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NICOTINE SKIN PENETRATION CHARACTERISTICS USING AQUEOUS & NON-AQUEOUS VEHICLES, ANIONIC POLYMERS, AND SILICONE MATRICES

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SUMMARY

Nicotine is a rational candidate for transdermal delivery for smoking withdrawal. In vitro experiments were performed to characterize nicotine skin penetration and some factors affecting skin penetration. These included pH, non-aqueous solvents, and anionic polymers. Nicotine penetrated skin rapidly, and fairly high doses can be delivered transdermally. A 30% aqueous solution vehicle, as has been administered transdermally in clinical trials, produced very rapid initial absorption but the absorption rate decreased with time. Because nicotine has such high skin permeability, one objective in developing a delivery system would be to control the delivery rate, rather than allowing skin permeability to be rate-limiting. A feasible approach to a rate-controlled delivery system was to use vulcanized polydimethylsiloxane as a monolithic matrix.

INTRODUCTION

Nicotine is used therapeutically to alleviate the effects of nicotine withdrawal during smoking cessation. It allows the nicotine-dependent user to

focus on the behavioral and psychological components of their smoking habit before going on to nicotine withdrawal. Nicotine is currently administered in the form of a chewing gum, in which it is bound to an ion-exchange resin. The drug is released from the gum by interaction with saliva and is then absorbed through the oral mucosa or after swallowing. The most frequent side effects associated with the gum are sore throat or mouth, hiccups, and nausea. A potential advantage of administering nicotine transdermally is to reduce these side effects. The transdermal route may also be more acceptable to patients because it would not have the unpleasant taste of the gum. In addition, transdermal delivery provides continuous dosing, even during periods of sleep, so morning cigarette craving might be reduced.

Two published studies have addressed transdermal nicotine delivery. An 8 mg transdermal dose administered to 10 cigarette smokers in a 30% aqueous solution reduced cigarette craving over a 90 minute test period.[1] Saliva nicotine concentrations in a single subject administered nicotine transdermally as described above, reached peak levels at 90 min and declined to baseline levels by 4 hr.[2] Apparently nicotine was rapidly absorbed through the skin using this vehicle.

These studies showed that a transdermal product may be effective for delivering nicotine, but little information is available on the skin penetration characteristics of nicotine and the effects of the applied vehicle. This information is required for optimization of the delivery profile. This study was done to characterize nicotine skin penetration using aqueous vehicles of various pH and non-aqueous vehicles. In addition, some preliminary approaches to preparing formulations with which transdermal delivery could possibly be controlled were studied. In developing a transdermal delivery system, the aim is

generally to manipulate skin penetration rates so as to achieve therapeutic doses. The usual dose of the gum is 10-12 pieces (2 mg each) per day. Systemic absorption after chewing a 2 mg piece of gum was estimated to be 0.86 mg.[3] An average daily systemic dose by gum administration would then be 10-15 mg/day.

MATERIALS AND METHODS

Reagents used were: nicotine base (Sigma), nicotine bitartrate (Sigma), nicotine salicylate (Pfaltz and Bauer), polyethylene glycol 400 (Kodak), propylene glycol (Fisher), light mineral oil (Penreco), dimethylpolysiloxane (DMPS-2X, viscosity 20 centistokes; DMPS-12M, viscosity 12500 centistokes; Sigma), alginic acid (Sigma), polycarbophil (*Carbopol 934P,* B.F. Goodrich), and silicone rubber elastomer (*Silastic 382, Medical grade,* Dow Corning). The silicone matrices were prepared by dispersing nicotine base within the silicone fluid, adding 2 drops/10g of the catalyst (*382 catalyst M,* Dow Corning), and allowing to cure at room temperature overnight.

Nicotine concentrations in all experiments were determined by HPLC. The mobile phase consisted of 0.2M monobasic sodium phosphate in water / methanol / tetrahydrofuran / sodium heptanesulfonate (79/20/1/0.05). At a flow rate of 1.4 ml/min the retention time on a 25 cm x 4.5 mm octylsilane (*Zorbax,* DuPont) column was 8-10 min. Detection was by uv absorbance at 260 nm.

Octanol/buffer partition coefficients were determined using 0.1M phosphate and 0.1M glycine buffers to which nicotine base (0.1% and 1%) was added. Equal volumes of octanol and buffer were tumble-mixed at room temperature (22-23°) for 24 hr. After separating the phases the buffer pH was measured and nicotine concentrations in both phases were determined.

In vitro skin penetration experiments were performed using diffusion cells in which the reservoir was constantly stirred and maintained at 37° with water-jacket or dry block heating. In the experiments in which the pH dependence was evaluated, the reservoir was the same pH as the donor. In other experiments, saline was used as the reservoir. If solutions were used as the donor, the volume was 0.5 ml, unless otherwise stated. The elastomeric matrices were affixed to the skin with an adhesive transfer tape, which did not impede diffusion. The skin surface area available for diffusion was 1.8 cm^2. Human skin specimens were obtained from an organ bank. Of 11 skin donors 4 were female, all were white, and the average age was 39 yrs (S.D.=11). Skin specimens were almost exclusively from thigh and calf areas. The average thickness of the specimens was 0.4 mm, which would include the entire epidermis and part of the dermis, based on average skin layer thicknesses. Skin was stored at -20° indefinitely. Sink conditions were maintained by removing the entire reservoir volume (7-9 ml) and replacing it with drug-free buffer or saline. Nicotine diffusion rates were measured as the rate of nicotine appearance in the reservoir.

RESULTS

pH Dependency

Nicotine is dibasic, with pKa values reported in separate references as 6.16 and 10.96[4], and 3.15 and 7.87.[5] Therefore, when the vehicle pH is below 10, as in these experiments, nicotine is mostly ionized. The profile of octanol/buffer partition coefficient vs pH reflected the increasing ionization with decreasing pH (Figure 1). The pH/partition profiles for 0.05% and 0.5% total nicotine concentrations were identical. Skin penetration rates using aqueous buffer vehicles showed a similar pH

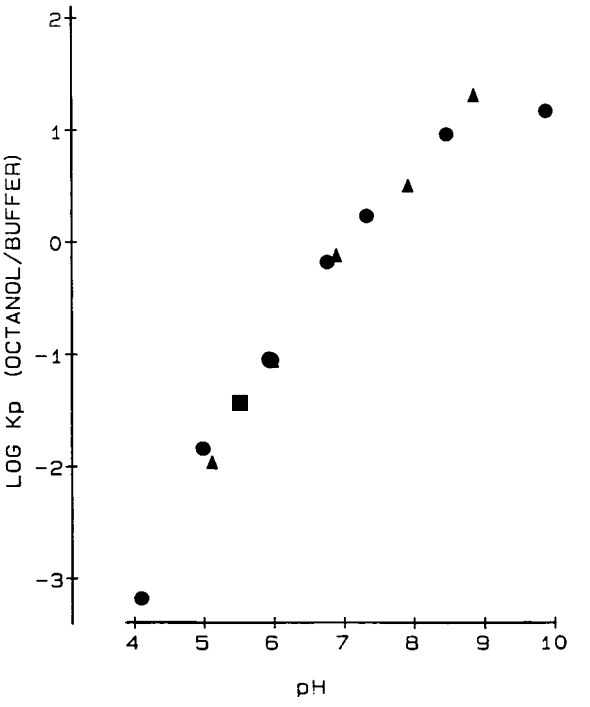

FIGURE 1

Log octanol/buffer partition coefficient (Kp) versus pH for nicotine at 0.05% (▲) and 0.5% (●) total concentration. For one determination (■) nicotine was added as the tartrate salt.

profile (Figure 2). At a fixed nicotine concentration in the vehicle, nicotine flux could be varied 10-fold by adjustment of the pH from 4 to 10. Vehicles of more extreme pH would probably be too irritating to be acceptable for clinical application. Further variations in flux can be expected by adjusting the nicotine concentration in the vehicle.

Effects of Salt Form

Nicotine flux was also measured using aqueous vehicles containing the water-soluble nicotine bitartrate and salicylate salts. Data are summarized in Table 1. At pH 8.5 the rates of nicotine skin penetration were independent of the applied salt form.

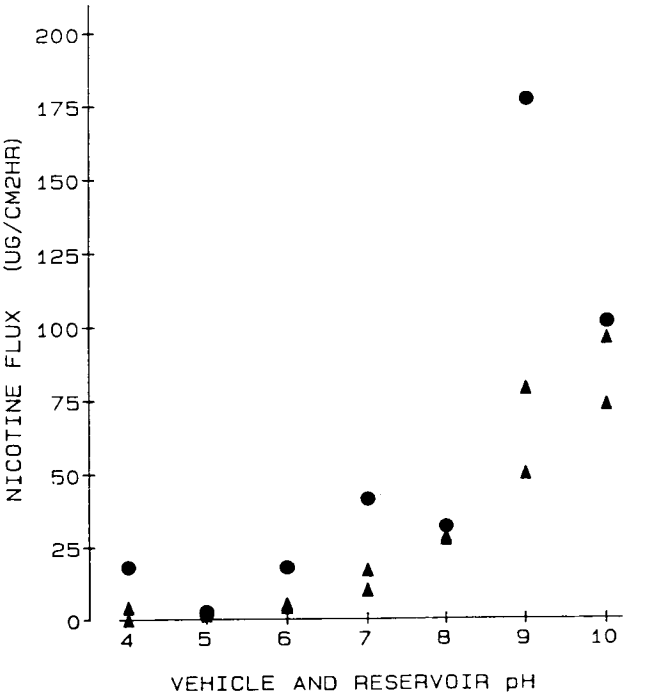

FIGURE 2

Effect of pH on nicotine penetration through skin from two separate donors. The nicotine concentration in the vehicle was 1%.

TABLE 1

Nicotine Skin Penetration from Aqueous Vehicles (0.1 M PO_4 Buffer) at pH 5 and 8.5 Containing 1% Nicotine, Added as the Base or Salt Form.

	Nicotine Flux ($\mu g/cm^2 hr$)	
Nicotine	pH 5	pH 8.5
Base	2.0 ± 0.3	58.8 ± 10.4
Tartrate	38.8 ± 13.3	61.2 ± 12.2
Salicylate	10.4 ± 4.2	56.0 ± 19.7

TABLE 2

Skin Penetration of Nicotine from Non-aqueous Vehicles Containing 1% Nicotine Base.

Vehicle	Nicotine Flux ($\mu g/cm^2 hr$)
Polyethylene Glycol 400	101.1 ± 3.0
Dimethylpolysiloxane (12M)	127.6 ± 19.6
Dimethylpolysiloxane (2X)	132.4 ± 24.7
Mineral Oil	97.0 ± 14.3
Propylene Glycol	16.6 ± 2.4

At pH 5, however, flux was higher for the salts than for the base. It is possible that nicotine partitions into skin as ion pairs[6], and that some ion pairs (i.e. nicotine bitartrate) may partition to a greater extent than others. The octanol/buffer partition coefficient of nicotine at pH 5 was measured with nicotine bitartrate in phosphate buffer. The partition coefficient was the same when nicotine bitartrate or nicotine base were added to the buffer (Figure 1).

Non-aqueous Vehicles

Nicotine base was added to various non-aqueous vehicles at 1% concentration and skin penetration rates were measured. Results are summarized in Table 2. Since the nicotine concentration was the same in all vehicles, the differences in flux presumably reflect differences in the skin/vehicle partition coefficients (specifically, thermodynamic activity coefficient). Again, further manipulation of flux could be expected by varying the nicotine concentration in the vehicle.

30% Aqueous Solution

The only reported clinical trials of transdermal nicotine[1,2] were done using an aqueous vehicle containing 30% nicotine, and applying 26 µl to the skin. Since skin

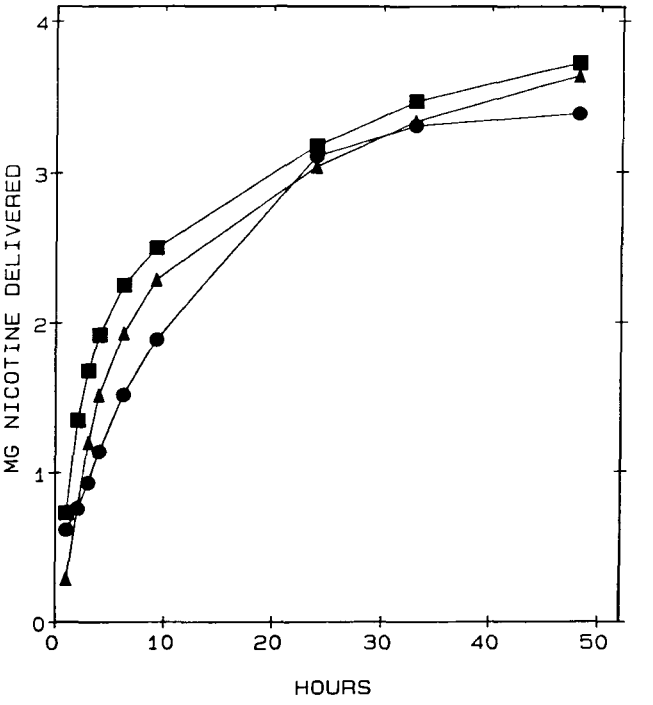

FIGURE 3

Skin penetration profile for 3 skin specimens upon which 26 µl of a 30% nicotine aqueous solution was placed.

penetration data for that formulation were not published, it was evaluated here. The solution pH was 10.5. Amount penetrating vs time profiles are shown in Figure 3. A plot of flux vs time (Figure 4) shows that initially skin penetration was very rapid. Because a finite dose was applied, the flux decreased as the vehicle concentration was depleted.

As described in the previous sections, the skin penetration characteristics of nicotine are such that very high permeation rates are possible, depending on the pH, the nicotine concentration in the vehicle, and on the solvent used as the vehicle. A transdermal delivery system should provide

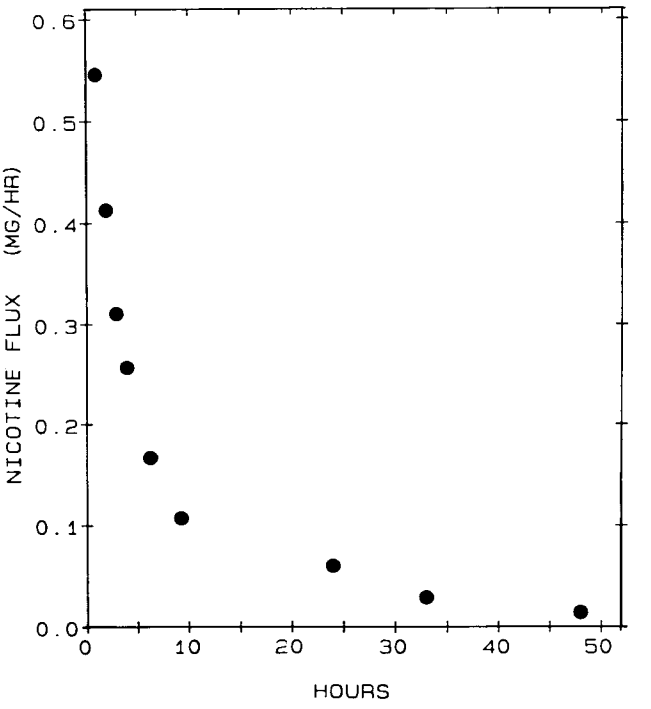

FIGURE 4

Using the data from Figure 3, flux was calculated at each sample time and averaged.

control of the diffusion rate, in contrast to that seen with a 30% aqueous solution. Two approaches to controlling the delivery rate were evaluated.

Effects of Anionic Polymers

Association of nicotine base with an anionic polymer in the vehicle might be expected to reduce flux. To examine this, various concentrations of the carboxylic acid polymers, polycarbophil and alginic acid, were added to water with 1% nicotine. The final vehicle pH depended on the polymer/nicotine concentration ratio. Polycarbophil vehicles were viscous and alginic acid vehicles were not. The major determinant of nicotine flux was the vehicle pH (Figure 5). With vehicles containing alginic

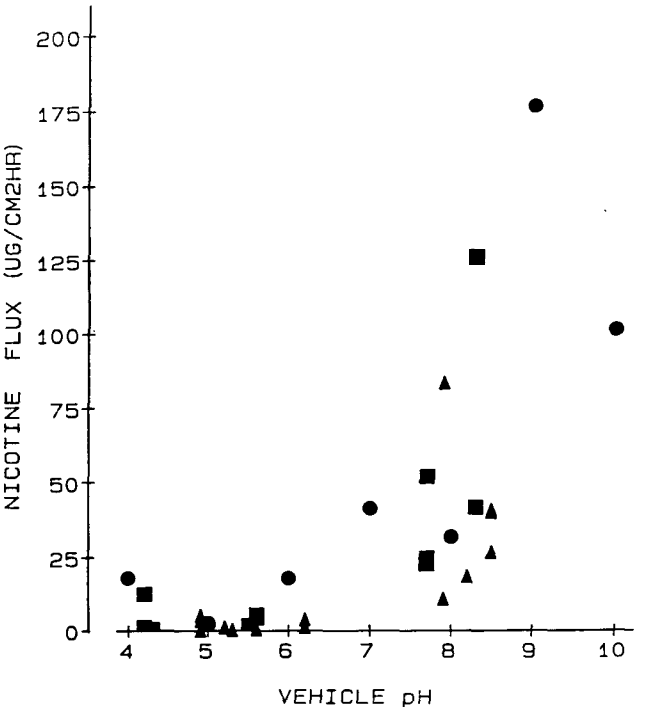

FIGURE 5

Nicotine skin penetration from vehicles where the pH was controlled by buffer (●), alginic acid (■), or polycarbophil (▲).

acid and nicotine in 1:1 weight proportions, nicotine flux increased in proportion to increasing nicotine concentrations (Table 3). A comparison of nicotine penetration rates through skin or a cellulose dialysis membrane (*Spectrapor 1*, MW cutoff 6000-8000 Spectrum) showed that skin was clearly still the rate-determining barrier, using a polycarbophil vehicle (Table 4). These data suggest that the addition of anionic polymers to aqueous nicotine vehicles does not deter diffusion from those vehicles, independently of the effects of the polymer on the vehicle pH. However, addition of polycarbophil to non-aqueous vehicles reduced nicotine flux through skin (Table 5).

TABLE 3

Concentration Dependence of Nicotine Skin Penetration from Alginic Acid/Nicotine (1/1, w/w) Aqueous Solutions.

Nicotine Concentration (%)	Solution pH	Nicotine Flux ($\mu g/cm^2 hr$)
1	≈7.7	33.3 ± 7.7
5	≈7.9	183.9 ± 21.2

TABLE 4

Nicotine Penetration Through Skin and Cellulose Membranes from Aqueous Polycarbophil Vehicles.

		Nicotine Flux ($\mu g/cm^2 hr$)	
Vehicle	pH	Skin	Cellulose Membrane
1% Nicotine, 0.5% Polycarbophil	7.9 - 8.2	37.7 ± 18.8	493.1, 442.8
1% Nicotine, 1.5% Polycarbophil	5.3 - 5.6	0.6 ± 0.1	291.7, 443.2

TABLE 5

Effects of Polycarbophil on Nicotine Skin Penetration Using Non-aqueous Vehicles.

Vehicles (1% Nicotine)	Nicotine Flux ($\mu g/cm^2 hr$)
PEG 400	10.1 ± 3.0
0.5% Polycarbophil in PEG 400	9.9 ± 3.6
1% Polycarbophil in PEG 400	4.0 ± 0.6
2% Polycarbophil in PEG 400	1.4 ± 0.3
Propylene Glycol	16.6 ± 2.4
1% Polycarbophil in PG	6.1 ± 0.4
2% Polycarbophil in PG	1.5 ± 0.2

TABLE 6

Nicotine Release Rates from Silicone Matrices and Skin Penetration Rates from Dimethylpolysiloxane Solutions and Silicone Matrices.

Vehicle	Nicotine Conc.(%)	Release Rate ($\mu g/cm^2 hr$)	Skin Penetration Rate ($\mu g/cm^2 hr$)	Lag Time (hr)
Dimethylpolysiloxane	1		163	0
Dimethylpolysiloxane	5		781	0
Silicone Matrix	1	37.3	21.4 ± 1.6	2.2 ± 1.2
Silicone Matrix	2	29.2	26.0 ± 4.7	2.2 ± 1.0
Silicone Matrix	3	34.8	32.4 ± 3.6	2.0 ± 0.8
Silicone Matrix	4	30.3	33.4 ± 2.9	2.3 ± 1.0
Silicone Matrix	5	Burst	217	0

Silicone Matrices

The other approach to control the delivery rate was to incorporate nicotine within a silicone elastomeric matrix (*Silastic*), wherein nicotine diffusion is rate-limiting. Systems were evaluated by measuring diffusion through skin from the silicone matrices or by measuring release rates into the reservoir in the absence of skin. Results are given in Table 6. At nicotine concentrations of 1-4% the release rates and skin penetration rates were approximately equal, demonstrating that the delivery system controlled the skin penetration rates. Skin penetration rates using 1% nicotine in the silicone matrix were much lower than with 1% nicotine in dimethylpolysiloxane. Release rates and skin penetration rates did not increase with increasing concentrations from 1-4%. This could be due to incomplete dissolution of nicotine in the silicone polymer, entrappping nicotine droplets when vulcanized. At 5% nicotine concentration

the silicone matrix did not completely vulcanize and remained fluid. Nicotine release into the reservoir exhibited a burst, and skin penetration rates were high.

DISCUSSION

The skin penetration of nicotine from aqueous vehicles was consistent with pH/partitioning theory in that flux was related to the degree of ionization. At the pH of these experiments nicotine was mostly ionized, but nevertheless skin penetration rates were fairly high. Oakley and Swarbrick[6] previously proposed that nicotine can partition into skin as ion pairs, and our results with different salt forms at pH 5 may reflect differences in ion pair partitioning, although the octanol/buffer partition coefficient did not confirm this. These studies demonstrated that nicotine penetrates skin rapidly from aqueous and non-aqueous vehicles. This was especially evident when a 30% aqueous solution was used as the vehicle, as has been administered in clinical trials. Therefore, a goal in developing a transdermal delivery system would be to control the delivery rate. Although the nicotine gum uses an ion exchange mechanism to control nicotine release, and polycarbophil has been shown to be useful as a cation exchanger to sustain the release of other drugs,[7] in aqueous vehicles polycarbophil and alginic acid did not control nicotine skin penetration rates aside from their effects on the vehicle pH. In non-aqueous solvents, however, these anionic polymers did reduce nicotine flux. Another approach to control the transdermal delivery rate was to incorporate nicotine base in a silicone elastomeric matrix. This appears to be a feasible approach.

Since pharmacodynamic data relating nicotine dosing or blood level profiles with efficacy are not available, the optimal dose or dosing profile by

transdermal delivery is not known. The average systemic dose by intermittent administration of the 2 mg gum is probably in the 10-15 mg/day range. A flux of 50 $\mu g/cm^2hr$, which was attained in this study, is equivalent to 1 mg/hr or 24 mg/day, if the coverage area is 20 cm^2. It remains to be determined whether sustained nicotine delivery is effective in treating smoking withdrawal.

ACKNOWLEDGEMENTS

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