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Skin permeation enhancement effects of linoleic acid and Azone on narcotic analgesics

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Summary

Hairless mouse skin permeation of narcotic analgesics (NAs), oxymorphone (OX), hydromorphone (HY), and morphine (MO), was examined in vitro using linoleic acid (LA) or Azone (AZ) as a skin permeation enhancer. The enhancement effect of LA was compared with AZ in non-aqueous binary or ternary solvent systems and aqueous gel preparations. Both enhancers significantly improved the permeation of NAs in all preparations. The rate of permeation of OX, HY and MO was almost similar when their permeation across skin was studied simultaneously. LA, like AZ, enhances the permeation of vehicle components of the formulation, indicating a non-specific enhancement effect. The ternary solvent systems developed, containing triacetin (50% w/w or more), may have a lower potential for causing skin irritation problems than binary solvent systems containing enhancer and propylene glycol (PG).

Introduction

The transdermal route for drug administration is limited by the barrier properties of the stratum corneum (SC). Only the most potent drugs with low daily dose and appropriate physicochemical characteristics are candidates for transdermal delivery. To improve the permeation of drugs across the skin, the barrier properties of the stratum corneum may be manipulated by using skin permeation enhancers, e.g. AZ and fatty acids (Schaefer et al., 1982; Barry, 1983; Cooper, 1984; Hadgraft, 1984; Hadgraft, 1985; Loftsson et al., 1987; Cooper, 1985; Aungst, 1986). As a result, less potent drugs with higher daily dose requirements (e.g. OX) or those with less favorable physicochemical properties for permeation may also be considered for transdermal delivery. In this study the permeation enhancement effects of linoleic acid (LA), an essential fatty acid, on the permeation of morphine (MO), oxymorphone (OX), and hydromorphone (HY) across hairless mouse skin were studied and compared with the effects of Azone (AZ). The physicochemical properties of the narcotic analgesics are shown in Table I (Moffat (Ed.), 1986; Roy and Flynn, 1988).

The opioid narcotic analgesics including salt forms of MO, OX and HY, are used orally and

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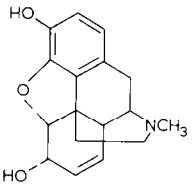
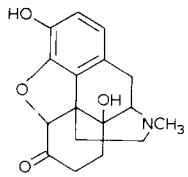
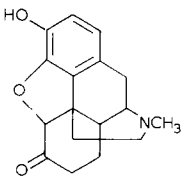
TABLE 1

Physicochemical properties of narcotic analgesics

Compound	Structure	mol. wt.	m.p. (°C)	Water soly. (mg/ml)	P.C. (oct/pH 7.4)
Morphine		285.3	254	0.345	0.7
Oxymorphone		301.3	248–249	1.5	1
Hydromorphone		285.3	265–267	1.9	1.28

parenterally as pain killers. The effects of orally administered NAs are significantly reduced, compared to parenteral administration, due to high first-pass metabolism by the liver. The bioavailability ratios for the salts of MO, OX and HY are 0.15 (Houde et al., 1965), 0.16 (Beaver, et al., 1977), and 0.62 (Beaver et al., 1978), respectively. A successful transdermal delivery system containing a safe permeation enhancer may provide a convenient alternative for administering the NAs to patients with chronic pain.

Materials and Methods

Oxymorphone base was obtained from Mallinckrodt (St. Louis, MO), morphine base from Penick Corp. (Lyndhurst, NJ), and hydromorphone hydrochloride from Knoll Pharmaceutical Co. (Whippany, NJ). Hydromorphone base was extracted from an alkalinized aqueous solution of hydromorphone hydrochloride with methylene chloride. Azone was obtained as a courtesy of Nelson Research Corp. (Irvine, CA). Carbopol 940 was obtained from BF Goodrich Co. (Cleveland, OH). PEG 400 was provided as a courtesy of Stepan Co. (Maywood, NJ). Purified triacetin (TA) was supplied by Aldrich Chemical Co. (Milwau-

TABLE 2

Effect of LA and AZ on permeation of morphine across hairless mouse skin from binary solvent systems containing PG and 1% w/w morphine base [a]

Vehicle (% w/w)	$\%D_{24}$	*EF* $\%(D_{24}/D_{24(\text{control})})$
PG(control)	0.24	1
LA : PG (2 : 98)	66.9 ± 0.8	279
LA : PG (20 : 80)	48.1 ± 4.2	204
AZ : PG (2 : 98)	41.2 ± 2.8	172
AZ : PG (20 : 80)	83.1 ± 5.8	346

[a] Values are the mean ± S.D. of 3–4 determinations

kee, WI). ICI Americas (Wilmington, DE) provided polysorbate 20. HPLC grade acetonitrile, and reagent grade linoleic acid were purchased from Fisher Scientific (Pittsburgh, PA). Propylene glycol (PG) was obtained from Captree Chemicals (Old Bethpage, NY). All other chemicals were of analytical grade. Hairless mice (SKH : hr-1) were obtained from Skin Cancer Hospital, Temple University (Philadelphia, PA).

TABLE 3

Effect of LA and Azone concentration on the simultaneous permeation of NAs across hairless mouse skin form ternary solvent systems containing equal amounts of MO, OX, and HY (0.5% w/w) [a]

Vehicle	Compound	$\%D_{24}$	*EF* $\%(D_{24}/D_{24(control)})$
TA : PG	MO	0.9 ± 0.5	1
(62.5 : 37.5)	OX	1.2 ± 0.4	1
(Control)	HY	1.0 ± 0.5	1
	PG	4.6 ± 0.8	1
	TA	1.4 ± 0.1	1
LA : TA : PG	MO	44.4 ± 7.1	49.3
(20 : 50 : 30)	OX	48.0 ± 7.3	40.0
	HY	39.1 ± 7.1	39.1
	PG	72.4 ± 9.5	15.7
	TA	26.6 ± 4.4	19.0
LA : TA : PG	MO	46.7 ± 2.8	51.9
(10 : 60 : 30)	OX	49.3 ± 3.1	41.0
	HY	44.9 ± 2.6	44.9
	PG	57.0 ± 6.4	12.4
	TA	17.8 ± 2.1	12.7
LA : TA : PG	MO	56.1 ± 2.9	62.3
(5 : 65 : 30)	OX	56.8 ± 2.5	47.3
	HY	56.5 ± 2.5	62.8
	PG	54.7 ± 7.8	11.9
	TA	18.3 ± 1.0	13.1
AZ : TA : PG	MO	59.1 ± 7.3	65.7
(20 : 50 : 30)	OX	47.7 ± 6.8	39.8
	HY	53.9 ± 7.0	53.9
	PG	74.6 ± 10.4	16.2
	TA	18.1 ± 3.4	12.9
AZ : TA : PG	MO	14.4 ± 8.0	16.0
(10 : 60 : 30)	OX	11.5 ± 6.4	9.6
	HY	12.6 ± 6.5	12.7
	PG	31.6 ± 17.9	6.9
	TA	4.9 ± 2.7	3.5
AZ : TA : PG	MO	2.6 ± 0.4	2.9
(5 : 65 : 30)	OX	3.0 ± 2.5	2.5
	HY	2.3 ± 2.3	2.3
	PG	11.0 ± 1.5	2.4
	TA	2.2 ± 0.3	1.6

[a] Values are the mean ± S.D. of 3–4 determinations.

Solubility measurement. The solubility of OX or MO in the solvent systems was measured by addition of excess amount of the drug to the solvent systems and several minutes sonication. After standing a few hours at room temperature, the solution was filtered through a nylon filter (0.45 μm) and assayed by HPLC.

Preparation of binary and ternary solutions. Four binary formulations (Table 2) were prepared by combining 2% or 20% w/w AZ or LA with PG. MO base (1% w/w) was added to each binary system and PG alone as a control followed by several minutes of sonication to obtain clear solutions. Ternary formulations containing multiple NAs (Table 3) were prepared by mixing 30% w/w PG with various ratios of LA (5–20% w/w) or AZ (5–20% w/w) and TA (65–50% w/w). The 3 NAs – MO, OX and HY – were added to the solvent systems which were then sonicated for several minutes to obtain clear solutions. Due to phase separation at a high drug concentration, all experiments with ternary solvent systems were carried out at drug concentrations less than their saturation solubilities.

Preparation of aqueous gel formulations. Aqueous carbopol gel systems (AGs) were prepared by dispersing 0.2–0.3% w/w Carbopol 940 in water containing 2–2.5% polysorbate 20 with constant stirring. The pH of the dispersions was adjusted to 4.8–5.0 with 1 N NaOH to form a clear gel. The AGs listed in Table 4 were prepared by addition of OX and 5–20% w/w LA or AZ to the carbopol gel. The final formulations were homogenized with a hand homogenizer.

Receiver solution. To provide sufficient sink conditions for the compounds especially when permeation is enhanced, an isotonic citrate phosphate buffer of pH 4.6 was selected as receiver solution instead of normal saline (pH 6.5). The buffer was prepared by dissolving 12.66 g of anhydrous dibasic sodium phosphate and 10.59 g of anhydrous citric acid in 1 liter of distilled water. The pH of the buffer was adjusted to 4.6 with 1 N sodium hydroxide. The osmolality was

TABLE 4

Effect of LA and AZ on the permeation of OX across hairless mouse skin from aqueous gel formulations containing 5% w/w OX [a]

Key: AGF_1 = aqueous gel formulation composed of 0.3% Carbopol 940 and 2.5% Polysorbate 20 in water, pH 4.8; AGF_2 = aqueous gel formulation composed of 0.2% Carbopol 940 and 2% Polysorbate 20 in water, pH 4.8–4.9; C = 0.2% Carbopol 940.

Gel system	$\%D_{24}$	EF $\%(D_{24}/D_{24(\text{control})})$
AGF(control)	0.7±0.2	1
0.3% Carb. 940	1.1±0.2	1.6
LA:AGF$_1$		
5:95	36.7±8.1	54
10:90	42.7±3.9	63
20:80	56.0±3.8	83
AZ:AGF$_2$		
5:95	61.4±8.8	61
10:90	63.3±6.7	63
20:80	67.7±6.8	68
AZ:C		
10:90	35.6±2.6	53

[a] Values are the mean±SD of 3–4 determinations.

measured by an osmometer (Osmette A from Precision System, Sudbury, MA), and adjusted to 300 mOsm/kg H_2O by adding approximately 0.8 g sodium chloride.

Skin membrane preparation. Female hairless mice (SKH:hr-1 obtained from Skin Cancer Hospital, Temple University) were sacrificed by spinal cord dislocation at the neck. The abdominal and dorsal sections of the skin were excised from the animal with a pair of surgical scissors. The adhering fat and other visceral debris were removed carefully from the undersurface with a pair of tweezers. The skin was clamped onto glass diffusion cells with the stratum corneum facing the donor compartment. To remove extraneous debris and leachable enzymes, the dermal side of the skin was in contact with the saline solution for 2 h before starting the diffusion experiment.

Diffusion cells. Standard Franz diffusion cells FDC-100 (Crown Glass Co., Somerville, NJ) with a receiver compartment volume of 8 or 10 ml were equipped with magnetic stirrer bars to provide 600 rpm of stirring. The effective diffusion areas of 8 or 10 ml cells are 1.76 or 3.14 cm^2, respectively.

Permeation procedure. One ml of non-aqueous solutions or about 1.5 ml of aqueous gel formulation was placed on the surface of the skin in the donor compartment. The donor compartment was covered with cellophane and Parafilm. At predetermined times, the entire receiver solution was withdrawn and replaced with fresh, warm (37 °C) receiver solution (isotonic citrate phosphate buffer of pH 4.6). The temperature of the receiver compartment was maintained at 37 °C during the experiment. The appearance of the drug in the receiver solution was monitored by determining its concentration by HPLC. All samples were prepared for assay by filtering through an 0.45 μm Vanex filter unit (Vangard International, Neptune, NJ). The permeation experiment was performed in triplicate or quadruplicate for each formulation.

Sample analysis. The sample concentrations of the narcotic analgesics were determined by reverse-phase HPLC methods. The methods for measuring MO, OX and HY contained in the diffusion samples, collectively or individually, are detailed in Table 5 as Methods I and II, respectively. Fig. 1 shows typical HPLC chromatograms.

Computation

Due to significant drug and vehicle depletion from the donor compartment, hydration, and time-dependent enhancement effect of the permeation enhancers, the experimental determination of steady-state flux values, under the described conditions, was not possible. However, to compare and to evaluate the effects of various enhancer systems on the in vitro permeation of drugs, the total percent of the dose that permeated through the skin in 24 h ($\%D_{24}$) was used for comparison. The enhancement factor (EF) was calculated by taking the ratio of $\%D_{24}$ from a solution containing enhancer over $\%D_{24}$ from the control solution (solution without enhancer). The cumulative percent of the dose ($\%D$) that permeated through the skin, or the ratio of flux value,

TABLE 5

Reverse-phase HPLC methods for quantitation of MO, OX, and HY in skin diffusion samples, collectively or individually (Methods I and II, respectively)

HP = Hewlett-Packard.

Method	Instruments	Stationary Phase	Mobile Phase	R.T. (min)
I	HP 1090 LC [a]	LC18-DB	Flow = 1, Time = 8 min	6.3 (MO)
	HP 3393A Integrator	4.6 mm × 25 cm	ACN 15%, 0.003 M amm. phos pH 3	6.8 (OX)
	Kratos Detector [b]	5 μm [c]	Flow = 2, time = 10 min	7.7 (HY)
	(Spectraflow 783)		ACN 40%, 0.003 M amm. phos pH 3	
			Flow = 2, time = 12 min	
			ACN 15%, 0.003 M amm. phos pH 3	
			Flow = 1, time = 13 min	
			Flow = 1.5	
II	HP 1090 LC [a]	CN	10% ACN	1.6 (MO)
	HP 7994A – Chem Station	3 μm [c]	90% 0.003125 M	1.7 (OX)
	HP 1040A – diode array [b]	3.3 cm	amm. phos. pH 3	2.2 (HY)

[a] 20 μl injection volume.
[b] Detection wavelength 220 nm.
[c] Packing particle size.

F_t, over initial concentration, C_0, (F_t/C_0) as a function of time was used for graphical comparison. The flux value was calculated at each sampling time using the following expression:

$$F_t = (V_r \cdot C_t)/(A \cdot t)$$

where V_r (cm^3) is the volume of the receiver compartment, C_t (μg/ml) is the drug concentration in the receiver solution at each sampling interval, A is the surface area of the skin (cm^2) and t (h) is the sampling interval.

Results and Discussion

Effect of linoleic acid and Azone on the permeation of morphine

The binary solvent systems containing LA or AZ (20 : 80 or 2 : 98 w/w enhancer : PG, Table 2) improved the permeation of MO significantly. The $\%D_{24}$ value for MO was higher from the binary system (PG : enhancer) containing 2% than that containing 20% LA ($\%D_{24} = 67$ vs 48) whereas AZ was more effective at 20% than at 2% ($\%D_{24} = 83$ vs 41). These differences between the binary systems, containing LA and AZ, may be explained partially by the solubility and thermodynamic activity of the drug in the solutions. Solubility of MO in the solvent systems containing LA is higher than the systems containing AZ (Fig. 2).Therefore, the thermodynamic activity of MO in these systems is not similar. Optimum permeation enhancement effects for fatty acids are observed when they are combined with a polar, water- and oil-miscible solvent, especially PG or alcohols (Cooper, 1984). The binary systems containing PG can be very irritating to human skin since PG is a known skin-irritant (Hadgraft, 1985). Therefore, we selected ternary solvent systems with more than 50% w/w TA or aqueous gel systems for further studies with LA and AZ.

Selection of TA as a cosolvent was based on the assumption that it may be needed also as a plasticizer in the preparation of transdermal patches and that replacing PG with such a less or non-irritating solvent may reduce the risk of irritation. TA is a solvent with low toxicity and irritation indices (Gosselin et al., 1984; Sweet (Ed.), 1987). TA has been used as a plasticizer in various polymer systems for coating controlled release dosage forms ("Aquacoat: Aqueous Polymer Dispersion", FMC Corp., Technical Information).

Preliminary comparative permeation studies using cosolvents such as TA, triethyl citrate, PEG

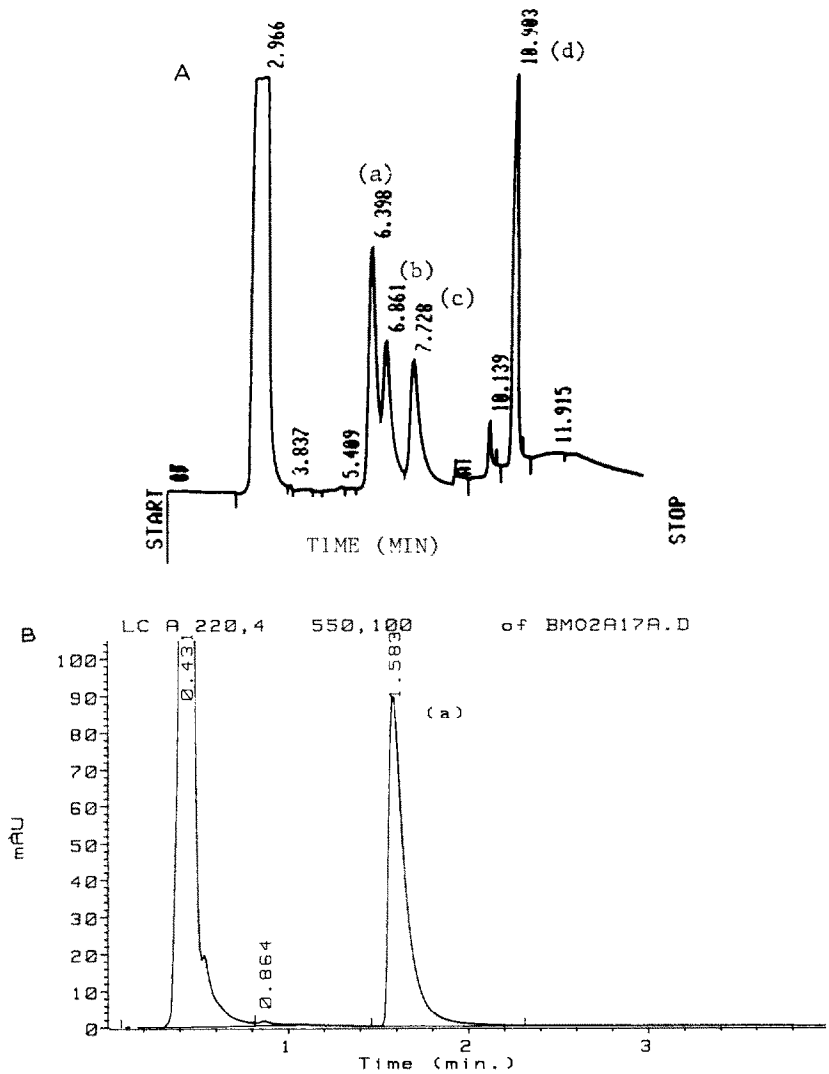


Fig. 1. Typical HPLC chromatograms for narcotic analgesics in diffusion samples using: (A) Method I: MO (a), OX (b), HY (c), TA (d). (B) Method II: MO (a).

400, mineral oil and dioctyl adipate in binary (LA : cosolvent) or ternary (LA : PG : cosolvent) solvent systems, indicated that MO had the best $\%D_{24}$ value from the systems containing TA.

Effect of linoleic acid and Azone on simultaneous permeation of NAs from non-aqueous ternary solvent systems. Table 3 shows the $\%D_{24}$ values of MO, OX and HY that permeated simultaneously from various formulations. Although the NAs differ in their water solubilities and partition coefficients (Table 1), the addition of LA or AZ to various mixtures of TA and PG improved the skin permeation of these compounds by about the same magnitude (Figs. 3, 4). In general, the enhancement effect of LA at 5% w/w concentration was better than at 20%, similar to the effect of 20% AZ and significantly better than the effect of AZ at 5–10% w/w ($P < 0.05$). The NAs permeation improved as concentration of AZ increased from 5% to 20%. At 20% AZ the permeation of MO improved 65.7- ($EF = 65.7$), for OX 39.8- and *HY* 54-fold compared to the control. The presence of

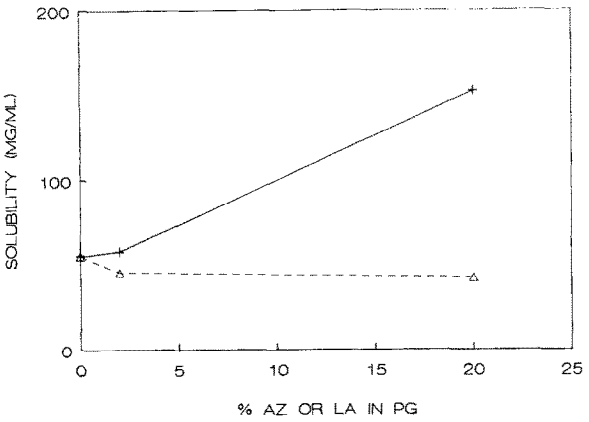


Fig. 2. Solubility of morphine in binary solvent systems. Key: (+), LA; (△) AZ.

LA in the formulation improved the solubility of NAs (partially due to production of a soluble salt), whereas increasing AZ concentration did not have much effect on the solubility (Fig. 5).

We have found that the required concentration of LA in binary or ternary solvent systems for optimum enhancement effect varies for different compounds (10% for procaterol (unpublished observation), 2% for propranolol (unpublished observation) and 2.5% for diltiazem in binary system with PG (Mauser et al., 1988). Increasing the OX concentration in the LA : PG : TA (20 : 30 : 50 w/w) solvent system resulted in a similar F_t/C_0 value (Fig. 6). Due to the interaction of LA (an acid) with OX (a base), the solvent system's prop-

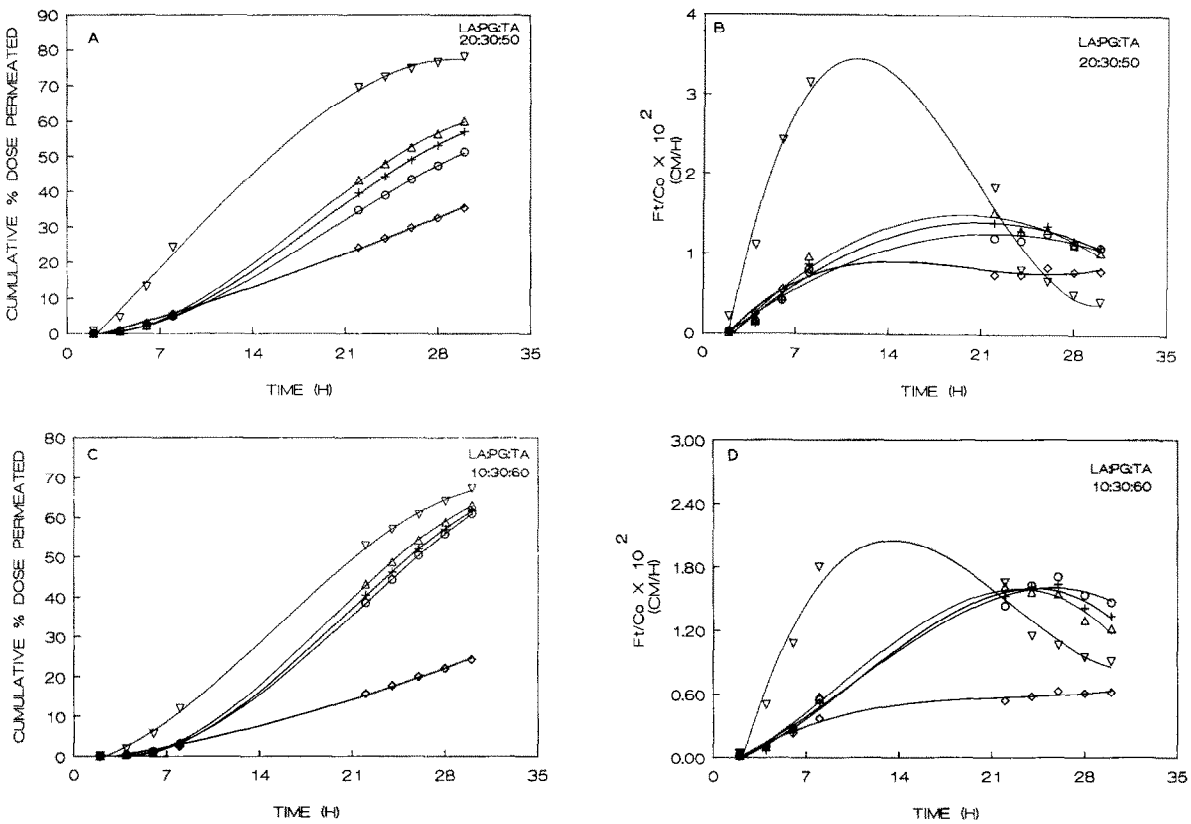


Fig. 3. Effect of LA on simultaneous permeation of solution components (MO, OX, HY, PG, TA) from: (A, B) 20 : 30 : 50, (C, D) 10 : 30 : 60, (E, F) 5 : 30 : 65 LA : PG : TA. Key: (+) MO, (△) OX, (○) HY, (▽) PG, (◇) TA; (G, H) 37.5 : 62.5, PG : TA (control): (+) MO, (▼) PG, (◆) TA. Data illustrate cumulative percent dose permeated and normalized flux versus time profiles. Line through the data points shows best curve fit.

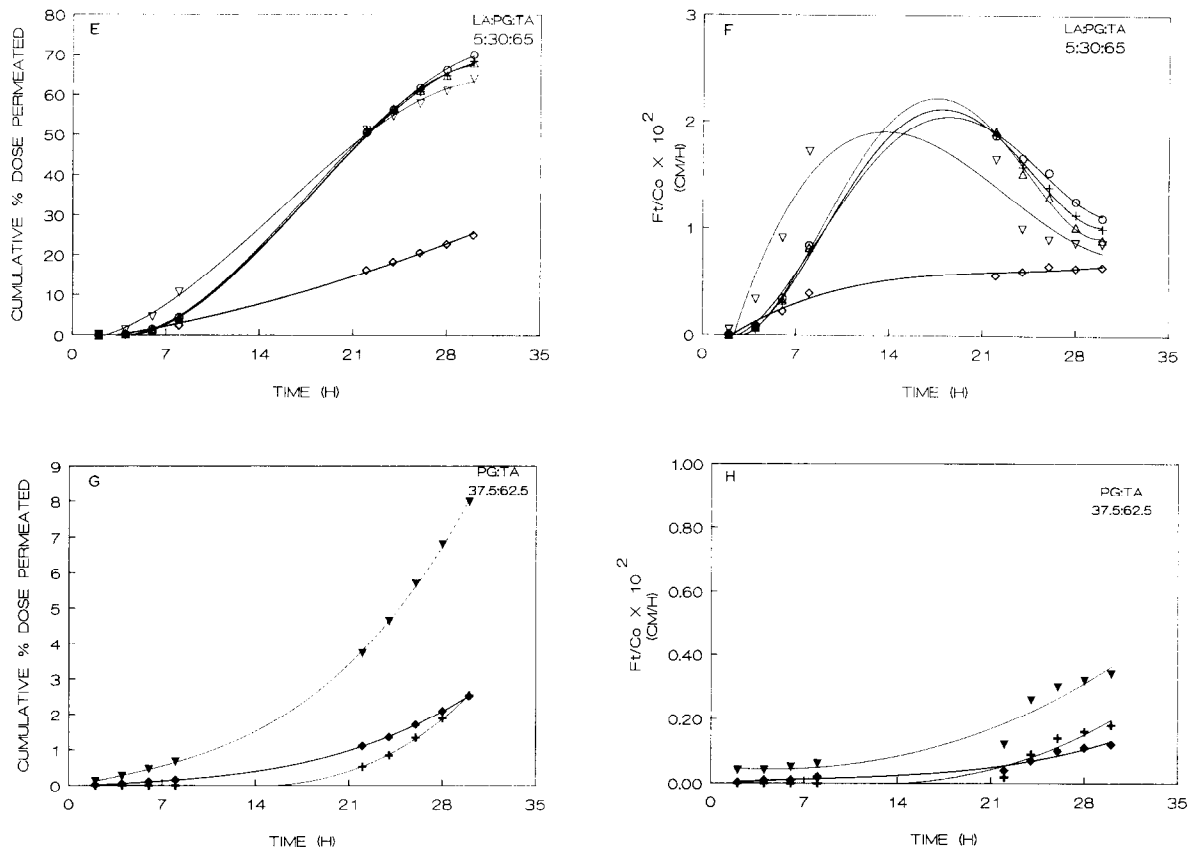


Fig. 3 (continued).

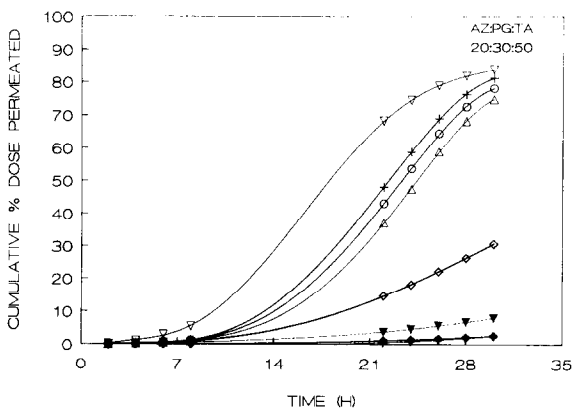


Fig. 4. Effect of AZ on simultaneous permeation of solution components (MO, OX, HY, PG, TA) from 20 : 30 : 50 AZ : PG : TA: (+) MO, (△) OX, (○) HY, (▽) PG, (◇) TA; 37.5 : 62.5 PG : TA (control): (+) MO, (▼) PG, (◆) TA. Data illustrates cumulative percent dose permeated. Line through the data points shows best curve fit.

erties should change with increasing drug concentration. However, these changes did not seem to affect the permeation of OX between con-

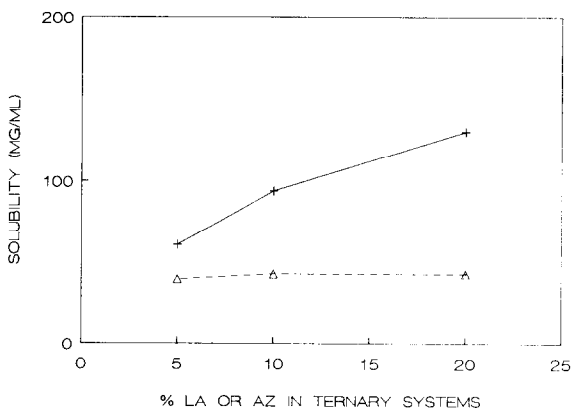


Fig. 5. Solubility of oxymorphone in ternary solvent systems. Key: % (+) LA or (△) AZ in PG (30): TA (50–65).

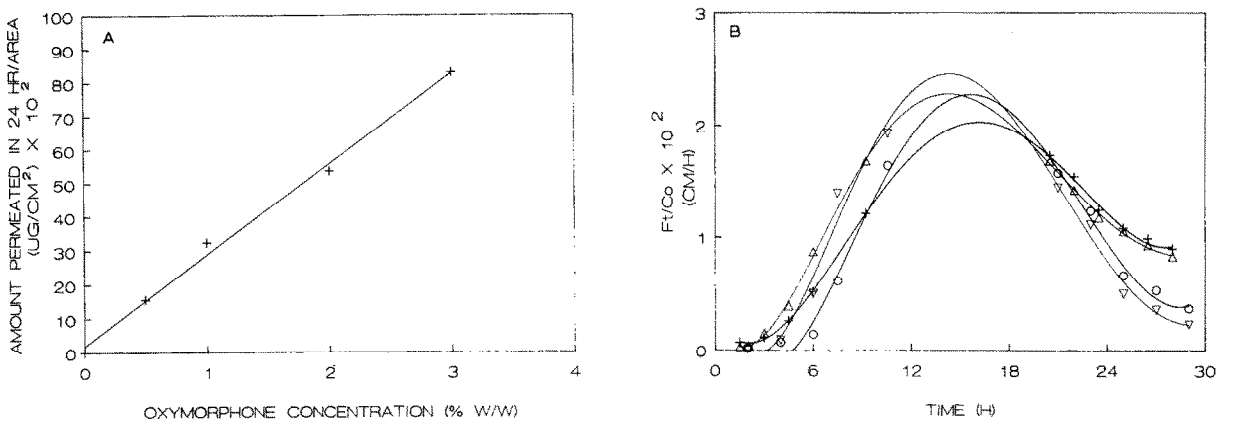


Fig. 6. Effect of increasing oxymorphone concentration in the ternary solvent system, LA : PG : TA (20 : 30 : 50), on drug permeation. Key: (A) (+) OX; (B) (+) 0.5%, (△) 1.0%, (○) 2.0%, (▽) 3.0%. Data illustrates (A) the total amount permeated in 24 hours; and (B) normalized flux versus time profiles. Line through the data points shows best curve fit.

centrations of 0.5–4% w/w. NAs' concentrations of 4% or over will cause phase separation of the ternary solvent system.

Effect of LA and AZ on permeation of vehicle components

AZ is reported to enhance the permeation of the vehicle components (Hadgraft, 1985). Fig. 4 shows the effect of AZ on the permeation of TA and PG. LA also enhances the permeation of vehicle components to various degrees. Fig. 3 shows the permeation of MO, TA and PG in the presence and absence of LA. The flux value of MO increases with time and reaches a maximum level before decreasing due to the depletion of the compound and/or vehicle components from the donor solution. Excessive depletion of MO and PG from the donor solution caused the flux values for MO and PG to decrease after about 10 h, whereas TA permeation reached a maximum at about 10 h and stayed almost constant until the end of the experiment.

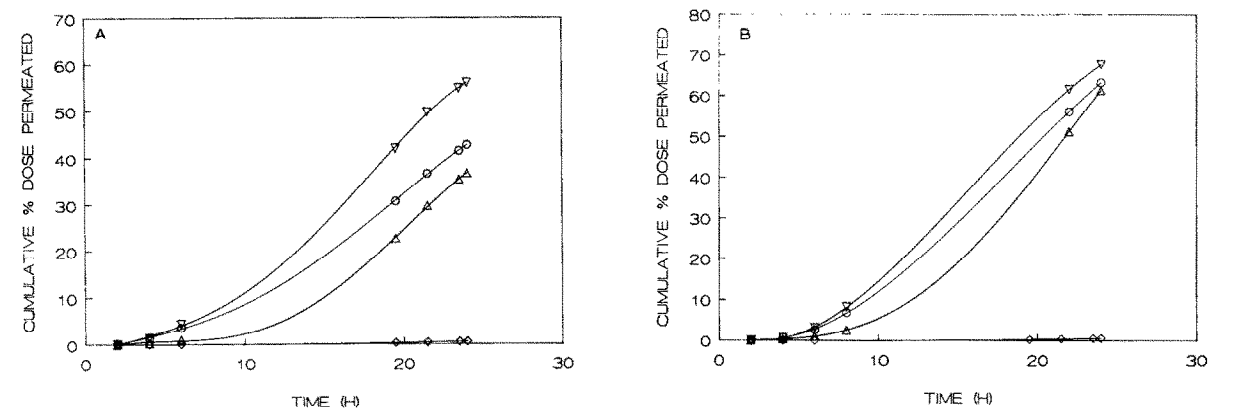


Fig. 7. Permeation of oxymorphone from aqueous gel formulations containing 5% w/w OX with (A) LA or (B) AZ. Key: (△) 5%, (○) 10%, (▽) 20% LA or AZ; (◇) AGF (control). Data illustrate cumulative percent dose permeated versus time. Line through the data points shows best curve fit.

The flux of LA from the ternary solvent system across skin was negligible. This is probably due to insolubility of LA in the receiver solution. A higher flux value for LA is expected in vivo. The in vitro flux of LA across human skin has been reported to be 0.036 $\mu g/cm^2/h$ when an 0.05 M phosphate buffer pH 7.5 containing 0.5% Pluronic F68 was used as a receiver solution (Hoelgaard and Mollgaard, 1982).

Effect of linoleic acid and Azone in aqueous gel formulations on the permeation of oxymorphone. AGs containing LA or AZ were very effective in enhancing the permeation of OX across hairless mouse skin. Fig. 7 and Table 4 show the effects of LA on oxymorphone's permeation. Increasing the concentration of LA from 0% to 20% w/w in the formulations containing 5% OX improved $\%D_{24}$ value 83 times ($EF = 83$). The systems containing AZ enhanced the permeation of OX similar to those containing LA but changing the AZ concentration from 5% to 20% w/w had less effect on the $\%D_{24}$ value.

The mechanism by which LA or other fatty acids enhance the permeation of drugs through the skin is not clearly understood. An increased fluidity of the stratum corneum (SC) lipids has been suggested (Cooper, 1984; Golden et al., 1987). The extraction of SC lipids by the formulation seems plausible. The requirement of a polar, but oil-miscible, solvent such as propylene glycol to elicit an optimum effect of LA as a permeation enhancer, leads to a speculation that the mixture (PG–LA) facilitates LA permeation into various portions of SC. This mixture may dissolve, plasticize or fluidize the SC lipids and cause the reduction of SC resistance to permeation of compounds. We have found that LA enhances the skin permeation of basic drugs (e.g. NAs (Mahjour et al., 1988), propranolol, procaterol, arecoline, etc.) more than neutral (nifedipine) or acidic (meclofenamic acid) compounds (unpublished observation). This may be due to the surface-active properties of the long-chain fatty acids when combined with basic drugs (soap formation) and/or due to the possibility of ion pair formation between fatty acids and the basic compounds.

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References

Aungst, B. and DiLuccio, R.C., Transdermal delivery of opioids. *U.S. Patent*, (1986) 4,626,539.

Barry, B.W., Properties that influence percutaneous absorption. In Swarbrick, J. (Ed.), *Dermatological Formulations: Percutaneous Absorption*, Marcel Dekker, New York, 1983, pp. 160–172.

Beaver, W.T., Wallenstein, S.L., Houde, R.W. and Rogers, A., Comparisons of the analgesic effects of oral and intramuscular oxymorphone and of intramuscular oxymorphone and morphine in patients with cancer. *J. Clin. Pharmacol.*, 17 (1977) 186–198.

Beaver, W.T., Wallenstein, S.L., Rogers, A. and Houde, R.W., Analgesic studies of codeine and oxycodone in patients with cancer. 1. Comparisons of oral with intramuscular codeine and of oral with intramuscular oxycodone. *J. Pharmacol. Exp. Ther.*, 207 (1978) 92–100.

Cooper, E.R., Increased skin permeability for lipophilic molecules. *J. Pharm. Sci.*, 73 (1984) 1153–1156.

Cooper, E.R., Penetrating topical pharmaceutical compositions containing 1-dodecyl-azacycloheptan-2-one. *U.S. Patent*, (1985) 4,557,934.

Golden, G.M., McKie, J.E. and Potts, R.O., Role of stratum corneum lipid fluidity in transdermal drug flux. *J. Pharm. Sci.*, 76 (1987) 25–28.

Gosselin, R.E., Smith, R.P. and Hodge, H.C., *Clinical Toxicology of Commercial Products*, Williams and Wilkins, Baltimore, 1984, p. II-203.

Hadgraft, J., Penetration enhancers in percutaneous absorption. *Pharm. Int.*, 5 (1984) 252–254.

Hadgraft, J., Percutaneous absorption. *Cosmetics and Toiletries*, 100 (1985) 32–38.

Hoelgaard, A. and Mollgaard, B.J., Permeation of linoleic acid through skin in vitro. *J. Pharm. Pharmacol.*, 34 (1982) 610–611.

Houde, R.W., Wallenstein, S.L. and Beaver, W.T., Clinical measurement of pain. In de Stevens, G. (Ed.), *Analgetics*, Academic Press, New York, 1965, pp. 75–122.

Loftsson, T., Gildersleeve, N. and Bodor, N., The effect of vehicle additives on the transdermal delivery of nitroglycerin. *Pharm. Res.*, 4 (1987) 436–437.

Mahjour, M., Mauser, B. and Fawzi, M.B., Comparative skin penetration enhancement effects of linoleic acid and azone for narcotic analgesics, Presented at *AAPS Third Annual Meeting and Exposition*, Orlando, FL, 1988.

Mauser, B., Mahjour, M. and Fawzi, M.B., In vitro skin permeation of diltiazem: effect of heat and skin penetration

enhancers. Presented at *AAPS Joint Eastern Regional Meeting*, Atlantic City, NJ, 1988.

Moffat, A.C. (Ed.), *Clarke's Isolation and Identification of Drugs*, Pharmaceutical Press, London, 1986, pp. 667–668, 790–791, 843.

Roy, S.D. and Flynn, G.L., Solubility and related physicochemical properties of narcotic analgesics. *Pharm. Res.*, 5 (1988) 580–586.

Schaefer, H., Zesch, A. and Stuttgen, G., Pharmacy of topical drugs. In *Skin Permeability*, Springer, New York, 1982, pp. 652–656.

Sweet, D. (Ed.), *Registry of Toxic Effects of Chemical Substances 1985–1986 Edition*, U.S. Department of Health and Human Services, Washington, 1987, p. 161.