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COMMUNICATION

In Vitro Study of Transdermal Nicotine Delivery: Influence of Rate-Controlling Membranes and Adhesives

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ABSTRACT

The objective of this study was to evaluate the influence of a rate-controlling membrane and adhesive on the in vitro permeation of nicotine. The physicochemical properties of the adhesive, including adhesion and rheology (viscosity), were also detected. Higher permeability of nicotine was observed through a hydrophilic membrane than through a hydrophobic membrane. Natural rubber and silicone were used as the adhesive bases, respectively. The silicone adhesive showed the highest adhesion among all adhesive formulations. To increase the adhesion of natural rubber, a tackifier (polyisoprene) and a secondary tackifier (terpene polymer; Px 1150®) were incorporated into the formulations to achieve acceptable adhesion. The nicotine permeation through silicone adhesive and three natural rubber adhesives with the secondary tackifier (2%, 4%, and 6% Px 1150) was close to that from a commercially available patch (Habitrol®), although the loading amount of nicotine was not the same. A longer lag time during the in vitro permeation study of nicotine was required for the adhesives prepared in our laboratory than for the commercially available patch.

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INTRODUCTION

Transdermal delivery of nicotine into the systemic circulation has been shown to facilitate tobacco withdrawal by mitigating or even preventing abstinence symptoms and diminishing craving (1,2). Transdermal nicotine delivery could eliminate oral discomfort and minimize gastrointestinal side effects. A transdermal nicotine drug delivery device has been available commercially for over a decade, and significant advances have been made in this field. A complete design for a transdermal device or patch incorporates a drug-loaded matrix or reservoir totally covered by a rate-controlling membrane. The entire skin-contacting surface of the patch is coated with adhesive (3). The topical bioavailability of a drug therefore depends, at least in part, on the rate of release from its formulated product, including the drug reservoir, rate-controlling membrane, and adhesive. The aim of this study was to evaluate the transdermal absorption of nicotine influenced by the rate-controlling membrane and pressure-sensitive adhesive (PSA). Furthermore, the physicochemical properties of the adhesive, such as adhesion and rheology, were characterized.

To verify the effect of the rate-controlling membrane on the transdermal transport of nicotine, both hydrophilic and hydrophobic membranes were employed in this study. For PSA, two types of material were used in this study, natural rubber and silicone. The tackifier was also incorporated in the adhesive, thus optimizing the physicochemical properites of the adhesive for use in the transdermal application of nicotine. Finally, in vitro permeation of nicotine from a commercial patch was determined for comparison with that from our designed devices.

MATERIALS AND METHODS

Materials

Nicotine was purchased from Sigma Company (St. Louis, MO). Polyisoprene was donated by Aldrich Company (USA). Natural rubber was supplied by Tong-Ho Company (Taiwan). Px 1150® terpene polymer was from Yasuhara Company (Japan). Dow Corning 355 silicone adhesive was obtained from Dow Corning Company (USA). Scotchpak 1009® and Scotchpak 1022® polyester film were purchased from 3M Company (USA). The eight rate-controlling membranes used in this study are listed in Table 1, which provides the thickness, typical porosity, pore size, and characteristics. The membranes were purchased from Millipore Company (USA), except for polysulfone (PS) membrane, which came from Gelman Company (USA).

Preparation of Adhesive

Nicotine and polymers (natural rubber, polyisoprene, and Px 1150) were accurately weighed and then dispersed in cyclohexane or *n*-hexane. This mixture was stirred for 24 hr until the polymer was dissolved and the solution was well mixed. Then, the mixture was poured uniformly onto the impermeable backing membrane (Scotchpak 1009) by constant volume in a glass ring. The adhesive film was kept at room temperature for 2 hr to

Table 1

Physicochemical Properties of Rate-Controlling Membranes

	Thickness (μm)	Porosity (%)	Pore Size (μm)	Characteristic
PS	152.4	—[a]	0.45	Hydrophilic
PVDF				
VVLP	125	70	0.10	Hydrophilic
HVLP	125	70	0.45	Hydrophilic
HVHP	125	75	0.45	Hydrophilic
SVLP	125	70	5.00	Hydrophilic
PTFE				
FGLP	175	70	0.20	Hydrophobic
FHWP	175	85	0.50	Hydrophobic
FSWP	200	85	3.00	Hydrophobic

PS, polysulfone; PVDF, polyvinylidene fluoride; PTFE, polytetrafluoroethylene.
[a] Not determined.

evaporate excess organic solvent. Finally, the release liner (Scotchpak 1022) was covered on the film to protect it.

In Vitro Permeation Study

The in vitro permeation flux was determined by using a modified Franz diffusion cell. The Wistar rat abdominal skin was mounted on the receptor compartment with the stratum corneum side facing upward into the donor compartment. A rate-controlling membrane was placed on the stratum corneum. In the in vitro permeation study of the effect of adhesive, the adhesive film was placed between the rate-controlling membrane and the stratum corneum. The top of the diffusion cell was covered with paraffin paper. The donor compartment of the cell was pipetted with 2 ml of 3% nicotine in pH 7 McIlvaine buffer. The receptor medium was 20 ml of pH 7.4 McIlvaine buffer. The available diffusion area of the cell was 2.54 cm^2. The diffusion cell was carried out at 37°C, and the receptor compartment was stirred by a magnetic stirrer at 700 rpm. The receptor medium was completely withdrawn and replaced with the fresh buffer at each scheduled sampling time. The sample withdrawn from the receptor compartment was then analyzed by high-performance liquid chromatography (HPLC).

Analytical Method

A 25 cm long, 3.9 mm inner diameter CN column (Merck®) was used as the analytical column. The drug sample was mixed with a suitable amount of *p*-phenylphenol as an internal standard. The mobile phase, consisting of 50% acetonitrile and 50% 0.002 M phosphate buffer at pH 7, was used at a flow rate of 1.2 ml/min. The column effluent was passed through the ultraviolet (UV) detector set at 260 nm (Waters® model 991 photodiode array detector). The retention times of *p*-phenylphenol and nicotine were 3.7 min and 4.7 min, respectively.

Determination of Adhesion

The adhesion measurement was made on an adhesive force meter (Gotech Co., Taiwan). After the removal of the release liner, the adhesive film (25 × 120 mm^2) was fixed onto a vertical stainless steel plate using a roller at the speed of 300 mm/min to press the film at a constant pressure. Then, the patch was ripped for 25 mm of the length. The end part of the ripped film was peeled away by a mechanical force at a speed of 300 ± 20 mm/min. The value of this force was detected as the adhesion (g/cm) (4).

Rheological Study

A rheology study was carried out at 37°C ± 1°C using a Brookfield DV-2 viscometer. The mixed solution of adhesive (0.5 ml) was placed in the sample cup of the viscometer. The reading was detected 30 sec after the measurement was made, when the level had stabilized.

RESULTS AND DISCUSSION

In Vitro Permeation Through Rate-Controlling Membrane

After the in vitro permeation study through the rate-controlling membrane, the slope of the resulting cumulative amount-time curve during 48 hr was computed. From these slopes, the flux (μg/cm^2/hr) was calculated; the data are shown in Figs. 1 and 2. The cumulative amount-time curves were all suitable to fit using a zero-order equation. Accordingly, controlled drug delivery may be observed for nicotine through a rate-controlling membrane since the development of systems for the sustained release of drugs has focused on those systems that result in either zero-order release or a drug release profile that is a simple function of time (5).

Fluxes of nicotine through the five membranes described as hydrophilic are shown in Fig. 1. The flux of nicotine through rat skin directly was significantly higher

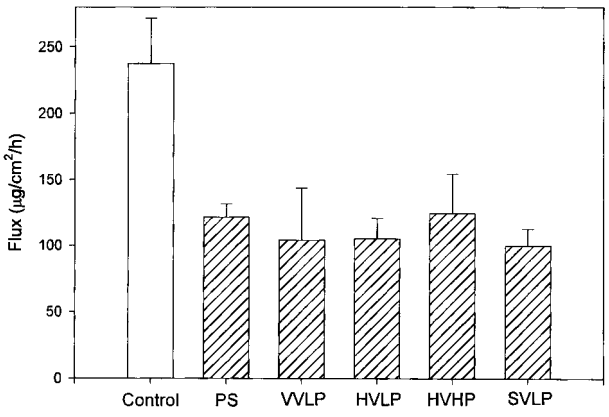

Figure 1. In vitro nicotine flux through hydrophilic membranes combined with rat skin. Values are means for three determinations.

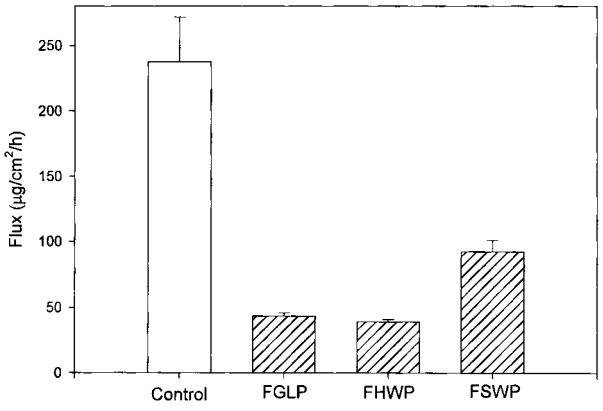

Figure 2. In vitro nicotine flux through hydrophobic membranes combined with rat skin. Values are means for three determinations.

than those through a rate-controlling membrane combined with rat skin, indicating a diffusion barrier property of these membranes. Although the PS membrane was thicker than the other hydrophilic membranes, a higher nicotine flux was observed, which may be due to the lack of a significant barrier property of PS membrane, mentioned previously (6). The porosity of the HVHP membrane was higher than that of the HVLP membrane, resulting in the higher nicotine flux of the HVHP membrane. Comparing three polyvinylidene fluoride (PVDF) membranes with the same thickness and porosity, but different pore size, including VVLP (0.1 μm), HVLP (0.45 μm), and SVLP (0.5 μm) membranes, no significant difference in nicotine flux was observed among these three membranes. The permeation of the drug through the hydrophilic membrane, such as the HVLP membrane, is via the pore structure within the membrane (7). The pores are large enough for the drug molecules to diffuse freely. Therefore, the pore size of 0.1 μm is enough for nicotine molecules to pass through since the higher pore sizes of hydrophilic membranes may restrict the diffusion amounts of nicotine to the level of the 0.1-μm pore size.

As for the hydrophilic membranes, the hydrophobic polytetrafluoroethylene (PTFE) membranes showed barrier properties to the diffusion of nicotine (Fig. 2). The flux of nicotine through the FSWP membrane with a 3.0-μm pore size was significantly higher than for the FGLP membrane (0.2 μm) and FHLP membrane (0.5 μm), although the thickness of the FSWP membrane was the highest among the three hydrophobic membranes. This indicates the diffusion of nicotine is influenced by the pore size of the hydrophobic membrane, which is different from the result for hydrophilic membranes. The hydrophobic membrane hinders nicotine diffusion into the receptor medium more profoundly than the hydrophilic membrane, as seen after the comparison of nicotine flux shown in Figs. 1 and 2. This may be due to the poor wetting of the membranes by the aqueous donor fluid in the diffusion cell beneath the membrane (6).

Characterization of Adhesive and In Vitro Nicotine Permeation Through Adhesive

Adhesive is usually described as a material that adheres to a surface with light pressure and leaves no residue when removed (3). In this study, various formulations of adhesive were prepared. The physicochemical properties of these adhesives, including adhesion and viscosity and the in vitro nicotine permeation through adhesives, were determined. Various adhesive formulations are listed in Table 2. Since organic tackifier is always needed in the rubber adhesive (8), 10% polyisoprene was added in the formulation of rubber adhesive in this study. In the investigation of physicochemical characterizations, it was observed that, increasing the concentration of natural rubber from 5% to 15% (formulations B to D) in the adhesive, the adhesion decreased from 169.7 g/cm to 117.9 g/cm (Table 3). However, an opposite trend was shown in the viscosity (rheology) of these three adhesive formulations. In the study of in vitro nicotine permeation through an adhesive, the adhesive was sandwiched between rat skin and a PS membrane. As shown in Table 3, the nicotine flux decreased after the addition of an adhesive layer. It indicates that the adhesive acts as a diffu-

Table 2

Compositions of Natural Rubber Adhesive Formulations

Formulation	Natural Rubber (%)	Polyisoprene (%)	Px 1150 (%)
A[a]	0	0	0
B	5	10	0
C	10	10	0
D	15	10	0
E	10	5	0
F	10	15	0
G	10	10	4
H	10	10	4
I	10	10	6

[a] No adhesive existed when performing the in vitro permeation study. Each value represents the mean ± SD.

Table 3

Physicochemical Properties and Data of In Vitro Permeation Study of Various Adhesive Formulations

Formulation	Adhesion (g/cm)	Viscosity (10^3 cps)	Flux (μg/cm²/hr)	Lag Time (hr)
A	—[a]	—	121.56 ± 9.97	0.62 ± 1.42
B	169.7 ± 40.0	3.78 ± 0.52	93.12 ± 18.73	2.26 ± 0.32
C	125.6 ± 19.0	6.21 ± 0.59	106.59 ± 26.62	2.48 ± 0.49
D	117.9 ± 33.0	Over range	87.40 ± 7.97	1.53 ± 0.34
E	11.6 ± 2.9	7.50 ± 0.94	99.22 ± 12.89	2.15 ± 0.62
F	169.6 ± 29.0	6.05 ± 0.18	79.79 ± 6.97	2.07 ± 0.29
G	150.2 ± 30.3	7.06 ± 0.83	73.25 ± 16.50	2.17 ± 0.28
H	263.2 ± 34.6	6.70 ± 1.09	71.30 ± 11.97	1.81 ± 0.40
I	393.2 ± 59.0	6.90 ± 0.63	69.29 ± 4.39	2.16 ± 0.18
J	758.3 ± 189.1	—	71.48 ± 6.81	2.10 ± 0.20
Habitrol	—	—	70.07 ± 1.41	0.58 ± 0.14

[a] Not determined.
Each value represents the mean ± SD.

sion barrier for nicotine. There was no significant difference among the nicotine permeations of these three adhesives (formulations B to D), although a shorter lag time was detected in the formulation with 15% natural rubber.

Various concentrations of the tackifier polyisoprene were also incorporated into the adhesive, and the result of the analysis of physicochemical properties and in vitro permeation of nicotine is shown in Table 3 (formulations C, E, and F). The adhesion significantly increased following the increase of polyisoprene concentration without interfering with the viscosity of the adhesive. However, the permeation of nicotine was slightly decreased when the concentration of polyisoprene reached the 15% level. The adhesion force required to adhere the patch onto skin surface should be greater than 200 g/cm (9). Nevertheless, formulations B to F did not achieve an acceptable adhesion force. Accordingly, the terpene polymer (Px 1150), as a secondary tackifier, was incorporated into the adhesive to increase the adhesion force of the adhesive. The adhesion achieved the acceptable level when adding 4% (formulation H) and 6% (formulation I) Px 1150. The nicotine permeation through the adhesive was retarded after incorporation of Px 1150 tackifier. This indicates that tackifiers (either polyisoprene or Px 1150) generally inhibit the diffusion of nicotine molecules. This may be because the lipophilic tackifier increases the solubility of nicotine in the adhesive layer, which resulted in the lower nicotine amount partitioning into the skin, thus reducing the permeability of nicotine across skin.

Dow Corning 355 silicone base was also prepared as the adhesive (formulation J). Greater adhesion of the silicone adhesive is observed compared to the adhesion of natural rubber adhesives. The commercially available nicotine patch (Habitrol®) was also used to perform the in vitro nicotine permeation study. The flux of nicotine from Habitrol was close to the flux from formulations G, H, I, and J, although the loading amount of nicotine was 52.5 mg for Habitrol compared to 60.0 mg for our donor preparation. This demonstrates that bioequivalence may be achieved between a commercially available patch and the formulations prepared in this study. However, the commercial patch showed a shorter lag time than formulations G, H, I, and J, indicating a rapid onset after the administration of the commercial patch. Judging from the adhesives of formulations G to J, formulation H showed a shorter lag time and suitable adhesion compared with others.

CONCLUSION

In summary, the nicotine cumulative amount-time profiles in the in vitro permeation through a rate-controlling membrane all fit well using a zero-order equation, indicating controlled drug delivery may be achieved for nicotine transdermal transport. The pore size of the hydrophilic membrane did not influence the diffusion of nicotine. However, a different manner was observed for the hydrophobic membrane since the permeability of nicotine through the hydrophobic membrane with a larger pore size was significantly higher than that with a smaller pore size. Moreover, the flux of nicotine through a hydrophobic membrane was lower than that through a hy-

drophilic membrane because of the poor wetting of the hydrophobic membrane by the aqueous solution of the donor during the in vitro permeation experiment.

In the study of adhesives, both natural rubber and silicone base were used as the main materials of the adhesive. The adhesion decreased with an increase of natural rubber proportions in the adhesive formulation. There was no significant difference in nicotine permeation when the amount of natural rubber in the formulation was changed. Polyisoprene as a tackifier was also incorporated into the adhesive base of natural rubber. The adhesion slightly increased following the increase of polyisoprene, whereas the nicotine flux was reduced when the concentration of polyisoprene reached the level of 15%. To achieve the acceptable adhesion value of 200 g/cm, a secondary tackifier of terpene polymer (Px 1150) was added to the adhesive. The acceptable adhesion value was achieved when the concentration of Px 1150 was above 4%. However, the permeation of nicotine was decreased after the incorporation of Px 1150 regardless of the Px 1150 concentration. The highest adhesion value was found in the silicone-based adhesive. Moreover, the fluxes of nicotine through silicone adhesive and three natural rubber adhesives with a secondary tackifier were almost the same as with the nicotine flux from a commercially available patch. Nevertheless, the commercial nicotine patch showed a shorter lag time and lower variation in nicotine permeability. Formulation I, which showed nicotine flux similar to that of Habitrol and suitable adhesion (263.2 g/cm), can possibly be developed for an ideal transdermal nicotine delivery system.

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