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Physicochemical aspects of the transdermal delivery of Bupranolol

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Summary

The skin absorption of Bupranolol has been measured in an assessment of the feasibility of delivering this drug transdermally. Basic physicochemical parameters such as partitioning are influenced by the presence of oleic and lauric acids. It is possible to enhance the transfer of Bupranolol across a model isopropyl myristate membrane by an ion pair mechanism involving these two fatty acids. They did not, however, significantly enhance transfer across in vitro human skin. A kinetic model based on physicochemical parameters can predict satisfactorily the transdermal delivery of this β-blocker

Introduction

A knowledge of the physicochemical and pharmacokinetic parameters of a drug are important in assessing the feasibility of transdermal drug delivery. The physicochemical features control the rates of diffusion and partitioning within the delivery system and the skin, and the pharmacokinetics the concentration of drug that builds up in the plasma. Bupranolol is a β-blocking agent which possesses the characteristic properties of this class of compound and its potential as a transdermal candidate can be assessed from its physicochemical properties.

It is a base ($pK_a = 9.6$) and as such will exist, in aqueous acid solution, as a protonated cation. It is possible to form ion pairs which will subsequently partition into a lipid membrane and the feasibility of this has been examined using two counter ions. Oleic acid and lauric acid were chosen. They are lipophilic in nature and oleic acid has been shown to be a potent penetration enhancer (Cooper, 1984; Golden et al., 1987). Initial studies concentrated on simple partitioning studies into isopropyl myristate (IPM) a lipid often regarded as a good model of skin constituents (Poulsen et al., 1968). Further studies were conducted to establish whether Bupranolol could be transported across a model lipid membrane as an ion pair. These experiments were conducted in a rotating diffusion cell and were compared with previously reported data.

Measurement of the absorption rate across excised human skin gives an indication of the total amounts of drugs that can be delivered transdermally. A recent report has indicated that it is more

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appropriate to use dermatomed skin rather than full thickness skin (Bronaugh and Stewart, 1986). The two have been compared. Ion pair transfer of Bupranolol has also been assessed in the in vitro skin cell.

It is possible to simulate the transdermal absorption of drugs provided some simple physicochemical and pharmacokinetic data are known. A transdermal patch for Bupranolol has been developed; the kinetics release of which are documented (Weiss et al., 1987). Using the release characteristics and known physicochemical and pharmacokinetic data, the plasma levels of Bupranolol following transdermal delivery have been simulated. They have then been compared with in vivo data in the literature.

Materials and Methods

Materials

Bupranolol was a gift from Schwarz Pharma AG. All reagents were of GPR grade and supplied by BDH Chemicals, except oleic acid and lauric acid which were biochemical grade. Isopropyl myristate (IPM) was supplied by Croda Chemicals. Cellulose nitrate 0.2 μm pore size membrane filters were obtained from Whatman.

Determination of partition coefficients

The partition coefficients were determined using a filter probe technique (Tomlinson, 1982) at 32° C and pH 7.4 and 8.0. The aqueous phase (20 ml) was buffered (McIlvaines) and the ionic strength adjusted to 0.6 M with sodium chloride. The volume of the organic phase was 2 ml. Both the buffer and the IPM were presaturated with one another.

The concentration of Bupranolol in the aqueous phase was monitored continuously in a flow through cell by UV spectrophometry (= 275 nm). Determinations were repeated 6 times. The effect of lauric and oleic acid on the partitioning of the drug was determined by adding 0.2 M fatty acid to the IPM prior to measurement.

Transfer across the model membrane

Experimental techniques using the rotating diffusion cell have been previously described in detail (Albery et al., 1976; Hadgraft et al., 1985). The donor phase consisted of 40 ml of a pH 8 phosphate-buffered solution (with 10% ethanol) of Bupranolol (6.7 mM). Ethanol was not required in the receptor phase (100 ml pH 7.4 phosphate buffer). The 0.2 μm cellulose nitrate separating the donor from the receptor phase was impregnated with IPM or 0.2 M fatty acid in IPM. The flux (J) of Bupranolol transferring across the membrane was determined spectrophotometrically and analysed according to the equation:

$$J = k \cdot A \cdot C_d$$

where A is the area of the filter and C_d the concentration of the drug in the donor compartment.

In vitro permeation across excised skin

Abdominal skin samples were obtained at autopsy from one male subject. Subcutaneous fat was removed by blunt dissection. Dermatomed skin samples were prepared by freezing between two flat steel plates and subsequently cutting a 330 μm thick slice using a Davies duplex 7 electric skin dermatome model GD 103.

The skin, either full thickness or dermatomed, was mounted horizontally in a Franz type glass diffusion cell. The area of skin available for diffusion was 1.8 cm^2. The donor phase was 1 ml pH 8 phosphate-buffered Bupranolol 15 mM containing 10% propanol. The receptor phase was degassed pH 7.4 phosphate buffer containing 10% alcohol. The cell was thermostatted at 37° C producing a skin surface temperature of 32° C.

In the experiments conducted with oleic acid, the enhancer was administered to the skin as a pretreatment by forming a thin film on the surface. 50 μl of an ethanolic solution of 0.1 M oleic acid was used. The ethanol evaporated leaving approximately 1.4 mg of oleic acid. Such a quantity would be expected to partition rapidly into the lipophilic regions of the outer layers of the stratum corneum. The Bupranolol appearing in the receptor phase was analysed by HPLC. The mobile phase consisted of: 5 mM heptane sulphonic acid in 830 ml methanol, 5 ml glacial acetic acid made up to 1 litre with water. An Apex 1 5 μm

ODS 250 × 4.6 mm i.d. column was used (Jones Chromatography). The flow rate used, 1.5 ml/min, gave a retention time of 4.2 min.

Results and Discussion

The partitioning data in Table 1 show that Bupranolol is comparable in lipophilicity to propranolol. The IPM/pH 7.4 partition coefficient of propranolol is 1.87 (Green et al., 1989). Oleic acid and lauric acid both increase the partitioning as a result of ion pair formation and a 100-fold increase in extraction is found. The increase is considerably higher than that found for propranolol (approximately 25-fold) (Green et al., 1989) presumably due to the different structural features of the two molecules. It is possible that there is an increased shielding of the charge of the ion pair formed between Bupranolol and the carboxylate anion. It was not possible to measure the partitioning at pH 8.0 in the presence of the acids due to emulsification problems.

Emulsification was not a problem in the rotating diffusion cell and transfer of Bupranolol from pH 8 to pH 4 aqueous solutions across an IPM membrane could be measured. In the absence of the carboxylic acid, the apparent rate constant was 6.11 $\mu m \cdot s^{-1}$. This was increased to 14.36 $\mu \cdot s^{-1}$ and 12.29 $\mu m \cdot s^{-1}$ by the presence of oleic acid and lauric acid, respectively. The increase in transfer rate is not as large as the increase in partition coefficient at pH 7.4. This is due to the fact that the partition coefficient will also be increased at pH 8.0 and it is the difference in values at pH 7.4 and pH 8.0 that creates the concentration gradient.

TABLE 1

Partitioning (at pH 7.4 and 8.0) and transfer rates (k) of Bupranolol across the model membrane

	IPM	IPM + Oleic acid	IPM + Lauric acid
pH 7.4	2.89	245.6	333.5
pH 8.0	8.26	–	–
$k/\mu m \cdot s^{-1}$	6.11	14.36	12.29

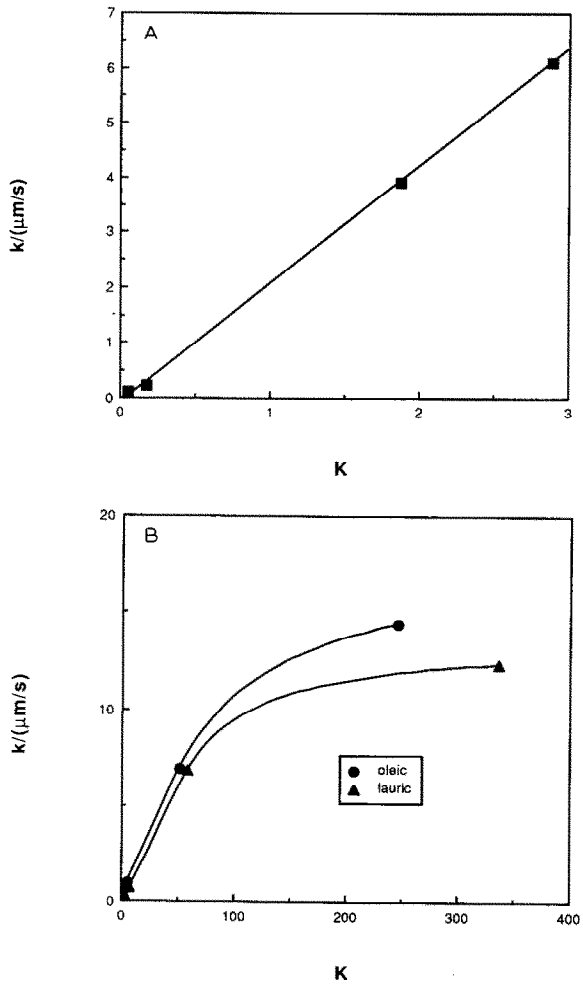

Fig. 1. Relationship between transfer rate in the rotating diffusion cell and pH 7.4 partition coefficient. A: the effect for 4 β-blockers without added acid. B: the effect of incorporating 0.2 M acid into the IPM membrane.

Fig. 1A shows the transfer rates for a range of β-blockers as a function of partition coefficient. In increasing lipophilicity the β-blockers are: metoprolol, oxprenolol, propranolol and Bupranolol (Green et al., 1989). Without oleic acid or lauric acid there is, as would be expected, a linear relationship between the transfer rate and the partition coefficient. When oleic acid and lauric acid are added, they ion pair to a differential amount at the two pHs on either side of the membrane. This results in the non-linear relationship between transfer rate and partition coeffi-

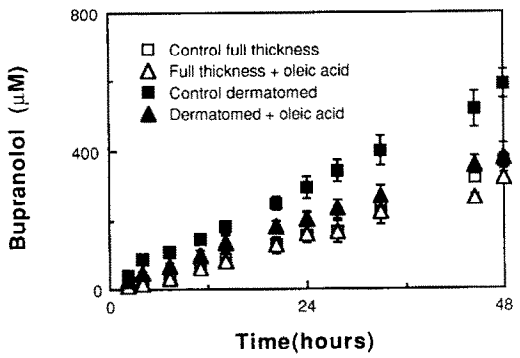

Fig. 2. In vitro penetration of Bupranolol across excised human skin. The effects of dermatoming the skin to 300 μm are shown together with the influence of oleic acid.

cient. However, there is still an apparent increase in transfer rate with lipophilicity (Fig. 1B). Both oleic acid and lauric acid appear equally efficient at enhancing the rate. This can be explained in terms of the similarities in pK_a, lipophilicity and molecular size of the two acids.

In vitro penetration across excised human skin is shown in Fig. 2 and Table 2. For all conditions the lag time for penetration is short showing that Bupranolol diffuses through skin rapidly.

Considering the experiments without oleic acid it is seen that the permeability is greater through the dermatomed skin. This implies that there is a contribution to the overall rate from diffusion of the Bupranolol through the dermis. In an assessment of the transdermal flux of Bupranolol it is more relevant to use dermatomed skin where the thickness chosen reflects the diffusional length from the skin surface to the dermal capillaries. A recent publication (Skelly et al., 1987) indicates that skin samples of less than 500 μm should be chosen but it may be necessary to choose thinner sections especially for lipophilic molecules. For these, the sections should be dermatomed to

TABLE 2

Permeability ($\times 10^{-4}$ cm/h) of Bupranolol in excised human skin (n = 3) (donor phase at pH 8.0)

	Full thickness	Dermatomed
Control	14.6 ± 1.6	23.5 ± 1.9
plus oleic acid	12.1 ± 1.7	16.5 ± 2.8

TABLE 3

Physicochemical and pharmacokinetic parameters for Bupranolol and the transdermal system

k_1 (h^{-1})	0.14
k_2 (h^{-1})	2.2
k_3 (h^{-1})	5.45
k_4 (h^{-1})	0.2
V_d (l)	375
k_0 ($\mu g/cm^2/h$)	18
k_a (h^{-1})	0.45
Apparent adhesive dose (mg)	7.2

around 200 μm which is more representative of the diffusional length to the blood supply. It is more difficult to produce thin samples but they do provide more relevant results. The transfer rate of Bupranolol, whose IPM–water partition coefficient at pH 7.4 is 2.89, would not be significantly affected by using 200 μm sections rather than 300 μm.

When oleic acid is present, it is surprising that the flux of Bupranolol is not increased. The in vitro results suggest that a permeability increase of approximately a factor of two would be expected. The decrease in skin permeability may be due to the ion pair which is formed being very stable in the lipid regions of the skin. The slowest step in

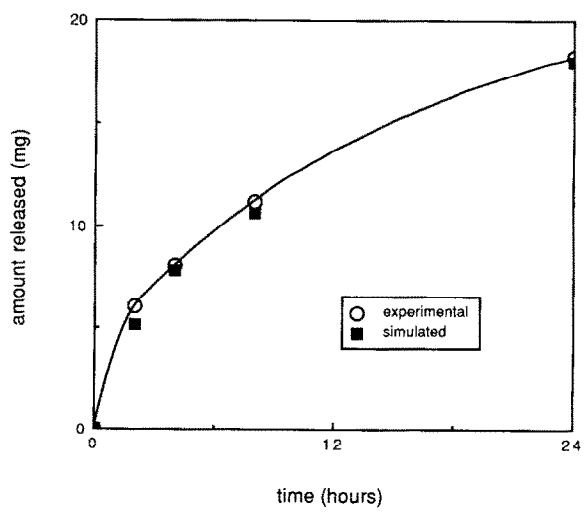

Fig. 3. The in vitro release of Bupranolol from a delivery system. The simulated data is obtained by using the rate constants k_0 and k_a given in Table 3.

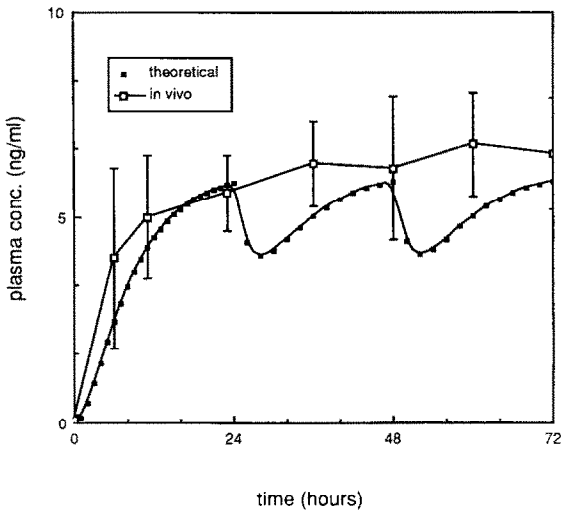

Fig. 4. The in vivo plasma levels of Bupranolol following transdermal delivery and the predicted levels given by the kinetic model and rate constants described in Table 3.

the transfer process is then the rate of partitioning from the stratum corneum to the viable tissue. The results demonstrate the difficulties in identifying model membranes which can be used to simulate skin. Transdermal delivery of Bupranolol can be modelled using the previously described kinetic description (Guy and Hadgraft, 1985). The rate constants are calculated from the physicochemical and pharmacokinetic properties of Bupranolol and are given in Table 3. The input function, k_i, from the device is obtained from the in vitro release characteristics of the delivery system. This may be modelled as the sum of a zero-order (k_0) and first-order process (k_a). The values of these terms are also given in Table 3 and the comparison between the experimental values (Weiss et al., 1987) and the calculated values using $k_0 + k_a$ are shown in Fig. 3. Comparison of the plasma levels predicted by the kinetic model and the measured in vivo concentrations is given in Fig. 4. The close agreement between the two demonstrates the utility in the kinetic model and its foundation on basic physicochemical parameters indicates its usefulness in predictive assessments.

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