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Improvement of buccal delivery of morphine using the prodrug approach

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Abstract

The feasibility of achieving buccal delivery of morphine using the prodrug approach was assessed by studies of bioactivation, in vitro permeation and in vivo absorption. The bioactivation of various morphine-3-esters was studied in human plasma and saliva. The in vitro permeation of morphine and various morphine-3-esters was studied using porcine buccal mucosa mounted in Ussing chambers and finally the in vivo absorption of the compounds evaluated following administration in rats. Both the results from the in vitro permeation and from the absorption of the prodrugs studied suggested a parabolic relationship to the lipophilicity of the compounds. In the in vitro studies the optimal permeation was achieved for the prodrug morphine-3-propionate having a log P value of approximately 0.7. In contrast to that optimal in vivo absorption was obtained for the prodrug morphine-3-acetate having a log P value of 0.2. This discrepancy could however be explained by the enzymatic stability of the two esters in saliva, since it was found that morphine-3-propionate was more rapidly hydrolysed in saliva than was morphine-3-acetate. The study demonstrates that the buccal delivery of morphine can be markedly improved by using ester prodrugs with higher lipophilicity than morphine itself. However, the enzymatic stability of the prodrugs in saliva also play an important role for the overall improvement in absorption properties. © 1997 Elsevier Science B.V.

Keywords: Morphine; Ussing-chamber; In vitro permeation; Buccal absorption Prodrug; Ester

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1. Introduction

Morphine is widely considered to be the prototype opioid analgesic. It is used extensively in the management of pain. Following peroral administration morphine is almost completely absorbed from the gastro-intestinal tract (Brunk and Delle, 1974; Yeh, 1975), however, due to extensive first-pass metabolism the systemic bioavailability is low and variable (19–47%) (Säwe et al., 1981, 1985; Osborne et al., 1990).

Following parenteral administration side-effects may occur as a consequence of high peak plasma levels. In addition peroral administration is inappropriate to patients suffering from nausea, vomiting or dysphagia and parenteral administration might be difficult in some patients due to decreased venous access, emaciation or coagulation defects.

Buccal or sublingual administration may offer a means of mitigating some of these problems. A necessity for buccal or sublingual administration of morphine is, however, that it is capable of penetrating the oral mucosa at a sufficiently high rate to ensure therapeutic plasma levels.

Recent studies on buccal administration of morphine have revealed contradictory results. Thus, when comparing the bioavailability of morphine after buccal and intramuscular administration Bardgett et al. (1983) and Bell et al. (1985) found a 19 and 46% higher bioavailabilty after buccal than after intramuscular administration respectively, whereas Fisher et al. (1987) and Simpson et al. (1989) found the bioavailability after buccal administration of morphine to be only 7.6 and 3% relative to that of intramuscular morphine, respectively.

Results from studies comparing the absolute bioavailability of morphine following different routes of administration (Hoskin et al., 1989; Osborne et al., 1990) showed that the bioavailabilty of morphine was similar after peroral, buccal and sublingual administration suggesting that following buccal and sublingual administration morphine is swallowed dissolved in saliva and absorbed from the gastro-intestinal tract and not as intended from the buccal cavity.

This apparent poor absorption of morphine through the buccal mucosa might be explained by its poor lipophilicity and polar properties at physiological pH. The pK_a value of the amino function in morphine is 8.1 at 35°C (Roy and Flynn, 1989). Al-Sayed-Omar et al. (1987) have reported that the absorption of morphine through the buccal mucosa increases with increasing pH, due to a higher degree of ionisation of the amino function at low pH values. Further the $\log P$ value of morphine is only 0.15, where P is the partition coefficient between octanol and aqueous buffer of pH 7.4 at 35°C (Roy and Flynn, 1988).

The aim of the present study was to examine the prodrug approach to enhance penetration of morphine through the buccal mucosa in order to make buccal delivery of the drug possible. This approach has been used to improve the buccal and transdermal absorption of the opioid analgesic ketobemidone (Hansen et al., 1991, 1992a,b,c) and the transdermal penetration of morphine (Drustrup et al., 1991). To be a successful approach the biphasic solubility and hence the permeation characteristics of the drug compound should be improved. Further, the prodrug should be cleaved quantitatively by enzymes present in the mucosa and plasma to the parent drug during or immediately following penetration of the buccal mucosa and the pro-moiety released should be atoxic.

Bioreversible derivatization of morphine (**I**) can be achieved by esterification of its 3-phenolic or 6-alcoholic group or both. In the present study only mono esters formed at the 3-phenolic group were examined since it have been shown that the ester function at C-6 position is quite resistant to attack by enzymes whereas the ester group at C-3 is rapidly hydrolysed when exposed to enzymes (Drustrup et al., 1991). Thus, various aliphatic esters of morphine (**II–VI**) were prepared and characterized with respect to lipophilicity, chemical stability, bioactivation in saliva and plasma, ability to permeate porcine buccal mucosa as evaluated by diffusion experiments in vitro and the absorption properties following buccal administration in rats.

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2. Materials and methods

2.1. Apparatus

High-performance liquid chromatography (HPLC) was carried out using a system consisting of a Shimadzu Model LC-6A pump, a variable-wavelength UV-detector type Shimazdu SPD-6A, a 20-μl Rheodyne injection valve and a D-2000 ChromatoIntegrator Merck Hitachi.

The diffusion experiments were carried out using a modified Ussing chamber (Ussing, 1949). Measurements of the electrical properties of the buccal membrane were performed with a current clamp set-up equal to that described by Bindslev (1979).

2.2. Chemicals

Morphine hydrochloride was obtained from Nomeco A/S, Copenhagen. Bovine serum albumin and Folin and Coicalteu's Phenol reagent were obtained from Sigma (St. Louis, MO). All other chemicals used were of reagent grade.

The glucose bicarbonate ringer solution (GBR) (pH 7.4) used in the diffusion experiments had the following composition: Na^+, 141 mM; K^+, 5 mM; Ca^{2+}, 1.2 mM; Mg^{2+}, 1.2 mM; Cl^-, 122 mM; HCO_3^-, 25 mM; HPO_4^{2-}, 1.6 mM; $H_2PO_4^-$, 0.4 mM and glucose 10 mM.

2.3. Preparation of morphine esters

The 3-esters of morphine were prepared by reacting morphine hydrochloride with an acid anhydride in alkaline aqueous solution (method A) or with an acid chloride in a two phase system of aqueous bicarbonate-methylene chloride (method B). Method A is a modification of a procedure described by Welsh (1954) for the synthesis of morphine-3-acetate (M-3-A).

2.3.1. Method A

This method was used for the preparation of M-3-A and morphine-3-propionate (M-3-P).

2.3.1.1. M-3-A. Morphine hydrochloride (3.76 g, 10 mmol) was added to 200 ml of a 10% aqueous solution of sodium bicarbonate with pH being adjusted to 9.0 with 5 M sodium hydroxide. Acetic anhydride (10 ml) was added in one portion and the reaction mixture was stirred at room temperature for 2 h. The pH of the clear solution (about 7.3) was adjusted to 8.0 with 2 M sodium hydroxide. The solution was extracted with methylene chloride (2 × 150 ml). The combined extracts were dried over anhydrous sodium sulphate and evaporated in vacuo to afford morphine-3-acetate as an oil in 90% yield. The compound crystallized from ether–petroleum ether after standing for 3 days at −18°C. M.p. 104–105°C. Anal. : Calc. for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28.; Found: C, 69.79; H, 6.41; N, 4.26.

2.3.1.2. M-3-P. This compound was prepared in a similar way using propionic anhydride (13 ml) instead of acetic anhydride. The ester crystallized from ether–petroleum ether after standing for 2 days at −18°C and was obtained in a 80% yield. M.p. 85–86°C. Anal. : Calc. for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10.; Found: C, 70.35; H, 6.41; N, 4.26.

2.3.2. Method B

This method was used for the preparation of morphine-3-hexanoate (M-3-H) and morphine-3-octanoate (M-3-O)

2.3.2.1. M-3-H. Morphine hydrochloride (3.76 g, 10 mmol) was added to a mixture of methylene chloride (80 ml) and 1 M sodium bicarbonate (80 ml) followed by hexanoyl chloride (5.4 ml, 40 mmol). The mixture was stirred at room temperature until both phases became clear (about 2 h). The organic phase was separated washed with water, dried over anhydrous sodium sulphate and evaporated in vacuo to yield morphine-3-hexanoate as an oil. A crystalline fumarate salt was obtained by adding a solution of fumaric acid (10% excess) in 2-propanol to a solution of 3-*O*-hexanoyl morphine in ether. The fumarate salt which precipitated upon standing at −18°C overnight was filtered off and recrystallized from ethanol–ether (yield 69%). Anal. : Calc. for $C_{23}H_{29}NO_4$, $C_4H_4O_4$, 0.5 H_2O: C, 63.77 H, 6.74; N, 2.75.; Found: C, 63.56; H, 6.72; N, 2.73.

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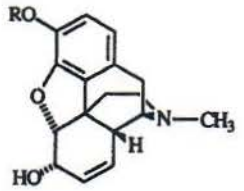
2.3.2.2. M-3-O. This compound and its fumarate salt (semihydrate) was prepared in a similar way using octanoyl chloride instead of hexanoyl chloride. Anal. : Calc. for $C_{25}H_{33}NO_4$, $C_4H_4O_4$, 0.5 H_2O:: C, 64.90 H, 7.14; N, 2.61.; Found: C, 64.80; H, 7.20; N, 2.54.

The structures of morphine (**I**) and the four esters (**II–V**) are shown in Scheme 1.

2.4. Analysis

In the hydrolysis studies and the in vitro permeation studies reversed-phase HPLC procedures were used for the quantitative determination of morphine and morphine esters. A Spherisorb-ODS 2 column (120 × 4.6 mm) (5-μm particles) was eluted with a mobile phase consisting of a mixture of Acetonitrile and 0.1% H_3PO_4 with 10^{-3}M triethylamine. The concentration of acetonitrile was adjusted for each compound in order to give suitable retention times. The injection volume was 20 μl. The flow rate was 1.0 ml/min and the column effluent was monitored at 215 nm. In each case adequate separation of morphine and ester was achieved. Quantitation of the compounds was done from measurement of peak heights in relation to those of standards chromatographed under the same conditions. Limit of quantisation was approximately 1 μg/ml.



	R	Name
I	—H	Morphine
II	—$COCH_3$	Morphine-3-acetate
III	—$COCH_2CH_3$	Morphine-3-propionate
IV	—$CO(CH_2)_4CH_3$	Morphine-3-hexanoate
V	—$CO(CH_2)_6CH_3$	Morphine-3-octanoate

Scheme 1. Chemical structure of morphine and the various esters investigated in this study. Compound, R and name, respectively: **I** H– morphine; **II** CH_3CO– morphine-3-acetate (M-3-A); **III** CH_3CH_2CO– morphine-3-propionate (M-3-P); **IV** $CH_3(CH_2)_4CO$– morphine-3-hexanoate (M-3-H); **V** $CH_3(CH_2)_6CO$– morphine-3-octanoate (M-3-O)

In the in vivo studies morphine serum concentrations were determined by radio-immuno-assay (Diagnostic Product Corporation). The limit of quantisation was 1 ng/ml. The cross reactivity of M-3-P, has earlier been estimated to 10% (Jørgensen et al., 1994). However, due to the very rapid hydrolysis of the esters in serum co-estimation of the esters is considered negligible. This radio-immuno-assay was also used to quantify morphine in the samples obtained from the in vitro permeation studies on morphine itself.

2.5. Determination of partition coefficients

The apparent partition coefficients, P of the compounds **I–V** were determined in an octanol/0.02 M phosphate buffer (pH 7.4) system at 21°C as earlier described by Hansen et al. (1991)

2.6. Stability of morphine esters

The stability of the morphine esters **II–IV** was studied at 37°C in 0.02 M phosphate buffer solutions (pH 7.4) with a ionic strength of 0.5. The reactions were initiated by adding 25–50 μl of a stock solution of the ester in acetonitrile to 10 ml of preheated buffer solution in screw-capped test tubes, the final concentration of the compound being 5×10^{-6}–10^{-4} M. The solutions were kept in a water bath and at appropriate intervals samples were taken and immediately analysed for contents of morphine and/or morphine ester.

2.7. Bioactivation of the esters in human plasma

The bioactivation of the morphine esters was studied at 37°C in human plasma diluted to 80 and 10% with 0.05 M phosphate buffer pH 7.4. The reactions were initiated by adding 50 μl of a stock solution of the ester in methanol to 5.0 ml of preheated plasma in screw-capped test tubes,

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the final concentration of the compound being 10^{-4} M. The solutions were kept in a water bath and at appropriate intervals samples of 250 μl were withdrawn and added to 250 μl of a 2% (w/v) solution of $ZnSO_4$ in water/methanol (1:1) in order to deproteinize the plasma. After mixing and centrifugation for 3 min at 13 000 rpm, 20 μl of the clear supernatant was analyzed for contents of morphine and/or morphine ester by HPLC as described above.

The bioactivation of M-3-A, M-3-P and M-3-H in human plasma both 80 and 10% proceeded too fast for the half-live to be accurately determined, however since the aim of these studies was merely to determine the rank order for the stability of the esters against enzymatic degradation in plasma, than to determine the exact half-lives no further studies were considered necessary.

2.8. Bioactivation of the esters in human saliva

The bioactivation of M-3-A and M-3-P was studied at 37°C in human whole saliva diluted to 80% with 0.05 M phosphate buffer pH 7.4. Saliva was collected from two female volunteers by expectoration into screw-capped test tubes. Salivation was stimulated by paraffin chewing using a 1.5-g paraffin wax sample with a melting point of about 49°C. Paraffin was moved from one side of the buccal cavity to the other in order to activate all salivary glands as described by Kerr (1961). Brushing of teeth was only allowed with toothpaste not containing fluoride and was performed at least 1 h prior to saliva collection, since the activity of esterases in the saliva as reported by Lindqvist et al. (1980) can be inhibited by several of the commonly used dental materials. Contents of protein in the saliva samples was determined by the method of Lowry (Lowry et al., 1951; Miller, 1959)

The reactions were initiated by adding 35 μl of the ester in methanol to 3.5 ml of preheated saliva in screw-capped test tubes, the final concentration of the compound being 10^{-4} M. The solutions were kept in a water bath and at appropriate intervals samples of 250 μl were withdrawn and added to 500 ml of a 2% (w/v) solution of $ZnSO_4$ in water/methanol (1:1) in order to deproteinize the saliva. After mixing and centrifugation for 3 min at 13 000 rpm, 20 μl of the clear supernatant was analyzed for content of morphine or morphine ester by HPLC as described above. The experiments were carried out in duplicate for each volunteer.

2.9. Permeation of buccal porcine mucosa in vitro

The diffusion experiments were carried out with morphine and the four morphine esters.

Initially the influence of various diffusion apparatus related parameters upon drug permeation was evaluated using the M-3-P. Thus, the influence of open-circuit versus short-circuit conditions was evaluated. Additionally, the possible appearance of edge damage of the tissue evaluated by comparing the fluxes obtained when using chambers with different diameter openings (0.64 and 0.95 cm^2). Further, the intra- and interindividual variation of porcine buccal mucosa were examined. The preliminary study was carried out as a factorial experiment.

The multiple analysis of variance was used the determine the significance of the possible influence of the different parameters tested upon permeation. $p < 0.05$ was considered significant.

None of the parameters tested were found to significantly influence the permeation. Hence, it was decided to carry out the subsequent studies using open-circuit conditions, chambers with a diameter opening of 0.95 cm^2, and mucosa from different pigs in each chamber.

Buccal tissue was removed from pigs at the abattoir immediately after sacrificing and was transported in GBR solution at 0°C. Prior to mounting in the Ussing chambers the connective tissue was carefully excised using a pair of scissors and a tissue slicer. Mounting the tissue in the Ussing Chambers was completed within 90 min from the death of the animal. During the experiment the tissue was bathed on both sides by 10.0 ml of GBR solution maintained at 37°C by water-jacketed reservoirs. The bathing solutions were circulation by gas lift with 95%O_2/5%CO_2, which at the same time provided oxygenation of the tissue.

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Since preliminary studies showed that the potential difference and the short-circuit current across the tissue stabilized within 60 min after mounting, the tissue was preincubated with GBR solution for 60 min prior to addition of drug to the mucosal half-chamber. The initial concentration of the compounds studied was equivalent to approximately 1 mg of morphine base per ml GBR solution. Morphine was used as the hydrochloride salt (trihydrate), M-3-A and M-3-P as the free bases and M-3-H and M-3-O as the fumarate salts (semihydrates).

Following addition of drug in GBR solution, samples of 1 ml were withdrawn from the serosal half-chamber at 5, 15, 30, 45, 60, 90, 120, 150 and 180 min, the volume being replaced with drug free GBR solution. Samples were stored at −20°C until analysis for content of morphine and ester. The permeation studies of each compound were done in quadruplicate.

2.10. Absorption from the buccal cavity in vivo

Morphine, M-3-A, M-3-P and M-3-H were administered buccally to separate groups of four male Sprague–Dawley rats weighing from 350 to 420 g. During the experiments the rats were anaesthetized with urethane (1.25 g/kg, i.p.). Prior to drug administration the esophagus was ligated through a small incision in the breast. The ligation prevents the solution administered buccally from being swallowed. In order to ensure that no leakage from the oral cavity to the nasal cavity occurred the rats were maintained on their back with their head raised. The rats were ventilated by room temperature atmospheric air (2 ml, 75 times per min) during the whole experiment. ECG was recorded prior to each blood sampling.

The compounds were given in doses equivalent to 1.5 mg morphine base/kg. Morphine was given as the hydrochloride salt (trihydrate), whereas the prodrugs were given as the free bases. The compounds were dissolved/suspended in GBR solution (morphine, M-3-A and M-3-P appeared as solutions, whereas M-3-H appeared as a suspension), which was applied between the cheek and lower gum in a volume of 250 μl/kg with a pipette equipped with a prolonged tip.

Blood samples (300 μl) were withdrawn from a catheter in the jugularis vein prior to and 15, 30, 60, 90, 120, 180 and 240 min following administration. The plasma samples obtained after centrifugation for 15 min at 3000 rpm were stored at −20°C until analyzed for contents of morphine by radio-immuno-assay as described above.

2.11. Calculations

The pseudo-first order rate constants for the hydrolysis and the bioactivation of the ester prodrugs were calculated from the slopes of the linear plots of the logarithm of residual ester against time.

In the permeation studies the cumulative amounts of morphine measured in the receptor phase divided by the surface area of the diffusion chamber were plotted against time of sampling. The steady-state fluxes (F_{ss}) were obtained from the slopes of the linear portion of these plots.

In the absorption studies the areas under the plasma concentration time profiles were calculated using the trapezoidal rule.

3. Results

3.1. Stability and bioactivation

In both the hydrolysis and bioactivation studies the hydrolysis of the morphine esters proceeded with quantitative formation of morphine.

The rates of hydrolysis of all esters were found to follow first order kinetics at the initial concentrations used. The observed half-lives for the hydrolysis and bioactivation are listed in Table 1.

Protein content in saliva from the two volunteers was found to be 1.18 and 1.71 mg/ml, respectively.

3.2. Permeation and absorption studies

Morphine did not permeate the porcine buccal mucosa in vitro to any measurable extent. For all four esters studied only morphine could be detected in the receptor solution. In the preliminary studies carried out with M-3-P the mean ± S.D

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Table 1
Half-lives of hydrolysis of various morphine esters in 0.02 M phosphate buffer solutions (pH 7.4), in human plasma and in human saliva at 37°C

Compound	Buffer pH 7.4 (h)	Plasma 80% (min)	Plasma 10% (min)	Saliva 80%* (min)
M-3-A	34.9	<0.2	0.8	59.6 (15.4)
M-3-P	40.0	<0.2	0.3	16.0 (4.8)
M-3-H	~150	<0.2	0.2	nd**
M-3-O	nd**	0.4	nd**	nd**

Values are given as mean and (S.D.).
* Values corrected to a protein content of 1 mg/ml.
** Not determined.

steady state flux was calculated to be 0.49 ± 0.31 ng/cm^2/min ($n = 16$).

The steady state fluxes for morphine obtained after application of the prodrug esters in the donor chamber are listed in Table 2 together with the AUC values obtained after buccal administration in rats and the log P values. Fig. 1 shows the steady-state fluxes obtained in the permeation study and the AUC values obtained in the absorption study as functions of log P, respectively.

4. Discussion

The morphine esters studied all underwent enzymatic hydrolysis. As can be seen from Table 1, the half-lives of hydrolysis in pure buffer solutions at pH 7.4 ranged from 35 to about 150 h, whereas in human plasma half-lives of a few seconds have been found. The hydrolysis in human saliva proceeded as can be seen from Table 1 considerably slower than in plasma. In both plasma and saliva M-3-A was found to be more stable than M-3-P.

In the in vitro permeations studies on morphine esters only morphine could be detected in receptor medium, indicating that the bioactivation takes place during the passage of the esters through the buccal membrane. This hypothesis is further confirmed by results presented by Groth et al. (1997), who studied the bioactivation of M-3-P in different tissue homogenates including buccal tissue from pig, rabbit and rat.

From Table 2 and Fig. 1 it can be seen that all the ester prodrugs tested were able to permeate porcine buccal mucosa, whereas the parent drug,

Table 2
Partition coefficients (P) between octanol and 0.05 M phosphate buffer pH 7.4, steady-state fluxes (F_{ss}) through porcine buccal mucosa and areas under the plasma concentration time profiles (AUC) following buccal administration in rats

Compound	Log P	F_{ss} (ng/cm^2/min	AUC (μg/ml/min)
Morphine	−0.06	nm*	4.98 (0.45)
M-3-A	0.17	0.14 (0.04)	18.57 (2.59)
M-3-P	0.66	0.44 (0.15)	12.65 (3.72)
M-3-H	2.04	0.96 (0.33)	2.31 (0.69)
M-3-0	3.06	0.29 (0.28)	nd**

Values are given as mean and (S.D.).
* Not measurable.
** Not determined.

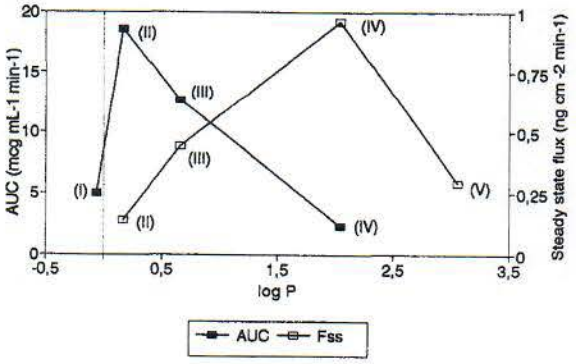

Fig. 1. Steady-state fluxes (F_{ss}) through porcine buccal mucosa and areas under the plasma concentration–time profiles (AUC) following buccal administration in rats for morphine (I) and the acetate (II), propionate (III), hexanoate(IV) and octanoate (V) esters as function of their octanol-buffer pH 7.4 partition coefficient (log P).

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morphine was not able to permeate the buccal mucosa to any measurable extent. The plot of the steady-state fluxes vs. the log P values (Fig. 1) shows that the apparent permeability increases with increasing log P up to a log P value of about 2 whereafter the permeability decreases. The data suggest a parabolic dependence of permeation on lipophilicity which cannot, however, be assessed with certainty from the data available. However, the same tendency was seen in a study on permeation of morphine and morphine esters through a human buccal cell culture grown on filters (Jacobsen, 1995) and in a study on permeation of ketobemidone prodrugs through porcine buccal mucosa (Hansen et al., 1992a). Thus, the results confirm the importance of lipophilicity in the passive diffusion of drug substances across biomembranes including the buccal epithelial cells. Thus, at low log P values the diffusion across the lipoidal epithelial cells seems to be the rate-limiting step, whereas when lipophilicity of the drug substance increases the rate-limiting step of the process becomes the diffusion across the aqueous boundary layer as argued by Ho et al. (1992). This hypothesis is further substantiated by the results of Jacobsen (1995), who as mentioned also found that the apparent permeability of morphine and morphine esters through human buccal cells grown on filters showed a parabolic dependence of log P, whereas the permeability of the cell layer, if ignoring or eliminating the permeation through the aqueous boundary layer, increased with increasing log P values.

Table 2 and Fig. 1 also show the influence of lipophilicity on buccal absorption judged by the areas under the plasma concentration time profiles. Apparently the absorption as well as the permeability varies parabolic with the lipophilicity. M-3-A and M-3-P are both absorbed to a greater extent than the parent drug, whereas the amount of M-3-H absorbed is lesser. The latter might be explained by the fact that this compound was applied in the buccal cavity as a suspension and thus the rate-limiting step of absorption might be the dissolution of the compound and not the diffusion across the buccal mucosa. In contrast to what was seen in the in vitro permeability studies the optimal log P for absorption seems to be about 0.2. This should, however, be interpreted with regards to the enzymatic stability of the esters in saliva. From Table 1 it can be seen that the acetate ester is more stable against enzymatic degradation than are the esters with longer carbon chains. Thus, the lower absorption fraction obtained following buccal administration of the propionate ester compared to the acetate ester might be due to the fact that propionate ester is more readily degraded by enzymes present in saliva to the parent compound, morphine, which is poorly absorbed through the buccal mucosa.

5. Conclusion

The results obtained in the present study show that the permeation of morphine through porcine buccal mucosa and the buccal absorption of morphine in rats can be markedly improved by using ester prodrugs with higher lipophilicity. However, under in vivo conditions, the enzymatic stability of the prodrugs in saliva do also play an important role for the overall improvement in absorption properties.

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