Structure-Activity Relationship of Chemical Penetration Enhancers

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Contents

4.1 **Introduction** 39

4.2 **Fatty Acids** 40
4.2.1 Effect of Carbon Chain Length 40
4.2.2 Saturated and Unsaturated Fatty Acids 41
4.2.3 Branched Versus Unbranched Fatty Acids 41
4.2.4 Position of Double Bond 42
4.2.5 Geometric Isomers 42
4.2.6 Number of Double Bonds 42

4.3 **Fatty Alcohols** 43
4.3.1 Fatty Acids Versus Fatty Alcohols 44

4.4 **Terpenes** 45

4.5 **Pyrrolidones** 47

4.6 **Surfactants** 49

4.7 **Recent Studies** 50

Conclusions 51

References 51

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4.1 Introduction

Transdermal drug delivery offers several advantages over the conventional routes of administration. Elimination of hepatic first-pass effects, reduced side effects through optimization of the blood concentration profile, and extended duration of activity are some of the benefits of transdermal delivery. However, the highly organized structure of the stratum corneum forms an effective barrier to the permeation of a diverse range of agents, which must be modified if poorly penetrating drugs are to be administered. The stratum corneum consists of dead, anucleate, keratinized cells embedded in a lipid matrix.

The use of chemical penetration enhancers would significantly increase the number of candidates suitable for transdermal delivery. According to the lipid-protein partitioning (LPP) theory (Williams and Barry 1991a), chemical penetration enhancers would act by one or more of three major mechanisms: (a) disruption of the stratum corneum lipid matrix, (b) interaction with intracellular protein, and (c) improvement in partitioning of a drug or solvent into the stratum corneum. The LPP theory was extended to recognize (d) disruption of the corneocyte envelope by compounds such as phenol and hydrocarbons; (e) effects on protein junctions, such as desmosomes; and (f) alteration of the partitioning between stratum corneum components (proteinaceous) and the

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lipid in the diffusion pathway (Menon et al. 1998; Magnusson et al. 2001).

Compounds with a wide variety of chemical structures have been evaluated as skin penetration enhancers. These compounds include fatty acids, fatty alcohols, terpenes, pyrrolidones, surfactants, amides, Azone and its derivatives, urea and its derivatives, sulfoxides, alkanes, and esters. The differences in the structure and physicochemical properties among each class of the enhancers were accounted for their penetration enhancement potencies. Structure-activity relationship (SAR) represents an attempt to correlate the structure or physicochemical property of a compound with its enhancement activity. The physicochemical descriptors include molecular shape, size, lipophilicity, hydrophilicity, molecular geometry, electronic, and steric effects that have strong influence in the biological activity of the compounds. SAR is currently being applied in many disciplines pertaining to drug design, proteomics, and environmental risk assessment. In this chapter, the relationship between the chemical structure and skin permeation enhancement effect of some of the extensively studied penetration enhancers such as fatty acids, fatty alcohols, terpenes, pyrrolidones, and surfactants has been discussed.

4.2 Fatty Acids

Saturated and unsaturated fatty acids have been established as effective enhancers for transdermal permeation of drugs (Aungst et al. 1986; Tanojo et al. 1997a; Thomas and Panchagnula 2003). The chemical formulae of some of the commonly used fatty acids are presented in Table 4.1. The SAR of fatty acids is discussed in detail in this section.

Table 4.1 Chemical formulae of commonly used fatty acids

Name	Formula
Saturated fatty acids	
Caprylic acid	$CH3(CH2)_6COOH$
Capric acid	$CH3(CH2)_8COOH$
Lauric acid	$CH3(CH2)_{10}COOH$
Myristic acid	$CH3(CH2)_{12}COOH$
Palmitic acid	$CH3(CH2)_{14}COOH$
Stearic acid	$CH3(CH2)_{16}COOH$
Unsaturated fatty acids	
Oleic acid	$CH3(CH2)_7CH=CH(CH2)_7COOH$
Linoleic acid	$CH3(CH2)_4CH=CHCH2CH=CH(CH2)_7COOH$
Linolenic acid	$CH3CH2CH=CHCH2CH=CHCH2CH=CH(CH2)_7COOH$

4.2.1 Effect of Carbon Chain Length

There are many reports on the effect of carbon chain length of fatty acids on the percutaneous permeation enhancement of drugs. Aungst et al. (1986) studied the effect of carbon chain length of saturated fatty acids (C7–C18) on the penetration of naloxone through human skin. As the carbon chain length increased from C7 to C12, there was an increase in the permeation of naloxone. An increase in the carbon chain length beyond C12 decreased the flux of naloxone. Maximum permeation was observed with C9–C12.

Ogiso and Shintani (1990) examined the effect of a series of saturated fatty acids on the permeation of propranolol through rabbit skin using gel formulations. Lauric acid and myristic acid were the most effective agents among the fatty acids used in increasing the penetration of propranolol, and the enhancement was significantly larger than those in short and long-chain fatty acids. Lee et al. (1993) investigated the effect of a series of saturated fatty acids (C6–C18) and unsaturated fatty acids (oleic and linoleic acid) on the permeation of the 5-fluorouracil prodrug Tegafur across hairless mouse skin. The fatty acids enhanced the skin permeation of Tegafur in the ethanol/panasate 800 (tricaprylin) (40:60) binary vehicle in the following order: oleic acid>C12>linoleic acid>C10>C8>C6>no fatty acid>C14>C16>C18. All fatty acids increased the skin permeation of Tegafur in the ethanol/water (60:40) binary vehicle. The skin permeation of Tegafur decreased in the following order: C12>C10>linoleic acid>oleic acid>C8>C6>no fatty acid. The skin permeation of Tegafur in the presence of fatty acids was significantly higher with ethanol/panasate 800 (40:60) when compared with

ethanol: water (60:40). These results suggest that the vehicle plays an important role in the skin permeation enhancement effect of fatty acids.

The skin permeation enhancement of a number of fatty acids, namely, straight chain saturated, monounsaturated, and polyunsaturated acids, was evaluated using human stratum corneum (Tanojo et al. 1997a). Saturated fatty acids with 6–12 carbons showed a parabolic correlation between enhancement effect and chain length, with a maximum at nonanoic-decanoic acids (with 9 and 10 carbons). A parabolic relationship between carbon chain length of fatty acids and skin permeation enhancement was also observed with thiamine disulfide (Komata et al. 1992), testosterone (Yu et al. 1991), and indomethacin (Chien et al. 1988).

Kandimalla et al. (1999) studied the effect of saturated fatty acids (C9–C14) on the permeation of melatonin across excised rat skin. A sharp increase in the permeation of melatonin was observed, as the fatty acid chain length increased from 9 to 10 carbons. A further increase in the permeation of melatonin was observed when the chain length was increased to 11. However, the permeation of melatonin decreased when the chain length was increased beyond 11 carbons. It can be observed that the permeation of melatonin has a parabolic relationship with the chain length of the saturated fatty acids. In general, medium chain fatty acids have showed greater permeation enhancement effect compared to short or long-chain fatty acids.

It has been proposed that fatty acids with a certain chain length, that is, around 12 carbons, possess an optimal balance between partition coefficient or solubility parameter and affinity to skin (Ogiso and Shintani 1990). Shorter chain fatty acids would have insufficient lipophilicity for skin permeation, whereas longer chain fatty acids would have much higher affinity to lipids in stratum corneum and thereby retard their own permeation and that of other permeants. The parallel effect with the permeation enhancement suggests that the mode of action of saturated fatty acids as enhancers is dependent on their own permeation across the stratum corneum (Tanojo et al. 1997a).

The mechanism by which fatty acids increase skin permeability appears to involve disruption of the lipids that fill the extracellular spaces of the stratum corneum (Aungst 1989; Barry 2001). Treatment of rabbit stratum corneum with various unsaturated fatty acids resulted in a shift to higher frequency for the C-H asymmetric stretch peak near 2920 cm^{-1} on Fourier transform infrared spectroscopy (FTIR) spectra, which primarily results from the acyl chains of intercellular lipid in the stratum corneum (Morimoto et al. 1996).

4.2.2 Saturated and Unsaturated Fatty Acids

The effect of saturated long-chain fatty acids [stearic acid (C18), myristic acid (C14), and lauric acid (C12)] on the percutaneous transport of thiamine disulfide from propylene glycol was studied through excised rat skin (Komata et al. 1992). The permeation of thiamine disulfide was enhanced 31 times by C12 and 1.4 times by C14 and suppressed to 80 % of its original value by C18. However, with unsaturated fatty acids, the permeation of indomethacin was enhanced in the following order: C20 > C22 > C18 = C16 > C14, and the flux values were correlated well with the uptake of these compounds into the stratum corneum (Morimoto et al. 1996). Oleic acid (C18, unsaturated) has been shown in several studies to be an effective skin permeation enhancer, whereas stearic acid (C18, saturated) is not a good skin permeation enhancer. Chi et al. (1995) reported an increase of 6.5-fold to 17.5-fold in the permeation rate of flurbiprofen by unsaturated fatty acids, while no significant increase was observed with saturated fatty acids. Thus, saturated and unsaturated fatty acids behave differently on the skin permeation enhancement.

4.2.3 Branched Versus Unbranched Fatty Acids

Aungst (1989) reported that maximum flux of naloxone was observed with C9–C12 branched and unbranched fatty acids through human skin.

The branched and unbranched isomers of C5–C14 fatty acids showed similar effects. However, isostearic acid [$(CH_3)_2CH(CH_2)_{14}COOH$] was a more effective permeation enhancer than stearic acid. The higher permeation enhancement effect of isostearic acid than stearic acid was attributed to its lower melting point and greater solubility in propylene glycol (Aungst 1995).

4.2.4 Position of Double Bond

Tanojo et al. (1997a) studied the effect of position of double bond on the percutaneous absorption of para amino benzoic acid in human stratum corneum using cis-octadecenoic acid with a double bond at 6th, 9th, 11th, or 13th position counted from the carboxyl head group. There was no significant difference in the effect of these acids on the permeation of para amino benzoic acid. Morimoto et al. (1996) studied the effect of double bond positions of unsaturated fatty acids (C18) on the permeation of indomethacin through rat skin. The permeation of indomethacin with oleic acid (cis-9), asclepic acid (cis-11), and petroselinic acid (cis-6) was not affected by the position of the double bonds.

4.2.5 Geometric Isomers

The effect of geometric isomers of unsaturated fatty acids on the permeation of indomethacin through rat skin was studied (Morimoto et al. 1996). The indomethacin flux with elaidic acid (trans-9-octadecenoic acid) was significantly lower than that of oleic acid (cis-9-octadecenoic acid). The flux of salicylic acid enhanced by trans isomers of 9-octadecenoic acid was lower than that of their cis-isomers (Golden et al. 1987). However, there was no significant difference between cis and trans unsaturated C16–C18 fatty acid isomers in their effects on naloxone flux across human skin (Aungst 1989). The discrepancy in these results may be due to the difference in the properties of drugs employed and the variation in the skin species used for the studies.

4.2.6 Number of Double Bonds

A significant increase in the flux of naloxone was observed as the number of double bonds in the C18 fatty acid increased from one (oleic acid) to two (linoleic acid) (Aungst et al. 1986). An increase in the number of double bonds to three (linolenic acid), however, did not increase the flux further. Tanojo et al. (1997a) investigated the effect of number of double bonds (in cis-conformation) in straight chain polyunsaturated acids on the permeation of para amino benzoic acid in human stratum corneum. Polyunsaturated fatty acids such as linoleic, linolenic, and arachidonic acid with, respectively, two, three, and four double bonds produced a significantly higher permeation of para amino benzoic acid than the monounsaturated fatty acid. However, there was no significant difference in the permeation enhancement effects among the polyunsaturated fatty acids. Carelli et al. (1992) also reported that the enhancement of flux of alprazolam by linoleic acid was greater than that of oleic acid through hairless mouse skin. However, the flux of indomethacin was not affected by the number of double bonds (Morimoto et al. 1996).

Kandimalla et al. (1999) investigated the effect of oleic acid, linoleic, and linolenic acid on the permeation of melatonin across excised rat skin. As the number of double bonds increased, there was a slight increase in the permeation of melatonin. The flux of melatonin with linolenic acid was significantly higher than that of oleic acid ($P<0.05$). However, there was no significant difference in the flux values of linoleic acid and linolenic acid ($P>0.05$). Fang et al. (2003) studied the effect of oleic acid, linoleic acid, and linolenic acid on the permeation of flurbiprofen through the mouse skin. The permeation of flurbiprofen increased with an increase in the number of double bonds in the fatty acid.

Oleic acid has been reported to be an effective skin penetration enhancer for polar and nonpolar drugs (Narishetty and Panchagnula 2004; Goodman and Barry 1988). Cis-unsaturated fatty acids (e.g., oleic acid, linoleic acid, and linolenic acid) have been reported to form separate domains within the stratum corneum lipids that effectively

decrease the diffusional path length or the resistance (Ongpipattanakul et al. 1991; Tanojo et al. 1997b). The formation of separate domains would provide permeability defects within the bilayer lipids and facilitate the permeation of hydrophilic permeants. The presence of double bonds in the structure has been proposed to cause the formation of kinks in the lipid matrix to allow water permeation across the skin (Potts and Francoeur 1990). An increase in the number of double bonds increases the flux of drugs, possibly by causing more kinks in the lipid structure of the skin.

Recently, Ibrahim and Li (2010) evaluated the effects of fatty acids (e.g., oleic acid, lauric acid, decanoic acid, and undecanoic acid) commonly present in cosmetic and topical formulations on permeation enhancement across human epidermal membrane (HEM) lipoidal pathway when the fatty acids saturated the SC lipid domain without cosolvents (E_{max}). E_{max} of fatty acids was shown to increase with their octanol solubilities and decrease with their lipophilicities. Solid fatty acids (saturated fatty acids) had lower enhancement efficiency when compared to the liquid fatty acids (unsaturated fatty acids). E_{max} of solid fatty acids was shown to depend on their melting points, an important parameter to the effectiveness of the enhancers. The estradiol uptake results suggested that enhancer-induced permeation enhancement across HEM was related to enhanced partitioning into the SC lipid domain.

4.3 Fatty Alcohols

The chemical formulae of some of the commonly used fatty alcohols are presented in Table 4.2. The effect of saturated alcohols (C8-OH to C18-OH) on the flux of naloxone from propylene glycol was investigated through human skin (Aungst et al. 1986). A parabolic effect of alkyl chain length was observed with C10-OH and C12-OH being most effective. The effect of a series of straight chain alkanols on the transdermal delivery of levonorgestrel through excised rat and human cadaver skin was investigated by Friend and coworkers (1988). The flux of levonorgestrel increased as the alkyl chain increased from C2 to C4, but decreased as the chain length increased above 1-butanol.

Table 4.2 Chemical formulae of commonly used fatty alcohols

Name	Formula
Saturated fatty alcohols	
Octanol	$CH3(CH2)_7OH$
Capric alcohol	$CH3(CH2)_9OH$
Lauryl alcohol	$CH3(CH2)_{11}OH$
Myristyl alcohol	$CH3(CH2)_{13}OH$
Cetyl alcohol	$CH3(CH2)_{15}OH$
Unsaturated fatty alcohols	
Oleyl alcohol	$CH3(CH2)_7CH=CH(CH2)_8OH$
Linoleyl alcohol	$CH3(CH2)_4CH=CHCH2CH=CH(CH2)_8OH$
Linolenyl alcohol	$CH3CH2CH=CHCH2CH=CHCH2CH=CH(CH2)_8OH$

Lee et al. (1993) examined the effect of a series of fatty alcohols in ethanol/panasate 800 and ethanol/water on the permeation of Tegafur across hairless mouse skin. All fatty alcohols, except the C18-OH, increased the skin permeation of Tegafur in the ethanol/panasate 800 (60:40) binary vehicle. The degree of permeation percentage of Tegafur obtained was same at 12 h (64.1–67.9 % of dose) in all cases, and no significant difference between them was observed. However, all fatty alcohols significantly enhanced the skin permeation of Tegafur with ethanol/water (60:40) binary vehicle. The flux of Tegafur increased with an increase in alkyl chain length, reached a maximum permeation in C12-OH, and then decreased as the alkyl chain length increased further. The skin permeability of Tegafur was in the following order: C12-OH > C10-OH > C9-OH > C8-OH > C14-OH > C16-OH > C18-OH > no fatty alcohol. Fatty alcohols with 9, 10, and 12 carbon atoms provided the greatest permeation enhancement of Tegafur at 12 h in the ethanol/water (60:40) binary vehicle. These results suggest that the vehicle plays an important role in the permeation enhancement effect of fatty alcohols.

The effect of n-alkanols on the permeation of a polar, nonelectrolyte penetrant, nicotinamide through hairless mouse skin was investigated by Kai et al. (1990). The enhancement versus alkanol chain length profile was parabolic,

C6-OH being the maximum. The alkanol flux after a 6-h contact period, versus carbon number, was also a parabolic function. Alkanol uptake on the other hand increased with increasing chain length. The authors suggested that the primary mechanism by which alkanols increase percutaneous absorption is extraction of stratum corneum intercellular lipids. Sloan et al. (1998) studied the fluxes of theophylline through hairless mouse skin from suspensions in straight alkyl chain alkanols. The flux of theophylline was the lowest from methanol (C1-OH), increased by almost 100-fold from pentanol (C5-OH), hexanol (C6-OH), heptanol (C7-OH), octanol (C8-OH), and nonanol (C9-OH), and then decreased tenfold from undecanol (C11-OH).

The effect of saturated fatty alcohols (C8-OH to C14-OH) on the permeation of melatonin across excised hairless rat skin was investigated (Kanikkannan and Singh 2002). All saturated fatty alcohols increased the permeation of melatonin through hairless rat skin, and the permeation of melatonin was found to be related to the carbon chain length of the fatty alcohols. An increase in the flux of melatonin was observed when the fatty alcohol chain length increased from 8 to 10 carbons. However, the flux of melatonin decreased when the chain length was increased beyond ten carbons. The maximum permeation of melatonin was observed with decanol. The parabolic relationship between carbon chain length of fatty alcohol and skin permeation enhancement was also observed for testosterone (Yu et al. 1991) and indomethacin (Chien et al. 1988).

The effect of number of double bonds in the C18 fatty alcohol on the permeation of naloxone across human skin was studied (Aungst et al. 1986). The permeation of naloxone was increased with an increase in the number of double bonds. Like fatty acids, fatty alcohols also act by disrupting the stratum corneum lipid matrix (Barry 2001). The influence of hydrocarbon chain branching on the effectiveness of alkanol skin permeation enhancers was investigated using corticosterone as a model drug across hairless mouse skin (Chantasart et al. 2004). The branched-chain alkanols showed lower enhancer potency than the 1-alkanols of the same molecular formula; the potency decreases as the hydroxyl group moves from the end of the chain toward the center of the enhancer alkyl chain. The authors also reported that the intrinsic potencies of the 1-alkyl enhancers (1-alkanols, 1-alkyl-2-pyrrolidones, and 1-alkyl-2-azacycloheptanones) are essentially the same and independent of their alkyl chain length at their isoenhancement concentrations (Warner et al. 2001; Warner et al. 2003; Chantasart et al. 2004).

Ding et al. (2006) investigated the relationship between the skin permeation enhancement of alkanols and their physicochemical parameters including octanol-phosphate buffered saline (PBS, pH 7.4). The authors established the correlation equations between enhancement potencies and the physicochemical parameters relevant to lipophilicity and position of hydroxyl group for 16 alkanols (e.g., 1-hexanol, 1-heptanol, 1-octanol, 1-nonanol, 2-nonanol, 3-nonanol, 4-nonanol, and 5-nonanol) using stepwise multiple linear regression analysis. The enhancement potency of alkanols increased as their lipophilicity increased but decreased as the hydroxyl group moves from the end of the alkyl chain toward the center.

It has been reported that the most effective chain lengths (C10–C12) correspond to the length of the steroid nucleus of cholesterol, suggesting that these may act by disrupting ceramide-cholesterol or cholesterol-cholesterol interaction (Brain and Walters 1993). Ackermann et al. (1987) studied the permeation of a series of alkanols (C1-OH to C8-OH) across the nude mouse skin. The permeability coefficients of alkanols increased linearly as the chain length increases. Further, the permeability coefficients of n-alkanols correlated well with their ether-water partition coefficients. These results could be used to explain the permeation enhancement effect of different alkanols. The increase in the enhancement effect of lower alkanols with increase in the alkyl chain length may be attributed to the increased permeation of alkanols through the skin.

4.3.1 Fatty Acids Versus Fatty Alcohols

Fatty acids have a higher melting point than their corresponding fatty alcohols, but lower solubility

parameters. If the enhancement by these fatty acids and alcohols was solely due to solubility effects, then it would be expected that the alcohols would be more effective than the acids, whereas the reverse is true for alkyl chains up to C18. This suggests that more specific interactions must occur (Brain and Walters 1993). Introduction of double bonds into long alkyl chains modifies the effect significantly, and, for the C18 compounds, there was little difference between the corresponding fatty acids and alcohols. There was a greater concentration dependence of permeation enhancement for lauric acid than lauryl alcohol (Aungst et al. 1986).

4.4 Terpenes

Terpenes are naturally occurring compounds, which consists of isoprene (C_5H_8) units. Terpenes are classified according to the number of isoprene units they contain: monoterpenes (C_{10}) have two isoprene units, sesquiterpenes (C_{15}) have three, and diterpenes (C_{20}) have four. The structural formulae of different types of terpenes (hydrocarbon, ketone, alcohol, oxide, and cyclic ether terpenes) evaluated as skin penetration enhancers are shown in Fig. 4.1.

Terpenes have been widely studied as skin penetration enhancers for various drugs (Williams and Barry 1991a; Okabe et al. 1989; Gao and Singh 1998; Godwin and Michniak 1999). Okabe et al. (1989) studied ten cyclic monoterpenes as penetration enhancers for lipophilic drug indomethacin in rats. The absorption of indomethacin from gel ointment was substantially enhanced by hydrocarbon terpenes such as d-limonene. However, the oxygen-containing terpenes did not affect the permeation of indomethacin. Only those cyclic monoterpenes with a lipophilic index (log k') of greater than 0 exhibited absorption promoting effects, suggesting that the lipophilicity of these compounds plays an important role in drug transport across the skin. But the alcohol and ketone terpenes were less effective for lipophilic drugs such as diazepam (Hori et al. 1991) and estradiol (Williams and Barry 1991b).

Williams and Barry (1991b) evaluated a series of terpenes as skin penetration enhancers for the hydrophilic drug 5-fluorouracil in human skin. Cyclic terpenes were chosen from the chemical classes of hydrocarbons, alcohols, ketones, and oxides. Of the terpenes studied, hydrocarbons were poor enhancers and alcohols and ketones were more effective. The epoxides showed mild enhancing activity, whereas the cyclic ethers were very effective; ascaridole, 7-oxabicyclo[2.2.1] heptane, and 1,8-cineole all induce a near 90-fold increase in the permeability coefficient of 5-fluorouracil. The five-membered cyclopentene oxide showed higher enhancing activity than the six-membered cyclohexene oxide.

The effect of 12 sesquiterpenes on the permeation of 5-flurouracil was studied across human skin (Cornwell and Barry 1994). Pretreatment of epidermal membranes with sesquiterpene oils or using solid sesquiterpenes saturated in dimethyl isosorbide enhanced the absorption of 5-fluorouracil. Enhancers containing polar functional groups were generally more effective than pure hydrocarbons, and enhancers with the least "bunched" structures were the most active.

Obata et al. (1990) reported that percutaneous absorption of hydrophilic diclofenac sodium was substantially enhanced in the presence of l-menthol and dl-menthone, while it was little enhanced by d-limonene and p-menthane. Overall, the skin permeation-enhancing effect of terpenes depends on the physicochemical properties of the drugs. In general hydrocarbon terpenes are effective for lipophilic drugs and oxygen-containing terpenes are effective for hydrophilic drugs. Okamoto and coworkers (1987, 1988) evaluated the compounds containing azacyclo ring and acyclic terpene hydrocarbon chains as enhancers for a variety of drugs. These studies demonstrated that azocyclo ring size (C5–C6) has little effect on the potency of the enhancers, whereas the length of hydrophobic terpene chain has a significant effect; a chain length of 12 carbons provided maximum effect.

El-Kattan et al. (2000) investigated the effect of terpene lipophilicity (log P 1.06–5.36) (terpene-4-ol, verbenone, fenchone, carvone, menthone, alpha-terpineol, cineole, geraniol, thymol, cymene, d-limonene, and nerolidol) on the percutaneous absorption of hydrocortisone from hydroxypropyl methyl cellulose gel formulations using hairless

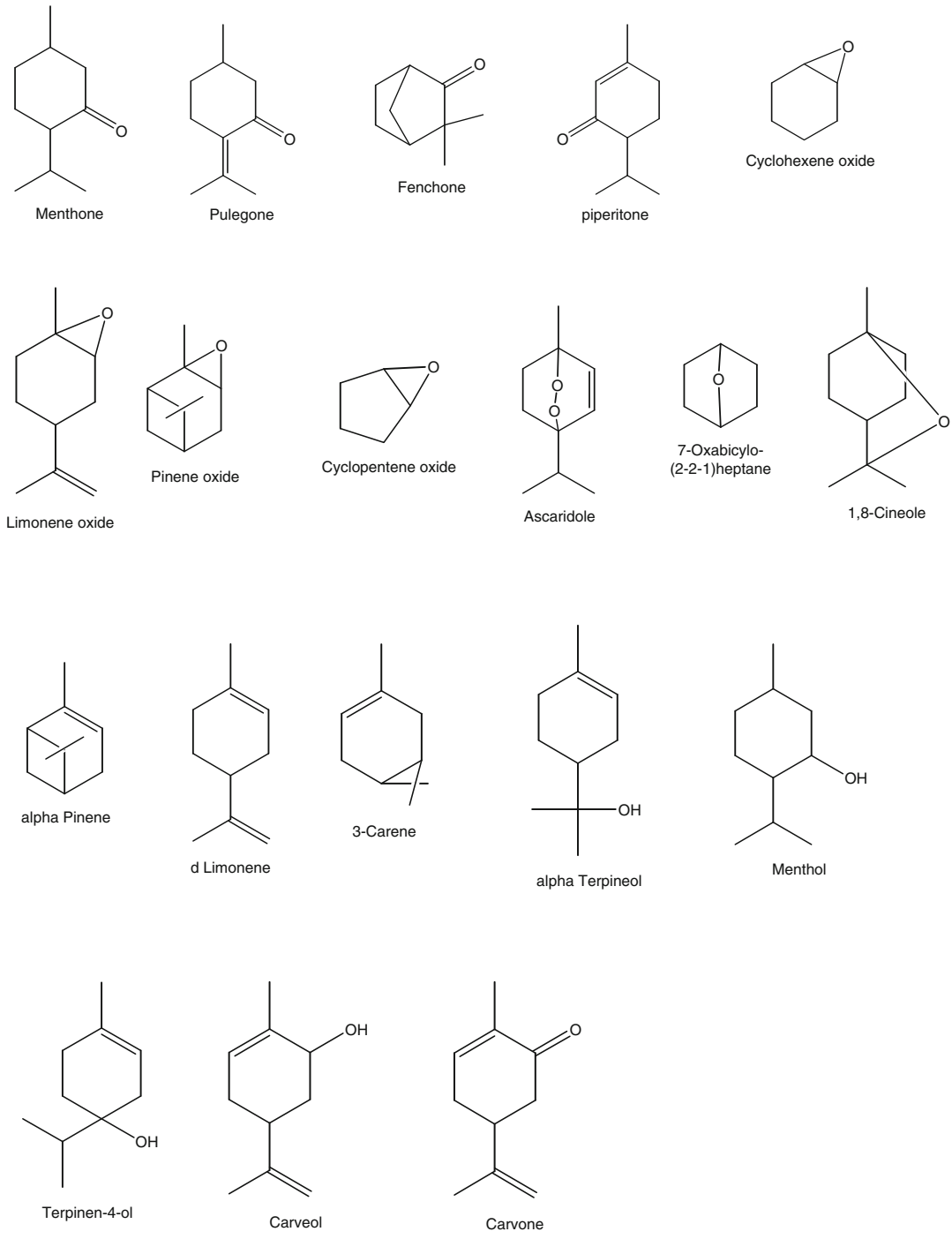

Fig. 4.1 Structural formulae of various types of terpenes (hydrocarbon, ketone, alcohol, oxide, and cyclic ether terpenes) evaluated as skin penetration enhancers

mouse skin in vitro. A linear relationship was found between the log P of terpene and the cumulative amount of hydrocortisone in the receptor compartment after 24 h. An increase in terpene lipophilicity was associated with an increase in the cumulative amount of hydrocortisone transported.

The effects of terpene enhancers (fenchone, thymol, d-limonene, and nerolidol) on the percutaneous absorption of drugs with different lipophilicities (nicardipine hydrochloride, hydrocortisone, carbamazepine, and tamoxifen) were studied (El-Kattan et al. 2001). Nerolidol (highest lipophilicity) provided the highest increase in the flux of the model drugs. The lowest increase in the flux was observed with fenchone (lowest lipophilicity). The results indicated that these four enhancers were more effective at enhancing the penetration of hydrophilic drugs rather than lipophilic drugs. The terpenes act mainly by disrupting the lipid matrix of the stratum corneum (Williams and Barry 1991b). Spectroscopic studies have also suggested that terpenes could exist within separate domains in stratum corneum lipids (Cornwell et al. 1996).

Kang et al. (2007) investigated the effects of physicochemical properties of terpenes on the permeation of a model drug (haloperidol) through the human stratum corneum using 49 terpenes. A full spectrum of terpenes was selected to include monoterpene, sesquiterpene, diterpene, triterpene, and tetraterpene with various functional groups such as hydrocarbons, alcohols, aldehydes, esters, ketones, and oxides. Liquid terpenes produced better enhancing effects than solid terpenes. Triterpenes and tetraterpenes showed poor penetration-enhancing effects compared to other types of terpenes. Terpenes with aldehyde and ester functional groups tend to increase $\text{Log}K_p$, while those with acid functional groups tend to decrease $\text{Log}K_p$. In general, terpenes with higher LogP values were found to be more effective enhancers than those with lower LogP.

Recently, Chantasart et al. (2009) investigated the effects of oxygen-containing terpenes as skin permeation enhancers on the lipoidal pathways of HEM. The enhancement (E(HEM)) effects of menthol, thymol, carvacrol, menthone, and cineole on the transport of a model drug, corticosterone, across HEM were determined. It was found that the enhancer potencies of menthol, thymol, carvacrol, and menthone were essentially the same and higher than that of cineole based on their aqueous concentration in the diffusion cell chamber at E(HEM) = 4. Thymol and carvacrol also had the same E(HEM) = 10 concentration further supporting that they had the same enhancer potency based on the aqueous concentration. The amount of terpene absorbed into the HEM stratum corneum (SC) intercellular lipid under the same conditions indicated that the intrinsic potencies of the studied terpenes are the same based on their concentration in the SC.

4.5 Pyrrolidones

Pyrrolidones and their derivatives have been investigated as potential skin penetration enhancers (Williams and Barry 2004). 2-Pyrrolidone and N-methyl-2-pyrrolidone (NMP) have been evaluated as penetration enhancers for a variety of drugs (Hoelgaard et al. 1988; Bhatia and Singh 1997). Figure 4.2 presents the chemical structures of some pyrrolidones, which have been evaluated as skin penetration enhancers. Aoyagi et al. (1991) synthesized a new group of 2-pyrrolidone enhancers containing a short alkyl group, such as methyl, ethyl, propyl, or butyl group, at the 1-position and a dodecyl group at the 3-position of a 2-pyrrolidone ring. The enhancing effect of these compounds was evaluated using indomethacin as a model drug. The length of the short alkyl group at the 1-position greatly impacted the enhancing activity of the 2-pyrrolidone derivatives. 1-Propyl and 1-butyl-3-dodecyl-2-pyrrolidone provided the greatest permeation enhancement effects for indomethacin through the skin.

The skin permeation enhancement activity of a series of alkyl substituted pyrrolidones was evaluated using phenol red as a model drug across rat skin in vitro and in vivo (Sasaki et al. 1988, 1990a, b, 1991). A correlation between the flux of phenol red and partition coefficient of the pyrrolidones was observed. The percutaneous penetration enhancement of 6-mercaptopurine by nine azacycloalkanone derivatives with an alkyl or terpene chain was studied using excised guinea pig skin (Okamoto et al. 1988). The number of carbonyl groups in the chain influenced the enhancing activity more effectively than the ring size.

It has been reported that pyrrolidone derivatives alter the liposomal membrane made with stratum corneum lipid (Kim et al. 1993). Yoneto

et al. (1995) studied the effects of 1-ethyl, 1-butyl, 1-hexyl, and 1-octyl-2-pyrrolidones on the transport of beta-estradiol, hydrocortisone, and corticosterone across hairless mouse skin. The results showed a 3.5-fold increase in enhancement potency per methylene group introduced at the 1-N position. The authors reported that the 1-alkyl-2-pyrrolidones may act via the intercalation of the alkyl group of the enhancer into the highly ordered interfacial region of the lipid bilayers, inducing significant disorder and enhancing microenvironmental fluidity. The authors studied the fluidizing effects of alkyl pyrrolidones upon the stratum corneum lipid liposome bilayer using steady-state anisotropy and fluorescence lifetime studies (Yoneto et al. 1996). The results suggested that the alkyl pyrrolidones might induce a general fluidizing effect upon the lipid bilayer. As a continuing effort to understand the mechanism of action, the authors studied the influence of the alkyl pyrrolidones on permeant partitioning into hairless mouse stratum corneum under the isoenhancement concentration conditions using beta-estradiol as the model drug (Yoneta et al. 1998). The results suggested that inducing a higher partitioning tendency for beta-estradiol into the lipoidal pathway of hairless mouse stratum corneum is a principal mechanism of action of the alkyl pyrrolidones in enhancing percutaneous absorption.

The transdermal permeation-enhancing effects of 16 pyrrolidinone derivatives toward

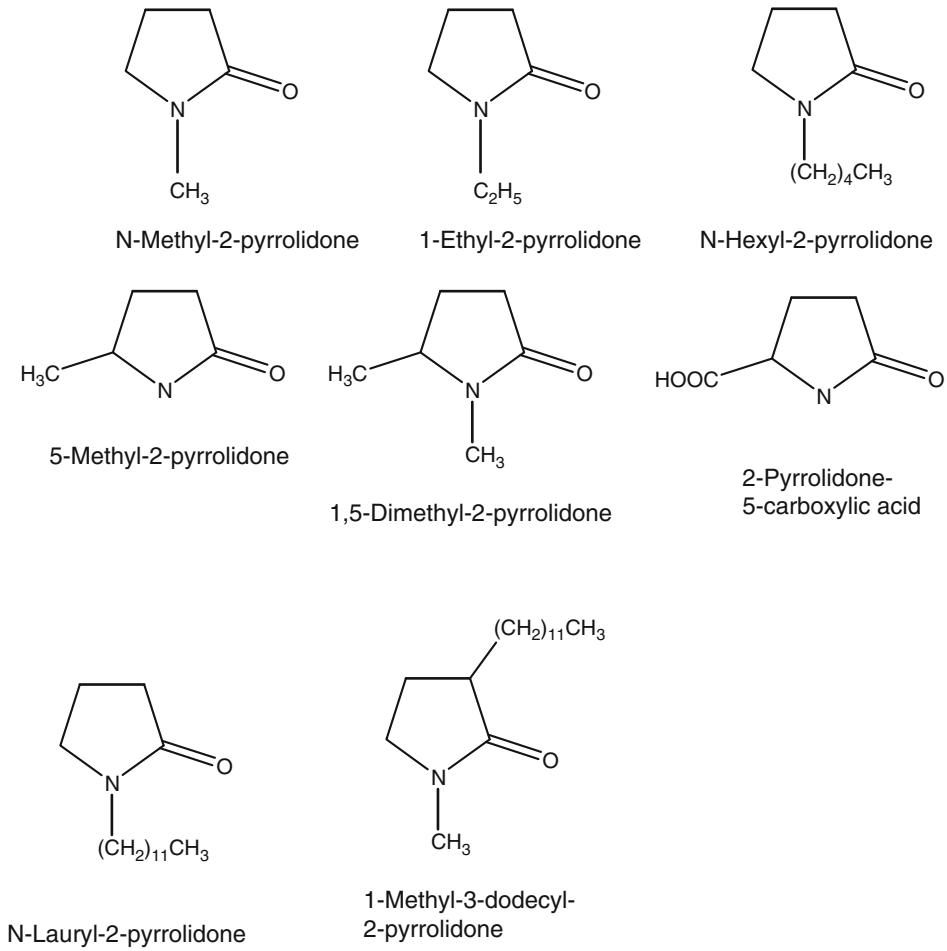

Fig. 4.2 Structural formulae of pyrrolidone enhancers

hydrocortisone have been measured using hairless mouse skin in vitro (Ghafourian et al. 2004). Enhancement ratios were calculated for the permeability coefficient [ER(kp)] and the 24-h receptor concentration ER(Q24, μM). The relationships of log ER(kp) and log ER(Q24) surface area squared (SA^2) indicate that larger pyrrolidinone derivatives are better enhancers for hydrocortisone penetration. Surface area is often correlated with hydrophobicity of molecules, and with this pyrrolidinone series, the correlation between SA^2 and log P had an r^2 value of 0.809. The correlation of log ER (kp) with log P was found to be a weak positive correlation.

4.6 Surfactants

Surfactants generally consist of a lipophilic alkyl or aryl chain with a hydrophilic head group. Surfactants may be classified according to the nature of the head group as anionic, cationic, nonionic, or zwitterionic. Surfactants have been used as skin permeation enhancers in several studies (Lopez et al. 2000; Park et al. 2000; Nokhodchi et al. 2003). In general, the penetration enhancement of drugs by surfactants is in the following order: cationic surfactants > anionic surfactants > nonionic surfactants. Ashton et al. (1992) compared the effects of dodecyl trimethyl ammonium bromide (DTAB), sodium lauryl sulfate (SLS), and polyoxyethylene fatty ether (Brij 36T™, Croda, USA) on the flux of methyl nicotinamide across excised human skin. The permeation enhancement of methyl nicotinamide was in the following order: DTAB > SLS > Brij 36 T ™. However, Brij 36 T ™ exhibited a smaller, but more immediate effect on the permeation of methyl nicotinate, resulting in the highest degree of flux enhancement over the first 24-h period. Walters et al. (1988) investigated the influence of several polyethoxylated nonionic surfactants on the transport of methyl nicotinate across hairless mouse skin in vitro. The surfactants having a linear alkyl chain greater than C8 and an ethylene oxide chain length (E) of less than E14 caused significant increases in the flux of methyl nicotinate. Surfactants having branched or aromatic moieties in the hydrophobic portion were ineffective. Maximum enhancement of flux was obtained using polyoxyethylene (10) lauryl ether (Brij 36T™). The authors proposed two possible modes of surfactant action. The surfactant may first penetrate into the intercellular regions of the stratum corneum, enhance fluidity, and solubilize and extract lipid components. Later, penetration of the surfactant into the intracellular matrix followed by interaction and binding with the keratin filaments may result in a disruption of order within the corneocyte. The structural aspect required for the latter mechanism may explain, to some extent, the maximum activity seen with the C12 surfactant.

The effect of 17 polyoxyethylene (POE) alkyl ethers on the transport of ibuprofen across rat skin was studied (Park et al. 2000). The transdermal flux through excised rat skin was found in the decreasing order of POE(5)cetyl/oleyl ether (110.24 μg/cm²/h) > POE(2) lauryl ether (99.91 μg/cm²/h) > POE(2)oleyl ether (67.46 μg/cm²/h) > POE(10)stearyl ether (66.19 μg/cm²/h). The enhancers containing the EO chain length of 2–5, hydrophilic lipophilic balance (HLB) value of 7–9, and an alkyl chain length of C16–C18 were effective promoters of ibuprofen flux.

The effects of various cationic surfactants (alkyl trimethyl ammonium halides, alkyl dimethylbenzylammonium halides, and alkyl pyridinium halides) on the permeation of radiolabeled water and lidocaine through excised human epidermis have been studied (Kushla and Zatz 1991). All surfactants increased the flux of water and lidocaine by two- to fourfold compared to the initial control period. However, there was no significant difference in the enhancing effects of these three hexadecyl derivatives. The maximum flux enhancement was observed from those derivatives with an alkyl chain length of 12–14 carbons. Cooper and Berner (1984) reported that the optimal chain length for skin barrier impairment might be attributed to the factors such as solubility of the surfactant in the donor vehicle, the critical micellar concentration, the stratum corneum-vehicle partition coefficient, and the binding affinity of the surfactant for epidermal keratin. An optimum chain length of 12–14

carbons may represent compromise between water solubility and lipophilic character. Furthermore, stratum corneum keratin may bind preferentially with carbon chains of specific length.

Cappel and Kreuter (1991) compared the enhancement potential of polysorbates 20, 21, 80, and 81. The results of these studies showed that polysorbates had a lesser effect on the transdermal permeation of methanol. Maximum permeation enhancement was achieved in the presence of polysorbates 21 and 81, which enhanced the permeation of methanol of two- to threefold, indicating that the more lipophilic polysorbates alter the barrier properties of the skin to a greater extent than their hydrophilic analogs.

Lopez et al. (2000) investigated the influence of the polar functional group on the skin permeation enhancement effects of nonionic surfactants. Their results indicated that the nature of the enhancer head group greatly influences cutaneous barrier impairment. Sorbitan monolaurate (Span®20, Croda, USA) showed greater permeation enhancement of all compounds compared to polysorbate 20 (Tween®20, Croda, USA). Ionic surfactants interact well with keratin filaments in the corneocytes and make them more permeable and increase the diffusion coefficient of the drug (Barry 2001). Surfactants may also modify peptide or protein material in the bilayer domain of the stratum corneum (Williams and Barry 1991a).

Kitagawa et al. (2001) studied the effects of the double-chained cationic surfactants dimethyldialkylammoniums (CH3)2 N+ (CnH(2n + 1))2 on the permeation of benzoic acid across excised guinea pig skin. Out of five dimethyldialkylammoniums tested ($n = 10$–18), dimethyldidecylammonium ($n = 10$) showed dose-dependent enhancement effects at concentrations of more than 20 μM. Compared with the significant enhancement effects of dimethyldialkylammoniums with relatively shorter alkyl chains, those of long-chain dimethyldialkylammoniums ($n = 16$, 18) were much less. The results suggest that dimethyldialkylammoniums with relatively shorter alkyl chains, which form either vesicles with looser molecular packing or micelles and appear to be present as surfactant monomers in higher ratios than those with longer alkyl chains, favor the interaction with the skin.

4.7 Recent Studies

Ibrahim and Li (2009) investigated the enhancement effects of a wide variety of compounds from different classes (e.g., oleic acid, octanol, oleyl alcohol, isopropyl myristate, iso-menthone, 1-octyl-2-pyrrolidone, and laurocapram) on the transdermal permeation of corticosterone across HEM. The potencies of these chemical enhancers-maximum enhancement, E_{max}, were compared at their highest thermodynamic activity in equilibrium with HEM. A relationship between the maximum intrinsic enhancement factor (E_{max}) and enhancer lipophilicity (K_{oct}) was observed with the enhancers, in which the enhancer potency decreased with increasing enhancer lipophilicity. The E_{max} versus K_{oct} relationship suggests that the potency of an enhancer is relatively independent of specific interactions between the enhancer and SC lipids. These results also suggest that the solubility of the enhancer in SC is an important factor for transdermal permeation enhancement. E_{max} of the nonalkyl chain enhancers was found to be lower than that of the alkyl chain enhancers when compared at the same lipophilicity. This study also proposed the possibility of using enhancer solubility in silicone as a predictive tool for determining the potency of an enhancer.

Iyer et al. (2007) constructed quantitative structure-activity relationship (QSAR) models for four different skin penetration enhancer data sets of 61, 44, 42, and 17 compounds using classic QSAR descriptors and 4D fingerprints. Three data sets involved skin penetration enhancement of hydrocortisone and hydrocortisone acetate, and the fourth data set involved skin penetration enhancement of fluorouracil. Significant QSAR models could be built using multidimensional linear regression fitting and genetic function model optimization for all four data sets when both classic and 4D fingerprint descriptors were used in the trial descriptor pool. Overall, the

QSAR models for the penetration enhancer systems appear meaningfully different from one another, suggesting that there were distinct mechanisms of skin penetration enhancement that depend on the chemistry of both the enhancer and the penetrant.

Golla et al. (2012) used a combination of genetic algorithms (GA) and quantitative structure-property relationship (QSPR) techniques to develop the computer-aided molecular design (CAMD) algorithm for virtual design of chemical penetration enhancers for transdermal drug delivery. The target properties of chemical penetration enhancers were identified by literature survey and analysis of their molecular properties. Using a database of 272 chemical penetration enhancers cited in the literature as seed molecules, new molecules were generated using genetic operators such as crossover, mutation, and functional group addition. QSPR models developed using artificial neural networks (ANNs) were used to predict the target physicochemical properties including skin penetration coefficient, octanol/water partition coefficient, melting point, skin sensitization, and skin irritation of the newly generated molecules. To validate the design methodology results, identified potential chemical penetration enhancers were tested experimentally for toxicity and skin permeation. Four molecules were found to be effective in enhancing insulin permeation through the skin with minimal or no toxic effects. This approach appears to have a few major drawbacks. Some of the virtually designed chemical penetration enhancers were not effective in transporting insulin through the skin, and the authors attributed this to lack of accurate knowledge of chemical penetration enhancer-drug interaction in the predesign stage. Another major impediment to experimental validation of the newly generated chemicals is the lack of commercial availability of the chemicals.

Conclusions

A large number of chemical compounds have been evaluated as skin penetration enhancers. The list of potential drugs that can be effectively delivered via transdermal route continues to increase. Structure-permeation enhancement relationship studies have significantly increased our understanding of the effect of penetration enhancers for different types of drugs. In general, a parabolic relationship between the carbon chain length of fatty acids and fatty alcohols and skin permeation enhancement has been observed with several drugs. Solid fatty acids (saturated fatty acids) had lower enhancement efficiency when compared to the liquid fatty acids (unsaturated fatty acids). Terpenes with higher LogP values were found to be more effective enhancers than those with lower LogP. With pyrrolidones, the number of carbonyl groups in the chain influenced the enhancing activity more effectively than the ring size. In general, ionic surfactants produced a greater flux of drugs than nonionic surfactants. Unfortunately, many of the penetration enhancers that showed good permeation enhancement effect also cause skin irritation (Kanikkannan and Singh 2002). The practical use of chemical penetration enhancers requires careful balancing of their benefits and risks, i.e., penetration rates and irritation. Further studies are needed in the areas of evaluation of skin permeation enhancement vis-a-vis skin irritation in order to choose penetration enhancers, which possess optimum enhancement effect with no skin irritation.

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