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Research Article

Transdermal Delivery of Narcotic Analgesics: Comparative Permeabilities of Narcotic Analgesics Through Human Cadaver Skin

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Relationships between the *in vitro* permeation rates of select narcotic analgesics through human skin and their physicochemical properties were investigated by following the permeation kinetics of six representative compounds in small diffusion cells. The relative permeability coefficients of three phenylpiperidine analogues, meperidine, fentanyl, and sufentanil, all measured on a single piece of skin, were 3.7×10^{-3}, 5.6×10^{-3}, and 1.2×10^{-2} cm/hr, respectively. Using membranes from the same skin section, the permeability coefficients of three opioid alkaloids, morphine, codeine, and hydromorphone, were considerably lower, at 9.3×10^{-6}, 4.9×10^{-5}, and 1.4×10^{-5} cm/hr, respectively. The high permeability coefficients of the former compounds are due to their highly lipophilic nature as reflected in high octanol/water partition coefficients and low solubility parameters. Generally, the permeability coefficients of the narcotics increase as the lipophilicity increases. When viewed in literature perspective, the data suggest that aqueous tissue control of transport is approached in the case of the phenylpiperidine analogues, all of which have $K_{octanol/water}$ values greater than 40. Permeability coefficients of fentanyl and sufentanil were also determined as a function of pH over the pH range 7.4 to 9.4, in this instance with membranes prepared from additional samples of skin. The permeability coefficients of each drug varied less than threefold over the pH range, a behavior consistent with the highly hydrophobic natures of the compounds. The low permeability coefficients of morphine, codeine, and hydromorphone coupled with their low potencies make these drugs poor transdermal candidates. It appears that fentanyl and sufentanil can be successfully transdermally delivered.

KEY WORDS: narcotic analgesics; permeability coefficients; melting points; solubility parameters; partition coefficients; cadaver skin; *in vitro* diffusion; transdermal drug delivery.

INTRODUCTION

Naturally occurring opioid alkaloids such as morphine, codeine, and hydromorphone and synthetic piperidine analogues such as meperidine, fentanyl, and sufentanil are used clinically for the relief of postsurgical pain, cancer pain, and other pain (1–4). By and large these narcotics (i) have short durations of action due to rapid metabolism and, in some instances, large volumes of distribution, (ii) tend to be sedative in their current oral and parenteral doses, (iii) are inefficiently absorbed orally due to first-pass metabolism, (iv) tend to depress respiration at the peak levels reached following their administration, (v) tend to be nauseating and have other dose- and route-related side effects (5), and, worst of all, (vi) are subject to drug abuse and the development of drug dependencies. Thus, in part due to the inadequacies of the drugs themselves and in part to a deep and abiding concern in the prescribing community over their addictive potential, the drugs tend to be used ultraconservatively in the clinical setting, with the result that acute and chronic pain are not as well controlled as they might be (6–9).

Transdermal delivery offers a means of mitigating some of the above drawbacks of the narcotics such as the all too frequent dosing required to sustain their therapeutic levels. Side effects which result from the peaks of pulsatile delivery can be eliminated. To these ends, a clinically adequate permeability of the potent narcotic analgesic, fentanyl, has been reported by Michaels *et al.* (10). This work sets a precedent for using *in vitro* permeability screening with cadaver skin as the first experimental step toward substantiating transdermal feasibility. The approach presupposes that excised skin retains the essential barrier attributes of living skin, a premise buttressed by over two decades of percutaneous absorption research (11–18). No other reports concerning the skin permeability of narcotics and the dependency thereof on physicochemical properties appear in the literature. Therefore, characterization of the *in vitro* skin permeation rates of some

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representative narcotic analgesics, namely, morphine, hydromorphone, codeine, meperidine, fentanyl, and sufentanil, has been undertaken. Other candidates suitable for transdermal delivery may surface.

MATERIALS AND METHODS

Materials. Fentanyl and sufentanil were received as gifts from Janssen Pharmaceutica, (N.J.). Meperidine hydrochloride, morphine sulfate, hydromorphone hydrochloride, codeine phosphate were obtained from the University of Michigan Hospital (Ann Arbor). The *N,O*-bis(trimethylsilyl)-acetamide (BSA) used in derivatizing morphine for assay was obtained from Pierce Chemical Co. (Rockford, Il.). Citrate–phosphate buffers having pH values between 7.4 and 7.5 were used in the permeation studies which were prepared from reagent-grade chemicals and distilled water. All buffer solutions were prepared to be isoosmotic with physiological fluids. The free-base form of each drug was used in the skin permeation studies to avoid introducing ionic species other than those already associated with the buffer system. The free bases of fentanyl and sufentanil were obtained directly from Janssen. Free-base forms of morphine, hydromorphone, codeine, and meperidine were prepared for the studies in the manner indicated previously (19) (by extracting basified aqueous solutions of the drugs with an organic solvent). Sharp melting points and chromatographic analysis (19) indicated that the free bases so formed were highly pure.

All permeation studies were done from saturated solutions of the drugs formed by first equilibrating excesses of the free-base forms of the drugs with the pH 7.4 buffer and then filtering off the excess solid solute. To do this, each drug solution was prepared from a weighed amount of narcotic exceeding its solubility. The slurries were than stirred vigorously and continuously for periods exceeding 24 hr. Previous work (20) indicated that overnight stirring was more than sufficient time to establish saturated states for these drugs. The pH in each case was again measured after the equilibrium, and in no instance did it drift by more than 0.1 unit (pH's were ≤ 7.5) from the initial value. In the previous work (20) it was also determined that, at pH 7.4, the free bases of fentanyl, sufentanil, and morphine are the saturated solid. The total solubility at this pH is thus equal to the saturated free-base concentration plus that amount of ionized species necessary to satisfy the dissociation equilibrium. pK_a values for codeine and meperidine found in the literature are both above 8, and therefore these two drugs also have solubilities which are established against their saturated free-base species at pH 7.4. Presumably the same is true for hydromorphone, given its structural similarity to morphine and codeine. Solubilities were determined in the pH 7.4 buffer medium on every solution used in the permeation analysis. These solubilities and the pK_a's of the compounds are listed in Table I. The solubilities reported in Table I are slightly different from those found previously, because a different ionic strength was used.

Skin Preparation. Human cadaver skin was used in the permeation studies. Samples of whole skin were removed from the abdomen of human cadavers within 48 hr postmortem using a dermatome set at a 200-μm thickness. The skins were wrapped in plastic film and stored in a freezer at −20°C (21). The frozen skins were thawed and cut into squares before mounting in the diffusion apparatus. Epidermal layers were separated from the full-thickness skin by immersing each skin section in water at 60°C for 30 sec (22). The epidermis was then teased off with forceps. The separated epidermal layer was used as such in the diffusion studies.

Skin Permeation Method. Each skin section was mounted carefully between the half-cells of a diffusion cell, each of a 3-ml capacity, and fastened with a rigid clamp. The two half-cells were filled with buffer and the temperature of the diffusion-cell contents was maintained at 37°C by circulating constant-temperature water (Lauda K-2/RD, Beckman Instrument) through glass jackets surrounding the each half-cell. The cell compartments were then rinsed with buffer and the donor compartment was charged with a saturated solution of one of the permeants dissolved in a physiological phosphate buffer (pH ≃ 7.4). Cadaver skin permeability coefficients of fentanyl and sufentanil were also determined as a function of donor pH. In this initiative, the pH of the physiological phosphate buffer was varied from 7.4 to 9.4.

Table I. Physicochemical Properties,[a] Diffusion, and Partition Coefficients of Narcotic Analgesics

Parameter	Morphine	Hydromorphone	Codeine	Fentanyl	Sufentanil	Meperidine
MW (g/mol)	285.3	285.3	299.3	336.5	387.5	247.0
M.P. (°C)	255	266	155	84	97	35
Solubility parameter, ∂_2 $(cal/cm^3)^{1/2}$	13.1	11.7	10.9	9.8	9.7	9.6
Solubility in buffer (pH 7.4, 25°C) (mg/ml)	0.72	2.25	2.14	0.051	0.034	6.55
pK_a (37°C)	8.1	8.1[b]	8.1	8.9	8.5	8.5
$K_{octanol/water}$ (pH 7.4)	0.70	1.28	2.95	717	2842	38.9
Apparent skin diffusion coefficients[c] (cm^2/sec)	8.9×10^{-12}	4.7×10^{-12}	6.1×10^{-12}	2.4×10^{-11}	2.3×10^{-11}	3.9×10^{-11}
Apparent $K_{membrane/water}$ ($P\,h_{sc}/D_{sc}$)	0.29	0.83	2.2	144.9	64.8	26.2

[a] From Ref. 19.

[b] pK_a of hydromorphone is assumed to be the same as morphine and codeine owing to its structural similarity.

[c] The apparent diffusivity is based on the Daynes and Barrer lag time equation [Eq. (3)].

The recorded pH's were measured after effecting saturation of the donor medium with the respective permeants, prior to starting the experiment. Stirring was set at 150 rpm throughout the experiment. At predetermined times, 200 μl of receiver content was withdrawn and replaced with previously warmed (37°C) fresh buffer. Owing to low levels of permeation as well as less assay sensitivity for morphine, hydromorphone, and codeine, the whole contents of the receiver compartment were withdrawn at each sampling interval. The receiver was rinsed once with previously warmed buffer, which was added to the sample, and was then filled with fresh buffer. Samples were taken from the donor compartment at the beginning and at the end of each experiment to assure that the depletion of donor drug did not exceed 10% during the course of an experiment. The samples were assayed by gas–liquid chromatography (GLC) using a nitrogen selective detector.

Meperidine, Fentanyl, and Sufentanil Extraction. Fourteen micrograms of codeine, the internal standard, 0.5 ml of 2 *M* NaOH, and 4 ml of extracting solvent (hexane:ethanol, 95:5%) were added to the 200 μl of sample in a 15-ml culture tube. The sample was then vortexed for 5 min to mix the phases intimately and was centrifuged. The organic phase was transferred to another test tube with the aid of a Pasteur pipette and evaporated to dryness at 40°C. Residue was reconstituted in 200 μl of toluene and an aliquot of 2 μl of the formed solution was injected into the GLC.

Morphine, Codeine, and Hydromorphone Extraction. Each sample (≈3 ml) was basified with sodium bicarbonate buffer (pH 9) and the aqueous phase was then extracted with dichloromethane/*n*-butanol (9:1). The organic phase was separated and evaporated to dryness at 40°C under a gentle stream of dry air. The residue was reconstituted in 40 μl of toluene. The morphine was derivatized with bovine serum albumin (BSA) using a standard procedure (23) before injecting a sample into the gas chromatograph.

Gas Chromatographic Assay. A Hewlett–Packard GC-5890 gas chromatograph (Hewlett Packard, N.J.) equipped with a nitrogen-phosphorous detector was used. Chromatographic resolution was achieved using a 10-m × 0.32-mm-ID, 0.25-μm cross-linked 50% phenyl methyl silicone fused silica capillary column. Helium was used as a carrier and makeup gas. The split ratio was 25:1. The gas chromatograph was also equipped with a Hewlett Packard 7673-A autosampler. Peak heights were evaluated on a Hewlett Packard 3390-A integrator.

The flow rates set for the carrier gas and the makeup gas were 2.5 and 45 ml/min, respectively, in all assays. The column temperature was set at 150°C for 1 min and was programmed to reach 255°C at a rate of 10°C/min. Both the injector and the detector temperatures were maintained at 295°C. Aliquots (2 to 3 μl) of the samples were injected and the purge of excess solvent was carried out at a flow rate of 60 ml/min beginning 1 min after the sample was injected and continuing to the end of the analysis. The run time was 15 min. The coefficient of variation of each assay was checked and was never greater than 10%. The lower limit of quantitation for each narcotic assayed was less than 50 ng/ml. It is notable that no metabolites were detected for any of the narcotics using this sensitive GLC assay.

Data Analysis. The data were plotted as the cumulative amount of drug collected in the receptor compartment as a function of time. The effective permeability coefficient for a given run was calculated from Fick's first law:

$$\frac{dM}{dt} = J_T = A\,P\,\Delta C \tag{1}$$

In this equation J_T is the total flux in the steady state as micrograms per hour; A is the area of the membrane, 0.785 cm^2; P is the effective permeability coefficient as centimeters per hour; and ΔC is the concentration difference expressed between the diffusion cell's chambers, which was taken as the initial donor phase concentration as micrograms per cubic centimeter. The term *effective* (or apparent) is used in this paper in recognition of the fact that the skin and particularly its barrier layer, the stratum corneum, are heterogeneous elements. While the experimental values of P are clearly characteristic of the net resistance of the membrane with all its complexities, they are at the same time composite values bearing little resemblance to the "pure" permeabilities of the tissue's microscopic physical regimes. Moreover, the component parts of the permeability coefficient, diffusivity, partition coefficient, and thickness, which are essentially experimentally inseparable for complex membranes such as the skin, are particularly subject to interpretation. The present lack of knowledge concerning the geometrical arrangements of the skin's phases prevents us from confidently assigning tortuosities to the various diffusion pathways. We do not even have functional estimates of the phase volumes of the regimes supporting diffusive conduction, let alone an understanding of each permeant's distributioning between the various phases of the skin during its permeation. Because of these and other comparable uncertainties, actual diffusion coefficients, thicknesses, and partition coefficients of the diffusive pathways taken by the compounds remain obscure. Thus all values estimated are "effective," with magnitudes subject to their manner of estimation and the geometries of the model chosen to represent the barrier. The complexities withstanding, if one makes parameter comparisons in the light of such realities, meaningful generalizations can be drawn about mass transfer processes across biological membranes.

Since J_T is also equal to

$$\frac{dM}{dt} = V\frac{dC}{dt} \tag{2}$$

where the term, V, is the receiver half-cell volume, 3.0 ml, the permeability coefficient can be directly estimated from the steady-state rate of change in concentration in the receiver half-cell.

RESULTS AND DISCUSSION

Solubilities of the narcotics in buffer (pH 7.4) are listed in the middle row in Table I. Table I also provides other essential physicochemical data to analyze the permeability of these compounds (19). The apparent diffusion coefficients ($D_{sc's}$) listed in Table I were calculated from the Daynes and Barrer lag time equation:

$$D_{sc} = \frac{h_{sc}^2}{6t_L} \quad (3)$$

where t_L is the lag time. To do these calculations, the stratum corneum thickness, h_{sc}, was set at 0.0010 cm, presumably a representative thickness for human skin (24). These are clearly relative values only as factors of nonlinearity of path and sorption are unaccounted for. If one could actually account for such factors, the diffusivities might be as much as two to three log orders greater than those presented in Table I. This is because nonlinearity of path (tortuosity) and permeant immobilization by way of sorption as the gradients are set up across a membrane both lengthen lag times. Because of the inverse relationship between lag time and diffusivity, diffusivities tend to be underestimated when either of these confounding factors is operative. However, for structurally related compounds, relative values of the diffusion coefficient are still meaningful and allow important comparisons. For example, the considerably lower apparent diffusion coefficients of the group of opioid alkaloids relative to the phenylpiperidine analogues indicates that the stratum corneum either offers more diffusional resistance, or is more adsorptive, or both to the former more rigid and considerably more polar opioid structures. The fact that the opioids are more polar is revealed in their low $K_{octanol/water}$ partition coefficients and in their relatively high aqueous solubilities at 25°C. It is notable, for instance, that the aqueous solubilities of all three opioids are higher than those of fentanyl and sufentanil despite the fact that the latter two compounds melt at far lower temperatures than do morphine, codeine, and hydromorphone (Table I).

Representative plots of the cumulative amounts of morphine, codeine, and hydromorphone permeated through human cadaver skin as a function of time are shown in Fig. 1. Figure 2 provides a similar set of curves for the phenylpiperidine analogues, fentanyl, meperidine, and sufentanil. It will be noted that steady-state fluxes of the latter compounds were established within a few hours, whereas the opioid alkaloids exhibited longer lag times, which in some runs approached 10 hr. The effective permeability coefficients (cm/hr) and steady-state fluxes (μg/cm²/hr) calculated using Eq. (1) and the terminal, linear portions of the curves are summarized in Table II. The slopes through these regions, the curves, which are equal to J_T for a run, were determined

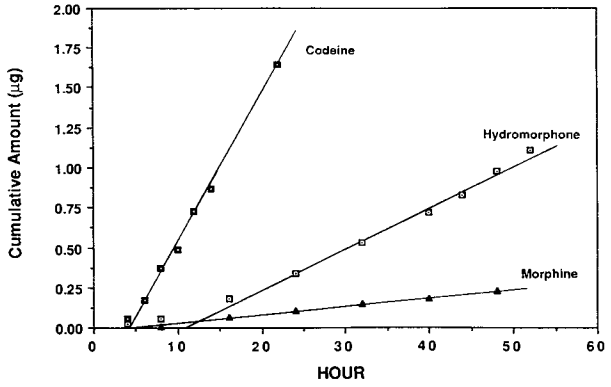

Fig. 1. Representative permeation profiles for the diffusion of morphine, hydromorphone, and codeine through human skin at 37°C.

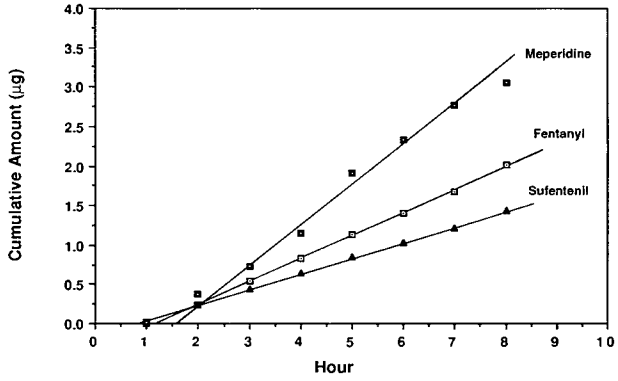

Fig. 2. Representative permeation profiles for the diffusion of meperidine, fentanyl, and sufentanil through human skin at 37°C.

using linear regression analysis. In most cases the coefficients of determination for the lines were better than 0.99. None were less than 0.98. The lag times reported in Table II were determined by extrapolating the steady-state curves to the X axis, as shown in Figs. 1 and 2. As seen in Table II, the permeability coefficients of the phenylpiperidine analogues were appreciably higher than those found for morphine and its analogues. Sufentanil exhibited the largest permeability coefficient among the compounds chosen for the studies. It also has a short diffusion lag time. Meperidine, which is hydrophobic but also relatively soluble due to its low melting point, exhibited the highest flux from saturated solution.

The permeability of fentanyl through human cadaver skin at 30°C has previously been reported to be 1.0×10^{-2} cm/hr at pH 8.0 using a tritiated radiolabeled tracer (10). In the present study, the permeability of fentanyl in different pieces of skin ranged between 5.6×10^{-3} cm/hr (pH 7.4) and 3.5×10^{-2} cm/hr (pH 9.0), with a value of 2.2×10^{-2} cm/hr at the very pH used by Michaels *et al.* Although the present values were obtained at a temperature 7°C higher than used previously, given the variability associated with such experiments, these results agree well with the Michaels *et al.* estimate. The fact that the past and present data are in remarkably close agreement demonstrates the essential integrity of the earlier results obtained by the radiolabeled tracer method. The similarity in results between the laboratories indicates that, under the conditions of the test, fentanyl is

Table II. *In Vitro* Skin Flux and Permeability Coefficients[a] of Six Narcotic Analgesics

Drug	J_T (μg/cm²/hr)	P (cm/hr)	t_L (hr)
Morphine	0.006 ± 0.002	$(9.3 \pm 3.6) \times 10^{-6}$	5.2 ± 2.4
Hydromorphone	0.032 ± 0.006	$(1.5 \pm 0.21) \times 10^{-5}$	9.9 ± 2.4
Codeine	0.09 ± 0.04	$(4.9 \pm 1.2) \times 10^{-5}$	7.6 ± 1.3
Fentanyl	0.26 ± 0.05	$(5.6 \pm 0.9) \times 10^{-3}$	1.9 ± 0.8[b]
Sufentanil	0.40 ± 0.06	$(1.2 \pm 0.1) \times 10^{-2}$	2.0 ± 0.8[b]
Meperidine	0.60 ± 0.14	$(3.7 \pm 0.9) \times 10^{-3}$	1.2 ± 0.2

[a] Values are the average ± SD of four or five diffusion experiments.
[b] These values were obtained on the same piece of skin and are in proper relative relationship to one another. Further research suggests that values three to four times this large are more typical for human skin.

unaffected by enzymes in the skin and is stable at pH 8.0 over the experimental period. It is important to note that at the point in the present studies where permeability coefficients for the narcotics were directly compared (Table II), all the results were obtained on a single section of cadaver skin in order to remove skin to skin variability from the comparisons.

Molecular weight dependencies for the diffusion of organic solutes through simple and complex membranes are well-documented phenomena (25). Since the diffusion of molecules through liquids is inversely proportional to their molecular weights to the square or cubic root and the dependency is generally not much more severe for a membrane, at least at the first level of consideration, one might expect higher permeability coefficients to be associated with the lower molecular weight drugs. However, as is evident in Table I, this is not the case with the narcotic analgesics. Rather, morphine, codeine, and hydromorphone, all of a similar, relatively low molecular weight, are the least permeable compounds of the six considered. This means only that other determinants of permeability dominate the overall behavior, with molecular size being a secondary, difficult-to-factor contributor to the permeation patterns.

It is well established that compounds with high partition coefficients, i.e., high lipophilicities, are likely to be the best permeants of skin. Since it is difficult to determine the actual skin/water partition coefficient of drugs, olive oil/water (24) and octanol/water ($K_{octanol/water}$) (26–28) partition coefficients have been used instead as alternative scales for ranking the lipophilicities of compounds for skin permeation analysis. We have chosen the latter for these purposes. The $K_{octanol/water}$ partition coefficients reported were experimentally determined at pH 7.4. It can be seen from Table III that, at this pH, the compounds range from 85 to 97% ionized. Knowing the pK_a's, the intrinsic partition coefficients of the free-base (unionized) species of these narcotics were calculated from the partition coefficients at pH 7.4 (column 4 in Table III). It can be seen that the rank order of the intrinsic free-base partition coefficients is the same as is experimentally determined at pH 7.4. Even the ratios of values are roughly the same. Consequently, the experimental rather than the pK_a normalized values of the partition coefficients are used in the analysis, a choice without material impact on conclusions drawn from the work.

The permeability coefficients of fentanyl and sufentanil through human cadaver skin sections of 200-μm thickness as a function of pH at 37°C, along with estimated degrees of ionization of the compounds, are summarized in Table IV. The permeability coefficient of fentanyl increases only 2.5-fold when ionization ranges from 97 to 24%. For sufentanil, the permeability coefficient increases only twofold when the degree of ionization drops from 93 to 11.2%. This insensitivity to pH as ionization is suppressed is consistent with the unusually high hydrophobicities of these compounds. The data further suggest that the free-base species of these drugs permeate the skin more readily than their ionized forms. This is consistent with the expectation for a membrane which is believed to behave, to a good first approximation, as a lipoidal barrier.

In order to see which of the interrelated physicochemical properties listed in Table I best correlate with the experimental permeability coefficients, plots of permeability coefficients of the six narcotics against their $K_{octanol/water}$ partition coefficients and their solubility parameters are given in Figs. 3, 4, and 5, respectively. It can be seen from Fig. 3 that the permeability coefficients systematically change with the melting point, with the compounds having the lowest melting points exhibiting the highest permeability coefficients. In a previous paper (19) it was shown that, at least for these compounds, melting points reflect relative hydrophobicities, apparently because the attribute, hydrophobicity, is associated with a low level of intracrystalline interaction. Thus this is one of several possible correlations reflecting upon the graded polarities of the compounds in the study.

The permeability coefficient relationship with partition coefficient is complex, but upon careful analysis and with the background of the literature, it is the most revealing of all parameters here considered. It has been shown many times that a membrane/water partition coefficient appears explicitly in the equations for the permeation of lipid membranes placed between aqueous media (10,25,29). The stratum corneum, at its first level of behavior, acts as a lipid membrane. It is also well established that the cell mass of the epidermis beneath the stratum corneum contributes an aqueous resistance to diffusion (10,25,27). Moreover, it is known that if lipophilicity is increased indefinitely, a point is reached where the true aqueous boundary layers and the aqueous

Table III. Partition Coefficient (Octanol/Water) of NarcoticAnalgesics

Narcotic	pH (% ionization)	$K_{(o/w)1}$ (Expt)	$K_{(o/w)2}$[a] (Calc.)
Morphine	7.4 (85.3)	0.70	4.2 (5.7)[b]
Hydromorphone	7.4 (85.3)	1.28	7.7
Codeine	7.4 (85.3)	2.95	17.7
Meperidine	7.4 (92.7)	38.9	529
Fentanyl	7.4 (97)	717	23,390
Sufentanil	7.4 (92.7)	2,842	38,621

[a] $K_{(o/w)2} = K_{(o/w)1}$ [antilog(pK_a − pH) + 1], where $K_{(o/w)2}$ is the intrinsic partition coefficient of free base (nonionized).
[b] From Ref. 44.

Table IV. Permeability Coefficients[a,b] for Fentanyl and Sufentanil Through Cadaver Skin (200-μm Thickness)[c] as a Function of pH at 37°C

	Fentanyl		Sufentanil	
pH	% ionization	$P \times 10^2$ (cm/hr)	% ionization	$P \times 10^2$ (cm/hr)
7.4	96.9	1.3 ± 0.3	92.6	1.6 ± 0.1
8.0	88.9	2.2 ± 0.2	76.0	2.3 ± 0.2
8.5	71.5	2.8 ± 0.2	50.0	3.0 ± 0.4
9.0	44.3	3.5 ± 0.6	24.0	3.4 ± 0.2
9.4	24.0	3.3 ± 0.6	11.2	3.4 ± 0.7

[a] Values at each pH are the average of four or five diffision experiments.
[b] Value ± SD of result.
[c] Site: thigh.

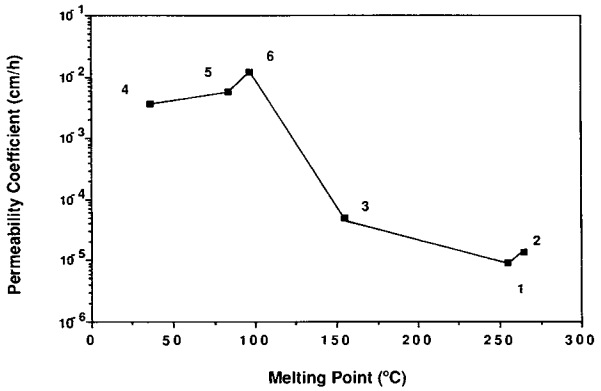

Fig. 3. Relationship between melting point and permeability coefficients of narcotic analgesics. Morphine (1), hydromorphone (2), codeine (3), meperidine (4), fentanyl (5), and sufentanil (6). This shows that the low melting compounds collectively have the highest permeability coefficient (see text).

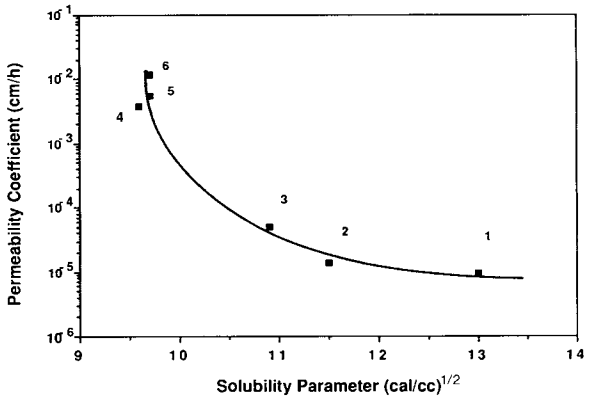

Fig. 5. Relationship between solubility parameter (∂_2) and permeability coefficients of narcotic analgesics. Morphine (1), hydromorphone (2), codeine (3), meperidine (4), fentanyl (5), and sufentanil (6). Low solubility parameters go hand to hand with low melting points and high oil/water partition coefficients. All parameters reflect the same quality, hydrophobicity, in quantitatively different ways.

strata of the skin together assume rate control. At this point the permeability coefficient is predicted to become essentially independent of partition coefficient. These permeability factors seem to be operative with respect to the permeation of the narcotic analgesics. From morphine to meperidine the permeability coefficients grow rapidly and reasonably linearly with partition coefficient, an expectation of stratum corneum control. However, permeability coefficients from meperidine through sufentanil are of the same magnitude. This suggests they are approaching an anticipated upper attainable limit associated with aqueous tissue control of transport (Fig. 4). Using meperidine as the marker, the onset of the aqueous strata control appears to be near a $K_{\text{octanol/water}}$ value of 40 (Fig. 4). Similar results have been previously observed and interpreted for *n*-alkanols, phenols, and the 21-*n*-alkyl esters of hydrocortisone (30). The upper limit in the permeability coefficient of 10^{-2} cm/hr upon which interpretation of these data is based is established for human skin through the work of Scheuplein and Blank (31). These workers showed that the permeability coefficients of homologous *n*-alkanols through cadaver membranes freed of epidermis are all of the order of 10^{-2} cm/hr (32). Since the narcotics are physically much larger, one can expect a limiting permeability coefficient of lesser magnitude than found for the alkanols.

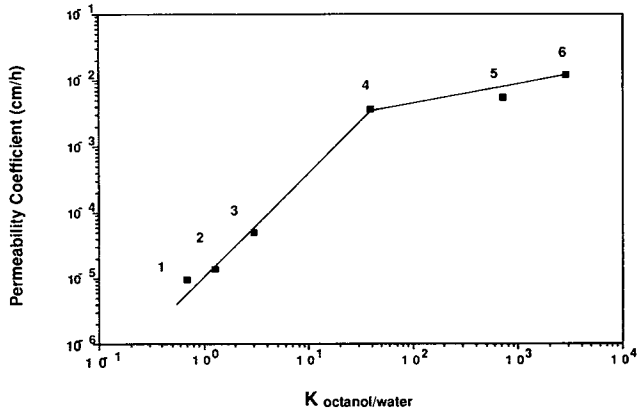

Fig. 4. Relationship between $K_{\text{octanol/water}}$ and permeability coefficients of narcotic analgesics. Morphine (1), hydromorphone (2), codeine (3), meperidine (4), fentanyl (5), and sufentanil (6). This relationship shows a distinct biphasic character consistent with a mechanism change from stratum corneum control to aqueous strata control.

High permeability coefficients for the narcotics (Table II) are associated with high $K_{\text{octanol/water}}$ partition coefficients (Table III). One can use the data at hand to estimate $K_{\text{membrane/water}}$ partition coefficients to be compared with the $K_{\text{octanol/water}}$ values. These can be calculated from the following equation:

$$K_{\text{membrane/water}} = \frac{Ph_{\text{sc}}}{D_{\text{sc}}} \tag{4}$$

where P is the experimental permeability coefficient. The calculated $K_{\text{membrane/water}}$ values presented in Table I, where $K_{\text{octanol/water}}$ values are also found. Although the values for the narcotics estimated from Eq. (4) are somewhat lower than the measured $K_{\text{octanol/water}}$ values, the partition coefficients calculated in this fashion nevertheless have essentially the same rank order. The solubility parameters (∂_2) of these compounds, which provide another reflection of lipophilicity (19), also tend to vary systematically with $K_{\text{octanol/water}}$, albeit in the opposite direction.

Interestingly, when the permeability coefficients are plotted against the solubility parameters of the compounds (Fig. 5), a monotonically changing pattern of permeability is apparent. The compounds with solubility parameters in the range of 9.6–9.8 (cal/cm^3)$^{1/2}$ are grouped together at the high end of the permeability scale. This is apparently another reflection of the general relationship between lipophilicity and permeability. Low solubility parameters are synonymous with a highly lipophilic character. It is notable that the permeability coefficients of series of alkanoic acids through porcine skin are reportedly parabolically related to solubility parameters, with the peak permeability near a solubility parameter of 10 (cal/cm^3)$^{1/2}$ (33,34). Interestingly, the cadaver skin permeability coefficients of the narcotics

also exhibit their maximum near the solubility parameter of 10 $(cal/cm^3)^{1/2}$. Since the solubility parameters of phenylpiperidine analogues are close to what may be an optimum for skin, one can expect these compounds to be relatively soluble in the skin's lipoidal phases. Consequently high permeability coefficients are to be expected for these drugs, and this is as seen.

Figure 6 makes a last important point about permeability. In this plot fluxes of the narcotics from their saturated solutions (in units of $\mu g/cm^2/day$), as found in Table V, are plotted against the $K_{octanol/water}$ partition coefficients of the compounds. A maximum in delivery is seen. This maximum results from the fact that the aqueous solubility of low melting meperidine is disproportionately large. The plot evidences the interplay which takes place among delivery, the mass transfer coefficient, and solubility. The intermolecular force factors which lend polarity to molecules and tend to make permeability coefficients low are the same factors which contribute positively to *aqueous* solubilities. Consequently, due to some cross-canceling of these factors, the actual spread of fluxes from saturated solutions is much smaller than the spread in permeability coefficients themselves, by a full order of magnitude. The pattern is highly irregular because the melting behavior of the solids, which also impacts on solubility, is anomalous and not well correlated with lipophilicity (35).

Using the data gathered in this research and previous studies, a comparison of the drug delivery possibilities for the six narcotic analgesics can be made. This is provided in Table V. Daily dosages (5) of the compounds are listed in this table alongside calculated fluxes of the compounds from saturated aqueous solutions. These together allow one to estimate the patch sizes which would be needed to deliver passively the drugs through an intact skin from media containing the compounds at unit thermodynamic activity (last column in Table V). This is done by dividing the daily dose (μg/day) by the respective 24-hr steady-state delivery rates ($\mu g/cm^2$/day) obtained using saturated solutions. It does not matter that the stated solubilities were determined at 25°C instead of 35°C as an experimental convenience, because relative solubilities remain in virtually exact proportion between the two temperatures and because solubilities at the lower temperature actually yield conservative patch size estimates, not overestimates. It is apparent from the estimates that reasonably sized patches are projected only for the most potent analgesics, fentanyl and sufentanil. These size estimates may actually be on the high side because the lowest permeability coefficient for each of these drugs obtained in these studies was used in the size estimation. One also anticipates that higher permeabilities can be obtained through judicious formulation of the compounds. It may be that meperidine, the low relative potency of which is mainly responsible for the large patch size estimated, could also be used transdermally, but only if its flux is dramatically boosted through formulation techniques. Patch sizes for the opioids are so large that, as a group, these appear totally unsuited for transdermal delivery from passive delivery systems, despite recent reports to the contrary (36).

Table V. A Comparison of Narcotic Analgesics with Respect to Potency, Dosage, Flux, and Patch Size

Drug	Potency (analgesics)	Daily dose im (mg/day)	Flux from saturated aqueous solution ($\mu g/cm^2$/day)	Estimated patch size (cm^2)
Morphine	1.0	10.0	0.16	62,500
Hydromorphone	6.7	2.0	0.76	2,631
Codeine	0.08	65	2.52	25,794
Fentanyl	80.0	1.2	6.85	175[a]
Sufentanil	800.0	0.78	9.81	79[a]
Meperidine	0.10	150	528.0	258

[a] The values for fentanyl and sufentanil reported here for a particular section of human skin are among the lowest seen in our extensive studies. All the data we have gathered on these two compounds suggest patch size for fentanyl and sufentanil should be less than 50 and 20 cm^2, respectively. Data on the permeability of these two compounds as functions of skin site, gender, age, pH, etc., are to be published separately.

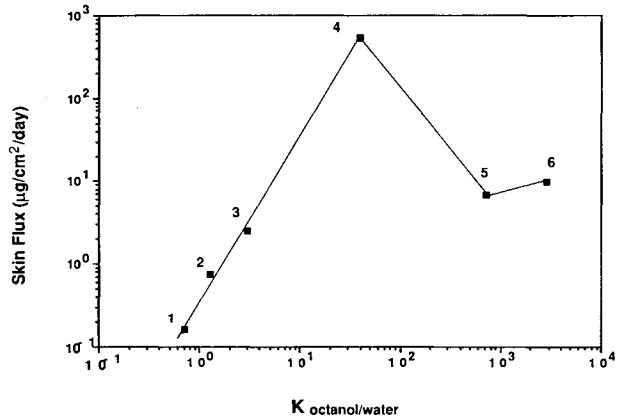

Fig. 6. A plot of skin flux from saturated solutions versus $K_{octanol/water}$ partition coefficients. Morphine (1), hydromorphone (2), codeine (3), meperidine (4), fentanyl (5), and sufentanil (6). Here the interplay of the solubility factor as well as the permeation factor comes into play, compressing the difference between the polar opioids and the phenylpiperidine analogues.

As evident from Table V, the present paper is concerned largely with determining the feasibility of transdermal delivery of narcotics, although, in the instance of fentanyl, feasibility had already been established by Michaels *et al.* (10). Here the known daily dosages of the drugs are measured against attainable delivery rates. There are other approaches to the determination providing that one has a firm assessment of the limiting, unit activity flux. One can, for instance, take the pharmacokinetic approach. To do this one must know the clearance rate of the drug and its therapeutic plasma concentration. Existing data, also for fentanyl, can be used to illustrate the estimation technique. The published clearance rate for fentanyl is 53 liters/hr (37). The literature further indicates that the analgetic plasma level for fentanyl is somewhat in excess of 1 ng/ml (38–40). The elimination rate of the drug at its analgetic concentration in the body, K_o, is the product of these parameters, roughly 50 μg/hr. This is also the minimally necessary replacement rate to maintain a therapeutic steady state for the drug. This deliv-

ery rate amounts to a 1.2-mg/day total requirement, a quantity virtually the same as the daily dose listed in Table V. Clearly, then, a patch operating to give 50 to 100 μg/hr (equivalent to 2 to 5 μg/cm^2/hr for a 20-cm^2 patch) meets the therapeutic requirement. The validity of the dosing estimate was borne in early clinical studies by White *et al.* (44.4 μg/hr) (39) and Kay (52.8 μg/hr) (41) and subsequently reinforced by Nimmo and Todd (1.5 μg/kg/hr ≃ 100 μg/hr for a 150-lb patient) (42) and Gourlay *et al.* (≃58 μg/hr) (43). In all these studies fentanyl was used successfully to suppress pain when administered intravenously more or less continuously.

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