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KINETIC EVALUATION OF TRANSDERMAL NICOTINE DELIVERY SYSTEMS

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ABSTRACT

The skin permeation and release kinetics of nicotine from four nicotine-releasing transdermal delivery systems (TDS) marketed recently was investigated under identical conditions to evaluate the effect of system design and the interchangeability of these products. In the study, hairless rat skin was first used as an animal model to evaluate the permeation mechanisms of various TDS's, which were then verified by studying the permeation through human cadaver skin. Three of the four TDS's were found to deliver nicotine at zeroth-order permeation kinetics at steady state with permeation rate ranging from 0.072 - 0.197 mg/cm^2/hr, while the fourth one produced a triphasic zeroth-order permeation rate profile. Three TDS's released nicotine at non-linear manner, which could be described by a linear Q vs. $t^{1/2}$ relationship, while one TDS yielded a constant release at steady state. The different skin permeation profiles of nicotine delivered by these TDS's could be explained by the difference in their system designs and structural compositions.

INTRODUCTION

Nicotine has been known to stimulate the release of neurotransmitters and hormones, such as acetylcholine, norepinephrine,

dopamine, growth hormone, ACTH and cortisol etc., leading to some alterations of the metabolic activities in the body (1,2). However, clear explanations have not been provided for the biobehavioral effects of nicotine. Even though the mechanism underlying the modifications of human behavior by nicotine is still a mystery (3,4), it is well known that the persistent smoking behavior is resulted from the development of nicotine addition, for which nicotine is categorized as a psychoactive substance. When an addict stops smoking, nicotine addiction often manifests some smoking withdrawal syndromes, such as craving, frustration, anxiety, decreased heart rate and weight gain (5). Prolonged consumption of nicotine is reportedly associated with a wide variety of health hazards, like cardiovascular diseases, pulmonary diseases and cancer (1,2,6). Heart rate and blood pressure have been found to increase significantly, which can be directly related to the nicotine level in the circulation (7). On the other hand, reduction in nicotine can lead to a significant decrease in lower respiratory tract inflammation (8). Nicotine is also regarded as a precursor for carcinogenesis triggered by the tobacco-specific nitrosamines (9,10). Drug metabolism and pharmacokinetics have also been reportedly disrupted by the nicotine from cigarette smoking (11).

Due to the undesirable effects of smoking outlined above, various methods have been devised to help smokers quit smoking. Among these, nicotine-replacement therapy is considered as the most efficient method for reducing tobacco craving as a result of substantial minimization of withdrawal syndromes (12). Nicotine replacement has even been regarded as the first effective treatment, as a cessation aid, for appropriately motivated and instructed subjects (13). Recently, four nicotine-releasing transdermal delivery systems (TDS's), designed to achieve the transdermal controlled delivery of nicotine over a 24-hr or 16-hr period, received regulatory approval for marketing in the United States as an effective and a safe treatment for smoking cessation. The TDS's are designed to be applied, once-a-day, to an alternate skin site on the trunk, upper or lower arm. Double-blind, placebo-controlled,

randomized clinical studies of TDS's have demonstrated the effectiveness of TDS's. By measuring the carbon monoxide concentration in the exhaled air and the occurrence of withdrawal syndromes during treatments, the percentage of abstinence and subjective satisfaction can be determined (12,14-17). The results obtained have revealed that TDS's can provide effective assistance in smoking cessation with minimal occurrence of withdrawal syndromes. Abstinence percentages ranging from 20-80% have been achieved in the active patch-treated group compared to only 10-30% in the placebo patch-treated groups. The abstinence percentage was found declining with the duration of post-treatment. Significant variation among various studies was observed, which can probably be explained by the differences in the sampling periods, the provision of behavioral therapy, and the nature of populations used for the studies.

Since the data supplied in the product information and patient instructions for the various marketed TDS's were collected under different study conditions, a question has been raised on the interchangeability among these TDS products, especially when a pharmacy runs out of the original product. No scientific data is available for medical profession to make sound judgment. Even though the in-vitro skin permeation of nicotine through human epidermis, membranes and laminates has been recently reported (18), no study is done for comparing these nicotine-releasing TDS products. A systematic series of kinetics studies were thus initiated in this laboratory to investigate and compare the mechanisms and rate profiles of the release and skin permeation kinetics of nicotine from these TDS's under identical conditions. In order to elucidate the kinetics of release and skin permeation of nicotine from these TDS's, the investigations were carried out to *(1)* characterize the mechanism and kinetics of skin permeation of nicotine from solution medium, which has no influence of drug delivery systems, *(2)* evaluate the intra- and inter-subject variability in the skin permeation of nicotine, *(3)* assess the pharmaceutical equivalence and interchangeability among the various TDS products.

MATERIALS AND METHODS

Materials

The nicotine-releasing transdermal delivery systems studied in this investigation consisted of:

1) System A [Nicoderm^{R} (lot 141103)]/ Marion Merrell Dow (Kansas City, MO)
2) System B [Habitrol^{R} (lot 1028200)]/ Basel Pharmaceutical (Summit, NJ)
3) System C [Prostep^{R} (lot 92/042)]/ Lederle Laboratories (Pearl River, NY)
4) System D [Nicotrol^{R} (lot 03052G)]/ Warner-Lambert Co. (Morris Plains, NJ)

The system characteristics of these four TDS's are compared in Table 1.

Skin Source:

1) Female hairless rat (fuzzy Hsd:fz, 6- to 8-week old) supplied by Harlan Sprague Dawley, Inc. (Indianapolis, IN)
2) Female human cadaver skin (39-year-old) obtained from Ohio Valley Tissue and Skin Center (Cincinnati, OH)

Permeation System:

Valia-Chien skin permeation cell assembly fabricated by Crown Glass Co. (Somerville, NJ)

Reagent:

1) (-)Nicotine, as the reference standard, was purchased from Sigma Chemical Co. (St. Louis, MO)
2) Na_2HPO_4, KH_2PO_4 and NaCl , used for preparation of isotonic phosphate buffer system, were reagent grade and purchased from Fisher Scientific (Fair Lawn, NJ)

Analytical Instrument

HPLC assembly by Millipore Corporation (Marlborough, MA) was used, which consisted of:

1) HPLC pump 510
2) Waters Intelligent sample processor 712

TABLE 1
Comparison in System Characteristics of TDS's

	Drug Releasing Area (cm^2)	Loading Dose Per Unit Surface (mg/cm^2)	Dosage Rate[a] ($mg/cm^2/day$)	Daily Dosage (mg/day/patch)	Intended Treatment Duration (hr)
System A	7	5.0	1.0	7.0	24
System B	10	1.8	0.7	7.0	24
System C	7	4.0	3.1	21.7	24
System D	10	0.83	0.5	5.0	16

[a] *Expected daily dosage of nicotine to be delivered from one unit surface of drug releasing area calculated from the information provided in the manufacturer's packaging insert*

3) Data module 730

4) Programmable system controller 721

5) $_{\mu}$Bondapak C_{18} column (3.9 mm x 150 mm)

in connection with detector, Spectroflow 783 (by Kratos Analytical, Ramsey, NJ)

Procedure

For skin permeation kinetics studies of nicotine, skin specimens (full-thickness,3.5x3.5 cm^2 each) were freshly excised from various body regions of a hairless rat and mounted individually between the half-cells of the Valia-Chien (V-C) permeation cell assembly thermostated at body temperature by circulating water at 37°C through the water jacket. To verify the results obtained from the animal model, the permeation through human cadaver skin from each TDS was also conducted. Skin specimen dematomed to 13.4 microns in thickness from the thigh region of the human cadaver and stored in nitrogen freezer(-70°C), was firstly defrosted at room temperature for 10 minutes and then thawed in 20°C distilled water for 10 minutes to remove preservatives. The skin specimen was cut into pieces (3.5x3.5 cm^2 each) and mounted in the same manner as for hairless rat skin. For the skin permeation kinetics of nicotine from the solution phase, the donor half-cell was filled with isotonic phosphate buffer solution (at pH 5.0), which had nicotine (50 mg/ml) dissolved in it. For the skin permeation kinetics of nicotine from TDS, a nicotine-releasing TDS was applied on the stratum corneum surface of the skin. In both cases, the receptor half-cell of each V-C cell was filled with 3.3 ml of isotonic phosphate buffer solution (at pH 7.4).

For release studies of nicotine from TDS's, no skin specimen was used and the drug-releasing surface of a TDS was in direct contact with the receptor solution (which was maintained at pH 5.0 to simulate the skin's surface pH).

Analytical methods

Concentrations of nicotine in the samples, taken from the receptor solution at predetermined intervals, were determined by a reverse-phase

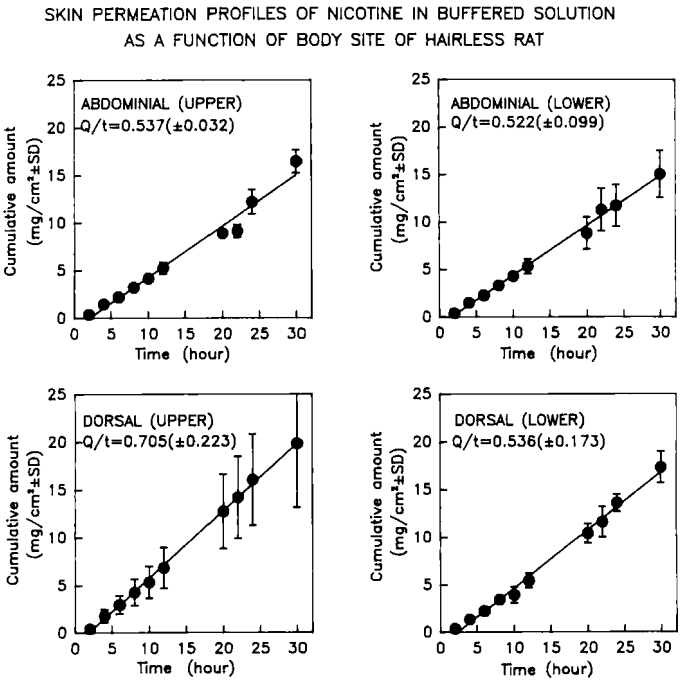

FIGURE 1
Hairless rat skin permeation profiles of nicotine from the donor solution (pH 5.0) containing 50 mg/ml of nicotine and the effect of body regions.

high-performance liquid chromatography outlined above. The sensitivity was determined to be 10 *u*g/ml. The detector wavelength was set at 260*n*m. A well-separated peak was detected at the retention time of 3.0 minutes. The mobile phase used was a combination of 40% phosphate buffer (pH=7.4) 30% methanol and 30% acetonitrile.

RESULTS and DISCUSSIONS

Skin permeation kinetics

Nicotine is a small molecule (MW=162) and lipophilic in nature, so it is expected to permeate readily through the skin barrier. Skin permeation kinetics studies of nicotine in buffered solution indicated that nicotine permeates through the skin specimens, excised from various body regions, by a zeroth-order kinetics process (Figure 1). The differences among the rates of permeation across the abdominal (upper

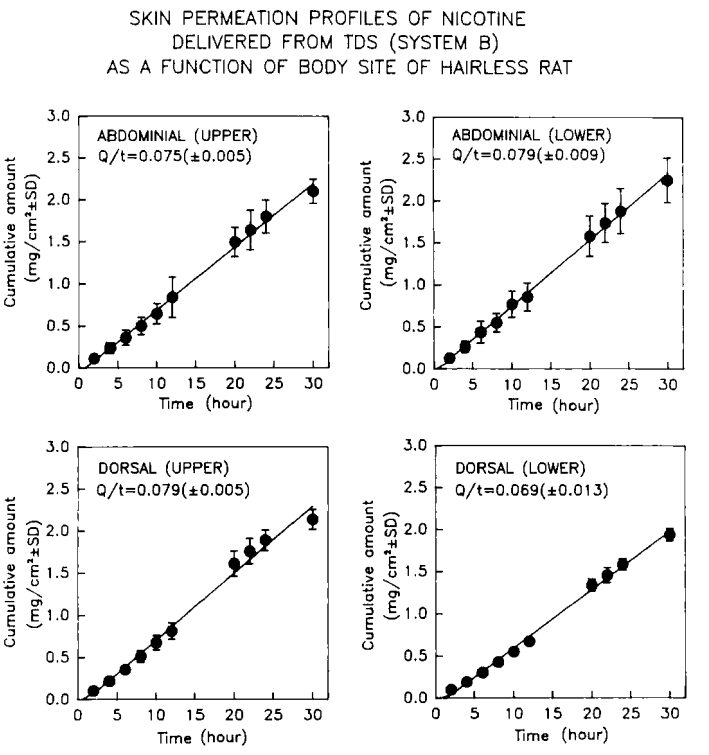

FIGURE 2
Hairless rat skin permeation profiles of nicotine delivered from the transdermal delivery system (TDS) B and the effect of body regions

and lower) and dorsal (upper and lower) skin from the same rat are found not statistically significant, which implies that the rate of permeation is relatively independent of the body region on the same subject.

The inter-subject variability in skin permeation rate of nicotine was also evaluated at different days using three hairless rats, for which the skin specimens from the same body region (upper abdomen) were used. The results indicated that the variability is also statistically insignificant. The skin permeation profiles in Figure 2 show that nicotine delivered by system B also permeates through the skin specimens from various body regions by zeroth-order kinetics. But, the rate of permeation reduces by 7-8 times. The intra- and inter-subject variabilities on the skin

permeation kinetics of nicotine from buffered solution and TDS's are summarized in Table 2. The comparison shows that the intra- and inter-variabilities for the skin permeation rate are substantially lower for nicotine from TDS's than from solution (9.21 - 9.63% vs. 13.2 - 30.6%). The decrease in skin permeation rate by TDS with the reduced variabilities can be attributed to the controlled release of nicotine from the TDS, which shifts the rate-limiting step for skin permeation from solely the stratum corneum to the controlled delivery by TDS.

Following the assessment that the subject variabilities in permeation rates by system B are insignificant, skin permeation profiles of nicotine delivered by systems A, B, C and D were then investigated and the results are compared in Figure 3. All of the four TDS's achieve zeroth-order permeation kinetics at steady state, but in different fashion. Two of the TDS's (systems B, C) attain the steady-state permeation profiles throughout the 30-hour period, whereas systems A and D give biphasic and triphasic permeation profiles, respectively, with rate varying from one phase to another.

The human cadaver skin permeation kinetics of nicotine delivered from these TDS's was also investigated; A biphasic permeation profile was observed for all four TDS's (Figure 4). The initial permeation of nicotine from these TDS's through the human cadaver skin are always faster in the beginning (with rate ranging from 0.068 to 0.289 mg/cm^2/hr), which lasts for 6-16 hours, followed by a permeation rate ranging from 0.029 to 0.165 mg/cm^2/hr for the remaining 30-hour period. It is interesting to note that the permeation rates obtained at steady state for human cadaver skin are in good agreement with those for hairless rat skin (Figures 3 & 4). This suggests that hairless rat skin is a good skin model for in-vitro permeation kinetics studies of nicotine through human skin.

The lag times for the skin permeation of nicotine delivered by the TDS's are found statistically insignificant in terms of the site and subject of application (Table 2). The length of lag time required for skin permeation to reach the steady state is noted to decrease with the use of

TABLE 2

Intra- and Inter-Subject Variability in Skin Permeation Kinetics of Nicotine from Buffered Solution and Transdermal Delivery System[d]

	PERMEATION RATE[a] (mg/cm^2/hr+/-SD)		LAG TIME[a] (hour+/-SD)	
SKIN REGION[b]				
Abdominal	Solution	TDS	Solution	TDS
upper	0.537 (0.032)	0.075 (0.005)	1.984 (0.324)	0.917 (0.980)
lower	0.522 (0.099)	0.079 (0.009)	1.483 (0.366)	0.624 (0.783)
Dorsal				
upper	0.705 (0.223)	0.079 (0.005)	1.825 (0.161)	1.118 (0.475)
lower	0.536 (0.173)	0.069 (0.013)	2.417 (0.300)	1.358 (0.073)
mean[e]	0.575 (0.176)	0.076 (0.007)	1.927 (0.507)	1.009 (0.748)
CV	30.6%	9.21%		
HAIRLESS RAT[c]				
	Solution	TDS	Solution	TDS
#1	0.463 (0.037)	0.069 (0.011)	1.259 (0.123)	1.587 (0.552)
#2	0.598 (0.018)	0.074 (0.001)	1.850 (0.111)	0.862 (0.752)
#3	0.537 (0.032)	0.075 (0.005)	1.984 (0.324)	0.917 (0.980)
mean	0.535 (0.071)	0.073 (0.007)	1.697 (0.601)	1.122 (0.877)
CV	13.2%	9.63%		

a Mean(+/-one standard deviation) values were each determined from triplicate experiments

b Skin specimens excised from 4 body regions from the same animal

c Skin specimens excised from the upper abdominal skin region of three rats sacrificed in 3 consecutive days.

d Transdermal delivery system B was evaluated as the model TDS in these studies

e n=12

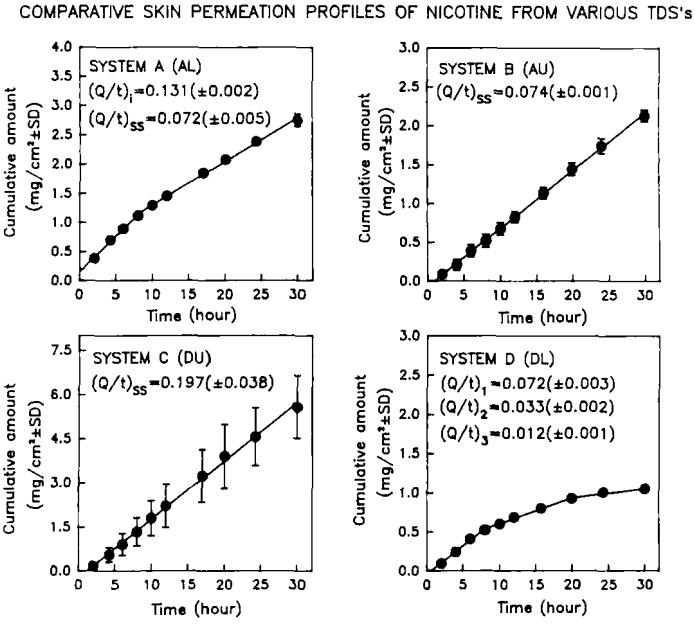

FIGURE 3
Hairless rat skin permeation profiles of nicotine delivered from the four marketed transdermal delivery systems

controlled-release drug delivery systems. The elevated coefficient of variation (74.1 - 78.2% vs. 26.3 - 35.4%) observed may be resulted from the variability in TDS application to the skin surface.

Release kinetics

In order to gain more insight of the release mechanisms of nicotine from the TDS's and their roles on transdermal delivery, the drug release kinetics study was also investigated, for which nicotine was released into a solution medium with pH simulating the skin surface pH (5.0). The results in Figure 5 indicate that while systems A, B and D release the nicotine loading gradually, at a nonlinear manner, throughout the course of 12-hr release study, system C releases all its nicotine loading within one hour. Except system A which deviates from this type of kinetics at steady state, the release profiles of nicotine from systems B, C, D appear to follow the polymer matrix diffusion-controlled process as shown by the

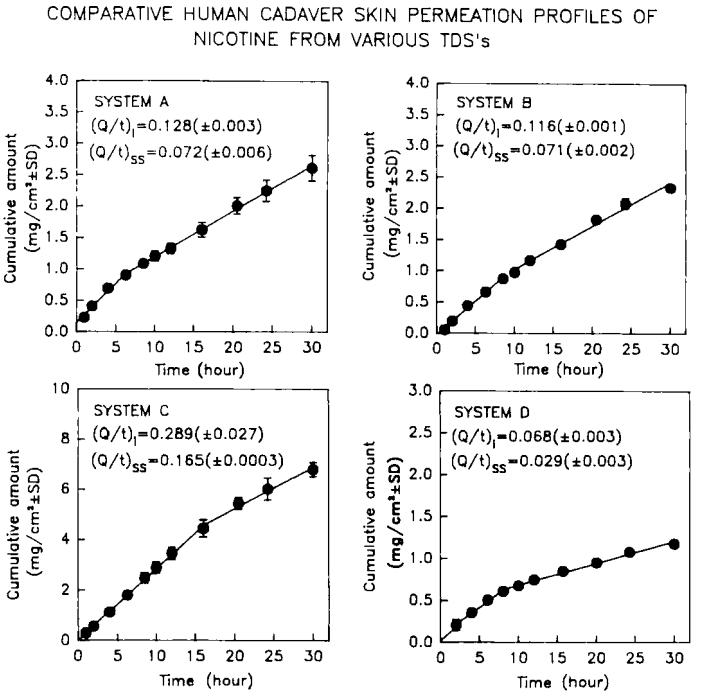

FIGURE 4
Human cadaver skin permeation profiles of nicotine delivered from the four marketed transdermal delivery systems

linear Q vs. $t^{1/2}$ relationship (Figure 6). The relationship is presented mathematically as followed (19,20):

$$Q = R \times t^{1/2} \quad \text{.....(1)}$$

where Q is the cumulative amount of nicotine released from a unit drug-releasing area of TDS, R is drug release flux and is defined by:

$$R = [(2A - C_p) \times C_p \times D_p]^{1/2} \quad \text{.....(2)}$$

where A is the initial loading of nicotine in an unit volume of the TDS, C_p is the solubility of nicotine in the polymer, Dp is the diffusivity of nicotine in the polymer matrix.

The differences in system designs and structural compositions contribute to the unique release profiles observed in Figures 5 & 6. Based on the product information provided by manufacturers, system A is

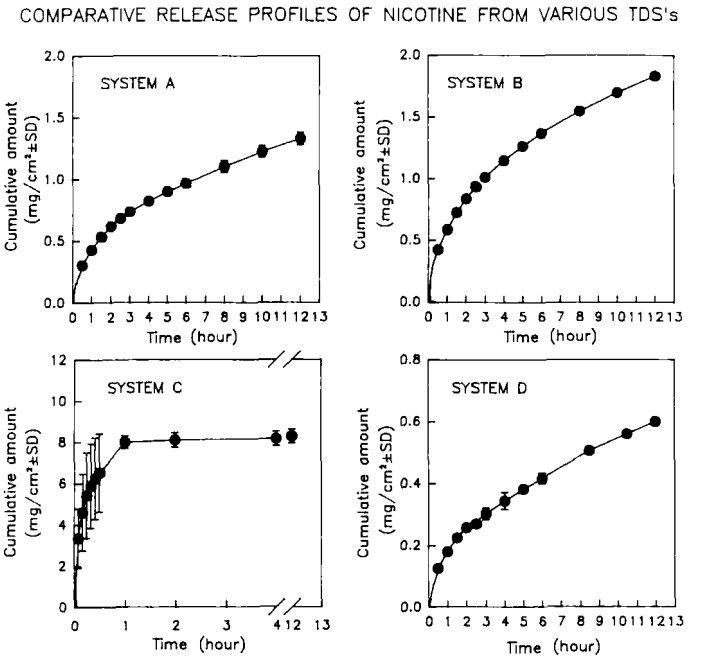

FIGURE 5
Release profiles of nicotine into buffered solution (pH 5.0) from the four marketed transdermal delivery systems

constructed from a nicotine reservoir in an ethylene-vinyl acetate copolymer matrix covered by a rate-controlling polyethylene membrane having a polyisobutylene adhesive surface. Nicotine is also purposely dispersed in the adhesive surface to create a rapid initial release. Thus, it releases nicotine in $\underline{Q \text{ vs. } t}^{1/2}$ manner in the first 3 hours (Figure 6) and then gradually shifts to $\underline{Q \text{ vs. } t}$ pattern (Figure 5). System C, which has nicotine dispersed in a hydrogel matrix surrounded by a peripheral adhesive pad, releases the nicotine loading dosat a very high release flux when it comes into contact with a solution medium (Figure 6). System B has its methacrylic acid copolymer solution of nicotine dispersed in a pad of nonwoven viscose and cotton, on which a layer of surface adhesive is laminated. System D contains nicotine in a layer of rate-controlling adhesive dispersing in a structural nonwoven material.

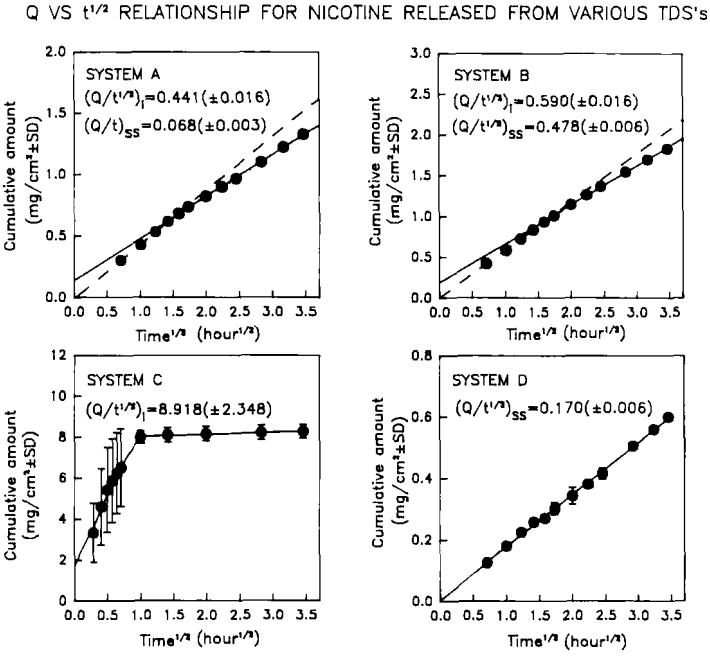

FIGURE 6

Linear Q vs. $t^{1/2}$ relationship for the controlled release profiles of nicotine from the four marketed transdermal delivery systems

Though sharing some similarity in system design, the variations in structural composition of system B gave a biphasic release pattern, with initial release flux of 0.590 and steady-state flux of 0.478 $mg/cm^2/hr^{1/2}$. On the other hand, system D produced a monophasic release pattern, with a steady-state release flux of 0.170 $mg/cm^2/hr^{1/2}$ (Figure 6). The nicotine release profile of system B could be attributed to the fact that nicotine diffusing into the surface adhesive during storage is firstly released, which is then followed by a matrix diffusion-controlled release of nicotine from the reservoir.

Correlation of skin permeation with release kinetics

For system A, the initial release of nicotine from the adhesive is controlled by matrix diffusion process, which contributes to the higher

initial permeation rate (0.128 mg/cm^2/hr) for the first 6-hour period. At steady state, the process is then shifted to a membrane-controlled permeation process with nicotine in drug reservoir permeates through the rate-controlling polyethylene membrane. A constant release rate of 0.068 (+/-0.003) mg/cm^2/hr was obtained, which was found to be very close to the skin permeation rate of [0.072 (+/-0.006) mg/cm^2/hr] of system A. The agreement of permeation rate with release rate indicates that at steady-state, the skin permeation kinetics of nicotine from system A is primarily determined by its release from the system.

On the other hand, the release of nicotine from systems B, C, D appears to follow solely matrix diffusion mechanism throughout the release process. The hydrophillic "gel composition" in system C, which becomes swollen in contact with aqueous medium and, as expected, yields a substantially high release flux of nicotine (Figure 6). The constant skin permeation profile observed (Figures 3 & 4) is apparently due to the fact that the stratum corneum is a non-sink medium and thus serves as a rate-limiting barrier for skin permeation of nicotine released to the stratum corneum surface from the TDS's. The high release flux of nicotine observed with system C (8.92 mg/cm^2/hr$^{1/2}$) may also explain the higher permeation rate of system C (0.289 mg/cm^2/hr for human cadaver skin and 0.197 mg/cm^2/hr for hairless rat skin), which is about 2 to 6 fold greater than those by the other systems (Figures 3 & 4). In other words, the skin permeation of nicotine from system C is relatively less controlled by the system itself as compared to other TDS's.

Similarly, skin-limiting permeation was also observed to operate when system B was used as the delivery device for nicotine. Nicotine was delivered through human cadaver skin at the initial rate of 0.116 mg/cm^2/hr for the first 8 hours and then at the steady-state rate of 0.071 mg/cm^2/hr throughout the period of 8-30 hours, which was very much the same as the rate of permeation across the hairless rat skin (0.074 mg/cm^2/hr) throughout the course of 30-hr permeation studies. The release flux of nicotine from system B is much lower than that by system

C, but it is greater than systems A and D (Figure 6). Even though the pharmacodynamic of these TDS's was not studied in this investigation, it should be pointed out that the availability of nicotine delivered from transdermal patch potentially determines the propensity for toxic manifestations (21).

Unlike systems B and C, the skin permeation of nicotine delivered by system D is primarily determined by the matrix diffusion- controlled release of nicotine from the system. The observed bi- and triphasic decline in the permeation profile of nicotine could be attributed to the substantial reduction in loading dose, thus, in the release flux of nicotine, as predicted from Equation (2).

In summary, both release flux and skin permeation rate data (through the human cadaver and hairless rat skin) of nicotine show the following order: system C>> system A≈system B> system D. They follow the relationship that the higher the release flux, the higher the rate of permeation through the skin (19,20).

The in-vitro skin permeation experiment could have one problem inherent with the experimental setup, for which the actual surface area of TDS in contact with the stratum corneum surface is larger than the dermal surface in exposure to the receptor solution. This setup permits the drug molecules in the reservoir, which surrounds the region perpendicular to the dermal surface exposed to the receptor solution, also release by lateral diffusion. This leads to a value of permeation rate and the amount of dose delivered higher than that calculated on the basis of the dermal area exposed to the receptor solution. This complication could become more significant for systems with high release flux. Since, in clinical situation, the entire drug releasing area of a TDS is applied to the skin of a patient, the drug molecules are mostly undergoing unidirectional diffusion; so, the in-vitro rate of delivery determined tends to be higher than the in-vivo rate. It may explain the observation that the in-vitro rates of permeation obtained in this investigation are approximately 1.5 - 2.0 times higher than the in-vivo rates of delivery reported by the manufacturers in their product

information. With this difference in mind, further studies are planned to be conducted under in-vivo conditions. At the present time, the scientific data generated in this series of investigations study serves to provide a good insight into the mechanisms and kinetics of nicotine delivery and the effects of system design and structural composition.

CONCLUSIONS

Based on the data collected, it is concluded that at steady state, nicotine is delivered to the skin by matrix diffusion-controlled process from three nicotine-releasing transdermal delivery systems (TDS's) and by membrane permeation-controlled process from one TDS; through these processes, the skin permeation of nicotine is thus modulated over a period of at least 24 hours. The skin permeation rate of nicotine varies from one system to another, which is the result of variation in the system design and structural composition of these TDS's. The human skin permeation data suggest that systems A and B are very much the same in both the permeation profiles and permeation rates of nicotine and thus, they could be considered interchangeable. On the other hand, the in-vitro skin permeation data generated do not support the interchangeability between systems C and D or between system C or D and system A or B. The conclusion is very different from that reported earlier for nitroglycerin-releasing TDS's (22).

Statistically, there is no difference in the skin permeation kinetics of nicotine among subjects and skin regions of application. A short lag time has been achieved for the skin permeation of nicotine from these TDS's. Furthermore, the hairless rat skin used in this investigation appears to be an acceptable skin model for studying the permeation kinetics of nicotine across the human cadaver skin.

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