Pharmacokinetics and Metabolism of Transdermal Oxybutynin: *In Vitro* and *in Vivo* Performance of a Novel Delivery System

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Purpose. The purpose of this work was to characterize *in vitro/in vivo* delivery and pharmacokinetics of oxybutynin (OXY) and its active metabolite, *N*-desethyloxybutynin (DEO), by a novel matrix transdermal system (TDS).

Methods. Two *in vivo,* randomized, three-way crossover trials examined single/multiple OXY TDS doses. Abdomen, buttock, and hip application sites were compared and dose proportionality was evaluated. Model independent pharmacokinetics, elimination rate constants, and metabolite/drug ratios were derived from both plasma OXY and DEO concentrations.

Results. Single/multiple applications of the OXY TDS to the abdomen yielded mean C_{max} OXY concentrations of 3.4 ± 1.1/6.6 ± 2.4 ng/mL and median t_{max} of 36/10 h, with steady state achieved during the second application. Plasma OXY and DEO concentrations decreased gradually after C_{max} until system removal. Buttock and hip applications resulted in bioequivalent OXY absorption. AUC ratios of DEO/OXY were 1.5 ± 0.4 (single dose) and 1.3 ± 0.3 (multiple dose). Mean *in vitro* OXY skin absorption (186 μg/h) was comparable to the estimated *in vivo* delivery (163 μg/h) over 96 h.

Conclusions. Sustained delivery over 4 days and multiple sites allow a convenient, well-tolerated, twice-weekly OXY TDS dosing. A low incidence of anticholinergic side effects is expected during clinical use because of the avoidance of presystemic metabolism and low DEO plasma concentrations. The consistent delivery, absorption, and pharmacokinetics should result in an effective treatment of patients with overactive bladder.

KEY WORDS: oxybutynin; transdermal; pharmacokinetics; *N*-desethyloxybutynin; bioequivalence.

INTRODUCTION

Oxybutynin (OXY) is a tertiary amine that has anticholinergic and direct spasmolytic effects on the bladder smooth muscle. (1) It is widely used in the treatment of urge urinary incontinence associated with detrusor instability (2–4). However, after oral administration, many patients discontinue its use because of unacceptable anticholinergic side effects, in particular dry mouth (5). These side effects have been associated with relatively high plasma concentrations of the primary metabolite of OXY, *N*-desethyloxybutynin (DEO), which circulates in concentrations approximately 4 to 10 times those of the parent compound (6–9). In radioligand binding studies, the average pK_i for OXY and DEO in bladder smooth muscle were identical (8.2 ± 0.1); however, salivary gland pK_i for DEO was significantly greater ($p < 0.05$) than for OXY (8.7 ± 0.1 vs 8.5 ± 0.1; Ref. 10). The greater affinity of DEO for the muscarinic receptors of the salivary glands may contribute to the anticholinergic side effect, dry mouth.

Presystemic metabolism of OXY occurs primarily because of extensive hepatic first-pass metabolism with a small contribution by intraluminal gastrointestinal metabolism, resulting in oral bioavailability of approximately 6% of the oral dose (11). Transdermal administration of OXY avoids that extensive presystemic metabolism (12). Transdermal delivery not only reduces DEO formation, with the potential for reduced incidence of anticholinergic side effects, but also allows for a convenient twice-weekly dosing regimen. Sustained OXY delivery also results in more stable plasma drug concentrations over a 3- to 4-day dosing interval.

This article describes the results of two trials in healthy volunteers; the trials characterize the performance of the transdermal system (TDS) and support initial *in vitro* estimates of the transdermal delivery of OXY. Plasma concentrations of OXY and DEO were measured after single- and multiple-dose applications to determine absorption from three application sites, the abdomen, buttock, and hip, and to evaluate the dose proportionality of three sizes of the OXY TDS.

METHODS AND MATERIALS

Subjects

Twenty-four healthy subjects, 11 males and 13 females, enrolled in the single-dose, bioequivalence trial. Subjects ranged in age from 20 to 77 years (mean age 49 years) and weighed 56 to 89 kg (mean weight 74 kg). All 24 subjects completed the trial. Twenty-six healthy subjects, 13 males and 13 females, were enrolled in the multiple-dose, steady-state trial. Subjects ranged in age from 20 to 65 years (mean age 33 years) and weighed 54 to 88 kg (mean weight 69 kg). Two subjects withdrew early, one because of treatment-related adverse events (mild headache), and the second for nonstudy-related reasons. One subject's TDS was inadvertently removed 36 h early. The data from these three subjects were not included in the pharmacokinetic analysis.

Treatments

OXY (free base), a tertiary amine, is soluble in alcohol, but relatively insoluble in water and has a molecular weight of 357 Daltons. The OXY TDS (Watson Laboratories, Inc., Salt Lake City, UT, USA) is a matrix-type TDS containing 12, 24, or 36 mg of OXY and triacetin (permeation enhancer) dissolved in an acrylic block-copolymer adhesive with surface areas of 13, 26, or 39 cm^2, respectively (13). The systems were designed to deliver drug continuously over 96 h.

Study Design

Both trials were conducted in accordance with the U.S. Code of Federal Regulations (21 CFR 50, 56, and 312), the ethical principles stated in the Declaration of Helsinki, and the applicable Guideline for Good Clinical Practice. Institutional Review Board approval was obtained (Bio-Kinetic

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Clinical Applications IRB, Springfield, MO, USA; Integ-Review, Austin, TX, USA), and all subjects provided written informed consent prior to study participation.

The randomized, three-way crossover, single-dose, bioequivalence trial was conducted by Bio-Kinetic Clinical Applications, Inc., Springfield, MO, USA, and consisted of three treatment periods during which a single 39-cm^2 OXY TDS was worn for 96 h on the abdomen, buttock, or hip. Treatment periods were separated by at least 7 days to allow for drug washout. Venous blood samples (7 mL/sample) for analysis of plasma OXY and DEO concentrations were collected before TDS application (0), and at 1, 2, 4, 6, 8, 10, 12, 24, 36, 48, 60, 72, 84, 96, 96.5, 97, 98, 99, 100, 102, 104, 108, and 120 h after TDS application.

The randomized, three-way crossover, multiple-dose, steady-state trial was conducted by MDS Pharma, Inc. (formerly Phoenix International Life Sciences, Inc.), Cincinnati, OH, USA, and included sequential application to the lower abdomen of three 13-, 26-, or 39-cm^2 OXY TDSs. The first two systems were worn for 84 h each, followed by a third 96-h application, alternating left or right application sites. Venous blood samples (7 mL/sample) for analysis of plasma OXY and DEO concentrations were collected before the first TDS application (0), at 84 h after the first and second applications, and at 1, 2, 4, 6, 10, 12, 24, 36, 48, 60, 72, 84, 96, and 120 h after application of the third TDS in each treatment period. Each treatment period was separated by 14 days to allow for drug washout.

Analytical and *in Vitro* Experimental Methods

Plasma was harvested from blood samples and frozen until assayed for OXY and DEO concentrations by MDS Pharma, Inc. (Lincoln, NE, USA), using a validated high-performance liquid chromatography/mass spectrophotometry/mass spectrophotometry (LC/MS/MS) method. OXY and DEO were extracted by solid phase extraction from 1.0 mL of plasma spiked with 5 ng of oxybutynin-D5 (OXY-D_5) and 5 ng of *N*-desethyloxybutynin-D5 (DEO-D_5) as internal standards. Organic solvent eluent was evaporated at 55°C with samples reconstituted in methanol/ammonium formate solution and analyzed with LC-MS/MS using an AB/MDS Sciex API-4000 system running in positive mode. Selected ions were 142.3 m/z (daughter ion of 358.3 m/z) for OXY, 96.1 m/z (daughter ion of 330.0 m/z) for DEO, 147.3 m/z (daughter ion of 363.4 m/z) for OXY-D_5, and 101.1 m/z (daughter ion of 335.2 m/z) for DEO-D_5. Calibration curves were constructed using OXY and DEO and were linear over the assay range (0.05–50 ng/mL), with the lower limit of quantitation for OXY and DEO at 0.05 ng/mL, using a 1-mL plasma sample. The overall precision (% CV) for the calibration standards and quality controls were all within 10% and 14%, respectively, at all concentrations.

Residual OXY content in used and control (unused) systems and analyses of *in vitro* permeation of OXY were determined by a validated high-performance liquid chromatography method as described previously (12). DEO is not observed in used TDSs or during cadaver skin flux experiments. *In vitro* human cadaver skin flux studies were performed over 96 h using modified Franz nonjacketed permeation cells as described previously (12). Interval and cumulative *in vitro* skin flux are expressed as μg/39 cm^2/h and μg/39 cm^2.

Pharmacokinetics and Statistical Analysis

Plasma concentration time profiles for OXY and DEO were characterized in terms of $AUC_{0\text{-}t}$ (area under the time-concentration curve from time 0 to time t), $AUC_{0\text{-}\infty}$ (area under the time-concentration curve from time 0 to infinity), C_{max} (maximal plasma drug concentration), and t_{max}(time to maximal plasma drug concentration), as appropriate. Steady-state parameters were derived during the third TDS application in the multiple-dose study. These model independent pharmacokinetic parameters were determined using standard methods of direct observation of the time-concentration curves, trapezoidal method for AUC, and apparent elimination rate constant k (estimated by linear regression of the log-transformed plasma concentration data in the terminal log-linear phase of the plasma concentration profile). Correction of AUC for measurable drug concentrations at time "0" was performed by subtracting the amount C/k from the trapezoidal AUC calculation. Absorption kinetics were estimated by Wagner-Nelson analysis of plasma concentrations and estimated elimination rate constant (14). Interval absorption rates were estimated based on percentage absorption over the predefined intervals corresponding to the *in vitro* skin flux studies and the nominal overall estimate of dose from the analysis of used TDS. Bioequivalence of the three application sites was determined by evaluating the test: reference ratio of C_{max} and $AUC_{0\text{–}\infty}$ for OXY and DEO using an analysis of variance model appropriate for a three-period crossover design using the abdominal site as reference. The antilogs of the confidence limits from $\log_e$-transformed data were used to obtain the 90% confidence intervals (CI) for the test: reference ratio of geometric means. Using a paired t test, attainment of steady state was assessed by comparing the plasma OXY concentrations 84 h after the second and third TDS applications with the plasma concentrations 84 h after the first TDS application. A test for overall dose proportionality of $AUC_{0\text{–}96}$ was performed using the classic weighted regression approach. This approach requires dose linearity and zero intercept to assert dose proportionality. $AUC_{0\text{–}96}$ was weighted by one/dose. The model for initial assessment tests was $Y = a + b\,(dose) + c\,(dose^2)$. When the coefficient for the quadratic term c is not significantly different from zero, dose linearity is claimed. The next model of interest was $Y = a + b\,(dose)$. If the intercept a is not significantly different from zero, dose proportionality may be claimed. Differences in t_{max} between application sites and between system sizes were determined using the Wilcoxon signed rank test. The estimated daily transdermal delivery rate in both studies was calculated as the total OXY delivered (determined by residual analysis of the used systems) over the 96-h wear period divided by 4 days. Statistical analysis was performed using the SAS statistical package (version 6.12, SAS Institute, Cary, NC, USA). Significance was assumed at $p < 0.05$.

RESULTS

After the initial TDS application, mean plasma OXY and DEO concentrations gradually increased over 24 to 36 h, reaching a relatively stable level for approximately 24 h before declining slightly over the remaining duration of the 96-h wear period (Fig. 1). A lag time of approximately 2 h was observed before the appearance of drug in the plasma after

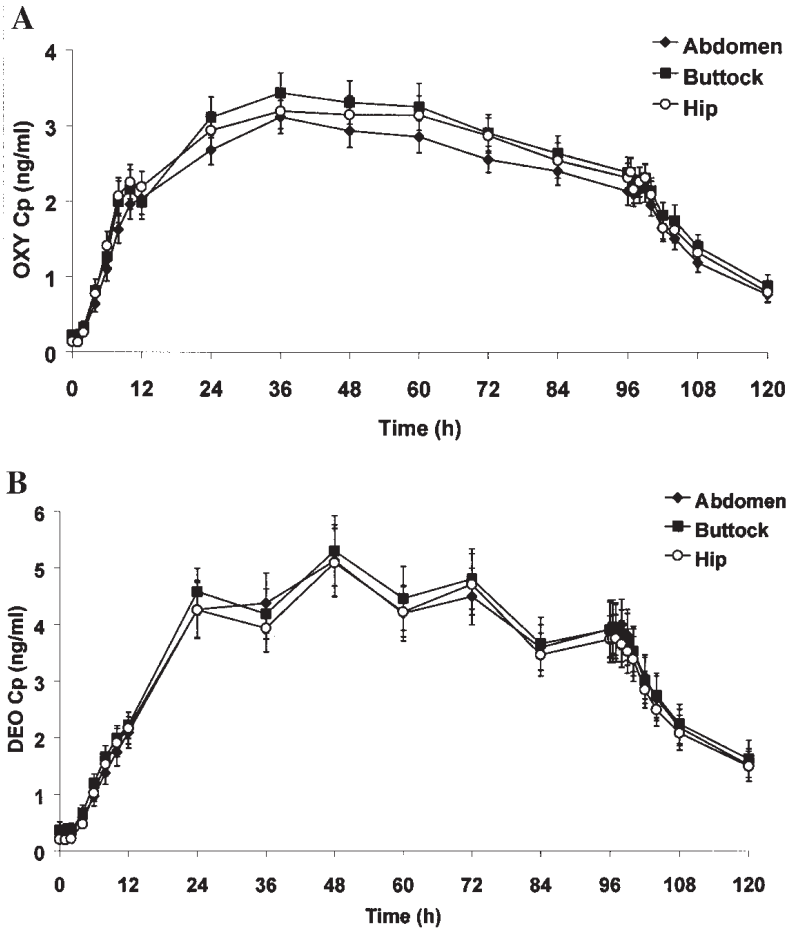

Fig. 1. Mean (± SEM) plasma OXY (A) and DEO (B) concentrations following a single-dose, 96-h TDS application to the abdomen, buttock, and hip (n = 24).

initial TDS application. A transient increase in plasma concentrations was observed 30 min after system removal, followed by a rapid decline in OXY and DEO plasma concentrations. Plasma DEO concentrations were approximately 1.5 times greater than OXY concentrations, regardless of the application site. Comparable plasma concentration profiles were observed for the three application sites.

Pharmacokinetic parameters are summarized in Table I. Mean OXY C_{max} values ranged from 3.4 ± 1.1 to 4.0 ± 1.5 ng/mL at the three application sites, with DEO concentrations approximately 1.5 times greater. Mean OXY $AUC_{0-\infty}$ values were 14% higher after TDS application to the buttock (324 ng · h/mL) and 10% higher after application to the hip (311 ng · h/mL) compared with the abdomen (284 ng · h/mL). Mean DEO $AUC_{0-\infty}$ values were 16% higher after TDS application to the buttock (504 ng · h/mL) and 12% higher after TDS application to the hip (488 ng · h/mL) compared with the abdomen (435 ng · h/mL). OXY absorption after TDS application to the buttock and the hip was bioequivalent to the abdominal application site. The 90% CI for the OXY C_{max} and $AUC_{0-\infty}$ ratios between application sites were within the acceptable range (0.80, 1.25) for bioequivalence (Table II). Median OXY and DEO C_{max} occurred within 36 to 48 h of TDS application to the abdomen, buttock, and hip. Median OXY and DEO t_{max} times were not significantly different between the buttock and abdominal application sites (p = 0.8462 and 0.3573, respectively) and between the hip and abdominal application sites (p = 0.7908 and 0.6938, respectively). The average estimated total OXY dose (mean ± SD) delivered to the abdomen (13.1 ± 2.6 mg), buttock (15.5 ± 2.5

Table I. Single-Dose OXY and DEO Pharmacokinetic Parameters (Mean ± SD, n = 24)

Pharmacokinetic parameter	Abdomen		Buttock		Hip	
	OXY	DEO	OXY	DEO	OXY	DEO
C_{max} (ng/mL)	3.4 ± 1.1	5.0 ± 2.7	4.0 ± 1.5	5.8 ± 2.9	3.7 ± 1.3	5.7 ± 3.3
AUC_{0-120} (ng · h/mL)	268 ± 93	389 ± 208	303 ± 119	448 ± 240	293 ± 111	436 ± 243
$AUC_{0-\infty}$ (ng · h/mL)	284 ± 104	435 ± 259	324 ± 136	504 ± 311	311 ± 126	488 ± 301
t_{max} (median, h)	36.0	48.0	48.0	48.0	48.0	48.0
(range, h)	12–96.5	24–96.5	24–84	24 ± 97	8 ± 72	24 ± 102
Ratio DEO:OXY ($AUC_{0-\infty}$)	1.5 ± 0.4		1.5 ± 0.4		1.5 ± 0.5	

Table II. Pharmacokinetic Parameter Ratios and Confidence Intervals Demonstrating Application Site Bioequivalence

Variable	Comparison (test: reference)	Pharmacokinetic parameter	Ratio	90% CI
OXY	Buttock: abdomen	$AUC_{0-\infty}$	1.1361	1.0641, 1.2129
		C_{max}	1.1519	1.0668, 1.2439
	Hip: abdomen	$AUC_{0-\infty}$	1.0891	1.0203, 1.1625
		C_{max}	1.0802	1.0005, 1.1661
DEO	Buttock: abdomen	$AUC_{0-\infty}$	1.1657	1.0765, 1.2623
		C_{max}	1.2033	1.0885, 1.3301
	Hip: abdomen	$AUC_{0-\infty}$	1.1097	1.0250, 1.2014
		C_{max}	1.1257	1.0186, 1.2440

mg), and hip (14.1 ± 2.3 mg) application sites were comparable, with estimated average daily OXY doses of 3.3 ± 0.7, 3.9 ± 0.6, and 3.5 ± 0.6 mg/day, respectively.

Comparison of the estimated cumulative extent of absorption and interval absorption rates from *in vitro* and *in vivo* analyses are shown in Fig. 2. The initial lag time and relatively higher transdermal absorption of OXY during the initial 24 h after application are demonstrated consistently in both the *in vitro* and *in vivo* studies. Absorption of OXY is continuous over the entire 96-h application period, with a slow decrease in OXY absorption rate after the initial 24 h. Estimated *in vitro* interval rates increased from 208 μg/h in the first 6 h to 383 and 337 μg/h in the following 6–12 and 12–24 h intervals. These interval rates corresponded to lower *in vivo* estimates of 225, 262, and 187 μg/h for the respective intervals during the first 24 h of application. In both cases, the rate slowly declined over the following 24-h intervals and yielded average *in vitro* and *in vivo* estimates of approximately 186 and 163 μg/h over the entire 96-h application period.

Consistent plasma OXY and DEO concentrations were observed 84 h after each of the three TDS applications in the multiple-dose trial (Table III). Mean steady-state plasma concentrations increased according to TDS surface area but showed similar profiles for OXY and DEO (Fig. 3). Steady-state pharmacokinetic parameters are summarized in Table IV. C_{max} and AUC parameters increased in a linear, dose-proportional manner according to TDS surface area. No statistically significant differences were observed in the comparison of dose-normalized AUC_{0-96} ($p = 0.3$ for OXY and DEO). Median OXY and DEO t_{max} values were 10 and 24 h, respectively, for all three system sizes tested and were not significantly different ($p \geq 0.4744$ and 0.7449 for OXY and DEO, respectively) between system sizes. Average DEO:OXY AUC_{0-96} ratios were 1.3 after application of the 13-, 26-, and 39-cm^2 systems. The test:reference ratios for the comparisons between dose-normalized C_{max} and AUC_{0-96} ranged from 1.03 to 1.08, with 95% CI between 0.90–1.24 (Table V).

Adverse events (AEs) were minimal after single TDS applications. The most frequently reported AEs were headache (three subjects, 13%) and dry mouth (two subjects, 8%). One subject experienced a mild application site rash. During the multiple-dose study, application site reactions (19 subjects, 73%) and headaches (seven subjects, 27%) were the most common AEs. Mild reactions were reported by 14 subjects during one application period only, and mild to moderate reactions reported during one or two periods in the other five subjects. Reactions included erythema, pruritus, burning sensation, pain, and hyperpigmentation. All reactions resolved after the patch was removed.

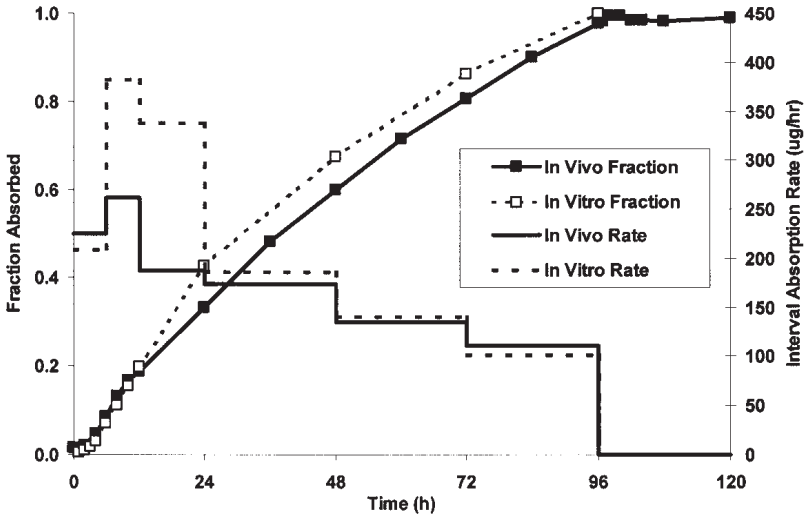

Fig. 2. Fraction absorbed and interval absorption rates estimated from *in vitro* cadaver skin flux experiments and single-dose *in vivo* TDS administration.

Table III. Mean (SEM) Plasma OXY and DEO Concentrations (ng/mL) Measured 84 h after Application of the Three Consecutive TDSs in the Multiple-Dose Study (n = 23)

TDS application # and duration	13 cm^2 system		26 cm^2 system		39 cm^2 system	
	OXY	DEO	OXY	DEO	OXY	DEO
First (84 hr)	1.1 ± 0.1	1.4 ± 0.2	1.8 ± 0.1	2.3 ± 0.2	2.8 ± 0.2	3.7 ± 0.4
Second (84 hr)	1.1 ± 0.1	1.5 ± 0.1	2.1 ± 0.1	3.0 ± 0.2	2.9 ± 0.2	4.2 ± 0.5
Third (96 hr)	0.9 ± 0.1	1.3 ± 0.1	1.7 ± 0.1	2.5 ± 0.2	2.6 ± 0.2	4.0 ± 0.5

DISCUSSION

Characterization of the performance of novel drug delivery systems in healthy volunteers under both single- and multiple-dose conditions provides important information to validate the safe and effective use of these delivery systems in patient populations. The results reported here support the use of multiple application sites, the rapid attainment of steady-state conditions, the dose-proportional increase in plasma concentrations with increasing TDS size, and the twice-weekly dosing regimen for OXY TDS. The predictive value of the *in vitro* model was demonstrated by the comparison to *in vivo* interval flux rates and the absorbed fraction of OXY, thereby allowing for a better prediction of performance for future product innovations.

The OXY TDS matrix design results in OXY delivery through the skin, which is controlled by the stratum corneum (15–17). Upon application of the TDS, skin hydration occurs followed by diffusion of both OXY and the permeation enhancer into the stratum corneum. An interaction of OXY and the permeation enhancer with the lipids in the skin controls the rate of drug diffusion through the stratum corneum. Over the application wear time, OXY content and concentration in the TDS gradually decreases, resulting in a slow decline of OXY diffusion into the skin. From the interval flux comparison data, it appears that skin permeability is highest during the initial 24 h of TDS application. This suggests a greater permeation enhancement effect during the initial 24 h and may reflect a more rapid release of enhancer from the TDS compared with OXY release. The difference in initial interval flux probably reflects skin deposition of oxybutynin that occurs *in vivo*, reducing initial *in vivo* absorption compared to the *in vitro* flux measurement. The total *in vivo* reduction in OXY content over the 96-h wear period was 43% (15.6 mg/36

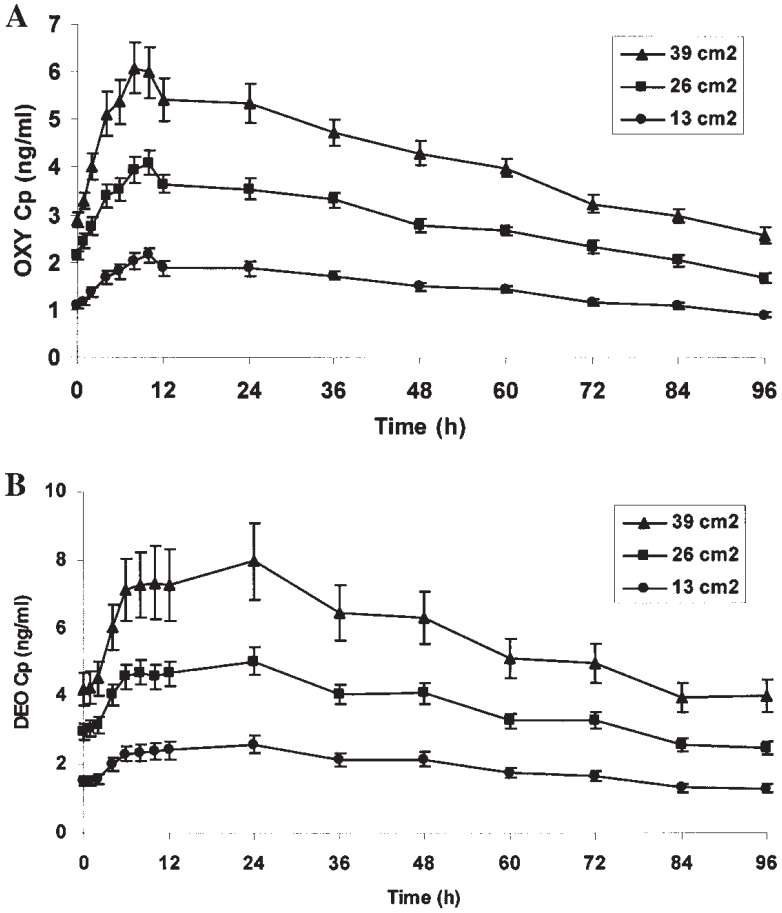

Fig. 3. Steady-state mean (± SEM) plasma OXY (A) and DEO (B) concentrations during application of 13, 26, or 39 cm^2 TDS (n = 23).

Table IV. Steady-State OXY and DEO Pharmacokinetic Parameters (Mean ± SD) Measured during Application of the Third System Application (n = 23)

Pharmacokinetic parameter	13 cm^2 system		26 cm^2 system		39 cm^2 system	
	OXY	DEO	OXY	DEO	OXY	DEO
C_{max} (ng/mL)	2.3 ± 0.8	2.7 ± 1.3	4.4 ± 1.3	5.3 ± 1.7	6.6 ± 2.4	8.5 ± 5.4
C_{avg} (ng/mL)	1.5 ± 0.4	2.0 ± 0.9	2.9 ± 0.6	3.8 ± 1.2	4.2 ± 1.1	5.8 ± 3.3
$AUC_{0–96}$ (ng · h/mL)	143 ± 39	188 ± 82	274 ± 59	361 ± 119	408 ± 108	561 ± 321
$AUC_{0–96}$ (ng · h/mL) (dose normalized)	429 ± 118	564 ± 245	410 ± 89	542 ± 179	408 ± 108	561 ± 321
t_{max} (median, h)	10.0	24.0	10.0	24.0	10.0	24.0
(range, h)	6–60	4 ± 72	6–36	1–60	1–84	0–84
Ratio DEO/OXY ($AUC_{0–96}$)	1.3 ± 0.3		1.3 ± 0.3		1.3 ± 0.4	

mg total content of the 39 cm^2 TDS), indicating that the OXY TDS is an efficient delivery system. The demonstrated linear dose-proportionality of OXY between systems of varying surface area is also consistent with the TDS matrix design.

The bioequivalence of OXY delivery at multiple anatomic application sites provides dosing flexibility for patients and may contribute to improved local tolerability. Despite known regional differences in skin thickness and lipid content, transdermal drug delivery from permeation-enhanced systems has been shown to be bioequivalent at various sites of application (18), including the central body regions, the upper arm, and the thigh. In the current studies, the buttock and hip application sites clearly demonstrated bioequivalence compared with the abdomen. Mild to moderate localized skin irritation is commonly reported for TDSs, with only rare occurrence of more severe bullous or ulcerative reactions. Dmochowski *et al.* (19) have shown that the OXY TDS is well tolerated, having a low incidence of moderate (7%) and severe (1%) erythema (20). With bioequivalent absorption, TDS-induced erythema may be reduced through the use of additional buttock and hip application sites.

The short half-life of OXY requires a controlled drug delivery system for the development of a product with a convenient dosing regimen. OXY TDS provides continuous drug delivery and promotes steady-state conditions with the first patch application. Zero-order OXY delivery would lead to steady-state conditions in approximately 16 to 20 h after initial administration, which is consistent with the plasma concentrations obtained after the first OXY TDS application. Fluctuations in plasma concentrations of OXY are expected over the dosing interval because of minor changes in transdermal flux over the 96-h wear period. Fluctuations observed with OXY TDS remain minimal, however, compared with oral immediate-release OXY or oral controlled-release OXY (21).

Table V. Dose-Normalized C_{max} and $AUC_{0–96}$ Ratios and Confidence Intervals Demonstrating Linear Dose Proportionality between OXY TDS System Sizes

	Pharmacokinetic parameter	Test: reference	Ratio	95% CI
OXY	C_{max}	13 cm^2: 39 cm^2	1.0765	0.9550–1.2135
	$AUC_{0–96}$		1.0698	0.9791–1.1688
	C_{max}	26 cm^2: 39 cm^2	1.0471	0.9289–1.1803
	$AUC_{0–96}$		1.0363	0.9485–1.1323
DEO	C_{max}	13 cm^2: 39 cm^2	1.0355	0.9015–1.1895
	$AUC_{0–96}$		1.0695	0.9600–1.1914
	C_{max}	26 cm^2: 39 cm^2	1.0811	0.9411–1.2418
	$AUC_{0–96}$		1.0729	0.9631–1.1953

A key benefit of OXY TDS delivery arises from the avoidance of presystemic metabolism whereby there is a significant reduction in circulating levels of the primary active metabolite DEO. DEO has been associated with the high incidence of anticholinergic side effects that are observed following the oral administration of OXY (6–9). Despite a minimal reduction in gastrointestinal metabolism by oral controlled-release OXY, hepatic first-pass metabolism results in poor overall oral bioavailability and high plasma levels of the active DEO metabolite. Our data demonstrated that lower DEO plasma concentrations are consistently observed during each TDS application, supporting the previous clinical findings that OXY TDS treatment results in minimal anticholinergic side effects (19). Addition *in vivo* preclinical evaluations of the relative effects of DEO and OXY on parotid gland and detrusor muscle activity are required to fully understand the clinical implications of the increased affinity of DEO for parotid tissue compared to OXY (10).

These studies confirm the rationale for the improved anticholinergic side effect profile that accompanies the previously reported therapeutic efficacy of transdermal delivery of OXY for patients with overactive bladder (19,20).

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