimethyl dialkylammoniums

Enhancement effects of the double-chained cationic surfactants of n-dimethyldialkylammoniums $(CH_3)2N_1(CnH_{2n11})2$on the permeation of anionic salicylate through excised guinea pig dorsal skin at pH 7.4. n-dimethyldidecylammonium (2C10), which seemed to form micelles, had dose-dependent enhancement effects and about a ninety-fold increase in the permeabilityn-Dimethyldilaurylammonium ($2C_{12}$), seemed to form bilayer vesicles, induced about a twenty five-fold increase in the permeability [123-125].

Sodium dodecyl sulfate

Sodium dodecyl sulfate (SDS) and dodecyl trimethylammonium bromide (C_{12}TAB) Patist et al. have previously shown that SDS micellar stability may be tailored by the addition of oppositely charged surfactants such as alkyltrimethylammonium bromides (C_nTABs). The long-chain TABs enhance SDS micellar stability, as measured by relaxation time, by up to 2000 times. Addition of C12TAB to SDS leads to stabilization of micelles and sub-micellar aggregates and such stabilization decreases and even virtually eliminates sub-micellar aggregates [126,127].

Polyoxyethylene-23-lauryl ether, polyoxyethylene-2-oleyl ether and polyoxyethylene-2-stearyl ether

Poloxamer gels containing piroxicam including surfactants as enhancers are good preparations to promote the percutaneous absorption of drugs [114].

Cremophor RH 40®

Cremophor RH 40® shifts the drug distribution to the stratum corneum. Cremophor RH 40® enhanced the flufenamic acid content in the stratum corneum 2-fold. The amount of flufenamic acid after pretreatment with Cremophor RH 40® is on a higher level in the stratum corneum [84].

Propylene glycol, 2-(2-ethoxy-ethoxy) ethanol (Transcutol®)

The optimum formulation containing 2.5% Transcutol as the penetration enhancer shows 1.7-fold enhancement in flux and permeation coefficient as compared to marketed cream and ointment formulation. In order to further improve the permeation rate of Acyclovir from the microemulsion, enhancer like Transcutol in the concentration ranging from 1% to 5% was employed. Results indicate significant improvement in the permeation pattern of ACV with the incorporation of enhancers. The presence of Transcutol in the formulations also results in an increase in the mean cumulative amount. The enhancing ability of Transcutol has been attributed to its ability to pass through the skin and get incorporated into the multiple-lipid bilayers, thereby swelling the intercellular lipids [84,86].

Conclusion

Skin permeation enhancement technology is a new and rapidly developing field which would significantly increase the number of candidates suitable for Transdermal Drug Delivery. Research in this area has proved the use of surfactant on the enhancement of permeation of drugs through skin. The techniques such as Differential scanning calorimeter, Fourier Transform Infrared, Nuclear magnetic resonance, Electron microscopy etc. have been very helpful in elucidating the mechanism of action and structure activity relationship of Penetration enhancers. Majority of studies reported indicate that the chemical structure of Penetration enhancers plays an important role on the permeation enhancement of drugs for some enhancers such as fatty acids, fatty alcohols and terpenes. Further studies are needed in the areas of evaluation of skin permeation enhancement vis-à-vis skin irritation in order to choose penetration enhancers which possess optimum enhancement effect with no skin irritation. A judicious selection of penetration enhancer would be very helpful in the successful development of topical and transdermal products.

Declaration

The author(s) declare that they have no competing interests or financial benefit from this work.

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