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DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY®
Vol. 29, No. 8, pp. 843–853, 2003

RESEARCH PAPER

Acrylic Matrix Type Nicotine Transdermal Patches: In Vitro Evaluations and Batch-to-Batch Uniformity

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ABSTRACT

Nicotine transdermal patches (NTPs) were fabricated using an acrylic pressure sensitive adhesive emulsion to form a transparent matrix film. An automated thin layer chromatography (TLC) plate scraper was used to control the thickness of the cast nicotine matrix film. The in vitro release behavior and permeation of nicotine across abdominal human epidermis (HE) from the NTPs was studied using United States Pharmacopeia (USP) dissolution apparatus 5 (paddle over disk) and modified Franz-diffusion cell, respectively. The release of nicotine from the NTPs showed a good linear correlation with the square root of time ($R^2 > 0.99$). This indicated a matrix diffusion controlled-release mechanism. The surface morphology of the matrix of the NTP was uniform and nonporous before and after release, indicating that the dried adhesive nicotine matrix was a homogeneous single-phase film. Neither the nicotine content in the range 4.70–8.41% w/w nor the film thicknesses of the NTPs affected the apparent diffusion coefficient of nicotine in the acrylic matrix. A good relationship between the amount of nicotine permeated across the HE and the square root of time was also observed with $R^2 > 0.98$. This study also showed that the NTPs provided a good delivery system with more than 65% of the nicotine delivery being controlled by the device. Moreover, the release of nicotine from six production batches met the criteria of USP 24. This finding presented a good potential of this method for upscaling to industrial manufacturing.

Key Words: Nicotine transdermal patch; Adhesive matrix; In vitro release and skin permeation; Rate control; Batch-to-batch uniformity.

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DOI: 10.1081/DDC-120024180
0363-9045 (Print); 1520-5762 (Online)

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INTRODUCTION

Transdermal drug delivery systems (TDDS) can be classified into two types: membrane controlled and matrix systems.[1] Drug release from membrane-controlled TDDS is relatively constant as long as the drug solution in the reservoir remains saturated. In the case of a matrix TDDS, the release rate of the drug decreases with time, as the drug in the skin-contacting side of the matrix is depleted.[2] However, systems using monolithic adhesive matrices are particularly interesting due to the ease of fabrication and the lack of dose dumping which was experienced when the membrane type was employed.[3]

Nicotine transdermal patches (NTPs) are used for smoking cessation therapy. They can deliver and maintain plasma concentrations of nicotine needed for up to 24 h. Two types of NTPs, membrane and monolithic matrix, were studied by Ho and Chien.[4] Polyacrylate adhesive polymers are most widely used as a matrix film for fabricating TDDS.[5–10] Particularly, emulsion-type acrylate polymers can be used for transdermal delivery of hydrophilic drugs that are not soluble in conventional adhesive solutions.[11]

In vitro evaluations of TDDS typically include characterizing drug permeation across a membrane such as human skin and drug release from the device. In vitro skin permeation studies are used to investigate the rate and amount of the drug permeating across the skin into a receptor compartment. On the other hand, in vitro release testing is commonly used as a quality control test to characterize the TDDS and is applied not only to assure batch-to-batch uniformity of drug release but also to support scale-up and postapproval changes.[12] The data obtained from both in vitro tests can be integrated to evaluate the degree of rate control of the TDDS, which was demonstrated by Guy and Hadgraft.[13]

In this work, we report the in vitro release and skin permeation of nicotine from NTPs formulated using acrylic, pressure-sensitive, adhesive emulsion to form the polymer matrix. Moreover, the reproducibility of nicotine released from these NTPs was also investigated as specified in United States Pharmacopeia (USP) 24.[14]

MATERIALS AND METHODS

Materials

Acrylic, pressure-sensitive, adhesive emulsion (Acrylax®-1061) and siliconized paper were a gift from Neoplast Co., Ltd., Patumthani, Thailand. Polyolefin backing membrane (CoTran®™ #9722) was a gift from 3 M Pharmaceuticals (St. Paul, MN), Methanol, HPLC grade, and (−)-Nicotine (purity ≥99%) were purchased from Baker Inc. (Phillipsburg, NJ), and Fluka (Buchs, Switzerland), respectively. Other reagents used were of analytical grade and used as received.

Nicotine Transdermal Patches (NTPs)

Preparation of NTP

Six formulations of NTPs, the compositions of which shown in Table 1, were prepared for the tests. For each preparation, nicotine was dispersed and evenly mixed with acrylic, pressure-sensitive, adhesive emulsion (solid content 55% w/w) in a glass tube. The mixture was centrifuged at 3000 rpm for 10 min so as to remove air bubbles and then poured on a sheet (15 × 15 cm) of polyolefin backing membrane that had been fixed onto a clean glass plate. The mixture was evenly cast using an automatic TLC plate scraper (Model 022.1602, Camag, Muttenz, Switzerland), which was preadjusted for a fixed gap between the scraper and the backing membrane (Table 1). The film was dried at 50°C for 2 hr and then covered with siliconized paper. The sheets of dried nicotine adhesive laminates were wrapped in aluminum foil and stored at 8°C in a refrigerator. For a batch-to-batch uniformity testing, a fixed size of 15 × 55 cm of each batch would be prepared.

Determination of Nicotine Content

A 1-cm diameter NTP was placed into an Erlenmeyer flask, followed by 200 mL of distilled

Table 1. Formulations of nicotine transdermal patches.

Formulation	Nicotine added (g)	Acrylic PSA emulsion[a] (g)	Gap width of TLC scraper (mm)
A	1.10	34.36	1.00
B	1.50	33.64	1.00
C	2.00	32.73	1.00
D	4.00	29.09	1.00
E	1.50	33.64	0.50
F	1.50	33.64	1.50

PSA = pressure-sensitive adhesive.
[a]Solid content 55% w/w.

water and magnetically stirred for 48 hr to reach its maximal release. The solution was collected and analyzed using spectrophotometer at a wavelength of 259 nm. The total amount of nicotine released divided by the area gave the nicotine content per unit area.

Thickness of Adhesive Matrix Film

The thickness of the patch was measured using an electronic digital caliper (Model 500-136, Mitutoyo, Kawasaki, Japan). The thickness of the adhesive matrix was determined from the difference in thickness between the patch and the backing membrane plus with siliconized release liner.

The other parameter indicating the thickness of NTPs is weight/area (W/A) ratio of matrix film. The NTP was cut in a 1-cm diameter circle and weighed. The weight of the NTP minus the weight of the backing membranes and divided by area provided the W/A ratio of matrix film.

Scanning Electron Microscopic Studies

The surface morphology of the nicotine adhesive matrix film was characterized before and after release testing. Samples of the dried adhesive matrix films were mounted on aluminum stubs using a two-sided adhesive tape, gold-coated in a vacuum evaporator, and photographed using a scanning electron microscope (Jeol Model JSM-5800LV, Tokyo, Japan).

In Vitro Release Studies

A USP dissolution apparatus 5 (paddle over disk) (Hanson Research, Northridge, CA) was used to characterize nicotine released from the patches. A 3.2-cm diameter NTP, with the matrix facing up, was mounted on a 41.2-mm diameter by 3.3-mm thick stainless steel disk using two-sided adhesive tape. The release studies were performed in 900 mL of distilled water at $32^\circ \pm 0.5^\circ$C at a rotation speed of 50 rpm. Samples (7 mL) were collected and replaced with distilled water at 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, and 24 hr. The amount of nicotine released was analyzed spectrophotometrically at a wavelength of 259 nm (Spectronic 601, Hanson Research, Northridge, CA).

In Vitro Skin Permeation Studies

Preparation of Skin Membrane

Thai Human abdominal skin was obtained from a 46-year-old Thai male within 24 hr of the death. The human epidermis (HE) was taken after the whole skin had been soaked in water at 60°C for 2 min and was stored at −20°C until use. Prior to use, the HE was hydrated by soaking in pH 7.4 phosphate buffer 30 min.

In Vitro Permeation System

A 6-mL modified Franz-diffusion cell (diameter 1 cm) was used. Each of the cells was stationed in a cell-mounting block (Franz 9-cell drive console, Crown Glass Company, Somerville, NJ) having a receptor compartment that was thermostatically maintained at 37°C. The receptor medium, phosphate buffer pH 7.4, was stirred at 600 rpm. A piece of hydrated skin was mounted on the diffusion cell by facing the stratum corneum surface to the donor compartment and equilibrating for at least 20 min prior to use. Then, the nicotine patches (diameter 0.84 cm) were placed on the skin, which was fixed with an O-ring and fastened tight with a clamp. The amount of nicotine permeated was quantitated by collecting 0.4 mL samples at 1.5, 2, 4, 6, 8, 10, 12, and 24 hr. The volume of receptor fluid withdrawn was replaced with fresh phosphate buffer pH 7.4. The concentration of nicotine in the receptor compartment was analyzed by high-performance liquid chromatography (HPLC).

Analysis of Nicotine

The concentration of nicotine in the receptor fluid was determined using high performance liquid chromatography (Model LC200, Perkin Elmer, Norwalk, CT). Reversed-phase HPLC using a C-18 column (Spherisorb® ODS-2, 5 micron, 4.6×250 mm, Waters Corporation, Milford, MA) was employed. The mobile phase was 0.05 M sodium acetate:methanol (88:12 v/v) containing 0.5% triethylamine; the pH was adjusted to 4.2 with glacial acetic acid. The HPLC conditions were as follows: flow rate 1 mL/min, UV detector (Model 785A, Perkin Elmer, Norwalk, CT) at a wavelength of 259 nm, and paracetamol was the internal standard. The retention times of nicotine and paraceta-

Table 2. Characteristics of nicotine transdermal patches.

Formulation	Adhesive matrix thickness[a] (mm)	Weight/Area ratio[b] (mg/cm^2)	Nicotine content[c]	
			(mg/cm^2)	% w/w[d]
A	0.333 ± 0.0124	35.4 ± 0.67	1.66 ± 0.11	4.70
B	0.319 ± 0.0094	34.2 ± 0.61	2.11 ± 0.06	6.17
C	0.320 ± 0.0182	34.7 ± 1.10	2.94 ± 0.40	8.41
D	0.350 ± 0.0176	35.6 ± 1.50	6.03 ± 0.45	17.04
E	0.135 ± 0.0062	13.9 ± 0.13	0.84 ± 0.01	6.12
F	0.510 ± 0.0178	57.3 ± 0.97	3.66 ± 0.18	6.39

[a]Mean ± SD of 12 determinations.
[b]Mean ± SD of five determinations.
[c]Mean ± SD of three determinations.
[d]% nicotine content = (nicotine content × 100)/(weight/area ratio).

mol were approximately 5.3 and 8.4 min, respectively. Under these conditions, good linearity and reproducibility were shown over the range 1–400 μg/mL of nicotine-free base.

Statistical Analysis

The permeation/release rates for nicotine were calculated using linear regression analysis of the relationship between the nicotine permeated/released and the square root of time. Analysis of variance (SPSS program for MS Windows, release 8.0) was used to determine the significant difference between release and permeation rates of nicotine, and parameters in batch-to-batch uniformity testing, such as nicotine content and W/A ratio of matrix film and nicotine release rate.

RESULTS AND DISCUSSION

Characteristics of Nicotine Transdermal Patches (NTPs)

The characteristics of the adhesive matrix NTPs are shown in Table 2. All formulations of NTPs were colorless, transparent, and had a smooth surface. All NTPs had a unique odor characteristic of nicotine and typical adhesive properties. The thickness and W/A ratio of the nicotine adhesive matrix films demonstrated low standard deviations. This indicated good reproducibility in the production of the NTPs. Nicotine recovery from the NTPs was in the range of 82–85%. The loss of nicotine was due to its high vapor pressure and evaporation during drying process.[15] The surface morphology of the nicotine adhesive matrix film of NTP formulation B before and after release testing are shown in Figs. 1A and 1B, respectively. A rough surface was observed and no pore formation occurred after release studies, indicating that nicotine was soluble in the acrylic adhesive matrix.

In Vitro Release Characteristic of NTPs

The nicotine contents in NTPs formulations A–D were 4.70, 6.17, 8.41, and 17.04% w/w, respectively. All formulations had a thickness in the range of 0.319–0.350 mm. The release profiles of nicotine from the NTPs with various nicotine contents are presented in Fig. 2A. The nicotine released shows a good linear correlation with the square root of time ($R^2 > 0.99$) (Fig. 2B), and indicated a matrix diffusion controlled-release mechanism. The release of nicotine from the adhesive matrix can be described by Eq. (1)[7,16]:

$$M_t = 4M_\infty \left(\frac{Dt}{\pi L^2}\right)^{1/2}, \ 0 \le M_t/M_\infty < 0.6 \qquad (1)$$

where M_t is the amount of drug released at a given time, M_∞ is the amount of drug released at infinite time, D is the diffusion coefficient of the drug in the adhesive matrix, L is the thickness of the adhesive matrix, and t is the time. An approximation of the equation could be shown by plotting the cumulative amount of nicotine released per unit area and the square root of time ($t^{1/2}$) as presented by Eq. (2)

$$M_t = kt^{1/2} \qquad (2)$$

where k is the nicotine release rate.

The release parameters of nicotine from the NTP formulations A–D are summarized in Table 3. The total amount of nicotine released after 24 hr from

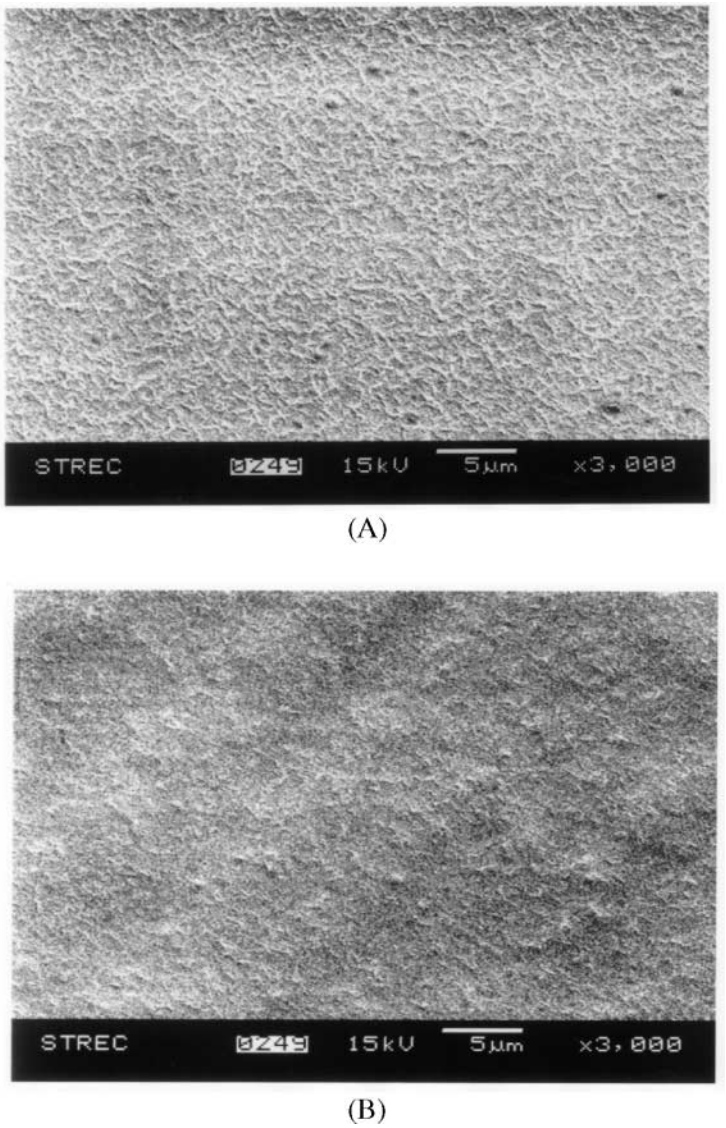

Figure 1. Scanning electron micrographs of NTP before (A) and after (B) in vitro release study.

NTPs loading various nicotine contents was about 77% of the nicotine content while the complete release (99%) was observed for the NTP formulation D. It was found that the release rate of nicotine was significantly increased ($p < 0.05$) when the nicotine content in the adhesive matrix increased. An increase in the nicotine content in the polymer matrix provided a reduction of the relative amount of polymer as a diffusional barrier. In addition, a good linear relationship between the release rate and the nicotine content in the range of 4.7–8.41% w/w was observed with R^2 higher than 0.99 (Fig. 3). However, the nicotine release from the NTP formulation D (17.04% w/w) deviated from this relationship, suggesting that the nicotine release from this formulation could not be explained by Eq. (1). This was due to the initial burst release of nicotine without the matrix controlled at the high concentration of nicotine.[7] This release behavior can be described using percolation theory. The increase of drug loading provided an infinite cluster in the system, leading to the complete release and the change of release behavior of drug.[17–19]

The effect of thickness of the adhesive matrix on the release of nicotine was also studied. The thickness of the adhesive matrix film of the NTP formulations E, B, and F were 0.135, 0.319, and 0.510 mm, respectively, while the nicotine contents were relatively constant (6.12–6.39% w/w). The nicotine release profiles from various adhesive matrix

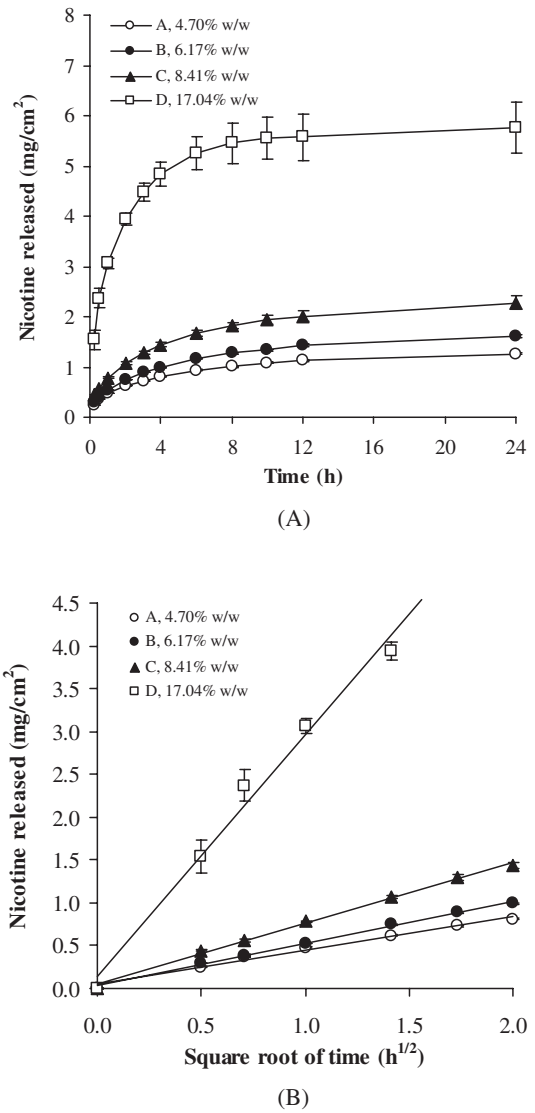

Figure 2. Nicotine cumulative-release profiles (A) and relationship between the amount of nicotine released and $t^{1/2}$ (B) from NTPs loading various nicotine contents. Each point represents the mean ± SD of triplicate experiments.

thicknesses of the NTPs are presented in Fig. 4A. The plot between the nicotine released vs. $t^{1/2}$ showed straight lines that followed Eq. (2) (Fig. 4B). It was found that the amount of nicotine released is proportional to the thickness of the adhesive matrix. On the other hand, the percentage of total nicotine released was inversely proportional to the thickness of the adhesive matrix (Table 3). The three formulations of the NTPs gave similar release rate, which were in the range of 0.474–0.577 $mg/cm^2/h^{1/2}$ (Fig. 3 and Table 3). These results indicate that the increase in thickness of the NTP did not remarkably affect the nicotine release rate, which was a function of the nicotine content.[20]

The apparent diffusion coefficient of nicotine in the adhesive polymer matrix can be calculated from Eq. (1) (Table 3). The value of the apparent diffusion coefficient of nicotine in the adhesive polymer matrix was in the range of $3.37–3.70 \times 10^{-9}$ cm^2/sec. It can be seen that neither the nicotine content in the range of 4.70–8.41% w/w nor the thickness of adhesive matrix film affected the apparent diffusion coefficient of nicotine in the acrylic adhesive matrix. Similar results were also reported by Roy et al.[7]

In Vitro Nicotine Permeation Across Human Epidermis (HE)

The skin permeation profiles of nicotine from the NTP formulations A–C across human epidermis (HE) are shown in Fig. 5A. The relationship was not linear, indicating the permeation of nicotine did not follow zero order kinetics. However, a good relationship between the amount of nicotine permeated and the square root of time was observed with R^2 greater than 0.98 (Fig. 5B). These results indicate that the matrix film-skin system formed a

Table 3. Release characteristics of nicotine transdermal patches.

Formulation	Release rate[a] ($mg/cm^2/h^{1/2}$)	Total nicotine released at 24 h[a] (mg/cm^2)	Apparent diffusion coefficient (cm^2/sec)
A	0.376 ± 0.0031	1.29 ± 0.021 (77.89%)[b]	3.46×10^{-9}
B	0.493 ± 0.0022	1.62 ± 0.028 (76.64%)	3.37×10^{-9}
C	0.711 ± 0.0191	2.28 ± 0.125 (77.52%)	3.61×10^{-9}
D	2.574 ± 0.0551	5.97 ± 0.522 (99.00%)	10.87×10^{-9}
E	0.512 ± 0.0672	0.74 ± 0.016 (88.33%)	3.69×10^{-9}
F	0.591 ± 0.0026	2.51 ± 0.023 (68.55%)	3.70×10^{-9}

[a]Mean ± SD of three determinations.
[b]Percentage of nicotine released from the NTPs.

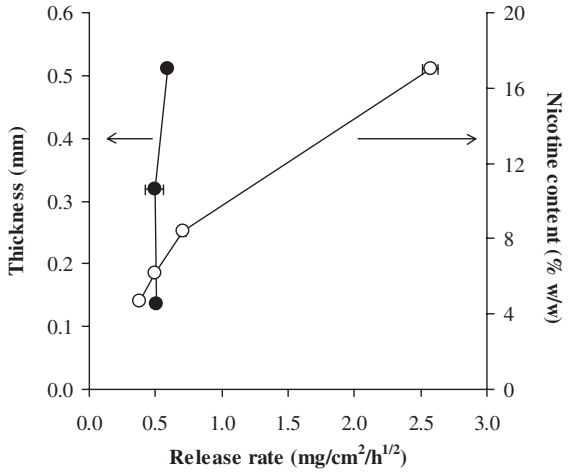

Figure 3. Relationship between nicotine release rate and thickness or nicotine content of NTPs. Each point represents the mean ± SD of triplicate experiments.

single homogeneous polymeric film. The transport of nicotine across the HE can be described by Eqs. (1) and (2). The nicotine skin permeation rates from NTP formulations A–C are presented in Table 4. It can be seen that the nicotine permeation rate was statistically increased ($p < 0.05$) when the nicotine content increased. This was due to the greater release rate of nicotine from NTPs having a high nicotine content. Besides, the nicotine permeation rate showed a good correlation with the nicotine content ($R^2 > 0.99$), which is similar to the release behavior of nicotine from the NTPs.

The residual nicotine in the NTP was investigated after 24 hr of skin permeation. The difference between the nicotine content and the residual nicotine left in the NTP was the amount of nicotine release onto the HE, corresponding to the dose delivered. The amount of nicotine released onto the HE from the NTP formulations A–C is showed in Table 4. It was observed that the higher the nicotine content, the greater the amount of nicotine released onto the skin. The percentage of the amount of nicotine released onto the HE was about 50–59% of the total amount of nicotine in the patch. These values were lower than the % nicotine release in the in vitro release test. This was due to differences between the condition of skin permeation and in vitro release test. The water-based type of acrylic adhesive matrix could rapidly absorb the surrounding water in the release testing media, leading to not only a faster release rate, but also the higher quantity of nicotine released from the NTPs when compared with those adhered to the skin.

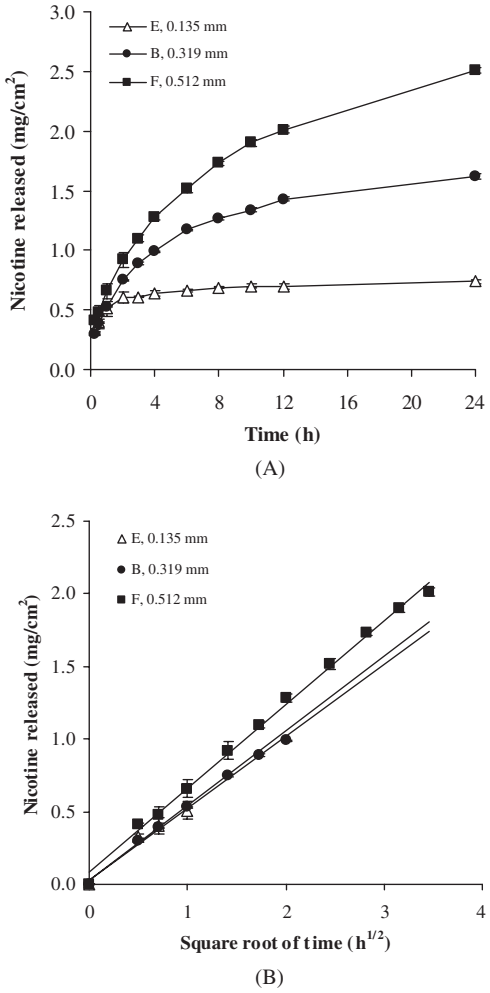

Figure 4. Nicotine cumulative-release profiles (A) and relationship between the amount of nicotine released and $t^{1/2}$ (B) from NTPs having various adhesive matrix thicknesses. Each point represents the mean ± SD of triplicate experiments.

Rate Control Studies of NTPs

The fractional rate control provided by the transdermal drug delivery device and skin, which was proposed by Guy and Hadgraft,[13] can be determined using the data from the release and permeation tests and the following equations:

$$\text{Fractional control by device } (F_d) = \frac{A_{T;\text{tapp}}}{A_{d;\text{tapp}}} \quad (3)$$

$$\text{Fractional control by skin } (F_s) = (1 - F_d) \quad (4)$$

where $A_{T;\text{tapp}}$ is the dose delivered or the amount of drug released into and across the skin in the intended application period, $A_{d;\text{tapp}}$ is the amount of

Table 4. In vitro skin permeation rate and mass balance of nicotine from NTPs.

Formulation	Permeation rate ($\mu g/cm^2/h^{1/2}$)	Amount of nicotine at 24 h (mg/cm^2)		
		Permeated	Residue in the patch	Released onto the HE
A	118.93 ± 9.24 ($R^2 = 0.9898$)	0.43 ± 0.036	0.82 ± 0.026	0.84 ± 0.026
B	173.17 ± 7.25 ($R^2 = 0.9874$)	0.63 ± 0.022	1.05 ± 0.058	1.06 ± 0.058
C	235.43 ± 19.05 ($R^2 = 0.9929$)	0.91 ± 0.091	1.20 ± 0.037	1.74 ± 0.036

Each value represents the mean ± SD of three determinations.

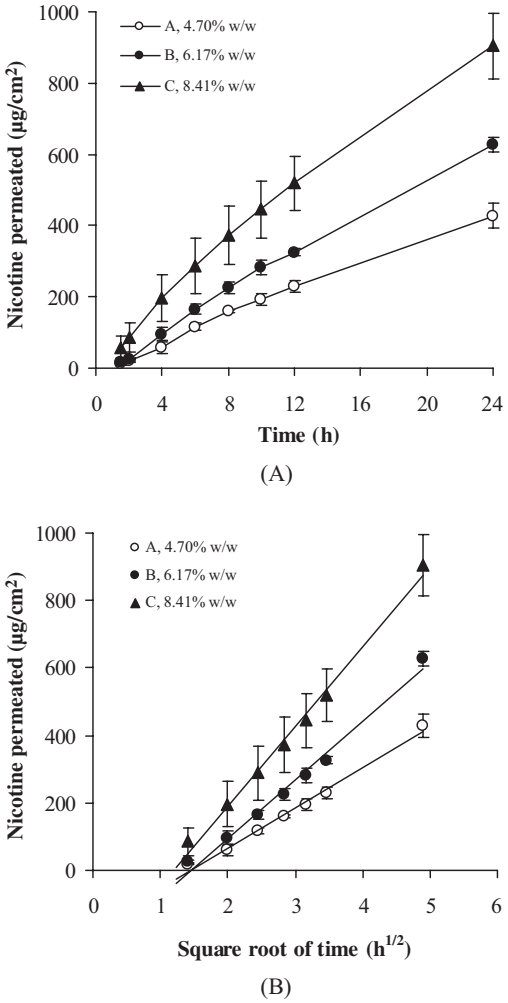

Figure 5. Nicotine skin-permeation profiles (A) and relationship between the amount of nicotine permeated and $t^{1/2}$ (B) across the human epidermis from NTPs having various nicotine contents. Each point represents the mean ± SD of triplicate experiments.

drug released into an aqueous sink at the intended application period.

Table 5 shows the fractional rate controls provided by the device and skin of nicotine delivery

Table 5. Rate control of nicotine delivered from nicotine transdermal patches.

Formulation	$A_{d;24}$ (mg/cm^2)	$A_{T;24}$ (mg/cm^2)	F_d	F_s
A	1.29	0.84	0.65	0.35
B	1.62	1.06	0.65	0.35
C	2.28	1.74	0.76	0.24

$A_{d;24}$ = the amount of nicotine released into distilled water at 24 h.
$A_{T;24}$ = the nicotine released onto the human epidermis at 24 h.
F_d (Fractional control by device) = $A_{T;24}/A_{d;24}$.
F_s (Fractional control by skin) = $1 - F_d$.

from the NTPs. The fractional rate control of the NTPs was more than 0.65, whereas the fractional rate control of skin was about 0.24–0.35. This indicated that the nicotine delivered from the NTPs across the HE was mainly controlled by the release of nicotine from the devices. These findings suggested that the human epidermis was not the only rate-limiting step of nicotine permeation but depended on the release of nicotine onto the skin. The nicotine skin permeation controlled by the device may provide a lower variation of nicotine blood levels due to regional differences in skin absorption of nicotine.

Batch-to-Batch Uniformity

Batch-to-batch uniformity of NTP formulation B was investigated using several parameters such as nicotine content, weight/area (W/A) ratio of matrix film, and in vitro nicotine release rate. The nicotine content and W/A ratio of matrix film were the parameters of choice for this evaluation because of the effect on the nicotine permeation rate.[21] In vitro release testing has been used as a quality control tool to assure batch-to-batch uniformity of production of TDDS.[12]

Table 6. Nicotine content, weight/area ratio of matrix film, and nicotine release rate of NTP formulation B obtained from batch-to-batch uniformity testing.

	Nicotine content (mg/cm^2)		W/A ratio of matrix film (mg/cm^2)		Release rate ($mg/cm^2/h^{1/2}$)	
Batch no.	Mean ± SD[a]	% CV[a]	Mean ± SD[b]	% CV[b]	Mean ± SD[a]	% CV[a]
1	2.11 ± 0.074	3.51	35.3 ± 1.2	3.40	0.57 ± 0.017	2.98
2	2.21 ± 0.092	4.16	34.7 ± 0.7	2.02	0.57 ± 0.016	2.81
3	1.97 ± 0.068	3.45	34.3 ± 0.8	2.33	0.52 ± 0.016	3.08
4	2.03 ± 0.068	3.35	34.5 ± 0.5	1.45	0.52 ± 0.020	3.85
5	2.15 ± 0.102	4.74	35.4 ± 0.9	2.54	0.56 ± 0.017	3.04
6	2.18 ± 0.099	4.54	35.6 ± 0.9	2.53	0.58 ± 0.006	1.03

[a]$n = 6$.
[b]$n = 10$.

Intrabatch variation of the NTP can be determined by using the coefficient of variation (% CV) of three parameters, nicotine content, W/A ratio of matrix film, and nicotine release rate in each batch and are shown in Table 6. The nicotine release rate calculated by Eq. (2) for the six batches of the NTPs was in the range of 0.52–0.58 $mg/cm^2/h^{1/2}$. All batches of the NTPs had a nicotine content in the range of 1.97–2.21 mg/cm^2 and provide the W/A ratio of matrix film in the range of 34.3–35.6 g/cm^2. It can be seen that the % CV of the three parameters of each batch was less than 5. This indicated a low intrabatch variation in the production of the NTP.

The means of the three parameters of the six batches were significantly different ($p < 0.05$) when tested using analysis of variance (ANOVA). The variation of content and release rate may depend on other factors, such as the mixing step of nicotine in the adhesive emulsion, which affected the uniformity of nicotine in the cast adhesive film. However, the industrial production of pharmaceutical preparations was accepted when the quality control parameters were in the range of ±10% variation, such as the content of nicotine in the transdermal system.[14] In addition, the criteria of the release of nicotine from transdermal device were recently defined in the USP 24. Thus, nicotine release profiles from six batches were evaluated using the criteria of the USP nicotine release test 3 (Table 7), and are shown for the percentage of the labeled amount of the dose absorbed in vivo.[14] The dose absorbed in vivo can be substituted by the amount of nicotine released onto the HE from the in vitro skin permeation test because this parameter showed a good correlation with the in vivo permeation parameter.[22,23] The percentage of the labeled amount of 1.06 mg/cm^2 nicotine released in vitro over time of the six batches of the NTPs is presented in Fig. 6. From these results, all nicotine release profiles were within the criteria of the USP 24 (Table 7). This indicated a good batch-to-batch reproducibility of the production method.

Table 7. Percentage of the labeled amount of the dose absorbed in vitro of nicotine released from NTP formulation B.

Time (h)	USP specification: amount released	Amount released from NTP formulation B[a] (%)
1	35–75%	55.4 ± 2.74
2	55–95%	77.2 ± 3.82
4	Not less than 73%	104.2 ± 5.69

[a]Data are means ± SD, $n = 36$ from six batches.

CONCLUSION

Nicotine transdermal patches fabricated from acrylic, pressure-sensitive, adhesive emulsion was a single-phase adhesive matrix and showed good uniformity. Nicotine release and permeation across human epidermis from the NTPs showed a linear correlation with the square root of time, indicating a matrix diffusion controlled-release mechanism. Increasing the nicotine content of the NTPs resulted in an increase in the release rate of nicotine. However, an increase in the thickness of the adhesive matrix with a constant nicotine content did not have an effect on nicotine release. Neither the nicotine content in the range 4.70–8.41% w/w nor the film thicknesses of the NTPs had any affect on the value of the apparent diffusion coefficient of nicotine in the acrylic

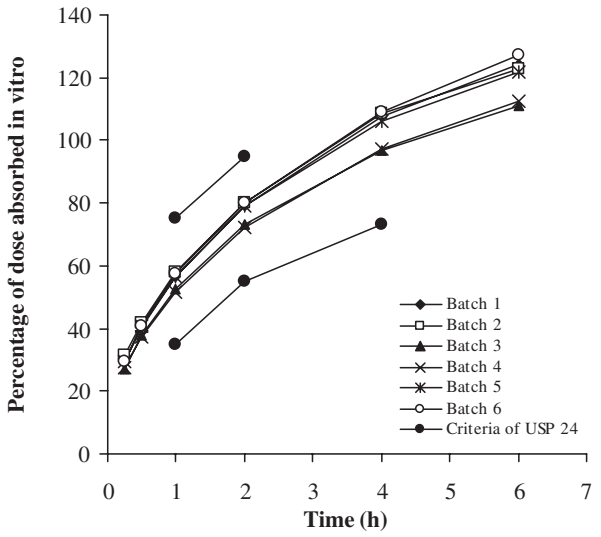

Figure 6. Percentage of the labeled amount of 1.06 mg/cm^2 nicotine absorbed in vitro from six batches of NTPs.

matrix film. This study also showed that the nicotine skin permeation across human epidermis was mainly controlled by the nicotine release from the device to the skin.

ACKNOWLEDGMENTS

The authors express appreciation to the Institute for Tobacco Consumption Control, Department of Medical Services, Ministry of Public Health (Bangkok, Thailand) for research funding and to the Department of Pathology, Faculty of Medicine, Khon Kaen University (Khon Kaen, Thailand) for the provision of the human skin. We also thank 3M Pharmaceuticals (St. Paul, MN) for polyolefin backing membrane and Neoplast Co., Ltd. (Patumthani, Thailand) for acrylic, pressure-sensitive, adhesive emulsion as well as siliconized paper.

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