

Percutaneous absorption in diseased skin: an overview

Audris Chiang,* Emilie Tudela and Howard I. Maibach

ABSTRACT: The stratum corneum's (SC) functions include protection from external hazardous environments, prevention of water loss and regulation of body temperature. While intact skin absorption studies are abundant, studies on compromised skin permeability are less common, although products are often used to treat affected skin. We reviewed literature on percutaneous absorption through abnormal skin models. Tape stripping is used to disrupt water barrier function. Studies demonstrated that physicochemical properties influence the stripping effect: water-soluble drugs are more affected. Abrasion did not affect absorption as much. Freezing is commonly used to preserve skin. It does not seem to modify water absorption, but still increases the penetration of compounds. Comparatively, heating the skin consistently increased percutaneous absorption. Removing SC lipids may increase percutaneous absorption of drugs. Many organic solvents are employed to delipidize. Delipidization with chloroform-methanol increased hydrophilic compound permeability, but not lipophilic. Acetone pre-treatment enhanced hydrophilic compound penetration. More data is needed to determine influence on highly lipophilic compound penetration. Sodium lauryl sulfate (SLS) induces irritant dermatitis and is frequently used as a model. Studies revealed that SLS increases hydrophilic compound absorption, but not lipophilic. However, skin irritation with other chemicals increases lipophilic penetration as much as hydrophilic. Animal studies show that UV exposure increases percutaneous absorption whereas human studies do not. Human studies show increased penetration in psoriatic and atopic dermatitis skin. The data summarized here begin to characterize flux alteration associated with damaged skin. Understanding the degree of alteration requires interpretation of involved conditions and the enlarging of our database to a more complete physicochemical spectrum. Copyright © 2012 John Wiley & Sons, Ltd.

Keywords: percutaneous penetration; absorption; damaged skin; hydrophilic; human

INTRODUCTION

The stratum corneum (SC) has important functions such as host protection from foreign chemicals, water loss prevention, and body temperature regulation. While skin absorption studies on healthy intact skin are abundant, data on permeability of chemicals in compromised skin are less common. Many drugs are used to treat skin diseases where the cutaneous barrier is damaged and it is likely that the pharmacokinetics and pharmacodynamics of such drugs would be modified. Thus it is important to obtain well-characterized models to characterize percutaneous absorption through diseased skin.

MATERIALS AND METHODS

We review percutaneous absorption through abnormal skin based on data in the literature. The medical literature was searched using the medical database Pubmed, utilizing the subjects 'skin' and 'absorption' combined with various descriptions of compromised skin ('tape strip', 'abrasion', 'frozen', 'burn', 'delipidized', 'irritated', 'diseased', etc.). In almost all instances in the literature, the damage preceded the application of the described penetrant. Authors typically provided either K_p or percentage dose absorption (see tables). Except where stated to the contrary, dosing was finite. As a model, some used damaged animal or human skin, utilizing *in vivo* or *in vitro* methods, whereas others studied clinical diseases, such as psoriasis and atopic dermatitis. The clinical relevance of this data, in terms of its toxicologic impact, mandates that these

alterations in penetration be accounted for in terms of blood and intra-organ exposure.

MECHANICAL DAMAGE: TAPE STRIPPING, ABRASION

Tape Stripping

The SC is a major skin protective barrier; consequently its removal should, in theory, increase percutaneous drug absorption. Tape stripping is a common method used to increase transepidermal water loss (TEWL) by mechanical damage. In older studies, the degree of SC removal was given as number of strips, or as glistening, indicating removal of the water barrier. Today, SC removal can be quantified with protein and related assays (Dreher *et al.*, 1998). Standard stripping methods are discussed by Löffler (Löffler *et al.*, 2004). Table 1 summarizes tape-stripped absorption studies based on degree of penetration compared with normal skin.

Feldmann and Maibach (1965) studied the effect of stripping and occlusion on penetration of hydrocortisone ($4 \mu\text{g cm}^{-2}$) in human forearm *in vivo*. Percentages of applied dose recovered

*Correspondence to: A. Chiang, University of California Medical School, San Francisco, CA 94143-0989, USA.
E-mail: audrischiang@berkeley.edu

University of California Medical School, San Francisco, CA, 94143-0989, USA

Table 1. Summary of literature in absorption studies in tape-stripped or abraded skin

Disease model	<i>In vivo/vitro</i>	Skin	Method	Penetrant	Result	Author	Year
TS (NM)	<i>In vivo</i>	Human	Urine	¹⁴ C-HC	x2	Feldmann and Maibach	1965
TS (NM)	<i>In vivo</i>	Human	Urine	Azodrin	x14	Maibach and Feldmann	1974
TS (NM)	<i>In vivo</i>	Human	Urine	Baygon	x3	Maibach and Feldmann	1974
TS (NM)	<i>In vivo</i>	Human	Urine	Diquat	x10	Maibach and Feldmann	1974
TS (NM)	<i>In vivo</i>	Human	Urine	2,4-D	x6	Maibach and Feldmann	1974
TS (NM)	<i>In vivo</i>	Human	Urine	Guthion	x4	Maibach and Feldmann	1974
TS (NM)	<i>In vivo</i>	Human	Urine	Parathion	x9	Maibach and Feldmann	1974
TS (NM)	<i>In vitro</i>	Human	Flux, K_p	Angiotensin II (infinite dose study)	↑ (x25–69)	Akomeah <i>et al.</i>	2008
TS (NM)	<i>In vitro</i>	Human	Flux, K_p	Butyl paraben	x3	Akomeah <i>et al.</i>	2008
TS (NM)	<i>In vitro</i>	Human	Flux, K_p	Caffeine	x19	Akomeah <i>et al.</i>	2008
TS (NM)	<i>In vitro</i>	Human	Flux, K_p	Methyl paraben	x5	Akomeah <i>et al.</i>	2008
TS (3–10)	<i>In vitro</i>	Mouse	Diffusion cells	PEGs	↑ (MW cut-off)	Tsai <i>et al.</i>	2003
TS (4–5)	<i>In vitro</i>	Mouse	Diffusion cells	PEGs	↑ (MW cut-off)	Tsai <i>et al.</i>	2001a
TS (8)	<i>In vivo</i>	Guinea pig	PPIX-fluo	ALA	↑	Goff <i>et al.</i>	1992
TS (10)	<i>In vivo</i>	Rat	Microdialysis	SA	x20	Benfeldt	1999
TS (12)	<i>In vivo</i>	Rat	Diffusion cells	³ H ₂ O	x20	Bronaugh and Stewart	1985
TS (12)	<i>In vitro</i>	Human	Diffusion cells	³ H ₂ O	x20	Bronaugh and Stewart	1985
TS (12)	<i>In vitro</i>	Rat	Diffusion cells	³ H-Cort, ¹⁴ C-NA	x2.5, x11	Bronaugh and Stewart	1985
TS (15)	<i>In vitro</i>	Rat	Diffusion cells, K_p	³ H ₂ O	↑	Scott <i>et al.</i>	1986
TS (15)	<i>In vitro</i>	Rat	Diffusion cells, K_p	³ H ₂ O	↑	Scott <i>et al.</i>	1986
TS (15)	<i>In vivo</i>	Rat	Chamber, TEWL	H ₂ O	↑	Scott <i>et al.</i>	1986
TS (15)	<i>In vivo</i>	Guinea pig	Urine	¹⁴ C-BA	x2.1	Moon <i>et al.</i>	1990
TS (15)	<i>In vivo</i>	Guinea pig	Urine	¹⁴ C-HC	x3	Moon <i>et al.</i>	1990
TS (15)	<i>In vitro</i>	Mouse	Diffusion cells	ALA	x100	Van den Akker <i>et al.</i>	2003
TS (15)	<i>In vitro</i>	Mouse	Diffusion cells	ALAHE	x200	Van den Akker <i>et al.</i>	2003
TS (15)	<i>In vitro</i>	Mouse	Diffusion cells	ALAME	x200	Van den Akker <i>et al.</i>	2003
TS (20)	<i>In vivo</i>	Mouse	PPIX-fluo	ALA	↑	Van den Akker <i>et al.</i>	2000b
TS (20)	<i>In vivo</i>	Mouse	PPIX-fluo	ALAHE	↑	Van den Akker <i>et al.</i>	2000b
TS (20)	<i>In vivo</i>	Mouse	PPIX-fluo (CS)	ALA	↑	Van den Akker <i>et al.</i>	2002
TS (20)	<i>In vivo</i>	Mouse	PPIX-fluo (CS)	ALAHE	↑	Van den Akker <i>et al.</i>	2002
TS (20)	<i>In vivo</i>	Rat	Plasma	Bucladesine	—	Van den Akker <i>et al.</i>	2002
TS (20)	<i>In vivo</i>	Human	Urine, plasma	¹⁴ C-MPA	↑	Mafune <i>et al.</i>	1995
TS (20)	<i>In vivo</i>	Rat	Microdialysis	SA (in absorptive ointment)	x30	Günther <i>et al.</i>	1998
TS (20)	<i>In vivo</i>	Rat	Microdialysis	SA (in hydrophilic poloid)	x0.8	Murakami <i>et al.</i>	1998
TS (20)	<i>In vivo</i>	Rat	Microdialysis	SA (in poloid)	x2.0	Murakami <i>et al.</i>	1998
TS (20)	<i>In vivo</i>	Rat	Microdialysis	SA (in solbase)	x1.6	Murakami <i>et al.</i>	1998
TS (20)	<i>In vivo</i>	Rat	Microdialysis	SA (in white petrolatum)	x46.2	Murakami <i>et al.</i>	1998
TS (20)	<i>In vivo</i>	Rat	Microdialysis	BA, alkyl-BA	x1.0	Murakami <i>et al.</i>	1998
TS (20)	<i>In vitro</i>	Guinea pig	Diffusion cells	SA	↑	Kitagawa and Li	1999
TS (20)	<i>In vivo</i>	Human	Microdialysis	KT	x157	Benfeldt <i>et al.</i>	1999
TS (20)	<i>In vitro</i>	Mouse	Diffusion cells	¹⁴ C- <i>n</i> -butanol	x22	Inoue <i>et al.</i>	2000
TS (25)	<i>In vitro</i>	Mouse	Diffusion cells	¹⁴ C-ethanol	x15.7	Behl <i>et al.</i>	1982
TS (25)	<i>In vitro</i>	Mouse	Diffusion cells	³ H-H ₂ O	x148.3	Behl <i>et al.</i>	1982
TS (25)	<i>In vitro</i>	Mouse	Diffusion cells	³ H-H ₂ O	x323	Behl <i>et al.</i>	1982

TS (25)	<i>In vitro</i>	Mouse	Diffusion cells	¹⁴ C-hexanol	x7.8	↑	Behl <i>et al.</i>	1982
TS (25)	<i>In vitro</i>	Mouse	Diffusion cells	³ H-methanol	x134.7	↑	Behl <i>et al.</i>	1982
TS (25)	<i>In vitro</i>	Mouse	Diffusion cells	¹⁴ C-octanol	x2.1	↑	Behl <i>et al.</i>	1982
TS (25)	<i>In vitro</i>	Rat	Diffusion cells	Diclofenac	↑	↑	Takahashi <i>et al.</i>	2001
TS (25–30)	<i>In vitro</i>	Human	Flow-through cells, <i>K_p</i>	8-MOP	x3	↑	Anigbogu <i>et al.</i>	1996
TS (30)	<i>In vitro</i>	Guinea pig	Diffusion cells	¹⁴ C-NA, MN, BN	↑	↑	Osamura <i>et al.</i>	1984
TS (30)	<i>In vivo</i>	Guinea pig	Glass plate	¹⁴ C-NA, MN, BN	↑	↑	Osamura <i>et al.</i>	1984
TS (1–50)	<i>In vivo</i>	Human	Microdialysis	Aciclovir	x440	↑	Morgan <i>et al.</i>	2003
TS (1–50)	<i>In vivo</i>	Human	Microdialysis	Penciclovir	x1300	↑	Morgan <i>et al.</i>	2003
AB	<i>In vivo</i>	Human	γ -Radiation	⁸⁵ Strontium	x200	↑	Ilyin <i>et al.</i>	1975
AB	<i>In vivo</i>	Rat, monkey, human	Excreta, plasma	Diflorasone diacetate- ³ H	—	—	Wickrema Sinha <i>et al.</i>	1978
AB	<i>In vivo</i>	Rat	Urine	³ H-Cort, ¹⁴ C-NA	x3, x7	↑	Bronaugh and Stewart	1985
AB	<i>In vivo</i>	Rat	Diffusion cells	³ H ₂ O	x20	↑	Bronaugh and Stewart	1985
AB	<i>In vitro</i>	Human	Diffusion cells	³ H ₂ O	x11	↑	Bronaugh and Stewart	1985
AB	<i>In vitro</i>	Rat	Diffusion cells	³ H-Cort, ¹⁴ C-NA	x2, x10	↑	Bronaugh and Stewart	1985
AB	<i>In vitro</i>	Human	Diffusion cells	BA	x2.1	↑	Bronaugh and Stewart	1985
AB	<i>In vitro</i>	Human	Diffusion cells	Caffeine	x1.6	↑	Bronaugh and Stewart	1985
AB	<i>In vitro</i>	Human	Diffusion cells	³ H-Cort, ¹⁴ C-NA	x3.9, x11.5	↑	Bronaugh and Stewart	1985
AB	<i>In vitro</i>	Human	Diffusion cells	Phenol	x1.7	↑	Bronaugh and Stewart	1985
AB	<i>In vitro</i>	Human	Diffusion cells	Propylene glycol	x5.3	↑	Bronaugh and Stewart	1985
AB	<i>In vitro</i>	Human	Diffusion cells	Urea	x7.1	↑	Bronaugh and Stewart	1985
AB	<i>In vitro</i>	Rat	Diffusion cells	BA	x2	↑	Bronaugh and Stewart	1985
AB	<i>In vitro</i>	Rat	Diffusion cells	Caffeine	x1.6	↑	Bronaugh and Stewart	1985
AB	<i>In vitro</i>	Rat	Diffusion cells	Phenol	x3.7	↑	Bronaugh and Stewart	1985
AB	<i>In vitro</i>	Rat	Diffusion cells	Propylene glycol	x4	↑	Bronaugh and Stewart	1985
AB	<i>In vitro</i>	Rat	Diffusion cells	Urea	x5.1	↑	Bronaugh and Stewart	1985
AB	<i>In vivo</i>	Monkey, guinea pig	Urine	¹⁴ C-Cort	—	—	McMaster <i>et al.</i>	1985
AB	<i>In vitro</i>	Rat	Diffusion cells, <i>K_p</i>	³ H ₂ O	↑	↑	Scott <i>et al.</i>	1986
AB	<i>In vivo</i>	Rat	Chamber, TEWL	H ₂ O	↑	↑	Scott <i>et al.</i>	1986
AB	<i>In vivo</i>	Rat	Plasma	Bucladesine	↑	↑	Mafune <i>et al.</i>	1995
AB	<i>In vitro</i>	Human	Flux, <i>K_p</i>	Acyclovir	↑ (x36–220)	↑	Akomeah <i>et al.</i>	2008
AB	<i>In vitro</i>	Human	Flux, <i>K_p</i>	Angiotensin II (infinite dose study)	↑ (x57–93)	↑	Akomeah <i>et al.</i>	2008
AB	<i>In vitro</i>	Human	Flux, <i>K_p</i>	Butyl paraben	x3	↑	Akomeah <i>et al.</i>	2008
AB	<i>In vitro</i>	Human	Flux, <i>K_p</i>	Caffeine	x64	↑	Akomeah <i>et al.</i>	2008
AB	<i>In vitro</i>	Human	Flux, <i>K_p</i>	Methyl paraben	x6	↑	Akomeah <i>et al.</i>	2008

Disease model: AB, abrasion; (NM), not mentioned; TS, tape stripping; (—), number of removals.

Method: CS, contralateral flank site; *K_p*, permeation/permeability coefficient; PpIX-fluo, protoporphyrin IX fluorescence; TEWL, transepidermal water loss.

Penetrant: ALA, 5-aminolevulinic acid; ALAHE, ALA hexyl ester; ALAME, ALA methyl ester; ALAPE, ALA pentyl ester; alkyl-BA, 4-methyl, 4-ethyl, 4-*n*-propyl benzoic acid; BA, benzoic acid; BN, butyl nicotinate; ¹⁴C, 14 carbon; Cort, cortisone; ³H, tritium; H₂O, water; HC, hydrocortisone; KT, un-ionized ketotifen; MN, methyl nicotinate; MPA, methylprednisolone aceponate; 8-MOP, 8-methoxypsoralen; NA, nicotinic acid; SA, salicylic acid; PEGs, polyethylene glycols; 2,4-D, 2,4-dichlorophenoxyacetic acid

Result: x, ratio of penetration; ↑, increase of penetration; ↓, decrease of penetration; —, no change; MW, molecular weight.

in the urine over 10 days were analyzed. Stripping the skin doubled this amount and significantly altered the absorption rate curve, whereas stripping and occlusion increased absorption by 32 times that of unmodified skin. Anigbogu *et al.* (1996) found a 3-fold increase in the flux of 8-methoxypsoralen *in vitro* after complete removal of full-thickness human membranes by 25–30 strips. Moon *et al.* (1990) observed that hydrocortisone and benzoic acid absorption in dorsolateral guinea pig skin *in vivo* increased 3 and 2 times for each drug after tape stripping, respectively. Inoue *et al.* (2000) observed a 22-fold ketotifen penetration increase by 20 times tape-stripped mouse skin. Günther *et al.* (1998) assayed *in vivo* methylprednisolone aceponate penetration through human skin by urine excretion of radiolabeled substances. Less than 0.5% of the administered dose was absorbed through intact inflamed skin, whereas absorption increased to ~15% (30-fold) after removal of the SC by tape stripping.

Using microdialysis *in vivo*, Benfeldt (1999) quantified the penetration of salicylic acid. Tape stripping resulted in a 180-fold increase in dermal concentration and a 20-fold increase in systemic absorption. Morgan *et al.* (2003) investigated penetration of penciclovir and aciclovir, chosen for their water solubility, using microdialysis in 0–40 times tape-stripped volunteer skin. Tape stripping increased penciclovir absorption by 1300-fold and aciclovir absorption by 440-fold compared with normal intact skin. They observed a strong correlation between penciclovir absorption and barrier disruption.

Goff *et al.* (1992) observed that stripped guinea pig skin was highly sensitive to percutaneous treatment with 5-aminolevulinic acid (ALA) compared with healthy skin. Van den Akker *et al.* (2000b) showed that removing mouse SC by tape stripping *in vivo* increased the penetration of ALA and 5-aminolevulinic hexyl ester (ALAHE). In another *in vivo* study using mouse skin, tape stripping before ALA application resulted in an increase of detectable protoporphyrin IX (PpIX) fluorescence outside the application area, indicating that tape stripping also improved ALA circulation penetration. However, tape stripping did not increase ALAHE-induced PpIX fluorescence outside the application area (van den Akker *et al.*, 2002). In an *in vitro* study van den Akker also showed that penetration of ALA and the ALA esters was higher, 100- and 200-fold respectively, through tape-stripped rather than through normal mouse skin (van den Akker *et al.*, 2003, 2004).

Some studies demonstrated a stripping effect on the function of certain drugs' chemical properties. In their *in vitro* study using guinea pig skin, Kitagawa and Li (1999) observed that tape stripping decreased the dependency of permeability coefficients on alkyl chain length of 4-alkyl-benzoic acid substituents. Murakami *et al.* (1998) found a highly variable effect when examining effects of five ointment bases with salicylic acid on intact and tape-stripped dorsal rat skin. They showed a 46.2-fold increase for the water-soluble ointment (polyethylene glycols), compared with only a 2-fold increase for the poloid and hydrophilic poloid ointments vs no increase for the white petroleum ointment and rather a decrease for the absorptive (oil-type emulsion containing water) ointment.

Tsai *et al.* (2001a, 2003) demonstrated that larger molecules, with greater molecular weights, were able to better penetrate compromised skin than normal skin. Tape stripping increased the molecular weight cut-off (maximum molecular weight) for polyethylene glycols (PEGs) penetration through hairless mouse skin.

Physicochemical properties are important determinants of stripping effects. Gattu and Maibach (2010, 2011) review studies comparing such properties and resulting absorption rates.

Table 2 summarizes tape-stripped absorption studies based on the degree of hydrophilicity of compounds. The log of the octanol–water coefficient ($\log K_{\text{oct}}$) values of compounds characterizing lipophilicity referenced in this article's tables were obtained from Gattu and Maibach (2010, 2011).

Maibach and Feldmann (1974) studied pesticide penetration enhancement in tape-stripped skin. Pesticides whose penetration was more clearly enhanced at 14-fold were also the most hydrophilic, with a $\log K_{\text{oct}}$ value of -0.2 , while pesticides least affected by tape stripping were lipophilic with $\log K_{\text{oct}}$ values of 1.5 and 2.8. As can be seen from Table 2, most water-soluble drugs are more affected by stripping.

Abrasion

Abrasion by means of a metal grader, brush brittle or a needle drawn across the skin's surface has been shown by transmission electron microscopy to loosen the SC (Akomeah *et al.*, 2008). Table 1 summarizes literature results in abrasion absorption studies based on degree of penetration compared with normal skin.

Bronaugh and Stewart (1985) compared the *in vitro* permeation of compounds through skin damaged by tape stripping and abrasion lines with a hypodermic needle. Water permeation through tape-stripped rat skin was much higher (80.6%) than through intact skin (4.1%) in terms of dose absorbed. For human skin, the values were 56.9 vs 2.7%, respectively. Needle abrasion produced an intermediate effect. Mafune *et al.* (1995) evaluated the *in vivo* bucladesine percutaneous absorption in rats with normal, stripped and full-thickness abraded skin. Bucladesine absorption was low through normal skin but rapid and nearly complete through damaged skin. Skin absorption was higher in abraded skin than in tape-stripped skin. In an *in vivo* study, Ilyin *et al.* (1975) found a 200-fold strontium absorption increase through abraded human skin compared with undamaged skin. Scott *et al.* (1986) used a scalpel blade, sandpaper abrasion, adhesive tape stripping and suction blister top removal for superficial rat skin alterations. These alterations increased water permeation with suction blister top removal being the most effective, tape stripping the second most, followed by sandpaper abrasion, and the least effective being the scalpel blade. However, Wickrema Sinha *et al.* (1978) found no significant differences in the *in vivo* permeation of diflorasone through normal and scalpel-rubbed abraded guinea pig and monkey skin.

McMaster *et al.* (1985) attempted to ascertain whether simply rubbing enhanced *in vivo* absorption. They applied hydrocortisone in hydrophilic ointment to a retroauricular skin area in the guinea pig and on the abdomen of the rhesus monkey. Rubbing with 100 strokes using a metal spatula caused no significant absorption increase. Table 2 summarizes human abrasion absorption studies based on degree of hydrophilicity (defined by $\log K_{\text{oct}}$ values) of compounds.

Akomeah *et al.* (2008) and Bronaugh and Stewart (1985) examined effects of tape stripping and abrasion on human epidermis and found that the more hydrophilic substances caffeine, tritiated water, acyclovir, urea, and nicotinic acid, with lower K_{oct} values, had greater skin permeation than the more lipophilic substances benzoic acid, cortisone, phenol, methyl paraben and butyl paraben, with higher K_{oct} values. However, the degree of permeation enhancement was different between the two sources. Akomeah

Table 2. Summary of literature in human absorption studies in tape-stripped or abraded skin comparing absorption enhancement to K_{oc} values indicating hydrophilicity

Disease model	In vivo/vitro	Penetrant	Molecular Weight	log K_{oc}	Enhancement Factor	Measured	Author	Year
TS	In vivo	HC	362	1.6	2	% Applied dose found in urine	Feldmann and Maibach	1965
TS	In vivo	Azodrin	223	-0.2	14	% Applied dose found in urine	Maibach and Feldmann	1974
TS	In vivo	Baygon	209	1.5	3	% Applied dose found in urine	Maibach and Feldmann	1974
TS	In vivo	Diquat	184	1.4	10	% Applied dose found in urine	Maibach and Feldmann	1974
TS	In vivo	2,4-D	221	2.8	6	% Applied dose found in urine	Maibach and Feldmann	1974
TS	In vivo	Guthion	317	2.8	4	% Applied dose found in urine	Maibach and Feldmann	1974
TS	In vivo	Parathion	291	3.8	9	% Applied dose found in urine	Maibach and Feldmann	1974
TS	In vitro	Tritiated water	22	1.38	21.00	% Dose absorbed	Bronaugh and Stewart	1985
TS	In vivo	0.1% methylprednisolone	472	3.8	30	% Applied dose found in urine	Günther <i>et al.</i>	1998
TS	In vivo	SA	138	2.3	157	Area under concentration vs Time curve by microdialysis	Benfeldt <i>et al.</i>	1999
TS	In vivo	Acyclovir	225	-1.8	440	Area under concentration vs time curve by microdialysis	Morgan <i>et al.</i>	2003
TS	In vivo	Penciclovir	253	-2.12	1300	Area under concentration vs time curve by microdialysis	Morgan <i>et al.</i>	2003
TS	In vitro	Angiotensin II (infinite dose)	1,046	-1.7	25-69	Flux	Akomeah <i>et al.</i>	2008
TS	In vitro	Butyl paraben	194	3.6	3.00	Flux	Akomeah <i>et al.</i>	2008
TS	In vitro	Caffeine	194	-0.07	19	Flux	Akomeah <i>et al.</i>	2008
TS	In vitro	Methyl paraben	152	1.96	5.00	Flux	Akomeah <i>et al.</i>	2008
AB	In vivo	Strontium	152	1.9	200	Whole body external radiation	Ilyin <i>et al.</i>	1975
AB	In vitro	Caffeine	194	0	1.60	% Dose absorbed	Bronaugh and Stewart	1985
AB	In vitro	Tritiated water	22	1.38	12.50	% Dose absorbed	Bronaugh and Stewart	1985
AB	In vitro	BA	122	1.9	2.10	% Dose absorbed	Bronaugh and Stewart	1985
AB	In vitro	Cortisone	360	1.6	3.90	% Dose absorbed	Bronaugh and Stewart	1985
AB	In vitro	NA	123	-0.2	11.50	% Dose absorbed	Bronaugh and Stewart	1985
AB	In vitro	Phenol	92	1.482	1.70	% Dose absorbed	Bronaugh and Stewart	1985
AB	In vitro	Propylene glycol	76	-1.7	5.30	% Dose absorbed	Bronaugh and Stewart	1985
AB	In vitro	Urea	60	-2.6	7.10	% Dose absorbed	Bronaugh and Stewart	1985
AB	In vitro	Caffeine	194	-0.07	64.00	Flux	Akomeah <i>et al.</i>	2008
AB	In vitro	Methyl paraben	152	1.96	6.00	Flux	Akomeah <i>et al.</i>	2008
AB	In vitro	Angiotensin II (infinite dose)	1046	-1.7	57-93	Flux	Akomeah <i>et al.</i>	2008
AB	In vitro	Butyl paraben	194	3.57	3.00	Flux	Akomeah <i>et al.</i>	2008
AB	In vitro	Acyclovir	225	-1.56	35-220	Flux	Akomeah <i>et al.</i>	2008

For abbreviations, see Table 1.

et al. (2008) found that abrasion produced a higher enhancement factor than tape stripping, while Bronough and Stewart (1985) observed the opposite. This discrepancy can be explained by differing abrasion methods employed by the authors. Akomeah *et al.* used a bristle brush made from hog skin applied to the skin for 25 s, while Bronough and Stewart drew a needle across the surface, which only damaged 6.4% of the surface area. Variability in damage methodology highlights inconsistency across *in vitro* permeability studies (Gattu and Maibach, 2010).

Human studies showed that tape stripping and abrasion both lead to increased skin absorption. Studies *in vivo* and *in vitro* with human and animal skin show that tape stripping increases skin penetration of most hydrophilic and lipophilic compounds (more so for hydrophilic than lipophilic). Few studies define abrasion and percutaneous absorption so it is difficult to draw conclusions, but abrasion does not seem to affect absorption as much as tape stripping. However it is important to compare similar models to each other and note that *in vivo* studies are more easily interpretable than *in vitro* studies.

FREEZING OR HEATING, BRANDING

Freezing

Table 3 summarizes absorption studies in frozen skin. Some evidence suggests that freezing skin for *in vitro* absorption studies alters its permeability. Swarbrick found an increased chromone acid absorption through frozen skin (-17°C) compared with fresh human skin (Swarbrick *et al.*, 1982). Kempainen *et al.* (1986) studied the absorption of T-2 toxin in fresh (4°C) and frozen (-60°C) human and monkey skin *in vitro*. For both species, the permeability rate increased 2.5-fold when stored at -60°C for no longer than 12 days. Similar results were obtained by Hawkins and Reifenrath (1984). The penetration of *N,N*-diethyl-*m*-toluamide was determined using pig skin after freezing for 1–6 weeks at -80°C . Absorption rate increased linearly with storage time. Using iontophoresis, Hadzija *et al.* (1992) studied the influence of frozen storage on salicylic acid permeability through rat skin. They observed a 3-fold increased permeability compared with freshly excised skin. The permeability was also found to be storage-time dependent.

Brain *et al.* (2005) studied the percutaneous penetration of diethanolamine (DEA) through frozen human skin (at least 1 week at -20°C) and fresh skin *in vitro*. They observed increased penetration through frozen skin when DEA was applied as an infinite dose in aqueous solution. However, DEA permeation from the leave-on formulation was similar and very low for both frozen and fresh skin. Sintov and Botner (2006) studied the transdermal delivery of diclofenac in vehicles using frozen (-20°C) rat, guinea pig and pig skin. In rat skin, they observed a decreased permeability through frozen compared with fresh (4°C) with microemulsion, and no significant difference when an aqueous solution was applied. In guinea pig skin, freezing also decreased permeability compared with fresh skin with microemulsion, but increased in permeability with aqueous solution. Permeability increased in pig skin when an aqueous solution was applied. However, application of the microemulsion vehicle resulted in similar drug penetration fluxes regardless of skin storage condition. The authors suggested that freezing and thawing procedures only modify the aqueous pathways of the lipid bilayers.

Harrison *et al.* (1984) found no significant difference in water penetration between fresh human skin and skin stored at -20°C for up to 466 days. Berenson and Burch (1951)

believed that water transfer rate through isolated skin was not significantly altered after several post-mortem days even after being frozen for at least 1 month and then thawed, provided there was no corneum deterioration. It is probable that the permeation of chemicals, which is highly metabolized by skin, may be greatly affected by freezing since freezing and thawing can destroy metabolic activity.

Bronaugh *et al.* (1986a) assayed the *in vitro* water permeation through frozen and unfrozen cadaver skin stored for a year. Significant changes in water absorption were seen only with the skin of two donors out of nine after 2 months storage at -20°C . Kasting and Bowman (1990a, b) compared *in vitro* samples of human fresh allograft skin properties with human frozen skin (-150°C) properties they had analyzed in a previous study. The fresh skin samples had a slightly higher median resistance and a 45% lower median permeability to sodium ions than the frozen skin samples. However, the difference was not statistically significant and the electrical behavior of the two tissues was similar enough to support the use of frozen tissue in iontophoresis studies.

Thus freezing does not seem to modify skin water absorption but leads to an increased penetration of other compounds, perhaps by having an effect on the lipid bilayer structure. More studies with compounds of different water solubility are needed to address this issue. As freezing is the most commonly used method to conserve skin, understanding its effects is very important.

Heating, Branding

Moderate to severe burns produce bulla, resulting in denuded skin with complete destruction of barrier function. For burn patient management, it is essential to restore barrier function and prevent further tissue fluid loss from within the body or secondary infections from foreign toxic agents. Table 3 summarizes absorption studies in burned skin.

Experimentally, heating or branding has no significant effect on permeation until burn temperature reaches 70°C (Flynn *et al.*, 1980; Behl *et al.*, 1981; Boosalis *et al.*, 1987). At higher temperatures, a notable increase in permeation rate was observed. Permeability of methanol increased over 50 times the control rate by 150°C scalding. Flynn *et al.* (1980) investigated the influence of scald burns at 60 – 98°C on mouse skin permeability. The higher the temperature, the greater the permeability (with a sharp transition between 70 and 80°C). They also noted a greater effect on more polar compounds. Behl *et al.* (1980) utilized 60°C scalded or branded mouse skin in their *in vitro* study and demonstrated that the duration of burning had a marginal effect on the permeability of skin when assessed immediately after burning. After 4–5 days of maturation, Flynn *et al.* (1980) found a 50% increase in the permeability of methanol and a 300–400% increase in the permeability of butanol through hairless mouse excised eschars induced by 15 s of 80°C applied metal. Thereafter, permeabilities tended to increase to reach 20 and 12 times for methanol and butanol, respectively.

Boosalis *et al.* (1987) found increased serum concentrations and urinary excretion of silver in burn patients treated with topical silver sulfadiazine. Although the use of silver sulfadiazine, to control burn wound bacteria, remains of overriding importance, the consistent absorption of small amounts of silver through the burn wound treated with silver sulfadiazine, depositing in normal tissues, is a source of rising concern

Table 3. Summary of literature in absorption studies in frozen or burned skin

Disease model	In vivo/vitro	Skin	Method	Penetrant	Result	Author	Year
FR	In vitro	Human	Water transfer	H ₂ O	—	Berenson and Burch	1951
FR	In vitro	Rat	Iontophoresis	Salicylic acid	x3	Hadzija <i>et al.</i>	1992
FR (−17 °C)	In vitro	Human	Diffusion cells	Chromone acid	↑	Swarbrick <i>et al.</i>	1982
FR (−20 °C)	In vitro	Human	Diffusion cells	H ₂ O	—	Harrison <i>et al.</i>	1984
FR (−20 °C)	In vitro	Human	Diffusion cells	³ H-H ₂ O	—	Bronaugh <i>et al.</i>	1986a
FR (−20 °C)	In vitro	Human	Diffusion cells	DEA (infinite dose)	↑	Brain <i>et al.</i>	2005
FR (−20 °C)	In vitro	Human	Diffusion cells	DEA (leave-on)	—	Brain <i>et al.</i>	2005
FR (−20 °C)	In vitro	Rat	Diffusion cells, microemulsion	Diclofenac	↓	Sintov and Botner	2006
FR (−20 °C)	In vitro	Rat	Diffusion cells, aqueous solution	Diclofenac	—	Sintov and Botner	2006
FR (−20 °C)	In vitro	Guinea pig	Diffusion cells, microemulsion	Diclofenac	↓	Sintov and Botner	2006
FR (−20 °C)	In vitro	Guinea pig	Diffusion cells, aqueous solution	Diclofenac	↑	Sintov and Botner	2006
FR (−20 °C)	In vitro	Pig	Diffusion cells, microemulsion	Diclofenac	↑	Sintov and Botner	2006
FR (−20 °C)	In vitro	Pig	Diffusion cells, aqueous solution	Diclofenac	↓	Sintov and Botner	2006
FR (−60 °C)	In vitro	Monkey, human	Diffusion cells	T-2 toxin	x2.5	Kemppainen <i>et al.</i>	1986
FR (−80 °C)	In vitro	Pig	Diffusion cells	m-Deet	x1.1–1.4	Hawkins and Reifenrath	1984
FR (−150 °C)	In vitro	Human	Diffusion cells	²² NaCl	x0.55	Kasting and Bowman	1990a
FR (−150 °C)	In vitro	Human	Iontophoresis	²² NaCl	x0.56	Kasting and Bowman	1990b
BU	In vivo	Human	Plasma, urine	Povidone-iodine	↑	Balogh <i>et al.</i>	1985
BU	In vivo	Human	Serum, urine	Silver sulfadiazine	↑	Boosalis <i>et al.</i>	1987
BU	In vivo	Human	Plasma	AgNO ₃ Silver Solution	x50	Wan <i>et al.</i>	1991
BU	In vivo	Human	Urine	AgNO ₃ Silver Solution	x5	Wan <i>et al.</i>	1991
BU	In vivo	Human	Water evaporation	H ₂ O	x1.33	Chen <i>et al.</i>	2007
BU (60 °C)	In vivo	Human	Serum	Topical epinephrine	↑	Papp <i>et al.</i>	2009
BU (60 °C)	In vitro	Mouse	Diffusion cells	³ H-H ₂ O	x1.52	Behl <i>et al.</i>	1980
BU (60 °C)	In vitro	Mouse	Diffusion cells	³ H-methanol	x1.5	Behl <i>et al.</i>	1980
BU (60 °C)	In vitro	Mouse	Diffusion cells	¹⁴ C-ethanol	x1.45	Behl <i>et al.</i>	1980
BU (60 °C)	In vitro	Mouse	Diffusion cells	¹⁴ C- <i>n</i> -butanol	x3.16	Behl <i>et al.</i>	1980
BU (80 °C)	In vitro	Mouse	Diffusion cells	³ H-methanol	x1.7	Flynn <i>et al.</i>	1980
BU (80 °C)	In vitro	Mouse	Diffusion cells	¹⁴ C-butanol	x4.5	Flynn <i>et al.</i>	1980
BU (60–98 °C)	In vitro	Mouse	Diffusion cells	³ H-H ₂ O, ¹⁴ C- <i>n</i> -alkanols	↑	Flynn <i>et al.</i>	1980

Disease model: BU, burning; FR, freezing.

Penetrant: ¹⁴C, ¹⁴ carbon; DEA, diethanolamine; H₂O, water; m-Deet, N,N-diethyl-m-toluamide.

Result: x, ratio of penetration; ↑, increase of penetration; ↓, decrease of penetration; —, no change.

(Fuller *et al.*, 1994). Such absorption may lead to hypersensitivity reactions, such as neutropenia and erythema multiforme (Lockhart *et al.*, 1983). Wan *et al.* (1991) determined that urinary excretion of silver and silver concentrations in plasma increased with the application of a standard solution of silver containing AgNO_3 .

Balogh *et al.* (1985) found in an *in vivo* study that the application of povidone-iodine resulted in higher iodine levels in the plasma and higher iodine excretion in the urine of burn patients than traumatized patients. However, they also found no clinical signs of iodine intoxication and no significant changes in thyroid hormones T3, T4, and TSH, concluding that topical treatment with povidone-iodine does not significantly inhibit thyroid function.

In an *in vivo* study comparing the effect of topical epinephrine application between burn and nonburn patients, Papp *et al.* found an increase in serum epinephrine concentrations for burn patients compared with nonburn patients. Increased epinephrine concentrations in burn patients suggest increased absorption properties in burned skin (Papp *et al.*, 2009).

Chen *et al.* (2007) studied water loss for burn wounds and found that evaporation from naked burn wounds was about one-third higher than from normal skin. All addressed results were similar: heating or branding the skin consistently increased percutaneous absorption. However, more *in vivo* studies are needed to verify this. Urinary excretion of topically applied drugs may be a useful *in vivo* verification method.

DELIPIDIZATION

Stratum corneum barrier function depends on its lipid and protein mosaic conformation (Fukuyama *et al.*, 1976). Removing SC lipids should increase the percutaneous absorption of drugs. Many organic solvents are employed to delipidize by extraction of fatty materials, resulting in karyopkneses on histology (Kronevi *et al.*, 1981). Some are water-soluble (e.g. alcohols, acetone), some are hydrophobic (e.g. hexane, chloroform), and some are mixtures of solvents. Table 4 delineates degree of skin absorption compared with normal skin following delipidization and Table 5 summarizes human delipidization absorption studies based on degree of hydrophilicity (defined by $\log K_{\text{oct}}$ values) of compounds.

In vitro water permeation experiments with excised skin have shown increased rates (Berenson and Burch, 1951; Mali, 1956; Onken and Moyer, 1963; Scheuplein and Ross, 1970; Matoltsy *et al.*, 1968). These effects are solvent-specific. Acetone alone was less effective in increasing water permeation, but when mixed with diethyl ether it was much more effective (Berenson and Burch, 1951; Mali, 1956). Wolfram *et al.* (1972) studied the physical properties of SC induced by ether extraction in guinea pig skin *in vitro* and suggested that the removal of lipids from the surface of the skin produces a pronounced weakening and swelling when the skin is subsequently immersed in water, reflecting the weaker more permeable properties of ether delipidized skin. Scheuplein and Ross (1970) graded the effectiveness of delipidizing solvent on water permeation as follows: ethanol < diethyl ether < chloroform < chloroform-methanol mixture. Butanol and butyric acid penetration through the octanol-treated skin nearly quadrupled. *In vivo* studies are rare and results are variable depending on the animal species and solvents used.

Chloroform-Methanol Delipidization

In an *in vivo* study, Bucks *et al.* (1983) showed that solvent trichloroethane did not enhance the penetration of hydrocortisone 24 h after delipidization, possibly owing to the lipophilic nature of hydrocortisone or the regeneration of the barrier within 24 h. However, a hairless guinea pig study showed a 5-fold increase in hydrocortisone after chloroform-methanol (2:1) treatment (Moon *et al.*, 1990). Rastogi and Singh (2001) investigated the effect of delipidization by chloroform and methanol (2:1) on hydrophilic compounds water, urea and inulin. Epidermal permeability increased with increasing lipid extraction. The enhancement in the permeability coefficient was 49, 215 and 4 for water, urea and inulin, respectively, using chloroform-methanol for 40 min. Moon observed the *in vivo* hydrocortisone and benzoic acid absorption in delipidized guinea pig skin. Absorption increased 5.2–2.7 times for each drug after defatting with chloroform and methanol (2:1; Moon *et al.*, 1990). Harada *et al.* (1992) investigated the *in vitro* penetration of salicylic acid from pH buffer solutions through human and shed snake skin. Lipid depletion with chloroform and methanol mixture considerably increased the permeability of the ionized form of salicylic acid in both skins. Moreover, as seen in Table 6, lipid depletion dramatically increased the permeability of snake skin to compounds with low lipophilicity but not for the more lipophilic compounds. They attributed the increased penetration rate of more hydrophilic compounds to an increased water penetration rate that they also observed in both species. Using the same delipidization procedure, Inoue *et al.* (2000) found a 100-fold ionized ketotifen penetration increase through mouse skin. However there was no difference for the nonionized ketotifen penetration rate. Fang *et al.* (2003) investigated the drug uptake in skin of flurbiprofen across chloroform-methanol delipidized vs intact skin from various enhancer-containing hydrogels. They found an increase in flurbiprofen amount in skin using all the studied enhancer-containing hydrogels for delipidized skin compared with intact skin. As observed with tape stripping in their *in vitro* study using guinea pig skin, Kitagawa and Li (1999) showed that delipidization by chloroform-methanol decreased the dependency of the permeability coefficients on the alkyl chain length of 4-alkyl-benzoic acid substituents. Akomeah *et al.* (2008) measured penetration of compounds with various lipophilicities after solvent damage. Delipidization produced greater enhancing effects for hydrophilic molecules with lower K_{oct} values, like caffeine, than for lipophilic molecules with greater K_{oct} values, such as methyl paraben and butyl paraben. Delipidization with a chloroform-methanol mixture seems to increase the permeability of hydrophilic compounds but does not affect the permeability of lipophilic compounds.

Acetone Delipidization

In their penetration study using microdialysis in rats, Benfeldt and Serup (1999) did not find an increase in salicylic acid penetration after acetone-induced delipidization but suggested that penetration would have increased if the acetone skin treatment had been longer and more intense. In an *in vivo* study on human skin by Benfeldt *et al.* (1999), they found a 2-fold increase of salicylic acid penetration. Tsai *et al.* (2001b) demonstrated *in vitro* that permeability barrier disruption by

Table 4. Summary of literature in absorption studies in defatted skin

Disease model	In vivo/vitro	Skin	Method	Penetrant	Result	Author	Year
D (acetone, ether, alcohol)	<i>In vitro</i>	Human	Diffusion cells	H ₂ O	↑	Berenson and Burch	1951
D (acetone)	<i>In vivo</i>	Rat	Urine, liver, blood	¹⁴ C-mannitol	↑	Lauer <i>et al.</i>	1997
D (acetone)	<i>In vivo</i>	Rat	Urine, liver, blood	³ H-PG	↑	Lauer <i>et al.</i>	1997
D (acetone)	<i>In vivo</i>	Human	Microdialysis	SA	x2.2	Benfeldt <i>et al.</i>	1999
D (acetone)	<i>In vivo</i>	Rat	Microdialysis	SA	x0.6	Benfeldt and Serup	1999
D (acetone)	<i>In vitro</i>	Mouse	Diffusion cells	PEGs	↑ (MW cut-off)	Tsai <i>et al.</i>	2001a
D (acetone)	<i>In vitro</i>	Mouse	Diffusion cells	³ H-CAF	x11	Tsai <i>et al.</i>	2001b
D (acetone)	<i>In vitro</i>	Mouse	Diffusion cells	³ H-ES	x2	Tsai <i>et al.</i>	2001b
D (acetone)	<i>In vitro</i>	Mouse	Diffusion cells	³ H-HC	x19	Tsai <i>et al.</i>	2001b
D (acetone)	<i>In vitro</i>	Mouse	Diffusion cells	³ H-PG	—	Tsai <i>et al.</i>	2001b
D (acetone)	<i>In vitro</i>	Mouse	Diffusion cells	³ H-S	x7	Tsai <i>et al.</i>	2001b
D (acetone)	<i>In vitro</i>	Human	TEWL	H ₂ O	—	Abrams <i>et al.</i>	1993
D (hexane)	<i>In vitro</i>	Human	TEWL	H ₂ O	—	Abrams <i>et al.</i>	1993
D (hexane-methanol)	<i>In vitro</i>	Human	TEWL	H ₂ O	x2.7	Abrams <i>et al.</i>	1993
D (chloroform-methanol)	<i>In vitro</i>	Human	TEWL	H ₂ O	x8.5	Abrams <i>et al.</i>	1993
D (chloroform-methanol)	<i>In vivo</i>	Guinea pig	Urine	¹⁴ C-BA	x2.7	Moon <i>et al.</i>	1990
D (chloroform-methanol)	<i>In vivo</i>	Guinea pig	Urine	¹⁴ C-HC	x5.2	Moon <i>et al.</i>	1990
D (chloroform-methanol)	<i>In vitro</i>	Snake	Diffusion cells	AAP	x80.44	Harada <i>et al.</i>	1992
D (chloroform-methanol)	<i>In vitro</i>	Snake	Diffusion cells	Butyl-PABA	x1.24	Harada <i>et al.</i>	1992
D (chloroform-methanol)	<i>In vitro</i>	Snake	Diffusion cells	DNCB	x1.23	Harada <i>et al.</i>	1992
D (chloroform-methanol)	<i>In vitro</i>	Human	Diffusion cells	³ H-H ₂ O	x41	Harada <i>et al.</i>	1992
D (chloroform-methanol)	<i>In vitro</i>	Snake	Diffusion cells	³ H-H ₂ O	x45	Harada <i>et al.</i>	1992
D (chloroform-methanol)	<i>In vitro</i>	Human	Diffusion cells	SA, ionized SA	x3.2; x17.3	Harada <i>et al.</i>	1992
D (chloroform-methanol)	<i>In vitro</i>	Snake	Diffusion cells	SA, ionized SA	x2.9; x24.5	Harada <i>et al.</i>	1992
D (chloroform-methanol)	<i>In vitro</i>	Snake	Diffusion cells	SAA	x10.27	Harada <i>et al.</i>	1992
D (chloroform-methanol)	<i>In vitro</i>	Guinea pig	Diffusion cells	BA, alkyl-BA	↑	Kitagawa and Li	1999
D (chloroform-methanol)	<i>In vitro</i>	Mouse	Diffusion cells	KT	x1.2	Inoue <i>et al.</i>	2000
D (chloroform-methanol)	<i>In vitro</i>	Mouse	Diffusion cells	KTH ⁺	x91	Inoue <i>et al.</i>	2000
D (chloroform-methanol)	<i>In vitro</i>	Pig	Diffusion cells	¹⁴ C-urea	x215.65	Rastogi and Singh	2001
D (chloroform-methanol)	<i>In vitro</i>	Pig	Diffusion cells	³ H-H ₂ O	x48.72	Rastogi and Singh	2001
D (chloroform-methanol)	<i>In vitro</i>	Pig	Diffusion cells	³ H-inulin	x3.90	Rastogi and Singh	2001
D (chloroform-methanol)	<i>In vitro</i>	Rat	Diffusion cells	Diclofenac	↑	Takahashi <i>et al.</i>	2001
D (chloroform-methanol)	<i>In vitro</i>	Mouse	Diffusion cells	flurbiprofen from CMCNa-containing hydrogel	x3	Fang <i>et al.</i>	2003
D (chloroform-methanol)	<i>In vitro</i>	Mouse	Diffusion cells	flurbiprofen from DMPC-containing hydrogel	x37	Fang <i>et al.</i>	2003

(Continues)

Table 4. (Continued)

Disease model	In vivo/vitro	Skin	Method	Penetrant	Result	Author	Year
D (chloroform-methanol)	<i>In vitro</i>	Mouse	Diffusion cells	flurbiprofen from Limonene-containing hydrogel	x7	Fang <i>et al.</i>	2003
D (chloroform-methanol)	<i>In vitro</i>	Mouse	Diffusion cells	flurbiprofen from Linolenic acid-containing hydrogel	x3	Fang <i>et al.</i>	2003
D (chloroform-methanol)	<i>In vitro</i>	Human	Flux, K_p	Angiotensin II (infinite dose)	↑ (x44–75)	Akomeah <i>et al.</i>	2008
D (chloroform-methanol)	<i>In vitro</i>	Human	Flux, K_p	Butyl paraben	x4.16	Akomeah <i>et al.</i>	2008
D (chloroform-methanol)	<i>In vitro</i>	Human	Flux, K_p	Caffeine	x10.93	Akomeah <i>et al.</i>	2008
D (chloroform-methanol)	<i>In vitro</i>	Human	Flux, K_p	Methyl paraben	x3.85	Akomeah <i>et al.</i>	2008
D (trichloroethane)	<i>In vivo</i>	Human	Urine	^{14}C -HC	—	Bucks <i>et al.</i>	1983
D (ethanol/propylene glycol)	<i>In vitro</i>	Pig	Diffusion cells	Aspirin	↑	Levang <i>et al.</i>	1999
D (ether/ethanol)	<i>In vitro</i>	Guinea pig	Fluorometric absorption spectrophotometric procedures	Aluminum chloride, Aluminum chlorohydrate	↑	Putterman <i>et al.</i>	1981
D (ethanol)	<i>In vitro</i>	Human	Flux, K_p	Butyl paraben	x3.75	Akomeah <i>et al.</i>	2008
D (ethanol)	<i>In vitro</i>	Human	Flux, K_p	Caffeine	x15.46	Akomeah <i>et al.</i>	2008
D (ethanol)	<i>In vitro</i>	Human	Flux, K_p	Methyl paraben	x4.08	Akomeah <i>et al.</i>	2008

Disease model: D, delipidization.
 Penetrant: AAP, acetaminophen; alkyl-BA, 4-methyl, 4-ethyl, 4-*n*-propyl benzoic acid; BA, benzoic acid; ^{14}C , ^{14}C , 14 carbon; CAF, caffeine; DNCB, dinitrochlorobenzene; ES, estradiol; H_2O , water; HC, hydrocortisone; KT, ketotifen; KTH^+ , ionized ketotifen; PABA, *p*-aminobenzoate; PEGs, polyethylene glycols; PG, progesterone; S, sucrose; SA, salicylic acid; SAA, salicylamide.
 Result: x, ratio of penetration; ↑, increase of penetration; ↓, decrease of penetration; —, no change; MW, molecular weight.

Table 5. Summary of literature in human absorption studies in delipidized skin comparing absorption enhancement to K_{oc} values indicating hydrophilicity

Disease model	<i>In vivo/vitro</i>	Penetrant	Molecular Weight	log K_{oc}	Enhancement factor	Measured	Author	Year
D (acetone)	<i>In vivo</i>	SA	138	2.3	2	Area under concentration vs time curve by microdialysis	Benfeldt <i>et al.</i>	1999
D (chloroform-methanol)	<i>In vitro</i>	Angiotensin II (infinite dose)	1046	-1.7	44-75	Flux	Akomeah <i>et al.</i>	2008
D (chloroform-methanol)	<i>In vitro</i>	Butyl paraben	194	3.57	4.16	Flux	Akomeah <i>et al.</i>	2008
D (chloroform-methanol)	<i>In vitro</i>	Caffeine	194	-0.07	10.93	Flux	Akomeah <i>et al.</i>	2008
D (chloroform-methanol)	<i>In vitro</i>	Methyl paraben	152	1.96	3.85	Flux	Akomeah <i>et al.</i>	2008
D (ethanol)	<i>In vitro</i>	Butyl paraben	194	3.57	3.75	Flux	Akomeah <i>et al.</i>	2008
D (ethanol)	<i>In vitro</i>	Caffeine	194	-0.07	15.46	Flux	Akomeah <i>et al.</i>	2008
D (ethanol)	<i>In vitro</i>	Methyl paraben	152	1.96	4.08	Flux	Akomeah <i>et al.</i>	2008
D (trichloroethane)	<i>In vivo</i>	Hydrocortisone (^{14}C -HC)	362	1.6	Not significant	% Applied dose found in urine	Bucks <i>et al.</i>	1983

For abbreviations see Table 4.

acetone treatment significantly enhanced mouse skin permeability to hydrophilic and amphiphilic compounds, including sucrose, caffeine and hydrocortisone, but not to highly lipophilic compounds, such as estradiol and progesterone. This is summarized in Table 7. They concluded that the enhancement in skin permeability to hydrophilic and amphiphilic compounds by delipidization was due to the increase in SC diffusivity at higher TEWL levels. The discrepancy between caffeine and hydrocortisone for enhancement relative to hydrophilicity may be explained by the small molecular weight of caffeine (MW = 194) compared with that for sucrose (MW = 342) and hydrocortisone (MW = 362), facilitating greater penetration enhancement at a minor degree of barrier disruption than that for sucrose and hydrocortisone. They also demonstrated, that it increases the molecular weight cut-off of PEG penetration through the hairless mice skin (Tsai *et al.*, 2001a). They showed that not only did the quantity of each penetrating chemical increase, but there was also a greater variety of chemicals that could penetrate skin with a compromised barrier.

Lauer *et al.* (1997) studied the *in vivo* percutaneous absorption of mannitol and progesterone through hairless and hairy rat skin. Hairless rat skin was more permeable to both compounds than hairy rat skin, although the difference was less dramatic for progesterone. The authors suggest the explanation that nonfollicular pathways predominate in lipophilic compound transport, whereas follicular pathways predominate for polar compounds. They repeated this experiment post acetone delipidization, and mannitol and progesterone penetration increased. With mannitol, absorption was more pronounced in hairy than in hairless rat skin. As an explanation for the acetone pre-treatment results, the authors consider the possibility that acetone pre-treatment has different effects on the permeability of the follicular and intrafollicular compartments.

Acetone skin pre-treatment enhances penetration for hydrophilic compounds. More data is needed to determine the influence on the permeability of highly lipophilic compounds.

Other Types of Delipidization

Tsai *et al.* (2003) reported that treatment by sodium dodecyl sulfate increased the molecular weight cut-off of polyethylene glycol penetration through hairless mouse skin. Levang *et al.* (1999) studied the effect of the solvent system ethanol, propylene glycol and combinations thereof on the *in vitro* aspirin percutaneous absorption: 80% ethanol-20% propylene glycol increased the percutaneous absorption of aspirin by increasing lipid extraction and perturbing the macroscopic barrier properties of pig skin.

Putterman *et al.* (1981) demonstrated that the *in vitro* absorption of aluminum to guinea pig SC increased for ether-ethanol delipidized skin compared with intact skin. Excised SC is opened up by delipidization, creating artificial diffusion shunts or increasing the internal surface absorption area.

Abrams *et al.* (1993) compared the resultant changes in TEWL after delipidization of the skin by acetone, chloroform-methanol, hexane or hexane-methanol. The results revealed that delipidizing skin with chloroform-methanol or hexane-methanol induced a significantly greater change in TEWL than delipidizing with acetone or hexane. Also, the results showed that no individual lipid class extracted by chloroform-methanol or hexane-methanol played a significant role in changing TEWL. The authors suggest

Table 6. Harada *et al.*'s (1992) absorption study in delipidized snake skin comparing absorption enhancement with K_{oct} values, indicating hydrophilicity

Disease model	<i>In vivo/vitro</i>	Penetrant	Molecular weight	$\log K_{\text{oct}}$	Enhancement factor	Measured
D (chloroform–methanol)	<i>In vitro</i>	AAP	151	0.76	80.44	↑ Amount penetrated vs time curve
D (chloroform–methanol)	<i>In vitro</i>	Butyl-PABA	193	3.16	1.24	↑ Amount penetrated vs time curve
D (chloroform–methanol)	<i>In vitro</i>	DNCB	202	2.24	1.23	↑ Amount penetrated vs time curve
D (chloroform–methanol)	<i>In vitro</i>	SAA	137	1.34	10.27	↑ Amount penetrated vs time curve

For Abbreviations see Table 4.

Table 7. Tsai *et al.*'s (2001b) absorption study in delipidized mouse skin comparing absorption enhancement with K_{oct} values, indicating hydrophilicity

Disease model	<i>In vivo/vitro</i>	Penetrant	Molecular weight	$\log K_{\text{oct}}$	Enhancement factor	Measured
D (acetone)	<i>In vitro</i>	^3H -CAF	194	−0.02	11	↑ Amount penetrated vs time curve
D (acetone)	<i>In vitro</i>	^3H -ES	272	2.7	2	↑ Amount penetrated vs time curve
D (acetone)	<i>In vitro</i>	^3H -HC	362	1.5	19	↑ Amount penetrated vs time curve
D (acetone)	<i>In vitro</i>	^3H -PG	314	3.9	—	— Amount penetrated vs time curve
D (acetone)	<i>In vitro</i>	^3H -S	342	−3.7	7	↑ Amount penetrated vs time curve

For abbreviations see Table 4.

based on these results that the mechanism by which chloroform–methanol and hexane–methanol induce a change in TEWL involves more than pure lipid extraction.

All these studies showed that skin delipidization with solvents such as chloroform–methanol mixture or acetone enhances skin penetration for many compounds, particularly hydrophilic ones. Further data is required to evaluate the influence of delipidization on highly lipophilic compounds; *in vivo* data in man and rhesus monkey would be welcome. Microdialysis may be a relevant method to evaluate the effect of delipidization on percutaneous absorption through human skin.

CHEMICAL IRRITATION

Most chemicals and drugs may alter the skin when applied topically, although the nature and concentration of the chemicals are important factors. Surfactants such as sodium lauryl sulfate (SLS) may change the composition of the SC by extracting lipids and converting α -keratin to β -keratin, producing swelling and hydration of the SC (Fulmer and Kramer, 1986; Imokawa *et al.*, 1989; Froese *et al.*, 1990; Putterman *et al.*, 1977). Studies regarding absorption in chemically irritated skin are summarized in Table 8. Table 9 summarizes human irritation absorption studies based on degree of hydrophilicity (defined by $\log K_{\text{oct}}$ values) of compounds.

Berensen and Burch (1951) treated with alkali (0.1 M NaOH up to 24 h) following the extraction of lipids from excised human skin and found no further change in water diffusion rate. They also observed no significant variation following the addition of 0.001 M potassium cyanide.

In an *in vivo* human experiment, Malten and Thiele (1973) studied the effect of sequential skin exposures to alkali and phosphate solution on water loss from skin. NaOH (pH 12) and

Na_3PO_4 (pH 12) caused an increase in water loss of ~350%. They also observed marked inflammation. They presumed the effect was due to a conformational collapse of the protein in this layer and a consequent increase in porosity from the damaged ductal epithelium of the exocrine glands.

Petitot *et al.* (2007, 2010) studied percutaneous penetration of uranyl nitrate through chemically burned rat skin. They found no significant difference in uranium concentration between 10 N NaOH burned skin and intact skin. Percutaneous absorption of uranium increased with increased impairment of the stratum corneum caused by various concentrations of nitric acid HNO_3 and 10 N hydrofluoric acid (HF).

Under certain conditions phenol damages skin, leading to increased penetration rates. Phenolic compounds interact with skin by protein denaturation. Roberts *et al.* (1977) examined the influence of concentration and structure of phenolic compounds on human skin permeability. The 3-fold concentration of phenol for damage was 1.5% w/v. For higher concentrations, the steady state K_p increased as a result of SC damage.

Solomon and Lowe (1979) produced an abnormal epidermidis using three methods: (1) ultraviolet (UV) light irradiation; (2) topical vitamin A acid; and (3) topical acetic acid. Topical application of retinoic acid to hairless mice produced an acanthotic epidermidis with an increased mitotic index and topical application of acetic acid promoted epidermal DNA synthesis and hyperplasia. *In vitro* absorption of hydrocortisone significantly increased through abnormal epidermis. These observations may be attributed to epidermal proliferation and altered keratinization. There is also evidence that results for topical application of retinoic acid may reflect abnormalities in the cell membrane phospholipid structure. Acetic acid may also induce abnormal cell membrane lipids. Thus increased absorption of hydrocortisone could be due to a combination of abnormal cell membrane phospholipids and an abnormal SC.

Table 8. Summary of literature in absorption studies in chemical irritated skin

Chemical	In vivo/vitro	Skin	Method	Penetrant	Result	Author	Year
NaOH, KCN	<i>In vitro</i>	Human	Water transfer	H ₂ O	—	Berenson and Burch	1951
NaOH, Na ₃ PO ₄	<i>In vivo</i>	Human	TEWL	H ₂ O	↑	Malten and Thiele	1973
10N NaOH,	<i>In vivo</i>	Rat	Blood	uranyl nitrate	—, x4, x5, x6, x6	Petitot <i>et al.</i>	2007
2N HNO ₃ ,							
5N HNO ₃ ,							
14N HNO ₃ ,							
10N HF							
10N NaOH,	<i>In vivo</i>	Rat	Urine	uranyl nitrate	—, x9, x6, x3, x3	Petitot <i>et al.</i>	2007
2N HNO ₃ ,							
5N HNO ₃ ,							
14N HNO ₃ ,							
10N HF							
2N HNO ₃ ,	<i>In vitro</i>	Rat	TEWL	H ₂ O	—, x2, x7	Petitot <i>et al.</i>	2010
5N HNO ₃ ,							
14N HNO ₃							
2N HNO ₃ ,	<i>In vitro</i>	Rat	Diffusion cells	uranyl nitrate	x2, x2, x290	Petitot <i>et al.</i>	2010
5N HNO ₃ ,							
14N HNO ₃							
SLS (0.5%)	<i>In vivo</i>	Guinea pig	Urine, fecal	¹⁴ C-AC	—	Wilhelm <i>et al.</i>	1991b
SLS (0.5%)	<i>In vivo</i>	Guinea pig	Urine, fecal	¹⁴ C-HC	x2.6	Wilhelm <i>et al.</i>	1991b
SLS (0.5%)	<i>In vivo</i>	Guinea pig	Urine, fecal	¹⁴ C-IB	x1.9	Wilhelm <i>et al.</i>	1991b
SLS (0.5%)	<i>In vivo</i>	Guinea pig	Urine, fecal	¹⁴ C-IM	x1.6	Wilhelm <i>et al.</i>	1991b
SLS (0.5%)	<i>In vitro</i>	Guinea pig	Diffusion cells	¹⁴ C-AC (saturated)	x3.4	Wilhelm <i>et al.</i>	1991a
SLS (0.5%)	<i>In vitro</i>	Guinea pig	Diffusion cells	¹⁴ C-HC (saturated)	x5.9	Wilhelm <i>et al.</i>	1991a
SLS (0.5%)	<i>In vitro</i>	Guinea pig	Diffusion cells	¹⁴ C-IB (saturated)	x3.9	Wilhelm <i>et al.</i>	1991a
SLS (0.5%)	<i>In vitro</i>	Guinea pig	Diffusion cells	¹⁴ C-IM (saturated)	x4.6	Wilhelm <i>et al.</i>	1991a
SLS (2%)	<i>In vivo</i>	Guinea pig	urine	¹⁴ C-BA	x2.1	Moon <i>et al.</i>	1990
SLS (2%)	<i>In vivo</i>	Guinea pig	urine	¹⁴ C HC	x4	Moon <i>et al.</i>	1990
SLS (0.1%)	<i>In vitro</i>	Human	Diffusion cells	BA	—	Nielsen <i>et al.</i>	2007
SLS (0.1%)	<i>In vitro</i>	Human	Diffusion cells	Caffeine	x5	Nielsen <i>et al.</i>	2007
SLS (0.1%)	<i>In vitro</i>	Human	Diffusion cells	Glyphosate	x24	Nielsen <i>et al.</i>	2007
SLS (0.1%)	<i>In vitro</i>	Human	Diffusion cells	Malthion	x2	Nielsen <i>et al.</i>	2007
SLS (0.1%)	<i>In vitro</i>	Human	Diffusion cells	Dimethoate	x1.85	Nielsen	2005
SLS (0.1%)	<i>In vitro</i>	Human	Diffusion cells	Methiocarb	—	Nielsen	2005
SLS (0.1%)	<i>In vitro</i>	Human	Diffusion cells	Paclobutrazol	x2	Nielsen	2005
SLS (0.1%)	<i>In vitro</i>	Human	Diffusion cells	Pirimicarb	x1.8	Nielsen	2005
SLS (0.3%)	<i>In vitro</i>	Human	Diffusion cells	Dimethoate	x2.75	Nielsen	2005
SLS (0.3%)	<i>In vitro</i>	Human	Diffusion cells	Methiocarb	—	Nielsen	2005
SLS (0.3%)	<i>In vitro</i>	Human	Diffusion cells	Paclobutrazol	x2	Nielsen	2005

(Continues)

Table 8. (Continued)

Chemical	In vivo/vitro	Skin	Method	Penetrant	Result	Author	Year
SLS (0.3%)	<i>In vitro</i>	Human	Diffusion cells	Pirimicarb	x1.7	Nielsen	2005
SLS (0.25%)	<i>In vitro</i>	Human	Diffusion cells	³ H ₂ O	x1.8	Frankild <i>et al.</i>	1995
SLS (0.25%)	<i>In vitro</i>	Human	Diffusion cells	¹⁴ C-HC	—	Frankild <i>et al.</i>	1995
SLS (0.25%)	<i>In vitro</i>	Human	Diffusion cells	⁶³ Ni	—	Frankild <i>et al.</i>	1995
SLS (2%)	<i>In vitro</i>	Human	Diffusion cells	³ H ₂ O	x3.3	Frankild <i>et al.</i>	1995
SLS (2%)	<i>In vitro</i>	Human	Diffusion cells	¹⁴ C-HC	—	Frankild <i>et al.</i>	1995
SLS (2%)	<i>In vitro</i>	Human	Diffusion cells	⁶³ Ni	—	Frankild <i>et al.</i>	1995
SLS (10%)	<i>In vitro</i>	Human	Diffusion cells	³ H ₂ O	x4.2	Frankild <i>et al.</i>	1995
SLS (10%)	<i>In vitro</i>	Human	Diffusion cells	¹⁴ C-HC	x4.3	Frankild <i>et al.</i>	1995
SLS (10%)	<i>In vitro</i>	Human	Diffusion cells	⁶³ Ni	↑	Frankild <i>et al.</i>	1995
SLS (1%)	<i>In vivo</i>	Human	TS	Metronidazole	↓	Ortiz <i>et al.</i>	2008
SLS (1%)	<i>In vivo</i>	Human	microdialysis	Metronidazole	x3	Ortiz <i>et al.</i>	2008
SLS (1%)	<i>In vitro</i>	Human	Diffusion cells	5-FU (infinite dose)	x4.8	Copoví <i>et al.</i>	2006
SLS (1%)	<i>In vitro</i>	Human	Diffusion cells	PHE (infinite dose)	x2.2	Copoví <i>et al.</i>	2006
SLS (1%)	<i>In vitro</i>	Human	Diffusion cells	PHB (infinite dose)	x1.2	Copoví <i>et al.</i>	2006
SLS (1%)	<i>In vitro</i>	Human	Diffusion cells	PHP (infinite dose)	x0.97	Copoví <i>et al.</i>	2006
SLS (5%)	<i>In vitro</i>	Human	Diffusion cells	5-FU (infinite dose)	x16.8	Copoví <i>et al.</i>	2006
SLS (5%)	<i>In vitro</i>	Human	Diffusion cells	PHE (infinite dose)	x2.4	Copoví <i>et al.</i>	2006
SLS (5%)	<i>In vitro</i>	Human	Diffusion cells	PHB (infinite dose)	x1.3	Copoví <i>et al.</i>	2006
SLS (5%)	<i>In vitro</i>	Human	Diffusion cells	PHP (infinite dose)	x1.04	Copoví <i>et al.</i>	2006
SLS (5%)	<i>In vivo</i>	Human	TS	PEGs	x3	Jakasa <i>et al.</i>	2006b
SLS (1%)	<i>In vivo</i>	Human	Microdialysis	SA	x46	Benfeldt <i>et al.</i>	1999
SLS (2%)	<i>In vivo</i>	Human	Microdialysis	SA	x146	Benfeldt <i>et al.</i>	1999
SLS (2%)	<i>In vivo</i>	Human	Microdialysis	SA	x83	Benfeldt and Serup	1999
SLS (0.24%)	<i>In vitro</i>	Rat	Diffusion cells	5-FU	x2.1	Borrás-Blasco <i>et al.</i>	2004
SLS (0.24%)	<i>In vitro</i>	Rat	Diffusion cells	Antipyrine	—	Borrás-Blasco <i>et al.</i>	2004
SLS (0.24%)	<i>In vitro</i>	Rat	Diffusion cells	Pentoxifylline	x1.1	Borrás-Blasco <i>et al.</i>	2004
SLS (0.24%)	<i>In vitro</i>	Rat	Diffusion cells	Salicylamide	x1.03	Borrás-Blasco <i>et al.</i>	2004
SLS (0.24%)	<i>In vitro</i>	Rat	Diffusion cells	4-Ethylaniline	—	Borrás-Blasco <i>et al.</i>	2004
SLS (0.24%)	<i>In vitro</i>	Rat	Diffusion cells	4- <i>n</i> -Butylaniline	—	Borrás-Blasco <i>et al.</i>	2004
SLS (0.24%)	<i>In vitro</i>	Rat	Diffusion cells	IM	x0.97	Borrás-Blasco <i>et al.</i>	2004
SLS (0.5%)	<i>In vitro</i>	Rat	Diffusion cells	5-FU	x7.5	Borrás-Blasco <i>et al.</i>	2004
SLS (0.5%)	<i>In vitro</i>	Rat	Diffusion cells	Antipyrine	—	Borrás-Blasco <i>et al.</i>	2004
SLS (0.5%)	<i>In vitro</i>	Rat	Diffusion cells	Pentoxifylline	x3.1	Borrás-Blasco <i>et al.</i>	2004
SLS (0.5%)	<i>In vitro</i>	Rat	Diffusion cells	Salicylamide	x1.04	Borrás-Blasco <i>et al.</i>	2004
SLS (0.5%)	<i>In vitro</i>	Rat	Diffusion cells	4-Ethylaniline	—	Borrás-Blasco <i>et al.</i>	2004
SLS (0.5%)	<i>In vitro</i>	Rat	Diffusion cells	4- <i>n</i> -Butylaniline	—	Borrás-Blasco <i>et al.</i>	2004
SLS (0.5%)	<i>In vitro</i>	Rat	Diffusion cells	IM	—	Borrás-Blasco <i>et al.</i>	2004
SLS (1%)	<i>In vitro</i>	Rat	Diffusion cells	5-FU	x7.8	Borrás-Blasco <i>et al.</i>	2004
SLS (1%)	<i>In vitro</i>	Rat	Diffusion cells	Antipyrine	x5.4	Borrás-Blasco <i>et al.</i>	1997
SLS (1%)	<i>In vitro</i>	Rat	Diffusion cells	Pentoxifylline	x4.5	Borrás-Blasco <i>et al.</i>	1997
SLS (1%)	<i>In vitro</i>	Rat	Diffusion cells	Salicylamide	x1.8	Borrás-Blasco <i>et al.</i>	1997

SLS (1%)	<i>In vitro</i>	Rat	Diffusion cells	4-Ethylaniline	x1.15	↑	Borrás-Blasco <i>et al.</i>	1997
SLS (1%)	<i>In vitro</i>	Rat	Diffusion cells	4- <i>n</i> -Butylaniline	x0.95	↓	Borrás-Blasco <i>et al.</i>	1997
SLS (1%)	<i>In vitro</i>	Rat	Diffusion cells	IM	x1.04	↑	Borrás-Blasco <i>et al.</i>	1997
SLS (5%)	<i>In vitro</i>	Rat	Diffusion cells	5-FU	x8.3	↑	Borrás-Blasco <i>et al.</i>	1997
SLS (5%)	<i>In vitro</i>	Rat	Diffusion cells	Antipyrine	x5.1	↑	Borrás-Blasco <i>et al.</i>	1997
SLS (5%)	<i>In vitro</i>	Rat	Diffusion cells	Pentoxifylline	x4.4	↑	Borrás-Blasco <i>et al.</i>	1997
SLS (5%)	<i>In vitro</i>	Rat	Diffusion cells	Salicylamide	x1.8	↑	Borrás-Blasco <i>et al.</i>	1997
SLS (5%)	<i>In vitro</i>	Rat	Diffusion cells	4-Ethylaniline	x1.2	↑	Borrás-Blasco <i>et al.</i>	1997
SLS (5%)	<i>In vitro</i>	Rat	Diffusion cells	4- <i>n</i> -Butylaniline	x0.97	↓	Borrás-Blasco <i>et al.</i>	1997
SLS (5%)	<i>In vitro</i>	Rat	Diffusion cells	IM	x1.03	↑	Borrás-Blasco <i>et al.</i>	1997
SLS (0.5%)	<i>In vitro</i>	Rat	Diffusion cells	Diazepam	x1.48	↑	Shokri <i>et al.</i>	2001
SLS (1%)	<i>In vitro</i>	Rat	Diffusion cells	Diazepam	x5.12	↑	Shokri <i>et al.</i>	2001
SLS (2.5%)	<i>In vitro</i>	Rat	Diffusion cells	Diazepam	x4.96	↑	Shokri <i>et al.</i>	2001
SLS (5%)	<i>In vitro</i>	Rat	Diffusion cells	Diazepam	x9.81	↑	Shokri <i>et al.</i>	2001
SLS (0.5%)	<i>In vitro</i>	Rat	Diffusion cells	Lorazepam	x2.99	↑	Nokhodchi <i>et al.</i>	2003
SLS (1%)	<i>In vitro</i>	Rat	Diffusion cells	Lorazepam	x10.05	↑	Nokhodchi <i>et al.</i>	2003
SLS (2.5%)	<i>In vitro</i>	Rat	Diffusion cells	Lorazepam	x5.36	↑	Nokhodchi <i>et al.</i>	2003
SLS (5%)	<i>In vitro</i>	Rat	Diffusion cells	Lorazepam	x11.3	↑	Nokhodchi <i>et al.</i>	2003
SLS (5%)	<i>In vivo</i>	Mouse	Blood, TS	¹⁴ C-Foscarnet	↑	↑	Piret <i>et al.</i>	2000
SDS	<i>In vitro</i>	Mouse	Diffusion cells	PEGs	↑ (MW cut-off)	↑	Tsai <i>et al.</i>	2003
BC (0.5%)	<i>In vitro</i>	Rat	Diffusion cells	Diazepam	x2	↑	Shokri <i>et al.</i>	2001
BC (1%)	<i>In vitro</i>	Rat	Diffusion cells	Diazepam	x7.98	↑	Shokri <i>et al.</i>	2001
BC (2.5%)	<i>In vitro</i>	Rat	Diffusion cells	Diazepam	x3	↑	Shokri <i>et al.</i>	2001
BC (5%)	<i>In vitro</i>	Rat	Diffusion cells	Diazepam	x3.42	↑	Shokri <i>et al.</i>	2001
BC (0.5%)	<i>In vitro</i>	Rat	Diffusion cells	Lorazepam	x3.98	↑	Nokhodchi <i>et al.</i>	2003
BC (1%)	<i>In vitro</i>	Rat	Diffusion cells	Lorazepam	x7.66	↑	Nokhodchi <i>et al.</i>	2003
BC (2.5%)	<i>In vitro</i>	Rat	Diffusion cells	Lorazepam	x5.02	↑	Nokhodchi <i>et al.</i>	2003
BC (5%)	<i>In vitro</i>	Rat	Diffusion cells	Lorazepam	x7.16	↑	Nokhodchi <i>et al.</i>	2003
CTAB (0.5%)	<i>In vitro</i>	Rat	Diffusion cells	Diazepam	x1.27	↑	Shokri <i>et al.</i>	2001
CTAB (1%)	<i>In vitro</i>	Rat	Diffusion cells	Diazepam	x1.16	↑	Shokri <i>et al.</i>	2001
CTAB (2.5%)	<i>In vitro</i>	Rat	Diffusion cells	Diazepam	x1.87	↑	Shokri <i>et al.</i>	2001
CTAB (5%)	<i>In vitro</i>	Rat	Diffusion cells	Diazepam	x2.23	↑	Shokri <i>et al.</i>	2001
CTAB (0.5%)	<i>In vitro</i>	Rat	Diffusion cells	Lorazepam	x4.67	↑	Nokhodchi <i>et al.</i>	2003
CTAB (1%)	<i>In vitro</i>	Rat	Diffusion cells	Lorazepam	x3.02	↑	Nokhodchi <i>et al.</i>	2003
CTAB (2.5%)	<i>In vitro</i>	Rat	Diffusion cells	Lorazepam	x4.96	↑	Nokhodchi <i>et al.</i>	2003
CTAB (5%)	<i>In vitro</i>	Rat	Diffusion cells	Lorazepam	x9.82	↑	Nokhodchi <i>et al.</i>	2003
Tween 80 (0.5%)	<i>In vitro</i>	Rat	Diffusion cells	Diazepam	x4	↑	Shokri <i>et al.</i>	2001
Tween 80 (1%)	<i>In vitro</i>	Rat	Diffusion cells	Diazepam	x5.68	↑	Shokri <i>et al.</i>	2001
Tween 80 (2.5%)	<i>In vitro</i>	Rat	Diffusion cells	Diazepam	x4.3	↑	Shokri <i>et al.</i>	2001
Tween 80 (5%)	<i>In vitro</i>	Rat	Diffusion cells	Diazepam	x3.05	↑	Shokri <i>et al.</i>	2001

(Continues)

Table 8. (Continued)

Chemical	In vivo/vitro	Skin	Method	Penetrant	Result	Author	Year
Tween 80 (0.5%)	In vitro	Rat	Diffusion cells	Lorazepam	x2.29	Nokhodchi et al.	2003
Tween 80 (1%)	In vitro	Rat	Diffusion cells	Lorazepam	x3.75	Nokhodchi et al.	2003
Tween 80 (2.5%)	In vitro	Rat	Diffusion cells	Lorazepam	x1.93	Nokhodchi et al.	2003
Tween 80 (5%)	In vitro	Rat	Diffusion cells	Lorazepam	x1.56	Nokhodchi et al.	2003
HPE-101 (3%)	In vivo	Mouse	PpIX-fluo	ALA	x3.6	Van den Akker et al.	2000b
HPE-101 (3%)	In vivo	Mouse	PpIX-fluo	ALAHE	x11	Van den Akker et al.	2000b
HPE-101 (3%)	In vivo	Mouse	PpIX-fluo (CS)	ALA	—	Van den Akker et al.	2002
HPE-101 (3%)	In vivo	Mouse	PpIX-fluo (CS)	ALAHE	—	Van den Akker et al.	2002
Vit A, acetic acid	In vitro	Mouse	Skin biopsy	¹⁴ C-HC	↑	Solomon and Lowe	1979
DNCB (5%)	In vivo	Guinea pig	Glass chamber	¹⁴ C-NA, MN, BN	↑	Osamura et al.	1984
Imipramine	In vitro	Human	Diffusion cells	Caffeine	x3	Nangia et al.	1993
Imipramine	In vitro	Human	Diffusion cells	HC	x10	Nangia et al.	1993
Imipramine	In vitro	Human	Diffusion cells	IM	—	Nangia et al.	1993
Norephedrine	In vitro	Human	Diffusion cells	Caffeine	x2	Nangia et al.	1993
Norephedrine	In vitro	Human	Diffusion cells	HC	x4	Nangia et al.	1993
Norephedrine	In vitro	Human	Diffusion cells	IM	↓	Nangia et al.	1993
GA (1%)	In vitro	Human	Diffusion cells	5-FU (infinite dose)	x4.1	Copovi et al.	2006
GA (1%)	In vitro	Human	Diffusion cells	PHE (infinite dose)	x1.9	Copovi et al.	2006
GA (1%)	In vitro	Human	Diffusion cells	PHB (infinite dose)	x1.3	Copovi et al.	2006
GA (1%)	In vitro	Human	Diffusion cells	PHP (infinite dose)	x0.98	Copovi et al.	2006
GA (5%)	In vitro	Human	Diffusion cells	5-FU (infinite dose)	x17.9	Copovi et al.	2006
GA (5%)	In vitro	Human	Diffusion cells	PHE (infinite dose)	x2.2	Copovi et al.	2006
GA (5%)	In vitro	Human	Diffusion cells	PHB (infinite dose)	x1.2	Copovi et al.	2006
GA (5%)	In vitro	Human	Diffusion cells	PHP (infinite dose)	x0.91	Copovi et al.	2006
LA (1%)	In vitro	Human	Diffusion cells	5-FU (infinite dose)	x5.5	Copovi et al.	2006
LA (1%)	In vitro	Human	Diffusion cells	PHE (infinite dose)	x1.8	Copovi et al.	2006
LA (1%)	In vitro	Human	Diffusion cells	PHB (infinite dose)	x1.2	Copovi et al.	2006
LA (1%)	In vitro	Human	Diffusion cells	PHP (infinite dose)	x0.74	Copovi et al.	2006
LA (5%)	In vitro	Human	Diffusion cells	5-FU (infinite dose)	x18.1	Copovi et al.	2006
LA (5%)	In vitro	Human	Diffusion cells	PHE (infinite dose)	x2.8	Copovi et al.	2006
LA (5%)	In vitro	Human	Diffusion cells	PHB (infinite dose)	x1.2	Copovi et al.	2006
LA (5%)	In vitro	Human	Diffusion cells	PHP (infinite dose)	x0.85	Copovi et al.	2006

Chemical: BC, benzalkonium chloride; CTAB, cetyltrimethylammonium bromide; DNCB, 2,4-dinitro-1-chlorobenzene; GA, glycolic acid; HPE-101, 1-[2-(decylthio)ethyl]azacyclopentan-2-one; KCN, potassium cyanide; LA, lactic acid; NaOH, sodium hydroxide; Na₃PO₄, sodium phosphate; SDS, sodium dodecyl sulfate; SLS, sodium lauryl sulfate; vit A, vitamin A.

Method: CS, contralateral site; PpIX-fluo, protoporphyrin IX fluorescence; TS, tape stripping.

Penetrant: AC, acitretin; ALA, 5-aminolevulinic acid; ALAHE, ALA hexylester; BA, benzoic acid; BN, butyl nicotinate; ¹⁴C, 14 carbon; EMLA[®], eutectic mixture of lidocaine (2.5%) and prilocaine (2.5%); 5-FU, 5-fluorouracil; ³H, tritium; H₂O, water; HC, hydrocortisone; IB, ibuprofen; IM, indomethacin; MN, methyl nicotinate; NA, nicotinic acid; Ni, nickel; PEGs, polyethylene glycols; PHE, 2-phenyl-ethanol; PHB, 4-phenyl-butanol; PHP, 5-phenylpentanol; SA, salicylic acid.

Result: x, ratio of penetration; ↑, increase of penetration; ↓, decrease of penetration; —, no change; MW, molecular weight.

Table 9. Summary of literature in human absorption studies in delipidized skin comparing absorption enhancement with K_{oc} values, indicating hydrophilicity

Chemical	<i>In vivo/vitro</i>	Penetrant	Molecular weight	$\log K_{oc}$	Enhancement factor	Measured	Author	Year
SLS 0.1%	<i>In vitro</i>	BA	122	1.83	Not significant	K_p	Nielsen <i>et al.</i>	2007
SLS 0.1%	<i>In vitro</i>	Caffeine	194	0.16	↑	K_p	Nielsen <i>et al.</i>	2007
SLS 0.1%	<i>In vitro</i>	Glycophosphate	170	-1.7	↑	K_p	Nielsen <i>et al.</i>	2007
SLS 0.1%	<i>In vitro</i>	Malathion	330	2.75	↑	K_p	Nielsen <i>et al.</i>	2007
SLS 0.1%	<i>In vitro</i>	Dimethoate	229	0.7	↑	Total pp	Nielsen	2005
SLS 0.1%	<i>In vitro</i>	Methiocarb	225	3.34	Not significant	Total pp	Nielsen	2005
SLS 0.1%	<i>In vitro</i>	Paclobutrazol	293	3.2	↑	Total pp	Nielsen	2005
SLS 0.1%	<i>In vitro</i>	Pirimicarb	238	1.7	↑	Total pp	Nielsen	2005
SLS 0.3%	<i>In vitro</i>	Dimethoate	229	0.7	↑	Total pp	Nielsen	2005
SLS 0.3%	<i>In vitro</i>	Methiocarb	225	3.34	Not significant	Total pp	Nielsen	2005
SLS 0.3%	<i>In vitro</i>	Paclobutrazol	293	3.2	↑	Total pp	Nielsen	2005
SLS 0.3%	<i>In vitro</i>	Pirimicarb	238	1.7	↑	Total pp	Nielsen	2005
SLS 0.25%	<i>In vitro</i>	Tritiated H_2O	22	1.38	↑	Total pp	Nielsen	2005
SLS 0.25%	<i>In vitro</i>	^{14}C - HC	364	1.4	Not significant	Total pp	Frankild <i>et al.</i>	1995
SLS 0.25%	<i>In vitro</i>	Nickel	134	0.05	Not significant	Total pp	Frankild <i>et al.</i>	1995
SLS 2%	<i>In vitro</i>	Tritiated H_2O	22	1.38	↑	Total pp	Frankild <i>et al.</i>	1995
SLS 2%	<i>In vitro</i>	^{14}C - HC	364	1.4	Not significant	Total pp	Frankild <i>et al.</i>	1995
SLS 2%	<i>In vitro</i>	Nickel	134	0.05	Not significant	Total pp	Frankild <i>et al.</i>	1995
SLS 10%	<i>In vitro</i>	Tritiated H_2O	22	1.38	↑	Total pp	Frankild <i>et al.</i>	1995
SLS 10%	<i>In vitro</i>	^{14}C - HC	364	1.4	↑	Total pp	Frankild <i>et al.</i>	1995
SLS 10%	<i>In vitro</i>	Nickel	134	0.05	↑	Total pp	Frankild <i>et al.</i>	1995
SLS 1%	<i>In vivo</i>	Metronidazole	171	0	↓	Concentration in stratum corneum sampled by TS	Ortiz <i>et al.</i>	2008
SLS 1%	<i>In vivo</i>	Metronidazole	171	0	↑	Area under concentration vs time curve by microdialysis	Ortiz <i>et al.</i>	2008
SLS 1%	<i>In vivo</i>	SA	138	2.3	↑	Area under concentration vs time curve by microdialysis	Benfeldt <i>et al.</i>	1999
SLS 2%	<i>In vivo</i>	SA	138	2.3	↑	Area under concentration vs time curve by microdialysis	Benfeldt <i>et al.</i>	1999
SLS 5%	<i>In vivo</i>	PEG	282-590	1.6	↑	K_p sampled by TS	Jakasa <i>et al.</i>	2006b
SLS 5%, GA 5%, LA 5%	<i>In vitro</i>	5-FU (infinite dose)	130	-0.95	↑	Amount penetrated vs time	Copovi <i>et al.</i>	2006
SLS 5%, GA 5%, LA 5%	<i>In vitro</i>	PHE (infinite dose)	122	1.34	↑	Amount penetrated vs time	Copovi <i>et al.</i>	2006
SLS 5%, GA 5%, LA 5%	<i>In vitro</i>	PHB (infinite dose)	150	2.33	↑	Amount penetrated vs time	Copovi <i>et al.</i>	2006
SLS 5%, GA 5%, LA 5%	<i>In vitro</i>	PHP (infinite dose)	164	2.89	↑, ↓, ↓	Amount penetrated vs time	Copovi <i>et al.</i>	2006

For abbreviations see Table 8.

Osamura *et al.* (1984) compared skin penetration of nicotinic acid compounds through several skin conditions in the guinea pig. They produced allergic contact dermatitis by sensitization with 2,4-dinitro-1-chlorobenzene in ethanol. The release of nicotinic acid and methyl nicotinate from water and olive oil was greatest in tape-stripped skin, followed by irritated, allergic and normal skin condition.

Sodium lauryl sulfate induces irritant dermatitis and has frequently been used as a model of irritant dermatitis besides being used as a drug penetration enhancer. Moon *et al.* (1990) in an *in vivo* study in hairless guinea pigs showed more than a 2-fold increase of hydrocortisone and benzoic acid through SLS-irritated skin. Benfeldt and Serup and Benfeldt *et al.* (1999) used microdialysis to study salicylic acid penetration in rats and humans. SLS-induced irritant dermatitis resulted in an 83-fold increase in penetration ratio for rats, and 46- and 146-fold increases for SLS 1 and 2%, respectively, in humans. Piret *et al.* (2000) observed a reduced Herpes simplex virus type 1 lesion score after addition of 5% SLS to a foscarnet topical gel formulation applied on mice. They attributed the improved efficacy to an increased penetration of the antiviral with SLS.

Wilhelm reported increased *in vitro* penetration for studies performed with saturated drug solutions of indomethacin, hydrocortisone and ibuprofen, individually, through SLS-induced contact dermatitis in guinea pig but not with acitretin. The enhancement was higher for hydrophilic drugs than for lipophilic ones (Wilhelm *et al.*, 1991a). This result was confirmed *in vivo* (Wilhelm *et al.*, 1991b). Likewise, Borrás-Blasco *et al.* (1997, 2004) showed that pre-treatment with SLS did not affect the skin permeability coefficient of most lipophilic compounds, but increased the permeability of hydrophilic to moderately lipophilic compounds, as can be seen in Table 10. In an *in vitro* study carried out on human skin, Nielsen demonstrated that limited damage to the skin (SLS 0.3%) increases the permeability coefficient as well as total percutaneous penetration of chemicals, most significantly for those compounds that, owing to their physicochemical characteristics (the most hydrophilic as well as the most lipophilic), have low penetration rates through intact skin (Nielsen *et al.*, 2007). However, in an *in vitro* study on human skin, Copoví *et al.* (2006) studied penetration enhancer effects of SLS, glycolic acid and lactic acid on infinite doses of 5-fluorouracil and different compounds belonging to the phenylalcohols. None of the pretreatment chemicals increased the penetration of the most lipophilic compound 5-phenyl-pentanol. For the other compounds, the increase

in permeability depended on the concentration of pre-treatment and the lipophilicity of the tested compounds. The most hydrophilic compound, 5-fluorouracil, consistently had the greatest increase in permeability. Nielsen (2005) investigated *in vitro* percutaneous penetration of pesticides varying in lipophilicity through slightly irritated human skin by SLS 0.1 and 0.3%. Increasing the concentration of SLS did not increase penetration of lipophilic pesticides significantly. He noted that hydrophilic compounds had enhanced penetration through the epidermis while lipophilic compounds had enhanced penetration through the dermis and damage increased penetration for both compounds through the dermis. The observation that hydrophilic pesticides prefer depositing in the epidermis explains why these compounds are more sensitive to damage to the epidermis than lipophilic compounds are. Also, hydrophilic compounds had a more decreased lag time with damaged skin compared with lipophilic compounds. However, Frankild *et al.* (1995) did not find enhancement *in vitro* hydrocortisone penetration through SLS-treated human cadaver full-thickness skin. They hypothesized that using a full-thickness skin, including highly hydrated epidermis and dermis, may have acted as an artificial barrier for the lipophilic hydrocortisone. They found a significant dose effect of increased penetration of water and nickel, and a time-effect relationship between pre-treatment time and water penetration when SLS was applied as pre-treatment. The relationship between SLS and nickel was not seen with hydrocortisone until the concentration of SLS was increased to 10%, indicating possible unresponsiveness of damaged skin to increasing lipophilicity.

Ortiz *et al.* (2008) used tape stripping to sample the concentration of metronidazole 30 min after application and found a correlation between the concentration, degree of erythema, and TEWL. Jakasa *et al.* (2006b) assessed the influence of skin damaged by 5% SLS on percutaneous penetration of PEG of varying molecular weights. SLS caused a 3-fold increase in the permeability coefficient for all molecular weights of hydrophilic PEGs, an increase compared with that found by Ortiz *et al.*, possibly owing to a more severe barrier damage because of higher SLS concentration. These results suggest that SLS increases penetration of hydrophilic compounds in skin more than lipophilic ones.

Shokri *et al.* (2001) noted increased diazepam permeability through rat skin *in vitro* using different surfactants: SLS, cetyltrimethylammonium bromide, benzalkonium chloride and Tween 80, each tested at concentrations of 0.5, 1, 2.5 and 5%.

Table 10. Borrás-Blasco *et al.*'s (1997) absorption study in irritated rat skin comparing absorption enhancement with K_{oct} values, indicating hydrophilicity

Chemical	<i>In vivo/vitro</i>	Penetrant	Molecular weight	$\log K_{\text{oct}}$	Enhancement factor	Measured
SLS 5%	<i>In vitro</i>	5-FU	130	-0.95	8.3	↑ K_p from amount penetrated vs time
SLS 5%	<i>In vitro</i>	Antipyrine	188	0.23	5.1	↑ K_p from amount penetrated vs time
SLS 5%	<i>In vitro</i>	Pentoxifylline	278	0.72	4.4	↑ K_p from amount penetrated vs time
SLS 5%	<i>In vitro</i>	Salicylamide	137	1.23	1.9	↑ K_p from amount penetrated vs time
SLS 5%	<i>In vitro</i>	4-Ethylaniline	121	1.97	1.2	↑ K_p from amount penetrated vs time
SLS 5%	<i>In vitro</i>	4- <i>n</i> -Butylaniline	149	3	0.97	↓ K_p from amount penetrated vs time
SLS 5%	<i>In vitro</i>	IM	358	4.42	1.03	↑ K_p from amount penetrated vs time

For abbreviations see Table 8.

The critical micellar concentration (CMC) of SLS and Tween 80 are 0.03 and 0.01% by weight in water, respectively. The presence of propylene glycol raised the CMC of nonionic surfactants by approximately a factor of 10. The highest enhancement ratio for permeation was obtained for 5% concentration of SLS, followed by 1% concentration of benzalkonium chloride and 1% concentration of Tween 80 (Shokri *et al.*, 2001). These results were similar for lorazepam (Nokhodchi *et al.*, 2003). However, increasing surfactant concentration resulted in decreased penetration for both substances. The increase in enhancement ratio for low concentrations is attributed to the ability of surfactant molecules to penetrate the skin and increase its permeability. Lower permeation in enhancer systems beyond 1% concentration is attributed to the ability of surfactant molecules to form micelles, a dampening effect of higher concentrations of surfactants.

Van Den Akker *et al.* (2000b) reported that the use of 1-[2-(decylthio)ethyl]azacyclopentan-2-one (HPE-101), a penetration enhancer that increases disorder in the SC lipids, accelerated the penetration of ALA and ALAHE through mouse skin.

Nangia *et al.* (1993) studied the *in vitro* effects of irritants norephedrin and imipramine on the permeation of compounds with diverse chemical properties: caffeine, indomethacin and hydrocortisone. Norephedrin treatment increased the permeation of caffeine and hydrocortisone but decreased indomethacin absorption. Treatment with imipramine also increased caffeine and hydrocortisone permeation but did not increase indomethacin permeation.

Thus, skin irritation with SLS increases skin absorption for hydrophilic compounds but not for lipophilic compounds. However, skin irritation from other chemicals increases hydrophilic penetration as much as lipophilic.

ULTRAVIOLET IRRADIATION

Table 11 summarizes absorption studies in ultraviolet irradiated skin. UV irradiation causes various skin effects. In hairless mouse skin, UV light increases mitosis, DNA synthesis and epidermal hyperplasia. UV light can also alter cutaneous lipids, leading to decreased phospholipids which are essential as membrane components.

Bronaugh and Stewart (1985) observed the effect of UV irradiation on skin absorption. The backs of rats were irradiated with a UV lamp, producing a mild erythema with 1.5 min and severe erythema with 6 min of irradiation. Percutaneous penetration

with mild erythema resulted in a 3.2-fold increase in nicotine absorption. The severe erythema resulted in 51% absorption of the applied dose. The higher degree of absorption obtained *in vivo* is due to changes in skin barrier during the study. Unlike abrasion or tape-stripping damage that occurs instantaneously, UV irradiation causes progressive damage. This progressive damage occurring from physiological response cannot be simulated in a diffusion cell experiment, so in an *in vitro* system, damage to the skin can be adjusted by varying physical damage to the skin, such as number of abrasion lines. Lamaud and Schalla (1984) measured hydrocortisone absorption after ultra-violet B (UVB) irradiation in hairless rat. Compared with normal skin, UV irradiation increased hydrocortisone concentrations in all skin layers examined by biopsy. Solomon and Lowe (1979) performed an *in vitro* study after UVC irradiation in mice and observed increased absorption of 0.1% hydrocortisone. Ultraviolet light can alter cutaneous lipids, leading to a decrease in phospholipids, and thus increase in absorption.

Van den Akker *et al.* (2004) found that chronic UVB-exposure induced changes in the mouse skin that resulted in a 10-fold increase of percutaneous penetration for 5-aminolevulinic acid compared with normal mouse skin. This increase is still less than through tape-stripped skin. However, in an *in vitro* study, Berenson and Burch (1951) found no difference in the rate of water diffusion through human skin. Günther *et al.* (1998) also found no difference in the *in vivo* skin penetration of methylprednisolone aceponate on healthy and UVB-inflamed human skin.

Animal studies show that UV exposure leads to an increased percutaneous absorption whereas human studies do not. UV irradiation offers the possibility of inducing a defective skin-barrier function and an inflammatory reaction without mechanical perturbation of the skin. However, elevated skin temperature from increased blood flow may have contributed to the increased drug penetration. More studies are needed to properly conclude the effect of UV exposure on absorption in the skin.

DISEASED SKIN

Limited data suggest penetration through clinically diseased skin is enhanced to a modest degree compared with intact skin, if at all, while noncomparative data suggest an increased severity of clinical disease may enhance penetration. Table 12 summarizes absorption studies in diseased skin. Table 13 summarizes human

Table 11. Summary of literature in absorption studies in ultraviolet irradiated skin

Disease model	<i>In vivo/vitro</i>	Skin	Method	Penetrant	Result		Author	Year
UVA + UVB	<i>In vivo</i>	Rat	Urine	¹⁴ C-NA	x7.5	↑	Bronaugh and Stewart	1985
UVA + UVB	<i>In vitro</i>	Rat	Diffusion cells	¹⁴ C-NA	x2.5	↑	Bronaugh and Stewart	1985
UVA	<i>In vitro</i>	Human	Water transfer	H ₂ O	—	—	Berenson and Burch	1951
UVB	<i>In vivo</i>	Rat	Biopsy, TEWL	¹⁴ C-HC	↑	↑	Lamaud and Schalla	1984
UVB	<i>In vivo</i>	Human	Urine, plasma	¹⁴ C-MPA	—	—	Günther <i>et al.</i>	1998
UVB	<i>In vitro</i>	Mouse	Diffusion cells	ALA	x10	↑	Van den Akker <i>et al.</i>	2004
UVC	<i>In vitro</i>	Mouse	Skin biopsy	¹⁴ C-HC	↑	↑	Solomon and Lowe	1979

Disease model: UVA, ultraviolet-A; UVB, ultraviolet-B; UVC, ultraviolet-C.

Method: TEWL, transepidermal water loss.

Penetrant: ALA, 5-aminolevulinic acid; ¹⁴C, 14 carbon; H₂O, water; HC, hydrocortisone; MPA, methylprednisolone aceponate; NA, nicotinic acid.

Result: x, ratio of penetration; ↑, increase of penetration; —, no change.

Table 12. Summary of literature in absorption studies in clinically diseased skin

Disease model	<i>In vivo/vitro</i>	Skin	Method	Penetrant	Result	Author	Year
PSOR	<i>In vivo</i>	Human	Flame photometry, TEWL	H ₂ O	x2–5.6	Grice <i>et al.</i>	1973
PSOR	<i>In vivo</i>	Human	Urine	³ H-TA	x3–x10	Schaefer	1977
PSOR	<i>In vivo</i>	Human	Urine	¹⁴ C-HC	—	Wester <i>et al.</i>	1983
PSOR	<i>In vivo</i>	Human	Urine	¹⁴ C-Dithranol	—	Wester <i>et al.</i>	1987
PSOR	<i>In vivo</i>	Human	Serum	Electrolytes	↑	Shani <i>et al.</i>	1985
PSOR	<i>In vitro</i>	Human	Diffusion cells	Anthrakin	↑	Wang <i>et al.</i>	1987
PSOR	both	Human	Diffusion chambers, urine	¹⁴ C-Lonapalene	↑	Lehman <i>et al.</i>	1992
PSOR	<i>In vitro</i>	Human	Flow-through cells, K _p	8-MOP	x2	Anigbogu <i>et al.</i>	1996
PSOR	<i>In vivo</i>	Human	Skin biopsy	5-MOP	↑	Colombo <i>et al.</i>	2003
PSOR	<i>In vivo</i>	Human	TS	¹²³ I-PAI-2	x10	Gould <i>et al.</i>	2003
PSOR, AD, CD	<i>In vivo</i>	Human	Plasma	Lidocaine, Prilocaine	↑	Juhlin <i>et al.</i>	1989
PSOR, AK	<i>In vitro</i>	Human	PpIX-fluo	ALA	↑	Smits <i>et al.</i>	2005
PSOR, IRR, ECZ	<i>In vivo</i>	Human	Urine (TTCA)	CS ₂	↑	Drexler <i>et al.</i>	1995
PSOR, LU, SP	<i>In vivo</i>	Human	Urine	¹⁴ C-5-FU	x15–75	Erlanger <i>et al.</i>	1970
AD	<i>In vivo</i>	Human	Wealing response	DMSO	↑	Yoshiike <i>et al.</i>	1993
AD	<i>In vitro</i>	Human	Diffusion chamber	Theophylline	↑	Yoshiike <i>et al.</i>	1993
AD	<i>In vivo</i>	Human	TS	Red 215 dye	↑	Hata <i>et al.</i>	2002
AD	<i>In vivo</i>	Human	TS	Yellow 4 dye	↑	Hata <i>et al.</i>	2002
AD	<i>In vivo</i>	Human	TS	1% SLS	x2	Jakasa <i>et al.</i>	2006a
AD	<i>In vivo</i>	Human	TS	PEG	↑	Jakasa <i>et al.</i>	2006a
AD	<i>In vivo</i>	Human	TS	SLS 1%	x1.5	de Jongh <i>et al.</i>	2006
AD	<i>In vivo</i>	Human	TS	Metronidazole	—	Ortiz <i>et al.</i>	2009
AD	<i>In vivo</i>	Human	Microdialysis	Metronidazole	x2.4	Ortiz <i>et al.</i>	2009
AD	<i>In vivo</i>	Human	¹²⁵ I-cortisol RIA, serum	HC	↑	Turpeinen <i>et al.</i>	1988
AD, SD	<i>In vivo</i>	Human	¹²⁵ I-cortisol RIA, serum	HC	↑	Turpeinen <i>et al.</i>	1986
AD, SD	<i>In vivo</i>	Human	Serum	HC	↑	Turpeinen	1988
ECZ	<i>In vitro</i>	Monkey	Diffusion cells	³ H-HC	x2	Bronaugh <i>et al.</i>	1986b
ECZ	<i>In vitro</i>	Monkey	Diffusion cells	TA	x1.3	Bronaugh <i>et al.</i>	1986b
EFAD	<i>In vitro</i>	Mouse	Humidity chamber	¹⁴ C-HC	x2–3	Solomon and Lowe	1978
EFAD	<i>In vivo</i>	Rat	Urine	¹⁴ C-HC	↑	Lambrey <i>et al.</i>	1987
UVB-SC	<i>In vivo</i>	Mouse	PpIX-fluo	ALA	↑	Van den Akker <i>et al.</i>	2000a
UVB-SC	<i>In vivo</i>	Mouse	PpIX-fluo	ALAPE	↑	Van den Akker <i>et al.</i>	2000a
CAC	<i>In vivo</i>	Mouse	PpIX-fluo	ALA	↑	Moan <i>et al.</i>	2001
CAC	<i>In vivo</i>	Mouse	PpIX-fluo	ALAHE	↑	Moan <i>et al.</i>	2001
CAC	<i>In vivo</i>	Mouse	PpIX-fluo	ALAME	↑	Moan <i>et al.</i>	2001
ADI, XRI, CI	<i>In vivo</i>	Human	LDF, TEWL	HN	↑	Lavrijsen <i>et al.</i>	1993
DD, EKV	<i>In vivo</i>	Human	LDF, TEWL	HN	—	Lavrijsen <i>et al.</i>	1993
Erythroderma	<i>In vivo</i>	Human	Plasma cortisol	HC	↑	Aalto-Korte	1995
Strained skin	<i>In vivo</i>	Human	Urine (BEAA)	BEE	↑	Korinth <i>et al.</i>	2003
Erythematous, BDE	<i>In vivo</i>	Human	Urine	o-Toluidine	↑	Korinth <i>et al.</i>	2006
Erythema	<i>In vivo</i>	Human	Hemoglobin adducts	o-Toluidine, Aniline	x3.5	Korinth <i>et al.</i>	2007

Erythema	In vivo	Human	Hemoglobin adducts	Aniline	x1.2	Korinth <i>et al.</i>	2007
MF	In vivo	Human	Urine	¹⁴ C-Carmustine	↑	Zackheim <i>et al.</i>	1977
BCC	In vivo	Human	Microdialysis	ALA	x2.5	Wennberg <i>et al.</i>	2000

Disease model: AD, atopic dermatitis; ADI, autosomal dominant ichthyosis vulgaris; AK, actinic keratosis BCC, basal cell carcinoma; BCNU, 1,3-bis(2-chloroethyl)-1-nitrosourea; BDE, burned dishydrotic eczema; CAC, colon adenocarcinoma; CD, contact dermatitis; CI, autosomal recessive congenital ichthyosis; D, dermatitis; DD, dyskeratosis follicularis (Darier's disease); ECZ, eczema; EFAD, essential fatty acid deficiency; EKV, erythrodermatitis; IRR, irritation; LU, leg ulcer; MF, mycosis fungoides; PSOR, psoriasis; SD, seborrheic dermatitis; SP, spinalioma; UVB-SC, ultraviolet-B induced skin cancer; XRI, X-linked recessive ichthyosis.

Method: BEAA, butoxyethoxyacetic acid; LDF, laser-Doppler flowmetry; PpIX-fluo, protoporphyrin IX fluorescence; RIA, radioimmunoassay, TEWL, transepidermal water loss; TS, tape stripping; TTCA, 2-thiothiazolidine-4-carboxylic acid.

Penetrant: ALA, 5-aminolevulinic acid; ALAHE, ALA hexylester; ALAME, ALA methylester; ALAPE, ALA pentyl ester; BEE, 2-(2-butoxyethoxy)ethanol; ¹⁴C, 14 carbon; CS₂, carbon disulfide; DMSO, dimethyl sulfoxide; 5-FU, 5-fluorouracil; ³H, tritium hydrogen; H₂O, water; HC, hydrocortisone; HN, hexyl nicotinate; ¹²⁵I, iodine 125; M-³H, Methoxyl tritium hydrogen; 5-MOP, 5-methoxypsoralen; 8-MOP, 8-methoxypsoralen; PAI-2, plasminogen activator inhibitor type 2; PEG, polyethylene glycols SLS, sodium lauryl sulfate; TA, triamcinolone acetonide.

Result: x, ratio of penetration; ↑, increase of penetration; ↓, decrease; —, no change.

disease absorption studies based on degree of hydrophilicity (defined by log K_{oct} values) of compounds. Lack of data and inconsistent results may be explained by difficulty in obtaining specimens of diseased skin, difficulty in reproduction and variability in skin damage (Gattu and Maibach, 2011).

Essential Fatty Acid-deficient Animal

Essential fatty acid deficiency (EFAD) results in epidermal hyperproliferation with acanthosis and hyperkeratosis. EFAD mice have been used as a model of experimental epidermal hyperproliferation. Solomon and Lowe (1978) used EFAD hairless mice to determine percutaneous absorption of a 0.1% solution of 4-¹⁴C-hydrocortisone. They showed significant increase (2- to 3-fold) *in vitro* absorption through EFAD compared with normal hairless mouse skin. Lambrey *et al.* (1987) studied hydrocortisone absorption in EFAD rat model. On the first day, 19% of the total applied radioactive hydrocortisone was recovered in the urine of the EFAD rats, while 1% was recovered from control.

Altered Skin

Drexler *et al.* (1995) showed that persons with skin disease or skin irritation absorb more carbon disulfide via the skin than persons with normal skin. Korinth *et al.* (2003) found an enhancement in percutaneous absorption of 2-(2-butoxyethoxy) ethanol in printing workers with strained skin. Korinth *et al.* (2006) observed that the relationship between skin lesions and internal exposure to lipophilic aromatic amine *o*-toluidine was relatively higher in workers with damaged epidermal barrier such as skin burns and particularly with dyshidrotic eczema, than in workers with normal or slightly erythematous skin. In an *in vivo* study on rubber industry workers exposed to aniline and *o*-toluidine, Korinth *et al.* (2007) found that hemoglobin–aromatic amines-adduct levels were significantly higher in workers with erythema than in workers with healthy skin.

Psoriasis

Psoriasis has a compromised barrier function by means of partly or completely damaged SC (Grice *et al.*, 1973; Schaefer, 1985; Schaefer *et al.*, 1984), which may result in increased TEWL. Grice *et al.* studied TEWL and its sodium and potassium content in normal and psoriatic skin. The TEWL ranged from 2.0 to 5.6 $\mu\text{g}/\text{cm}^2/\text{h}$ in 6 psoriatic patients, while the mean TEWL in 15 normal subjects was $0.3 \pm 0.1 \mu\text{g}/\text{cm}^2/\text{h}^1$. This demonstrated electrolyte barrier preservation in active psoriasis despite serious impairment of the water barrier (Grice *et al.*, 1973). Wang *et al.* (1987) investigated the release and permeation of anthralin with an *in vitro* Franz diffusion cell unit. The study showed that involved psoriatic skin was much more permeable to anthralin than uninvolved psoriatic skin and that the rate-limiting step to permeation of anthralin products was their release rates rather than their permeability.

Shani *et al.* (1985), who measured the penetration of electrolytes through the skin of healthy and psoriatic patients who had bathed in the Dead Sea, found significant increases in the levels of serum Br, Rb, Ca, Zn only in the psoriatic group. Erlanger *et al.* (1970) observed a 15- to 20-fold-increased penetration of 5-fluorouracil ointment on psoriatic patient skin compared with healthy skin. Anigbogu *et al.* (1996), in

Table 13. Summary of literature in human absorption studies in diseased skin comparing absorption enhancement with K_{oct} values, indicating hydrophilicity

Disease model	<i>In vivo/vitro</i>	Penetrant	Molecular weight	$\log K_{\text{oct}}$	Enhancement factor	Measured	Author	Year
Atopic dermatitis	<i>In vivo</i>	Metronidazole	171	0	Not significant	Concentration in stratum corneum sampled by TS	Ortiz <i>et al.</i>	2009
Atopic dermatitis	<i>In vivo</i>	Metronidazole	171	0	2.4	Area under concentration vs time curve by microdialysis	Ortiz <i>et al.</i>	2009
Uninvolved skin atopic dermatitis patients	<i>In vivo</i>	PEG	150-590	1.6	2	D (diffusion coefficient), K_p	Jakasa <i>et al.</i>	2007
Uninvolved skin atopic dermatitis patients	<i>In vivo</i>	1% SLS	262	5.4	2	D sampled by TS	Jakasa <i>et al.</i>	2006a
Uninvolved skin atopic dermatitis patients	<i>In vivo</i>	Red 215 dye	423	Lipophilic	Increased	Photoacoustic spectrometry sampled by TS	Hata <i>et al.</i>	2002
Uninvolved skin atopic dermatitis patients	<i>In vivo</i>	Yellow 4 dye	524	Hydrophilic	Increased	Photoacoustic spectrometry sampled by TS	Hata <i>et al.</i>	2002
Psoriasis	<i>In vivo</i>	Hydrocortisone (^{14}C -HC)	362	1.6	Not significant	% Applied dose found in urine	Wester <i>et al.</i>	1983
Mycosis fungoides	<i>In vivo</i>	BCNU/carmustine	218	1.5	Increased	% Applied dose found in urine	Zackheim <i>et al.</i>	1977

For abbreviations see Table 12.

an *in vitro* study, found a greater than 2-fold increase in the equilibrium uptake of 8-methoxypsoralen in psoriatic skin compared with normal skin. The 8-methoxypsoralen aqueous/plaque partition coefficient was also greater than 2-fold. Colombo *et al.* (2003) also noted an increase in 5-methoxypsoralen penetration through psoriatic human skin.

Schaefer *et al.* (1977) noted that triamcinolone acetonide penetration was 3- to 10-fold higher in psoriatic human compared with healthy skin. Gould *et al.* (2003) showed in an *in vivo* study that psoriatic skin promoted greater penetration of plasminogen activator inhibitor type 2 than uninvolved skin. Smits *et al.* (2005) investigated the fluorescence in psoriatic and actinic keratosis lesions before and after fractionated photodynamic therapy with topical 5-aminolevulinic acid. After ALA application, psoriatic plaques and actinic keratosis lesions showed higher fluorescence compared with nonlesional skin. This increase was more pronounced in psoriasis than in actinic keratosis.

However, Wester *et al.* (1983, 1987) reported in an *in vivo* experiment that involved psoriatic skin was no more permeable to hydrocortisone or dithranol than normal skin, suggesting one of the following: psoriasis may not have a penetration barrier defect, the penetration of lipophilic compounds may not be sensitive to damaged skin, or the vasoconstriction activity of the drug might have counteracted the disrupted barrier properties.

Although the Lehman *et al.* (1992) study was not designed to determine the difference in permeability between normal and psoriatic skin, they observed that the *in vitro* penetration of lonapalene through cryopreserved normal skin achieved only one-half the peak flux observed from the *in vivo* urinary excretion rate, suggesting that psoriatic plaque may be more permeable than normal skin.

Aalto-Korte (1995) followed TEWL and percutaneous absorption of hydrocortisone in psoriatic patients undergoing treatment and observed a decline in both after 4–6 days, indicating that improvement of skin barrier function led to a decreased absorption rate.

These studies show that skin penetration is often increased in psoriatic skin. As most of psoriasis treatments are based on topical therapy, particular attention should be given to this issue.

Atopic Dermatitis

Atopic dermatitis demonstrates a barrier defect attributed to abnormalities in barrier ceramides (Di Nardo *et al.*, 1998), resulting in increased TEWL (Linde, 1992). Correlations between TEWL values and skin permeability of compounds have been suggested (Levin and Maibach, 2005). Penetration may not be enhanced through atopic dermatitis skin (Ortiz *et al.*, 2009), but some studies show an enhancement through uninvolved skin of atopic dermatitis patients.

Turpeinen *et al.* (1988) studied percutaneous absorption of hydrocortisone in 18 young adults after the acute phase of atopic dermatitis by measuring serum cortisol levels using a (^{125}I) cortisol radioimmunoassay kit. Endogenous secretion of cortisol was suppressed using dexamethasone. Patients with widespread and high-grade dermatitis showed a median serum concentration of 314 nmol/l in the remission group. The plasma cortisol concentration was higher in exacerbation than in remission, showing that acute atopic dermatitis may leave skin more sensitive to hydrocortisone penetration than when in remission. Two other studies also showed greater increased

absorption of topical 1% hydrocortisone in children with severe dermatitis than moderate dermatitis, and also higher in moderate dermatitis than in mild dermatitis (Turpeinen *et al.*, 1986; Turpeinen, 1988). Aalto-Korte and Turpeinen (1993) found that cortisol rise was correlated to the severity of dermatitis and TEWL. However, variation was observed among patients, making it difficult to predict permeability by clinical diagnosis alone and emphasizing the need for TEWL measurement.

Previously, Juhlin noticed that blanching reactions owing to EMLA[®] (eutectic mixture of 5% lidocaine and prilocaine) were accentuated in dry and eczematous skin of patients with atopic dermatitis (Juhlin and Rollman, 1984). In another *in vivo* study on psoriatics and dermatitis patients, he showed that the absorption of EMLA[®] through diseased skin was faster than through normal skin with higher plasma concentrations: 1000 times more in atopic dermatitis than in healthy subjects (Juhlin *et al.*, 1989). A prompt but shorter anesthetic effect in diseased patients was also observed.

De Jongh *et al.* (2006), in an *in vivo* study, found a 1.5-fold higher diffusivity for SLS in atopic persons than nonatopics. Jakasa *et al.* (2006a) also observed a 2-fold increase in percutaneous penetration of SLS with atopic dermatitis patients compared with control subjects in an *in vivo* study. In another study, Jakasa found that other lipophilic compounds, polyethylene glycols, also had modest enhancement (Jakasa *et al.*, 2006b). This showed that even noninvolved skin of atopic patients have altered barrier characteristics with greater SLS penetration than controls. Similarly, Yoshiike *et al.* (1993) reported increased theophylline penetration not only in involved but also in uninvolved atopic dermatitis skin compared with control subjects. Hata *et al.* (2002) noted that penetration of hydrophilic yellow dye increased in proportion to severity of disease. This emphasizes the importance of considering risks of exposure in patients with a history of atopy, even when patients do not manifest the active disease (Gattu and Maibach, 2010). Thus, similar to psoriatic skin, atopic dermatitis leads to increased chemical absorption.

Exfoliative Dermatitis

In exfoliative dermatitis, a significant amount of sodium was absorbed from a corn starch bath in a 0.275 M sodium bicarbonate solution. Hydrocortisone penetration was greater than 50% (~50-fold increase).

Aalto-Korte and Turpeinen (1995) evaluated hydrocortisone skin penetration in patients with erythroderma using plasma cortisol level. Their data showed that 24 h absorption of hydrocortisone in patients was significantly higher than the penetration of hydrocortisone in normal skin (4–19 vs 1% respectively).

Eczema

Using monkey skin *in vitro*, Bronaugh *et al.* (1986b) found that percutaneous absorption of hydrocortisone through eczematous skin was twice that of normal skin.

Mycosis Fungoides

Zackheim *et al.* (1977) measured *in vivo* percutaneous absorption of 1,3-bis(2-chloroethyl)-1-nitrosourea (Carmustine) in five patients with mycosis fungoides. Absorption through diseased skin was shown to be 1- to 5-fold greater than through normal

skin. Increased permeation was explained as an impaired SC barrier, represented by parakeratosis, inter-/intracellular edema, vascular dilatation or other changes often found in lesions of mycosis fungoides affected skin.

Keratinisation Disorders

Lavrijsen *et al.* (1993) characterized the SC barrier function of patients with keratinization disorders – autosomal dominant ichthyosis vulgaris, X-linked recessive ichthyosis, autosomal recessive congenital ichthyosis, dyskeratosis follicularis (Darier's disease) and erythrokeratoderma variabilis – using among other things the vascular response to hexyl nicotinate penetration into the skin as determined by laser-Doppler flowmetry. A significant decrease in lag time was found in the three forms of ichthyosis compared with the healthy controls. Comparison between patient groups showed significant differences between recessive congenital ichthyosis and dyskeratosis follicularis/erythrokeratoderma variabilis but not between congenital ichthyosis and the other types of ichthyosis. They attributed the decreased lag time to an acceleration of hexyl nicotinate flux through diseased skin. However, no difference was found between healthy and dyskeratosis follicularis or erythrokeratoderma variabilis patients.

Skin Cancer

Van den Akker *et al.* (2000a) studied the penetration of ALA and 5-aminolevulinic pentyl ester (ALAPE) through UVB-induced early mouse skin cancer. ALA and ALAPE penetration were higher on UVB-induced visible lesions than on normal or UVB-induced altered skin as interpreted from the enhanced PpIX (protoporphyrin IX) production induced by ALA and ALAPE. In UVB-induced altered skin and visible lesions, ALAPE-induced PpIX fluorescence levels are higher compared with ALA, demonstrating better skin penetration properties. This can be explained by the fact that ALA esters are more lipophilic, and therefore may have better penetration properties than ALA. Wennberg *et al.* (2000), utilizing microdialysis, studied the topical penetration of aminolevulinic acid in patients with basal cell carcinoma. He reported a 2.5-fold increase of blood perfusion in basal cell carcinomas compared with healthy areas. Moan *et al.* (2001) showed that the mouse skin overlaying tumors (human colon adenocarcinoma cell line) was more permeable to ALA than normal skin. They also found that the tumor to normal tissue ratio of PpIX fluorescence levels produced was higher for ALA esters (ALAHE, ALAME) than ALA, although the amount of PpIX produced solely in the tumor by the ALA esters was not necessarily greater than ALA.

CONCLUSION

Skin can be damaged by many methods that affect skin penetration. Tape stripping, which may lead to a near complete removal of SC, increases absorption of lipophilic and hydrophilic compounds. Freezing, commonly used to preserve skin, does not seem to modify skin water absorption but leads to an increase in penetration for other compounds. More studies are needed to confirm if freezing has a more profound effect on lipophilic compounds.

Delipidization with a chloroform–methanol mixture seems to increase permeability of all hydrophilic compounds, but not lipophilics. Acetone skin pre-treatment enhances hydrophilic

compound penetration but not as much for highly lipophilic compounds. The literature on the effect of lipid extraction on percutaneous penetration is not complete. Abrams *et al.* (1993) studied the phenomena *in vitro* with human skin, concluding that the more effective the stratum corneum lipid solvation is, the greater the TEWL enhancement. This is an indirect measurement of water barrier function. Conversely, Bucks *et al.* (1983) delipidized human skin *in vivo*, noting no such effect. Much experimental work remains to be done before a general theory can be postulated.

Skin irritation with SLS increases hydrophilic compound skin absorption, but not lipophilic. However, skin irritation from other chemicals increases lipophilic penetration as much as hydrophilic.

Few studies have documented UV irradiation and skin penetration, but all animal studies reported increased absorption. Altered or diseased skin such as psoriasis, atopic dermatitis or skin cancer, increases skin permeability. Differences may exist in various diseases as well as varying degrees of severity of each disease.

As different methods are used in these studies, our conclusions should be interpreted with caution. Even if results are similar, skin kinetics may be different between species or anatomic sites and it is important to note not only mean values but also the range of these results. Keep in mind that hair follicles are a contributing factor, especially in animals. There are also possible metabolic differences between species. This information, when significant amounts of data become available, may help explain some of the enhancement factors noted here. Many questions regarding chemical relation to physical chemistry require further research. Further studies *in vivo* on human skin are needed to confirm the results noted here. As microdialysis does not trap all the penetrant and alters the skin physiology itself, clinical interpretation of results should be done with caution. Microdialysis studies showed higher penetration rates than traditional sampling techniques or urinary excretion (Gattu and Maibach, 2011). Microdialysis may become a method of choice to assess skin penetration *in vivo* once we better comprehend how to relate perfusion through the dermal compartment to total flux.

The impact of this large, but incomplete, data set relates to quantity of a chemical/drug entering the body – and hence exposes blood and internal organs. Traditionally the toxicologist accounts for differences from normal skin with safety factors. As seen in the tables, in some instances damaged skin leads to minimal increases in flux, whereas in other instances, marked increases have been observed. Thus a perhaps somewhat arbitrary safety factor may be inappropriate. As additional experiments are carried out, most readily interpreted from *in vitro* and *in vivo* skin, a more appropriate safety factor may be established.

Taken together, the data summarized here begin to characterize flux alteration associated with damaged skin. We note that there is insufficient experimental data available to hypothesize possible mechanisms of enhancement for the several types of damaged skin overviewed here. Understanding the degree of alteration requires interpretation of the conditions involved (*in vitro*, *in vivo*, animal, man, etc.) and the enlarging of our database to a more complete physicochemical spectrum.

REFERENCES

- Aalto-Korte K. 1995. Improvement of skin barrier function during treatment of atopic dermatitis. *J. Am. Acad. Dermatol.* **33**: 969–972.
- Aalto-Korte K, Turpeinen M. 1993. Transepidermal water loss and absorption of hydrocortisone in widespread dermatitis. *Br. J. Dermatol.* **128**: 633–635; doi: 10.1111/j.1365-2133.1993.tb00258.x.
- Aalto-Korte K, Turpeinen M. 1995. Quantifying systemic absorption of topical hydrocortisone in erythroderma. *Br. J. Dermatol.* **133**: 403–408; doi: 10.1111/j.1365-2133.1995.tb02668.x.
- Abrams K, Harvell JD, Shriner D, Wertz P, Maibach HI, Rehfeldt SJ. 1993. Effect of organic solvents on *in vitro* human skin water barrier function. *J. Invest. Dermatol.* **101**: 609–613; doi: 10.1111/1523-1747.ep12366068.
- Akomeah FK, Martin GP, Muddle AG, Brown MB. 2008. Effect of abrasion induced by a rotating brush on the skin permeation of solutes with varying physicochemical properties. *Eur. J. Pharm. Biopharm.* **68**: 724–734; doi: 10.1016/j.ejpb.2007.06.005.
- Anigbogu A, Williams A, Barry B. 1996. Permeation characteristics of 8-methoxypsoralen through human skin; relevance to clinical treatment. *J. Pharm. Pharmacol.* **48**: 357–366; doi: 10.1111/j.2042-7158.1996.tb05933.x.
- Balogh D, Bauer M, Riccabona G. 1985. The influence of povidone–iodine treatment on thyroid hormones in severe burns. *J. Hosp. Infect.* **6**: 147–153; doi: 10.1016/S0195-6701(85)80061-X.
- Behl CR, Flynn GL, Kurihara T, Smith W, Gatmaitan OG, Higuchi WI, Ho NF, Pierson CL. 1980. Permeability of thermally damaged skin: I. immediate influences of 60 °C scalding on hairless mouse skin. *J. Invest. Dermatol.* **75**: 340–345.
- Behl CR, Flynn GL, Barrett M, Walters KA, Linn EE, Mohamed Z, Kurihara T, Ho NF, Higuchi WI. 1981. Permeability of thermally damaged skin: II. Immediate influences of branding at 60 °C on hairless mouse skin permeability. *Burns*. **7**: 389–399.
- Behl CR, Barrett M, Flynn GL, Kurihara T, Walters KA, Gatmaitan OG, Harper N., Higuchi WI, Ho NF, Pierson CL. 1982. Hydration and percutaneous absorption III: Influences of stripping and scalding on hydration alteration of the permeability of hairless mouse skin to water and *n*-alkanols. *J. Pharm. Sci.* **71**: 229–234.
- Benfeldt E. 1999. *In vivo* microdialysis for the investigation of drug levels in the dermis and the effect of barrier perturbation on cutaneous drug penetration: studies in hairless rats and human subjects. *Acta Derm. Venerol. Suppl. (Stockh.)* **206**: 1–59.
- Benfeldt E, Serup J. 1999. Effect of barrier perturbation on cutaneous penetration of salicylic acid in hairless rats: *in vivo* pharmacokinetics using microdialysis and non-invasive quantification of barrier function. *Arch. Dermatol. Res.* **291**: 517–526; doi: 10.1007/s004030050447.
- Benfeldt E, Serup J, Menné T. 1999. Effect of barrier perturbation on cutaneous salicylic acid penetration in human skin: *in vivo* pharmacokinetics using microdialysis and non-invasive quantification of barrier function. *Br. J. Dermatol.* **140**: 739–748; doi: 10.1046/j.1365-2133.1999.02859.x.
- Berenson G, Burch G. 1951. Studies of diffusion of water through dead human skin; the effect of different environmental states and of chemical alterations of the epidermis. *Am. J. Trop. Med. Hyg.* **31**: 842–853.
- Boosalis M, McCall J, Ahrenholz D, Solem L, McClain C. 1987. Serum and urinary silver levels in thermal injury patients. *Surgery* **101**: 40–43.
- Borrás-Blasco J, López A, Moran M, Díez-Sales O, Herráez-Domínguez M. 1997. Influence of sodium lauryl sulphate on the *in vitro* percutaneous absorption of compounds with different lipophilicity. *Eur. J. Pharm. Sci.* **5**: 15–22; doi: 10.1016/S0928-0987(96)00184-4.
- Borrás-Blasco J, Díez-Sales O, López A, Herráez-Domínguez M. 2004. A mathematical approach to predicting the percutaneous absorption enhancing effect of sodium lauryl sulphate. *Int. J. Pharm.* **269**: 121–129; doi: 10.1016/j.ijpharm.2003.09.021.
- Brain KR, Walters KA, Green DM, Brain S, Loretz LJ, Sharma RK, Dressler WE. 2005. Percutaneous penetration of diethanolamine through human skin *in vitro*: application from cosmetic vehicles. *Food Chem. Toxicol.* **43**: 681–690; doi: 10.1016/j.fct.2004.12.021.
- Bronaugh R, Stewart R. 1985. Methods for *in vitro* percutaneous absorption studies V: permeation through damaged skin. *J. Pharm. Sci.* **74**: 1062–1066; doi: 10.1002/jps.2600741008.
- Bronaugh R, Stewart R, Simon M. 1986a. Methods for *in vitro* percutaneous absorption studies. VII: use of excised human skin. *J. Pharm. Sci.* **75**: 1094–1097; doi: 10.1002/jps.2600751115.
- Bronaugh R, Weingarten D, Lowe N. 1986b. Differential rates of percutaneous absorption through the eczematous and normal skin of a monkey. *J. Invest. Dermatol.* **87**: 451–453; doi: 10.1111/1523-1747.ep12455487.
- Bucks D, Maibach H, Menczel E, Wester R. 1983. Percutaneous penetration of hydrocortisone in humans following skin delipidization by 1:1:1 trichloroethane. *Arch. Dermatol. Res.* **275**: 242–245.
- Chen J, Han CM, Su GL, Tang ZJ, Su SJ, Lin XW. 2007. Randomized controlled trial of the absorbency of four dressings and their effects on the evaporation of burn wounds. *Chin. Med. J.* **120**: 1788–1791.

- Colombo G, Zucchi A, Allegra F, Colombo P, Zani F, Santi P. 2003. *In vitro* and *in vivo* study of 5-methoxypsoralen skin concentration after topical application. *Skin Pharmacol. Appl. Skin Physiol.* **16**: 130–136; doi: 10.1159/000069025.
- Copoví A, Díez-Sales O, Herráez-Domínguez JV, Herráez-Domínguez M. 2006. Enhancing effect of alpha-hydroxyacids on 'in vitro' permeation across the human skin of compounds with different lipophilicity. *Int. J. Pharm.* **314**: 31–36; doi: 10.1016/j.ijpharm.2006.01.033.
- de Jongh C, Jakasa I, Verberk M, Kezic S. 2006. Variation in barrier impairment and inflammation of human skin as determined by sodium lauryl sulphate penetration rate. *Br. J. Dermatol.* **154**: 651–657; doi: 10.1111/j.1365-2133.2005.06989.x.
- Di Nardo A, Wertz P, Giannetti A, Seidernari SL. 1998. Ceramide and cholesterol composition of the skin of patients with atopic dermatitis. *Acta Derm. Venereol.* **78**: 27–30; doi: 10.1080/00015559850135788.
- Dreher F, Arens A, Hostýnek J, Mudumba S, Ademola J, Maibach H. 1998. Colorimetric method for quantifying human stratum corneum removed by adhesive-tape stripping. *Acta Derm. Venereol.* **78**: 186–189; doi: 10.1080/000155598441495.
- Drexler H, Ulm K, Hubmann M, Hardt R, Göen T, Mondorf W, Lang E, Angerer J, Lehnert G. 1995. Carbon disulphide. III. Risk factors for coronary heart diseases in workers in the viscose industry. *Int. Arch. Occup. Environ. Health* **67**: 243–252.
- Erlanger M, Martz G, Ott F, Storck H, Rieder J, Kessler S. 1970. Cutaneous absorption and urinary excretion of 6-¹⁴C-5-fluorouracil ointment applied in an ointment to healthy and diseased human skin. *Dermatologica* **140**(suppl. 1): 7–14.
- Fang JY, Hwang TL, Leu YL. 2003. Effect of enhancers and retarders on percutaneous absorption of flurbiprofen from hydrogels. *Int. J. Pharm.* **250**: 313–325; doi: 10.1016/S0378-5173(02)00540-9.
- Feldmann R, Maibach H. 1965. Penetration of ¹⁴C hydrocortisone through normal skin: the effect of stripping and occlusion. *Arch. Dermatol.* **91**: 661–666; doi: 10.1001/archderm.1965.01600120093023.
- Flynn GL, Behl CR, Walters KA, Gatmaitan OG, Wittkowsky A, Kurihara T, Ho NF, Higuchi WI, Pierson CL. 1980. Permeability of thermally damaged skin III: influence of scalding temperature on mass transfer of water and *n*-alkanols across hairless mouse skin. *Burns* **8**: 47–58; doi: 10.1016/0305-4179(81)90089-9.
- Frankild S, Andersen K, Nielsen G. 1995. Effect of sodium lauryl sulfate (SLS) on *in vitro* percutaneous penetration of water, hydrocortisone and nickel. *Contact Dermatitis* **32**: 338–345; doi: 10.1111/j.1600-0536.1995.tb00622.x.
- Froebe CL, Simion FA, Rhein LD, Cafan RH, Kligman A. 1990. Stratum corneum lipid removal by surfactants: relation to *in vivo* irritation. *Dermatologica* **181**: 277–283.
- Fukuyama K, Inoue N, Suzuki H, Epstein W. 1976. Keratinization. *Int. J. Dermatol.* **15**: 473–489; doi: 10.1111/j.1365-4362.1976.tb00713.x.
- Fuller FW, Parrish M, Nance FC. 1994. A review of the dosimetry of 1% silver sulfadiazine cream in burn wound treatment. *J. Burn Care Rehabil.* **15**: 213–223; doi: 10.1097/00004630-199405000-00003.
- Fulmer AW, Kramer GJ. 1986. Stratum corneum lipid abnormalities in surfactant-induced dry scaly skin. *J. Invest. Dermatol.* **86**: 598–602; doi: 10.1111/1523-1747.ep12355351.
- Gattu S, Maibach HI. 2010. Enhanced absorption through damaged skin: an overview of the *in vitro* human model. *Skin Pharmacol. Physiol.* **23**: 171–176; doi: 10.1159/000288163.
- Gattu S, Maibach HI. 2011. Modest but increased penetration through damaged skin: an overview of the *in vivo* human model. *Skin Pharmacol. Physiol.* **24**: 2–9; doi: 10.1159/000314995.
- Goff B, Bachor R, Kollias N, Hasan T. 1992. Effects of photodynamic therapy with topical application of 5-aminolevulinic acid on normal skin of hairless guinea pigs. *J. Photochem. Photobiol. B* **15**: 239–251; doi: 10.1016/1011-1344(92)85128-H.
- Gould A, Sharp P, Smith D, Stegink A, Chase C, Kovacs JC, Penglis S, Chatterton BE, Bunn CL. 2003. Increased permeability of psoriatic skin to the protein, plasminogen activator inhibitor 2. *Arch. Dermatol. Res.* **295**: 249–254; doi: 10.1007/s00403-003-0425-4.
- Grice K, Sattar H, Baker H. 1973. The cutaneous barrier to salts and water in psoriasis and in normal skin. *Br. J. Dermatol.* **88**: 459–463; doi: 10.1111/j.1365-2133.1973.tb15450.x.
- Günther C, Kecskes A, Staks T, Täuber U. 1998. Percutaneous absorption of methylprednisolone aceponate following topical application of Advantan lotion on intact, inflamed and stripped skin of male volunteers. *Skin Pharmacol. Appl. Skin Physiol.* **11**: 35–42.
- Hadzija B, Ruddy S, Ballenger E. 1992. Effect of freezing on iontophoretic transport through hairless rat skin. *J. Pharm. Pharmacol.* **44**: 387–390; doi: 10.1111/j.2042-7158.1992.tb03630.x.
- Harada K, Murakami T, Yata N, Yamamoto S. 1992. Role of intercellular lipids in stratum corneum in the percutaneous permeation of drugs. *J. Invest. Dermatol.* **99**: 278–282; doi: 10.1111/1523-1747.ep12616623.
- Harrison S, Barry B, Dugard P. 1984. Effects of freezing on human skin permeability. *J. Pharm. Pharmacol.* **36**: 261–262; doi: 10.1111/j.2042-7158.1984.tb04363.x.
- Hata M, Tokura Y, Takigawa M, Sato M, Shioya Y, Fujikura Y, Imokawa G. 2002. Assessment of epidermal barrier function by photoacoustic spectrometry in relation to its importance in the pathogenesis of atopic dermatitis. *Lab. Invest.* **82**: 1451–1461.
- Hawkins GJ, Reifenrath W. 1984. Development of an *in vitro* model for determining the fate of chemicals applied to skin. *Fundam. Appl. Toxicol.* **4**: S133–144; doi: 10.1016/0272-0590(84)90145-3.
- Ilyin L, Ivannikov A, Parfenov Y, Stolyarov V. 1975. Strontium absorption through damaged and undamaged human skin. *Health Phys.* **29**: 75–80; doi: 10.1097/00004032-197507000-00009.
- Imokawa G, Akasaki S, Minematsu Y. 1989. Importance of intercellular lipids in water-retention properties of the stratum corneum: induction and recovery study of surfactant dry skin. *Arch. Dermatol. Res.* **281**: 45–51; doi: 10.1007/BF00424272.
- Inoue K, Ogawa K, Suzuki Y, Okada J, Kusai A, Ikeda M, Nishimura K. 2000. The skin permeation mechanism of ketotifen: evaluation of permeation pathways and barrier components in the stratum corneum. *Drug Dev. Ind. Pharm.* **26**: 45–53.
- Jakasa I, de Jongh C, Verberk M, Bos J, Kezic S. 2006a. Percutaneous penetration of sodium lauryl sulphate is increased in uninvolved skin of patients with atopic dermatitis compared with control subjects. *Br. J. Dermatol.* **155**: 104–109; doi: 10.1111/j.1365-2133.2006.07319.x.
- Jakasa I, Verberk M, Bunge A, Kruse J, Kezic S. 2006b. Increased permeability for polyethylene glycols through skin compromised by sodium lauryl sulphate. *Exp. Dermatol.* **15**: 801–807; doi: 10.1111/j.1600-0625.2006.00478.x.
- Jakasa I, Verberk MM, Esposito M, Bos JD, Kezic S. 2007. Altered penetration of polyethylene glycols into uninvolved skin of atopic dermatitis patients. *J. Invest. Dermatol.* **127**: 129–134; doi: 10.1038/sj.jid.5700582.
- Juhlin L, Rollman O. 1984. Vascular effects of a local anesthetic mixture in atopic dermatitis. *Acta Derm. Venereol.* **64**: 439–440.
- Juhlin L, Hägglund G, Evers H. 1989. Absorption of lidocaine and prilocaine after application of a eutectic mixture of local anesthetics (EMLA) on normal and diseased skin. *Acta Derm. Venereol.* **69**: 18–22.
- Kasting G, Bowman L. 1990a. DC electrical properties of frozen, excised human skin. *Pharm. Res.* **7**: 134–143.
- Kasting G, Bowman L. 1990b. Electrical analysis of fresh, excised human skin: a comparison with frozen skin. *Pharm. Res.* **7**: 1141–1146.
- Kemppainen B, Riley R, Pace J, Hoerr F. 1986. Effects of skin storage conditions and concentration of applied dose on [³H]-T-2 toxin penetration through excised human and monkey skin. *Food Chem. Toxicol.* **24**: 221–227; doi: 10.1016/0278-6915(86)90232-2.
- Kitagawa S, Li H. 1999. Effects of removal of stratum corneum, delipidization and addition of enhancers, ethanol and L-menthol, on skin permeation of benzoic acid and its 4-*n*-alkyl substituents in excised guinea pig dorsal skin. *Chem. Pharm. Bull. (Tokyo)* **47**: 44–47.
- Korin G, Göen T, Kaemeyer M, Broding HC, Drexler H. 2003. Skin strain and its influence on systemic exposure to a glycol ether in offset printing workers. *Contact Dermatitis* **49**: 248–254; doi: 10.1111/j.0105-1873.2003.0242.x.
- Korin G, Weiss T, Angerer J, Drexler H. 2006. Dermal absorption of aromatic amines in workers with different skin lesions: a report on 4 cases. *J. Occup. Med. Toxicol.* **1**: 17; doi: 10.1186/1745-6673-1-17.
- Korin G, Weiss T, Penkert S, Schaller K, Angerer J, Drexler H. 2007. Percutaneous absorption of aromatic amines in rubber industry workers: impact of impaired skin and skin barrier creams. *Occup. Environ. Med.* **64**: 366–372; doi: 10.1136/oem.2006.027755.
- Kronevi T, Wahlberg JE, Holmberg B. 1981. Skin pathology following epicutaneous exposure to seven organic solvents. *Int. J. Tissue React.* **3**: 21–30.
- Lamaud E, Schalla W. 1984. Influence of UV irradiation on penetration of hydrocortisone. *In vivo* study in hairless rat skin. *Br. J. Dermatol.* **27**(suppl.): 152–157; doi: 10.1111/j.1365-2133.1984.tb15595.x.
- Lambrey B, Schalla W, Kail N, Lahmy J, Schaefer H. 1987. Influence of an essential fatty acid deficient diet on absorption of topical hydrocortisone in the rat. *Br. J. Dermatol.* **117**: 607–615; doi: 10.1111/j.1365-2133.1987.tb07493.x.

- Lauer A, Elder J, Weiner N. 1997. Evaluation of the hairless rat as a model for *in vivo* percutaneous absorption. *J. Pharm. Sci.* **86**: 13–18; doi: 10.1021/js960350c.
- Lavrijsen A, Oestmann E, Hermans J, Boddé H, Vermeer B, Ponc M. 1993. Barrier function parameters in various keratinization disorders: trans-epidermal water loss and vascular response to hexyl nicotinate. *Br. J. Dermatol.* **129**: 547–553; doi: 10.1111/j.1365-2133.1993.tb00482.x.
- Lehman P, Tomlinson R, Johnson J, Olerud J, Akers W, Franz T. 1992. Percutaneous absorption and metabolism of lonapalene in psoriatic skin. *Pharm. Res.* **9**: 1145–1151.
- Levang A, Zhao K, Singh J. 1999. Effect of ethanol/propylene glycol on the *in vitro* percutaneous absorption of aspirin, biophysical changes and macroscopic barrier properties of the skin. *Int. J. Pharm.* **181**: 255–263; doi: 10.1016/S0378-5173(99)00055-1.
- Levin J, Maibach H. 2005. The correlation between transepidermal water loss and percutaneous absorption: an overview. *J. Control. Release* **105**: 291–299; doi: 10.1016/j.jconrel.2004.11.035.
- Linde YW. 1992. Dry skin in atopic dermatitis. *Acta Derm. Venereol. Suppl. (Stockh.)* **177**: 9–13.
- Lockhart SP, Rushworth A, Azmy AA, Raine PA. 1983. Topical silver sulphadiazine: side effects and urinary excretion. *Burns Incl. Therm. Inj.* **10**: 9–12; doi: 10.1016/0305-4179(83)90121-3.
- Löffler H, Dreher F, Maibach H. 2004. Stratum corneum adhesive tape stripping: influence of anatomical site, application pressure, duration and removal. *Br. J. Dermatol.* **151**: 746–752; doi: 10.1111/j.1365-2133.2004.06084.x.
- Mafune E, Takahashi M, Takasugi N. 1995. Effect of vehicles on percutaneous absorption of bucladesine (dibutyl cyclic AMP) in normal and damaged rat skin. *Biol. Pharm. Bull.* **18**: 1539–1543.
- Maibach HI, Feldmann RJ. 1974. Systemic absorption of pesticides through the skin of man. In *Occupational Exposure to Pesticides: Report to the Federal Working Group on Pest Management from the Task Group on Occupational Exposure to Pesticides*, Task Group on Occupational Exposure to Pesticides (ed.). Federal Working Group on Pest Management: Washington, DC; 120–127.
- Mali J. 1956. The transport of water through the human epidermis. *J. Invest. Dermatol.* **27**: 451–469.
- Malten K, Thiele F. 1973. Evaluation of skin damage. II. Water loss and carbon dioxide release measurements related to skin resistance measurements. *Br. J. Dermatol.* **89**: 565–569.
- Matoltsy A, Downes A, Sweeney T. 1968. Studies of the epidermal water barrier. II. Investigation of the chemical nature of the water barrier. *J. Invest. Dermatol.* **50**: 19–26.
- McMaster J, Maibach H, Wester R, Bucks D. 1985. Does rubbing enhance *in vivo* dermal absorption? In *Percutaneous Absorption*, Bronaugh RL, Maibach HI (eds). Marcel Dekker: New York; 359.
- Moan J, Ma L, Iani V. 2001. On the pharmacokinetics of topically applied 5-aminolevulinic acid and two of its esters. *Int. J. Cancer* **92**: 139–143; doi: 10.1002/1097-0215(200102)9999:9999<:AID-IJC1154>3.0.CO;2-K.
- Moon K, Wester R, Maibach H. 1990. Diseased skin models in the hairless guinea pig: *in vivo* percutaneous absorption. *Dermatologica* **180**: 8–12; doi: 10.1159/000247977.
- Morgan C, Renwick A, Friedmann P. 2003. The role of stratum corneum and dermal microvascular perfusion in penetration and tissue levels of water-soluble drugs investigated by microdialysis. *Br. J. Dermatol.* **148**: 434–443; doi: 10.1046/j.1365-2133.2003.05163.x.
- Murakami T, Yoshioka M, Okamoto I, Yumoto R, Higashi Y, Okahara K, Yata N. 1998. Effect of ointment bases on topical and dermal delivery of salicylic acid in rats: evaluation by skin microdialysis. *J. Pharm. Pharmacol.* **50**: 55–61; doi: 10.1111/j.2042-7158.1998.tb03305.x.
- Nangia A, Camel E, Berner B, Maibach H. 1993. Influence of skin irritants on percutaneous absorption. *Pharm. Res.* **10**: 1756–1759.
- Nielsen J. 2005. Percutaneous penetration through slightly damaged skin. *Arch. Dermatol. Res.* **296**: 560–567; doi: 10.1007/s00403-005-0555-y.
- Nielsen J, Nielsen F, Sørensen J. 2007. Defense against dermal exposures is only skin deep: significantly increased penetration through slightly damaged skin. *Arch. Dermatol. Res.* **299**: 423–431; doi: 10.1007/s00403-007-0788-z.
- Nokhodchi A, Shokri J, Dashbolaghi A, Hassan-Zadeh D, Ghafourian T, Barzegar-Jalali M. 2003. The enhancement effect of surfactants on the penetration of lorazepam through rat skin. *Int. J. Pharm.* **250**: 359–369; doi: 10.1016/S0378-5173(02)00554-9.
- Onken H, Moyer C. 1963. The water barrier in human epidermis. Physical and chemical nature. *Arch. Dermatol.* **87**: 584–590.
- Ortiz PG, Hansen SH, Shah VP, Menné T, Benfeldt E. 2008. The effect of irritant dermatitis on cutaneous bioavailability of a metronidazole formulation, investigated by microdialysis and dermatopharmacokinetic method. *Contact Dermatitis* **59**: 23–30; doi: 10.1111/j.1600-0536.2008.01348.x.
- Ortiz PG, Hansen SH, Shah VP, Menné T, Benfeldt E. 2009. Impact of adult atopic dermatitis on topical drug penetration: assessment by cutaneous microdialysis and tape stripping. *Acta Derm. Venereol.* **89**: 33–38; doi: 10.2340/00015555-0562.
- Osamura H, Jimbo Y, Ishihara M. 1984. Skin penetration of nicotinic acid, methyl nicotinate, and butyl nicotinate in the guinea pig – comparison of *in vivo* and excised skin, and the effects of four dermatologic conditions. *J. Dermatol.* **11**: 471–481.
- Papp AA, Uusaro AV, Ruokonen ET. 2009. The effects of topical epinephrine on haemodynamics and markers of tissue perfusion in burned and non-burned patients requiring skin grafting. *Burns* **35**: 832–839; doi: 10.1016/j.burns.2008.10.001.
- Petitot F, Gautier C, Moreels AM, Frelon S, Paquet F. 2007. Percutaneous penetration of uranium in rats after a contamination on intact or wounded skin. *Radiat. Prot. Dosim.* **127**: 125–130; doi: 10.1093/rpd/ncm261.
- Petitot F, Moreels AM, Paquet F. 2010. Evolution of the percutaneous penetration and distribution of uranyl nitrate as a function of skin-barrier integrity: an *in vitro* assessment. *Drug Chem. Toxicol.* **33**: 316–324; doi: 10.3109/01480540903431457.
- Piret J, Désormeaux A, Cormier H, Lamontagne J, Gourde P, Juhász J, Bergeron MG. 2000. Sodium lauryl sulfate increases the efficacy of a topical formulation of foscarnet against herpes simplex virus type 1 cutaneous lesions in mice. *Antimicrob. Agents Chemother.* **44**: 2263–2270; doi: 10.1128/AAC.44.9.2263-2270.2000.
- Putterman GJ, Wolejsza NF, Wolfram MA. 1977. The effect of detergent on swelling of stratum corneum. *J. Soc. Cosmet. Chem.* **28**: 521–532.
- Putterman GJ, Strassburger J, Fitzgerald JJ. 1981. *In vitro* sorption of aluminum complex to guinea pig stratum corneum. *J. Invest. Dermatol.* **77**: 319–324; doi: 10.1111/1523-1747.ep12482522.
- Rastogi S, Singh J. 2001. Lipid extraction and transport of hydrophilic solutes through porcine epidermis. *Int. J. Pharm.* **215**: 241–249; doi: 10.1016/S0378-5173(01)00766-9.
- Roberts M, Anderson R, Swarbrick J. 1977. Permeability of human epidermis to phenolic compounds. *J. Pharm. Pharmacol.* **29**: 677–683; doi: 10.1111/j.2042-7158.1977.tb11434.x.
- Schaefer H. 1985. Short-contact therapy. *Arch. Dermatol.* **121**: 1505–1509; doi: 10.1001/archderm.121.12.1505.
- Schaefer H, Zesch A, Stüttgen G. 1977. Penetration, permeation, and absorption of triamcinolone acetonide in normal and psoriatic skin. *Arch. Dermatol. Res.* **258**: 241–249; doi: 10.1007/BF00561126.
- Schaefer H, Schalla W, Lamaud E. 1984. Pharmacological and pharmacokinetic aspects in logical and systemic therapy of psoriasis. In *Current Research Problems in Psoriasis*, Kröger H, Stüttgen G (eds). Grosse: Berlin; 104–110.
- Scheuplein R, Ross L. 1970. Effects of surfactants and solvents on the permeability of epidermis. *J. Soc. Cosmet. Chem.* **21**: 853–873.
- Scott R, Dugard P, Doss A. 1986. Permeability of abnormal rat skin. *J. Invest. Dermatol.* **86**: 201–207; doi: 10.1111/1523-1747.ep12284280.
- Shani J, Barak S, Levi D, Ram M, Schachner ER, Schlesinger T, Robberecht H, Van Grieken R, Avrach WW. 1985. Skin penetration of minerals in psoriatics and guinea-pigs bathing in hypertonic salt solutions. *Pharmacol. Res. Commun.* **17**: 501–512; doi: 10.1016/0031-6989(85)90123-7.
- Shokri J, Nokhodchi A, Dashbolaghi A, Hassan-Zadeh D, Ghafourian T, Barzegar-Jalali M. 2001. The effect of surfactants on the skin penetration of diazepam. *Int. J. Pharm.* **228**: 99–107; doi: 10.1016/S0378-5173(01)00805-5.
- Sintov A, Botner S. 2006. Transdermal drug delivery using microemulsion and aqueous systems: influence of skin storage conditions on the *in vitro* permeability of diclofenac from aqueous vehicle systems. *Int. J. Pharm.* **311**: 55–62; doi: 10.1016/j.ijpharm.2005.12.019.
- Smits T, Robles C, van Erp P, van de Kerkhof P, Gerritsen M. 2005. Correlation between macroscopic fluorescence and protoporphyrin IX content in psoriasis and actinic keratosis following application of aminolevulinic acid. *J. Invest. Dermatol.* **125**: 833–839; doi: 10.1111/j.0022-202X.2005.23843.x.
- Solomon A, Lowe N. 1978. Percutaneous absorption in experimental epidermal proliferation. *Arch. Dermatol.* **114**: 1029–1030; doi: 10.1001/archderm.114.7.1029.

- Solomon A, Lowe N. 1979. Percutaneous absorption in experimental epidermal disease. *Br. J. Dermatol.* **100**: 717–722; doi: 10.1111/j.1365-2133.1979.tb08078.x.
- Swarbrick J, Lee G, Brom J. 1982. Drug permeation through human skin: I. Effect of storage conditions of skin. *J. Invest. Dermatol.* **78**: 63–66; doi: 10.1111/1523-1747.ep12497937.
- Takahashi K, Sakano H, Yoshida M, Numata N, Mizuno N. 2001. Characterization of the influence of polyol fatty acid esters on the permeation of diclofenac through rat skin. *J. Control. Release* **73**: 351–358; doi: 10.1016/S0168-3659(01)00359-5.
- Tsai J, Hung P, Sheu H. 2001a. Molecular weight dependence of polyethylene glycol penetration across acetone-disrupted permeability barrier. *Arch. Dermatol. Res.* **293**: 302–307; doi: 10.1007/s004030100229.
- Tsai J, Sheu H, Hung P, Cheng C. 2001b. Effect of barrier disruption by acetone treatment on the permeability of compounds with various lipophilicities: implications for the permeability of compromised skin. *J. Pharm. Sci.* **90**: 1242–1254; doi: 10.1002/jps.1077.
- Tsai J, Shen L, Sheu H, Lu C. 2003. Tape stripping and sodium dodecyl sulfate treatment increase the molecular weight cutoff of polyethylene glycol penetration across murine skin. *Arch. Dermatol. Res.* **295**: 169–174; doi: 10.1007/s00403-003-0414-7.
- Turpeinen M. 1988. Influence of age and severity of dermatitis on the percutaneous absorption of hydrocortisone in children. *Br. J. Dermatol.* **118**: 517–522; doi: 10.1111/j.1365-2133.1988.tb02461.x.
- Turpeinen M, Salo O, Leisti S. 1986. Effect of percutaneous absorption of hydrocortisone on adrenocortical responsiveness in infants with severe skin disease. *Br. J. Dermatol.* **115**: 475–484; doi: 10.1111/j.1365-2133.1986.tb06242.x.
- Turpeinen M, Mashkilleysen N, Björkstén F, Salo O. 1988. Percutaneous absorption of hydrocortisone during exacerbation and remission of atopic dermatitis in adults. *Acta Derm. Venereol.* **68**: 331–335.
- Van den Akker J, de Bruijn H, Beijersbergen van Henegouwen G, Star W, Sterenberg H. 2000a. Protoporphyrin IX fluorescence kinetics and localization after topical application of ALA pentyl ester and ALA on hairless mouse skin with UVB-induced early skin cancer. *Photochem. Photobiol.* **72**: 399–406.
- Van den Akker J, Iani V, Star W, Sterenberg H, Moan J. 2000b. Topical application of 5-aminolevulinic acid hexyl ester and 5-aminolevulinic acid to normal nude mouse skin: differences in protoporphyrin IX fluorescence kinetics and the role of the stratum corneum. *Photochem. Photobiol.* **72**: 681–689; doi: 10.1562/0031-8655(2000)072<0681:TAOAAH>2.0.CO;2.
- Van den Akker J, Iani V, Star W, Sterenberg H, Moan J. 2002. Systemic component of protoporphyrin IX production in nude mouse skin upon topical application of aminolevulinic acid depends on the application conditions. *Photochem. Photobiol.* **75**: 172–177; doi: 10.1562/0031-8655(2002)075<0172:SCOPIP>2.0.CO;2.
- Van den Akker J, Holroyd J, Vernon D, Sterenberg H, Brown S. 2003. Comparative *in vitro* percutaneous penetration of 5-aminolevulinic acid and two of its esters through excised hairless mouse skin. *Lasers Surg. Med.* **33**: 173–181; doi: 10.1002/lsm.10212.
- Van den Akker J, Holroyd J, Vernon D, Sterenberg H, Brown S. 2004. Chronic UVB exposure enhances *in vitro* percutaneous penetration of 5-aminolevulinic acid in hairless mouse skin. *Lasers Surg. Med.* **34**: 141–145; doi: 10.1002/lsm.20004.
- Wan AT, Conyers RA, Coombs CJ, Masterton JP. 1991. Determination of silver in blood, urine, and tissues of volunteers and burn patients. *Clin. Chem.* **37**: 1683–1687.
- Wang J, Patel B, Ehmann C, Lowe N. 1987. The release and percutaneous permeation of anthralin products, using clinically involved and uninvolved psoriatic skin. *J. Am. Acad. Dermatol.* **16**: 812–821; doi: 10.1016/S0190-9622(87)70106-6.
- Wennberg A, Larkö O, Lönnroth P, Larson G, Krogstad A. 2000. Delta-aminolevulinic acid in superficial basal cell carcinomas and normal skin – a microdialysis and perfusion study. *Clin. Exp. Dermatol.* **25**: 317–322; doi: 10.1046/j.1365-2230.2000.00652.x.
- Wester R, Bucks D, Maibach H. 1983. *In vivo* percutaneous absorption of hydrocortisone in psoriatic patients and normal volunteers. *J. Am. Acad. Dermatol.* **8**: 645–647; doi: 10.1016/S0190-9622(83)70072-1.
- Wester R, Mobayen M, Ryatt K, Bucks D, Maibach H. 1987. *In vivo* percutaneous absorption of dithranol in psoriatic and normal volunteers. In *4th International Symposium on Psoriasis: Proceedings of the Fourth International Symposium*, Farber EM, Farber N, Morhenn J (eds). Elsevier: New York; 429.
- Wickrema Sinha A, Shaw S, Weber D. 1978. Percutaneous absorption and excretion of tritium-labeled diflorasone diacetate, a new topical corticosteroid in the rat, monkey and man. *J. Invest. Dermatol.* **71**: 372–377.
- Wilhelm K, Surber C, Maibach H. 1991a. Effect of sodium lauryl sulfate-induced skin irritation on *in vitro* percutaneous absorption of four drugs. *J. Invest. Dermatol.* **96**: 963–967; doi: 10.1111/1523-1747.ep12476269.
- Wilhelm K, Surber C, Maibach H. 1991b. Effect of sodium lauryl sulfate-induced skin irritation on *in vivo* percutaneous penetration of four drugs. *J. Invest. Dermatol.* **97**: 927–932; doi: 10.1111/1523-1747.ep12491710.
- Wolfram MA, Wolejsza NF, Laden K. 1972. Biomechanical properties of delipidized stratum corneum. *J. Invest. Dermatol.* **59**: 421–426; doi: 10.1111/1523-1747.ep12627597.
- Yoshiike T, Aikawa Y, Sindhvananda J, Suto H, Nishimura K, Kawamoto T, Ogawa H. 1993. Skin barrier defect in atopic dermatitis: increased permeability of the stratum corneum using dimethyl sulfoxide and theophylline. *J. Dermatol. Sci.* **5**: 92–96; doi: 10.1016/0923-1811(93)90076-2.
- Zackheim H, Feldmann R, Lindsay C, Maibach H. 1977. Percutaneous absorption of 1,3-bis (2-chloroethyl)-l-nitrosourea (BCNU, carmustine) in mycosis fungoides. *Br. J. Dermatol.* **97**: 65–67.