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Transdermal delivery of some anti-emetics

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Abstract

One group of drugs that could be usefully delivered by the transdermal route are the anti-emetics. Representative examples of this class of drugs have been examined and their potential for transdermal delivery assessed. This has been achieved by an examination of their physicochemical properties from which skin permeability can be predicted using a range of mathematical models. The results have been compared with data in the literature for the penetration of the drugs across rat skin. The predicted permeabilities have then been equated with the known clearance kinetics of the drugs to calculate probable plasma levels. In this way the feasibility of delivering these drugs transdermally can be assessed.

Keywords: Transdermal delivery; Anti-emetic; Skin penetration

A recent paper by Calpena et al. (1994) has highlighted the possibility of delivering some anti-emetic drugs via the transdermal route. There are clear advantages if this can be achieved but the data available in the literature are sparse. The paper considers a number of anti-emetics, which are given together with some physicochemical parameters in Table 1.

Permeability determinations were conducted with drug concentrations at 5 mg ml^{-1}. An ethanol/water (70:30) donor and receptor medium was used. Hairless rat skin was chosen as the membrane. In addition, experiments were conducted over a 180 h period. Rodent skin is very susceptible to breakdown over extended periods and the barrier function would be expected to be compromised. In any feasibility studies the choice of conditions is important. Hairless rat skin will not usually provide results which are directly comparable to human skin. High concentrations of ethanol will extract skin lipids and potentially provide over-estimates of the permeability coefficients. For this reason it was decided to examine the same compounds using theoretical approaches to evaluate permeability coefficients. The different approaches chosen were those that have been published by Potts and Guy (1992) and Pugh and Hadgraft (1994).

The method of Potts and Guy of calculating the permeability coefficient (k_p) uses a simple equation based on a knowledge of the octanol

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Table 1
Physico-chemical properties of the anti-emetics

Drug	MW	m.p. (°C)	pK_a	Log K_{oct} (Calpena et al., 1994)	Log K_{oct} (Medchem)
Alizapride	339.9	207.0	9.15	3.05	2.74
Bromopride	344.26	152.5	9.35	1.53	2.07
Clebopride	507.9	162.0	8.59	2.57	2.81
Domperidone	425.92	242.5	8.06	4.45	4.06
Metoclopramide	354.3	182.0	8.77	2.03	1.87
Metopimazine	445.61	170.5	8.64	3.66	2.22
Scopolamine	303.35	59.0	7.55	0.76	0.26

water partition coefficient (K_{oct}) and the molecular weight (MW) of the permeant:

$$\log k_p(\text{cm h}^{-1}) = -2.7 + 0.71 \cdot \log K_{oct} - 0.0061 \cdot \text{MW}$$

From the Medchem database (Medchem software release 3.4, Biobyte Corp., Claremont, CA) a series of K_{oct} values can be identified for the compounds. It is therefore possible to calculate a prediction interval (PI) for the estimated k_p value. PI values tend to be high because they have to account for experimental error in the log k_p predictor term. (Bolton, 1984)

An alternative approach is to break the molecules into their component fragments. Two methods, the '11 predictor' and 'SMILES' fragmentation methods (Pugh and Hadgraft, 1994), have been identified for this. The results depend on the method of fragmentation and have been described in detail. Since the predictors are simply the numbers of each fragment present in the molecule, they contain no experimental error. The estimated log k_p is then associated with a confidence interval (Bolton, 1984) which tends to be lower than the prediction interval of the method of Potts and Guy.

The three different methods of calculation give estimates of log k_p, the reliability of which can be weighted using the reciprocal of the variance of the regression (Finney, 1964). The values obtained and the relative weightings are given in Table 2.

Table 2
A comparison between the different theoretical approaches for estimating k_p in human skin

Drug	Method	Log k_p (cm h^{-1})	Weight ($1/s^2$)
Alizapride	1	−6.73	1.42
	2	−4.57	2.38
	3	−2.56	87.9
Bromopride	1	−3.00	4.12
	2	−1.95	70.62
	3	−1.93	10.0
Clebopride	1	−3.46	6.34
	2	−2.16	4.57
	3	−3.19	31.77
Domperidone	1	−3.80	4.20
	2	−4.40	2.00
	3	−2.40	40.62
Metoclopramide	1	−2.76	4.61
	2	−1.95	4.96
	3	−3.00	96.17
Metopimazine	3	−3.72	–
Scopolamine	1	−3.68	18.56
	2	−3.95	22.61
	3	−3.00	57.60

Method 1, 11 predictor (Pugh and Hadgraft, 1994); method 2, SMILES (Pugh and Hadgraft, 1994); method 3, Potts and Guy (1992).

Table 3
Weighted mean values for the predicted human skin permeability (95% CI) and those for hairless rat skin (Calpena et al., 1994).

Drug	Weighted log k_p (CI)	Log k_p hairless rat (CI)
Alizapride	−2.68 (0.36)	−2.24 (0.37)
Bromopride	−2.53 (0.16)	−2.11 (0.15)
Clebopride	−3.12 (0.52)	−2.13 (0.38)
Domperidone	−2.61 (0.50)	−2.55 (0.18)
Metoclopramide	−2.94 (0.33)	−2.02 (0.15)
Metopimazine	−2.72 (1.47)	−2.29 (0.15)
Scopolamine	−3.35 (0.34)	−2.38 (0.27)

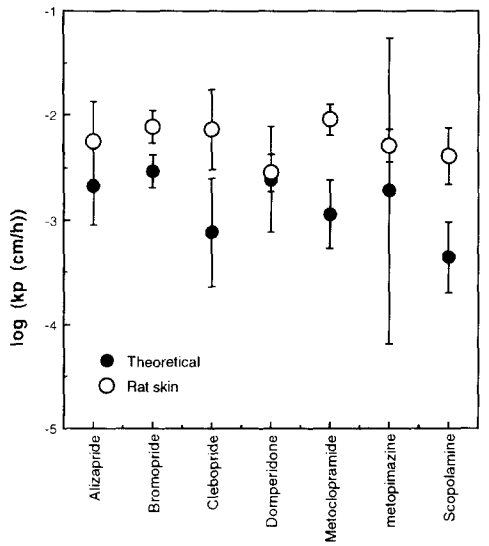

Fig. 1. A graphical comparison between the determined k_p values using the theoretical approach and the in vitro hairless rat data.

Metopimazine contains fragments which do not appear in the Pugh and Hadgraft paper and therefore it was not possible to calculate k_p values using methods 1 and 2.

Using the relative weights it is then possible to calculate a weighted mean value with 95% confidence interval. These are provided in Table 3.

In general, the data for the rat skin are significantly higher than the estimated values in human skin. This is shown graphically in Fig. 1.

From the permeability data and known clearance kinetics it is possible to estimate the expected plasma levels of these drugs. If the values for rat skin are taken it is very easy to over-estimate the plasma levels and obtain optimistic expectations of delivering these drugs transdermally.

Steady-state plasma levels (C_p) can be obtained using the simple equality:

$$JA = \mathrm{Cl}C_p$$

where J is the flux per unit area through the skin. A is the area of the of the transdermal patch and Cl denotes the clearance rate.

The flux J is calculated assuming no enhancement and using the simple equation:

$$J = k_p C_{app}$$

where C_{app} is the applied concentration. For an initial estimation, C_{app} has been taken as 5 mg

Table 4
Flux values, clearance kinetics (from Calpena et al., 1994) and estimated steady-state plasma levels

Drug	k_p (cm h^{-1})	Flux across skin (mg cm^{-2} h^{-1})	Cl (l h^{-1})	C_p (ng ml^{-1})
Alizapride	2.09×10^{-3}	1.04×10^{-2}	26.2	6.4
Bromopride	2.95×10^{-3}	1.48×10^{-2}	61.3	3.9
Clebopride	7.59×10^{-4}	3.79×10^{-3}	18.5	3.3
Domperidone	2.45×10^{-3}	1.23×10^{-2}	42.1	4.7
Metoclopramide	1.15×10^{-3}	5.74×10^{-3}	38.5	2.4
Metopimazine	1.91×10^{-4}	9.53×10^{-4}	174	0.1
Scopolamine	4.47×10^{-4}	2.23×10^{-3}	45	0.8

Table 5
A comparison of estimated plasma levels and those required therapeutically

Drug	C_p (ng ml^{-1}) from Calpena et al. (1994)	C_p (ng ml^{-1}) from Table 4	Therapeutic values (ng ml^{-1})
Alizapride	2.0–28.5	6.4	160
Bromopride	1.2–16.9	3.9	11.6
Clebopride	3.5–50.0	3.3	1.0
Domperidone	0.6–9.0	4.7	18
Metoclopramide	2.1–30.0	2.4	35
Metopimazine	0.3–4.0	0.1	15
Scopolamine	0.8–12.0	0.8	0.1

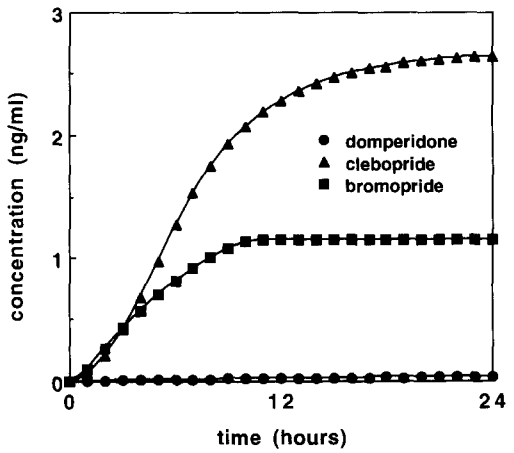

Fig. 2. A comparison between the predicted plasma levels using the kinetic model.

ml^{-1} and it has been assumed that at this concentration all the drug will be in solution. An area of 16 cm^2 was chosen. These two values were selected to make direct comparison with the estimates in the paper of Calpena et al. (1994). The flux and steady-state plasma levels are given in Table 4.

The estimated plasma levels from Calpena et al. (1994) and the therapeutic plasma concentrations required can be compared with the values given in Table 4. The comparison is provided in Table 5.

Those compounds which are within a factor of 5 of the therapeutic levels are potentially attainable. In order of feasibility, it is considered that the following drugs would warrant further investigation: scopolamine (already on the market for travel sickness), clebopride, bromopride, and domperidone.

One of the problems with this approach is that it does not take into account potential solubility constraints that the compounds may have. This problem has been addressed in a previous publication (Hadgraft et al. (1990)) and an estimate of the capacity of the skin can be obtained using:

$$\log[SC] = 1.911(10^3/MP) - 2.956$$

where [SC] is the 'solubility' of the drug in the stratum corneum ($\mu g\ cm^{-2}$) and MP represents the melting point (K). Using this value and the kinetic model proposed by Guy and Hadgraft (1983), it is possible to calculate the maximum attainable flux through the skin. This is given in Table 6.

These results suggest that problems of solubility constraints may occur. For the potentially identified materials: scopolamine, clebopride, bromopride and domperidone, it is the last of the group which may require formulation with a co-solvent to increase the solubility of the drug in the skin lipids.

Another problem which is not addressed by the analysis above is the fact that very lipophilic materials can be prevented from transferring from the stratum corneum to the viable tissue. This is modelled in the kinetic analysis published by Guy and Hadgraft (1983). Concentrating on the three compounds bromopride, clebopride and domperidone it is possible to simulate the build up of these drugs in the plasma as a function of time. The modelled data are shown in Fig. 2.

Steady-state plasma levels for clebopride and

Table 6
Estimated maximum fluxes through human skin based on a solubility constraint

Drug	[SC] ($\mu g\ cm^{-2}$)	J_{max} ($\mu g\ cm^{-2}$)	C_p (max) ($ng\ ml^{-1}$)
Alizapride	10.6	1370	0.8
Bromopride	34.3	4400	1.1
Clebopride	27.4	3090	2.7
Domperidone	5.6	674	0.3
Metoclopramide	17.5	2230	0.9
Metopimazine	22.5	2660	0.2
Scopolamine	631	84500	30.1

The associated steady-state plasma levels are given.

bromopride are reached within 24 h whereas domperidone is so lipophilic that the steady-state levels (0.3 ng ml^{-1}) would take a substantial time to be established.

It may be concluded that the likely candidates for transdermal anti-emetic activity are scopolamine, clebopride and bromopride. There may be other drug entities showing this pharmacological activity which could also be considered.

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