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REVIEW ARTICLE

Permeation Enhancers for Transdermal Drug Delivery

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ABSTRACT

The transdermal route has been recognized as one of the highly potential routes of systemic drug delivery and provides the advantage of avoidance of the first-pass effect, ease of use and withdrawal (in case of side effects), and better patient compliance. However, the major limitation of this route is the difficulty of permeation of drug through the skin. Studies have been carried out to find safe and suitable permeation enhancers to promote the percutaneous absorption of a number of drugs. The present review includes the classification of permeation enhancers and their mechanism of action; thus, it will help in the selection of a suitable enhancer(s) for improving the transdermal permeation of poorly absorbed drugs.

Key Words: *Percutaneous absorption; Permeation enhancer; Skin; Stratum corneum; Transdermal.*

INTRODUCTION

The skin is very effective as a selective penetration barrier. Percutaneous absorption involves the passage of the drug molecule from the skin surface into the stratum corneum under the influence of a concentration gradient and its subsequent diffusion through the stratum corneum and underlying epidermis, through the dermis, and into the blood circulation. The skin behaves as a passive barrier to the penetrant molecule. The stratum corneum provides the greatest resistance to penetration, and it is the rate-limiting step in percutaneous absorption.

Penetration enhancers are the substances that facilitate the absorption of penetrant through the skin by temporarily diminishing the impermeability of the skin. Ideally, these materials should be pharmacologically inert, nontoxic, nonirritating, nonallergenic, compatible with the drug and excipients, odorless, tasteless, colorless, and inexpensive and have good solvent properties. The enhancer should not lead to the loss of body fluids, electrolytes, and other endogenous materials, and skin should immediately regain its barrier properties on its removal.

No single penetration enhancer can possess all the required properties. However, many enhancers exhibit

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many of these attributes, and they have been tested in clinics or in research laboratories. Several scientists are engaged in transdermal permeation studies using various enhancers for several drug moieties. The present review is an attempt to classify the penetration enhancers and to explain the mechanism of action; this will help in selection of a proper enhancer(s) for transdermal absorption of drugs. This review discusses a few important permeation enhancers used in transdermal drug delivery.

TERPENES, TERPENOIDS, ESSENTIAL OILS

Terpenes and terpenoids are usually the constituents of volatile oil. Their chemical structure consists of repeated isoprene (C_5H_8) units and is classified according to the number of isoprene units: Monoterpenes have two isoprene units (C_{10}), sesquiterpenes have three (C_{15}), and diterpenes have four (C_{20}). Terpenes may also be classified as acyclic/linear, monocyclic, and bicyclic.

Terpenes have been utilized for a number of therapeutic purposes, such as in antispasmodics, carminatives, perfumery, and others, but a few reports also suggest their potential as percutaneous absorption enhancers (1).

L-Menthol (present in a high proportion in peppermint oil) has been shown to increase the skin absorption of testosterone by forming a eutectic mixture with the drug, thereby lowering its melting point drastically from 153.7°C to 39.9°C, as reflected by differential scanning calorimetry (DSC) studies, increasing its solubility and hence its absorption. In further studies, menthol also has been shown to increase the absorption of ceramides and cholesteryl oleate. Menthol affects skin permeation by a dual mechanism: by forming a eutectic mixture with the penetrating compound, thereby increasing its solubility, and by altering the barrier properties of the stratum corneum (2).

Hydrogel-based patches of propranolol hydrochloride were formulated with and without menthol as an enhancer (in concentrations of 1%, 5%, 10% w/v). Permeability of propranolol hydrochloride across hairless mouse skin was significantly higher from patches containing menthol. Menthol preferentially distributes into the intercellular spaces of stratum corneum and possibly causes the reversible disruption of lipid domains, thus enhancing the permeation of drugs (3).

In combination with 15% ethanol, 1-menthol (1%) increased the permeability coefficient of methyl paraben about 16 times, while it decreased that of butyl paraben to one-fifth of the control value through guinea pig dorsal skin. A spin label study with stratum corneum showed that these permeation enhancers increased the fluidity of the lipid bilayer of stratum corneum, thus enhancing the permeation of hydrophilic substances (4).

The mechanism of 1-menthol as an enhancer was examined using diclofenac as a hydrophobic drug (which permeated through the lipid pathway in the stratum corneum) and diclofenac sodium as a hydrophilic drug (which permeated through the pore pathway) through ethanol-treated and untreated silicone membranes, which are models for lipid and pore pathways of skin. Results indicated that it enhanced the permeation of both salts of the drug by both the lipid and pore pathways (5). Kobayashi et al. (6) studied the in vitro permeation of four drugs using excised hairless rat skin. Addition of 1-menthol to water and 40% ethanol improved the diffusion coefficient of morphine hydrochloride, atenolol, nifedipine, and vinpocetine in lipid and pore pathways of the stratum corneum, whereas the addition of ethanol to water and 5% menthol improved the drug solubility in the vehicle and increased the contribution of the pore pathway to whole skin permeation.

The effect of three essential oils (eucalyptus, peppermint, turpentine oil) on the permeation of 5-fluorouracil (5-FU) were studied using excised rat skin. Although all three oils enhanced the permeation of drug, their effect was less than that of azone. Eucalyptus oil was found to be the most active, causing a 60-fold increase, while peppermint and turpentine oil showed 48- and 28-fold increases, respectively. Mode of action of these enhancers may be due to a combined process of partition and diffusion, the latter being dominant (7). Some cyclic terpenes have also been investigated as penetration enhancers. Cineole, d-limonene, and α-pinene were studied using human cadaver skin for their absorption-enhancing effect on two neuroleptic drugs, chlorpromazine (CPZ) and haloperidol (8). None of the three improved the penetration profile of CPZ; d-limonene even reduced its transdermal permeation. Permeation of haloperidol was increased by both cineole and d-limonene; α-pinene provided no change in its permeation profile. Coapplication of terpenes (1,8-cineole, menthone, limonene, nerolidol) with 5-FU, both at saturation, in a propylene glycol (PG)/water cosolvent system increased drug flux significantly (9). Terpene activity depended on PG content, with maximum flux obtained with formulations containing 80% PG. A dual mechanism of permeation was proposed, one due to increased lipid disruption in the stratum corneum by terpenes and the second due to the increased drug partitioning contributed by the high PG content.

Eucalyptol (1,8-cineole) increased the flux of indomethacin (lipophilic) and urea (hydrophilic) to a great extent through full-thickness rat skin (10). A high concentration (10% eucalyptol) is needed to increase the permeation of low molecular weight heparin-enoxaparin sodium across human skin (11). Flux of haloperidol from methylcellulose gel formulation increased 6.16-fold across rabbit skin when cineole was included in the formulation (12).

Percutaneous permeation of ketoprofen was investigated from two systems containing d-limonene and oleic acid. Percutaneous absorption was higher with d-limonene, but it also produced greater skin damage (13). In the case of verapamil hydrochloride, a higher concentration of d-limonene (20%) was effective in enhancing its permeation significantly (14).

The acetone extract of *Amomum cardamomum* and *Elettaria cardamomum* produced the best effect in enhancing the penetration of indomethacin and prednisolone across rabbit skin. Further studies revealed that the increase in permeation was due to the presence of the monoterpenes terpineol and acetyl terpineol (15,16). The penetration index of piroxicam from piroxicam gel after 1 hr pretreatment with 10% cardamom oil in alcohol/pH 7.4 buffer was 340.9 times higher than that from untreated rabbit abdominal skin (17).

Long-chain sesquiterpene nerolidol in a 2% concentration produced a twofold increase in the permeation of enoxaparin sodium (11). Another unsaturated sesquiterpene, α-bisabolol was studied for its permeation enhancement properties on model compounds 5-FU and triamcinolone acetonide using human skin samples. Skin pretreated with bisabolol in PG was 17 times more permeable to 5-FU and 73 times more permeable to triamcinolone compared to untreated skin due to increased lipid fluidity of stratum corneum (18).

PYRROLIDONES

Pyrrolidones and their derivatives have great potential to be used as transdermal permeation enhancers. The most common *N*-methyl-2-pyrrolidone (NMP) has been used widely to enhance the skin absorption of many drugs, for example, insulin (19), ibuprofen, and flurbiprofen (20). By the use of NMP, the flux of the anti-inflammatory drug ibuprofen increased 16 times and that of flurbiprofen increased 3 times through cadaver skin. Kim and Chien (21,22) studied the effect of NMP on the skin permeation of the anti-HIV drugs zalcitabine, didanosine, and zidovudine using hairless rat skin at 37°C. Addition of 1% v/v of NMP in ethanol : tricaprylin (TCP) (50 : 50) cosolvent system could not significantly increase the permeation rate of these drugs. Addition of viscous TCP probably reduced the thermodynamic activity of the enhancer to distribute from the vehicle to the skin. NMP enhanced the permeation of anti-inflammatory drugs like ketoprofen through mouse skin (23) and produced satisfactory analgesic and antiphlogistic effects pharmacodynamically, suggesting effective blood levels of ibuprofen had been reached (24).

2-Pyrrolidone and NMP were assessed in enhancing the topical bioavailability of a model steroid betamethasone-17-benzoate, using dimethylisosorbide (DMI) as the standard solvent. Pyrrolidones produced higher stratum corneum reservoirs compared with DMI, but because of their irritation potential, they are less preferred clinically (25).

The influence of skin permeation of various enhancers prepared from 2-pyrrolidone containing a short alkyl group at the 1 position and a dodecyl group at the 3 position of the pyrrolidone ring was studied. The length of the short alkyl group at the 1 position considerably influenced the enhancing activity. 1-Propyl and 1-butyl-3-dodecyl-2-pyrrolidone showed the effective enhancement of penetration of indomethacin through the skin in 60 wt% ethanolic solution (26). Effects of 1-ethyl, 1-butyl, 1-hexyl, 1-octyl-2-pyrrolidone were tested on transport of steroids like β-estradiol, hydrocortisone, and corticosterone across hairless mouse skin. It was found that there was a 3.5-fold increase in enhancement potency per methylene group introduced at the 1-N position. A semilog linear relationship was shown between enhancement potency and carbon number of alkyl chain. This result suggests that the enhancer action resides in the alkyl group (27).

In general, 2-pyrrolidone enhances the transdermal permeation of caffeine through polar routes of skin by increasing its diffusivity and reduces the passage through the nonpolar route by decreasing diffusivity and partitioning (28). One of its derivatives, *N*-dodecyl-2-pyrrolidone, has been shown to increase the permeability coefficient of hydrophilic methyl paraben about seven times while decreasing that of butyl paraben. Perturbation of stratum corneum lipid lamellae seems to be related to the enhancement of absorption of hydrophilic paraben (4). Fatty acid esters of *N*-(2-hydroxyethyl)-2-pyrrolidone (HEP) produced a twofold increase in permeation of hydrocortisone through mouse skin (29). The ester linkage was cleaved by the hydrolytic enzymes of plasma and skin homogenates.

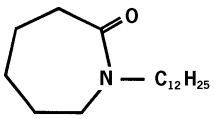

Figure 1. Azone.

Azone (1-dodecylazacycloheptan-2-one) (Fig. 1) forms one of the major classes of percutaneous permeation enhancers. It has been reported that the choice of solvent is very important while using azone as a permeation enhancer. When azone was used in combination with PG, the flux of methotrexate (30) and piroxicam (31) increased significantly. Patches containing 0.05% w/v of cyclosporin A, an otherwise nonimmunosuppressive concentration, also showed good immunosuppression when azone was included in PG (32).

Flux of edatrexate across hairless mouse skin was enhanced when laurocapram was used in isopropyl alcohol (30). Azone (2%) in PG promoted the absorption of 5-FU by almost 100-fold, but in combination with Tween 20, the effect was less pronounced (33). Azone in combination with PG greatly increased the permeation of the polar compound mannitol, but had a moderate effect on the permeation of hydrocortisone, a relatively nonpolar steroid. It proved to be a poor enhancer for the nonpolar steroid progesterone, with a high partition coefficient through human skin (34).

Mura et al. (35) investigated the effect of several enhancers on clonazepam permeation from Carbopol hydrogel through a cellulose nitrate membrane. Maximum drug release was obtained from formulations containing clonazepam and methyl β-cyclodextrin in a vehicle composed of water, PG, Tween 80, and azone.

Azone alone enhances the skin permeation of a wide variety of drugs, like indomethacin, urea, methadone, 5-FU, propranolol hydrochloride (10,36,37). It produced 3.56-fold enhancement in the permeation of haloperidol from its gel formulations through rabbit skin (12). Singh et al. (38) reported that ephedrine patches containing laurocapram showed an increased flux of ephedrine through rat skin and epidermis with a reduced time lag.

Azone is less effective than oleic acid in increasing the transdermal permeation of amino acids through hairless mouse skin (39). But, in the case of insulin, the enhancement is almost double that produced by dodecyl-L-pyroglutamate (19). Compared with terpenes, azone is the most effective penetration enhancer for low molecular weight heparin across human skin. The enhancing power of enhancers decreased in the order laurocapram > nerolidol > eucalyptol (11).

An experiment on transdermal permeation of β-blockers revealed that azone possesses lipid-fluidizing ability and shows a strong facilitating effect on drug permeation (40). It has no direct effect on the stratum corneum proteins; rather, it increases the moisture content in the stratum corneum (41). Laurocapram dramatically alters the lipid structure of stratum corneum, but it does not interact with proteins. It is directly partitioned into the lipid bilayer, disrupting it, increases its fluidity, and hence promotes drug penetration. Azone is always more effective when used in combination with PG. PG promotes intracellular transport, while azone improves intercellular drug transport. Azone/PG increase penetration through the stratum corneum by affecting both the hydrophilic and lipophilic routes of penetration. Azone increases the fluidity of the lipid layer, while PG increases the water content of the proteinaceous region and helps azone partition into the aqueous region. A combination of these two helps the penetration of hydrophilic drugs greatly (42).

The chemical structure of azone is considered to be a hybrid of two potent permeation enhancers—pyrrolidone and decylmethylsulfoxide. The polar ring and the long alkyl chain present at position 1 are necessary for its action. By replacing this long alkyl chain by an alkenyl (terpene) chain, four new analogues (i.e., 1-geranylazacycloheptan-2-one [GAH], 1-farnesylazacycloheptan-2-one [FAH], 1-geranylazacyclopentan-2,5-dione [GAPD], and 1-farnesylazacyclopentan-2-one [FAP]) (Fig. 2) were tested on the percutaneous permeation of mitomycin C through hairless mouse and rat skin.

Experimental results revealed that GAH, FAH, FAP, and azone enhanced the permeation of mitomycin C 20 to 60 times that of the control (ethanol). The enhancing

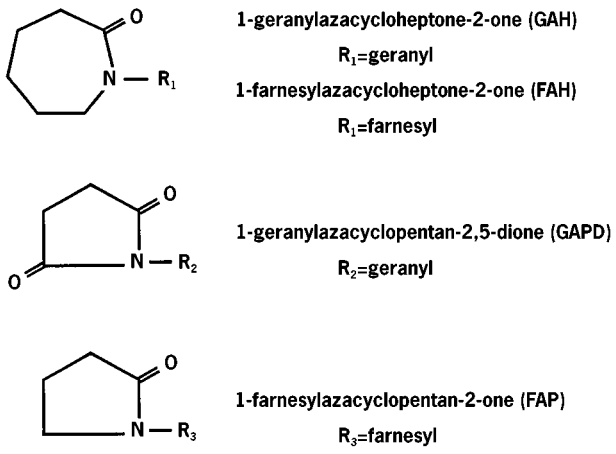

Figure 2. Structures of GAH, FAH, GAPD, and FAP.

effect with GAPD was only half of that of the other compounds, thereby dictating the importance of the polar group in the ring moiety on the potency of a compound as a penetration enhancer (43). Derivatives with a C-10 carbon terpene chain and an azacyclo ring with one carbonyl group reveal good enhancing effects. An increase in the length of the terpene chain and the number of carbonyl groups in the compound decreases the activity. Derivatives with an alkyl chain induce more severe primary irritation than those with an alkenyl chain; so, GAH, FAH, and FAP are the favorable enhancers, with a balance between enhancing and irritating activities (44).

Azone derivatives with varying azacyclo ring nucleus (keeping the side alkyl chain constant) were investigated for their permeation enhancer properties on six drugs with varying lipophilicities across full-thickness hairless mouse skin. *N*-Dodecyl-2-pyrrolidinone and *N*-dodecyl-2-piperdinone were most effective for hydrophilic drugs, and the least effective was 2-(1-nonyl)-1,3-dioxolane (42).

FATTY ACIDS AND ESTERS

A large number of fatty acids and their esters have been used as permeation enhancers. A general trend has been seen that unsaturated fatty acids are more effective in enhancing percutaneous absorption of drugs than their saturated counterparts. Chi et al. (45) reported an increase of 6.5-fold to 17.5-fold in the permeation rate of flurbiprofen through rat skin by unsaturated fatty acids, while no significant increase was observed with saturated fatty acids. Moreover, they have a greater enhancing effect on lipophilic drugs.

When Carbomer 934P was used for making a patch, the maximum flux of ketoprofen was obtained with 35% of oleic acid, while for Carbomer 940, 10% oleic acid produced maximum flux through full-thickness human skin (46). Moreover, oleic acid proved to be the best enhancer among azone, NMP, and PG for the permeation of ketoprofen (23). Permeation of another nonsteroidal anti-inflammatory drug (NSAID) was improved by the action of oleic acid and urea (45). Oleic acid in PG was markedly successful in increasing the permeation rate of 5-FU and estradiol through human skin. Results suggested that oleic acid remained in tissues for longer periods (33). Oleic acid (3%) was successful in enhancing the flux of the tetrapeptide melanotropin-hisetal across hairless mouse skin and human skin, but enhancement across human skin was much less (47,48). In the case of organophosphate poisoning, a patch of propionic acid and oleic acid (50:50) produced greater transdermal delivery of physostigmine than propionic acid alone (49).

Addition of oleic acid to an ethanol:water (50:50) cosolvent system markedly improved the skin permeation of zalcitabine, didanosine, and zidovudine, whereas addition of the same to ethanol:TCP (50:50) produced no enhancement across hairless rat skin. It was suggested that viscous TCP reduced the thermodynamic activity of oleic acid (22). Oleic acid was found to be the most efficient enhancer for piroxicam, followed by linoleic acid (50). Sodium oleate was found to be a better permeation enhancer than oleyl oleate when tested on indomethacin and urea (10).

Increased flux of metaproteronol sulfate was obtained when lauric acid was used. It increased both the partition coefficient and diffusivity of drug in skin (51). When lauric acid was added to an ethanol:water (60:40) system, the skin absorption of tegafur, alclofenac, and ibuprofen was increased (52). Capric acid, lauric acid, and neodecanoic acid were tested for their activity on naloxone, testosterone, benzoic acid, indomethacin, 5-FU, and methotrexate (53). All three fatty acids increased the skin diffusivity of naloxone, testosterone, indomethacin, and 5-FU through human skin. Capric acid also increased the diffusivity of PG, suggesting that increased solvent penetration could also be involved as a mechanism for increased skin absorption of the drug. These studies suggested that drug solubilization in the vehicle, increased partitioning, increased solvent penetration, and barrier disruption each can contribute to enhanced skin permeation rates in the presence of fatty acids. Myristic acid in combination with PG increased the permeation of oxymorphone through hairless guinea pig skin (54).

The fatty acid extract of cod liver oil was found to be as good a permeation enhancer as oleic acid. The most effective transdermal penetration enhancer was palmitoleic acid, which resulted in a 640-fold increase in hydrocortisone flux through hairless mouse skin. Incorporation of pure cod liver oil in a PG vehicle did not improve the hydrocortisone permeability, suggesting that the unsaturated fatty acids have to be in the free form to be able to act as skin permeation enhancers (55). A 1-hr pretreatment of rabbit abdomen skin with 10% oleic acid in PG greatly enhanced the absorption of piroxicam from its gel (56).

SULFOXIDES AND SIMILAR COMPOUNDS

Dimethyl sulfoxide (DMSO), the most important compound belonging to the category of sulfoxides and

similar compounds, enhances the transdermal permeation of a variety of drugs, like β-blockers, ephedrine hydrochloride, and papaverine hydrochloride (38,40,57). It also enhances the release of azapropazone from its ointments (58). Fourier transform Raman spectroscopic studies revealed that DMSO changes the stratum corneum keratin from alpha-helical to β-sheet conformation. At concentrations greater than 60% v/v, at which DMSO enhances the flux, there was evidence of its interaction with stratum corneum lipids. It also produces alteration in protein structure, but may also be related to alterations in stratum corneum organization besides any increased drug-partitioning effect (59). In a study by Clancy et al. (60) using attenuated total reflectance–Fourier transform infrared (ATR-FTIR) and DSC, it was confirmed that DMSO treatment (of human skin) causes extensive lipid extraction and stratum corneum protein denaturation. DMSO showed a negligible enhancing effect on the diffusion of piroxicam (31). It was also found to be less effective than lauryl chloride in increasing the flux of timolol maleate through human skin (61).

Decylmethyl sulfoxide (DCMS) in combination with ethanol increased the flux of oxymorphone hydrochloride (54). A 4% aqueous solution of DCMS increased the permeation of 5-FU 35 times across human skin, but it was rapidly washed out of the tissues (33).

Various compounds of category *N*,*N*-dimethylamides also possess penetration-enhancing power and are also structurally related to sulfoxides. *N*,*N*-Dimethylformamide promotes absorption through the polar route by increasing both the diffusion and the partitioning of drug. It increases the permeation of caffeine (human skin) and ephedrine hydrochloride (rat skin and human epidermis) (28,38). Dimethylacetamide (DMA) enhances the permeation of indomethacin from creams and ointments in rats (62). *N*,*N*-Dimethyloctanamide and *N*,*N*-dimethyldecanamide were found to be the effective enhancers of the NSAIDs ibuprofen and naproxen from 50% aqueous PG vehicles across rat skin (63).

ALCOHOLS, GLYCOLS, AND GLYCERIDES

Ethanol is the most commonly used alcohol as a transdermal penetration enhancer. It increases the permeation of ketoprofen from a gel-spray formulation (64) and triethanolamine salicylate from a hydrophilic emulsion base (65). It also acts as a vehicle for menthol in increasing the penetration of methyl paraben (4).

Ethanol in combination with TCP and with water were used as two cosolvent systems for zalcitabine, didanosine, zidovudine, tegafur, alclofenac, and ibuprofen. The permeation rate of zalcitabine, didanosine, and zidovudine increased as the volume fraction of ethanol in the two cosolvent systems was increased, and it reached a maximum at 50–60% v/v of ethanol (22). Flux of tegafur, alclofenac, and ibuprofen was higher from the ethanol-water cosolvent system than from the ethanol-TCP system (52).

Ethanol acts as a penetration enhancer by extracting large amounts of stratum corneum lipids. It also increases the number of free sulphydryl groups of keratin in the stratum corneum proteins. Usually, pretreatment of skin with ethanol increases the permeation of hydrophilic compounds, while it decreases that of hydrophobic ones (41).

PG promoted the flux of heparin sodium (66), verapamil hydrochloride (67), and ketoprofen, but at higher concentrations, it inhibited the flux of ketoprofen (23). A saturated solution of terpenes in a PG-water cosolvent system enhanced the flux of 5-FU, terpene activity being dependent on PG content and with the maximum flux obtained from formulations containing 80% PG. Also, PG increases drug partitioning and drug permeation (9). PG, in combination with azone, increases the flux of methotrexate (30), piroxicam (31), cyclosporin A (32), and 5-FU (33). Flux of estradiol was 10 times higher when PG was used in conjunction with 5% oleic acid (33). Urea analogues were effective in enhancing the permeation of 5-FU only when PG was used as a vehicle (68).

PG solvates the keratin of the stratum corneum, occupying the hydrogen bonding sites. When it is used in combination with azone, large amounts of glycol enter the tissue and promote intracellular diffusion of drugs (42).

The effect of *n*-alkanols on a hairless mouse skin barrier and the transdermal permeation of nicotinamide were examined. It was seen that the flux of drug increased with increasing carbon chain length up to six carbon atoms. These alcohols promote skin permeation of drugs by causing lipid extraction from the stratum corneum (69). Flux of propranolol hydrochloride was increased 8.2-fold by 1-nonanol (70), and octyl alcohol was efficient in increasing the permeation of urea (10). Of the fatty alcohols tested, lauryl alcohol increased the transdermal permeation of propranolol hydrochloride, timolol maleate, ibuprofen, acetaminophen, and 5-FU (50,71,72). Lauryl alcohol is most effective in enhancing the permeation of drugs with greater hydrophilicities and large molecular size (73). Dodecyl alcohol (lauryl alcohol) acts by dis-

rupting the lipoidal bilayer. By changing the hydrophilic end of the chain, the duration of action can be changed remarkably (74).

Short-chain glycerides are also effective as permeation enhancers (e.g., TCP). For instance, glycerin tricaprylate (caprylic acid triglyceride) in combination with ethanol is used as a solvent system (22,52). TCP is an excellent hydrophobic vehicle and promoted the permeability of tegafur combined with ethanol (75). Glyceryl monocaprylate enhanced the partitioning of papaverine across hairless rat skins (76). Sefsol 318, a medium-chain glyceride, increased the permeation of papaverine hydrochloride by almost 820 times by increasing the fluidity of the lipoidal membrane of the stratum corneum (77).

MISCELLANEOUS ENHANCERS

Phospholipids

Phosphatidyl glycerol derivative increased the accumulation of bifonazole in skin and the percutaneous penetration of tenoxicam; phosphatidyl choline derivatives promoted the percutaneous penetration of erythromycin (78). Six phosphatidyl glycerol derivatives (PGE [from egg yolk], PGS [from soyabean], dimyristyl phosphatidyl glycerol [DMPG], dipalmityl phosphatidyl glycerol [DPPG], distearyl phosphatidyl glycerol [DSPG], dioleyl phosphatidyl glycerol [DOPG] derivatives); five phosphatidyl choline (PC) derivatives (PCS [from soyabean], PCE [from egg yolk], dioleyl PC [DOPC], dilinoleoyl PC [DLPC], hydrogenated PC [HPC]); and two phosphatidyl ethanolamine derivatives were studied using indomethacin. Results suggest that phospholipids containing unsaturated fatty acids in the hydrophobic group are strong permeation enhancers for percutaneous delivery of some topically applied drugs (79).

Lipid Synthesis Inhibitors

The barrier layer (i.e., stratum corneum) consists of a mixture of cholesterol, free fatty acids, and ceramides, and these three classes of lipids are required for normal barrier function. Addition of inhibitors of lipid synthesis enhances the delivery of some drugs like lidocaine and caffeine. Fatty acid synthesis inhibitors like 5-(tetradecyloxy)-2-furancarboxylic acid (TOFA) and the cholesterol synthesis inhibitors fluvastatin (FLU) or cholesterol sulfate (CS) delay the recovery of barrier damage produced by prior application of penetration enhancers like DMSO, acetone, and the like. It was concluded that modulation of lipid biosynthesis following the application of conventional chemical penetrant enhancers causes a further boost in the transdermal permeation (80).

Cyclodextrin Complexes

Cyclodextrin complexes of a number of drugs have been formed, and such a combination usually enhances the permeation of drugs. For instance, an inclusion complex of piroxicam with β-cyclodextrin increased the drug flux three times across hairless mouse skin (31), and a similar complex of clonazepam with methyl-β-cyclodextrin improved its release profile from Carbopol hydrogel through cellulose nitrate membrane (35).

In solution, cyclodextrin forms a complex with enhancers like quaternary ammonium salts and shifts their critical micellar concentration to higher values, thereby decreasing the toxic effect of such enhancers (81). Transdermal absorption of alprostadil (AP) from its β-cyclodextrin complex and *O*-carboxymethyl-*O*-ethyl-β-cyclodextrin (CME-β-CD) complex was compared across hairless mouse skin. HPE-101 (1-[2-(decylthio)ethyl] azacyclopentan-2 one) was included as a permeation enhancer in both cases. Flux from the latter complex was 10 times higher than from the former one. It was concluded that a combination of CME-β-CD and HPE-101 enhances the topical bioavailability of the drug (82).

Amino Acid Derivatives

Various amino acid derivatives have been investigated for their potential in improving percutaneous permeation of drugs. *N*-Dodecyl-L-amino acid methyl ester and *n*-pentyl-*N*-acetyl prolinate were studied. Application of these two enhancers on excised hairless mouse skin 1 hr prior to drug treatment produced greater penetration of hydrocortisone from its suspension (83). *n*-Pentyl-*N*-acetyl prolinate also enhances the flux of benzoic acid across human cadaver skin; it is nontoxic at low doses, but at higher doses produces dose-dependent central nervous system toxicity (84). Esters of omega amino acids like octyl-6-aminohexanoate and decyl-6-aminohexanoate enhanced the transdermal permeation of theophylline in aqueous and oily vehicles, respectively (85).

The effectiveness of the biodegradable penetration enhancer dodecyl *N*,*N*-dimethylamino isopropionate (DDAIP; dodecyl-*N*,*N*-dimethyl-L-alanine) was compared to dodecyl-*N*,*N*-dimethylamino acetate (DDAA), azone, and other known permeation enhancers. DDAIP showed a dose-dependent increase in the flux of 5-FU. Also, DDAIP produced better enhancement than DDAA

and azone (72). It increased the transdermal flux of indomethacin (86). Hydrogen bonding and dipole-dipole interactions were reported between the drug and DDAIP.

Clofibric Acid

Esters and amides of clofibric acid were studied for their permeation-enhancing property using nude mice skin. The best enhancement of hydrocortisone-21 acetate and betamethasone-17-valerate was observed with clofibric acid octyl amide when applied 1 hr prior to each steroid. Amide analogues are generally more effective than ester derivatives of the same carbon chain length (87).

Dodecyl-*N*,*N*-Dimethylamino Acetate

DDAA increased the transdermal permeation of a number of drugs, like propranolol hydrochloride and timolol maleate. It was found to be as effective an enhancer as azone, but it possesses an advantage over azone: Skin irritation with DDAA is reversed in a short time compared to azone (88). DDAA also increased the transdermal flux of 5-FU through snakeskin. Moreover, substitution of one of the hydrogen atoms of the acetate moiety with a methyl group greatly increased its penetration power (72). The increase in the flux of tetrapeptide-hisetal by DDAA was 1.5-fold more than azone across hairless mouse skin. The permeability-enhancing effect was due to changes in the lipid structure of the stratum corneum, like azone and oleic acid (47). The improvement in transdermal permeation of sotalol by DDAA was the same as that produced by iontophoresis (89). DDAA causes the disruption of the lipoidal bilayer of the stratum corneum. Its duration of action is shorter than that of azone and dodecyl alcohol because of the presence of hydrophilic groups (74). So, there is faster recovery of the skin structure and hence less irritation potential. It also exerts a hydrating effect on the skin (90).

Enzymes

Due to the importance of the phosphatidyl choline metabolism during maturation of the barrier lipids, the topical application of the phosphatidyl choline–dependent enzyme phospholipase C produced an increase in the transdermal flux of benzoic acid, mannitol, and testosterone. Three epidermal enzymes (triacylglycerol hydrolase [TGH], acid phosphatase, phospholipase A2) were also studied for their effect. Acid phosphatase was ineffective, TGH increased the permeation of mannitol, while phospholipase A2 increased the flux of both benzoic acid and mannitol (91).

Pretreatment of skin with papain produced reversible alterations in the protein structure of the stratum corneum. These alterations resulted in increased permeation of proteins of various molecular weights, with the effect decreasing with increasing molecular weight (92).

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