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In vitro comparative studies of two marketed transdermal nicotine delivery systems: Nicopatch® and Nicorette®

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Abstract

The aim of this work was to compare in vitro the performances at delivering nicotine of two transdermal delivery system (TDS): Nicorette (8.3 mg/10 cm^2 nicotine content) and Nicopatch (17.5 mg/10 cm^2). Release profiles were obtained using the FDA paddle method, and skin permeation profiles using Franz-type diffusion cells. Using the first method, nicotine release followed the polymer matrix diffusion-controlled process, as suggested by the linear Q versus $t^{1/2}$ relationship. Cumulative amounts released from Nicopatch were twice the amounts released from Nicorette, but the released fractions were almost equal for both TDS (∼50%). Using diffusion cells, skin permeation rates were constant over the time: they were not significantly different between both TDS and close to in vivo claimed releases: Nicorette should be considered as more efficient at delivering nicotine through skin than Nicopatch. However, cumulative permeated amounts were overestimated, indicating that the actual diffusion surface area exceeded the effective diffusion surface area of the cells. Reducing the trimmed TDS surface area led not only to a reduction of the cumulative permeated amounts, but also to a reduction of the permeation rates. Therefore, the usefulness of the method to evaluate skin permeation parameters of TDS is questioned.

Keywords: Nicotine; Patch; Transdermal delivery system; Franz-type diffusion cell; FDA paddle method; Skin permeation

1. Introduction

Nicotine is a cholinergic agonist which is prescribed as an adjunct to smoking cessation. It is available in various dosage forms: gum, nasal spray, inhaler and patch (or transdermal delivery systems, TDS) (Karnath, 2002). The efficacy of the nicotine replacement therapy on the relief of cigarette craving and withdrawal using TDS is dependent on the dosing parameters (Shiffman et al., 2000), which determines the nicotine plasma levels over the course of the day (Fant et al., 2000). Nicopatch from Pierre Fabre Santé and Nicorette from Pharmacia & Upjohn are two TDS marketed in France. As a common rule, a treatment consists of a daily skin application of the appropriate TDS during 4–8 weeks in order to deliver a dose adapted to the level of addiction (which usually corresponds to the largest TDS). This initial period is followed by a gradual therapeutic withdrawal, consisting in reducing the dose every 2–4 weeks using smaller TDS (20, 10 and finally 5 cm^2). For any TDS,

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Table 1
Nicotine patch specifications

TDS	Nicotine content (mg)	Surface area (cm^2)	Application duration (h)	Claimed in vivo release
Nicopatch	17.5	10	24	7 mg (= 700 μg cm^{-2}) over 24 h
Nicorette	8.3	10	16	5 mg (= 500 μg cm^{-2}) over 16 h

the initial concentration gradient between the nicotine reservoir and skin should be sufficiently high to maintain the required drug flux over the duration of the application, which implies that their contents are generally much larger than the drug amounts delivered. Nicopatch and Nicorette differ from each other in nicotine contents and in time duration for application (Table 1). However, calculated from the claimed in vivo release, the average release rates are almost equal. Furthermore, Nicopatch releases in vivo 40% of its content over 24 h and Nicorette 60% over 16 h. Considering that the nicotine content of Nicorette is half the one of Nicopatch, this should mean that Nicorette is more efficient at delivering nicotine than Nicopatch, or that the observed in vivo rates are the result of a skin rate-limiting effect. This work was carried out to clarify this point by comparing the nicotine release and skin permeation characteristics of the two TDS.

2. Materials and methods

2.1. Materials

(−)-Nicotine hemisulfate aqueous solution (40%, w/v nicotine free base content), used to prepare standards for spectrometric and HPLC determinations, was obtained from Sigma (Saint Quentin Fallavier, France). The transdermal delivery system used in this study were Nicorette® 5 mg/16 h (nicotine content: 8.3 mg/10 cm^2, lot #VE111D) from Pharmacia-Upjohn, France. Nicopatch® 7 mg/24 h (17.5 mg/10 cm^2, lot #HU165200). Abdominal female human skin was supplied by the plastic surgery department (Prof. Duport) from the Poitiers University Hospital, Poitiers, France. Skin plasties were stored at −20 °C within 2 h after surgery. They were slowly defrosted at +4 °C, dermatomed to 300 μm, rolled in aluminium foils and stored at −20 °C until use.

2.2. Dissolution test using the FDA paddle method

Nicotine release kinetics were evaluated according to the FDA paddle method (Shah et al., 1988), using a DTB 678A apparatus (Kontron Instruments), with a paddle stirring set at 50 rpm and a receptor phase consisting of 900 ml HCl 0.025 aqueous solution thermostated at 32 °C. Samples (2 ml) were collected from the receptor phase at regular time intervals over 24 h, in order to determine nicotine concentration by UV spectrophotometry at 254 nm. They were poured back to the receptor phase immediately after determination.

2.3. Nicotine skin permeation study using the Franz-type diffusion cells

The two TDS were trimmed to a diameter of 2.45 cm (surface area: 4.71 cm^2) and adhered to the stratum corneum of dermatomed skin mounted in all-glass Franz-type diffusion cells (mean effective surface area for diffusion: 0.77 cm^2, mean diameter: 0.99 cm). The skin and the TDS covered all the surface of the cell (diffusion surface and edge surface). The receptor compartment was filled with saline thermostated at 37 °C, stirred with small magnetic spin bars. Samples (0.23 ml) were collected from this compartment at appropriate time intervals in order to determine by HPLC nicotine concentration in the receptor phase. They were immediately replaced with the same volume of saline. The dilution was taken into account to calculate the cumulative amount of nicotine transferred into the receptor phase. Nicotine permeation studies were conducted for 32 h. Only data obtained up to 24 h were used for kinetic parameter calculation due to the possible loss of skin integrity after longer time periods.

2.4. "Edge effect" evaluation

The "edge effect" was studied using Nicorette TDS trimmed to three different diameters (areas): 1.2 cm

(1.13 cm^2), 1.8 cm (2.54 cm^2) and 2.45 cm (4.71 cm^2) in order to create an overlap of 0.1, 0.4 and 0.7 cm, respectively, over the edge of the Franz-type diffusion cells. Two series of experiments were carried out following the procedure described in Section 2.3: one series without skin (i.e. the TDS was directly adhered to the cells) in order to evaluate the effect of the patch surface area on the nicotine release kinetics, and one series with skin interposed between the TDS and the cells (and covering both the effective diffusion surface and the edge surface) in order to evaluate the effect of the patch surface area on the nicotine permeation kinetics. Release kinetics were studied over a 48-h period and permeation kinetics over a 24-h period.

2.5. HPLC nicotine determination

The chromatographic system consisted of a pump LC-10AT Shimadzu, an autosampler SP8780 Spectra-Physics and a spectrophotometer SpectroMonitor III MaxN® series. Nicotine was analyzed by isocratic reversed-phase HPLC using a C18 Column (300 × 39 mm, Waters), a mobile phase made of 0.8% (v/v) of 0.25 M sodium dodecyl sulfate solution, 1% (v/v) of 1 M sodium acetate solution, 61.2% of (v/v) water and 37% of (v/v) acetonitrile at a 2 ml min^{-1} flow rate and a 254 nm detection wavelength. Injection volume was 10 μl. Data were recorded and processed with an integrator SP4290 Spectra-Physics.

2.6. Data analysis

The cumulative amounts of nicotine released from TDS that were obtained either by using the FDA paddle method or by using the Franz-type diffusion cells were plotted versus time$^{1/2}$ ($t^{1/2}$) and computerized using Eq. (1) (Ho and Chien, 1993):

$$Q_R = F \times t^{1/2} \quad (1)$$

where Q_R is the cumulative released amount, i.e. the cumulative amount of nicotine released per cm^2 of the drug-releasing surface of the TDS (FDA paddle methods) or of the active surface of the Franz-type cells, and F is the drug release flux deduced from the slope of the Q_R versus $t^{1/2}$ curve. Cumulative released amounts obtained using the FDA paddle method were also expressed as percentage of the initial TDS surface area content and were referred to as percent cumulative amounts $Q_{R\%}$. The corresponding nicotine release flux was designated as percent release flux $F_{\%}$.

For skin permeation studies using Franz-type cells, the cumulative amount Q_P of nicotine that permeated through skin and reached the receptor phase was plotted versus t. Skin permeation rates R at steady state diffusion (i.e. after the lag times required for skin permeation to reach equilibrium) were deduced from the slope of the Q_P versus t curves.

Linearity of the Q_R versus $t^{1/2}$ or of the steady-state Q_P versus t relationship was assessed by calculating the correlation coefficient r. Data were compared by the Student's t-test (for two groups) or by one-way analysis of variance followed by the Bonferroni's multiple comparison test (for more than two groups), with the level of significance set at $P < 0.05$.

3. Results

3.1. Dissolution test (FDA paddle method)

At all time points of determination the cumulative released amounts Q_R were significantly higher for Nicopatch than for Nicorette (Fig. 1A). For both devices Q_R was not linearly related to t (Fig. 1A), but to $t^{1/2}$ (Fig. 1B). The nicotine release fluxes F were significantly different between Nicorette and Nicopatch (Table 2). Expressed as the percentage of the initial surface area contents of the respective devices, the percent cumulative amounts $Q_{R\%}$ were also significantly higher for Nicopatch than for Nicorette at all time points (Fig. 1C). However, values were very close, as well as the percent release fluxes $F_{\%}$ (Fig. 1D, Table 2). At 24 h, the fraction of nicotine released from the devices reached 55.7 ± 0.8% for Nicopatch and 51.3 ± 0.95% for Nicorette. Though very close, these two values were significantly different.

3.2. Skin permeation studies

At all time points of determination, the cumulative amounts Q_P of nicotine that permeated through skin were not significantly different between Nicopatch and Nicorette (Fig. 2). The Q_P versus t relationship was linear and skin permeation rates were not

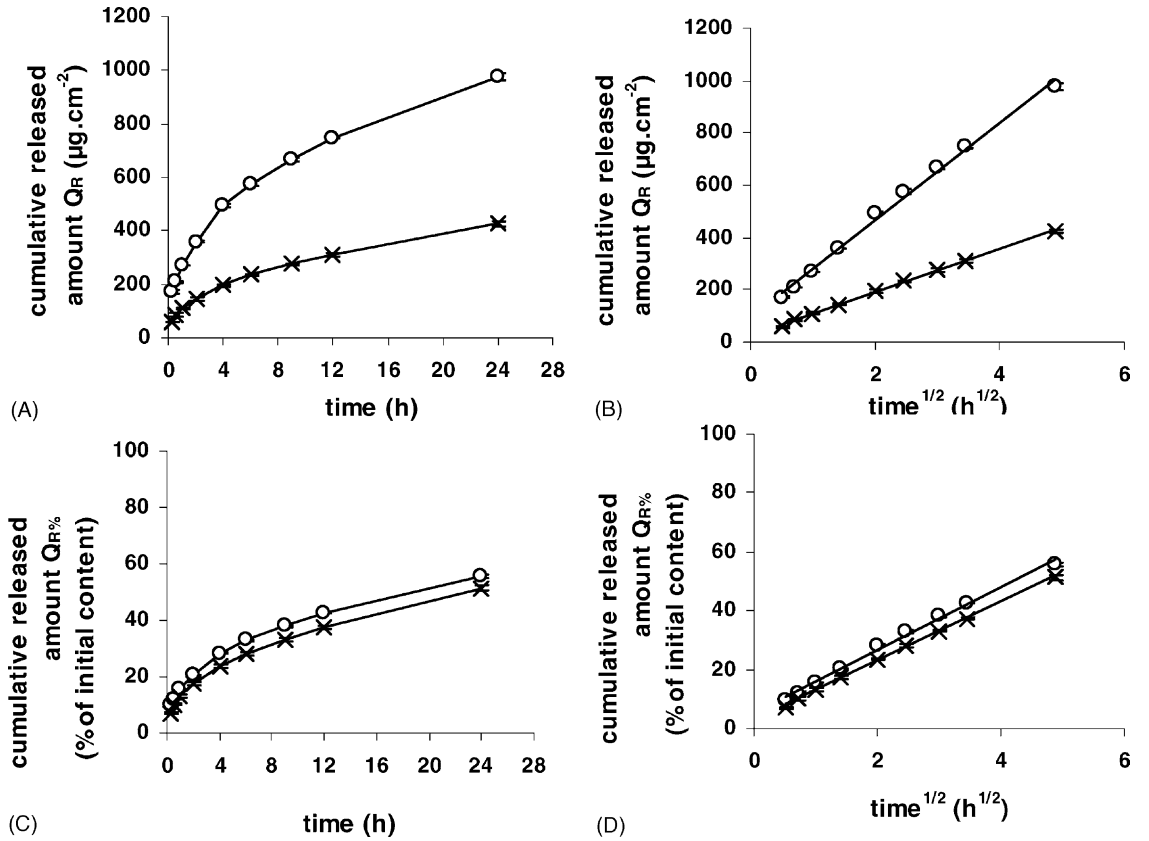

Fig. 1. Release profiles of nicotine from Nicopatch TDS (○) and from Nicorette TDS (×) obtained using the FDA paddle method and expressed as cumulative released amount per surface area unit vs. time (A) and vs. time$^{1/2}$ (B). Release profiles were also expressed as the percentage of initial nicotine content vs. time (C) and vs. time$^{1/2}$ (D). Means ± S.E.M., $n = 6$. Short error bars are superimposed with the symbols.

significantly different between the two TDS (Table 3). For Nicopatch, the cumulative amount of permeated nicotine was 709 ± 56 µg cm^{-2} (40% of the initial surface area content) at 24 h. For Nicorette, it was 501 ± 39 µg cm^{-2} (60% of the initial surface area content) at 16 h (recommended time for TDS withdrawal when used for treatment) and 717±58 µg cm^{-2} (86%) at 24 h. For both TDS, the cumulative amounts of permeated nicotine continued to increase after the recommended time for TDS withdrawal. In the case of Nicorette, the cumulative permeated amount was close to the surface area content of the device at 28 h (850 ± 69 µg cm^{-2}), and significantly higher at 32 h (957 ± 84 µg cm^{-2}).

Table 2
Release parameters obtained using the FDA paddle method ($n = 6$)

TDS	Release flux F (µg cm^{-2} h$^{-1/2}$) (mean[a] ± S.E.M.)	Percent release flux $F_{\%}$ (% h$^{-1/2}$) (mean[a] ± S.E.M.)	r
Nicopatch	186.5 ± 1.9	10.7 ± 0.1	0.9966 ± 0.0002
Nicorette	82.5 ± 1.8	9.9 ± 0.2	0.9987 ± 0.0002

[a] Significantly different by the Student's t-test.

Table 3
Skin permeation parameters obtained with Nicopatch TDS and Nicorette TDS using Franz-type diffusion cells ($n = 5$) and effect of the TDS surface area

TDS	Surface area (cm^2)	Skin permeation rate R ($\mu g\,cm^{-2}\,h^{-1}$) ± S.E.M.	r
Nicopatch	4.71	31.0 ± 2.4[a]	0.9900 ± 0.0026
Nicorette	4.71	31.6 ± 2.9[b]	0.9960 ± 0.0010
	2.54	20.7 ± 4.8[c]	0.8402 ± 0.0553
	1.13	12.3 ± 3.4[d]	0.9089 ± 0.0317

a and b are not significantly different by the Student's t-test. b and c, and c and d are not significantly different, b and d are significantly different by the Bonferroni's multiple comparison test.

3.3. "Edge effect" study

Without skin interposed between the TDS and the receptor compartment, the cumulative released amounts Q_R were not linearly related to t (Fig. 3A), but to $t^{1/2}$ (Fig. 3B, Table 4) whatever the surface area. The nicotine release fluxes F increased with increasing surface areas (Table 4). Cumulative released amounts Q_R at all time points of determination and nicotine release fluxes F were significantly higher than those obtained using the FDA paddle method. When the experiment was prolonged up to 48 h, cumulative released amounts Q_R were close to the surface content of the device ($830\,\mu g\,cm^{-2}$) at 48 h for the smallest surface area, and exceeded this value at 30 h for 2.54 cm^2 and at 24 h for 4.71 cm^2.

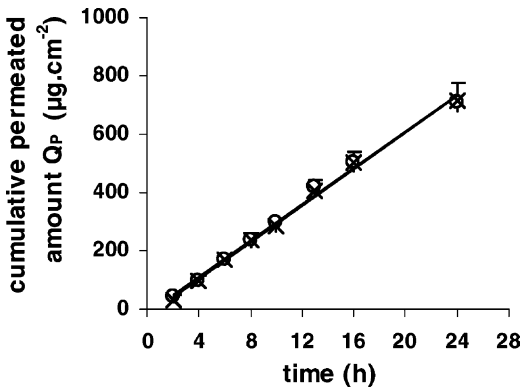

Fig. 2. Skin permeation profiles of nicotine delivered from Nicopatch TDS (○) and from Nicorette TDS (×) obtained using Franz-type diffusion cells. Both TDS were trimmed to a 4.71 cm^2 surface area. The cumulative amount Q_P of nicotine that permeated through skin was expressed per cm^2 of the active surface of the Franz-type diffusion cells. Means ± S.E.M., $n = 5$. The two regression curves are virtually superimposed.

Table 4
Effect of the Nicorette TDS surface area on nicotine release parameters obtained using Franz-type diffusion cells ($n = 4$)

Surface area (cm^2)	Release flux F ($\mu g\,cm^{-2}\,h^{-1/2}$) (mean ± S.E.M.)	r
4.71	166.5 ± 9.8[a]	0.9893 ± 0.0037
2.54	153.8 ± 9.3[b]	0.9975 ± 0.0005
1.13	119.0 ± 8.3[c]	0.9871 ± 0.0035

a and b, and b and c are not significantly different, a and c are significantly different by the Bonferroni's multiple comparison test.

The effect of the surface areas of trimmed Nicorette TDS on nicotine skin permeation is presented on Fig. 4. For the three surface areas studied, a linear Q_P versus t relationship was observed (Table 3). Skin permeation rates R decreased with decreasing surface areas.

4. Discussion

Using the FDA paddle method, the cumulative amount of nicotine released Q_R from Nicopatch was more than two-times higher than from Nicorette at all time points of determination over 24 h (Fig. 1A). For both TDS, Q_R was not linear with t, but with $t^{1/2}$ (Fig. 1A and B), suggesting a polymer matrix diffusion-controlled process (Ho and Chien, 1993). The nicotine release flux F from Nicopatch was 2.3 times higher than from Nicorette (Table 2). Expressed as percentage of initial surface area contents, however, percent cumulative released amounts $Q_{R\%}$ were almost similar (Fig. 1C and D), as well as percent release fluxes $F_{\%}$ (Table 2). Therefore, both TDS released nicotine with the same efficiency in term of

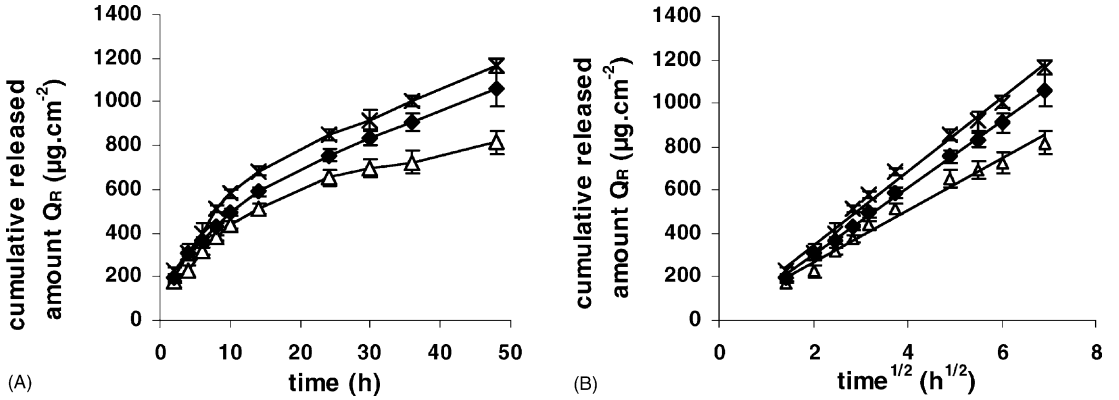

Fig. 3. Effect of the Nicorette TDS surface area on nicotine release profiles. The TDS was trimmed to 4.71 (×), 2.54 (◆) and 1.13 (Δ) cm^2 and was directly applied on Franz-type diffusion cells. Results were expressed as cumulative released amount per surface area unit vs. time (A) and vs. time$^{1/2}$ (B). Means ± S.E.M., $n = 4$.

the fraction of nicotine content released. Differences in Q_R values and F values stemmed only from the different nicotine contents between both TDS: the Nicopatch versus Nicorette release flux ratio (2.3) was close to the Nicopatch (1.75 mg cm^{-2}) versus Nicorette surface area content (830 µg cm^{-2}) ratio (2.1). It is interesting to notice that neither for Nicopatch, nor for Nicorette the cumulative amount of nicotine released after the recommended time of application (24 and 16 h, respectively), determined using the FDA paddle method, was equal to the claimed in vivo release specified in Table 1. For Nicopatch, the 24-h cumulative released amount was higher than the claimed 24-h in vivo release, and for Nicorette cumulative released amounts were lower than the claimed 16 h in vivo release even after 24 h. Such discrepancies between in vivo claimed release and in vitro release data were previously reported by Lewis et al. (1997). These authors showed that the FDA paddle method does not reflect the conditions of in vivo release from patches. It is not difficult to figure out that the complete soaking of TDS in an aqueous medium and the different physico-chemical properties between the aqueous medium and skin should have influence on the release rates.

In order to complete the comparison study between Nicopatch and Nicorette, skin permeation was evaluated on Franz-type diffusion cells. With this method, the devices are in situation closer to clinical application, as they are adhered onto the upper dry surface of the skin sample. The cumulative amount of nicotine that permeated through skin was linear versus time for both TDS (Fig. 2). Despite a 2.1 times higher drug content, Nicopatch provided the same skin permeation rate as Nicorette. Therefore, for Nicopatch at least, skin was the rate-limiting factor for nicotine delivery. Interestingly, skin permeation rates corresponded to the in vivo release claimed for Nicorette (31 µg cm^{-2} h^{-1}) and was close to the value claimed for Nicopatch (29 µg cm^{-2} h^{-1}). Previous studies carried out with Nicorette TDS using rat skin or human cadaver skin gave different skin permeation rates, though in the same magnitude order (Ho and Chien, 1993), confirming the importance of the choice of

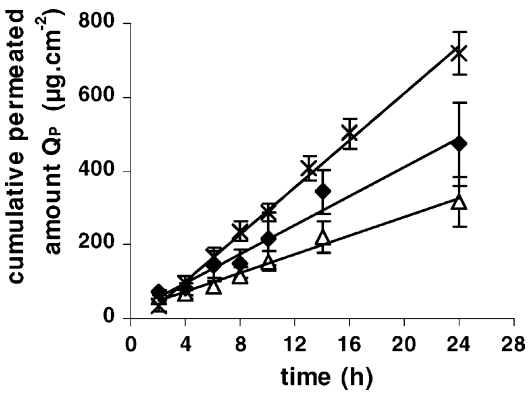

Fig. 4. Effect of the Nicorette TDS surface area on nicotine skin permeation profiles. The TDS was trimmed to 4.71 (×), 2.54 (◆) and 1.13 (Δ) cm^2 and was applied on skin mounted in Franz-type diffusion cells. Means ± S.E.M., $n = 5$.

skin origin to evaluate TDS (Qvist et al., 2000). The cumulative nicotine amount that permeated through skin was 40% of the content at 24 h (recommended time for TDS withdrawal) for Nicopatch and 60% at 16 h for Nicorette, which confirmed the claimed fractions of nicotine released in vivo for both TDS over the respective time periods (Table 1). Therefore, in term of efficiency at delivering nicotine through skin, Nicopatch should be considered as less efficient than Nicorette. In the case of these two TDS, the skin permeation rates and the skin permeated amounts determined using the Franz-diffusion cells mounted with human skin appeared to be predictive of in vivo skin permeation parameters. However, cumulative permeated amounts (reported to the effective surface area of the cells) were probably overestimated, since nicotine continued to permeate according to a sustained way long after the recommended withdrawal times. In the case of Nicorette, cumulative permeated amounts were obviously erroneous: when the skin permeation experiments were prolonged up to 32 h, Q_P after 28 h was higher than the actual nicotine content of the TDS (see Section 3.2). This observation was attributed to the edge effect previously reported by Hadgraft et al. (1991). For Nicorette at least, the actual diffusion surface area clearly exceeded the effective diffusion surface area of the cells.

In order to evaluate the edge effect on drug release flux F, release studies were performed with Nicorette using Franz-type diffusion cells. Cumulative released amounts Q_R were dependent on the surface area of the trimmed TDS and significantly higher than using the FDA paddle method at all time points of determination (Fig. 3A), whatever the surface area. With 2.54 and 4.71 cm^2, the cumulative released amounts even exceeded the actual TDS nicotine content after 30 and 24 h, respectively. The release profiles satisfactorily fitted the Q_R versus $t^{1/2}$ model (Fig. 3B) and F (Table 4) were significantly higher than using the FDA paddle methods (Table 2). Therefore, due to the edge effect, Franz-type diffusion cells led to an overestimation of drug release flux compared to the FDA reference method. The nicotine within the part of the patch overlapping the edge of the cell was responsible for an excess amount of drug diffusing within the TDS matrix and/or the skin towards the receptor phase. In order to minimize the influence of the edge effect on skin permeation data, Nicorette TDS were trimmed to two surface areas (1.13 and 2.54 cm^2) smaller than the cell surface area and were adhered to skin (4.71 cm^2) mounted in cells. This resulted in an underestimation of the cumulative permeated amount Q_P (Fig. 4) and of the skin permeation rates R (Table 3) compared to the claimed in vivo release (Table 1). Such a phenomenon was attributed to the skin reservoir effect, i.e. the accumulation of nicotine within skin (Benowitz, 1995; Benowitz et al., 1991). Therefore, skin permeation rates determined using Franz-type diffusion cells were not only dependent on the intrinsic release properties of the TDS and on the drug permeation through skin, but also on the relative surface areas of the trimmed TDS, of the piece of skin mounted in the cell and of the active diffusion surface, which questioned the validity of the method to evaluate skin permeation parameters of TDS.

In conclusion, based on the FDA paddle method, both TDS had release characteristics of a polymer matrix diffusion type. In term of amount, Nicopatch released more than two-times more nicotine than Nicorette in accordance with their respective contents. In term of release efficiency both TDS were similar: they released around 50% of their nicotine content at 24 h. Skin permeation rates of both TDS determined using the Franz-type diffusion cells were apparently equal and corresponded to the claimed in vivo releases. However, skin permeation data were probably erroneous, since the edge effect led to an overestimation of the cumulative amounts of nicotine that permeated through skin.

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