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Research Article

Contributions of Drug Solubilization, Partitioning, Barrier Disruption, and Solvent Permeation to the Enhancement of Skin Permeation of Various Compounds with Fatty Acids and Amines

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The contributions of several proposed mechanisms by which fatty acids and amines might increase skin permeation rates were assessed. Permeation rates of model diffusants with diverse physicochemical properties (naloxone, testosterone, benzoic acid, indomethacin, fluorouracil, and methotrexate) through human skin were measured *in vitro*. The enhancers evaluated were capric acid, lauric acid, neodecanoic acid, and dodecylamine. Increased drug solubility in the vehicle, propylene glycol (PG), in some cases accounted for the increases in flux in the presence of adjuvants, since permeability coefficients were unchanged. Partition coefficients of some drugs into isopropyl myristate or toluene were increased by the adjuvants, but this did not occur for combinations of an acid with a base (adjuvant-drug or drug-adjuvant). Increases in flux not accounted for by increases in drug solubility or partitioning were assumed to involve disruption of the barrier function of skin (increased skin diffusivity). All fatty acids increased skin diffusivity of naloxone, testosterone, indomethacin, and fluorouracil but not of methotrexate or benzoic acid. Dodecylamine increased skin diffusivity only for fluorouracil. Capric acid and dodecylamine, but not lauric acid or neodecanoic acid, increased the skin permeation rate of PG, suggesting that enhanced solvent penetration could also be involved as a mechanism for increased skin permeation of the drug. However, the increase in PG flux due to dodecylamine was nullified when methotrexate was added to the vehicle, possibly because of a dodecylamine/methotrexate interaction. These studies demonstrate that drug solubilization in the vehicle, increased partitioning, increased solvent penetration, and barrier disruption each can contribute to increased skin permeation rates in the presence of fatty acids and amines. The relative contributions of the mechanisms vary with the drug, the adjuvant, and the vehicle.

KEY WORDS: skin permeation; enhancer; fatty acid; membrane; transport; ion pairing; solvent drag.

INTRODUCTION

Numerous adjuvants have been used to increase skin permeation rates. These compounds have potential application for improving the skin penetration of poorly absorbed, systemically or topically active drugs. Their effects vary from drug to drug. Rational selection of a skin permeation enhancer and optimization of a skin permeation enhancing effect require an understanding of how drugs are affected by certain enhancers and how that varies from drug to drug. This depends at least partly on the mechanisms of permeation enhancement.

Fatty acids comprise one class of skin permeation enhancers for salicylic acid (1), acyclovir (2), naloxone (3), and several other drugs. The goals of this study were to compare the effects of fatty acids on the skin permeation rates of several drugs and to determine the contributions of various proposed mechanisms by which fatty acids might increase skin permeation rates.

One likely mechanism involved is reduction of skin resistance as a permeability barrier by disruption of the tightly packed lipid regions of the stratum corneum, which increases penetration through the intercellular lipid matrix (4). Differential scanning calorimetry and infrared spectroscopy indeed showed that skin permeability changes were proportional to physical changes in the stratum corneum lipids (5).

Another possible mechanism is increased skin/vehicle partitioning of the drug. A fatty acid adjuvant and an amine drug may form a lipophilic ion pair, thereby increasing drug partitioning into skin. Green and Hadgraft suggested this mechanism for the increased diffusion of β-blockers by fatty acids across an artificial isopropyl myristate membrane (6). They further showed that oleic acid and lauric acid each increased the isopropyl myristate/buffer partition coefficient of naphazoline, a base, providing evidence for an ion pairing role in skin penetration enhancement (7).

A third mechanism of skin permeation enhancement by adjuvants invokes increased solvent transport into or across

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the skin. If the adjuvant increases the penetration rate of the solvent, drug solubility in the skin and skin penetration of the drug would also increase if the drug has a high affinity for the solvent. In the case of oleic acid enhancement of molsidomine skin penetration, Yamada *et al.* demonstrated a correlation between the penetration rates of molsidomine and the polyhydric alcohol vehicle, and they proposed a solvent drag mechanism for permeation enhancement (8).

The skin permeation enhancing effects of fatty acids and a fatty amine were studied using six compounds as model diffusants. These compounds were naloxone base, testosterone, a nonionizable drug, and four acids, benzoic acid, indomethacin, fluorouracil, and methotrexate. The structures of these compounds are shown in Fig. 1. We have examined how the flux, solubility, partitioning, and skin diffusivity of each of these compounds are affected by adjuvants. The fatty acids studied as adjuvants were capric acid (C_{10}), lauric acid (C_{12}), and neodecanoic acid, a branched-chain C_{10} fatty acid. Capric acid and lauric acid were previously shown to be the most effective enhancers within a series of saturated, straight-chain fatty acids, using naloxone as the diffusant (3). In another study neodecanoic acid was as effective as capric acid and lauric acid in increasing naloxone skin penetration rates, but it appeared to have a lower skin irritation potential (10). Dodecylamine was examined to see whether a basic adjuvant had effects on acidic drugs similar to the effects of fatty acid adjuvants on basic drugs. We also evaluated the effects of adjuvants on the skin permeation of the vehicle. The solvent used as the vehicle was propylene glycol. Previous studies have shown that the skin permeability enhancing effects of fatty acids are greatest with propylene glycol vehicles (3,8).

MATERIALS AND METHODS

Materials. Capric acid, lauric acid, testosterone, indomethacin, 5-fluorouracil, and methotrexate [(+)-amethopterin trihydrate] were purchased from Sigma. Naloxone base was from DuPont Pharmaceuticals. Propylene glycol U.S.P. and benzoic acid were supplied by Fisher. Isopropyl myristate was obtained from Kodak. Dodecylamine and stearylamine were obtained from Fluka. Phenylethylamine base was from Aldrich. Triethylamine was from

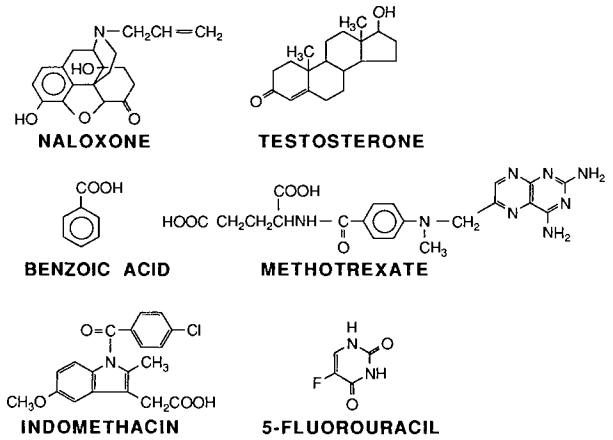

Fig. 1. Structures of the drugs used as model diffusants.

EM Science. Akzo Chemie America generously provided bis-(2-hydroxyethyl)oleylamine (Ethomeen O/12) and polyoxyethylene(5)oleylamine (Ethomeen O/15), which are referred to as PEG-2 oleamine and PEG-5 oleamine, respectively. Neodecanoic acid is a mixture of highly branched fatty acid isomers of the general formula R_3CCOOH, in which the average number of carbon atoms is 10. It was supplied by Exxon Chemicals. [^{14}C]Propylene glycol (1,2-propanediol, [1-^{14}C]; sp act, 40 mCi/mmol) was obtained from ICN Biomedicals. Human skin specimens, dermatomed to an approximate thickness of 0.4 mm, were obtained from an organ bank. The skin donor population consisted of 22 people, of which 2 were nonwhite and 7 were female. The donor age averaged 37 ± 15 years. The majority of specimens were from the thighs and the calves.

Skin Permeation. In vitro skin permeation rates were measured using glass diffusion cells in which human cadaver skin was clamped into a position separating donor and reservoir compartments. The reservoir was maintained at 37°C using a circulating water jacket or a dry block heater and was constantly stirred. The reservoir solution was selected to optimize drug solubility so that sink conditions were maintained. For indomethacin, fluorouracil, and methotrexate the reservoir was 0.1 *M* phosphate buffer at pH 7.4; saline was used for naloxone, benzoic acid, and propylene glycol; for testosterone the reservoir was 2% bovine serum albumin in saline. The entire reservoir volume (7–9 ml) was removed at the sampling times and replaced with drug-free solution. The donor vehicle volume was 0.5 ml. The donor chamber was sealed from the atmosphere with parafilm. The diffusional surface area was 1.8 cm^2. Each drug was evaluated using skin from at least three separate donors, and in most cases where direct comparisons of vehicles were made, the same skin donors were used to evaluate all vehicles.

The vehicles were propylene glycol or 0.5 *M* adjuvant in propylene glycol. The fatty acid or dodecylamine/propylene glycol mixtures were warmed to melt and dissolve the adjuvant. Clear solutions were obtained, unless indicated otherwise. The various drugs were then added to these vehicles in excess in saturated solubility. These suspensions were used for skin permeation experiments. Drug solubilities in the vehicles were determined after filtration and dilution or extraction. In some experiments, the drug was added to the vehicles in concentrations below saturation. The vehicles for measuring propylene glycol skin permeation had 2 μCi [^{14}C]propylene glycol/ml, and 0.5 ml was applied to the skin.

Partition Coefficients. Partition coefficients of the test drugs from propylene glycol vehicles, and the effects of fatty acids and dodecylamine, were examined using toluene and isopropyl myristate as the lipophilic phases. Octanol, which has a polarity similar to that of the lipids of skin (9), was not used because it was miscible with the propylene glycol vehicles. The saturated solutions used as vehicles in the skin permeation studies were filtered and diluted 10-fold with drug-free vehicle to give solutions with concentrations 1/10th of the drug solubility. These were equilibrated with equal volumes of isopropyl myristate or toluene by end-to-end mixing at room temperature (≈22°C) for at least 16 hr. The phases were then separated and diluted with methanol or extracted with 0.1 *N* NaOH (in the cases of fluorouracil and methotrexate), and the drug concentrations in both phases

were determined by HPLC. The solubility and partition coefficient data represent one to three determinations.

Analyses. Concentrations of naloxone, testosterone, benzoic acid, indomethacin, fluorouracil, and methotrexate in skin permeation samples and for partition coefficients were determined by HPLC. The assay conditions are outlined in Table I. The albumin in the samples from the testosterone skin permeation experiment was precipitated with 2 vol of methanol and was removed by filtration prior to HPLC analysis. [^{14}C]Propylene glycol concentrations were determined by counting 0.5-ml aliquots of the reservoir samples after the addition of 5-ml volumes of scintillation cocktail.

Data Analysis. The amount of drug permeating through skin during a sampling interval was calculated based on the measured reservoir concentration and volume. Plots of amount permeating vs time were made for each experiment. Flux was calculated as the slope of the linear portion of the plot and was normalized to 1-cm^2 surface area. [^{14}C]-Propylene glycol flux was expressed as the percentage of the applied amount delivered per hour and was not corrected for surface area. All flux data are reported as the mean ± SE of at least three determinations.

RESULTS

One goal of this study was to evaluate separately the effects permeation enhancing adjuvants have on drug solubility in the vehicle, partition coefficient, and skin diffusivity. The effects on solubility were measured directly. The permeability coefficient, P, was calculated as the flux, J, divided by the drug concentration in the saturated solution, C^s. P is a composite variable which includes drug partitioning into skin and the diffusion coefficient or diffusivity of the drug in the stratum corneum. Skin permeation rates are dependent on the stratum corneum/vehicle partition coefficients. These values are difficult to determine accurately. It was judged that the contribution of any mechanism that increases partitioning, such as ion pairing, would be evident in organic solvent/vehicle partition coefficients (K). The organic solvents were isopropyl myristate and toluene. Increases in P not accounted for by increases in K were assumed to involve increased skin diffusivity, indicative of barrier disruption.

Solubility, skin permeation, and partitioning data for the model compounds, and the effects of fatty acids and dodecylamine, are summarized in Table II.

Naloxone. The fatty acids increased naloxone solubility approximately 2- to 3-fold but increased naloxone flux 30- to 40-fold; P values increased at least 10-fold. In previous work naloxone solubility in lauric acid/propylene glycol solvent mixtures increased linearly with increasing lauric acid concentrations (3). This could be indicative of complexation or ion pair formation, but the effects of fatty acids on naloxone partitioning into isopropyl myristate or toluene were not indicative of formation of lipophilic ion pairs. Each fatty acid slightly increased $K^{toluene/PG}$, but there were no consistent effects on $K^{IM/PG}$. Furthermore, dodecylamine increased the partitioning of naloxone base into both isopropyl myristate and toluene. Considering the relative effects of dodecylamine on P (31-fold increase relative to control) and $K^{IM/PG}$ (72-fold increase) and $K^{toluene/PG}$ (19-fold increase), the effect of dodecylamine appears to be primarily on partitioning.

Testosterone. The effects of the fatty acid adjuvants on testosterone were to increase slightly C^s, $K^{IM/PG}$, and $K^{toluene/PG}$. Because the increases in P were consistently greater than the increases in K, some barrier disruption was evidenced. Dodecylamine decreased solubility in the vehicle, increased P (6-fold), and increased $K^{IM/PG}$ (14-fold) and $K^{toluene/PG}$ (22-fold). Since the increases in K were greater than the increase in P, there was no suggestion of dodecylamine increasing skin diffusivity.

Benzoic Acid. Benzoic acid represents a solute with high solubility in PG and high intrinsic skin permeability. None of the acid or amine adjuvants had a very great effect on any parameter determined.

Indomethacin. In the absence of an enhancer, the average flux for indomethacin was approximately 1000-fold lower than that of benzoic acid. However, permeability coefficients of indomethacin and benzoic acid were similar for vehicles containing capric acid or lauric acid. Neodecanoic acid was less effective in increasing indomethacin P. Each fatty acid had very little effect on indomethacin solubility. The increases in P were much greater than the increases in K, so increased skin diffusivity is likely. In the presence of dodecylamine, indomethacin solubility and flux increased to the same extent, so that there was no net change in P. Changes in K with dodecylamine were not consistent. The effect of dodecylamine on indomethacin skin permeation provides an example of an adjuvant apparently increasing flux solely by solubilizing the drug in the vehicle.

Table I. Chromatographic Methods Employed for Drug Analyses

Drug	Column	Mobile phase	Flow rate (ml/min)	Detection (nm)
Naloxone	C_8	Acetonitrile/THF/0.05 *M* phosphate buffer, pH 3 (10/0.8/89.2)[a]	1.4	284
Testosterone	C_8	Acetonitrile/0.1 *M* acetate buffer, pH 4 (50/50)	2.0	242
Benzoic acid	C_8	Acetonitrile/0.2 *M* acetate buffer, pH 3.5 (25/75)	1.4	230
Indomethacin	C_8	Acetonitrile/0.04 *M* phosphoric acid (55/45)	1.2	260
Fluorouracil	C_8	0.01 *M* acetate buffer/0.05% triethylamine, pH 4	1.2	266
Methotrexate	C_8	Methanol/THF/citrate phosphate buffer, pH 3.2 (15/4/81)	2.0	303

[a] All ratios are volume ratios.

Table II. Solubility (C^s), Flux (J), Permeability Coefficient (P), and Partition Coefficients (K) for Various Model Drugs Using Propylene Glycol Vehicles and Fatty Acid or Amine Adjuvants

	C^s (mg/ml)	J (μg/cm² hr)[a]	P (cm/hr)	$K^{IM/PG}$	$K^{toluene/PG}$
Naloxone					
PG	28.3	3.6 ± 1.2	1.3×10^{-4}	0.09	0.45
Capric acid/PG	70.0	111.4 ± 37.3	1.6×10^{-3}	0.04	0.74
Lauric acid/PG	62.0	136.1 ± 42.6	2.2×10^{-3}	0.13	0.75
Neodecanoic acid/PG	48.7	145.7 ± 63.1	3.0×10^{-3}	0.08	0.78
Dodecylamine/PG	6.2	25.1 ± 0.9	4.0×10^{-3} (31)[b]	6.47 (72)	8.52 (19)
Testosterone					
PG	67.8	4.0 ± 0.9	5.9×10^{-5}	0.18	0.18
Capric acid/PG	89.7	14.2 ± 3.4	1.6×10^{-4}	0.29	0.48
Lauric acid/PG	91.3	21.9 ± 4.3	2.4×10^{-4}	0.32	0.67
Neodecanoic acid/PG	74.0	21.4 ± 3.3	2.9×10^{-4}	0.25	0.39
Dodecylamine/PG	28.0	10.4 ± 0.8	3.7×10^{-4} (6)	2.49 (14)	4.04 (22)
Benzoic acid					
PG	250	557 ± 71	2.2×10^{-3}	0.20	0.20
Capric acid/PG	229	815 ± 82	3.6×10^{-3}	0.28	0.24
Lauric acid/PG	259	726 ± 89	2.8×10^{-3}	0.25	0.32
Neodecanoic acid/PG	271	648 ± 74	2.4×10^{-3}	0.27	0.32
Dodecylamine/PG	231	902 ± 166	3.9×10^{-3}	0.04	0.19
Indomethacin					
PG	7.6	0.5 ± 0.05	6.6×10^{-5}	0.30	0.17
Capric acid/PG	9.9	23.3 ± 3.4	2.4×10^{-3}	0.49	0.89
Lauric acid/PG	11.6	51.2 ± 16.7	4.4×10^{-3}	0.60	1.05
Neodecanoic acid/PG	8.8	5.8 ± 2.2	6.6×10^{-4}	0.48	0.85
Dodecylamine/PG	136.5	7.7 ± 1.2	5.6×10^{-5}	0.14	0.71
Fluorouracil					
PG	12.4	1.4 ± 0.4	1.1×10^{-4}	0.002	4×10^{-4}
Capric acid/PG	8.1	92.0 ± 3.5	1.1×10^{-2}	0.01	0.02
Lauric acid/PG	7.0	81.9 ± 4.9	1.2×10^{-2}	0.01	0.04
Neodecanoic acid/PG	8.6	45.6 ± 2.7	5.3×10^{-3}	0.01	0.01
Dodecylamine/PG	63.3	527.6 ± 30.0	8.3×10^{-3}	0.01	0.06
Methotrexate					
PG	2.7	7.0 ± 5.9	2.6×10^{-3}	—[c]	—
Capric acid/PG	2.4	8.8 ± 6.5	3.7×10^{-3}	—	—
Lauric acid/PG	3.5	10.1 ± 6.6	2.9×10^{-3}	—	—
Neodecanoic acid/PG	3.0	16.0 ± 4.7	5.3×10^{-3}	—	—
Dodecylamine/PG	54.1	131.8 ± 56.3	2.4×10^{-3}	—	—

[a] Mean ± SE.
[b] Numbers in parentheses are relative to the PG control.
[c] Partition coefficients were too low to measure.

Fluorouracil. Dodecylamine also solubilized (fivefold) fluorouracil, another drug with acidic functionality. However, unlike indomethacin, fluorouracil P was also increased (75-fold) by dodecylamine. Fluorouracil K values were very low, and increased in the presence of each fatty acid or amine adjuvant, to account at least partly for the increases in P. The fatty acids also greatly increased fluorouracil flux and P, and part of the increase in P may have been due to increases in K.

Methotrexate. For methotrexate, neither flux, C^s, nor P was markedly increased in the presence of fatty acids. The effects of dodecylamine on methotrexate were similar to those with indomethacin: increased solubility, proportional increase in flux, and no change in P. Partitioning of methotrexate into either isopropyl myristate or toluene was negligible using control or adjuvant vehicles.

Dodecylamine increased flux of methotrexate and indomethacin by solubilization without affecting P, but increased fluorouracil P, as well as C^s. This indicates that this adjuvant has apparently different mechanisms of promoting skin permeation, depending on the drug. To illustrate this further, the effects of dodecylamine were also studied at fixed concentrations of methotrexate (1 mg/ml) or fluorouracil (5 mg/ml) in the vehicle. Results are shown in Fig. 2. Dodecylamine did not increase methotrexate flux significantly, but fluorouracil flux increased 78-fold. These results are consistent with those using drug-saturated vehicles.

Other Bases as Permeation Enhancers. The effects of some other adjuvants with basic functionality were studied using indomethacin and fluorouracil as diffusants. Results are given in Table III, together with the previously presented results for control and dodecylamine vehicles. Because

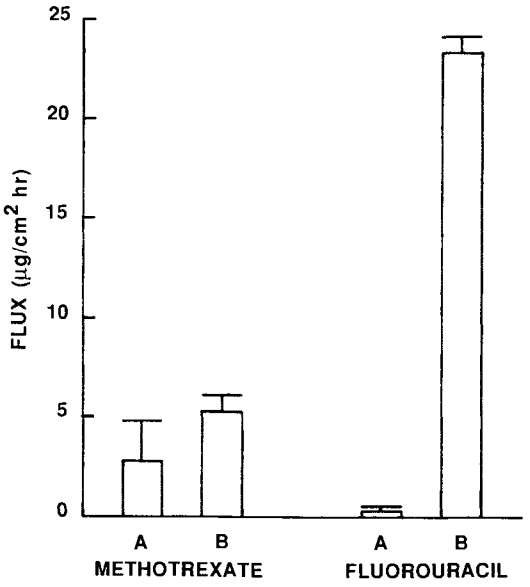

Fig. 2. Flux of methotrexate or fluorouracil from propylene glycol (A) or propylene glycol containing 0.5 *M* dodecylamine (B). Vehicles contained 1 mg/ml methotrexate or 5 mg/ml fluorouracil.

some of the vehicles were semisolid, solubility of the drug could not be measured. However, for those indomethacin vehicles for which solubility was determined, it was increased by each adjuvant. Indomethacin permeability coefficients, on the other hand, were increased only by NaOH (twofold) and triethylamine (fivefold). Indomethacin flux in the presence of phenylethylamine or stearylamine was the same as control. These adjuvants affected indomethacin and fluorouracil differently. Triethylamine and phenylethylamine both increased fluorouracil solubility and flux, but since these increases were proportional to each other, *P* was not affected. In contrast, PEG-2 oleamine and PEG-5 oleamine both increased *P* but did not affect fluorouracil solubility. Sodium hydroxide and stearylamine increased flux, but the vehicles were semisolid and C^s could not be measured. These results confirm that adjuvants affect different drugs in different ways.

Propylene Glycol Skin Permeation. The rate of skin penetration of the solvent can influence the permeation rate of dissolved solutes because the resistance of the barrier could change as it absorbs solvent and because drug partitioning into a solvent-soaked membrane may be different than into a dry or hydrated membrane. Propylene glycol skin permeation was characterized using fatty acid/PG or dodecylamine/PG vehicles. Results are given in Table IV. Each fatty acid increased the PG skin permeation rate, but only the effect of capric acid was statistically significant. Dodecylamine produced an even greater increase in PG skin permeation. However, in a vehicle saturated with methotrexate, the enhancing effect of dodecylamine was negated, as shown in Fig. 3. Presumably the adjuvants must penetrate into skin to exert their effects on the barrier properties of skin. Inhibition by methotrexate of the enhancing effect of dodecylamine on PG flux suggests that an interaction of dodecylamine and methotrexate occurs in the vehicle to inhibit dodecylamine skin penetration. Perhaps this is why dodecylamine did not affect methotrexate *P*, as shown in Table II.

DISCUSSION

Various mechanisms have been proposed to account for the effects of fatty acids on skin permeation. These include increased drug solubility in the vehicle, increased partitioning into the skin, increased solvent penetration, and barrier disruption. The dependence of flux on each of these variables can be illustrated with a diffusion equation in which drug flux through a membrane at steady state, from a saturated solution into a sink, is represented as

$$J = C^s K_m D/h$$

Table III. Effects of Various Basic Adjuvants on Solubility (C^s), Flux, and Permeability Coefficient of Indomethacin and Fluorouracil

	C^s (mg/ml)	Flux (μg/cm² hr)	*P* (cm/hr)
Indomethacin			
PG	7.6	0.5 ± 0.05	6.6×10^{-5}
Dodecylamine/PG	136.5	7.7 ± 1.2	5.6×10^{-5}
Triethylamine/PG	132.8	40.7 ± 21.8	3.1×10^{-4}
Phenylethylamine/PG	ND[a]	0.4 ± 0.2	ND
PEG-2 oleamine/PG	115.7	3.9 ± 0.9	3.4×10^{-5}
PEG-5 oleamine[b]/PG	125.8	1.2 ± 0.6	9.5×10^{-6}
NaOH/PG	88.7	12.6 ± 5.8	1.4×10^{-4}
Stearylamine/PG	ND	0.7 ± 0.06	ND
Fluorouracil			
PG	12.4	1.9 ± 0.5	1.5×10^{-4}
Dodecylamine/PG	63.3	527.6 ± 30	8.3×10^{-3}
Triethylamine/PG	47.7	10.4 ± 1.2	2.2×10^{-4}
Phenylethylamine/PG	59.1	9.7 ± 2.2	1.6×10^{-4}
PEG-2 oleamine/PG	16.0	272.7 ± 59.4	1.7×10^{-2}
PEG-5 oleamine[b]/PG	14.8	26.6 ± 4.4	1.8×10^{-3}
NaOH/PG	ND	12.5 ± 6.9	ND
Stearylamine/PG	ND	21.7 ± 11.0	ND

[a] Not determined.
[b] Adjuvant was not completely soluble at 0.05 *M*.

Table IV. Effects of Fatty Acid Adjuvants and Dodecylamine on Propylene Glycol Skin Penetration

Adjuvant (0.5 *M*)	Propylene glycol	
	Flux (%/hr)	Lag time (hr)
None	0.8 ± 0.4	3.5 ± 1.7
Capric acid	7.5 ± 1.6	3.0 ± 1.1
Lauric acid	1.4 ± 0.2	1.0 ± 0.5
Neodecanoic acid	1.6 ± 0.2	2.2 ± 1.8
Dodecylamine	15.7 ± 1.9	2.2 ± 0.7

J is the flux per unit area of membrane, K_m is the membrane/vehicle partition coefficient, C^s is the drug concentration in the vehicle at the solubility limit, D is the diffusion coefficient, and h is the membrane thickness. K_mD/h is the permeability coefficient (P). Increased drug diffusion rates in the presence of adjuvants could be due to changes in any of the variables K_m, C^s, D or h. D reflects, among other things, the structural properties of the skin. We evaluated the relative contributions of the proposed mechanisms of fatty acid skin permeation enhancers by examining their effects on drug solubility, partitioning, and permeability coefficient of diverse acidic, basic, and neutral permeants. We also examined the effects of amine and other basic adjuvants on these diverse model compounds.

Our results indicate that each of the proposed mechanisms (i.e., increased drug solubility in the vehicle, increased partition coefficient, barrier disruption, and increased solvent permeation) may be associated with the increased flux in the presence of fatty acid adjuvants and dodecylamine. The relative contributions of these mechanisms varied from drug to drug, however. Table V lists examples of the drugs for which these mechanisms appeared to contribute to increased flux. The most consistent effects were for acidic adjuvants to increase the solubility of the basic drug in the vehicle and for basic adjuvants to increase the solubilities of acidic drugs. For some drug/adjuvant combinations (e.g., indomethacin/dodecylamine) this effect completely accounts for the increase in flux, since the permeability coefficient was unchanged. However, it may be difficult to predict *a priori* which adjuvants will have only a solubilizing effect. For example, triethylamine and phenylethylamine increased fluorouracil flux by increasing only its solubility in the vehicle (P was unchanged). However, both of these adjuvants increased P for indomethacin (Table III).

Skin permeation could also be increased by increasing the partitioning of the drug into the skin. Ion pairing has been proposed in several publications as a possible mechanism of increasing partitioning. Lee and Kim (11) demonstrated that ion pairing could substantially increase the penetration of ionic drugs through synthetic hydrophobic membranes using nonaqueous vehicles with a low dielectric constant. An ion pairing mechanism was proposed for the enhancement of penetration of β-blockers across an isopropyl myristate membrane in the presence of fatty acids (6). Synthetic ion pairs of trospium, wherein the counterions were alkyl sulfates, had greater skin permeation rates than trospium chloride (12). The bioavailability of dermally applied diltiazem hydrochloride was increased by the inclusion of lipophilic, anionic counterions (13). Sodium salicylate increased the skin penetration and partition coefficient (octanol/pH 7.4 buffer) of isopropamide iodide, presumably by formation of a lipophilic ion pair (14). Oleic acid and lauric acid increased both the isopropyl myristate/buffer partition coefficient and the skin permeation rate of naphazoline, a base, but the partition coefficients of caffeine and methyl nicotinate were not affected by the fatty acids (7). We evaluated the possibility of increased partitioning into skin, by measuring partitioning into isopropyl myristate and toluene. There were several adjuvant/drug combinations which resulted in increased partitioning of the drug. We found no evidence of adjuvant and drug counterions forming more lipophilic ion pairs, however. On the contrary, the fatty acids increased the partition co-

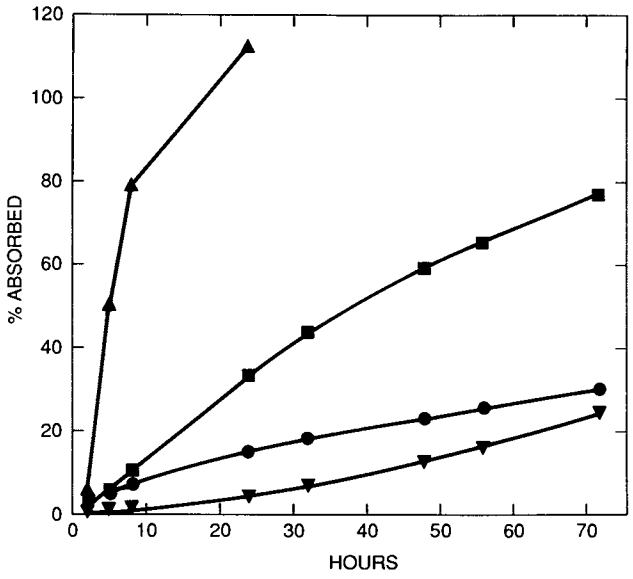

Fig. 3. Profiles of propylene glycol skin penetration from vehicles containing no adjuvant (●), 0.5 *M* lauric acid (■), 0.5 *M* dodecylamine (▲), or 0.5 *M* dodecylamine and saturated with methotrexate (▼).

Table V. Mechanisms Involved in the Skin Penetration Enhancing Effects of Fatty Acids and Dodecylamine and Those Drugs Affected via the Specified Mechanism

Mechanism	Adjuvant	
	Fatty acids	Dodecylamine
Increased drug solubility in vehicle	Naloxone	Indomethacin Fluorouracil Methotrexate
Increased partition coefficient	Indomethacin Fluorouracil	Naloxone Testosterone
Disrupted barrier function of skin	Naloxone Testosterone Indomethacin Fluorouracil	Fluorouracil
Increased skin penetration of solvent	Yes	Yes

efficients of the acidic drugs indomethacin and fluorouracil, and dodecylamine increased the partition coefficients of naloxone base. One difference in methodology between our work and those studies cited above (6,7,12–14) is that the donor vehicles used were entirely or predominantly aqueous. We did not evaluate the apparent pH of the vehicles and do not know if the drug or adjuvant were ionized, a requirement for ion pairing. Thus, although we show no evidence for ion pairing, we cannot state that it cannot contribute to enhanced skin permeation under other conditions.

The permeation rate of the solvent can also be an important factor influencing the permeation rate of the drug. A correlation between metronidazole and PG skin permeation rates from PG vehicles was described (15). Similar relationships were described for indomethacin (16), molsidomine (8), and narcotic analgesics (17) from fatty acid/PG vehicles and for nicorandil penetration from fatty acid ester/PG vehicles (18). The results of increased solvent penetration into the skin may include increased drug solubility in the skin and increased barrier disruption if the solvent itself is a penetration enhancer. Kadir *et al.* have shown that propionic acid vehicles enhanced the skin permeation of theophylline (19) and adenosine (20) because of rapid propionic acid skin penetration and solubilization of the drug in the skin–propionic acid medium. We did not measure PG skin permeation rates with all drug/adjuvant/vehicle combinations, but our data show that the permeation rate of the vehicle can be influenced by the presence of adjuvant or drug. Drug solubility in the membrane should be most influenced by the PG skin penetration rate for those drugs with a high affinity for PG, as evidenced by low partition coefficients. Some adjuvants can have the dual synergistic effects of increasing drug solubility in the vehicle and increasing the skin penetration rate of the vehicle.

The remaining proposed mechanism is disruption of the barrier function of the skin. Fatty acids can change the physical chemical characteristics of skin, as shown using differential scanning calorimetry and infrared spectroscopy for oleic acid-treated stratum corneum (5). Specifically, fatty acids seem to disrupt the packed structure of the intercellular lipids of the stratum corneum (4). We have not measured barrier disruption directly but have attributed any increase in P, not accompanied by a proportional increase in K, to increased diffusivity. The fatty acids were shown to increase skin diffusivity and permeation rates of naloxone, indomethacin, and fluorouracil. However, the effects of fatty acids were inconsistent; P values for benzoic acid and methotrexate were unaffected. To examine the relationship between compound structure and permeability enhancement, we calculated the increase in P in the presence of lauric acid ($P^{lauric}/P^{control}$) for each diffusant. The $P^{lauric}/P^{control}$ values were independent of whether the compounds had basic, neutral, or acidic functional groups (Table VI). There was also no relationship to their octanol/water partition coefficients or molecular weights. The effects of dodecylamine on barrier disruption also varied from drug to drug, and a significant disruption effect was indicated only for fluorouracil. One reason for the inconsistent effects on skin diffusivity from drug to drug is that the drug, adjuvant, and vehicle interact to each influence the penetration of the others. Susceptibility to permeation enhancement may also depend on the routes of drug permeation through skin, which may vary from drug to drug.

Table VI. Comparison of the Increase in Permeability Coefficient with Lauric Acid ($P^{lauric}/P^{control}$) for the Various Model Drugs and Some of Their Physical Chemical Properties

Diffusant	$P^{lauric}/P^{control}$	Log K (octanol/water)[a]	Molecular weight
Naloxone	16.92	1.53	327
Testosterone	4.07	3.32	288
Benzoic acid	1.27	1.95	122
Indomethacin	66.67	3.08	358
Fluorouracil	109.09	−0.92	130
Methotrexate	1.12	−1.85	454

[a] Values are from Ref. 21.

We conclude from these studies that fatty acid and amine adjuvants can increase skin permeation by a combination of several mechanisms. The relative contributions of those mechanisms vary depending on the drug and adjuvant. We are not yet able to predict which mechanism will predominate for any one drug/adjuvant/vehicle combination.

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