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Drug-delivery by ion-exchange. Stability of ester prodrugs of propranolol in surfactant and enzymatic systems

W.J. Irwin and K.A. Belaid

Drug Development Research Group, Pharmaceutical Sciences Institute, Aston University, Birmingham (U.K.)

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Summary

The degradation of *O*-acetyl and *O*-*n*-propanoyl propranolol with surfactants follows the pathways afforded by chemical hydrolysis and yields both propranolol, by hydrolysis, and the corresponding *N*-acyl propranolol by *O*-to-*N* rearrangement. The extent of rearrangement is controlled by the surfactant charge with cationic systems favouring rearrangement while anionic surfactants suppress this reaction. In contrast, in the presence of isolated esterases, the rearrangement becomes unimportant and is detected only with *O*-acetylpropranolol. Longer chain members of the series (*O*-*n*-propanoyl to *O*-*n*-decanoyl propranolol) act solely as precursors of propranolol in enzymatic systems with the rates of reaction showing a maximum at the *O*-*n*-hexanoyl derivative. Hydrolysis to propranolol is also observed with isolated intestinal segments and in everted sacs the serosal chamber showed greater activity than the mucosal compartment.

Introduction

Controlled drug delivery with liquid formulations may be achieved by the use of ion-exchange resins (Calmon and Kressman, 1957; Schacht, 1983). Release of drug from its resinate is initiated by an influx of competitive ions from the gastrointestinal tract and control of the release profile may be afforded by coating (Raghunathan et al., 1981; Motyka et al., 1985). We have previously described the interaction of a series of *O*-*n*-acyl propranolol esters with cationic exchange resins (Irwin and Belaid, 1987a and b; Irwin et al., 1987), the effect of coating on drug release (Irwin et al., 1988) and the hydrolytic stability of the series (Irwin and Belaid, 1988). Degradation was characterised by an *O*-to-*N* rearrangement which competed with hydrolysis and produced a very stable *N*-acyl amide derivative. The extent of the rearrangement was reduced with increasing chain length in the ester and could be eliminated entirely with the bulky *O*-pivaloyl analogue. In this paper we describe the stability of the esters in the presence of surfactants, isolated esterase enzyme and intestinal segments and show that under conditions which more closely resemble the in vivo

Correspondence: W.J. Irwin, Drug Development Research Group, Pharmaceutical Sciences Institute, Aston University, Aston Triangle, Birmingham B4 7ET, U.K.

situation the rearrangement is substantially less important and is not observed at all with *O-n*-propanoylpropranolol and higher analogues.

Experimental

Apparatus

HPLC analyses were undertaken using the system previously described (Irwin and Belaid, 1988). The mobile phases consisted of acetonitrile, diethylamine, orthophosphoric acid (88%) and water adjusted to pH 2.8. For *O-n*-acetylpropranolol these were in the ratio 65 : 0.15 : 0.1 : 34.75 and 65 : 0.2 : 0.1 : 34.7 for the longer *O-n*-alkyl components.

Methods

Degradation of O-acetyl and O-n-hexanoyl propranolol in surfactants

Solutions (40 mM) of *O*-acetylpropranolol and *O-n*-hexanoylpropranolol were prepared separately in acetonitrile and aliquots (1 ml) were delivered individually to the reaction vessels containing various concentrations of dodecyl trimethyl ammonium bromide (DTAB, $0–2 \times 10^{-2}$ M), in Britton-Robinson buffer (Mongay and Cerda, 1974) at pH 7.4 and 37 °C, to prepare the reaction mixtures (200 ml, 0.2 mM). Aliquots were withdrawn immediately and at intervals of 10–30 min. The samples were treated with an equal volume of internal standard (e.g. 7 mg ethyl paraben for *O*-acetylpropranolol and 10 mg of butyl paraben for the *O-n*-hexanoyl ester, both in 250 ml of 0.1 M HCl). Samples were analysed by HPLC but with a modified mobile phase free of the diethylamine moderator and comprising: acetonitrile, orthophosphoric acid (88%) and water in the ratio 42 : 2.0 : 56 for *O*-acetylpropranolol (methyl paraben) and 55 : 2.5 : 42.5 for the *O-n*-hexanoyl analogue (butyl paraben). Further experiments were undertaken with tetramethyl ammonium chloride ($1.7–10 \times 10^{-2}$ M), with sodium dodecyl sulphate ($0–17.5 \times 10^{-3}$ M) using a mobile phase of acetonitrile, orthophosphoric acid (88%) and water in the ratio 48 : 2.5 : 49.5 (ethyl paraben) and with Tween 80 (0–0.3% m/v) using acetonitrile, orthophosphoric acid (88%) and water 45 : 3.0 : 52 (propyl paraben).

Degradation of O-acylpropranolol pro-drugs with isolated esterase

Degradation studies were undertaken with *O*-acetyl, *O-n*-propanoyl, *O-n*-butanoyl, *O-n*-valeroyl, *O-n*-hexanoyl, *O-n*-octanoyl and *O-n*-decanoyl propranolols (Irwin and Belaid, 1987a) in a solution comprising 10% dimethylformamide (DMF) and McIlvaine buffer, pH 7.4, ionic strength 0.5 M (Elving et al., 1956), in the presence of a fixed amount of esterase enzyme at 37 °C. A stock solution of esterase enzyme (Sigma) was prepared by diluting the sample (1 ml, 10 mg · ml^{-1}, nominal activity 120 units · mg^{-1}), in phosphate buffer to 25 ml with buffer, pH 7.4, and the dilution (48 units · ml^{-1}), was stored for no more than 30 h at −4 °C until required. Stock solutions of the esters (20 mM) in neutralised DMF (10 ml) were separately prepared and aliquots of the ester stock solutions (1 ml) were individually delivered to the reaction vessels containing buffered DMF (98 ml, pH 7.4) equilibrated at 38 °C and the enzyme stock solution (1 ml) was added to prepare reaction mixtures with an ester concentration of 0.2 mM and an esterase activity of 0.48 units · ml^{-1}. At appropriate time intervals (2–10 min) samples were withdrawn from each reaction vessel and were treated with an equal volume of the internal standard, usually comprising ethyl paraben in a mixture of acetonitrile and 0.1 M HCl (1 : 1). This treatment deactivated the enzyme and quenched the degradation process. Samples were stored in a salt ice bath until analysed by HPLC.

The effect of the substrate initial concentration on the enzymatic degradation of *O*-pivaloylpropranolol was monitored using a stock solution of *O*-pivaloylpropranolol (60 mM) in neutralised DMF. Accurately measured volumes of this stock solution comprising 0.125, 0.25, 0.3, 0.4, 0.75 and 1 ml were individually placed in flasks and were diluted to 100 ml with pre-heated 10% buffered DMF, pH 7.4 at 37 °C, to provide reaction mixtures with initial ester concentrations of 0.075–0.6 mM. Samples (1 ml) were withdrawn from each flask and replaced with the esterase enzyme (1 ml) containing 120 units · ml^{-1}. Aliquots (1 ml) were

withdrawn from each flask immediately and at various intervals (10–20 min), diluted with the internal standard (1 ml; desimipramine, 2–16 mg in 100 ml prepared in acetonitrile and 0.1 M HCl; 1 : 1).

Degradation of O-acylpropranolols in serum

Blood samples (250 ml) were withdrawn from white New Zealand rabbits, were left for about 1 h to clot and were centrifuged at 4000 rpm and 4 °C for 20 min. The separated serum layers were divided into 9 ml portions and were stored frozen at −30 °C until use. Stock solutions of *O*-acetyl, *O*-*n*-propanoyl, *O*-*n*-butanoyl, *O*-*n*-valeroyl, *O*-*n*-hexanoyl and *O*-pivaloyl propranolol esters (2 mM) were prepared separately in neutralised DMF (10 ml). The ester stock solutions (1 ml) were added to vials containing serum (9 ml) at 37 °C to give ester concentrations of 0.2 mM. The vial was sealed, the reaction mixture stirred and aliquots (0.5 ml) were withdrawn immediately and at various intervals (2–15 min). The degradation processes were quenched by adding the sample to a mixture of acetonitrile and 0.1 M HCl (1 : 1; 2 ml). The agitated mixture was centrifuged at 4000 rpm for 20 min and the supernatant layer (1 ml) and the internal standard (1 ml; 13 mg of ethyl paraben in 200 ml of mobile phase) were mixed together and stored in a salt ice bath until analysed by HPLC.

Degradation by rat small, intestine

Four male Wistar rats, of average weight 370 g, were fasted overnight prior to the experiments but were allowed free access to water at all times. Fragments of everted small intestines (10 cm) were prepared as described previously (Crane and Wilson, 1958; Levy et al. 1967) but with minor modifications. The rats were anaesthetised with halothane and segments of the intestine, starting with the duodenum, were stripped from the mesentery, rinsed and maintained as rapidly as possible in cold, oxygenated Krebs bicarbonate solution, pH 7.4. Segments (10 cm) were measured when stretched slightly to give an average weight of 0.37 g. Segments were then sleeved onto a glass rod and carefully everted. Individual segments were placed in conical flasks containing *O*-acetylpropranolol (1 mM, 100 ml) in 10% DMF–Krebs bicarbonate solution, pH 7.4, equilibrated at 37 °C. Calcium chloride and magnesium sulphate were omitted from the buffer due to the formation of precipitates in the DMF solutions. Other segments of everted small intestines were first immersed in boiling water for 5 min and then placed in the *O*-acetylpropranolol solution (1 mM) as a control. Other flasks with drug solution but with no intestinal segments were also prepared. All flasks were flushed with 95% oxygen and 5% carbon dioxide mixture, sealed and transferred into a shaking water bath at 37 °C. Aliquots (2 ml) were withdrawn immediately and at various intervals (5–15 min). The degradation reaction was quenched by adding the internal standard (2 ml; 12 mg of ethyl paraben in 200 ml of acetonitrile and 0.1 M HCl; 1 : 1) and samples were analysed by HPLC.

Degradation of O-acylpropranolols in everted intestinal segments

The system (Crane and Wilson, 1958) comprised a test tube of 15 ml capacity fitted with a rubber stopper into which was inserted a glass cannula, two hypodermic needles and a teflon tubing attached to one of these needles. Intestinal segments (10 cm) were quickly removed from male Wistar anaesthetised rats, washed with Krebs bicarbonate solution, pH 7.4, and everted. One end of the everted intestinal segment was tied and the other end was bound securely to the cannula with a thread. Solutions of *O*-acetylpropranolol and *O*-pivaloylpropranolol (10 ml, 10 mM in 10% DMF–Krebs bicarbonate solution) as the mucosal fluid were pipetted separately into the tube and were thermally equilibrated at 37 °C. The 10% DMF–Krebs bicarbonate solution (2 ml) was placed into the intestinal sac, via the cannula, as the serosal fluid and the intestine was immersed into the mucosal fluid maintained at 37 °C. The solution was saturated with oxygen–carbon dioxide mixture (95 : 5) via one of the needle and vented through the other. After 40 min the intestinal sac was removed from the mucosal fluid and was washed on the outside rapidly with warm Krebs solution. The segment was then transferred to an identical tube and placed in a water bath.

Samples (1 ml) were immediately withdrawn from mucosal and serosal fluids and 20 μl aliquots were injected directly onto the HPLC column and the concentrations of the ester in both mucosal and serosal fluids in these samples were considered as 100%. Samples (0.1 ml) were withdrawn from the serosal compartment at various intervals (2–5 min) and 20 μl of each directly analysed as before to allow the degradation of the ester to be monitored. Aliquots (0.5 ml) were also withdrawn from the mucosal fluid at various intervals (2–5 min), treated with internal standard (0.5 ml) prepared in a mixture of acetonitrile 0.1 M HCl (1 : 1).

Discussion

The presence of surfactants in the solutions of the *O*-*n*-acyl propranolols resulted in a pronounced effect on the chromatographic resolution of the components. As shown in Fig. 1, the use of the mobile phases previously developed for the analysis of the *O*-*n*-acyl propranolols resulted in a significant reduction in the efficiency of the separation on successive injections of the samples containing surfactants. A decrease in the acetonitrile level and omission of the diethylamine modifier overcame this problem and Fig. 2 illustrates the effect of dodecyl trimethyl ammonium bromide (DTAB) on the degradation of *O*-acetylpropranolol. The degradation mirrors that in aqueous systems (Irwin and Belaid, 1988) with parallel hydrolysis (k_1), to yield propranolol, and *O*-to-*N* rearrangement (k_2), to give the *N*-acetyl analogue, being observed. The effect of varying the DTAB concentration on the degradation rate constants of both *O*-acetyl and *O*-*n*-hexanoyl propranolol is recorded in Table 1. With increasing amounts of surfactant the overall degradation rates ($k_1 + k_2$) increase to a maximum. Isolation of the individual rate constants reveals that this is almost solely due to an enhancement of the rearrangement process which rapidly becomes the dominant reaction, as shown by the k_1/k_2 ratio. In the case of *O*-acetylpropranolol this ratio increases over 30-fold whilst with the *O*-*n*-hexanoyl analogue an increase in excess of 800-fold is observed. This difference accords with literature data which indicate that

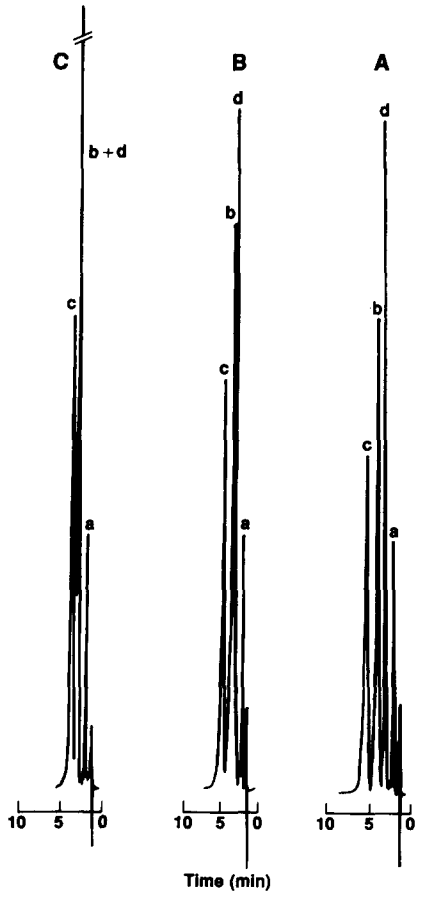

Fig. 1. High-performance liquid chromatograms showing the effect of successive injections of a mixture in dodecyl trimethyl ammonium bromide (DTAB) solution. A, 1st; B, 2nd; C, 5th injection. Components are: a, ethyl paraben; b, propranolol; c, *O*-acetylpropranolol; and d, *N*-acetylpropranolol. The mobile phase comprised acetonitrile : orthophosphoric acid (88%) : diethylamine : water (65 : 0.1 : 0.2 : 34.7) at pH = 2.5.

the more hydrophobic the substrate, the more pronounced are surfactant effects (Behme et al., 1965; Menger and Portnoy, 1967; Romsted and Cordes, 1968). The pK_a of *O*-acetylpropranolol in 0.02 M DTAB is found to be 7.66. This contrasts with the aqueous value of 8.52 (Irwin and Belaid, 1987b). The pK_a variation may be accounted for by the incorporation of the base into the micellar structure, shifting the ionisation equilibrium towards the unprotonated species and thus effectively reducing basicity. An increase in the proportion of unprotonated base could enhance the re-

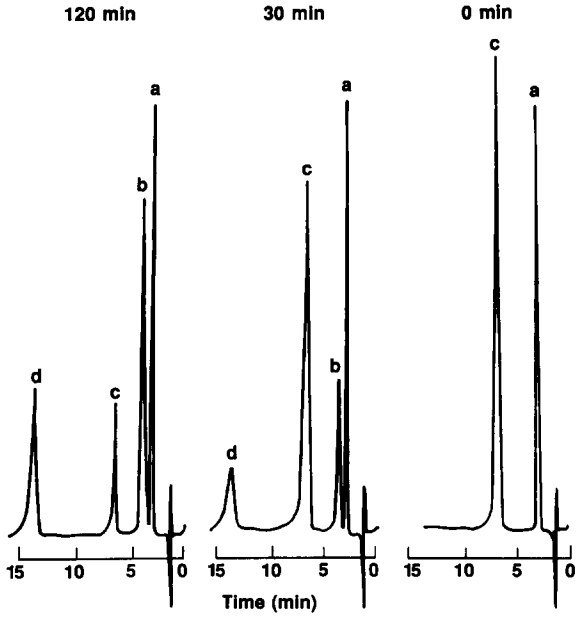

Fig. 2. HPLC showing the degradation of *O*-Acetylpropranolol in the presence of 1.42×10^{-2} M dodecyl trimethyl ammonium bromide at pH = 7.4 and 37 °C. The mobile phase comprised acetonitrile : orthophosphoric acid (88%) : water (42 : 2 : 56) at pH = 1.7. Components are: a, methyl paraben; b, propranolol; c, *O*-acetylpropranolol; d, *N*-acetylpropranolol.

arrangement but, although the presence of micelles may have a considerable effect on reaction rates (Romsted, 1977; Cipiciani et al., 1983; Fendler and Fendler, 1975), it is of interest to note that the greatest influence by the surfactant in this case appears to be below the critical micelle concentration of $1.42–1.59 \times 10^{-2}$ M (Mukerjee and Mysels, 1971). This suggests that ionic rather than micellar interactions may be responsible for the effect. To establish this point a non-surface active cation was added and Table 2 records the degradation rate constants for *O*-acetylpropranolol influenced by the presence of varying amounts of tetramethyl ammonium chloride (TAC). Analogous results are observed although over the concentration range examined the rearrangement reaction does not become dominant. The enhancement of the rearrangement in this case may be due to an increased carbonyl reactivity due to polari-

TABLE 2

Effect of tetramethyl ammonium chloride (TAC) concentration on the degradation of O-acetylpropranolol in buffer, pH 7.4, μ = 0.5 M and 37 °C

TAC ($M \times 10^2$)	$k_1 + k_2$ ($min^{-1} \times 10^3$)	k_1 ($min^{-1} \times ^3$)	k_2 ($min^{-1} \times 10^3$)	k_1/k_2
0.0	7.59	6.99	0.60	12.0
1.7	8.73	7.88	0.85	9.3
2.5	8.65	7.67	0.98	7.8
5.0	8.57	7.34	1.23	5.9
7.5	8.32	7.29	1.39	5.3
10.0	8.27	6.86	1.41	4.8

TABLE 1

Effect of dodecyl trimethyl ammonium bromide (DTAB) concentration on the degradation of O-acetyl and O-hexanoyl propranolol in buffer solution, pH = 7.4, μ = 0.5 M, and 37 °C

k_1, hydrolysis rate constant; k_2, rearrangement rate constant.

DTAB ($M \times 10^2$)	$k_1 + k_2$ ($min^{-1} \times 10^3$)		k_1 ($min^{-1} \times 10^3$)		k_2 ($min^{-1} \times 10^3$)		k_1/k_2	
	Acetyl	hexanoyl	Acetyl	hexanoyl	Acetyl	hexanoyl	Acetyl	hexanoyl
0.00	7.33	0.19	6.72	0.18	0.16	0.01	12.00	30.00
0.52	8.65	2.96	6.45	0.19	2.20	2.77	2.93	0.07
0.78	15.33	4.23	6.24	0.21	9.09	4.02	0.69	0.05
1.04	20.05	4.69	6.17	0.20	13.88	4.49	0.44	0.045
1.30	23.68	5.14	6.12	0.19	17.57	4.96	0.35	0.039
1.42	25.94	5.22	6.36	0.19	19.59	5.03	0.33	0.038
1.50	26.54	5.40	6.40	0.20	20.32	5.20	0.32	0.038
1.56	25.98	5.44	6.28	0.19	19.70	5.25	0.32	0.037
1.69	24.96	5.48	6.12	0.19	18.84	5.29	0.33	0.037
1.82	24.43	5.49	6.07	0.20	18.36	5.29	0.33	0.037

TABLE 3

Effect of sodium dodecyl sulphate (SDS) concentration on the degradation of O-acetylpropranolol in buffer, pH 7.4, $\mu = 0.5$ M and 37 °C

TAC ($M \times 10^3$)	$k_1 + k_2$ ($min^{-1} \times 10^3$)	k_1 ($min^{-1} \times 10^3$)	k_2 ($min^{-1} \times 10^3$)	k_1/k_2
0.0	7.45	6.81	0.64	11.0
1.0	5.99	5.60	0.394	14.0
2.0	2.77	2.64	0.128	21.0
3.0	2.26	2.18	0.082	26.5
5.0	1.72	1.67	0.048	35.0
8.5	1.53	1.48	0.041	36.5
11.5	1.46	1.42	0.041	35.0
14.5	1.45	1.41	0.042	34.0
17.5	1.50	1.46	0.043	34.0

sation of this group by an associated cationic centre $[C^{\delta+}=O^{\delta-} \ldots N^{+}(CH_3)_4]$.

The behaviour of the anionic surfactant sodium dodecyl sulphate was rather different. Here, as illustrated by Table 3, the overall degradation rate ($k_1 + k_2$) was significantly reduced; an effect due to the inhibition of both hydrolysis (k_1) and rearrangement (k_2) reactions. As indicated by the k_1/k_2 ratio, the rearrangement reaction was more susceptible to suppression in this anionic medium and the hydrolysis pathway at the plateau value was enhanced 3-fold over the surfactant-free system. Again, the effects are dominant at the lower concentrations used and little further effect is observed above 8.5×10^{-3} M, a value close to the CMC range ($5.8–8.2 \times 10^{-3}$ M) of this surfactant (Mukerjee and Mysels, 1971). The influence of SDS on the degradation of *O*-acetyl-propranolol may be related to the effect of anionic surfactants on the pK_a of the esters. The pK_a value of *O*-acetyl-propranolol in 0.02 M SDS was found to be 10.18, an enhancement which may be attributed to ion-pair formation between the protonated nitrogen and the anionic counter-ion. This interaction shifts the equilibrium in favour of ionisation and results in an increase in pK_a. The greater extent of ionisation in the SDS systems parallels the effect of a decrease in pH and results in less rearrangement. In contrast, a non-ionic surfactant (Tween 80) had a negligible effect on the degradation of *O*-acetylpropranolol.

In the presence of isolated esterase enzymes, the disappearance of the *O*-*n*-acyl propranolols followed first-order kinetics and the course of the reaction differed significantly from the pure chemical reactions. The specificity of the enzyme system, coupled with the moderate pH of 7.4 used in this case, resulted in a substantial inhibition of the competing rearrangement reaction. Indeed, with ester homologues of *O*-*n*-propranoyl and above no rearrangement was detected at all. This result suggests that, in contrast to chemical media where only *O*-pivaloylpropranolol generated solely propranolol, in a biological system all analogues other than *O*-acetyl are useful prodrugs. Table 4 shows the variation in first-order rate constants dependent upon the side-chain and reveals that the generation of propranolol under these conditions occurs at a maximum rate with the *O*-*n*-hexanoyl derivative although all compounds show an acceptable release of propranolol. The degradation rates of these esters in rabbit serum was also investigated at 37 °C. Complete conversion to propranolol was again observed with all esters larger than the acetyl derivative and in all cases the degradations could again be modelled by first-order kinetics. The sensitivity of the various ester derivatives to undergo enzyme-catalysed hydrolysis in the rabbit serum was also strongly influenced by the structure of the acyl moiety and this effect is also illustrated in Table 4. The observed order of susceptibility was the same as that obtained for the isolated esterases although a much smaller difference between the *O*-*n*-hexanoyl and

TABLE 4

Effect of side-chain on the degradation of O-n-acyl propranolols by esterase enzyme and in serum

O-*n*-acyl propranolol	Degradation rate constant ($min^{-1} \times 10^2$)	
	Esterase	Serum
Acetyl	0.096	0.838
Propanoyl	1.488	1.122
Butanoyl	4.308	2.582
Valeroyl	6.839	3.648
Hexanoyl	19.879	4.273
Octanoyl	3.966	1.837
Decanoyl	2.897	

the other esters was evident. These results are in agreement with those reported earlier (O'Neill and Carless, 1980) during a study of the influence of the side chain on the enzymatic hydrolysis of hydrocortisone esters. The rate of the ester cleavage was found to vary with the chain length and a similar optimum carbon number for a maximal hydrolysis rate was observed. The effect of substrate concentration on the initial velocity of degradation of *O*-pivaloylpropranolol is shown in Table 5. These data follow the Michaelis-Menten model, the Lineweaver-Burk transformation of which is:

$$\frac{1}{v} = \frac{1}{v_{max}} + \frac{K_m}{v_{max} \cdot [S]}$$

where [S] is the substrate concentration, v is the initial velocity of the reaction, v_{max} is the maximum initial velocity and K_m is the Michaelis constant (Engel, 1984). A double-reciprocal plot ($1/[S]$ against $1/v$) provides an excellent linear relationship and yields values of 0.209 mM for K_m and 2.527×10^{-3} mM · min^{-1} for v_{max}.

The presence of esterases in the gastrointestinal tract is well documented (Dawson and Pryse-Davies, 1963) and a limited enhancement of the hydrolysis of *O*-acetylpropranolol was observed when this compound was incubated with segments of small intestine. It was found that propranolol was produced at a somewhat faster rate with the active segments (k, 14.71×10^{-3} min^{-1}) than with boiled deactivated tissue (k, 8.646×10^{-3} min^{-1}). This apparent enzymic enhancement of the hydrolytic process makes it of interest to study the degradation of *O*-acetyl and *O*-pivaloyl propranolol using an everted small intestine. The time course reflecting the degradation of both esters in mucosal and serosal compartments of the everted sac is shown in Fig. 3. These degradation profiles follow first-order kinetics and the measured rate constants are recorded in the legend. The degradation of *O*-acetylpropranolol is significantly faster in both serosal and mucosal compartments than was observed in the isolated enzyme or serum systems (Table 4). The rate in the mucosal compartment is comparable to that observed on incubation with everted intestinal lengths (k, 14.71×10^{-3} min^{-1}). This rate is substantially increased in the serosal compartment and may be related to the presence of esterases in the intestinal epithelium as well as the gastric mucosa. *O*-Pivaloylpropranolol shows an analogous enhancement of hydrolysis in serosal fluid and although in chemical media it is considerably more stable than the *O*-acetyl analogue, in this medium the latter compound degrades with only a two-fold greater rate. These data suggest that bioactivation of the pro-drugs at useful rates is possible. Indeed, the

TABLE 5

Effect of substrate concentration on the initial reaction velocity for the enzymatic hydrolysis of O-pivaloylpropranolol

Initial concentration (mM)	Initial reaction velocity (mM · min^{-1} × 10^3)
0.60	1.805
0.45	1.786
0.30	1.522
0.24	1.347
0.18	1.157
0.15	1.050
0.075	0.660

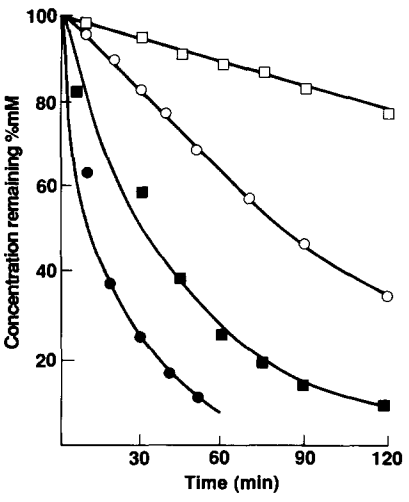

Fig. 3. Concentration–time profiles for the degradation of *O*-Acetyl and *O*-pivaloylpropranolol in everted rat small intestine during absorption at 37 °C. ●, serosal *O*-acetylpropranolol, 44.34×10^{-3} min^{-1}; ○, mucosal *O*-acetylpropranolol, 11.60×10^{-3} min^{-1}; ■, serosal *O*-pivaloylpropranolol, 21.67×10^{-3} min^{-1}; □, mucosal *O*-pivaloylpropranolol, 2.49×10^{-3} min^{-1}.

limited capacity of the enzyme systems located in the gastrointestinal mucosa (Levy et al., 1967) may result in an enhanced hydrolysis when the compounds are administered in a controlled release system such as ion-exchange resinates.

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