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PHARMACOKINETICS AND DISPOSITION

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Pharmacokinetic investigation of a nicotine sublingual tablet

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Abstract *Objective*: To evaluate the pharmacokinetics of a new 2-mg nicotine sublingual tablet under varying conditions of use.
Methods: The pharmacokinetics of the 2-mg nicotine sublingual tablet were investigated in four separate studies involving healthy adult volunteer smokers: (1) a multiple-dose comparison with 2-mg nicotine chewing gum ($n=24$; 13 males, 11 females), (2) a dose-proportionality study comparing single doses of 2, 4 and 6 mg ($n=21$, 10 males, 11 females), (3) an evaluation of the effect of incorrect tablet use, i.e. chewing the tablet followed by either immediate or delayed swallowing ($n=19$, 10 males, 9 females), and (4) the effect of oral and gastric pH on nicotine absorption from the tablet ($n=20$; 11 males, 9 females). Study parameters were maximal plasma concentration (C_{max}), time to C_{max} (t_{max}), and area under the plasma concentration–time curve (AUC).
Results: The plasma nicotine profiles were similar following repeated administration of the sublingual tablet and the 2-mg nicotine chewing gum (mean C_{max} 13.2 versus 14.4 ng/ml, median t_{max} 20 versus 20 min, mean $AUC_{11–12}$ 12.4 versus 13.5 ng/ml per hour) with no statistically significant difference between the two treatments. The pharmacokinetics of the 4- and 6-mg doses were non-linear compared to the 2-mg dose, probably as a result of more of the dose being swallowed and undergoing first-pass metabolism in the liver. The mean C_{max} for the 2-, 4- and 6-mg dose was 3.8 ± 1.0, 6.8 ± 2.1, and 9.0 ± 3.3 ng/ml, respectively, and in terms of dose proportionality the relative bioavailability of the 4- and 6-mg dose was 0.82 and 0.71, respectively. Incorrect tablet use, i.e. chewing the tablet and immediate swallowing decreased nicotine bioavailability both in terms of rate and extent. Mean C_{max} was 12.1 ng/ml (correct use), 10.3 ng/ml (chewing and immediate swallowing), and 12.1 ng/ml (chewing and delayed swallowing). Corresponding mean values for $AUC_{9–10}$ were 11.6, 9.6 and 11.2 ng/ml per hour. There were no significant differences between 'alkaline mouth' versus control, 'acidic mouth' versus control or 'alkaline stomach' versus control, but the rate of nicotine absorption was increased at alkaline compared to acidic oral pH (mean C_{max} 6.1 versus 4.9 ng/ml, $P=0.003$; median t_{max} 60 versus 90 min, $P=0.0002$).
Conclusion: The pharmacokinetic profile of the nicotine 2-mg tablet was similar to that of the 2-mg nicotine chewing gum. Absorption of nicotine from the tablet was nonlinear at higher doses (two or three tablets). Chewing the tablet and keeping the remains in the mouth or concurrent use of acidic beverages or antacids are equivalent to recommended sublingual use during normal oral pH conditions.

Key words Nicotine · Sublingual tablet · Pharmacokinetics

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Introduction

Nicotine is the psychoactive component in tobacco that maintains addiction to tobacco [1]. The majority of tobacco users are unable to stop smoking unaided because of tobacco withdrawal symptoms [2]. Nicotine replacement therapy (NRT), which substitutes some of the nicotine that would have been obtained from tobacco, reduces tobacco withdrawal symptoms and craving for cigarettes, thereby aiding smoking cessation [3]. Clinical guidelines in the United States and England now recommend that NRT should routinely be used by all smokers during cessation attempts [4, 5].

As nicotine undergoes extensive hepatic first-pass metabolism following oral administration [6], NRT

formulations have to use other modes of delivering nicotine to the blood stream. Four different NRT formulations are already in use: the transdermal patch, nicotine chewing gum, nasal spray and oral inhaler.

Transdermal nicotine patches offer a convenient and discreet form of NRT, maintaining relatively constant plasma nicotine levels throughout the day. However, they are relatively inflexible in that the wearer cannot self-titrate the dose of nicotine received. Nicotine chewing gum, nasal sprays, and oral inhalers have the advantage of flexible, ad libitum administration, but are not as discreet as the transdermal patch.

The recognition that smokers differ in terms of needs and wants [7] maintains the impetus to develop new forms of nicotine delivery in order to further increase the number of smokers who use NRT during cessation attempts. The recently developed nicotine sublingual tablet offers a new mode of buccal administration of NRT for smokers who prefer an oral dose form but are unable to use gum due to fillings, bridgework and dyspepsia or reject it for aesthetic reasons. In one smoking reduction trial the sublingual tablet was the most highly endorsed of five different nicotine replacement products, and was rated the most useful treatment for tobacco dependence [8]. One 6-month study with a further 6-month follow-up demonstrated that the tablet did not have any adverse effect on the oral mucosa during long-term administration [9].

The nicotine sublingual tablet contains 2 mg of nicotine which is bound to β-cyclodextrin. The tablet is designed to be placed under the tongue, where it slowly disintegrates. The nicotine-β-cyclodextrin complex dissolves, releasing free nicotine which penetrates the oral mucosa.

Four separate studies evaluated the pharmacokinetics of the nicotine sublingual tablet. As many smoking cessation trials have been conducted with nicotine chewing gum, one study compared the plasma nicotine levels achieved with the sublingual nicotine tablet versus the gum. A second study determined the bioavailability of nicotine from the sublingual tablet at three dose levels in order to assess dose proportionality. Although the tablet is designed for sublingual use, some individuals may use it incorrectly by either swallowing it immediately or chewing the tablet; the third study evaluated the effect of incorrect use on plasma nicotine levels. As it has previously been reported that the oral pH may affect buccal absorption of nicotine from nicotine chewing gum [10], the final study investigated the effect of oral and gastric pH on the bioavailability of nicotine from the sublingual tablet.

Materials and methods

Protocol

The studies were approved by the Ethics Committee of the Universities of Lund and Uppsala, and were conducted in accordance with the Helsinki Declaration. All participants provided written informed consent.

All volunteers were healthy adult smokers. Before entering the studies, subjects underwent screening evaluations including medical history, physical examination, laboratory tests and electrocardiogram. Participants had to abstain from nicotine for more than 12 h prior to treatment, and a minimum of 24 h elapsed between different treatments.

Blood samples (5 ml from an antecubital vein) were collected in heparinised venoject tubes which were centrifuged at 1000*g* for 10 min at 4 °C. The plasma was separated, frozen and stored at –20 °C until analysis. The nicotine concentration was determined using capillary gas chromatography following single-step liquid–liquid extraction of the plasma sample [11]. The limit of quantitation was 0.6 ng/ml. Normally the plasma samples were analysed twice. However, if the nicotine content differed by more than 10%, and the absolute difference was greater than 1 ng/ml, then a third analysis was performed. The median value was used in all calculations. The pharmacokinetic calculations were carried out using Siphar (SIMED, France). Any subject with a baseline plasma nicotine level greater than 4 ng/ml was excluded from the analysis.

The maximal plasma concentration (C_{max}) and time to C_{max} (t_{max}) were obtained from observed plasma nicotine concentration–time data. The area under the plasma concentration–time curve (AUC) of the last dosing interval was calculated using the trapezoidal rule. AUC extrapolated to infinity (AUC∞) was calculated using the equation $AUC\infty = AUC_{0-t} + C_t/\lambda z$, where C_t denotes the last value of the concentration–time curve and λz the terminal elimination rate constant. AUC_{0-t} was calculated using the trapezoidal rule and λz was obtained by linear regression analysis of the slope of the logarithmic plasma concentration–time curve. Following single-dose administration, C_{max} and AUC∞ were corrected for baseline nicotine concentration (cC_{max}, cAUC∞) using the equations $cAUC\infty = AUC\infty - C_0/\lambda z$ and $cC_{max} = C_{max} - C_0 e^{-\lambda z \cdot t_{max}}$, where C_0 denotes the baseline concentration.

Conventional bioequivalence criteria were used to evaluate differences between treatments in the studies of dose proportionality, recommended versus incorrect use and pH manipulation. Bioequivalence was stated if the 90% confidence interval (CI) of the ratio μ_{test}/μ_{ref} was fully contained within the interval 0.8–1.25 for C_{max} and AUC and 0.7–1.43 for t_{max}.

Study 1: Comparison with 2-mg nicotine gum

The aim of this crossover study was to compare the plasma nicotine profiles of the nicotine sublingual tablet (Nicorette Microtab, Pharmacia & Upjohn) and 2-mg nicotine polacrilex chewing gum (Nicorette, Pharmacia & Upjohn).

Twenty-four healthy volunteer smokers (13 males aged 20–48 years, 11 females aged 24–48, smoking more than ten cigarettes per day) were given repeated doses of the 2-mg nicotine sublingual tablet or 2-mg nicotine chewing gum once every hour for 11 h (total of 12 administrations). The tablets were placed sublingually and allowed to disintegrate; if anything was left of the tablet after 30 min, the remains were chewed and swallowed. Chewing of the gum was standardised by using a metronome; one piece of gum was chewed every 2 s for 30 min, and saliva was swallowed every minute. Each used gum was placed in a sealed container. Analysis of residual nicotine was performed spectrophotometrically. The amount of nicotine extracted was calculated as the difference between the amount of nicotine in unused gums (mean of ten pieces) and the residual amount in used gums (mean of eight pieces per subject).

Serial blood samples were drawn at 0, 2, 4, 6, 8, 9, 10 and 11 h to determine trough nicotine levels and at 10-min intervals between 11 and 12 h to determine nicotine levels during the last dosing interval. The study parameters C_{max} and t_{max} of the last dosing interval and AUC_{11-12} were analysed with ANOVA for treatment differences. Nicotine plasma concentrations at each time-point were tested for normality and a repeated measures ANOVA was performed.

Study 2: Dose proportionality

The dose proportionality of nicotine from the 2-mg nicotine sublingual nicotine tablet (Nicorette Microtab) was assessed in 21

healthy adult smokers (10 males aged 24–45 years, 11 females aged 22–48 years, smoking ≥20 cigarettes containing ≥1 mg nicotine per day) in an open, three-way crossover randomised trial. Subjects had to fast from midnight, and no food or drink were allowed until 60 min after treatment administration. Single doses of one, two or three tablets were administered sublingually in a randomised order, and allowed to disintegrate; saliva was swallowed once every minute.

Serial venous blood samples were drawn for determination of nicotine levels before (0) and at 10, 20, 30, 45, 60, 90 min and 2, 3, 4, 5, 6, 7, 8 h after drug administration. Study variables were AUC_∞ and C_{max}.

Dose proportionality was assessed as follows:

$$1.\ F_{rel} = \frac{AUC_\infty \text{ and } C_{max}(2\ tabl)}{\frac{2}{AUC_\infty \text{ and } C_{max}(1\ tabl)}}$$

$$2.\ F_{rel} = \frac{AUC_\infty \text{ and } C_{max}(3\ tabl)}{\frac{3}{AUC_\infty \text{ and } C_{max}(1\ tabl)}}$$

A 90% CI of F_{rel} within 0.8–1.25 indicated linear pharmacokinetics. F_{rel} of both study parameters was analysed with ANOVA. The CIs were calculated with the error taken from the ANOVA.

Study 3: Recommended versus incorrect tablet use

The objective of this open, three-way crossover, randomised study was to evaluate the bioavailability of nicotine from the sublingual nicotine tablet when used incorrectly, by chewing and either immediate or delayed swallowing.

Nineteen healthy smokers (ten males, nine females, aged 24–47 years, smoking more than ten cigarettes per day) were given one 2-mg nicotine sublingual tablet (Nicorette Microtab) every hour for 9 h (ten administrations). Subjects were instructed to either place the tablet sublingually and allow it to disintegrate, while swallowing the saliva once every minute, or chew and immediately swallow the tablet, or chew the tablet but delay swallowing for as long as possible.

Serial venous blood samples were drawn at baseline (0) and at 1, 2, 3, 4, 5, 6, 7, 8 and 9 h to determine trough nicotine levels and every 10 min between 9 and 10 h to determine nicotine levels during the last dosing interval. Conventional methodology of bioequivalence analysis was used to demonstrate equivalence/inequivalence between the test situations. The study variables C_{max} and t_{max} of the last dosing interval and AUC_{9-10} were analysed with ANOVA. A 90% CI was calculated for test/reference with the error taken from the ANOVA. Equivalence between test situations was stated if the 90% CI of the ratio test/reference was fully contained within the interval 0.8–1.25 (AUC and C_{max}) and 0.7–1.43 for t_{max}. Nicotine plasma concentrations were analysed at each time-point with a repeated measures ANOVA to evaluate treatment differences.

Study 4: Effect of oral and gastric pH on absorption

The effect of oral and gastric pH manipulation on the bioavailability of nicotine from the sublingual tablet was assessed in an open, randomised, four-way crossover study involving 20 healthy subjects (11 males aged 22–48 years, 9 females aged 23–47 years, smoking ten or more cigarettes per day).

Two 2-mg nicotine sublingual tablets (Nicorette, Microtab) were given as a single 4-mg dose on four occasions, with or without pH modifying agents, with a wash-out period of at least 48 h between each session. For 'acidic mouth', 10 ml of freshly prepared orange juice was taken every 30 s for 2 min prior to and for 30 min after tablet administration. 'Alkaline mouth' involved sucking antacid lozenges containing calcium and magnesium carbonate (Rennie, Nicholas) for 2 min prior to and 30 min after treatment administration. 'Alkaline stomach' was achieved by giving a single 150-mg dose of ranitidine (Zantac, Glaxo), an H_2-antagonist, 2 h before nicotine treatment plus administering 10 ml of an antacid mixture (Novaluzid, ASTRA-Hässle) before and 2, 4 and 6 h after the nicotine dose. One session without pH manipulation served as control. The oral pH was measured 30 min after nicotine administration by applying two indicator strips (Merck) to the buccal side of the oral cavity and comparing the colour change with a colour scale.

Serial venous blood samples were drawn before (0) and at 10, 20, 30, 45, 60, 75 and 90 min and 2, 3, 4, 5, 6, 7 and 8 h after nicotine administration to determine plasma nicotine concentrations. A possible effect of pH manipulation on the bioavailability of nicotine from the sublingual tablet was evaluated using conventional bioequivalence criteria. Study variables were pH, C_{max}, t_{max} and AUC∞. An ANOVA was used in the analysis of bioequivalence and for differences between treatments.

Results

Study 1: Comparison with 2-mg nicotine gum

In total, 22 and 21 subjects were eligible for analysis following tablet and gum administration, respectively; two and three subjects, respectively, were excluded because of high baseline plasma nicotine concentrations. The mean tablet disintegration time was 26 min. The mean ± SD amount of nicotine extracted from the gum was 1.55 ± 0.12 mg. The mean C_{max}, t_{max} and $AUC_{11-12\ h}$ obtained with the sublingual tablet and 2-mg chewing gum are shown in Table 1. There were no statistically significant differences between the two treatments for any pharmacokinetic measure. Once hourly administration of the sublingual tablet generated nicotine plasma concentrations of the same magnitude as once hourly administration of the 2-mg gum (Fig. 1, upper left). Five and six subjects reported adverse events (AE) following administration of the gum and tablet, respectively. The most frequently reported adverse events were hiccups and throat irritation; abdominal discomfort, cough, headache, nausea, feeling speeded (restless, excited) and tachycardia were occasionally reported.

Study 2: Dose proportionality

Of the 21 subjects, 17 were eligible for analysis; 4 were excluded because of high baseline nicotine levels (> 4 ng/ml). In a majority of the individual plasma concentration–time curves, two peaks were observed; the first probably reflected buccal absorption and the second absorption of swallowed nicotine (Fig. 1, lower left). The

Table 1 Pharmacokinetic parameters during the last dosing interval for the 2-mg nicotine sublingual tablet and the 2-mg nicotine chewing gum. Data are mean (with SD) unless otherwise indicated

Parameter	Sublingual tablet	2-mg gum
C_{max} [ng/ml]	13.2 (3.1)	14.4 (2.3)
Median t_{max} (range) [min]	20 (10–40)	20 (10–40)
AUC_{11-12} [ng/ml·h]	12.4 (3.0)	13.5 (2.3)

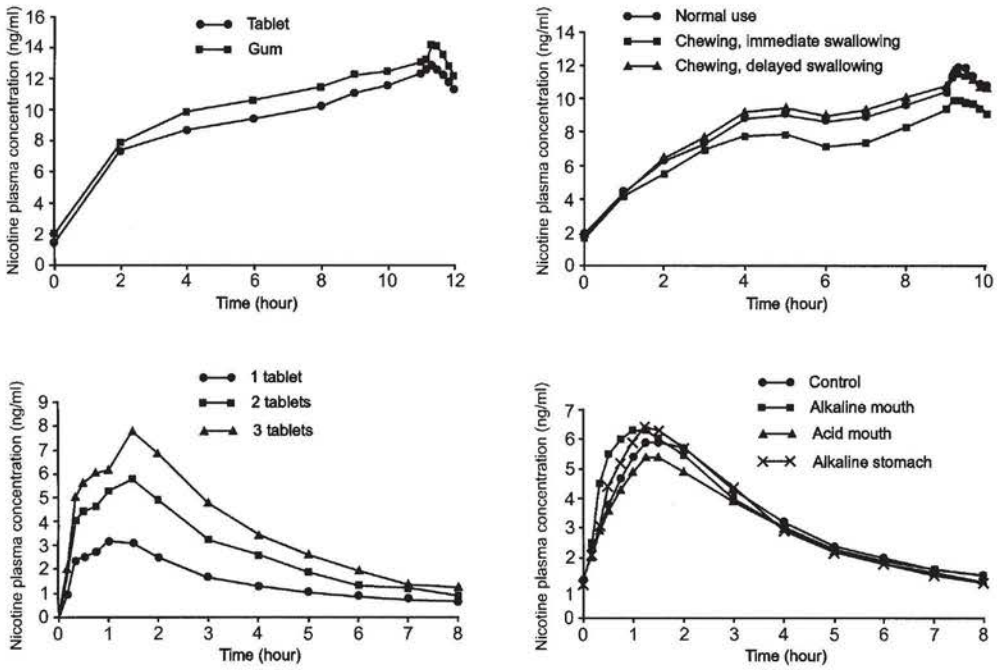

Fig. 1 Nicotine plasma concentrations following: multiple-dose administration (once hourly) of the sublingual tablet and the gum (*top left*); single-dose administration of one, two and three sublingual tablets (*bottom left*); multiple-dose administration (once hourly) during correct use (sublingual) and incorrect (chewing and either immediate or delayed swallowing) use of the sublingual tablet (*top right*); and single-dose administration of two sublingual tablets during acidic mouth, alkaline mouth and alkaline stomach conditions (*bottom right*)

mean C_{max} for one, two and three tablets was 3.8 ± 1.0 (range, 2.5–6.5), 6.8 ± 2.1 (range, 3.6–12.0) and 9.0 ± 3.3 ng/ml (range, 3.8–14.8), respectively. Normalised for dose, the corresponding C_{max} values for two and three tablets were 3.4 ± 1.0 (range, 1.8–6.0) and 3.0 ± 1.1 ng/ml (range, 1.3–4.9), respectively. The 90% CIs of the ratio for the dose-normalised C_{max}, using the one-tablet dose as reference, were 0.88 (0.78–1.00) and 0.76 (0.67–0.85) for the two- and three-tablet doses, respectively.

The AUC_{∞} was estimated at 17.0 ± 5.0 (range, 5.9–24.5), 27.6 ± 7.6 (range, 15.3–41.0) and 36.5 ± 13.1 ng/ml per hour (range, 16.3–63.9) after one, two and three tablets, respectively. In terms of dose proportionality, the relative bioavailability of nicotine from the two- and three-tablet doses was estimated at 0.82 (0.73–0.95) and 0.71 (0.63–0.82), respectively, demonstrating a deviation from linearity.

The incidence of adverse events increased with increasing dose; 10 adverse events were reported with one tablet, compared to 19 and 27 after two and three tablets, respectively. The most common adverse events were hiccups (15), heartburn (14) and nausea (11). All adverse events were mild to moderate, except for three cases at the highest dose (hiccups, heartburn and nausea) that were rated as severe.

Study 3: Recommended versus incorrect tablet use

During chewing and delayed swallowing, the median interval between chewing and swallowing was 20 min (range, 1–20 min). The plasma concentration–time profiles were similar for all three treatments; the mean C_{max}, t_{max} and AUC_{9-10} are shown in Table 2.

Comparison of the plasma nicotine concentrations achieved after recommended use and chewing and delayed swallowing did not reveal any statistically significant difference at any time point, whereas chewing and immediate swallowing resulted in significantly lower steady-state plasma concentrations compared to recommended use following the fourth tablet administration (Fig. 1, upper right). Although the median t_{max} was identical for all three treatments, the frequency distribution of individual t_{max} values demonstrated a shift towards shorter values with both chewing and immedi-

Table 2 Pharmacokinetic parameters during correct (sublingual) use and incorrect (chewing and either immediate or delayed swallowing) use of the 2-mg nicotine tablet. Data are mean (with SD) unless otherwise indicated

Parameter	Correct use	Chewing and immediate swallowing	Chewing and delayed swallowing
C_{max} [ng/ml]	12.1 (2.3)	10.3 (3.3)*,**	12.1 (2.9)
Median t_{max} (range) [min]	20 (10–60)	20 (10–60)	20 (10–60)
AUC_{9-10} [ng/ml·h]	11.6 (2.4)	9.6 (3.1)***,****	11.2 (2.7)

*$P = 0.0006$ versus correct use; **$P = 0.0004$ versus chewing and delayed swallowing; ***$P = 0.0002$ versus correct use; ****$P = 0.0009$ versus chewing and delayed swallowing

ate swallowing and chewing and delayed swallowing compared to recommended use.

The mean and 90% CIs for the ratio between chewing and delayed swallowing versus recommended use were 0.96 (0.89–1.07) for $AUC_{9-10\ h}$, 0.99 (0.93–1.10) for C_{max} and 0.77 (0.55–1.07) for t_{max}. Corresponding values for the ratios between chewing and immediate swallowing and recommended use were 0.80 (0.74–0.88), 0.82 (0.76–0.90) and 0.86 (0.62–1.19), respectively.

Chewing and immediate swallowing of the sublingual tablet produced slightly more adverse events than either recommended use or chewing and delayed swallowing (ten versus four and three). The most common events were hiccups and heartburn.

Study 4: Effect of oral and gastric pH on absorption

The mean oral pH at the end of the administration time (30 min) was 6.6 ± 0.6 in the control situation. Sucking antacid lozenges increased the oral pH to 7.2 ± 0.6 ($P = 0.0013$) whereas ingestion of orange juice decreased it to 5.9 ± 1.0 ($P = 0.0004$). However, the pH modifying agents had no effect on either the rate or the extent of nicotine bioavailability compared to the control situation (Table 3). Comparison of the two pH extremes, alkaline and acidic mouth, revealed a small but statistically significantly higher rate of nicotine absorption in alkaline mouth, demonstrated by a shorter t_{max} and higher C_{max} (Table 3, Fig. 1, lower right).

A total of 23 adverse events were reported by 17 subjects during the four treatment sessions. The majority of these were mild or moderate and transient, resolving within 30 min. Some of these were related to concurrent treatment with ranitidine and antacids.

Discussion

The studies reported here compare the pharmacokinetic profile of the 2-mg nicotine sublingual tablet with that of the 2-mg nicotine gum, and investigate the pharmacokinetic parameters of the sublingual tablet under varying conditions of use.

The results of the comparison of the nicotine sublingual tablet and the 2-mg chewing gum show similar pharmacokinetic characteristics (C_{max}, t_{max} and AUC) for the two nicotine preparations when used according to the same hourly dosing schedule. This may seem confusing since the amount of nicotine extracted from the gum is lower than the amount of nicotine in the tablet. The amount of nicotine reaching the systemic circulation is, however, similar since the absolute bioavailability of nicotine from the gum is higher (0.85) than from the tablet (0.65).

The 2-mg nicotine gum has consistently been shown to increase abstinence rates among smokers attempting to quit [3], and the similar plasma profile of the sublingual tablet suggests that it should also be an effective aid to smoking cessation. In placebo-controlled clinical trials, the nicotine sublingual tablet significantly reduced tobacco withdrawal symptoms and craving [12] and increased the 6-month abstinence rates [13].

In the dose-proportionality study (study 2) the ratio of the dose-normalised AUC_{∞}, using the one-tablet (2-mg) dose as a reference, was significantly lower than expected for the two- (4 mg) and three-tablet (6 mg) doses. The most plausible explanation is that a larger fraction of the higher doses was swallowed and subject to first-pass elimination. This is in agreement with one study where a single oral dose of three tablets (6 mg) produced maximum plasma levels of only 5.5 ng/ml (3.7–7.9) [14]. The increasing number of tablets used (one, two and three tablets, respectively) may have been associated with increased production of saliva. In addition, absorption via the oral mucosa may be capacity limited, contributing to this deviation from linearity.

Following single-dose administration of the sublingual tablet, two absorption phases were observed in a majority of the subjects (Fig. 1, lower left), the first reflecting absorption from the oral cavity and the second reflecting intestinal absorption. The plasma peaks resulting from the two processes were separated by approximately 1 h. Following multiple-dose administration, with a dosing interval of 1 h, the resulting C_{max} of the last dosing interval is the sum of the nicotine intestinally absorbed from the previous administration and buccally absorbed nicotine from the final administration. This is probably the reason for the earlier t_{max} following multiple-dose administration compared to single-dose administration.

The slightly lower bioavailability and lower C_{max} after chewing and immediate swallowing than recommended use in study 3 (C_{max}, 10.3 ± 3.3 ng/ml versus

Table 3 Pharmacokinetic parameters following administration of two 2-mg nicotine sublingual tablets during acidic mouth, alkaline mouth and alkaline stomach conditions. Data are mean (with SD) unless otherwise indicated

Parameter	Control	Acidic mouth	Alkaline mouth	Alkaline stomach
C_{max} [ng/ml]	5.6 (1.9)	4.9 (1.8)	6.1 (2.1)[a]	6.2 (2.2)[a]
Median t_{max} (range) [min]	75 (30–180)	90 (30–240)	60 (30–120)[b]	75 (30–120)
AUC_{∞} [ng/ml·h]	26.5 (9.4)	25.5 (10.0)	26.7 (10.8)	26.3 (10.0)

[a] Alkaline mouth and alkaline stomach significantly higher than acid mouth ($P = 0.0034$ and 0.0031, respectively)
[b] t_{max} in alkaline mouth was significantly earlier than in control ($P = 0.0029$), acid mouth ($P = 0.0002$) and alkaline stomach ($P = 0.0117$) conditions

12.1 ± 2.3 ng/ml) may also be explained by a larger fraction of the dose being swallowed and subject to first-pass metabolism. Chewing the tablet and keeping the remains in the mouth may theoretically increase the bioavailability, resulting in higher plasma nicotine peaks than those obtained after recommended sublingual use. However, similar peak plasma concentrations were obtained after both modes of administration indicating a capacity-limited absorption of nicotine via the buccal mucosa.

The effects of pH on the absorption of nicotine are well established in both animals [15, 16] and humans [10, 17, 18]. Nicotine in the form of the undissociated, lipid-soluble base readily penetrates cell membranes. As the pKa of nicotine is 8.0, under acidic conditions very little nicotine is present as the free base, whereas at pH 8 the proportion of free base is 50%. As mucosal absorption of nicotine is promoted by alkalinity and decreased with acidity, alkalinisation of the mouth and stomach by antacids and H_2-antagonists and the acidifying effect of acidic beverages (e.g. coffee, carbonated drinks and fruit juices) may influence the bioavailability of nicotine from the sublingual tablet. Since the smoking population is known to have an increased incidence of peptic ulcer disease [19] and gastroesophageal [20] and bile reflux [21], conditions which are commonly treated with antacids and H_2-antagonists, study 4 was designed to simulate situations close to everyday life in which pH-modifying agents and the nicotine sublingual tablet may be used simultaneously.

Our study demonstrated that simultaneous sucking on antacid lozenges, ingestion of acidic beverages such as orange juice or intake of antacid mixtures did not have any effect on the bioavailability of nicotine. Comparisons of the two pH extremes, alkaline mouth and acidic mouth, revealed a small but statistically significantly higher rate of nicotine absorption in alkaline mouth (as demonstrated by a shorter t_{max} and higher C_{max}) but this did not have any effect on the AUC.

This contrasts with results obtained by Henningfield et al. [10], in which rinsing with acidic beverages virtually eliminated nicotine absorption from nicotine chewing gum. However, several factors may explain the modest effect of pH on absorption of nicotine from the sublingual tablet. When the tablet is placed under the tongue, much of the nicotine released is likely to be absorbed locally. A local microclimate, protected by the tongue, may be created which may differ from the pH in the rest of the oral cavity. Nicotine, being a weak base, will have a weak buffering effect and increase the local pH. Moreover, saliva flow can be stimulated by taste (e.g. fruit candy and citric acid). As stimulated saliva is more alkaline than resting saliva [22], orange juice may increase the sublingual pH (as a result of saliva stimulation) whereas the acidifying effect of the juice will predominate in the rest of the oral cavity.

The adverse events reported were generally mild and tolerable when the tablet was administered according to the recommended dosage schedule (one or two tablets per hour, depending on the smoker's level of dependence on tobacco) and were similar to those previously described during treatment with nicotine gum.

In conclusion, the pharmacokinetic profile of the 2-mg nicotine sublingual tablet resembled that of 2-mg nicotine chewing gum. Buccal absorption of nicotine from the tablet was non-linear at higher doses (4 or 6 mg). Neither chewing the tablet and keeping the remains in the mouth nor concomitant administration of acidic beverages or antacids resulted in any changes in the pharmacokinetic parameters of nicotine. The sublingual route is a well-recognised mode of administration, particularly for drugs that undergo extensive first-pass hepatic metabolism, and the nicotine sublingual tablet offers a discreet, oral aid to smoking cessation.

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