International Journal of Pharmaceutics, 30 (1986) 63–72
Elsevier

IJP 00996

Enhanced percutaneous absorption via iontophoresis I. Evaluation of an in vitro system and transport of model compounds

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(Received July 29th, 1985)
(Modified version received December 2nd, 1985)
(Accepted December 5th, 1985)

Key words: iontophoresis—in vitro methodology—model compounds—hairless mouse—transdermal drug delivery

Summary

In vitro methodology was developed to investigate the iontophoretic transport of select ionic and non-ionic compounds across hairless mouse skin. Using sodium benzoate and a constant current of 0.1 mA, it was observed that alterations in the diffusion cell configuration and/or return electrode placement relative to the membrane had little effect on the transport of benzoate ions, thus permitting the use of a simple experimental design. Increases in applied current (from 0.0 to 0.2 mA) produced a linear increase in observed benzoate flux. The steady-state flux was also slightly increased (apparently linearly) with greater donor concentrations, but was reduced when competitive ions (NaCl) were added to the donor chamber. Employing a direct current of 0.1 mA and identical solutions, the iontophoretic flux enhancement ratios (flux with current/flux without current) were calculated for benzoate (22.61) and the phenethylamine cation (43.32, using reversed electrode polarity). The flux of a non-ionic compound (benzyl alcohol) was not significantly altered during the application of a 0.1 mA direct current. Upon termination of the current in benzoate iontophoresis experiments (0.1 mA × 3 h), subsequent fluxes were observed to be quite inconsistent. Many yielded values fairly close to the average control (no current exposure) flux for the benzoate ion. However, several of the residual fluxes were nearly 10-fold higher than the control, suggesting compromised skin barrier integrity of a variable nature. This occasional alteration in membrane transport resistance was not, however, observed in experiments performed with benzyl alcohol. It is speculated that the diffusional path followed specifically by ionized species undergoes sporadic current-related changes, and that the flux of the uncharged benzyl alcohol is not affected by alterations in this path. These results suggest that iontophoresis may be a convenient means by which to achieve constant and readily controllable transdermal delivery, locally or to the systemic circulation, for ionized drug species (including peptides). Transport rates may be optimized by adjustment of donor ionic composition and utilization of current densities and patterns deemed physiologically appropriate.

Introduction

Numerous literature reports have revealed successfully enhanced delivery of a variety of drugs across biological membranes by means of the technique of iontophoresis. This method involves the transport of charged substances into a tissue by the passage of a direct electrical current through an ionized drug solution and into the patient, using appropriate electrode polarity. As a diagnostic test for cystic fibrosis, iontophoresis is the method of choice for the delivery of pilocarpine

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(Gibson and Coole, 1959). In addition, the preferred method of producing external ear canal anesthesia is via lidocaine and epinephrine iontophoresis (Comeau et al., 1973). These latter two drugs have also been delivered iontophoretically to the oral mucosa to provide what has been termed profound surface anesthesia prior to extraction of loose deciduous teeth (Gangarosa, 1974). Other compounds which have been successfully administered by iontophoresis include methacholine, histamine, fluoride, idoxuridine, ara-AMP, vinca alkaloids, methylene blue, potassium iodide, dexamethasone, thymidine, penicillin, streptomycin and tetracycline (Gangarosa et al., 1977; Park et al., 1978; Gangarosa et al., 1980, Jenkinson et al., 1974; Pereyra, 1948; Csillik et al., 1982; Glass et al., 1979; Ragelis, 1981a and b).

While the majority of work reported to date involving iontophoretic drug delivery has been geared toward localization in surface tissues, the possibility exists that this technique may be useful for systemic drug administration as well. Iontophoresis, like any other means by which to enhance drug transport through the epidermal barrier, could conceivably expand the battery of compounds considered to be feasible candidates for delivery via the transdermal route. Moreover, in the quest for development of a transdermal delivery system for a given drug, the use of iontophoresis might obviate the need for 'chemical' penetration enhancers and thus eliminate those problems associated with the presence of such adjuvants. Alternatively, the coupling of iontophoresis with a chemical penetration enhancer may permit the use of lower quantities of either drug, enhancer, or current within the delivery system, potentially circumventing adverse reactions, toxicity problems, and formulation difficulties. With the many advantages inherent in the use of transdermal drug administration and with the reported successes of iontophoretic delivery, an investigation into the utility of this technique was initiated, by performing a mechanistic, in vitro examination of a number of system variables and their influence on ion transport through a model skin barrier.

Materials and Methods

Materials

Sodium benzoate, benzyl alcohol, phenethylamine and sodium chloride were used as received from the manufacturers. Aqueous solutions were prepared with deionized water which was purified further prior to use (Milli-Q water purification system, Millipore, Bedford, MA). The final resistivity of the water was 18 MΩ-cm.

Membrane

All diffusion studies involved abdominal skin, freshly excised (non-hydrated) from 20-week-old male hairless mice (Jackson).

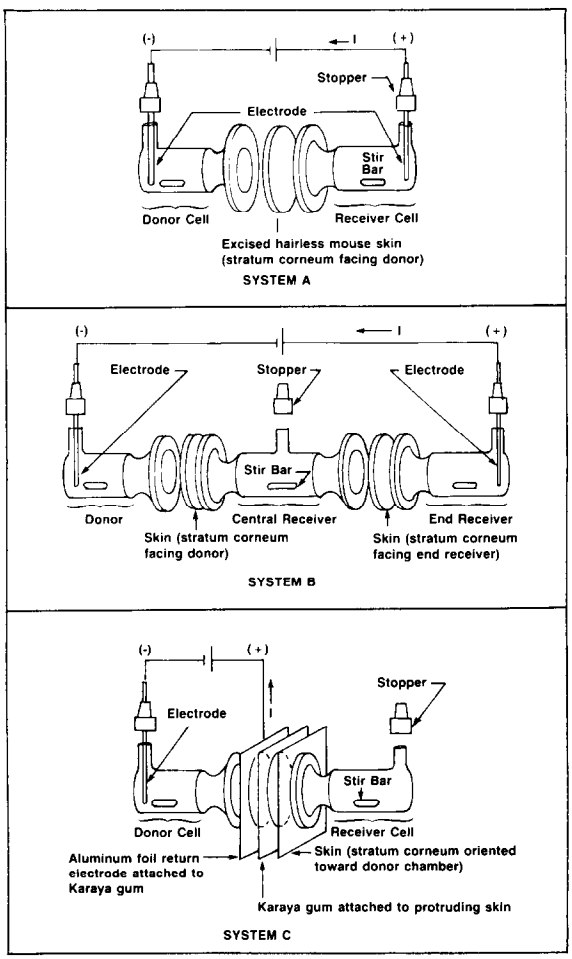

Fig. 1. Diffusion cell design and electrode configuration for various systems utilized for benzoic acid iontophoresis.

Power source

A device was constructed to provide an adjustable, constant direct current using a power source of 12 V.

Diffusion cells / electrode placement

Three different system designs were utilized in these studies. Systems A, B and C are illustrated in Fig. 1 and are described below.

System A. Excised mouse skin was sandwiched between donor and receiver chambers of horizontal glass diffusion cells (Bellco Glass, Vineland, NJ), with the stratum corneum facing the donor compartment. The total area available for transport was 1.77 cm^2. Each chamber held a volume of 5 ml and stirring was achieved with a teflon-coated stir bar, driven at 300 rpm by an external rotating magnet. The cell halves were held together with a pinch clamp, and the entire assembly was maintained at 37°C by immersion in a thermostatically controlled water bath. Platinum wire electrodes (22-gauge) were inserted into each chamber, with the positive electrode immersed in the donor compartment for cation iontophoresis and the return electrode immersed in the receiver compartment (containing normal saline). The electrode polarity was reversed for anion iontophoresis. At appropriate intervals, samples were removed from the receiver compartment and the concentration of the species of interest was determined by HPLC. The entire donor and receiver contents were removed and replaced with fresh solution at each sample time. Since in vivo iontophoresis would not generally involve placement of the return electrode on the dermis side of the skin, two additional experimental designs were utilized, where the configuration and/or location of the return electrode was altered in order to more closely simulate an in vivo situation or systemic compartment.

System B. This configuration involved three compartments separated by two pieces of skin, with both stratum corneum sides oriented toward the compartment containing an electrode. Again, the exposed surface area of each piece of skin was 1.77 cm^2. The 'central' and 'end receiver' compartments both contained normal saline. Compartment stirring, electrode construction and polarity were as described for System A. Because of this cell construction, entire compartment solution removal was not possible due to the introduction of air pockets against the membrane surfaces. For these systems, 1.0 ml portions were removed for assay from each saline compartment, and were replaced with the same volume of normal saline.

System C. The cell design here was identical to that of system A except for the placement of the return electrode. In this case, a large section of excised mouse skin was used (approximately 7 cm^2) so that excess skin protruded from the periphery of the clamped cell compartments. The area of skin exposed to the compartment media was 1.77 cm^2. The return electrode consisted of aluminum foil which was fixed to the stratum corneum side of the excess protruding skin by means of a layer of conductive Karaya gum. The dermis side of the protruding skin was protected from contact with the electrode with a layer of parafilm. The receiver compartment was filled with normal saline, and sampling was performed as described for either System A or B.

HPLC assays

Benzyl alcohol. Mobile Phase: 35% methanol
Column: Waters μBondapak C18, 30 cm
Wavelength: 258 nm
Flow Rate: 1 ml/min.

Benzoic acid. Mobile Phase: 75% 0.05 M KH_2PO_4, pH 2.5, 25% acetonitrile
Column: Rainin Microsorb C18, 10 cm
Wavelength: 230 nm
Flow Rate: 1 ml/min.

Phenethylamine. Mobile Phase: 45% (0.005 M heptane sulfonic acid, 0.1% glacial acetic acid, pH 3.0); 55% methanol
Column: Waters μBondapak C18, 30 cm
Wavelength: 258 nm
Flow Rate: 1 ml/min.

Calculations

Cumulative quantities of the species of interest appearing in the receiver chambers were plotted as a function of time, and steady-state flux values were calculated from the slope of the linear portions of these plots. Lag times were determined from the extrapolated time axis intercepts. Flux ratios were obtained by normalizing the iontophoretic fluxes with respect to controls, i.e. flux ratio = (flux without current)/(flux within current).

Results and Discussion

Effect of cell design and electrode configuration on benzoate flux

To evaluate the effects of the various diffusion cell configurations on observed flux, benzoate iontophoresis was performed using the three cell systems described in Fig. 1. In all cases the donor compartment consisted of 0.082 M benzoate (prepared using the sodium salt). The solutions were unbuffered to minimize competitive ion interference with the iontophoretic transport of benzoate ions. The inherent pH (~ 8.2) of the solution remained well above the pK_a of benzoic acid so that only ionized species were present. A constant current of 0.1 mA was utilized for this series of flux experiments. Since the sampling procedure used with Cell System B was different from that used with System C (in that only a fraction of the compartment volume was removed with each sample), it was observed that the different sampling procedures altered the measured flux. For purposes of comparison with data obtained from System B, an additional set of experiments was performed using the same System A cell design, except that only 1.0 ml samples were removed from the receiver chamber for each sample, subsequently being replaced with fresh saline. Table 1 lists the mean benzoate fluxes (J_{ss}) observed with each of the described techniques.

TABLE 1

BENZOATE FLUX ACROSS HAIRLESS MOUSE SKIN USING VARIOUS EXPERIMENTAL TECHNIQUES

I = 0.1 mA, donor = 10 mg/ml benzoic acid (from Na salt), receiver = saline.

System [a]	Sample size	J_{ss} [b] ($\mu g/cm^2 \cdot h$) ± S.D.	n [c]
A	Entire chamber	42.83 ± 3.31	15
C	Entire chamber	47.88 ± 6.42	3
A	1.0 ml	33.67 ± 0.92	2
B	1.0 ml	33.26 ± 5.33	3

[a] See Fig. 1 for cell/electrode configuration.
[b] Mean steady-state flux.
[c] Number of determinations.

As can be seen, for a given sampling procedure, the steady-state fluxes from the different configurations are nearly constant. A slightly lower steady-state flux is observed when only partial receiver contents were replaced with fresh medium (as opposed to total receiver volume replacement). This effect does not appear to be due to loss of sink conditions, since receiver concentrations were at all times at least three orders of magnitude lower than donor concentrations. The factors responsible for the differences in steady-state flux cannot be precisely identified from the data in hand. Suffice it to say, however, that these differences appear to be related only to the method of sampling, and not to the apparatus designs utilized.

The significance of these findings lies in the fact that essentially identical fluxes are maintained, even with drastic alterations in membrane/electrode configuration, as long as the same sampling technique is utilized. Since the use of System A was the least experimentally cumbersome, and because it also produced data identical to that of a design more representative of an in vivo situation (e.g. System C), this procedure (with total chamber media replacement at each sampling time) was utilized in all subsequent iontophoretic studies reported herein.

It should be mentioned that with the described experimental designs, the electrical potential drop across the hairless mouse skin membrane could not be accurately measured. The apparent voltage passing through the *entire* circuit was followed in a number of experiments, and was seen to be quite variable from mouse to mouse, even among replicate studies. This variability is likely due in large part to mouse-to-mouse differences in skin resistance, which would evoke corresponding differences in the membrane potential gradient, pro-

vided a constant current is maintained. Measured electrical potentials in the various experiments (monitoring total circuit voltages) were generally between 2 and 5 V.

Effect of applied current on benzoate flux

To probe further into the mechanistic aspects of iontophoretic transport, a series of experiments was performed in which the applied current was varied from 0 to 0.2 mA. The data reported in Table 2 suggest that there is a linear relationship between benzoate flux and the applied current. Theoretically, the conservation of charge within the system requires that:

$$I_T = F \cdot \sum_{i=1} z_i \cdot J_i \qquad (1)$$

where I_T = total current density; F = Faraday's constant; z_i = valence of species i; J_i = flux of species i.

Benzoate transport, then, is a function of the total current and the fluxes of other ions present (Cl^- and Na^+). However, the rates of transport of the other species are also dependent upon the total current. The fraction of this current carried by a particular ion (I_i/I_T) is empirically given by its transport (or transference) number, t_i so that:

$$J_i = \frac{t_i \cdot I_T}{z_i \cdot F} \qquad (2)$$

Under conditions in which a membrane separates solutions having different concentrations of species i, t_i is a complex function of the distributions of all mobile ionic species in the membrane as well as in the bathing solutions, in addition to the relative mobilities of the various species present (Schultz, 1980). However, in this set of experiments (where only I_T is varied), since the same donor and receiver concentrations were used and steady-state conditions were in effect, t_i may be viewed as a constant. The magnitude of t_i under these circumstances may be obtained from the slope of Fig. 2, yielding $t_i = 0.16$. Thus 16% of the total current is being carried by benzoate ions. The remaining fraction of the total current includes contributions from the other ionic species present in the system (e.g. Na^+, Cl^-, H^+, OH^-) as well as ionic species which may be present in the membrane itself.

TABLE 2

EFFECT OF CURRENT ON BENZOATE FLUX ACROSS HAIRLESS MOUSE SKIN

Donor-10 mg/ml benzoic acid (from Na salt), Receiver = saline.

Current (mA)	Mean flux data ± S.D.		
	J_{ss} ($\mu g/cm^2 \cdot h$)	n	Lag time (h)
0.00	1.89 ± 0.57	10	0.90 ± 0.25
0.05	25.40 ± 0.91	2	0.36 ± 0.01
0.10	42.83 ± 3.31	15	0.27 ± 0.14
0.15	65.78 ± 3.31	3	0.45 ± 0.02
0.20	86.41 ± 3.49	3	0.52 ± 0.21

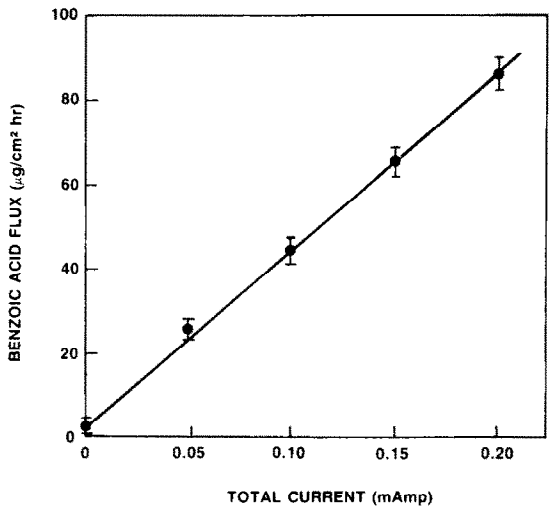

Fig. 2. Effect of applied current on benzoic acid iontophoresis. Donor = 10 mg/ml benzoic acid (from Na salt), receiver = saline.

Effect of variations in ionic composition of donor on benzoate flux

In the next segment of this study, the effects on benzoate flux induced by variations in species concentrations in the donor compartment were investigated. As illustrated in Fig. 3, increasing the concentration of sodium benzoate in the donor chamber produces a slight, apparently linear increase in benzoate flux. This effect was relatively

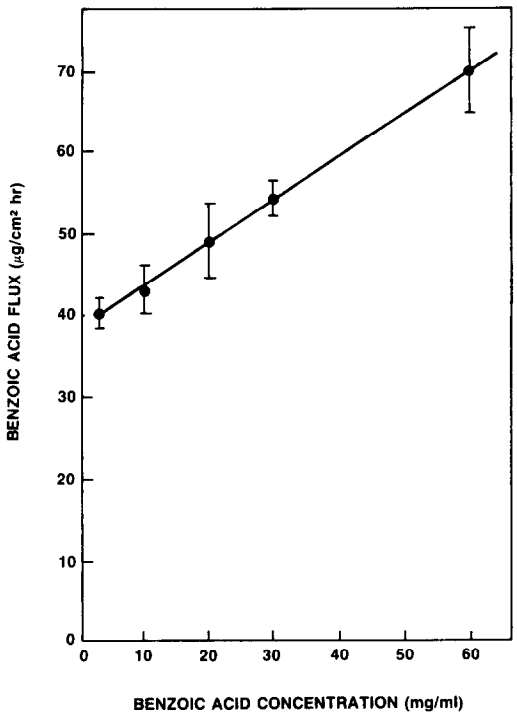

Fig. 3. Effect of donor concentration on benzoic acid iontophoresis. Donor solutions prepared with Na benzoate, receiver = saline.

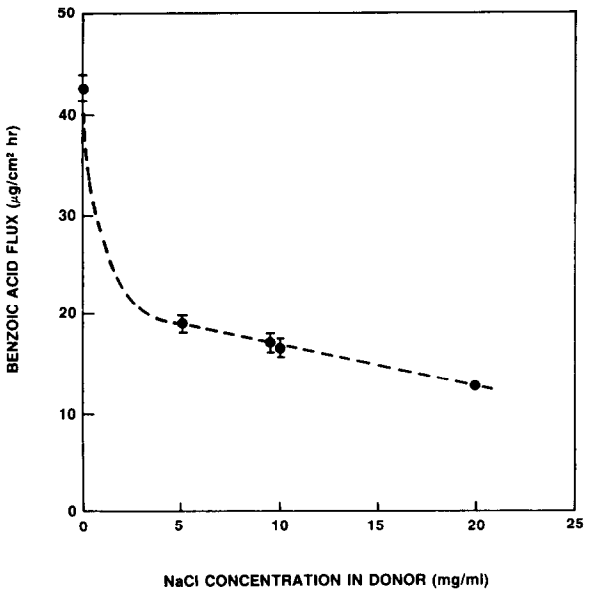

Fig. 4. Effect of competitive ions on benzoic acid iontophoresis. Donor benzoic acid concentration = 10 mg/ml (from Na salt), receiver = saline.

small over the concentration range examined: a 20-fold increase in benzoate content produced but a 1.7-fold increase in flux. A more dramatic effect was observed with the introduction of competitive ions, where benzoate flux was reduced by more than half when an approximately equimolar amount of NaCl was added to the donor benzoate solution (Fig. 4). Theoretically, the effect of alterations in ionic composition in the donor compartment is to cause a variation in the transport numbers (t_i) of all ionic species present in the system (including ions in the receptor as well as the donor chamber). Thus, as expected from the above discussion, the fractional contribution of benzoate ion transport to the total current (t_i, benzoate) is increased with greater concentrations of sodium benzoate, and is reduced with the addition of competitive ions (e.g. Na^+, Cl^-). A mechanistic model predicting the effect of variations in ionic composition on t_i is presently under investigation. The experimental findings do serve to suggest methods by which iontophoretic transport could be optimized. Although flux was seen to increase with greater concentrations of the species of interest, the effect was not large. Thus, in situations involving high drug cost or limited solubility, the use of lower quantities of drug in an iontophoretic device may not compromise drug delivery rates to the extent of that observed with purely passive diffusion devices. With respect to ionic composition, drug flux may be maximized by the avoidance of extraneous (competing) ions within an iontophoretic delivery system. If buffers or other ionic additives must be included, they could be selected so as to exhibit low transport numbers (perhaps via size variations), and thus they will interfere minimally with the fractional current carried by the drug.

Iontophoretic flux enhancement of model compounds

At this point it was decided to investigate the iontophoretic transport of species other than the benzoate ion through hairless mouse skin. A cation was selected (phenethylamine) as well as an uncharged molecule (benzyl alcohol). The same electrode polarity used for benzoic acid was maintained for the benzyl alcohol studies, while the polarity of the applied potential was reversed for

TABLE 3

IONTOPHORETIC FLUX ENHANCEMENT OF MODEL ANION, CATION AND NEUTRAL MOLECULE

Donor solution concentrations = 10 mg/ml, receivers = saline.

Species	Current (mA)	Mean flux data ± S.D.			
		J_{ss} ($\mu g/cm^2 \cdot h$)	n	Lag time (h)	Ratio [a]
Benzoic acid	0.10 [b]	42.83 ± 3.31	15	0.27 ± 0.14	22.61
	0.00	1.89 ± 0.57	10	0.90 ± 0.25	
Phenethylamine	0.10 [c]	31.45 ± 3.59	4	0.04 ± 0.22	43.32
	0.00	0.73 ± 0.03	3	0.02 ± 1.57	
Benzyl alcohol	0.10 [b]	104.88 ± 13.08	4	0.49 ± 0.09	1.14
	0.00	91.78 ± 25.86	12	0.36 ± 0.19	

[a] Flux with current/flux without current.
[b] Donor compartment contained cathode.
[c] Donor compartment contained anode.

phenethylamine, so that the donor electrode was positively charged for cation iontophoresis. To compare the extent of transport enhancement of the three compounds induced by the passage of 0.1 mA of current, individual flux ratios were calculated (i.e. flux with current/flux without current) using data from separate experiments. All runs (with and without current) were performed using donor concentrations of 10 mg/ml in distilled water. Table 3 lists the data observed for these three species. As anticipated, substantial flux enhancement occurred with both ionic species, while the passage of current appeared to have little effect on benzyl alcohol transport. Since both benzoate and phenethylamine exhibited quite favorable iontophoretic flux enhancement, it appears that drugs existing as either cations or anions in a physiologically acceptable vehicle may be viable candidates for iontophoretically assisted transdermal delivery. Molecular size constraints have not been established, although it is likely that large ions could exhibit lower transport numbers (and thus lower fluxes, all other factors being equal) than those associated with the relatively small species involved in this study.

Interestingly, there was a statistically significant ($P < 0.01$, t-test) reduction in lag time during benzoate iontophoresis (as compared with control data), although no such effect was observed with phenethylamine or benzyl alcohol ($\alpha = 0.05$). An unequivocal explanation of this finding, and of the fact that no such effect was observed for phenethylamine, cannot be offered based on the present body of data. However, if lag time reductions are demonstrable in an in vivo situation, the necessity or magnitude of a loading dose in a transdermal delivery device could conceivably be eliminated or reduced by the use of the iontophoretic technique. It should be pointed out that the data for each experiment reported thus far involved skin from separate mice for each individual experiment. Substantial mouse-to-mouse variability was observed, particularly noticeable in the benzyl alcohol data.

To investigate more precisely the effect of current on benzyl alcohol flux, a set of experiments was designed to reduce the variability observed in the previous studies. Using a single piece of mouse skin, benzyl alcohol transport was monitored for 3 h with no applied current (Stage I), followed by the passage of 0.1 mA of current for the next 3 h (Stage II), and finally an additional 3 h after external current termination (Stage III). Thus, three separate flux stages were followed using a single piece of mouse skin. Calculated fluxes from Stages II and III in each experiment were 'normalized' with respect to the Stage I flux from the same permeation run. This was done in an attempt to factor out inherent skin-to-skin flux variations. With the realization that progressive hydration of the mouse skin during the later stages of the experiments might influence benzyl alcohol

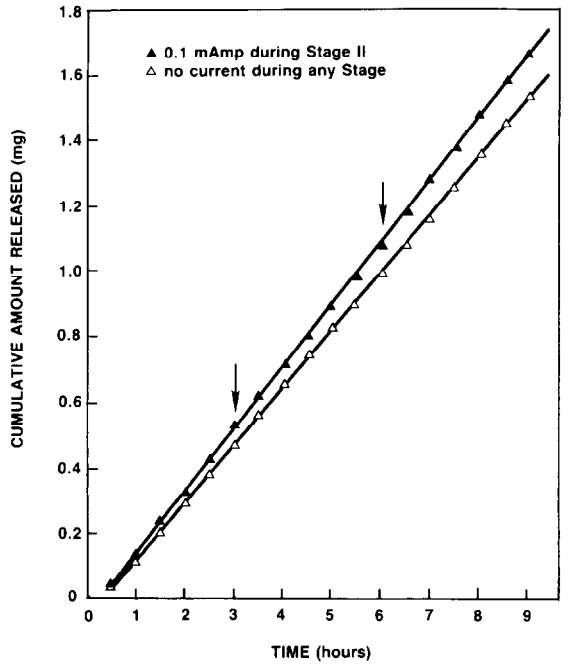

Fig. 5. Effect of current on benzyl alcohol flux across hairless mouse skin. Stage I = 0–3 h, Stage II = 3–6 h, Stage III = 6–9 h. Donor = 10 mg/ml benzyl alcohol, receiver = saline.

transport, a second group of studies was performed under identical conditions as just described, except that no externally applied current was used during any stage of the experiment. Fluxes were calculated for the same 3-h stages, and flux ratios, normalized with respect to Stage I were obtained. Fig. 5 illustrates representative flux plots from the two groups of experiments.

It was felt that this experimental design provided a means by which to separate normal hydration effects from changes resulting from the applied electrical field. Naturally, the latter effect would include electrical field-induced hydration (if that were to occur). Any differences between average Stage II/Stage I ratios (comparing experiments involving Stage II current to those with no current exposure) would imply an effect directly related to the presence of the electrical field. Similarly, differences between the average Stage III/I ratios would imply an effect related to *prior exposure* to an electrical field. Table 4 shows these ratios, grouped according to the presence or absence of an applied current during Stage II. There is no statistically significant difference within either of these sets of ratios when compared using a two-tailed t-test, $\alpha = 0.05$. Thus it can be stated that under the experimental conditions described, the passage of current produced no direct alterations or residual changes in the hairless mouse skin resistance to benzyl alcohol transport.

Benzoic acid flux reversibility

For an ionic species such as the benzoate anion which does exhibit iontophoretic flux enhancement, the question of reversibility arises. To address this issue, a series of experiments was performed using a two-stage design. The first 2.5 h during a given run involved the application of 0.1 mA of direct current, after which the electrodes were removed, with flux being followed for an additional 3 h. The three-stage experimental design described for benzyl alcohol was not utilized for benzoic acid, since large flux variability was

TABLE 4

FLUX RATIOS FROM VARIOUS STAGES DURING THREE-STAGE BENZYL ALCOHOL PERMEATION EXPERIMENTS

Stage I = 0.5–3 h; Stage II = 3–6 h; Stage III = 6–9 h. Donor solutions = 10 mg/ml benzyl alcohol, receivers = saline.

Ratio involved	Computed ratio				
	Expt. 1	Expt. 2	Expt. 3	Expt. 4	Ave. ± S.D.
II [a]/I	1.04	0.96	0.72	0.73	0.86 ± 0.14
II [b]/I	0.92	1.03	0.87	0.87	0.92 ± 0.07
III [a]/I	1.10	0.77	0.94	1.15	0.99 ± 0.15
III [b]/I	1.05	1.15	1.30	1.20	1.18 ± 0.09

[a] Control experiment (no exposure to external current during any stage).

[b] Experiment in which 0.1 mA current was applied during Stage II (donor compartment contained cathode).

observed in preliminary 'control' (no current) studies involving prolonged exposure to the aqueous media. This variability, generally exhibited as a non-linear increasing flux toward the later time periods in some experiments, was thought to possibly be related to the extent of hydration of the mouse skin.

Plots of cumulative benzoate transport as a function of time showed a continual decrease in flux after removal of the externally applied field, indicative of a typical 'burst effect' associated with solute desorption from an initially loaded membrane. The observed curvature was fairly reproducible; however, an occasional skin produced data showing a substantially slower decline in flux upon external current termination. To obtain accurate limiting flux values for the Stage II segment in this experimental design, an additional set of studies was performed, this time extending the duration of the second stage. Typical data from two such experiments are displayed in Fig. 6, and represent the two extremes observed in the limiting (Stage II) flux. Table 5 summarizes the fluxes calculated from the two segments of this group of studies.

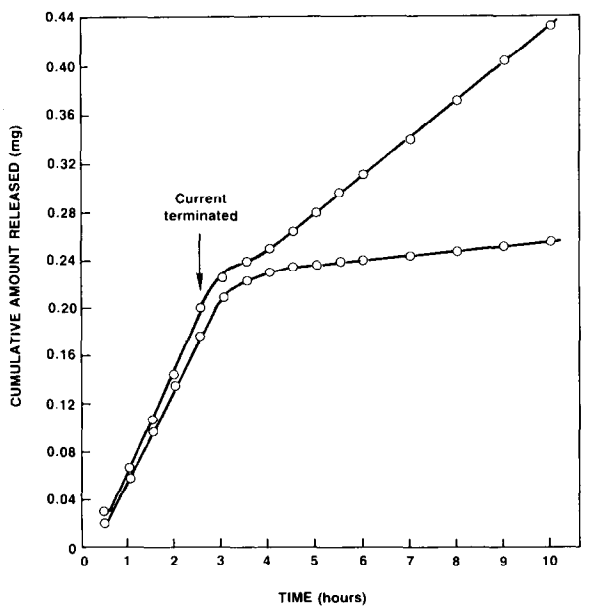

Fig. 6. Benzoic acid flux reversibility following exposure to current. Stage I = 0–2.5 h; current = 0.1 mA. Stage II = 2.5–10 h; no external current. Donor = 10 mg/ml benzoic acid (from Na salt), receiver = saline.

TABLE 5

BENZOATE FLUX ACROSS HAIRLESS MOUSE SKIN DURING TWO-STAGE PERMEATION STUDIES

Stage I: current = 0.1 mA. Stage III no externally applied current. Donor solutions = 10 mg/ml benzoic acid (from Na salt), receivers = saline.

Steady-state benzoate flux ($\mu g/cm^2 \cdot h$)	
Stage I	Stage II
42.77	3.18
42.60	3.01
42.22	5.19
35.24	17.85
46.19	3.76
44.69	2.20
40.32	10.59
48.80	17.25

As can be seen, there is substantial variation in the apparent steady-state benzoate fluxes following current termination, despite fairly consistent behavior during the initial current stage. About half of the skins approached fluxes reasonably close to the mean control (no current exposure) value (1.89 $g/cm^2 \cdot h$), suggesting minimal alteration in the benzoate permeability characteristics of these particular skin barriers as a result of the applied electrical field. The higher Stage II fluxes of the remaining skins suggest compromised barrier integrity of a variable nature. If damage was progressively being induced in these skins during the current stage, it did not appear to affect the iontophoretic transport, since deviations from linearity were not observed during this stage.

It should be noted that at the termination of several studies reported herein (particularly in experiments involving higher currents), the mouse skin was observed to possess faint dark patches, never of the same size or orientation. It is conceivable that although the total current passing through the exposed skin surface area is maintained at a constant level, local variations in current density could occur if there exist local variations in skin resistance. Attempts to identify structural changes in the protein or lipids of current-exposed stratum corneum segments are presently underway. By differential scanning calorimetry performed on isolated hairless mouse stra-

tum corneum, no discernible current-related differences in protein or lipid domains were observed. Preliminary histological findings suggest some alteration in epidermal cell shapes following exposure of excised skin to higher currents. Current-related alterations were also suggested in exploratory studies examining the stratum corneum's infrared spectrum (via attenuated total reflectance). It should be mentioned that the extent of any observed structural changes appeared to be a function of the magnitude of the applied current. Thus it may be possible to avoid induction of these structural alterations by appropriate titration of the current density. Certainly, the maximum current density and duration limitations will be dictated by parameters which are deemed acceptable from a patient safety standpoint. It should be noted that potential local tissue damage is most likely related to current density, and not total current. In theory, to deliver a particular dose of drug over a given time period, any size of epidermal surface area may be utilized, provided the total amperage is held constant (see Eqn. 2). The use of different surface areas will alter the current density but will not affect the quantity of drug delivered, thus providing a possible means by which an iontophoretic device may be optimized with respect to patient safety.

Acknowledgements

The authors would like to recognize Mrs. Sharon Cardinal for technical contributions, Mr. William F. Peterson for construction of the constant current devices, and Dr. Russell O. Potts for assistance in DSC and ATR studies.

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