International Journal of Pharmaceutics 367 (2009) 1–15

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Review

Transdermal drug pharmacokinetics in man: Interindividual variability and partial prediction

Sara Farahmand, Howard I. Maibach*

Department of Dermatology, School of Medicine, University of California, San Francisco, 90 Medical Center Way, Surge 110, Box 0989, San Francisco, CA 941143-0989, USA

ARTICLE INFO

Article history:
Received 10 July 2008
Received in revised form 7 November 2008
Accepted 11 November 2008
Available online 30 November 2008

Keywords:
Transdermal drug delivery
Pharmacokinetics
Interindividual variation
QSPR
Skin absorption
Transdermal patch

ABSTRACT

A database of human dermatopharmacokinetic parameters of 12 transdermal patches is established. The effect of system design, application site, and metabolism on pharmacokinetic data is discussed, and interindividual variability of data and its possible sources evaluated. Using multiple regression analysis, two equations based on drugs physicochemical characteristics are suggested for partial prediction of peak plasma concentration (C_{max}) after patch application. Patch application presumably decreases variance as rub-off, wash and exfoliation steps are diminished.

The results showed that interindividual variation, in terms of coefficient of variation (CV) of C_{max}, is inversely correlated with drugs molecular weight and lipophilicity in the range of $200 < MW < 400$ and $1.6 < \log K_{oct} < 4.3$. Multiple regression analysis of C_{max} against physichochemical parameters demonstrated the prominent contribution of hydrogen bonding acceptability of the molecules on their maximal plasma concentration after patch administration.

The findings suggest that the serum concentration profile for transdermal therapeutic systems (TTS) is a net result of the system performance, drug absorption and elimination. Thus, the variability in serum concentration is a function of variability of each process involved. This should be noted in explanation of effect of molecular features of drugs on their plasma concentration profile.

Contents

* Corresponding author. Tel.: +1 415 476 2468; fax: +1 415 753 5304.
E-mail addresses: maibachh@derm.ucsf.edu, farahmand.s@gmail.com (H.I. Maibach).

0378-5173/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2008.11.020

1. Introduction

Scopolamine was the first drug marketed as a transdermal therapeutic system (TTS). Incremental design developments resulted in a significant market growth of these products. Their advantages (reduced first pass effect and GI incompatibility, constant therapeutic drug level, and increased patient compliance) have increased their popularity.

Today, numerous drugs have been delivered successfully through transdermal patches: scopolamine, nitroglycerin, nicotine, clonidine, fentanyl, estradiol, testosterone, oxybutynin, and recently methylphenidate, selegiline, rivastigmine and rotigotine.

However, considering the efficient skin barrier properties, specific physicochemical properties are needed for a chemical to be a candidate for passive transdermal delivery. The molecules should be small (MW <500), have a low melting point (<200 °C), and have a log K_{oct} of ~2 (Vecchia and Bunge, 2003).

Predictive equations for skin permeability coefficients of drugs are mainly made based on the in vitro static cell experiments using animal or human skin (Potts and Guy, 1992; Cronin et al., 1999). Detailed analysis of the pharmacokinetics of transdermal drug delivery and its correlation with physicochemical characteristics of the delivered drugs is minimal. Moreover, there is considerable interindividual variation in transdermal penetration and pharmacokinetics, which could be one reason for imprecision in predicting dermatopharmacokinetics parameters of transdermally delivered drugs based on their molecular properties.

This study reviews the dermatopharmacokinetic parameters of the drugs marketed as several brands of transdermal patches, reports the interindividual variations in pharmacokinetics parameters such as C_{max} (maximal plasma concentration), and correlates the in vivo data and physicochemical characteristics of the drugs. Patches were chosen as they minimize the variance from three steps of penetration: rub-off, exfoliation and wash (Wester and Maibach, 1983).

2. Transdermal therapeutic systems (TTS)

Currently, at least 13 drugs are widely marketed as transdermal therapeutic system (Table 1). Each transdermal system was designed according to a therapeutic rationale based on existing pharmacokinetic/pharmacodynamic data.

3. Pharmacokinetic parameters of TTS after single-dose application

The single-dose pharmacokinetic profile for transdermal delivery includes three periods: (1) the time until plasma concentrations are achieved (lag time); (2) the plateau at constant steady-state plasma concentrations; and (3) a declining phase post patch removal.

The last phase may be prolonged due to the presence of a skin depot, and the drugs pharmacokinetic characteristics (Berner and John, 1994; Grond et al., 2000).

TTS pharmacokinetic evaluation is often accomplished through randomized crossover studies, comparing the pharmacokinetic profile of a transdermal system with that of an intravenous or oral dose, or comparing different products for bioequivalence studies.

Plasma concentration time profiles for most of the transdermal systems are characterized in terms of AUC_{0-t} (area under the time concentration curve from time 0 to time t), $AUC_{0-\Phi}$ (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). C_{max} occurs due to: (a) slight depletion in driving force of drug; (b) variation due to plasma assay/sampling; and (c) other reasons such as circulation variation. For any of these, C_{max} provides a practical estimate of C_{ss} (plasma concentration at steady state).

Table 2 (2.1 to 2.12) demonstrates the pharmacokinetic data of transdermal patches, after single-dose treatment.

Table 3 (3.1 to 3.5) presents metabolite pharmacokinetic data.

4. Correlation of physicochemistry and plasma concentration of drugs

Scheuplein and Blank, proposed that epidermal penetration depends on the structural features of the penetrant (Scheuplein and Blank, 1971). The epidermal transport of most solutes is restricted to passive diffusion across the stratum corneum. Studies have evaluated the role of molecular structure and physicochemistry in this process. Most attempts to develop predictive equations for permeability have focused on the contributions of molecular size and the solubility in stratum corneum lipids. The data availability, and relative success in addressing a wide range of biophysical processes involved in the skin permeation make molecular weight (MW) and logarithmically transformed octanol–water partition coefficient (log K_{oct}) the most widely used parameters for predicting skin penetration (Vecchia and Bunge, 2003). Melting point may also be considered as an important predictor of skin permeability coefficient as it correlates strongly with oil solubility of drugs (Yalkowsky, 1981; Barratt, 1995).

4.1. Predictive models for skin permeability

Two types of structure–activity models have been used to estimate the skin permeability coefficients of chemicals: empirical and theoretical. Theoretical models are based on the contributions of the possible routes of percutaneous penetration and the interactions of the elements of these routes with the penetrants. Empirical models rely on measured experimental permeability coefficients of series of chemicals and correlate them with the physicochemical properties.

The Guy and Hadgraft theoretical model (Guy and Hadgraft, 1985) is based on a linear pharmacokinetic model. The rate constants in this model have been chosen such that they may be related to the penetrants physicochemical properties. Equations have been derived which may be used predictively to estimate the concentration of drug in the plasma following transdermal application.

A database of in vitro skin permeability coefficient values has been consolidated and over 20 empirical equations have been published estimating permeability coefficients for chemicals penetrating the human skin from aqueous vehicles (Vecchia and Bunge, 2003). One of the most widely used empirical models was developed by Potts and Guy, predicting permeability coefficient (Kp) based on log K_{oct} and molecular weight (MW) (1) (Potts and Guy,

Table 1
Currently available transdermal therapeutic systems[a].

Drug	TDS name	Strength	TE code[b]	Company
Estradiol	Alora	0.025, 0.05, 0.075, 0.1 mg/24 h	BX	Watson
	Climara	0.025, 0.0375, 0.05, 0.06, 0.075, 0.1 mg/24 h	AB/AB2	Bayer HLTHcare
	Estraderm	0.05, 0.1 mg/24 h	BX	Novartis
	Estradiol	0.025, 0.0375, 0.05, 0.06, 0.075, 0.1 mg/24 h	AB/AB2	Mylan
	Vivelle	0.05, 0.1 mg/24 h	AB1	Novartis
	Vivelle-Dot	0.025, 0.0375, 0.05,0.075, 0.1 mg/24 h	BX/AB1	Novartis
	Menostar	14 μg/24 h	None	Bayer HLTHcare
Ethinyl estradiol/levonorgestrol	Climara Pro	0.045;0.015 mg/24 h	None	Bayer HLTHcare
Ethinyl estradiol/norelgestromin	Ortho Evra	0.02;0.15 mg/24 h	None	Ortho Mcneil
Ethinyl estradiol/norethindrone	Combipatch	0.05;0.14, 0.05;0.25 mg/24 h	None	Novartis
Clonidine	Catapress	0.1, 0.2, 0.3 mg/24 h	None	Boehringer ingelheim
Oxybutinin	Oxytrol	3.9 mg/24 h	None	Watson
Fentanyl	Duragesic	12.5,25, 50, 75,100 μg/ h	AB	Alza
	Fentanyl TDS	12.5,25, 50, 75,100 μg/ h	AB	Mylan
	Fentanyl TDS	25, 50, 75,100 μg/ h	AB	Watson
	Fentanyl TDS	25, 50, 75,100 μg/ h	AB	Lavipharm
	Fentanyl TDS	25, 50, 75,100 μg/ h	AB	Abrika Pharms
Methylphenidate	Daytrana	1.1, 1.6, 2.2, 3.3 mg/ h	None	Shire
Nicotine	Nicoderm CQ	7, 14, 21 mg/24 h	None	Sanofi Aventis US
	Nicotine	7, 14, 21 mg/24 h	None	Aveva
	Habitrol	7, 14, 21 mg/24 h	None	Novartis
	Prostep	11, 22 mg/24 h	None	Aveva
Nitroglycerin	Minitran	0.1, 0.2, 0.4, 0.6 mg/ h	AB1	3M
	NG TDS	0.1, 0.2, 0.4, 0.6 mg/ h	AB2	Mylan
	Nitrodur	0.1, 0.2, 0.3, 0.4, 0.6, 0.8 mg/ h	AB1	Key Pharms
	Nitroglycerin	0.2, 0.4, 0.6 mg/ h	AB2	Hercon labs
	Nitroglycerin	0.2, 0.4 mg/ h	AB1	Kremers Urban
Selegiline	EMSAM	6,9,12 mg/24 h	None	Somerset
Scopolamine	TD Scop	1 mg/72 h	None	Novartis
Testosterone	Androdrem	2.5, 5 mg/24 h	None	Watson
Rivastigmine	Exelon	4.6, 9.5,13.3,17.4 mg/24 h	None	Novartis
Rotigotine	Neupro	2,4,6 mg/24 h	None	Schwarz Pharma

[a] Reference: www.fda.gov/cvm/FOI.
[b] Therapeutic equivalence code.

1992).

$$\log \mathrm{Kp} = -2.72 + 0.71 \log K_{\mathrm{oct}} - 0.0061\,\mathrm{MW} \quad (1)$$

Variability in the proposed models is partly due to the experimental uncertainties and individual skin variations which limit the prediction of skin permeability coefficients.

However, correlation of in vivo skin permeation descriptors such as plasma concentration and molecular characteristics has not been evaluated in the literature.

According to the Eq. (2), after transdermal drug delivery, plasma concentration depends on J (steady-state flux of the drug per unit area) and is inversely related to the drug's Vd (volume of distribution):

$$C_{\mathrm{ss}} = \frac{A \times J}{\mathrm{Ke} \times \mathrm{Vd}} \quad (2)$$

where A is patch area, and Ke is the elimination rate constant (Berner, 1985).

As Fick's first law of diffusion describes steady-state diffusion through a membrane (3):

$$J = \frac{K \times D}{h \times C_0} \quad (3)$$

where K is the stratum corneum/formulation partition coefficient of the drug, D is its diffusion coefficient in the stratum corneum of path length h, and C_0 is the concentration of drug applied.

Therefore, the dependency of plasma concentration on flux (J), allows relation to the drug's physicochemical properties. Meanwhile as a component of drug clearance, volume of distribution is also related to drug's solubility characteristics, which emphasizes correlation of plasma concentration and structural features of drug molecules.

Here, using multiple regression analysis, an empirical model has been adopted for prediction of $C_{\max}$ of transdermally administered drugs upon their physicochemical properties such as $\log K_{\mathrm{oct}}$, MW or MV (molecular volume) and hydrogen bonding descriptors.

Table 2.1
Pharmacokinetic data for transdermal therapeutic system (TTS) scopolamine[a].

n[b]	Delivery rate (μg/h)	Duration of application (h)	$C_{\max}$ (ng/ml)	C_{ss} (ng/ml)	C_{avg} (ng/ml)	$T_{\max}$ (h)	Reference
8	5	72	0.1 (0.011–0.24)	NA	NA	8	Renner et al. (2005)
NA[c]	5	72	NA	NA	0.087	24	PDR (2006)

[a] TD Scop (reservoir); application site: behind the ear.
[b] Number of subjects.
[c] Not available.

Table 2.2
Pharmacokinetic data for transdermal therapeutic system (TTS) rivastigmine[a]. Data are presented as mean and inter-individual variability (standard deviation or range).

n	Delivery rate (mg/day)	Duration of application (day)	C_{max} (ng/ml)	$AUC_{0-\phi}$ (ng/ml h)	AUC_{0-24} (ng/ml h)	T_{max} (h)	Reference
40	9.5	1	6.8 ± 3.2	128 ± 51.7	NA	16 (8–24)	Lefèvre et al. (2007)
22	4.6	1	2.7 ± 1.2	NA	46.3 ± 17.2	8 (0–12.1)	Lefèvre et al. (2007)
22	9.5	1	7.9 ± 2.9	NA	127 ± 41.4	8 (3–16)	Lefèvre et al. (2007)
19	13.3	1	14.1 ± 6.3	NA	233 ± 83.2	8 (3–16)	Lefèvre et al. (2007)
13	17.4	1	19.5 ± 7.5	NA	345 ± 127	8 (0–12)	Lefèvre et al. (2007)
13	4.6	1	3.3 ± 1.4	NA	64.1 ± 24.6	8.2 ± 2.4	Mercier et al. (2007)
14	9.5	1	8.7 ± 3.3	NA	166.4 ± 50	8.1 ± 2.4	Mercier et al. (2007)
15	13.3	1	16 ± 6.3	NA	312.4 ± 110	8.2 ± 2.3	Mercier et al. (2007)
16	17.4	1	24.2 ± 9.7	NA	473.9 ± 163	8.3 ± 2.5	Mercier et al. (2007)

[a] Exelon (matrix); application site: upper or lower back, upper arm, chest.

Table 2.3
Pharmacokinetic data for transdermal therapeutic system (TTS) testosterone[a]. Data are presented as mean and inter-individual variability (standard deviation).

n	Delivery rate (mg/day)	Duration of application (day)	C_{max} (ng/dl)	C_{ss} (nmol/L)	AUC (ng/ml h)	T_{max} (h)	Reference
34	2*2.5	1	696.96 ± 299.5	18.1 ± 7.49	NA	8.1 ± 3.2	Meikle et al., 1996
12	2.5	4	525 ± 146	NA	73.2 ± 17.3	6.62 ± 3.21	Brocks et al., 1996
12	2*2.5	4	739 ± 309	NA	108 ± 52.6	8.54 ± 5.53	Brocks et al., 1996
12	3*2.5	4	1036 ± 422	NA	155 ± 63.6	6.61 ± 2.38	Brocks et al., 1996
NA	2*2.5	1	737.28	NA	108	8.54	McClellan and Goa, 1998

[a] Androderm (matrix); application site: back, stomach, upper arms, thighs.

4.2. Methods

As is usual in transdermal studies, the technique is based on multiple regression analysis (Potts and Guy, 1992; Abraham et al., 1995). Statistical analysis was conducted using SPSS software (SPSS 11.5, SPSS Science, Chicago, IL, USA)

It was assumed that a general linear model would apply of the type:

$$C_{max} = A + Bb + Cc + \cdots$$

C_{max} (maximal plasma concentration) is the mean of reported values for each drug, after being normalized to dose .When there were more than one brand for a drug, C_{max} corresponded to each brand was examined separately in each modeling trial (Table 4). A, represents a constant, and $B, C, \ldots$ are fitted coefficients to the parameters b, c, ... (such as molecular weight, $\log K_{oct}$, number of hydrogen bond donor or acceptor groups on the molecule, molecular volume, excess molar refraction and dipolarity/polarizability).

The molecules physicochemical descriptors are summarized in Table 4.

The values $A, B, C, \ldots$ were calculated as the coefficients in the best fit equation from the multiple regression analysis.

In order to determine the usefulness of a model, the following statistical information was considered:

1. r^2: The coefficient of determination: This represents the amount of the dependent variable (C_{max}) attributable to the values of the independent (predictor) variables.
2. p: This is the probability of error in concluding that a predictor has a real influence on C_{max}. A value <0.05 is generally considered acceptable.
3. Studentized residual (TRESID): The residual is the difference between observed and predicted values of C_{max}. Its normality has been tested to assure that the standard errors of regression coefficients are not biased.
4. Leverage (HI): High leverage is an indication of presence of unusual predictor values. A value $>3\upsilon/N$ is considered unusual (υ, number of independent predictors including the constant; N, number of data points).
5. Variance inflation factor (VIF): VIF > 10 confirms collinearity, which means that independent variables are highly related to

Table 2.4
Pharmacokinetic data for transdermal therapeutic system (TTS) selegiline[a]. Data are presented as mean and inter-individual variability (standard deviation or CV%).

n	Delivery rate (mg/day)	Duration of application (day)	C_{max} (ng/ml)	$AUC_{0-\phi}$ (ng/ml h)	AUC_{0-24} (ng/ml h)	T_{max} (h)	Reference
12	6	1	2.16 [78]	46.16 [61]	29.42 [66]	18.4 [37]	Azzaro et al. (2007)
6	6	1	1.42 ± .4	33.17 ± 16.56	31.64 ± 15.63	18 ± 6.93	Rohatagi et al. (1997a,b)

[a] EMSAM (matrix); application site: upper torso, thighs, outer arm.

Table 2.5
Pharmacokinetic data for transdermal therapeutic system (TTS) methylphenidate[a]. Data are presented as mean and inter-individual variability (range).

n	Delivery rate (mg/h)	Duration of application (h)	C_{max} (ng/ml)	AUC_{0-12} (ng/ml h)	T_{max} (h)	Reference
79	10/9h	9	20	145	7.1–8.8	Anderson and Scott (2006)
79	15/9 h	9	23.9	181	7.1–8.9	Anderson and Scott (2006)
79	20/9 h	9	30.5	229	7.1–8.10	Anderson and Scott (2006)
79	30/9 h	9	46.5	378	7.1–8.11	Anderson and Scott (2006)

[a] Daytrana (matrix); application site: hips.

Table 2.6
Pharmacokinetic data for transdermal therapeutic system (TTS) nitroglycerin[a]. Data are presented as mean and inter-individual variability (standard deviation or CV%).

TTS name	TTS type	n	Delivery rate (mg/h)	Duration of application (h)	C_{max} (ng/L)	$AUC_{0-\phi}$ (ng/L h)	T_{max} (h)	Reference
Adesitrin	Matrix	12	0.4	24	104 ± 19	NA	6 ± 4.52	Ponti et al. (1989)
Deponit	Matrix	17	0.2	24	255 ± 151	NA	3.6 ± 3.5	Wolff et al. (1985)
Minitran	Matrix	24	0.75	24	202.5 ± 125	NA	12.2 ± 6.8	Riedel et al. (1989)
NG-Lavipharm	Matrix	30	0.4	24	506 ± 492	5309 ± 2836	10 ± 6	Auclair et al. (1998a)
Nitroderm	Reservoir	12	0.4	24	102 ± 22	NA	6.8 ± 4.13	Ponti et al. (1989)
Nitro disc	Matrix	18	0.4	14	500	6100 ± 3700	NA	Sun et al. (1995)
Nitro-Dur2	Matrix	18	0.4	14	500	6100 ± 4200	NA	Sun et al. (1995)
Nitro-Dur1	Matrix	24	0.4	24	383 ± 269[70]	NA	NA	Noonan et al. (1986)
Nitro-Dur2	Matrix	24	0.4	24	432 ± 372[86]	NA	NA	Noonan et al. (1986)
Nitro-Dur	Matrix	10	0.4	24	100 ± 14	NA	2.5 ± 1.08	Ponti et al. (1989)
Transderm-Nitro	Reservoir	30	0.4	24	478 ± 500	4793 ± 2768	8 ± 5	Auclair et al. (1998b)
Transderm-Nitro	Reservoir	18	0.4	14	500	6300 ± 4800	NA	Sun et al. (1995)

[a] application site: chest, inner side of the upper arm, shoulder.

Table 2.7
Pharmacokinetic data for transdermal therapeutic system (TTS) Nitcotine[a]. Data are presented as mean and inter-individual variability (standard deviation).

TTS name	n	Delivery rate (mg/day)	Duration of application (h)	C_{max} (ng/ml)	$AUC_{0-\phi}$ (ng/ml h)	AUC_{0-24} (ng/ml h)	T_{max} (h)	Reference
Habitrol	20	21	24	21 ± 7.2	373.6 ± 128.8	NA	9.8 ± 2.3	Gupta et al. (1995)
Nicoderm	14	21	24	22.7 ± 4.3	533 ± 113	412 ± 87	9.6 ± 7.4	Gupta et al. (1993)
Nicoderm	20	14	24	12.2 ± 2.9	256 ± 53	193 ± 39	4.4 ± 2.1	Gupta et al. (1993)
Nicoderm	39	14	24	13.7 ± 2.18	277.67 ± 56.19	221.67 ± 41.95	5.66 ± .71	Prather et al. (1993)
Nicoderm	20	21	24	22.8 ± 4.8	393.8 ± 89.1	NA	5.2 ± 3.1	Gupta et al. (1995)
Nicoderm	10	21	11	16.4 ± 2.9	NA	0–8 h:104 ± 18	NA	Bur et al. (2005)
Nicolan	9	15 mg–3.5	24	8.02 ± 1.96	170 ± 36.5	NA	7.78 ± 4.27	Bannon et al. (1989)
Nicolan	9	30 mg–7	24	17.1 ± 5.03	310 ± 56.4	NA	7.78 ± 1.86	Bannon et al. (1989)
Nicolan	9	2*30 mg	24	28.9 ± 9.14	541 ± 99.7	NA	8.22 ± 3.07	Bannon et al. (1989)
Nicorette	12	10/16 h	16	9.15 ± 1.8	155.13 ± 29.51	NA	13.3 ± 3.4	Sobue et al. (2006)
Nicorette	12	15/16 h	16	20.58 ± 7.8	412.27 ± 193	NA	8.5 ± 4.8	Sobue et al. (2006)
Nicotine-Pharmacia Upjohn	25	15/16 h	16	11.9 ± 3.83	NA	165 ± 54	6.5 ± 2.7	Fant et al. (2000)
Nicotine-Novartis	25	21	24	17.6 ± 6.39	NA	290 ± 108	10 ± 3.7	Fant et al. (2000)
Nicotine-Alza	25	21	24	21.9 ± 8.86	NA	328 ± 144	3.8 ± 2.7	Fant et al. (2000)
Nicotinell	10	21	11	16 ± 3.4	NA	0–8 h:92 ± 16	NA	Bur et al. (2005)

[a] Application site: upper arm, trunk.

Table 2.8
Pharmacokinetic data for transdermal therapeutic system (TTS) clonidine[a]. Data are presented as mean and interindividual variability (standard deviation).

n	Delivery rate (mg/day)	Duration of application (day)	C_{max} (ng/ml)	C_{ss} (ng/ml)	AUC_{0-t} (ng/ml h)	Reference
10	0.2	7	.84 ± .36	NA	124.81 ± 68.9	Ito and O'Connor (1991)
6	0.1	7	NA	0.387 ± .134	NA	MacGregor et al. (1985)
6	0.2	7	NA	0.835 ± .31	NA	MacGregor et al. (1985)
6	0.3	8	NA	1.118 ± .55	NA	MacGregor et al. (1985)

[a] Catapress (reservoir); application site: upper arms, stomach, hips or buttocks.

Table 2.9
Pharmacokinetic data for transdermal therapeutic system (TTS) Fentanyl[a]. Data are presented as mean and inter-individual variability (standard deviation).

n	Delivery rate (μg/h)	Duration of application (h)	C_{max} (ng/ml)	AUC (ng/ml h)	T_{max} (h)	Reference
10	50	72	1.9 ± .3	115 ± 19	24.5 ± 3.4	Thompson et al. (1998)
8	50	<24	1.5 ± .2	112 ± 22	28.1 ± 4.3	Thompson et al. (1998)
22	75	24	1.5 ± 1	NA	24	Grond et al. (2000)
5	50	72	0.8 ± .4	74 ± 36	17 ± 7	Grond et al. (2000)
6	50	72	1 ± .5	126 ± 60	20 ± 10	Grond et al. (2000)
28	75	24	1.9 ± .9	NA	24	Grond et al. (2000)
5	75	24	1 ± .1	34 ± 4.3	21 ± 6.3	Grond et al. (2000)
40	50	72	1.4 ± .2	76	28	Grond et al. (2000)
40	75	72	1.8 ± .1	104	36	Grond et al. (2000)
20	75	72	1.6 ± .5	91 ± 33	32 ± 16	Grond et al. (2000)

[a] Duragesic (reservoir); application site: upper arms, back.

Table 2.10
Pharmacokinetic data for transdermal therapeutic system (TTS) oxybutynin[a]. Data are presented as mean and interindividual variability (standard deviation).

n	Delivery rate (mg/day)	Duration of application (day)	C_{max} (ng/ml)	AUC_{0-4d} (ng/ml h)	$AUC_{0-\phi}$ (ng/ml h)	T_{max} (h)	Reference
NA	3.9	4	3.2 ± 1	245 ± 59	NA	48	PDR (2006)
24	3.9	4	4 ± 1.5	120 h:303 ± 119	324 ± 136	48	Zobrist et al. (2003)
13	3.9	3.5	4.2 ± 1	24 h:10.8 ± 2.4	259 ± 57	NA	Appell et al. (2003)
18	3.9	4	R[b]: 1.2 ± .5; S[c]: 1.6 ± .4	R: 85.8 ± 26.4; S: 121.4 ± 34	NA	48	Zobrist et al. (2001)

[a] Oxytrol (matrix), application site: upper arms, stomach, hips, buttocks.
[b] R enantiomer.
[c] S enantiomer.

Table 2.11
Pharmacokinetic data for transdermal therapeutic system (TTS) Estradiol[a]. Data are presented as mean and interindividual variability (standard deviation).

TTS name	TTS type	*n*	Delivery rate (μg/day)	Duration of application (day)	C_{max} (pg/ml)	AUC_{0-t} (pg/ml h)	T_{max} (h)	Reference
Alora	Matrix	33	50	3.5	21.5 ± 9.4	2871.8 ± 1072.6	NA	Buch et al. (1999)
Climaderm	Matrix	26	50	7	71.1 ± 27.7	7257.9 ± 1994.4	28.9 ± 14.8	Baracat et al. (1996)
Climara	Matrix	39	100	7	256.4 ± 38.9	18255.3 ± 33.7	NA	Harrison and Harari (2002)
Estraderm	Matrix	21	50	4	38.9 ± 25.1	3192.1 ± 1646	32 ± 11.1	Rohr et al. (1999)
Estraderm	Reservoir	20	50	3	52 ± 3.6	2076 ± 132	48 (24–72)	Reginster et al. (2000)
Estraderm	Matrix	34	50	4	Cavg:36.9 ± 14.4	3678 ± 1409	NA	Müller et al. (1996)
Estraderm	Reservoir	34	50	4	Cavg:31.1 ± 8.2	3361 ± 858	NA	Müller et al. (1996)
Estradiol-Mylan	Matrix	39	100	7	291.9 ± 37.9	20717.9 ± 35.9	NA	Harrison and Harari (2002)
Estradot	Matrix-DOT	30	25	3.5	24 ± 9.8	1326.8 ± 496.5	38 ± 12.2	Hossain et al. (2003a)
Estradot	Matrix-DOT	30	37.5	3.5	34.8 ± 12.2	1893 ± 665.3	32.5 ± 13	Hossain et al. (2003a)
Estradot	Matrix-DOT	30	50	3.5	50.1 ± 18.5	2524.8 ± 969.3	28.5 ± 16.8	Hossain et al. (2003a)
Estradot	Matrix-DOT	30	100	3.5	96 ± 33.9	5333 ± 1946.9	33.7 ± 16.1	Hossain et al. (2003a)
Estradot	Matrix-DOT	11	50	3.5	54.8 ± 13.9	3569.4 ± 763.5	34.9 ± 19.5	Hossain et al. (2003b)
Estradot	Matrix-DOT	11	100	3.5	106.2 ± 35.9	6029.5 ± 2384.6	29.5 ± 19.6	Hossain et al. (2003b)
Evorel	Matrix	33	50	3.5	9.3 ± 4.4	1870.6 ± 665.05	NA	Buch et al. (1999)
Evorel	Matrix	30	50	4	49.6 ± 3.36	2668 ± 181.92	21.1 ± 4.46	Reginster et al. (1997)
Fempatch	Matrix	24	20	7	23[43]	0–240:2611[38]	41[75]	Boyd et al. (1996)
Oesclim	Matrix	24	50	4	55.03 ± 32.67	2982.32 ± 1903.12	27.48 ± 15.55	Guichard et al. (1999)
Oesclim	Matrix	24	100	4	116.84 ± 66	6342.22 ± 4082.15	26.98 ± 12.71	Guichard et al. (1999)
Menorest	Matrix	21	50	4	47.5 ± 21.3	3967.8 ± 1651.8	32 ± 13	Rohr et al. (1999)
Menorest	Matrix	11	100	3.5	101.6 ± 39.1	6068.5 ± 1762.2	27.3 ± 20.1	Hossain et al. (2003b)
Menorest	Matrix	30	50	4	55.7 ± 4.42	3712.4 ± 260.78	41.9 ± 4.89	Reginster et al. (1997)
Menostar	Matrix	NA	14	7	20.6	2296	42	PDR (2006)
Systen	Matrix	20	50	3	41 ± 7.6	1404 ± 156	12 (6–72)	Reginster et al. (2000)
Tradelia	Matrix	21	50	4	48 ± 20.3	3737.9 ± 1637.6	32 ± 9.2	Rohr et al. (1999)
Vivelle	Matrix	24	50	4	49.38 ± 35.71	2535.15 ± 1690.54	30.09 ± 18.52	Guichard et al. (1999)

[a] Application site: trunk except breasts and waist.

Table 2.12
Pharmacokinetic data for transdermal therapeutic system (TTS) ethinyl estradiol/levonorgestrel or norelgestromin[a]. Data are presented as mean and inter-individual variability (standard deviation or CV%).

TTS name	*n*	Delivery rate (μg/day)	Duration of application (day)	C_{max} (pg/ml)	AUC_{0-t} (pg/ml h)	Ethinyl estradiol		Reference
						C_{ss} (pg/ml)	T_{max} (h)	
Climara-pro	43	L:45 E:15	7	46.3	5720	NA	NA	Harrison et al. (2007)
Climara-pro	NA	L:45 E:15	7	54.3 ± 18.9	6340 ± 1740	NA	42	PDR (2006)
OrthoEvra/Evra	29	N:150 EE:20	7	NA	8543 ± 3488	56.7 ± 22.6	NA	Zacur et al. (2002)
OrthoEvra/Evra	31	N:150 EE:20	7	76.3 [36.7]	9793 [36.2]	Cavg:65.9[35.8]	105.03 [30.9]	Devineni et al. (2007)
OrthoEvra/Evra	37	N:150 EE:20	7	66.3 ± 23.9	8391 ± 2622	54 ± 16.5	48 (36–48)	Abrams et al. (2002)
OrthoEvra/Evra	29	N:150 EE:20	7	64.5 ± 21.6	8237 ± 3047	53 ± 18.7	86.9 ± 48.5	Abrams et al. (2001)

TTS Name	*n*	Delivery rate (μg/day)	Duration of application (day)	C_{max} (pg/ml)	AUC_{0-t} (pg/ml h)	Norelgestromin/levonorgestrel		Reference
						C_{ss} (pg/ml)	T_{max} (h)	
Climara-pro	43	L:45 E:15	7	194 ± 111	27.9 ± 19.1	NA	NA	Harrison et al. (2007)
Climara-pro	NA	L:45 E:15	7	136 ± 52.7	22.9 ± 8.86	NA	90	PDR (2006)
OrthoEvra/Evra	29	N:150 EE:20	7	NA	123 ± 32.3	830 ± .210	NA	Zacur et al. (2002)
OrthoEvra/Evra	31	N:150 EE:20	7	928 [41.1]	115 [39]	Cavg:766 [38.7]	78.7 [28.2]	Devineni et al. (2007)
OrthoEvra/Evra	37	N:150 EE:20	7	1170 ± 500	150 ± 57.9	990 ± .380	72 (48–72)	Abrams et al. (2002)
OrthoEvra/Evra	29	N:150 EE:20	7	940 ± 320	116 ± 43.8	730 ± 270	74.5 ± 31	Abrams et al. (2001)

[a] Application site: trunk except breasts and waist.

Table 3.1
Pharmacokinetic data for Rivastigmine active metabolite (NAP 2260-90). Data are presented as mean and inter-individual variability (standard deviation or range).

C_{max} (ng/ml)	AUC_{0-24} (ng/ml h)	$AUC_{0-\phi}$ (ng/ml h)	T_{max} (h)	Reference
2.27 ± .84	NA	54.3 ± 15.1	16 (8–28)	Lefèvre et al. (2007)
1.65 ± .6	32.1 ± 11.5	NA	8 (.5–16)	Lefèvre et al. (2008)
4.05 ± 1.6	75.5 ± 28.3	NA	12 (0–16)	Lefèvre et al. (2008)
7.47 ± 3.5	139 ± 57.4	NA	12 (0–24)	Lefèvre et al. (2008)
9.28 ± 3.2	185 ± 67.7	NA	12 (.5–16)	Lefèvre et al. (2008)

each other. Variables with VIF > 10 must be excluded from the analysis.

4.3. Results

Multiple regression anlaysis of C_{max} of 10 drugs (excluding fentanyl and clonidine), against physicochemical parameters (Table 4), yields the following equation as the best fitted model:

$$C_{max}\,(\text{ng/ml}) = 8.625\,\text{e}-07\,\text{HA} + 8.231\,\text{e}-07\,\log K_{oct} - 1.22\,\text{e}-06\,\text{HD} - 2.58\,\text{e}-06 \quad (4)$$

$n = 10$, $r = 0.974$, $F = 37.45$, SD = 0.82, $p = 0.000$

In this equation and elsewhere, HA is the total number of hydrogen bond acceptor groups on the molecule, $\log K_{oct}$ is logarithmically transformed octanol–water partition coefficient, and HD is the total number of hydrogen bond donor groups on the molecule.

All predictors had significant ($p < 0.05$) partial effect in the full model.

Inclusion of molecular weight failed to improve significantly the statistics of this equation. Furthermore, no linear correlation could be established between C_{max} and MW.

Further inclusion of Abraham's descriptors (Abraham and Martins, 2004) in the equation, led to the following model:

$$C_{max} = 6.055\,\text{e}-07\,\log K_{oct} + 8.691\,\text{e}-07\,\text{HA} + 1.075\,\text{e}-06\,V - 1.91\,\text{e}-06\,E - 2.84\,\text{e}-06 \quad (5)$$

$n = 10$, $r = 0.989$, $F = 56.49$, SD = 0.75, $P = 0.000$

where, V is the McGown characteristic volume in units of $(\text{cm}^3\,\text{mol}^{-1})/100$ and E is the solute excess molar refractivity in units of $(\text{cm}^3\,\text{mol}^{-1})/10$.

No collinearity was found between the variables in the model (VIF < 2 for all the variables in both models).

Studentized residuals showed a normal distribution according to Kolmogrov-Smirnov test of normality ($p > 0.05$).

Unusual leverage values were not found, which confirms that there is no serious outlier influence in the model.

5. Discussion

5.1. Dose proportionality

Evaluation of relationship between plasma concentration and the dose administered using different patch sizes has usually proved the dose proportionality of the systems (Ridout et al., 1988; Berner and John, 1994; Hossain et al., 2003a,b). Deviations from the dose proportionality seen for rivastigmine, were less pronounced with transdermal system application when compared to oral route of administration (Cummings et al., 2007).

5.2. Anatomical site

Dependency of the extent of skin absorption upon the anatomical application site in human is well known (Wester and Maibach, 1983). The best examples demonstrating the skin permeability variation at different sites are: scrotal skin which shows five-fold greater permeability to testosterone compared with other skin sites, and postauricular region which facilitates scopolamine penetration 20 times more effectively than other areas of the body (Berner and John, 1994). However several pharmacokinetic studies show bioequivalence of several anatomical sites after patch application: clonidine patch provides similar plasma concentration profile after application on arm and chest (MacGregor et al., 1985). The rate and extent of nicotine absorption from Nicoderm® 14 mg/day were similar after application on upper outer arm, upper back and upper chest (Gorsline et al., 1992). Abrams et al. showed that plasma concentrations of norelgestromin and ethinyl estradiol from the contraceptive patch remain within the reference ranges throughout the wear period regardless of the application site (Abrams et al., 2002). Absorption of fentanyl is also the same between the chest, abdomen and thigh (Grond et al., 2000).

Meanwhile, for rivastigmine, the highest plasma exposure is provided through the application on chest, upper arm and upper back rather than thigh and abdomen (Lefèvre et al., 2007). Besides, the findings of Harrison's study suggest that bioequivalence of the generic estradiol brand and Climara® at one anatomical site is not indicative of bioequivalence at another (Harrison and Harari, 2002).

Since various body regions have different sensitivities to drug application, patch application site is also important to minimize skin irritation. Skin Inflammation may affect the absorption; when the application site of methylphenidate patch was inflamed, the lag time was reduced to less than 1 h, the C_{max} and AUC were three-fold higher than normal and the T_{max} decreased to 4 h (Anderson and Scott, 2006). Most of the marketed transdermal patches are to be used on the trunk, arms, and thighs. However, hips are suggested for methylphenidate (PDR, 2006).

Most of the marketed transdermal patches are used on the trunk, arms, and thighs. However, hips are suggested for methylphenidate (PDR, 2006). The superior therapeutic efficacy of the patches applied over the particular organ on which the therapeutic effect is required, has not been proved yet (Tanner and Marks, 2008). The most important factors in choosing the application site, are adhesiveness (e.g. waist area is not suggested for patch application), and irritation potential (e.g. estradiol patch can be used on buttocks instead of abdomen to reduce the irritation potential (Berner and John, 1994). For some drugs such as methylphenidate, rivastigmine, and selegiline, rotation of the application site has been suggested in order to minimize irritation (PDR, 2006).

5.3. System design

The membrane-controlled (reservoir) and monolithic (matrix) systems are the main categories of transdermal systems. Matrix systems contain a drug reservoir that contacts the skin, whereas it is located behind a rate control membrane for reservoir systems (Fig. 1).

A reservoir TTS consists of the following main parts: a reservoir containing the drug, a backing layer (which mechanically fastens the whole system and prevents the drug from diffusing in undesired directions and from loss on storage), a semi-permeable membrane controlling the drug release form the reservoir, a pressure-sensitive biocompatible adhesive for mounting the TTS on the skin, and an antiadhesive layer, the release liner (usually, a siliconized film or

Table 3.2
Pharmacokinetic data for Selegiline active metabolites (N-DMS, R-AMPH, R-METAMPH). Data are presented as mean and inter-individual variability (standard deviation or CV %).

N-DMS				R-AMPH				R-Methamph				Reference
C_{max} (ng/ml)	$AUC_{0-\phi}$ (ng/ml h)	AUC_{0-24} (ng/ml h)	T_{max} (h)	C_{max} (ng/ml)	$AUC_{0-\phi}$ (ng/ml h)	AUC_{0-24} (ng/ml h)	T_{max} (h)	C_{max} (ng/ml)	$AUC_{0-\phi}$ (ng/ml h)	AUC_{0-24} (ng/ml h)	T_{max} (h)	
.791 [67]	22.96 [68]	11.29 [76]	19.58 [26]	.796[56]	42.69 [50]	7.45 [73]	29.17 [4]	2.17[52]	93.08 [59]	28.92 [19]	27.5 [15]	Azzaro et al. (2007)
0.52 ± .26	14.9 ± 10.2	13.58 ± 9.6	19.67 ± 6.74	.62 ± .35	32 ± 17.33	12.69 ± 11.06	26 ± 8.2	1.99 ± .7	82.71 ± 33.7	70.79 ± 28.86	24.3 ± 6.6	Rohatagi et al. (1997a,b)

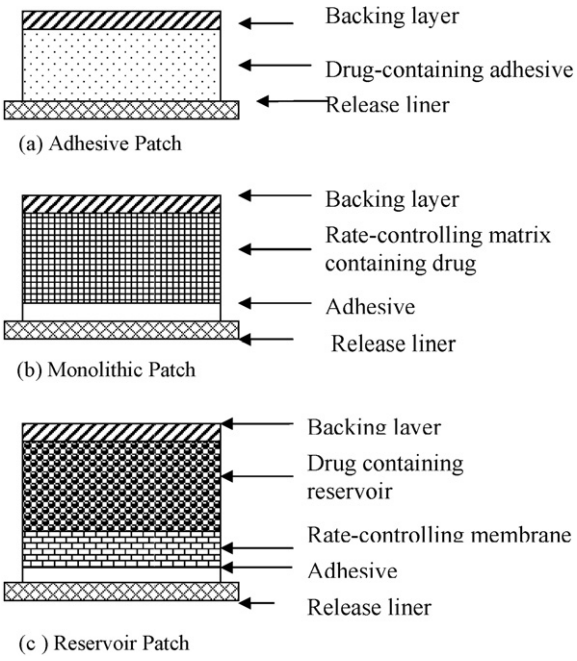

Fig. 1. Schematic structure of transdermal therapeutic systems.

paper protecting the adhesive and preventing the drug from loss prior to application). The latter film is removed immediately before application. Several matrix systems are possible: simple matrix (monolithic) where, drug is dispersed or dissolved in an adhesive polymer matrix which controls drug delivery; adhesive system, where, the drug is dispersed in an adhesive polymer matrix, which controls the drug delivery, and multilayer matrix system, where a concentration gradient is created by superposition of layers with various drug concentrations (Vasil'ev et al., 2001; Williams, 2003).

The drug in the reservoir compartment can be in the form of a solution, suspension, gel, or dispersed in a solid polymer matrix. Chemical permeation enhancers such as ethanol and propylene glycol (the most widely used) and others such as oleic acid, azone, dimethyl sulfoxide, 2-pyrrolidone, *N*-methyl-2-pyrrolidone, isopropyl myristate, transcutol (ethylcellosolve) and sodium lauryl sulfate have been incorporated in the patch formulations. They exert their influence on lipids in the stratum corneum as well as on lower dermal layers and possibly capillary beds (Williams, 2003).

Different types of polymers have been utilized in different layers of a patch: the release liner is often prepared from polymers such as ethylene vinyl acetate, coated papers, or from aluminium foil. Three classes of pressure-sensitive adhesives (PSA) are used: acrylate-based adhesives which are sensitive to pressure even without special additives like tackifiers or stabilizers, polyisobutylene (PIB) adhesives with less tack but high flexibility, and polysiloxane adhesives (Vasil'ev et al., 2001). Numerous materials can be used for the backing layer: for a small patch, the occlusive polyethylene, polyester or polyurethane backing may be selected. However, some water vapor transmission is desirable for larger patches to be worn for extended times, and so less occlusive polyvinylchloride films can be used (Williams, 2003). The design and material of the reservoir or a matrix containing the drug determine the release pattern. Polyvinyl pyrrolidone and polyvinyl acetate are among the most widely used matrix polymers. Diffusion of the permeant through a polymer matrix is also controlled by the degree of polymer cross-linking and by the level of hydration in the gel. For the reservoir systems, the release membrane can be prepared from a co-polymer of ethylene acetate with vinyl acetate. The proportion of vinyl acetate can affect the rigidity of the film and release

Table 3.3
Pharmacokinetic data for nitroglycerin active metabolites (1,2-GDN and 1,3-GDN). Data are presented as mean and inter-individual variability (standard deviation or range).

1,2-GDN			1,3-GDN			Reference
C_{max} (ng/L)	$AUC_{0-\phi}$ (ng/L h)	T_{max} (h)	C_{max} (ng/L)	$AUC_{0-\phi}$ (ng/L h)	T_{max} (h)	
3424 ± 1109	NA	9 ± 4	515 ± 161	NA	9 ± 4	Auclair et al. (1998a)
3011 ± 1109	NA	11 ± 6	522 ± 188	NA	8 ± 5	Auclair et al. (1998b)
3500	44600 ± 15800	NA	700	9300 ± 2900	NA	Sun et al. (1995)
3500	44300 ± 16100	NA	700	9700 ± 2900	NA	Sun et al. (1995)
3500	42800 ± 19300	NA	701	8700 ± 3000	NA	Sun et al. (1995)

Table 3.4
Pharmacokinetic data for oxybutynin active metabolite (*N*-desethyl oxybutynin). Data are presented as mean and inter-individual variability (standard deviation).

C_{max} (ng/ml)	AUC_{0-4d} (ng/ml h)	$AUC_{0-\phi}$ (ng/ml h)	T_{max} (h)	Reference
NA	NA	NA	NA	PDR (2006)
5.8 ± 2.9	448 ± 240	504 ± 311	48	Zobrist et al. (2003)
4.9 ± 2	24 h:13.4 ± 4.7	321 ± 114	NA	Appell et al. (2003)
R:1.2 ± .5; S:1.4 ± .7	R:83.9 ± 43 S:101.1 ± 52.6	NA	48	Zobrist et al. (2001)

Table 3.5
Pharmacokinetic data for estradiol active metabolite (estrone). Data are presented as mean and inter-individual variability (standard deviation).

C_{max} (pg/ml)	AUC_{0-t} (pg/ml h)	T_{max} (h)	Reference
NA	NA	NA	PDR (2006)
10.5 ± 5.8	558.8 ± 367.9	54.9 ± 19.6	Hossain et al. (2003a)
15.2 ± 6.5	852.3 ± 426.1	54.8 ± 20.2	Hossain et al. (2003a)
21.8 ± 10.1	1194.4 ± 559.4	52.8 ± 20.8	Hossain et al. (2003a)
41 ± 16.7	2380 ± 1072.5	58.8 ± 15.2	Hossain et al. (2003a)
75.6 ± 15.1	4661.8 ± 995.9	58.9 ± 12.5	Hossain et al. (2003b)
97 ± 27	6270.5 ± 1777	45.8 ± 22	Hossain et al. (2003b)
98.3 ± 21.2	6293.9 ± 1406.5	48 ± 18.6	Hossain et al. (2003b)
101.2 ± 52.5	9940.4 ± 59	NA	Harrison and Harari (2002)
98.7 ± 40.4	10075.6 ± 56.8	NA	Harrison and Harari (2002)

properties. Microporous release membranes such as cellulose ester films may also be used as the rate-limiting membrane (Vasil'ev et al., 2001; Williams, 2003).

Reservoir systems are mainly designed to shift the control of drug absorption rate to the delivery system rather than the skin. In theory, this may reduce interindividual variation if drug release from the system – through the rate control membrane – is much slower than permeation through the skin. However, in practice, membrane-controlled systems have less contribution in drug flux control. That is mostly because of drug partitioning into the adhesive layer during storage, which results in high initial release of the drug during the first hours of application (Berner and John, 1994). Meanwhile, presence of ethanol as an absorption enhancer in the reservoir causes pronounced fluctuations in plasma concentration–time profile of the drug, as shown for estradiol: in the immediate phase following TTS application, alcohol depletes rapidly, which leads to drug saturation. Estradiol concentration gradient becomes the prominent mechanism of drug flux. Finally, ethanol depletion reduces transdermal estradiol delivery. This explains the typical plasma concentration–time profile of estradiol reservoir TTS: an initial gradual increase during the first 2 days, reaching a maximum on day 2 or 3, and declining thereafter. Drug is released in a time-dependent manner from matrix systems (cumulative mass vs. square root of time are linear) and shows less fluctuations of the plasma estradiol level. Although the bioequivalence of the matrix and reservoir systems have been shown in terms of extent of absorption, the profiles of estradiol release and absorption rate are different, which is not expected to affect the clinical efficacy (Müller et al., 1996; Reginster et al., 2000).

Alcohol-enhanced membrane-controlled transdermal fentanyl and nitroglycerin have reduced the variation in skin drug permeation by 50% (Berner and John, 1994; Grond et al., 2000).

When, as is the usual case, the skin is the rate-limiting barrier to drug permeation, the burst effect associated with the patch membrane is negligible. But, in case of patch-controlled permeation, the initial burst from the patch membrane can decrease the lag time and allow more rapid drug absorption. This has been considered in scopolamine reservoir TTS design, which shortens the lag time from 2.6 h to 1.6 h (Berner, 1985).

5.4. Duration of application

The total drug amount absorbed from a patch is a function of patch surface area and the delivery rate. Because of the limitations of a loading dose in a patch and a practical patch size, a good permeant should have a flux in the region of 1 mg/cm^2/day (Williams, 2003).

The real duration of operation of an applied TTS is related to the time required to attain a stationary rate of drug release into the blood stream. The latter time, which depends on the chemical structure of the drug, its elimination half life, the epidermis hydration rate, and the rate of drug metabolism, varies from half an hour (e.g., for nitroglycerin) to a few days (clonidine). Hence, the usual TTS application time ranges from 1 day to 3–4 days. If the TTS is rapidly (within 2–3 h) replaced by a new one, the stationary drug supply to blood is not halted and the process may be continued for a long time depending on medical indications (Vasil'ev et al., 2001).

Along with the pharmacokinetic properties of a transdermal drug which determines its application period, there are few parameters that may also interfere with the time period that a patch can remain on the skin: Skin irritation, is an important cause of abrupt patch withdrawal for several drugs. Methyl phenidate, selegiline, clonidine, and rivastigmine are potential skin irritants. However, nature of adhesive materials, occlusion provided by the TTS and presence of chemical enhancers, may increase the risk of skin sensitization which can limit the application period (Anderson and Scott, 2006).

Table 4
TTS systems considered in the analysis, their dose-normalized C_{max}, and physicochemical descriptors.

TTS name	Dose-normalized C_{max} (ng/ml)	MW (g/mol)	log K_{oct}	E^a	S^b	HA[c]	HD[d]	V^e
TD Scop	1.4E−06	303.35	1.24	1.686	2.03	5	1	2.2321
Oxytrol	3.72E−06	357	4.3	1.52	1.41	4	1	3.0091
Androderm	8.21E−07	288.42	3.32	1.54	2.59	2	1	2.3827
Catapress	2.94E−05	231	0.53	1.6	1.5	3	2	1.5317
Exelon	9.49E−07	250.34	1.98	0.95	1.45	3	0	2.1176
OrthoEvra/Evra	1.96E−08	327.46	4	2.08	2.7	3	2	2.6783
Climara-pro	4.31E−10	312.44	3.11	1.9	2.84	2	1	2.5785
Daytrana	1.67E−06	233.31	3.65	1.01	1.77	3	1	1.9092
Duragesic	1.27E−03	336.5	4.05	1.83	1.75	2	0	2.8399
EMSAM	2.98E−07	187.3	2.7	0.866	1.01	1	0	1.7166
Climaderm	2.03E−10	272.39	4.01	1.8	1.74	2	2	2.1988
Climara	3.66E−10	272.39	4.01	1.8	1.74	2	2	2.1988
Alora	1.5E−06	272.39	4.01	1.8	1.74	2	2	2.1988
Estraderm	1.73E−09	272.39	4.01	1.8	1.74	2	2	2.1988
Estradiol-Mylan	4.17E−10	272.39	4.01	1.8	1.74	2	2	2.1988
Estradot	3.5E−09	272.39	4.01	1.8	1.74	2	2	2.1988
Evorel	3.97E−10	272.39	4.01	1.8	1.74	2	2	2.1988
Fempatch	1.64E−10	272.39	4.01	1.8	1.74	2	2	2.1988
Menorest	3.93E−09	272.39	4.01	1.8	1.74	2	2	2.1988
Menostar	1.03E−08	272.39	4.01	1.8	1.74	2	2	2.1988
Oesclim	2.34E−09	272.39	4.01	1.8	1.74	2	2	2.1988
Systen	2.73E−10	272.39	4.01	1.8	1.74	2	2	2.1988
Tradelia	3.84E−09	272.39	4.01	1.8	1.74	2	2	2.1988
Vivelle	2.47E−10	272.39	4.01	1.8	1.74	2	2	2.1988
Habitrol	E−06	162.23	1.17	0.865	0.88	2	0	1.371
Nicoderm	8.81E−07	162.23	1.17	0.865	0.88	2	0	1.371
Nicolan	5.29E−07	162.23	1.17	0.865	0.88	2	0	1.371
Nicorette	1.24E−06	162.23	1.17	0.865	0.88	2	0	1.371
Nicotine-Alza	1.04E−07	162.23	1.17	0.865	0.88	2	0	1.371
Nicotinell	3.81E−07	162.23	1.17	0.865	0.88	2	0	1.371
Nicotine-Novartis	8.38E−07	162.23	1.17	0.865	0.88	2	0	1.371
Nicotine-Pharmacia Upjohn	7.93E−07	162.23	1.17	0.865	0.88	2	0	1.371
Nitro disc	1.75E−05	227.11	1.62	0.494	2.04	9	0	1.23
Nitroderm	6.12E−06	227.11	1.62	0.494	2.04	9	0	1.23
Nitro-Dur	6E−06	227.11	1.62	0.494	2.04	9	0	1.23
Nitro-Dur 1	2.23E−05	227.11	1.62	0.494	2.04	9	0	1.23
Nitro-Dur2	2.17E−05	227.11	1.62	0.494	2.04	9	0	1.23
Minitran	6.48E−07	227.11	1.62	0.494	2.04	9	0	1.23
NG-Lavipharm	3.03E−05	227.11	1.62	0.494	2.04	9	0	1.23
Transiderm-Nitro	2.13E−05	227.11	1.62	0.494	2.04	9	0	1.23
Adesitrin	6.24E−06	227.11	1.62	0.494	2.04	9	0	1.23
Deponit	3.06E−05	227.11	1.62	0.494	2.04	9	0	1.23

[a,b,e]Abraham's descriptors are cited data of Abraham and Martins (2004); [a]excess molar refractivity ($cm^3\ mol^{-1}$)/10; [b]dipolarity/polarizability; [c,d]number of hydrogen bond acceptor and donor groups on the molecules (taken from pubchem database: www.ncbi.nlm.nih.gov); [e]McGown characteristic volume ($cm^3\ mol^{-1}$)/100.

Acute toxicity can also be a reason for abrupt patch removal for some drugs with a relatively narrow therapeutic window (e.g. fentanyl). This is of concern in special population such as children or elderly, where variable rates of permeation and metabolism are more prominent.

5.5. Metabolism

Although bypassing hepatic metabolism remains an important rationale for transdermal drug delivery, after penetration through stratum corneum, substances may be subjected to the metabolic properties of the viable epidermis. Metabolism of the chemical may result in significant modification of the molecule in terms of reduced or increased pharmacological and/or toxicological activity (Wester and Maibach, 1983).

Examples of cutaneous metabolism of drugs include steroids (estradiol, progesterone, testosterone) and nitroglycerin. In most cases metabolism is reduced compared to the oral administration, as it has also been demonstrated for stereoselective metabolism of oxybutynin, and for selegiline (Rohatagi et al., 1997a,b; Zobrist et al., 2001). For rivastigmine, although the extent of cutaneous metabolism is shown to be negligible (Tse and Laplanche, 1998), the plasma concentration profile of the main metabolite (NAP 226-90) correlated with the anatomical application site of the patch: when the patch is applied on the chest, upper back and upper arm, the greatest AUC was obtained for both the parent molecule and the metabolite (Lefèvre et al., 2007).

Regional variations in cutaneous metabolism may cause differences in drug bioavailability, as it is known for scrotal and non-scrotal application of testosterone transdermal system, where, the former results in increased systemic dihydrotestosterone concentration (Berner and John, 1994). Meanwhile, some excepients (e.g. permeation enhancers) in patch formulations affect skin metabolism. This can be explained through the inhibition or induction of enzymatic activity by these chemicals (e.g. inhibition of nitroglycerin and estradiol metabolism by alcohol). Another explanation would be the effect of the permeation enhancers such as alcohol, oleic acid, triolein, etc. on flux of the drug from the system which also may alter the rate and extent of metabolism (Berner and John, 1994). Therefore, the system characteristics might be considered as a potential reason for inter- and intra-individual variations in metabolism and bioavailability of transdermally administered drugs.

5.6. Interindividual variations

The main advantage that transdermal drug delivery possesses over oral dose regimens is avoiding the variability associated with

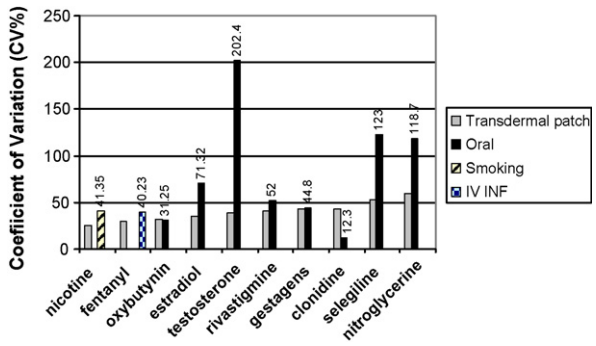

Fig. 2. Inter-individual variation of C_{max} in different routes of administration of drugs. (a) Oral mean CVs are calculated from the reported mean and standard deviations in the following references: Oxybutynin: Appell et al. (2003); Zobrist et al. (2001); estradiol: Amory et al. (2008); testosterone: Amory et al. (2008); rivastigmine: Lefèvre et al. (2008); gestagens: Sambol et al. (2006); clonidine: Fujimura et al. (1994); selegiline: Azzaro et al. (2007); nitroglycerin: Yu et al. (1988). (b) Smoking CV is calculated mean value from the reported mean and standard deviations in the following references: Gupta et al. (1995); Sobue et al. (2006). (c) IV INF CV is calculated from the reported mean and standard deviation in: Burlacu et al. (2007).

the gastrointestinal tract (effects of pH, motility, transit time and food intake). Nevertheless, in general drug permeation through human skin at a selected skin site can vary from 46% to 66% among individuals (Grond et al., 2000).

In order to study the variations, we chose transdermal patches rather than a volatile solvent vehicles (such as acetone) (Feldmann and Maibach, 1970) or a semi solid (cream/ointment), as the former provides: (1) fixed dose; (2) relatively abrupt removal (except for skin reservoirs); and (3) their relative freedom from other penetration steps: volatility (evaporation of the active); rub removal. Further, these systems are near or at maximum thermodynamic activity (saturation).

Examining the transdermal pharmacokinetic literature, almost all measurements reported in terms of means and standard deviation referring to data from different individuals. Here, mean coefficient of variation (CV) of C_{max} was calculated for transdermal drugs. The mean CV of values reported from several resources ranges from 26% (for nicotine) to 53% (for nitroglycerin) (Fig. 2, Table 5).

The mean CV of C_{max} is also calculated for the oral dosage form of these drugs (For fentanyl and nicotine CV of C_{max} after intravenous infusion and smoking is reported, respectively.) The CV values from non-transdermal routes of administration range from 12.3% (for clonidine) to 202% (for testosterone) (Fig. 2).

Table 5
C_{max} coefficient of variation and physicochemical data of drugs.

Drug	Mean CV (%)	MW[b]	log K_{oct}[c]
Nicotine	25.8[a]	162.23	1.17
Fentanyl	30.40	336.5	4.05*
Oxybutynin	31.85	357	4.3*
Estradiol	35.70	272.39	4.01
Testosterone	38.33	288.42	3.32
Rivastimine	41.24	250.34	1.98
Norelgestromine	42.80	327.46	4*
Levonorgestrel	42.80	312.44	2.97
Clonidine	42.90	231	0.53
Selegiline	53.08	187.3	2.7
Nitroglycerin	59.20	227.11	1.62*

[a] Each value is a mean of CV calculated for C_{max} values reported in different resources.

[b] Molecular weight (g/mol).

[c] Logarithmically transformed octanol–water partition coefficient are cited data of Hansch et al. (1995).

* Value reported for the neutral form.

The main factors controlling the interindividual variation in transdermal drug delivery can be categorized to four groups:

5.6.1. Study design and methodology
5.6.2. General subject factors
5.6.3. TTS system design
5.6.4. Kinetic variations of drug molecules

5.6.1. Study design and methodology

Design of crossover studies including subject randomization, treatment and wash out periods and sample size can affect the results obtained from different studies.

Meanwhile, different sensitivity, precision and robustness of different analytical methods should also be considered as a source of interindividual variations.

For some unstable drugs (such as nitroglycerin), standardization of the sampling procedure is essential to obtain reliable and less variable results.

5.6.2. General subject factors

Besides the genetic aspects of variations between individuals in absorption and metabolism of drugs, ethnicity, age, gender, body weight, compliance, general health and skin condition are among the main subject parameters affecting the plasma concentration profile of transdermally delivered drugs:

5.6.2.1. Age. Among the drugs administered transdermally, fentanyl's pharmacokinetics has been studied extensively in different age groups (ages 6–75 years) (Grond et al., 2000). Plasma profile at steady state was similar between children (ages 7–18 years) and adults, although the interindividual variability in kinetics was less in children. There were no marked differences found in C_{max} and AUC of elderly and adult group. However, the data suggest a longer delay and decay in the elderly patients (Grond et al., 2000).

Even though the effects of aging on barrier qualities of skin affect drug permeation, the variability could also be explained by differences in cytochrome p-450 3A4 activity in population of patients covering a wide age range (Solassol et al., 2005).

Renal function decreases with age, which might also increase interindividual variation, as shown for some topically applied lipophilic drugs (Roskos and Maibach, 1992).

5.6.2.2. Gender. Although there are significant differences in the general appearance of skin and the distribution of hair follicles between males and females, there is no convincing evidence to suggest major differences in barrier function (Tur, 1997).

Pharmacokinetic study of nicotine, demonstrated the higher values for apparent nicotine elimination rate constants in women (Prather et al., 1993).

Greater subcutaneous lipid in women compared with men could be hypothesized to affect transdermal drug delivery but it has not been confirmed. In general, bioavailability and protein binding do not appear to be significantly affected by gender (Schwartz, 2003).

Further studies are needed to address the gender effect on the efficiency of transdermal drug delivery.

5.6.2.3. Other. Formation of skin depot and duration of its effect varies in different subjects. This is known to cause interindividual variations in plasma concentration profile of clonidine after system removal: as for some subjects the plasma concentration rises whereas others decline (MacGregor et al., 1985). As CV of oral and transdermal clonidine are presented in Fig. 2, that is the only case where CV of transdermal route dominates the oral. The possibility of skin depot formation and related inter-subject variations should be considered in interpretation of this finding.

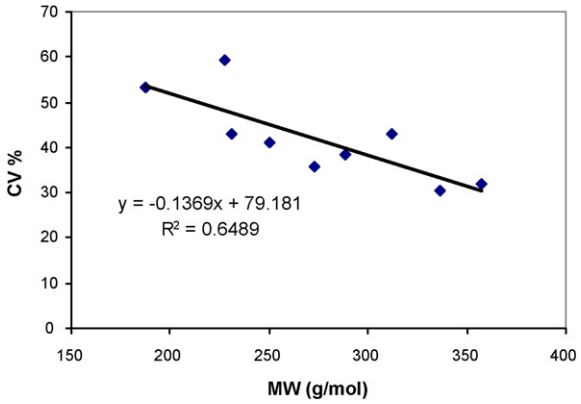

Fig. 3. Correlation of inter-individual variation and molecular weight of nine drugs.

Local blood flow is considered as a limiting factor for the exchange rate of transdermally applied nicotine. This explains the increased drug release from the TTS during exercise (Bur et al., 2005). Although under normal physiologic conditions, blood flow to and from the skin site of application has little influence on the rate of fentanyl absorption (Gupta et al., 1992).

Obesity could decrease the plasma level of transdermally administered nicotine in a study of 12 male subjects. However, in large clinical trials body weight had no effect on drug disposition (Prather et al., 1993).

5.6.3. TTS system design

As mentioned above, the membrane-controlled systems may reduce interindividual variation if the system is the rate controlling barrier rather than the skin. Alcohol-enhanced membrane-controlled transdermal systems have reduced the interindividual variation for fentanyl and nitroglycerin by 50% (Berner and John, 1994; Grond et al., 2000).

5.6.4. Kinetic variations of drug molecule

Nitroglycerin pharmacokinetic in humans after an intravenous infusion is characterized by high intra/inter-subject variation (Sun et al., 1995). For oral nitroglycerin, the coefficient of variation of C_{max} is around 112% (Fig. 2). These high variabilities in clearance may be due to apparent extensive tissue distribution and rapid plasma clearance. The same trend is seen for transdermal route, which may explain the highest mean CV value observed in this study compared to the other drugs (Fig. 2, Table 5).

High degree of variability in selegiline pharmacokinetic data after oral administration is attributed to the extensive rate of hepatic first pass metabolism (>90%) (Fig. 2). The avoidance of first pass effect following transdermal application, reduced the variability in selegiline exposure by 50% (Azzaro et al., 2007), though the mean CV of C_{max} remains high (53%). The same explanation might also be true for differences in CV values observed for oral and transdermal estradiol and testosterone (Fig. 2).

Finally, the variations of clonidine and fentanyl plasma concentration have been primarily attributed to interindividual variations in drug clearance, because similar interindividual variability is achieved during continuous intravenous infusion. However, it is partly due to different skin permeability (MacGregor et al., 1985; Gupta et al., 1992; Grond et al., 2000).

Since the absorption, disposition and clearance of the drugs are a function of physicochemical properties of their molecules, the correlation between mean Coefficient of variation (CV) in C_{max} of drugs and their molecular weight (MW) and $\log K_{oct}$ (logarithmically transformed octanol–water partition coefficient) was evaluated (Table 5, Figs. 3 and 4). C_{max} is selected as the most consistently reported parameter for all of the drugs, and as an important pharmacokinetic marker of plasma concentration profile.

Excluding nicotine (MW: 162.23; $\log K_{oct}$: 1.17), there appeared to be a significant negative correlation between CV and MW. (Pearson correlation coefficient: −0.806; p-value < 0.01) That means in the range of MW: 200–400 g/mol, by increasing molecular weight, interindividual variation in C_{max} of the drugs decreases (Fig. 3).

On the other hand, after exclusion of nicotine (MW: 162.23; $\log K_{oct}$: 1.17) and clonidine (MW: 231; $\log K_{oct}$: 0.53) a negative correlation was established between mean CV and $\log K_{oct}$ (Pearson correlation coefficient: −0.844; p-value < 0.01). Thus in the range of $\log K_{oct}$: 1.6–4.3, increase of lipophilicity results in reduced interindividual variation of C_{max} (Fig. 4).

Therefore, it can be hypothesized that for small and hydrophilic molecules in the mentioned range, higher degree of interindividual variation is expected. This could be explained by higher skin permeability, volume of distribution, and clearance for this type of molecules, which make the effect of subject variation during each process, even more prominent.

These findings support the effect of kinetic variations on general interindividual differences observed in plasma concentration after transdermal drug delivery.

Evaluation of CVs for different brands of each drug revealed that no significant correlation could be found between CV and system delivery rate and application period.

Taken together, the plasma concentration profile for TTS is a net result of the system performance and drug absorption and elimination. Thus, the variability in plasma concentration is a function of variability of each process involved, at least in theory.

5.7. Predictive models

The models obtained here, suggest the possibility of a determinant correlation between C_{max} of transdermally administered drugs and their molecular properties. Models were developed based on the available data for all the pharmacokinetically studied marketed drugs except fentanyl and clonidine, which showed exceptionally high C_{max} values.

As this trial evaluates the relationship of in vivo absorption data of transdermally applied drugs with their structural features, a small data set was available. Although this may reduce the predictive power of the model for further molecules, correlations are evaluated for a relevant data set which is corresponded to a group of drugs with proved clinical efficacy after transdermal absorption.

According to the standardized partial regression coefficients, the number of hydrogen bond acceptor groups (HA) has the largest contribution in predicting C_{max} in both equations, in the context of

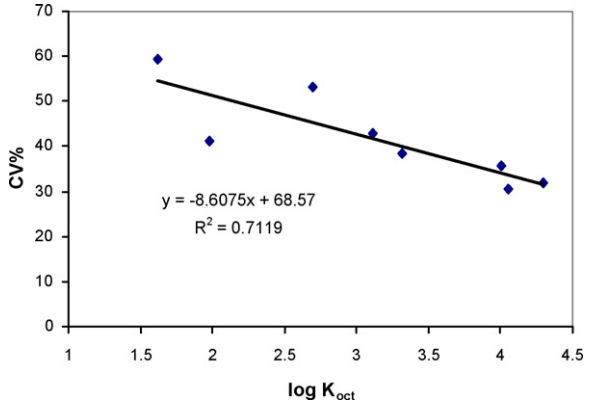

Fig. 4. Correlation of inter-individual variation and $\log K_{oct}$ of eight drugs.

the other predictor variables in the model. This finding is in accordance with the previous studies, where HA was determined to be a main parameter in predicting permeability coefficient (Cronin et al., 1999; Abraham and Martins, 2004). Eqs. (4) and (5) disclose that the C_{max} is positively correlated to the HA. Lipinski et al. proposed that large number of hydrogen bond acceptor sites may potentially delay skin permeation. Poor absorption or permeation is more likely when there are more than five hydrogen bond donors or ten hydrogen bond acceptors present on the molecule (Lipinski et al., 2001).

The issue is complicated further if the composite nature of $\log K_{oct}$ is considered, because it contains a degree of information regarding hydrogen bonding. Although no proven collinearity of variables was detected in the adopted models in the present study, there could be found a poor insignificant correlation between $\log K_{oct}$ and HA (r: −0.361, $p > 0.05$); the poor correlation coefficient does not demonstrate that $\log K_{oct}$ and HA are independent.

If C_{max} was just an indication of drug permeation rate, a negative correlation between C_{max} and HA could be expected. The positive correlation of HA and C_{max} (Eqs. (4) and (5)) suggests considering C_{max} as a complex parameter composed of absorption and elimination. If a high number of hydrogen bonding acceptor groups can impede the skin permeation, its effect on the clearance process should also be noted. The affinity of the drugs to body fluids which affects the volume of distribution is partly related to their molecular properties, such as hydrogen bonding. Assuming a linear single compartment model, the total amount of drug in the blood may be expressed as:

$$\frac{dS}{dt} = -k \times S + A \times J \tag{6}$$

where, k is the sum of the various elimination rate constants, A is the patch area, and J is the flux of drug across the skin (Berner, 1985). Increased number of hydrogen bond acceptor groups, may decrease the J, but may increase the k .Therefore, its net effect on blood concentration should be noted.

Moreover, the effects of hydrogen bonding capacity on protein binding and metabolism may also interfere with plasma concentration.

Predictivity of the permeation models based on physicochemical properties of molecules such as MW and $\log K_{oct}$ has been questioned by the fact that they give little information as to the actual structural features of solutes that influence skin permeability (Abraham et al., 1995). The following equation was suggested for prediction of $\log K_{oct}$ from molecular properties:

$$\log K_{oct} = 0.088 + 0.562\,R_2 - 1.054\pi_2^H + 0.034\,\Sigma\alpha_2^H - 3.46\,\Sigma\beta_2^H + 3.814V_x \tag{7}$$

where, R_2 is an excess molar refraction, π_2^H is the solute dipolarity/polarizability, $\Sigma\alpha_2^H$ and $\Sigma\beta_2^H$ and are the overall hydrogen bond acidity and basicity, and V_x is the McGown characteristic volume.

Therefore, a criticism of Eq. (5) could be that $\log K_{oct}$ (as a predictive variable in this equation) may found to be collinear with the other equation variables.

Although Eq. (5) could show the effect of molecular size on the C_{max}, inclusion of molecular weight in Eq. (4), failed to result in a significant correlation. Again, the complexity of C_{max} as an indicator of absorption and elimination, and/or narrow range of molecular weights of studied compounds (162–357), could explain this finding. In Barratt's predictive model for skin permeability coefficient, melting point is included as an independent variable in addition to the $\log K_{oct}$ and molecular volume (Barratt, 1995).

Inclusion of melting point in Eqs. (4) and (5), failed to improve the statistics of the Eqs. (4) and (5). Further, no linear correlation could be established between C_{max} and the melting point.

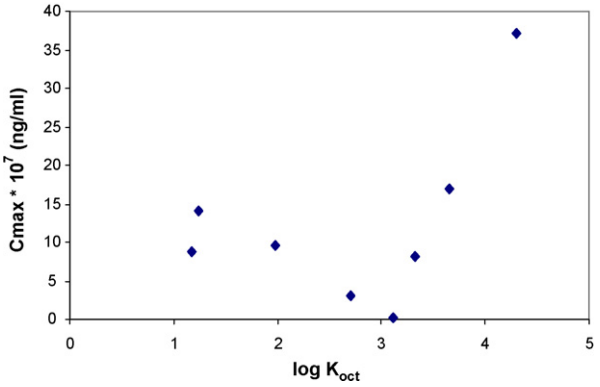

Fig. 5. Two-segmental linear correlation of C_{max} and $\log K_{oct}$ for eight drugs.

It has been known that melting point is a composite parameter that describes the propensity to accept or donate hydrogen bonds (Cronin et al., 1999). Thus, the effect of melting point is implied in the hydrogen bonding term of the suggested models (Eq. (4) and (5))

Note when C_{max} was plotted against $\log K_{oct}$, is the two segment linear correlation of C_{max} and $\log K_{oct}$ ($r^2 = 0.984$, $p < 0.05$) (Fig. 5). The outliers were clonidine, fentanyl and nitroglycerin, with high C_{max} values and estradiol with low C_{max} value. This significant pattern of correlation, suggests that $\log K_{oct} = 3$ is an inflection point below which $\log K_{oct}$ is negatively correlated with C_{max}, and above that, there is a positive correlation between C_{max} and $\log K_{oct}$. If log kp (skin permeability coefficient) was considered as the only parameter determining C_{max}, then according to Potts and Guy equation (Eq. (1))—which is applicable in the range of $-3 < \log K_{oct} < 6$, there should be a direct linear correlation between C_{max} and $\log K_{oct}$. This contrast, supports the fact that effects of physicochemical parameters on C_{max}, are expressed through different in vivo processes responsible for observed plasma concentration profiles (e.g. absorption, clearance, metabolism, etc.).

6. Future challenges

In the past 30 years, transdermal drug delivery has moved from a clinical reality, to the point where it represents a viable way of delivering a number of drugs with the potential to deliver many more using several enhancement approaches. Further research will be aimed to improve transdermal device design and enabling commercialization of intelligent TTS including feedback loops, synthesis and development of more efficient penetration enhancers, better understanding skin irritation, immunology, and metabolism, and improving fluxes for a wide variety of molecules. Recently, some evidence suggests that skin epithelial cells contain biochemical barrier systems such as influx and efflux pumps which could effect skin penetration of some substances (Schiffer et al., 2003). Further studies are suggested for clarification of clinical implications of skin active transporters, since these findings may evolve the transdermal drug delivery approaches in future.

Prediction of the in vivo blood concentration has become increasingly important in the development of transdermal therapeutic systems. Development and validation of QSPR models which consider the vehicle effect and use in vivo endpoints would be an economic alternative for costly and time-consuming in vitro and in vivo skin permeation studies.

7. Conclusion

The design of transdermal delivery systems was based on a hypothesized therapeutic rationale and knowledge of the

pharmacokinetics of the individual drugs. Characterization and optimization of these systems and their pharmacokinetic profile is still required.

Interindividual variation in pharmacokinetics remains an important challenge in transdermal drug delivery. Our results suggest increased interindividual variability by decreased MW and $\log K_{oct}$ values, in the range of $200 < MW < 400$ and $1.6 < \log K_{oct} < 4.3$. This could be explained by augmented vulnerability of smaller and more hydrophilic molecules in this range to permeation and elimination, the main sources of inter-subject variability.

In an attempt to develop a predictive model for maximal plasma concentration (C_{max}) based on physicochemical characteristics of drugs, two statistically significant empirical equations were established for 10 molecules. The results demonstrated that the number of hydrogen bond acceptor groups (HA) has the largest contribution in predicting C_{max} in both of the equations, in the context of the other predictor variables in the model.

These findings emphasize that the plasma concentration profile for TTS is a net result of the system performance and drug absorption and elimination. Thus, the variability in plasma concentration is a function of variability of each process involved. This should be noted in explanation of effect of molecular features of drugs on their plasma concentration profile.

Further theoretical evaluations are needed to confirm the power of suggested models in predicting in vivo parameters from the drugs structure. Meanwhile, detailed comparison of interindividual pharmacokinetic variability between TTS and other routes of drug administration can elucidate the possible correlation of interindividual variability and physicochemical characteristics of drugs. This will give insights for the future challenge of transdermal drug delivery: designing drugs with low variability. This in vivo human data provides an anchor for further examination of predictive models based on in vitro data.

Acknowledgements

We thank Professor Michael Abraham for his generous help in providing the unavailable molecular descriptors and Professors, Leslie Z. Benet, and David Verotta, for the helpful discussion and assistance in data analysis. We gratefully acknowledge Mr. Robert Gale and Dr. Bret Berner for providing enlightening comments and ideas for this work.

References

Abraham, M.H., Martins, F., 2004. Human skin permeation and partition: general linear free-energy relationship analyses. J. Pharm. Sci. 93, 1508–1523.

Abraham, M.H., Chadha, H.S., Mitchell, R.C., 1995. The factors that influence skin penetration of solutes. J. Pharm. Pharmacol. 47, 8–16.

Abrams, L.S., Skee, D.M., Natarajan, J., Wong, F.A., Anderson, G.D., 2002. Pharmacokinetics of a contraceptive patch (Evra/Ortho Evra) containing norelgestromin and ethinyloestradiol at four application sites. Br. J. Clin. Pharmacol. 53, 141–146.

Abrams, L.S., Skee, D.M., Natarajan, J., Wong, F.A., Leese, P.T., Creasy, G.W., Shangold, M.M., 2001. Pharmacokinetics of norelgestromin and ethinyl estradiol delivered by a contraceptive patch (Ortho Evra/Evra) under conditions of heat, humidity, and exercise. J. Clin. Pharmacol. 41, 1301–1309.

Amory, J.K., Kalhorn, T.F., Page, S.T., 2008. Pharmacokinetics and pharmacodynamics of oral testosterone enanthate plus dutasteride for 4 weeks in normal men: implications for male hormonal contraception. J. Androl. 29, 260–271.

Anderson, V.R., Scott, L.J., 2006. Methylphenidate transdermal system in attention-deficit hyperactivity disorder in children. Drugs 66, 1117–1126.

Appell, R.A., Chancellor, M.B., Zobrist, R.H., Thomas, H., Sanders, S.W., 2003. Pharmacokinetics, metabolism, and saliva output during transdermal and extended-release oral oxybutynin administration in healthy subjects. Mayo Clin. Proc. 78, 696–702.

Auclair, B., Sirois, G., Ngoc, A.H., Ducharme, M.P., 1998a. Novel pharmacokinetic modelling of transdermal nitroglycerin. Pharm. Res. 15, 614–619.

Auclair, B., Sirois, G., Ngoc, A.H., Ducharme, M.P., 1998b. Population pharmacokinetics of nitroglycerin and of its two metabolites after a single 24-hour application of a nitroglycerin transdermal matrix delivery system. Ther. Drug Monit. 20, 607–611.

Azzaro, A.J., Ziemniak, J., Kemper, E., Campbell, B.J., VanDenBerg, C., 2007. Pharmacokinetics and absolute bioavailability of selegiline following treatment of healthy subjects with the selegiline transdermal system (6 mg/24 h): a comparison with oral selegiline capsules. J. Clin. Pharmacol. 47, 1256–1267.

Baracat, E., Haidar, M., Castelo, A., Tufik, S., de Lima, G.R., Vieira, J.G., Peloso, U., Casoy, J., 1996. Comparative bioavailability study of a once-a-week matrix versus a twice-a-week reservoir transdermal estradiol delivery systems in postmenopausal women. Maturitas 23, 285–291.

Bannon, Y.B., Corish, J., Corrigan, O.I., Devane, J.G., Kavanagh, M., Mulligan, S., 1989. Transdermal delivery of nicotine in normal human volunteers: a single dose and multiple dose study. Eur. J. Clin. Pharmacol. 37, 285–290.

Barratt, M.D., 1995. Quantitative structure-activity relationships for skin permeability. Toxic. In Vitro 9, 27–37.

Berner, B., 1985. Pharmacokinetics of transdermal drug delivery. J. Pharm. Sci. 74, 718–721.

Berner, B., John, V.A., 1994. Pharmacokinetic characterization of transdermal delivery systems. Clin. Pharmacokinet. 26, 121–134.

Boyd, R.A., Zegarac, E.A., Eldon, M.A., Sedman, A.J., Forgue, S.T., 1996. Characterization of a 7 day 17 beta-estradiol transdermal delivery system: pharmacokinetics in healthy postmenopausal women. Biopharm. Drug Dispos. 17, 459–470.

Brocks, D.R., Meikle, A.W., Boike, S.C., Mazer, N.A., Zariffa, N., Audet, P.R., Jorkasky, D.K., 1996. Pharmacokinetics of testosterone in hypogonadal men after transdermal delivery: influence of dose. J. Clin. Pharmacol. 36, 732–739.

Buch, A.B., Shen, L.Z., Kelly, S.C., Russell, D.A., Sahota, R.S., Bixler, C.A., Moehrke, W., Powell, J.H., 1999. Significant differences in estradiol bioavailability from two similarly labelled estradiol matrix transdermal systems. Climacteric 2, 248–253.

Bur, A., Joukhadar, C., Klein, N., Herkner, G., Mitulovic, R., Schmid, E., Agneter, M., Müller, M., Brunner, 2005. Effect of exercise on transdermal nicotine release in healthy habitual smokers. Int. J. Clin. Pharmacol. Ther. 43, 239–243.

Burlacu, C.L., Frizelle, H.P., Moriarty, D.C., Buggy, D.J., 2007. Pharmacokinetics of levobupivacaine, fentanyl, and clonidine after administration in thoracic paravertebral analgesia. Regional Anesth. Pain Med. 32, 136–145.

Cronin, M.T.D., Dearden, J.C., Moss, G.P., Murray-Dickson, G., 1999. Investigation of the mechanism of flux across human skin in vitro by quantitative structure–permeability relationships. Eur. J. Pharm. Sci. 7, 325–330.

Cummings, J., Lefevre, G., Small, G., Appeldingemanse, S., 2007. Pharmacokinetic rationale for rivastigmine patch. Neurology 69, S10–S13.

Devineni, D., Skee, D., Vaccaro, N., Massarella, J., Janssens, L., LaGuardia, K.D., Leung, A.T., 2007. Pharmacokinetics and pharmacodynamics of a transdermal contraceptive patch and an oral contraceptive. J. Clin. Pharmacol. 47, 497–509.

Fant, R.V., Henningfield, J.E., Shiffman, S., Strahs, K.R., Reitberg, D.P., 2000. A pharmacokinetic crossover study to compare the absorption characteristics of three transdermal nicotine patches. Pharmacol. Biochem. Behav. 67, 479–482.

Feldmann, R.J., Maibach, H.I., 1970. Absorption of some organic compounds through the skin in man. J. Invest. Dermatol. 54, 399–404.

Fujimura, A., Ebihara, A., Ohashi, K., Shiga, T., Kumagai, Y., Nakashima, H., Kotegawa, T., 1994. Comparison of the pharmacokinetics, pharmacodynamics, and safety of oral (Catapres) and transdermal (M-5041T) clonidine in healthy subjects. J. Clin. Pharmacol. 34, 260–265.

Gorsline, J., Okerholm, R.A., Rolf, C.N., 1992. Comparison of plasma nicotine concentrations after application of Nicoderm (nicotine transdermal system) to different skin sites. J. Clin. Pharmacol. 32, 576–581.

Grond, S., Radbruch, L., Lehmann, K.A., 2000. Clinical pharmacokinetics of transdermal opioids: focus on transdermal fentanyl. Clin. Pharmacokinet. 38, 59–89.

Guichard, J.P., Sauron, R., Jones, A.B., 1999. Comparison of the pharmacokinetics of 17 beta-estradiol after a single 4-day application of Oesclim 50, Oesclim 100, and Vivelle 0.05 (Menorest 50) transdermal delivery systems. J. Clin. Pharmacol. 39, 811–816.

Gupta, S.K., Okerholm, R.A., Coen, P., Prather, R.D., Grosline, J., 1993. Single- and multiple-dose pharmacokinetics of Nicoderm (Nicotine Transdermal System). J. Clin. Pharmacol. 33, 169–174.

Gupta, S.K., Okerholm, R.A., Eller, M., Wei, G., Rolf, C.N., Gorsline, J., 1995. Comparison of the pharmacokinetics of two nicotine transdermal systems: nicoderm and habitrol. J. Clin. Pharmacol. 35, 493–498.

Gupta, S.K., Southam, M., Gale, R., Huang, S.S., 1992. System functionality and physicochemical model of fentanyl transdermal system. J. Pain Symptom Manage. 7, S17–26.

Guy, R.H., Hadgraft, J., 1985. Pharmacokinetic interpretation of the plasma levels of clonidine following transdermal delivery. J. Pharm. Sci. 74, 1016–1018.

Hansch, C., Leo, A., Hoekman, D., 1995. Exploring QSAR. ACS, Washington D.C, PP. 54, 158, 164, 178, 169, 124, 127, 113, 150, 6, 76 and 173.

Harrison, L.L., Harari, D., 2002. An evaluation of bioequivalence of two 7-day 17beta-estradiol transdermal delivery systems by anatomical site. J. Clin. Pharmacol. 42, 1134–1141.

Harrison, L.I., Zurth, C., Gunther, C., Karara, A.H., Melikian, A., Lipp, R., 2007. Simultaneous estradiol and levonorgestrel transdermal delivery from a 7-day patch: in vitro and in vivo drug deliveries of three formulations. Drug Dev. Ind. Pharm. 33, 373–380.

Hossain, M., Quebe-Fehling, E., Sergejew, T., Schmidt, G., Skerjanec, A., Ibarra de Palacios, P., Krinsky, L., 2003a. Dose proportionality study of four doses of an estradiol transdermal system. Estradot. Maturitas 46, 173–185.

Hossain, M., Quebe-Fehling, E., Sergejew, T., Schmidt, G., Skerjanec, A., Cohen, A., Krinsky, L., Ibarra de Palacios, P., 2003b. Comparative bioequivalence studies with Estradot and Menorest transdermal systems. Maturitas 46, 187–198.

Ito, M.K., O'Connor, D.T., 1991. Skin pretreatment and the use of transdermal clonidine. Am. J. Med. 91, S42–49.
Lefèvre, G., Sedek, G., Huang, H.L., Saltzman, M., Rosenberg, M., Kiese, B., Fordham, P., 2007. Pharmacokinetics of a rivastigmine transdermal patch formulation in healthy volunteers: relative effects of body site application. J. Clin. Pharmacol. 47, 471–478.
Lefèvre, G., Sedek, G., Jhee, S.S., Leibowitz, M.T., Huang, H.L., Enz, A., Maton, S., Ereshefsky, L., Pommier, F., Schmidli, H., Appel-Dingemanse, S., 2008. Pharmacokinetics and pharmacodynamics of the novel daily rivastigmine transdermal patch compared with twice-daily capsules in Alzheimer's disease patients. Clin. Pharmacol. Ther. 83, 106–114.
Lipinski, C.A., Lombardo, F., Dominy, B.W., Feeny, P.J., 2001. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv. Drug Deliv. Rev. 46, 3–26.
MacGregor, T.R., Matzek, K.M., Keirns, J.J., van Wayjen, R.G., van den Ende, A., van Tol, R.G., 1985. Pharmacokinetics of transdermally delivered clonidine. Clin. Pharmacol. Ther. 38, 278–284.
McClellan, K.J., Goa, K.L., 1998. Transdermal testosterone. Drugs 55, 253–2578, discussion 259.
Meikle, A.W., Arver, S., Dobs, A.S., Sanders, S.W., Rajaram, L., Mazer, N.A., 1996. Pharmacokinetics and metabolism of a permeation-enhanced testosterone transdermal system in hypogonadal men: influence of application site—a clinical research center study. J. Clin. Endocrinol. Metab. 81, 1832–1840.
Mercier, F., Lefèvre, G., Huang, H.L., Schmidli, H., Amzal, B., Appel-Dingemanse, S., 2007. Rivastigmine exposure provided by a transdermal patch versus capsules. Curr. Med. Res. Opin. 23, 3199–3204.
Müller, P., Botta, L., Ezzet, F., 1996. Bioavailability of estradiol from a new matrix and a conventional reservoir-type transdermal therapeutic system. Eur. J. Clin. Pharmacol. 51, 327–330.
Noonan, P.K., Gonzalez, M.A., Ruggirello, D., Tomlinson, J., Babcock-Atkinson, E., Ray, M., Golub, A., Cohen, A., 1986. Relative bioavailability of a new transdermal nitroglycerin delivery system. J. Pharm. Sci. 75, 688–691.
Physician's Desk Reference, 2006, 60th ed., Thompson PDR, New Jersey.
Ponti, F.D.E., Luca, C., Pamparana, F., 1989. Bioavailability study of three transdermal nitroglycerin preparations in normal volunteers. Curr. Ther. Res. 46, 111–120.
Potts, R.O., Guy, R.H., 1992. Predicting skin permeability. Pharm. Res. 9, 663–669.
Prather, R.D., Tu, T.G., Rolf, C.N., Grosline, J., 1993. Nicotine pharmacokinetics of Nicoderm (nicotine transdermal system) in women and obese men compared with normal-sized men. J. Clin. Pharmacol. 33, 644–649.
Reginster, J.Y., Donazzolo, Y., Brion, N., Lins, R., 2000. Estradiol pharmacokinetics after transdermal application of patches to postmenopausal women: matrix versus reservoir patches. Climacteric 3, 168–175.
Reginster, J.Y., Albert, A., Deroisy, R., Colette, J., Vrijens, B., Blacker, C., Brion, N., Caulin, F., Mayolle, C., Regnard, A., Scholler, R., Franchimont, P., 1997. Plasma estradiol concentrations and pharmacokinetics following transdermal application of Menorest 50 or Systen (Evorel) 50. Maturitas 27, 179–186.
Renner, U.D., Oertel, R., Kirch, W., 2005. Pharmacokinetics and pharmacodynamics in clinical use of scopolamine. Ther. Drug Monit. 27, 655–665.
Ridout, G., Santus, G.C., Guy, R.H., 1988. Pharmacokinetic considerations in the use of newer transdermal formulations. Clin. Pharmacokinet. 15, 114–131.
Riedel, D.J., Wick, K.A., Hawkinson, R.W., Kolars, C.A., Crowley, J.K., Armstrong, K.E., Chang, S.F., Harrison, L.I., de Dennis, S.R., 1989. Performance of a new transdermal nitroglycerin adhesive patch formulation. Clin. Ther. 11, 225–231.
Rohatagi, S., Barrett, J.S., DeWitt, K.E., Morales, R.J., 1997a. Integrated pharmacokinetic and metabolic modeling of selegiline and metabolites after transdermal administration. Biopharm. Drug Dispos. 18, 567–584.
Rohatagi, S., Barrett, J.S., McDonald, L.J., Morris, E.M., Darnow, J., DiSanto, A.R., 1997b. Selegiline percutaneous absorption in various species and metabolism by human skin. Pharm. Res. 14, 50–55.
Rohr, U.D., Nauert, C., Stehle, B., 1999. 17Beta-estradiol delivered by three different matrix patches 50 microg/day: a three way cross-over study in 21 postmenopausal women. Maturitas 33, 45–58.
Roskos, K.V., Maibach, H.I., 1992. Percutaneous absorption and age: implications for therapy. Drugs Aging 2, 432–449.
Sambol, N.C., Harper, C.C., Kim, L., Liu, C.Y., Darney, P., Raine, T.R., 2006. Pharmacokinetics of single-dose levonorgestrel in adolescents. Contraception 74, 104–109.
Scheuplein, R.J., Blank, I.H., 1971. Permeability of the skin. Physiol. Rev. 51, 707–747.
Schiffer, R., Neis, M., Holler, D., Rodriguez, F., Geier, A., Gartung, C., Lammert, F., Dreuw, A., Zwadlo-Klarwasser, G., Merk, H., Jugert, F., Baron, J.M., 2003. Active influx transport is mediated by members of the organic anion transporting polypeptide family in human epidermal keratinocytes. J. Invest. Dermatol. 120, 285–291.
Schwartz, J.B., 2003. The influence of sex on pharmacokinetics. Clin. Pharmacokinet. 42, 107–121.
Sobue, S., Sekiguchi, K., Kikkawa, H., Akasaki, M., Irie, S., 2006. Comparison of nicotine pharmacokinetics in healthy Japanese male smokers following application of the transdermal nicotine patch and cigarette smoking. Biol. Pharm. Bull. 29, 1068–1073.
Solassol, I., Caumette, L., Bressolle, F., Garcia, F., Thézenas, S., Astre, C., Culine, S., Coulouma, R., Pinguet, F., 2005. Inter- and intra-individual variability in transdermal fentanyl absorption in cancer pain patients. Oncol. Rep. 14, 1029–1036.
Sun, J.X., Piraino, A.J., Morgan, J.M., Joshi, J.C., Cipriano, A., Chan, K., Redalieu, E., 1995. Comparative pharmacokinetics and bioavailability of nitroglycerin and its metabolites from Transderm-Nitro, Nitrodisc, and Nitro-Dur II systems using a stable-isotope technique. J. Clin. Pharmacol. 35, 390–397.
Tanner, T., Marks, R., 2008. Delivering drugs by transdermal route: review and comment. Skin Res. Technol. 14, 249–260.
Thompson, J.P., Bower, S., Liddle, A.M., Rowbotham, D.J., 1998. Perioperative pharmacokinetics of transdermal fentanyl in elderly and young adult patients. Br. J. Anaesth. 81, 152–154.
Tse, F.L., Laplanche, R., 1998. Absorption, metabolism and disposition of [14C]SDZ ENA.713 an acetylcholinesterase inhibitor, in minipigs following oral, intravenous, and dermal administration. Pharm. Res. 15, 1614–1620.
Tur, E., 1997. Physiology of the skin—differences between women and men. Clin. Dermatol. 15, 5–16.
Vasil'ev, A.E., Krasnyuk, I.I., Ravikumar, Tokhmakhchi, V.N., 2001. Drug synthesis methods and manufacturing technology transdermal therapeutic systems for controlled drug release. Pharm. Chem. J. 35, 613–626.
Vecchia, B.E., Bunge, A.L., 2003. Evaluating the transdermal permeability of chemicals. In: Guy, R.H., Hadgraft, J. (Eds.), Transdermal Drug Delivery. Marcel Dekker, New York, pp. 25–57.
Wester, R.C., Maibach, H.I., 1983. Cutaneous pharmacokinetics: 10 steps to percutaneous absorption. Drug Metab. Rev. 14, 169–205.
Williams, A.C., 2003. Transdermal and Topical Drug Delivery. Pharmaceutical Press, London, pp. 178–187.
Wolff, M., Cordes, G., Luckow, V., 1985. In vitro and in vivo release of nitroglycerin from a new transdermal therapeutic system. Pharm. Res. 2, 23–29.
Yalkowsky, S.H., 1981. Solubility and partitioning V: dependence of solubility on melting point. J. Pharm. Sci. 70, 971–973.
Yu, D.K., Williams, R.L., Benet, L.Z., Lin, E.T., Giesing, D.H., 1988. Pharmacokinetics of nitroglycerin and metabolites in humans following oral dosing. Biopharm. Drug Dispos. 9, 557–565.
Zacur, H.A., Hedon, B., Mansour, D., Shangold, G.A., Fisher, A.C., Creasy, G.W., 2002. Integrated summary of Ortho Evra/Evra contraceptive patch adhesion in varied climates and conditions. Fertil. Steril. 77, S32–S35.
Zobrist, R.H., Quan, D., Thomas, H.M., Stanworth, S., Sanders, S.W., 2003. Pharmacokinetics and metabolism of transdermal oxybutynin: in vitro and in vivo performance of a novel delivery system. Pharm. Res. 20, 103–109.
Zobrist, R.H., Schmid, B., Feick, A., Quan, D., Sanders, S.W., 2001. Pharmacokinetics of the R- and S-enantiomers of oxybutynin and N-desethyloxybutynin following oral and transdermal administration of the racemate in healthy volunteers. Pharm. Res. 18, 1029–1034.