DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 19(20), 2765-2793 (1993)

Transdermal Nicotine Delivery Systems: Multi-institutional Cooperative Bioequivalence Studies

Senshang Lin and Yie W. Chien

Controlled Drug-Delivery Research Center, College of Pharmacy, Rutgers University, Piscataway, NJ 08855-0789, USA.

Wen-Chu Huang, Chau-Hsian Li, and Chin-Ling Chueh

Mackay Memorial Hospital, Taipei, Taiwan.

Russel Rhei-Long Chen

School of Pharmacy, National Taiwan University, Taipei, Taiwan.

Te-Man Hsu and Tsang-Shann Jiang

Sintong Chemical Industrial Co., Ltd., Taoyuan, Taiwan.

Jhili Wu and Kirti H. Valia

TBS Laboratories, Inc., Piscataway, NJ 08854, USA.

ABSTRACT

Nicotine transdermal delivery systems (nicotine-TDSs) have been evaluated clinically and found to provide effective assistance to smokers in

* To whom all the correspondences should be directed.

Controlled Drug-Delivery Research Center

Rutgers University, College of pharmacy

P.O. Box 789, Frelinghuysen Road

Piscataway, New Jersey 08855-0789

U.S.A.

smoking cessation with minimal occurrence of withdrawal symptoms. However, substantial skin reactions have been reported with the four nicotine-TDSs marketed recently. To reduce the skin reactions, a new type of nicotine-TDS has been recently developed. In vitro skin permeation studies demonstrated that this nicotine-TDS yields a constant skin permeation profile with a rate of permeation across the human cadaver skin comparable to the steady-state permeation rates attained by Habitrol™ and Nicoderm® systems. Clinical studies completed in two ethnic groups have demonstrated that this newly-developed nicotine-TDS is clinically effective and has yielded minimal skin irritation. As part of technical transfer program, a clinical study was initiated in 18 non-obese non-smoking Taiwanese, using Latin-square design, to compare the systemic bioavailability and pharmacokinetic profile of nicotine delivered transdermally from the nicotine-TDSs fabricated at technology licensee (Sintong nicotine-TDS) in comparison with that from the technology developer (TBS nicotine-TDS), using one marketed nicotine-TDS (Habitrol™ system) as the reference product. In vitro release and skin permeation studies of nicotine from the nicotine-TDSs manufactured at both licensor and licensee were found similar in kinetic profiles and comparable in rates. Since the patch size of these nicotine-TDSs studied was smaller than the marketed product used (10 cm^2 for both Sintong and TBS nicotine-TDSs, versus 20 cm^2 for Habitrol™ system), the daily doses of nicotine delivered to the volunteers are equivalent between Sintong and TBS nicotine-TDSs [9.58 (± 2.23) vs. 8.76 (± 1.88) mg/day/patch] but are lower than that from Habitrol™ system [15.13 (± 4.05) mg/day/patch]. Thus, for the statistical analysis of the pharmacokinetic parameters obtained need to be corrected for the difference in patch size and daily nicotine dose delivered. The results of statistical analysis suggested that Sintong and TBS nicotine-TDSs are bioequivalent to Habitrol™ system.

INTRODUCTION

Due to the undesirable effects of smoking on human health and clean environment, various methods have been devised to help smokers to quit

smoking. Among these, nicotine replacement therapy has been considered as the most efficient method for the reduction of tobacco craving by substantially minimizing withdrawal syndromes [1]. Nicotine replacement therapy has even been regarded as the first effective treatment, as a smoking cessation aid, for the appropriately motivated and properly instructed smokers [2]. Four nicotine-releasing transdermal delivery systems (nicotine-TDSs), which are designed to achieve the transdermal controlled delivery of nicotine over a 24-hr or 16-hr period, have recently received regulatory approval for marketing in the United States as an effective and safe treatment for smoking cessation [3-6]. The results obtained clinically have documented that these nicotine-TDSs can provide effective assistance to smokers in smoking cessation with minimal occurrence of withdrawal symptoms. However, substantial skin reactions have been reported with these marketed nicotine-TDSs [7-10].

To reduce the skin reactions, a new generation of nicotine-TDS, which also releases a counterirritant, has been recently developed [11]. Study was performed to compare the nicotine-TDS fabricated at the technology licensee (Sintong Chemical Industrial Co., Ltd.) with that from the technology developer (TBS Laboratories, Inc.), using a marketed nicotine-TDS (Habitrol™ system) as the reference product. In Vitro skin permeation studies demonstrated that this newly-developed nicotine-TDS yields a constant skin permeation profile of nicotine across the human cadaver skin with a rate [0.068 (± 0.003) mg/cm^2/hr] [12], which is comparable to the steady-state skin permeation rates from Nicoderm® system [0.072 (± 0.006) mg/cm^2/hr] and Habitrol™ system [0.071 (± 0.002) mg/cm^2/hr] investigated under the identical experimental conditions [13]. Clinical studies, which were performed first in USA [14] and then in Taiwan [15], demonstrated that this new nicotine-TDS is clinically effective and has yielded minimal skin irritation. Pharmacokinetic treatment of the plasma nicotine profiles generated in two ethnic groups and statistical analysis suggested that there is no demographic effect [12].

As part of technical transfer program, a bioequivalence study was initiated in 18 non-obese non-smoking Taiwanese. In this report, the results

of in vitro kinetic studies and clinical bioequivalence evaluations of these nicotine-TDSs will be discussed.

MATERIALS AND METHODS

Materials

The newly-developed nicotine-TDS, which is a multi-laminate adhesive-type transdermal nicotine delivery system having nicotine and counterirritant dispersed in the adhesive polymer [11], used in this series of investigations was fabricated by TBS Laboratories, Inc. (Piscataway, NJ) and by Sintong Chemical Industrial Co., Ltd. (Taoyuan, Taiwan), respectively, using the same formulation, identical process and similar equipment. For comparative studies, Habitrol™ system, which was used as the reference product, was obtained through Hurtado Health Center (New Brunswick, NJ) and also investigated using the same study protocol. Nicotine, as the reference standard, was purchased from Sigma Chemical Co. (St. Louis, MO). Na_2HPO_4, KH_2PO_4, and NaCl, used for the preparation of isotonic phosphate buffer system, were reagent grade and used as obtained from Fisher Scientific (Fair Lawn, NJ).

In Vitro Kinetic Studies

In Vitro skin permeation kinetics - The skin permeation system used for studying the skin permeation kinetics of nicotine was consisted of the hydrodynamically well-calibrated Valia-Chien (V-C) skin permeation cell [16], fabricated by Crown Glass Co. (Somerville, NJ), and synchronous driving assembly, engineered by Canton Industrial Co. (Edison, NJ). A circulating water bath (Model 80, Fisher Scientific, Fair Lawn, NJ) was used to provide temperature control for the water-jacketed V-C permeation cell.

Analytical instrument - HP-1090M assembly (Hewlett-Packard, Atlanta, GA) was the HPLC system used for the assay of nicotine. It consisted of diode-array detector and ODS Hypersil C_{18} column (5μm; 2.1 mm x 100 mm).

In Vitro permeation studies - The same experimental procedure and conditions reported earlier [13] were also used in this investigation.

In brief, the left posterior leg skin of male human cadaver (donor: JL092192, 43 years old) was first defrosted at room temperature for 10 min and then thawed in distilled water (20°C) for another 10 min to remove preservatives. The skin specimen was cut into pieces (3.5 by 3.5 cm^2 each) and unit of nicotine-TDS was applied onto the stratum corneum surface of the skin and then mounted individually between the half-cells of the V-C permeation cell, which was thermostated at body temperature by circulating water (37°C) through the water jacket. The receptor half-cell of each V-C cell was filled with 3.3 ml of isotonic phosphate buffer solution (pH 7.4), which was stirred by a starhead-shape magnet rotating at 600 rpm. Samples (300 μl each) were taken from the receptor solution at predetermined intervals and nicotine concentrations in the samples were assayed by HPLC method outlined later.

Dissolution studies - For studying the release kinetics of nicotine from the nicotine-TDSs, the in vitro dissolution method [17] modified from USP apparatus II by the Center for Drug Evaluation and Research, Food and Drug Administration (Rockville, MD) was used. Briefly, six units of tested nicotine-TDSs, following the removal of the protective release liner, were each sandwiched between a set of nickel-chromium wire gauze (Fisher Scientific, Springfield, NJ) and watch gauze glass (with its drug-releasing surface facing gauze) and clamped together by 3 pieces of plastic clips. The gauze-TDS-glass set was each carefully positioned (with the gauze side facing up and the glass side facing down) at the center bottom of the dissolution vessel, which contained 900 ml of a prewarmed distilled water (32°C) each. Lower down the paddles to a fixed position above the gauze-TDS-glass set and rotate them at a speed of 50 rpm. Samples (5 ml each) were taken at predetermined time intervals and the nicotine concentration in the samples were assayed by HPLC method outlined below.

Analytical methods - Concentrations of nicotine in the samples taken from the receptor solution or dissolution medium were determined by injecting a volume of sample (15 μl of the receptor solution or 8 μl of the dissolution medium into a reverse-phase HPLC outlined above. The detector was set at wavelength of 260 nm, while a combination of phosphate buffer (pH 7.4), methanol and acetonitrile (45:27.5:27.5 for permeation samples, 40:30:30 for dissolution samples) was used as the mobile phase. Under such condition, a well-separated peak was detected at the retention time of 1.3 min with the sensitivity of 5 μg/ml.

Clinical Studies

Subject's information - The studies were conducted at Mackay Memorial Hospital (Taipei, Taiwan) in a group of 16 subjects (9 females and 7 males, two other subjects dropped out of the studies). The mean value (± SD) of age and body weight of the subjects were 24.8 (± 2.3) years (ranging from 22 to 32) and 57.3 (± 8.4) kg (ranging from 50 to 80), respectively.

All subjects had a normal medical history and were in good health (confirmed by physical examination and appropriate laboratory testing of blood and urine before participation). Criteria for exclusion include: history of cardiovascular diseases, diabetes mellitus, peptic ulcer, liver or kidney disorder, skin allergies or other skin diseases, and current pregnancy or breast feeding.

Crossover studies - In order to evaluate the possible effect of the crossover of treatment periods as well as the changeover of treatments, the subjects were divided into six groups (n = 3 each) and each group of subjects was enrolled into the treatment from one period to the next. Therefore, the study design has the form of two 3 x 3 Latin squares (Table I).

The study protocol designed was approved for the protection of human subjects by the Institutional Review Board of Mackay Memorial Hospital and Department of Health. Before initiation of the study, written informed

Table I. The experimental design in the clinical studies of three nicotine-TDSs in six subject groups following three treatment periods

Treatment period	Latin square 1			Latin square 2		
	Subject group[a]					
	1	2	3	4	5	6
1	A	B	C	A	C	B
2	B	C	A	C	B	A
3	C	A	B	B	A	C

a. Treatment A: One Sintong nicotine-TDS [22.01 (± 1.01) mg/patch, 10 cm^2]; one-time application for 24 hours.
Treatment B: One TBS nicotine-TDS [22.40 (± 1.71) mg/patch, 10 cm^2]; one-time application for 24 hours.
Treatment C: One Habitrol™ system (34.98 (± 1.01) mg/patch, 20 cm^2]; one-time application for 24 hours.

consent was obtained from each subject prior to participation. The subjects were randomly assigned to one of six groups. And, each group of subjects was subjected to, using a different sequence of treatments, the following three treatments:

Treatment A: One unit of Sintong nicotine-TDS for 24 hour;

Treatment B: One unit of TBS nicotine-TDS for 24 hour;

Treatment C: One unit of Habitrol™ system for 24 hour.

All treatment were carried out in a 6-day restricted inpatient environment. The nicotine-TDS was applied onto the skin in the upper chest region and removed after treatment for 24 hours. During the course of study, serial blood samples (5 ml each), based on the study protocol designed, were withdrawn from the superficial forearm vein of each subject at 0, 2, 4, 6, 8, 10, 12, 24 and 48 hours for each single-dose treatment and collected into the pre-chilled heparinized glass tubes. Samples were centrifuged immediately following collection (10 min at 2500 rpm) and plasma samples were each immediately separated and stored in a freezer (at -20°C). A 24-hr washout

period was incorporated between two treatments, since the half-life of nicotine is around 2-3 hours.

Assay of Plasma Samples - The assay of nicotine and its major metabolite, cotinine, was conducted at University of California, Division of Clinical Pharmacology and Experimental Therapeutics (UCSF, San Francisco, California, USA) by a capillary gas chromatographic method [18]. Briefly, the procedure consisted of spiking the plasma samples (1.0 ml each) with internal standards and then recovering nicotine and cotinine by a 3-step extraction procedure. An aliquot of the extracts was injected into a gas chromatograph (GC) equipped with an automatic sampler, a split-splitless injection port, a fused silica capillary column (0.32 mm by 25 m) and a nitrogen-phosphorous detector. The detection limits were calibrated and found to be 0.5 ng/ml for nicotine and 5 ng/ml for cotinine. The inter-day and intra-day variabilities were determined and found to have a mean coefficient of variation of 1.1-7.8% for nicotine (1-100 ng/ml) and of 0.8-9.5% for cotinine (10-1000 ng/ml). Assay specificity was verified by comparing the data with those determined by GC-MS.

Assay of Residual Nicotine in Used Patches - All used nicotine-TDS patches were returned in original packages to Sintong Chemical Industrial Co., Ltd. for nicotine residue assay. Residual nicotine content in the used patches was first extracted into methanol and then analyzed by gas chromatograph (Hewlett Packard HP-5890 II) following standard method [14].

Data Treatments

Pharmacokinetic analysis - The plasma nicotine concentration-time profiles resulted from the transdermal delivery of nicotine from each of the three nicotine-TDSs were submitted to pharmacokinetic treatment to obtain the values of the following pharmacokinetic parameters:

1) C_{max}: peak plasma nicotine concentration;

2) t_{max}: time to reach the peak plasma nicotine concentration;

3) AUC: area under the plasma concentration-time curves calculated by trapezoidal rule.

Model fitting analysis - A general dynamic mathematical model, which was developed to describe the plasma concentration profile of drug following transdermal delivery, was applied for the modeling and analysis of plasma nicotine data generated in the clinical studies of three nicotine-TDSs to determine the pharmacokinetic parameters. The following equations have been derived to describe the concentration profiles of nicotine in the central compartment using one-compartment open model with transdermal continuous infusion of nicotine from the nicotine-TDSs:

(1) for absorption phase and plateau steady-state phase

$$C(t) = \frac{R_i}{VK_e}(1 - e^{-K_e t}) \quad (1)$$

(2) for elimination phase

$$C(t) = \frac{R_i}{VK_e}(1 - e^{-K_e T})\, e^{-K_e (t-T)} \quad (2)$$

where C is the plasma concentration of nicotine in central compartment; R_i is the rate constant for nicotine infusion; K_e is the first-order rate constant for elimination; V is the volume of distribution in central compartment; t is the time after patch application; and T is the total duration of patch application.

Using this one-compartment open model, the plasma data determined experimentally can be fitted with the theoretical line calculated from Equations (1) and (2) and the values of R_i/V and K_e are thus computed. Thereafter, the elimination half-life ($t_{1/2}$) and plasma nicotine concentration at steady state (C_{ss}) could be calculated from K_e and/or R_i/V values.

Statistic Analysis

The student t-test was used to determine the statistical significance of each pharmacokinetic parameter, which was obtained from the

pharmacokinetic treatment of plasma nicotine concentration profile, among the nicotine-TDSs. The effects of variation in the applications periods and treatment sequences of nicotine-TDSs on the transdermal bioavailability and pharmacokinetics of nicotine were assessed statistically.

RESULTS AND DISCUSSION

Skin Permeation Kinetics

The skin permeation kinetics of nicotine delivered by the nicotine-TDSs was investigated using the left posterior leg skin of human cadaver. The results indicated that nicotine delivered from both Sintong and TBS nicotine-TDSs permeate through the human cadaver skin at a permeation profile which can be well described by the zero-order kinetics (Figure 1). This constant skin permeation has been followed throughout the 30-hr skin permeation study ($r^2 \geq 0.99$). A skin permeation rate of 0.047 (± 0.003) mg/cm^2/hr was obtained for Sintong nicotine-TDS and 0.049 (± 0.003) mg/cm^2/hr for TBS nicotine-TDS, which are essentially no difference statistically ($P > 0.05$). The results indicate that Sintong and TBS nicotine-TDSs are equivalent kinetically, in addition to being pharmaceutically equivalent in system design and composition.

The skin permeation kinetics of nicotine from Habitrol™ system was also investigated under identical conditions. The results are also plotted in Figure 1, which show that the nicotine delivered from Habitrol™ system yields a biphasic permeation profile with fast rate for the initial 10 hours and slower rate at steady state. The initial rate of skin permeation is almost two times higher than that at steady state [$(Q/t)_i$ = 0.092 (± 0.003) and $(Q/t)_{ss}$ = 0.053 (± 0.001) mg/cm^2/hr]. The permeation profiles obtained here are in agreement with the observations reported in the literature [12,13]. The steady-state rate of permeation for nicotine delivered by Habitrol™ system [0.053 mg/cm^2/hr] is statistically no difference from those attained by Sintong and TBS nicotine-TDSs ($P > 0.02$). Therefore, Sintong and TBS nicotine-

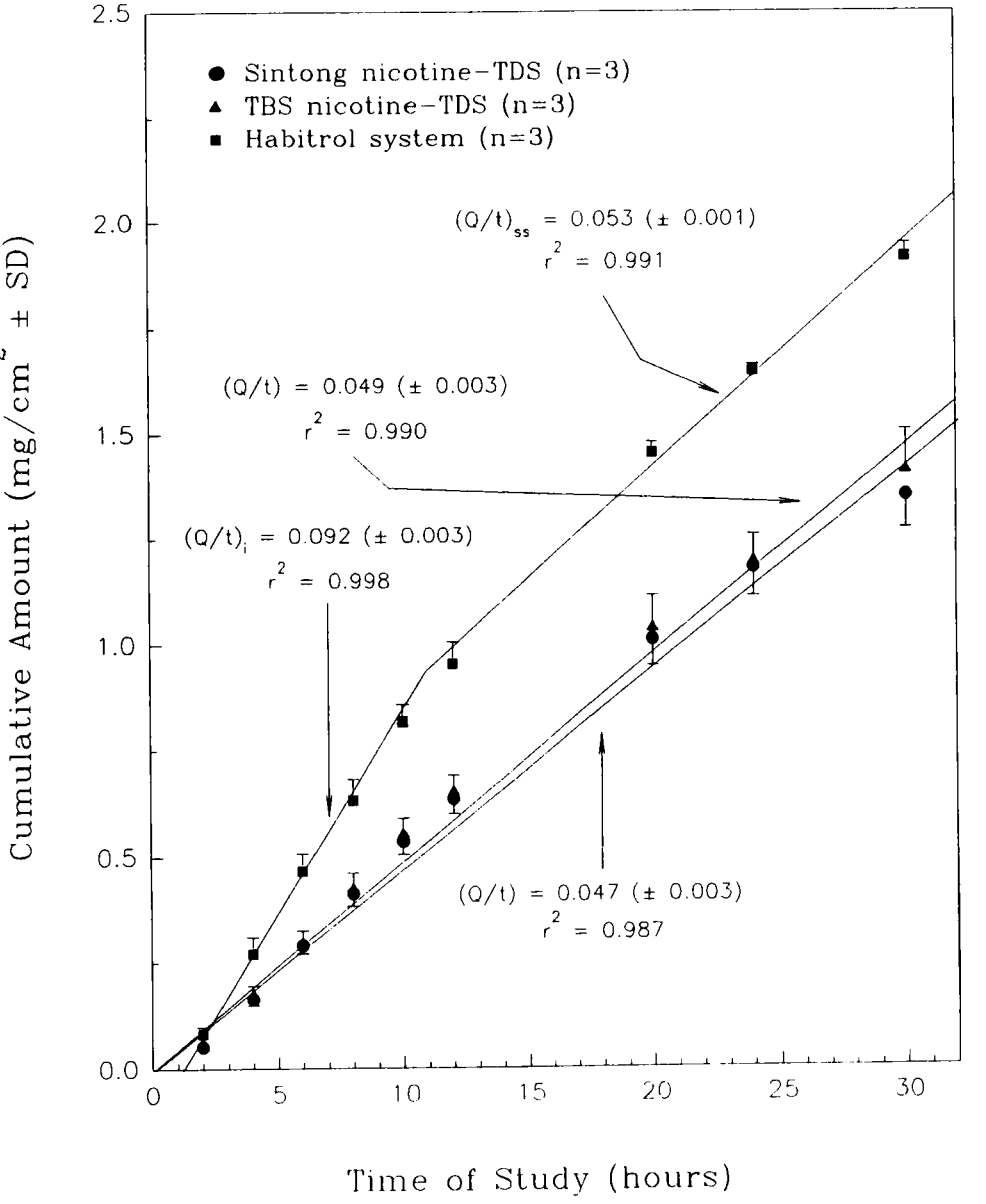

FIGURE 1

Comparative skin permeation profiles of nicotine delivered from the three nicotine-TDSs (n =3 each) through human cadaver skin.

TDSs are considered equivalent, kinetically, to Habitrol™ system at steady state.

Dissolution Kinetics

In order to gain a better insight into the mechanisms underlying the controlled release of nicotine from the nicotine-TDS and its role on the transdermal systemic delivery of nicotine, the release kinetics of nicotine was investigated. The results in Figure 2A indicate that all three nicotine-TDSs release nicotine gradually, at a nonlinear manner, throughout the course of 24-hr dissolution study. The release profiles of nicotine from all three nicotine-TDSs appear to follow the polymer matrix diffusion-controlled process [19]. As reported previously [12,13], a biphasic Q vs. $t^{1/2}$ relationship was also obtained in this investigation for all nicotine-TDSs (Figure 2B). The relationship can be presented mathematically [19] as follow:

$$Q = Rt^{1/2} \tag{3}$$

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

$$R = [\,(2A - C_p)\,C_p D_p\,]^{1/2} \tag{4}$$

where A is the initial loading of nicotine; C_p is the solubility of nicotine in the adhesive polymer; D_p is the diffusivity of nicotine in the polymer matrix. Nicotine was released from Sintong, TBS and Habitrol™ nicotine-TDSs, respectively, at initial release flux of 11.12 (± 0.92), 10.44 (± 0.46) and 8.86 (± 0.40) $\%/hr^{1/2}$ for the first 4 hours, which shifted to a lower rate of 1.25 (± 0.23), 1.36 (± 0.09) and 1.93 (± 0.13) $\%/hr^{1/2}$ for the remaining 20 hours. It is interesting to note that the release flux of nicotine from nicotine-TDSs at the initial state $[(Q/t^{1/2})_i]$ follows the order of: Sintong ≥ TBS > Habitrol™, while a reverse order is observed at steady state $[(Q/t^{1/2})_{ss}]$: Habitrol™ > TBS ≥ Sintong. The observed shifting phenomenon could be attributed to the

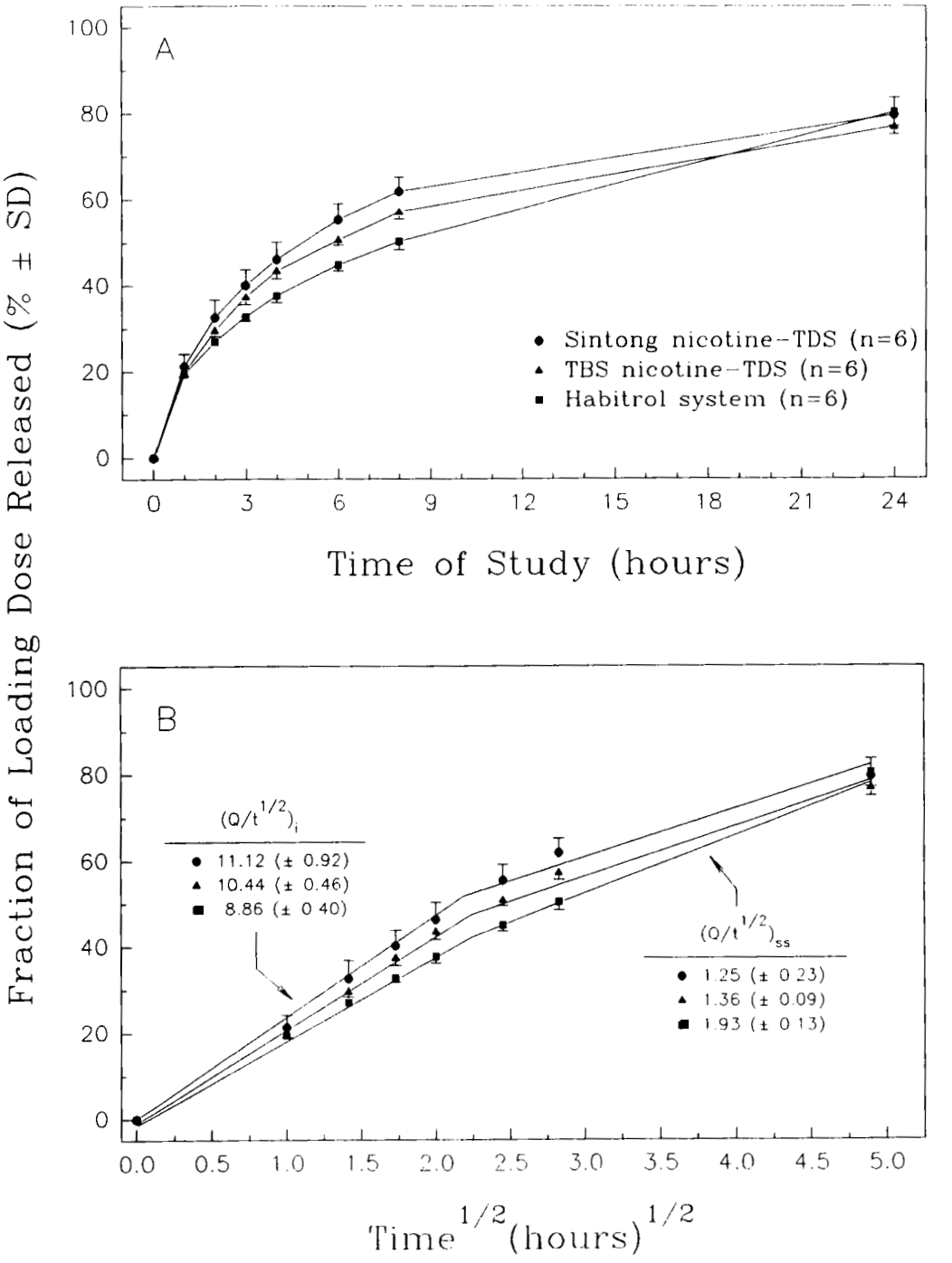

FIGURE 2
Cumulative release profile of nicotine from the three nicotine-TDSs (n = 6 each) as a function of time (A) and square root of time (B).

reduction in the loading dose of nicotine in drug reservoir compartment to a level having a significant effect on the magnitude of $(2A - C_p)^{1/2}$ (Equation 4). Statistical analysis, by student t-test, of the release fluxes of nicotine indicated that the differences between Sintong and TBS nicotine-TDSs is statistically insignificant ($P > 0.05$), but the different between Sintong nicotine-TDS and Habitrol™ system as well as between TBS nicotine-TDS and Habitrol™ system are statistically significant ($P < 0.001$).

Correlation of Skin Permeation with Release Kinetic

The release of nicotine from Sintong and TBS nicotine-TDSs, both are multi-laminate adhesive-type nicotine-TDS, appears to be controlled solely by adhesive polymer matrix diffusion process (Figure 2B). The observation of constant skin permeation profiles (Figure 1) is an indication that the skin permeation of nicotine, following the release of nicotine-TDS, is still controlled by the transport through the non-sink stratum corneum, which acts as a rate-limiting permeation barrier for the systemic delivery of nicotine, after its release to the surface of stratum corneum.

Clinical Evaluation

The plasma concentration profiles of nicotine in 16 Taiwanese volunteers following the transdermal delivery of nicotine from Sintong and TBS nicotine-TDSs (both are 10 cm^2 each) and Habitrol™ system (20 cm^2 are compared in Figure 3. As reported previously [20], plateau levels were attained within 6 hours of nicotine-TDS application and maintained throughout the course of 24-hr application. These plasma profiles are analyzed pharmacokinetically to calculate the pharmacokinetic parameters for each nicotine-TDS and statistically to determine the statistical significance of the following factors:

1) System-to-System bioequivalence: To study the bioequivalence in the systemic bioavailability and transdermal pharmacokinetics of nicotine among Sintong, TBS and Habitrol™ nicotine-TDSs in all groups of subjects.

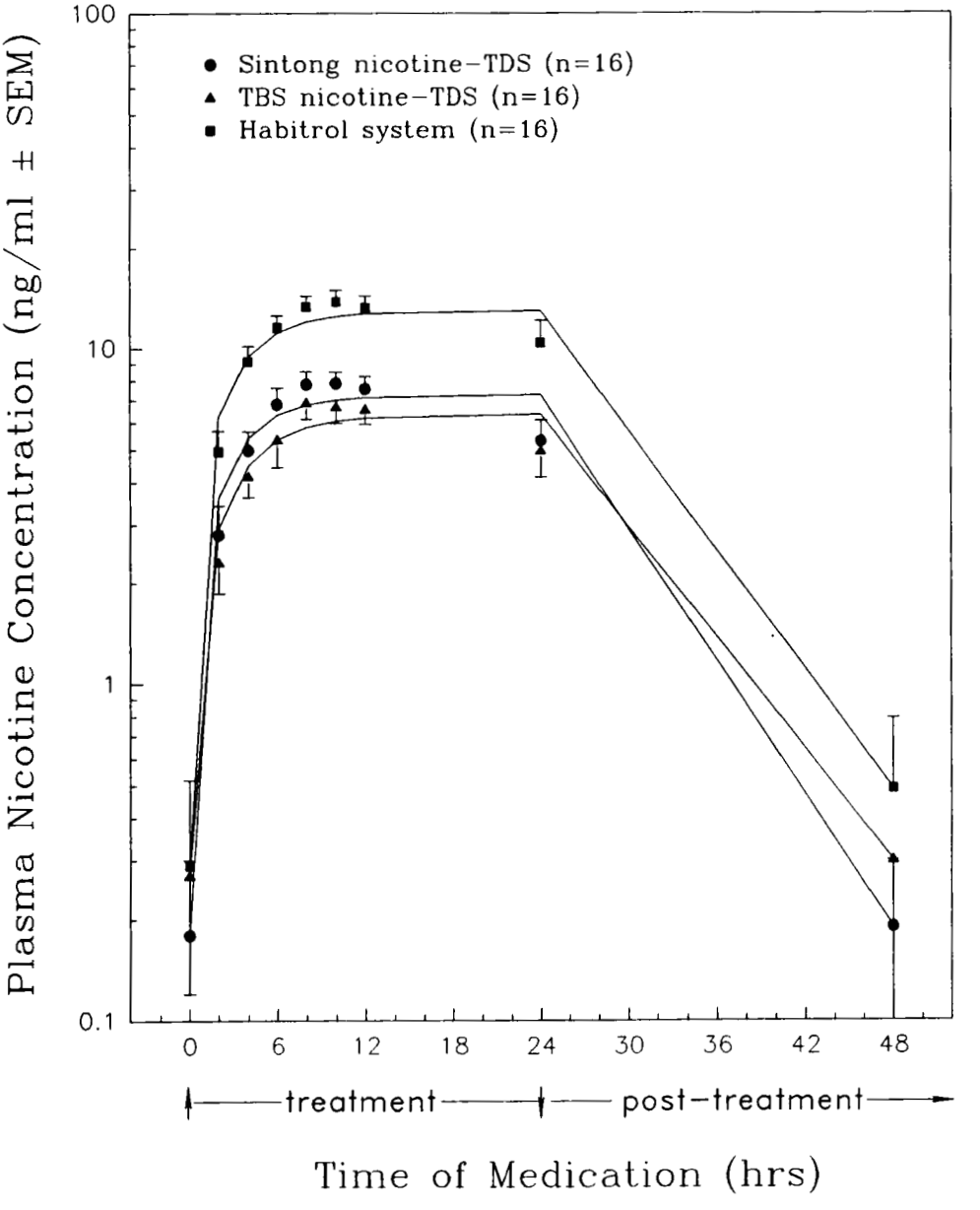

FIGURE 3

Comparative plasma profiles of nicotine in human volunteers (n = 16) during and after the 24-hr topical application of three nicotine-TDSs.

2) Period-to-Period variability: To investigate any effect of variation in the treatment periods for each nicotine-TDS on the systemic bioavailability and transdermal pharmacokinetics of nicotine in various groups treated with the same nicotine-TDS.

System-to-System Bioequivalence

Nicotine Pharmacokinetic Profiles - The results in Figure 3 indicate that the plasma concentration profiles of nicotine attained by the transdermal delivery of nicotine from all three nicotine-TDSs appear to be adequately described pharmacokinetically by the one-compartment open model, since most of the experimental data points, except three data sets, correlate well with the theoretical line calculated from Equations (1) and (2) with a correlation coefficient (r) of greater than 0.92. The pharmacokinetic parameters obtained by pharmacokinetic treatment are outlined in Table II (sections A and B). The results of statistical analysis suggest that the differences in pharmacokinetic parameters are statistically insignificant ($P > 0.2$) between Sintong and TBS nicotine-TDSs, but the differences in the values of C_{max}, $AUC^{0\rightarrow 24}$, R_i/V, C_{ss} and D_0 are significant ($P < 0.01$) between Sintong nicotine-TDS and Habitrol™ system as well as between TBS nicotine-TDS and Habitrol™ system (Table II-G). The higher mean values of C_{max}, $AUC^{0\rightarrow 24}$, R_i/V and C_{ss} observed for Habitrol™ system than for Sintong and TBS nicotine-TDSs can be attributed to the higher daily dose (D_0) of nicotine (15.13 vs. 9.58 and 8.76 mg/day/patch) delivered from the larger patch size for Habitrol™ (20 cm^2) than from other two nicotine-TDSs (10 cm^2). Hence, it makes good sense scientifically to correct the dose- and patch size-dependent pharmacokinetic parameters, such as C_{max}, AUC, R_i/V and C_{ss}, for the difference in patch size and daily dose delivered among these nicotine-TDSs (Table II, sections D and E). Statistical analysis, using student t-test, of all the corrected pharmacokinetic parameters indicated that except the values of $R_i/V/D_0$ and D_0/Area, the differences among all other parameters

Table II: Comparison in systemic bioavailability and pharmacokinetic parameters of nicotine delivered transdermally to Taiwanese volunteers (n = 16) from three nicotine-TDSs

	Sintong nicotine-TDS	TBS nicotine-TDS	Habitrol® system
A. Pharmacokinetic Parameters:			
C_{max} (ng/ml ± SEM)	8.86 (0.84)	7.66 (0.84)	15.58 (1.59)
t_{max} (hr ± SEM)	10.1 (1.1)	9.9 (1.0)	11.0 (1.4)
AUC(0→24) (ng/ml•hr ± SEM)	212.46 (22.04)	190.50 (23.98)	391.04 (44.43)
B. Model Fitting Parameters:			
C_{ss}(8→24) (ng/ml ± SEM)	7.20 (0.81)	5.89 (0.76)	13.72 (1.49)
R_i/V (ng/hr/ml ± SEM)	2.303 (0.325)	1.898 (0.229)	4.723 (0.651)
K_e (hr^{-1} ± SEM)	0.344 (0.047)	0.346 (0.039)	0.361 (0.046)
$t_{½}$ (hr ± SEM)	2.7 (0.5)	2.7 (0.6)	2.7 (0.6)
r	0.919	0.930	0.931
C. Daily Nicotine Dose Delivered:			
D_0 (mg/day/patch ± SD)	9.58 (2.23)	8.76 (1.88)	15.13 (4.05)
D. Parameters Normalized by Daily Nicotine Dose:			
C_{max}/D_0 (day•patch/ml x 10^{-6} ± SEM)	0.950 (0.100)	0.893 (0.109)	1.087 (0.148)
C_{ss}(8→24)/D_0 (day•patch/ml x 10^{-6} ± SEM)	0.823 (0.116)	0.721 (0.122)	0.969 (0.145)
AUC(0→24)/D_0 (day•patch•hr/ml x 10^{-6} ± SEM)	23.25 (3.00)	22.65 (3.45)	27.82 (4.37)
$R_i/V/D_0$ (day•patch/hr/ml x 10^{-6} ± SEM)	0.245 (0.027)	0.215 (0.018)	0.301 (0.032)
E. Parameters Normalized by Patch Size:			
D_0/Area (mg/cm^2/day/patch ± SEM)	0.958 (0.056)	0.876 (0.047)	0.757 (0.051)
C_{max}/Area (ng/ml/cm^2 ± SEM)	0.886 (0.084)	0.766 (0.084)	0.779 (0.080)
C_{ss}(8→24)/Area (ng/ml/cm^2 ± SEM)	0.720 (0.081)	0.589 (0.076)	0.686 (0.074)
AUC(0→24)/Area (ng/ml/cm^2•hr ± SEM)	21.25 (2.20)	19.05 (2.40)	19.55 (2.22)
R_i/V/Area (ng/hr/ml/cm^2 ± SEM)	0.230 (0.032)	0.190 (0.023)	0.236 (0.033)
F. In Vivo Delivery Rate vs Systemic Input Rate:			
D_0/Area/hr (µg/cm^2/hr ± SEM)	39.92 (2.33)	36.51 (1.96)	31.53 (2.11)
R_i/Area (µg/cm^2/hr ± SEM)	33.77 (5.00)	29.02 (4.42)	35.85 (5.35)

G. Statistic analysis

	t	p	t	p	t	p	t	p	t	p	t	p
	C_{max}		t_{max}		AUC(0→24)		R_i/V		K_e		C_{ss}	
Sintong vs TBS	1.018	0.317	0.173	0.864	0.704	0.487	1.032	0.311	-0.035	0.972	1.182	0.248
Sintong vs Habitrol®	-3.739	<0.001*	-0.510	0.614	-3.624	<0.001*	-3.183	0.004*	-0.268	0.791	-3.692	<0.001*
TBS vs Habitrol®	-4.418	<0.001*	-0.670	0.508	-4.013	<0.001*	-3.989	<0.001*	-0.257	0.799	-4.596	<0.001*
	D_0		C_{max}/D_0		AUC(0→24)/D_0		$R_i/V/D_0$		C_{ss}(8→24)/D_0		D_0/Area	
Sintong vs TBS	1.120	0.272	0.391	0.699	0.143	0.887	0.966	0.342	0.605	0.550	1.120	0.272
Sintong vs Habitrol®	-4.806	<0.001*	-0.770	0.448	-0.918	0.360	-1.300	0.204	-0.774	0.445	2.673	0.012*
TBS vs Habitrol®	-5.711	<0.001*	-1.064	0.296	-0.841	0.407	-2.316	0.028*	-1.304	0.202	1.734	0.093
	C_{max}/Area		AUC(0→24)/Area		R_i/V/Area		C_{ss}(8→24)/Area		D_0/Area/hr		R_i/Area	
Sintong vs TBS	1.017	0.317	0.674	0.505	1.032	0.311	1.182	0.248	1.120	0.271	0.714	0.481
Sintong vs Habitrol®	0.926	0.362	0.541	0.592	-0.126	0.900	0.309	0.759	2.674	0.012*	-0.281	0.781
TBS vs Habitrol®	-0.116	0.908	-0.154	0.879	-1.152	0.258	-0.914	0.368	1.734	0.093	-0.977	0.337

Note 1:
- C_{max}: peak plasma nicotine concentration
- t_{max}: time to reach the peak plasma nicotine concentration
- C_{ss}: steady-state plasma concentration observed during the plateau (steady state) period (8 to 24 hours)
- AUC(0→24): area under the plasma concentration-time curves calculated by trapezoidal rule from 0 to 24 hr
- R_i: nicotine input rate constant, V: volume of distribution, the R_i/V ratio was obtained from model fitting
- K_e: elimination rate constant obtained from model fitting
- $t_{½}$: elimination half-life (calculated from K_e)
- r: correlation coefficient of fitting
- D_0: daily nicotine dose delivered from each nicotine-TDS
- Area: size of patch (10 cm^2 for both Sintong and TBS nicotine-TDSs, 20 cm^2 for Habitrol® system)

Note 2:
a. Statistic analysis was performed using student t-test.
b. t: t value of student t-test
c. p: probability value of student t-test
d. * presents a significant difference of student t-test ($P < 0.05$).

are statistically insignificant ($P > 0.05$) (Table II-G). The difference in the $R_i/V/D_0$ values between TBS nicotine-TDS and Habitrol™ system are statistically significant ($P < 0.05$). And, the difference in the D_0/Area values between Sintong nicotine-TDS and Habitrol™ system are statistically significant ($P < 0.05$).

The assay of residual nicotine content in the used patches has provided the results on the amount of nicotine delivered to the skin from the nicotine-TDS, during the course of 24-hr topical application. The data in Table II-F indicate that the In vivo delivery rate of nicotine (D_0/Area/hr) from Sintong nicotine-TDS [39.92 (± 2.33) $\mu g/cm^2/hr$] is very much the same as those of TBS nicotine-TDS and Habitrol™ system [36.51 (± 1.96) and 31.53 (± 2.11) $\mu g/cm^2/hr$, respectively]. Statistical analysis, using student t-test, indicated that the difference in D_0/Area/hr between Sintong nicotine-TDS and Habitrol™ system is statistically significance ($P < 0.05$), while the differences between Sintong and TBS nicotine-TDSs as well as between TBS nicotine-TDS and Habitrol™ system are not statistically significant ($P > 0.05$) (Table II-G).

By dividing the value of R_i/V by the drug-releasing area of nicotine-TDS, and taking the volume of distribution [2.6 (± 0.9) l/kg] reported in the literature [20] and the body weight of each subject participating in this investigation into account, the systemic input rate of nicotine from the nicotine-TDS (R_i/Area) could be estimated. The data obtained (Table II-F) indicate that the systemic input rate of nicotine from Sintong nicotine-TDS [33.73 (± 5.00) $\mu g/cm^2/hr$] is very much the same as those of TBS nicotine-TDS and Habitrol™ system [29.02 (± 4.42) and 35.85 (± 5.35) $\mu g/cm^2/hr$, respectively], and the difference in the R_i/Area values among the nicotine-TDSs is not statistically significant ($P > 0.05$).

Cotinine Pharmacokinetic Profiles - Cotinine is the major inactive metabolite of nicotine and has a half-life of 16.9-22.7 hours [21]. The plasma profiles of cotinine following three nicotine-TDSs are compared in Figure 4,

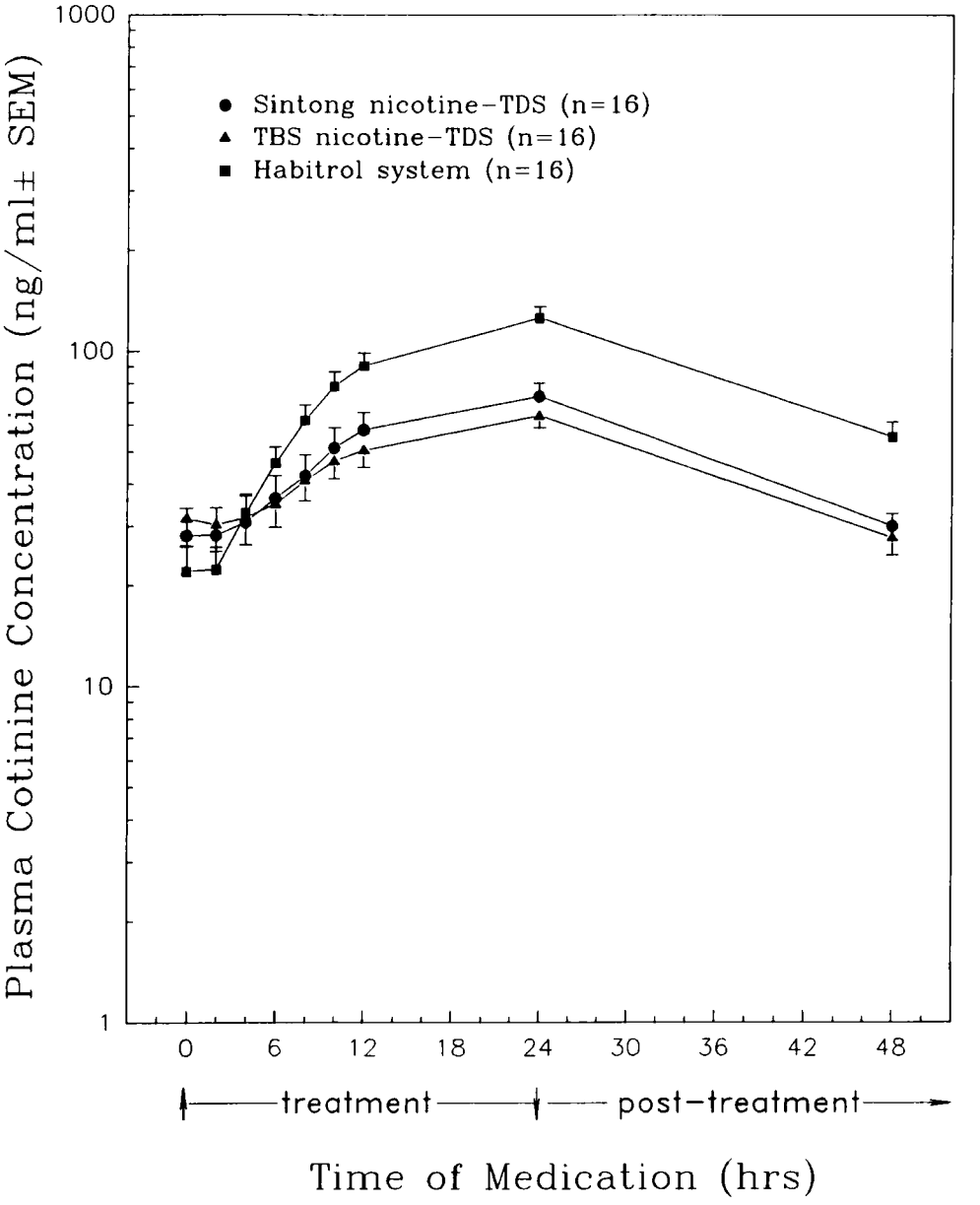

FIGURE 4

Comparative plasma profiles of cotinine, the major metabolite of nicotine, in human volunteers (n = 16) during and after the transdermal delivery of nicotine from three nicotine-TDSs applied topically for 24 hours.

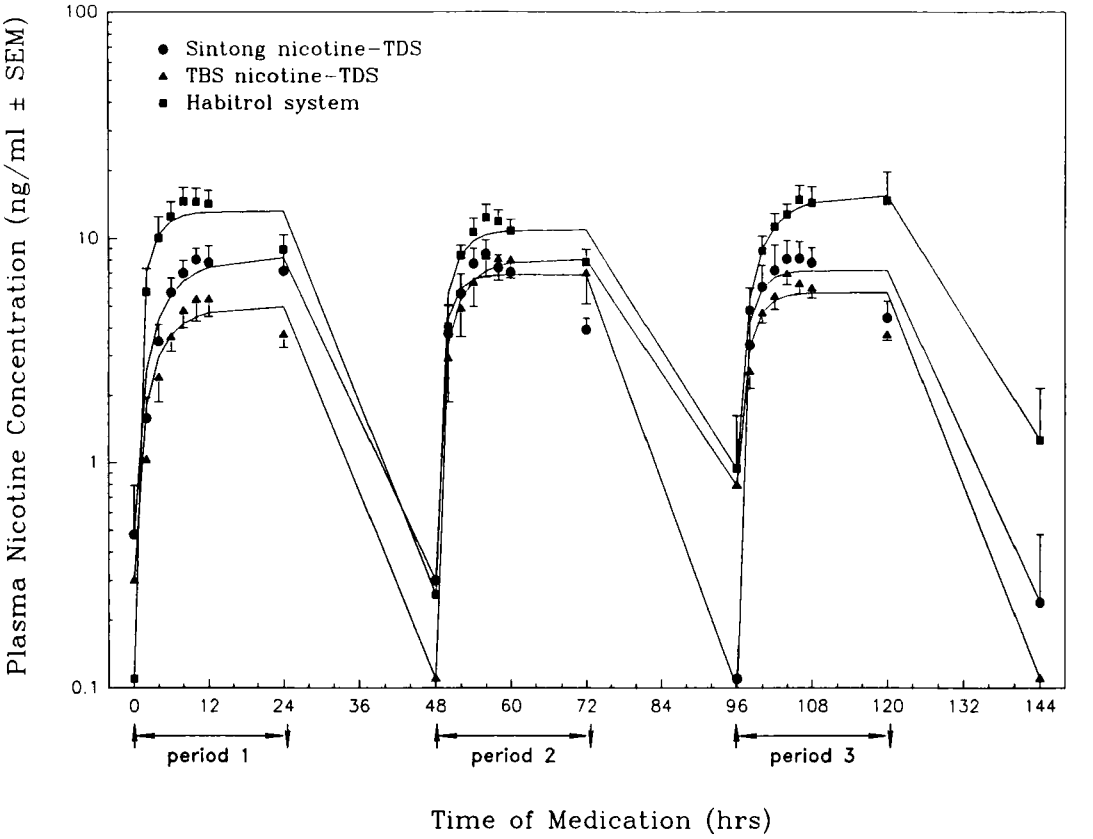

FIGURE 5
Comparative plasma profiles of nicotine in human volunteers (n = 5-6 per period) during and after three treatment periods of 24-hr topical application of three nicotine-TDSs, in sequence, by Latin square design.

which indicate that higher levels of cotinine were attained by Habitrol™ system than by Sintong and TBS nicotine-TDSs, even though the baseline levels among the three groups of subjects, during the pretreatment period, are statistically no difference. As expected, the difference in the plasma profiles of cotinine produced by Sintong and TBS nicotine-TDSs is statistically insignificant ($P > 0.05$).

Period-to-Period Variability

Effect of variation in the treatment periods for each nicotine-TDS has been evaluated and is discussed as follows:

Table III. Effect of variation in the treatment periods for each nicotine-TDS on transdermal pharmacokinetics of nicotine in Taiwanese volunteers (n = 5-6 per system)

1. Sintong nicotine-TDS

	1st period	2nd period	3rd period
A. Pharmacokinetic Parameters:			
C_{max} (ng/ml ± SEM)	9.00 (1.60)	8.88 (1.24)	8.68 (1.76)
t_{max} (hr ± SEM)	12.7 (2.3)	8.4 (1.0)	8.8 (1.0)
AUC(0-24) (ng/ml•hr ± SEM)	240.50 (49.18)	186.89 (20.49)	204.37 (36.97)
B. Model Fitting Parameters:			
C_{ss}(8-24) (ng/ml ± SEM)	8.39 (1.73)	6.63 (1.02)	5.98 (0.49)
R_i/V (ng/hr/ml ± SEM)	1.786 (0.333)	3.072 (0.928)	2.311 (0.360)
K_e (hr^{-1} ± SEM)	0.231 (0.044)	0.454 (0.093)	0.402 (0.092)
$t_{\frac{1}{2}}^{e}$ (hr ± SEM)	3.8 (1.0)	1.8 (0.5)	2.0 (0.3)
r	0.942	0.900	0.905
C. Daily Nicotine Dose Delivered:			
D_0 (mg/day/patch ± SD)	8.62 (1.43)	10.36 (1.24)	9.95 (1.21)
D. Parameters Normalized by Daily Nicotine Dose:			
C_{max}/D_0 (day•patch/ml x 10^{-6} ± SEM)	1.069 (0.233)	0.856 (0.087)	0.902 (0.158)
C_{ss}(8-24)/D_0 (day•patch/ml x 10^{-6} ± SEM)	1.001 (0.250)	0.708 (0.086)	0.669 (0.110)
AUC(0-24)/D_0 (day•patch•hr/ml x 10^{-6} ± SEM)	28.69 (7.12)	18.37 (1.81)	21.62 (3.64)
$R_i V/D_0$ (day•patch/hr/ml x 10^{-6} ± SEM)	0.202 (0.029)	0.317 (0.078)	0.239 (0.010)
E. In Vivo Delivery Rate vs Systemic Input Rate:			
D_0/Area/hr ($\mu g/cm^2$/hr ± SEM)	35.93 (1.79)	43.16 (5.16)	41.46 (5.05)
R_i/Area ($\mu g/cm^2$/hr ± SEM)	24.68 (4.89)	44.13 (11.49)	37.05 (10.35)

F. Statistic analysis

	t	p	t	p	t	p	t	p	t	p	t	p
	C_{max}		t_{max}		AUC(0-24)		R_i/V		K_e		C_{ss}	
1st vs 2nd period	0.054	0.958	1.556	0.154	0.896	0.394	-1.525	0.166	-2.422	0.042*	0.763	0.467
1st vs 3rd period	0.036	0.895	1.404	0.194	0.568	0.584	-1.043	0.328	-1.869	0.099	1.099	0.304
2nd vs 3rd period	0.098	0.925	-0.283	0.785	-0.352	0.734	0.764	0.474	0.396	0.706	0.578	0.584
	D_0		C_{max}/D_0		AUC(0-24)/D_0		$R_i/V/D_0$		D_0/Area/hr		R_i/Area	
1st vs 2nd period	-1.430	0.187	0.791	0.449	1.268	0.237	-1.596	0.149	-0.799	0.447	-1.776	0.136
1st vs 3rd period	-1.112	0.295	0.566	0.585	0.841	0.422	-0.980	0.360	-0.792	0.451	-1.211	0.261
2nd vs 3rd period	0.236	0.820	-0.254	0.806	-0.733	0.485	0.989	0.361	-0.212	0.839	0.458	0.663

(continued)

Sintong nicotine-TDS - The plasma concentration profiles of nicotine attained by the transdermal delivery of nicotine from Sintong nicotine-TDS following three separate periods of 24-hr treatment (with 5-6 subjects per period) are shown in Figure 5. All three sets of nicotine plasma data appear to be adequately described by the one-compartment open model used, since most of the experimental data points, except two data sets, correlate well with the theoretical line calculated from Equations (1) and (2). The results of pharmacokinetic treatment are outlined in Table III-1. Statistical analysis, by student t-test, of all the pharmacokinetic parameters indicated that except the values of K_e, there is no statistically-significant difference ($p > 0.05$) among

Table III. (continued)

2. IBS nicotine-TDS

	1st period	2nd period	3rd period
A. Pharmacokinetic Parameters:			
C_{max} (ng/ml ± SEM)	5.60 (1.04)	9.68 (1.81)	7.00 (0.65)
t_{max} (hr ± SEM)	10.0 (0.8)	11.3 (2.6)	8.3 (0.3)
AUC(0-24) (ng/ml•hr ± SEM)	141.12 (18.75)	253.37 (54.95)	160.53 (11.98)
B. Model Fitting Parameters:			
C_{ss}(8-24) (ng/ml ± SEM)	4.87 (0.77)	7.58 (2.69)	5.77 (0.49)
R_i/V (ng/hr/ml ± SEM)	1.349 (0.212)	1.952 (0.470)	2.425 (0.342)
K_e (hr^{-1} ± SEM)	0.282 (0.036)	0.350 (0.128)	0.414 (0.032)
$t_{\frac{1}{2}}$ (hr ± SEM)	2.6 (0.3)	4.0 (2.2)	1.7 (0.2)
r	0.941	0.930	0.919
C. Daily Nicotine Dose Delivered:			
D_0 (mg/day/patch ± SD)	8.28 (0.73)	8.54 (1.00)	9.31 (0.67)
D. Parameters Normalized by Daily Nicotine Dose:			
C_{max}/D_0 (day•patch/ml x 10^{-6} ± SEM)	0.658 (0.074)	1.190 (0.248)	0.752 (0.047)
C_{ss}(8-24)/D_0 (day•patch/ml x 10^{-6} ± SEM)	0.578 (0.046)	1.072 (0.441)	0.622 (0.039)
AUC(0-24)/D_0 (day•patch•hr/ml x 10^{-6} ± SEM)	16.89 (0.97)	31.76 (8.19)	17.39 (1.04)
$R_i/V/D_0$ (day•patch/hr/ml x 10^{-6} ± SEM)	0.161 (0.017)	0.239 (0.019)	0.256 (0.024)
E. In Vivo Delivery Rate vs Systemic Input Rate:			
D_0/Area/hr ($\mu g/cm^2$/hr ± SEM)	34.50 (3.06)	35.59 (4.16)	38.78 (2.81)
R_i/Area ($\mu g/cm^2$/hr ± SEM)	18.68 (2.81)	31.79 (12.05)	37.30 (5.81)

F. Statistic analysis

	t	p	t	p	t	p	t	p	t	p	t	p
	C_{max}		t_{max}		AUC(0-24)		R_i/V		K_e		C_{ss}	
1st vs 2nd period	-1.703	0.127	-0.408	0.694	-1.628	0.142	-0.669	0.525	-0.272	0.793	-0.770	0.467
1st vs 3rd period	-1.217	0.258	2.169	0.062	-1.032	0.332	-2.341	0.047*	-2.683	0.028*	-1.042	0.328
2nd vs 3rd period	1.404	0.191	1.160	0.273	1.635	0.133	-1.312	0.222	-0.967	0.359	0.529	0.609
	D_0		C_{max}/D_0		AUC(0-24)/D_0		$R_i/V/D_0$		D_0/Area/hr		R_i/Area	
1st vs 2nd period	-0.190	0.854	-1.690	0.130	-1.473	0.179	-1.151	0.287	0.217	0.834	-0.726	0.491
1st vs 3rd period	-1.004	0.346	-1.137	0.288	-0.479	0.645	-2.931	0.019*	-1.004	0.345	-1.331	0.216
2nd vs 3rd period	-0.635	0.540	1.744	0.117	1.735	0.113	-1.185	0.266	-1.110	0.296	-0.833	0.424

(continued)

all the other pharmacokinetic parameters when one treatment period is compared to another (Table III-1-F), with or without correcting the difference in daily nicotine dose delivered.

The data in Table III-1-E indicate that with the exception of the first treatment period, both systemic input rates in the second and third periods agree well with their correspondent in vivo delivery rates of nicotine from Sintong nicotine-TDS (Table III-1-E). The low correlation observed in the first period of treatment may be attributed to the difference in the volume of distribution between this group of subjects and that reported in the literature. However, statistical analysis, using student t-test, indicated that the difference

Table III. (continued)

3. Habitrol system

	1st period	2nd period	3rd period
A. Pharmacokinetic Parameters:			
C_{max} (ng/ml ± SEM)	15.90 (2.05)	12.92 (1.78)	17.86 (4.22)
t_{max} (hr ± SEM)	9.3 (1.0)	9.2 (0.8)	14.8 (3.8)
AUC(0→24) (ng/ml•hr ± SEM)	378.73 (51.56)	311.14 (31.59)	485.71 (121.74)
B. Model Fitting Parameters:			
C_{ss}(8→24) (ng/ml ± SEM)	13.67 (1.71)	10.89 (1.14)	16.62 (4.10)
R_i/V (ng/hr/ml ± SEM)	5.586 (1.263)	4.196 (0.652)	4.215 (1.381)
K_e (hr^{-1} ± SEM)	0.401 (0.080)	0.379 (0.035)	0.297 (0.113)
$t_{\frac{1}{2}}$ (hr ± SEM)	2.3 (0.6)	1.9 (0.2)	4.1 (1.6)
r	0.910	0.928	0.961
C. Daily Nicotine Daily Nicotine Dose:			
D_0 (mg/day/patch ± SD)	18.17 (2.07)	13.92 (0.42)	12.71 (1.03)
D. Parameters Normalized by Dose Delivered:			
C_{max}/D_0 (day•patch/ml x 10^{-6} ± SEM)	0.888 (0.067)	0.930 (0.124)	1.482 (0.428)
C_{ss}(8→24)/D_0 (day•patch/ml x 10^{-6} ± SEM)	0.775 (0.079)	0.784 (0.079)	1.388 (0.416)
AUC(0→24)/D_0 (day•patch•hr/ml x 10^{-6} ± SEM)	21.64 (2.64)	22.29 (1.95)	40.78 (12.39)
$R_i/V/D_0$ (day•patch/hr/ml x 10^{-6} ± SEM)	0.288 (0.050)	0.300 (0.043)	0.317 (0.081)
E. In Vivo Delivery Rate vs Systemic Input Rate:			
D_0/Area/hr ($\mu g/cm^2$/hr ± SEM)	37.84 (4.32)	29.00 (0.87)	26.48 (2.15)
R_i/Area ($\mu g/cm^2$/hr ± SEM)	47.51 (10.79)	29.36 (4.78)	28.34 (9.00)

F. Statistic analysis

	t	p	t	p	t	p	t	p	t	p	t	p
	C_{max}		t_{max}		AUC(0→24)		R_i/V		K_e		C_{ss}	
1st vs 2nd period	1.060	0.317	0.101	0.921	0.985	0.351	0.892	0.396	0.200	0.846	1.287	0.230
1st vs 3rd period	-0.452	0.662	-1.509	0.166	-0.880	0.402	0.715	0.493	0.740	0.478	-0.710	0.496
2nd vs 3rd period	-1.078	0.313	-1.433	0.190	-1.379	0.205	-0.010	0.991	0.692	0.508	-1.345	0.215
	D_0		C_{max}/D_0		AUC(0→24)/D_0		$R_i/V/D_0$		D_0/Area/hr		R_i/Area	
1st vs 2nd period	1.829	0.101	-0.340	0.742	-0.303	0.769	-0.229	0.824	1.829	0.100	1.431	0.186
1st vs 3rd period	2.207	0.055	-1.520	0.163	-1.684	0.126	-0.323	0.754	2.207	0.055	1.328	0.217
2nd vs 3rd period	1.087	0.309	-1.239	0.250	-1.469	0.180	-1.154	0.882	1.088	0.308	0.100	0.923

Note 1:

C_{max}: peak plasma nicotine concentration
t_{max}: time to reach the peak plasma nicotine concentration
C_{ss}: steady-state plasma concentration observed during the plateau (steady state) period (8 to 24 hours)
AUC(0→24): area under the plasma concentration-time curves calculated by trapezoidal rule from 0 to 24 hr
R_i: nicotine input rate constant, V: volume of distribution, the R_i/V ratio was obtained from model fitting
K_e: elimination rate constant obtained from model fitting
$t_{\frac{1}{2}}$: elimination half-life (calculated from K_e)
r: correlation coefficient of fitting
D_0: daily nicotine dose delivered from each nicotine-TDS
Area: size of patch (10 cm^2 for both Sintong and TBS nicotine-TDSs, 20 cm^2 for Habitrol™ system)

Note 2:

a. Statistic analysis was performed using student t-test.
b. t: t value of student t-test
c. p: probability value of student t-test
d. * presents a significant difference of student t-test ($P < 0.05$).

in D_0/Area/hr and R_i/Area values between any two of the treatment periods are not statistically significant ($P > 0.05$) (Table III-1-F).

The plasma profiles of cotinine, the major metabolite of nicotine, are also compared graphically in Figure 6.

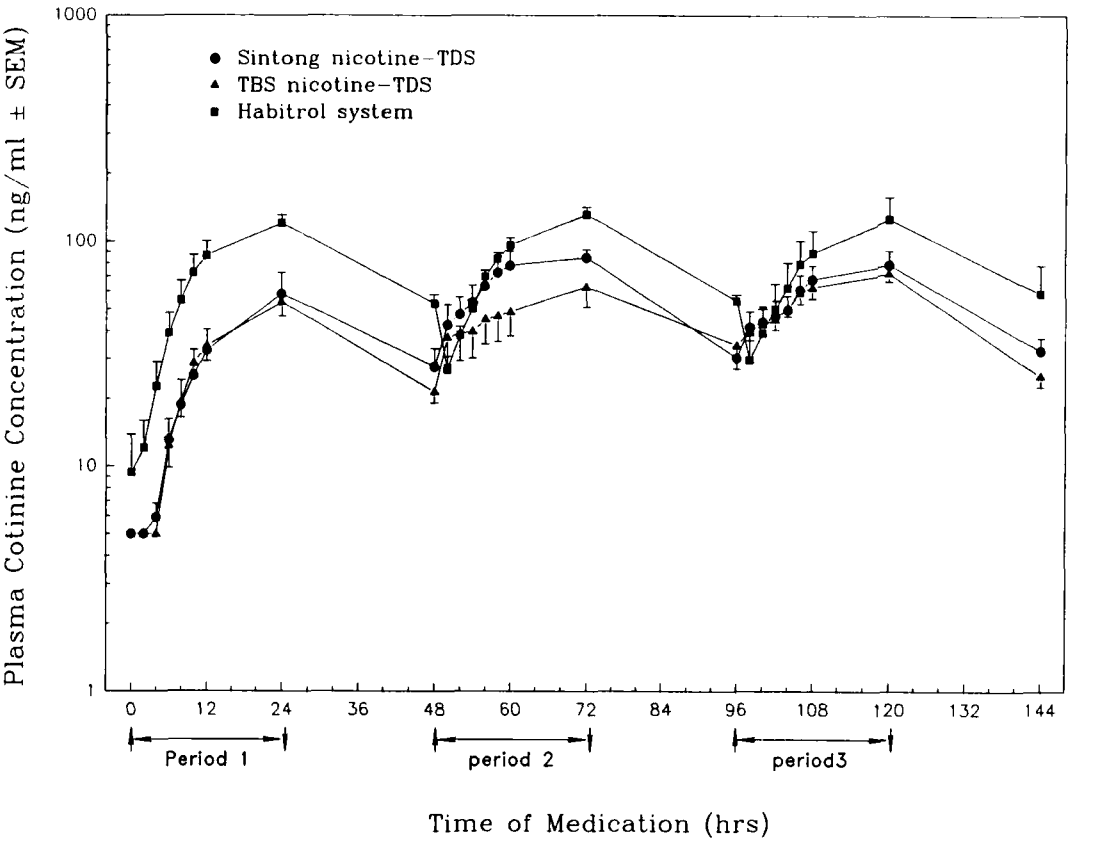

FIGURE 6

Comparative plasma profiles of cotinine, the major metabolite of nicotine, in human volunteers (n = 5-6 per period) during and after the transdermal delivery of nicotine from three nicotine-TDSs, each applied topically for 24 hours, in three treatment periods.

TBS nicotine-TDS - The plasma concentration profiles of nicotine attained by the transdermal delivery of nicotine from TBS nicotine-TDS following three separate periods of 24-hr treatment (with 5-6 subjects per period) are also shown in Figure 5. As observed for Sintong nicotine-TDS, all three sets of nicotine plasma data are adequately described by the one-compartment open model used, since most of the experimental data points, except one data set, correlate well with the theoretical line calculated from Equations (1) and (2). The results of pharmacokinetic treatment are outlined

in Table III-2. Statistical analysis, by student t-test, of all the pharmacokinetic parameters indicated that except the values of K_e, R_i/V and $R_i/V/D_0$, which are significant difference ($p < 0.05$) between 1st and 3rd periods of treatment, there is no statistically-significant difference ($p > 0.05$) among all the other pharmacokinetic parameters when one treatment period is compared to another (Table III-2-F), with or without correcting the difference in daily nicotine dose delivered.

The data in Table III-2-E indicate that with the exception of the first treatment period, both systemic input rates in the second and third periods agree well with their correspondent in vivo delivery rate of nicotine from TBS nicotine-TDS. However, statistical analysis, using student t-test, indicated that the difference in D_0/Area/hr and R_i/Area values between any two of the treatment periods are not statistically significant ($P > 0.05$) (Table III-2-F). The results are similar to the observation for Sintong nicotine-TDS (Table III-1-E).

The plasma profiles of cotinine, the major metabolite of nicotine, are also compared graphically in Figure 6.

Habitrol™ system - The plasma concentration profiles of nicotine attained by the transdermal delivery of nicotine from Habitrol™ system following three separate periods of 24-hr treatment (with 5-6 subjects per period) are also shown in Figure 5. As observed for Sintong and TBS nicotine-TDSs, all three sets of the nicotine plasma data are adequately described by the one-compartment open model used, since most of the experimental data points correlate well with the theoretical line calculated from Equations (1) and (2). The results of pharmacokinetic treatment are outlined in Table III-3. Statistical analysis, by student t-test, of all the pharmacokinetic parameters indicated that the differences in all the pharmacokinetic parameters between the treatment periods are statistically insignificant ($p > 0.05$) (Table III-3-F).

The data in Table III-3-E indicate that with the exception of the first treatment period both systemic input rates in the second and third period

agree well with their correspondent in vivo delivery rate of nicotine from Habitrol™ system (Table III-3-E). However, statistical analysis, using student t-test, indicated that the difference in D_0/Area/hr and R_i/Area values between any two of the treatment periods are not statistically significant ($P > 0.05$) (Table III-3-F). It is interesting to note that the results are similar to the observations for Sintong and TBS nicotine-TDSs (Tables III-1-E and III-2-E).

The plasma profiles of cotinine, the major metabolite of nicotine, are also compared graphically in Figure 6.

Skin Irritation Evaluation

The most common skin irritation associated with the use of marketed nicotine-TDSs is a mild short-lived erythema, pruritus, or burning at the site of patch application. In this clinical investigation, the average reported ratings of local erythema and edema for Sintong and TBS nicotine-TDSs, using a 4-point scale [none = 0, mild = 1, moderate = 2 and severe = 3], were found to have a primary irritation index (PII) of 0.13. This PII score is lower than that (PII = 0.69) of Habitrol™ system.

CONCLUSION

In summary, the transdermal pharmacokinetic profiles of nicotine delivered by three nicotine-TDSs evaluated were found to be adequately described by a one-compartment pharmacokinetic model with the transdermal continuous infusion of nicotine. Since the patch size of these nicotine-TDSs used in the clinical study were different (10 cm^2 for both Sintong and TBS nicotine-TDSs, but 20 cm^2 for Habitrol™ system) and thus, a variation in the daily dosage of nicotine delivered was observed [9.58 (± 2.23) mg/day/10 cm^2 for Sintong nicotine-TDS, 8.76 (± 1.88) mg/day/patch for TBS nicotine-TDS, and 15.13 (± 4.05) mg/day/patch for Habitrol™ system]; Therefore, some of the pharmacokinetic parameters obtained need to be corrected for the difference in patch size or daily dosage delivered. The results of statistical

analysis of these pharmacokinetic parameters suggested that Sintong nicotine-TDS and TBS nicotine-TDS are bioequivalent to one another, kinetically and pharmacokinetically; Furthermore, both nicotine-TDSs are pharmacokinetically bioequivalent to Habitrol™ system, an FDA- approved NDA product, even though they are different in system design and composition [12,13].

The variation in the periods of treatment with the same nicotine-TDS has produced no statistically-significant effect on most of the pharmacokinetic parameters determined.

The plasma concentration profiles of nicotine and its major metabolite, cotinine, attained by Sintong and TBS nicotine-TDSs are very similar, since they are pharmaceutically equivalent (They have the same patch size and identical system composition). This bioequivalence study has provided scientific evidence to demonstrate that the nicotine-TDS fabricated by Sintong, the technology licensee, is equivalent to that fabricated by TBS, the technology developer.

The plasma profiles achieved and maintained by both Sintong and TBS nicotine-TDSs can be increased to a level equivalent to Habitrol™ system by properly adjusting the patch size used from 10 cm^2 to, for example, 20 cm^2 as for Habitrol™ system.

ACKNOWLEDGMENT

The authors wish to express their appreciation to Sintong Chemical Industrial Co., Ltd. for their funding support of this multi-institutional cooperative clinical evaluation.

REFERENCES

1. T. Abelin, A. Buehler, Ph. Muller, K. Vesanen, and P.R. Imhof, Lancet, 1, 7-10 (1989).

2. M.J. Jarvis, M. Raw, M.A.H. Russell, and C. Feyerabend, Br. Med. J., 285, 537-540 (1982).

3. R.D. Hurt, G.G. Lauger, K.P. Offord, T.E. Kottke, and L.C. Dale, Mayo Clin. Proc., 65, 1529-1537 (1990).

4. J.E. Rose, E.D. Levin, F.M. Behm, C. Adivi, and C. Schur, Clin. Pharmacol. Ther., 47, 323-330 (1990).

5. Transdermal Nicotine Study Group from the Centers for Disease Control, JAMA, 266, 3133-3134 (1991).

6. J. Foulds, J. Stapleton, C. Feyerabend, C. Vesey, M. Jarvis, and M.A.H. Russell, Psychopharmacology, 106, 421-427 (1992).

7. Nicoderm® (nicotine transdermal system) product information, Marion Merell Dow, 1991.

8. Habitrol™ (nicotine transdermal system) product information, Ciba-Geigy, 1992.

9. Prostep™ (nicotine transdermal system) product information, Lederle, 1992.

10. Nicotrol™ (nicotine transdermal system) product information, Parke-Davis, 1992.

11. U.S. patent application pending (TBS Laboratories, Inc.).

12. S.S. Lin, H. Ho and Y.W. Chien, Development of a new nicotine transdermal delivery system: in vitro kinetic studies and clinical pharmacokinetic evaluations in two ethnic groups, J. Control. Rel. (in press)

13. H. Ho and Y.W. Chien, Drug Develop. Ind. Pharm., 19, 295-313 (1993).

14. J.D. Lane, E.C. Westman, G.V. Ripka, J. Wu, C.C. Chiang and J.E. Rose, Pharmacokinetics of a transdermal nicotine patch compared to nicotine gum, Drug Develop. Ind. Pharm. (in press)

15. H.S. Lin, T.M. Hsu, T.S. Jiang, and R.C. Chen, Pharmacokinetics and clinical studies of a transdermal nicotine patch, presented at 1992 int'l. symposium on "Biomedical Engineering in The 21st Century" Taipei, Taiwan, September 23-26, 1992.

16. Y.W. Chien and K.H. Valia, Drug Develop. Ind. Pharm., 10, 575-599 (1984).

17. N.W. Tymes, V.P. Shah, and J.P. Skelly, J. Pharm. Sci., 79, 601-602 (1990).

18. P. Jacob III, M. Wilson, and N.L. Benowitz, J. Chromatogr., 222, 61-70 (1981).

19. Y.W. Chien, Transdermal controlled systemic medications, Dekker, New York (1987), chapter 2.

20. K.J. Palmer, M.M. Buckley and D. Faulds, Drugs, 44, 498-529 (1992).

21. A.G. Gilman, T.W. Rall, A.S. Nies, and P. Taylor, Goodman and Gilman's the pharmacological basis of therapeutics, 8th edition, Pergamon press, New York (1990), p 1696.