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DRUG-DELIVERY BY ION-EXCHANGE.

PART II: PHYSICO-CHEMICAL PROPERTIES OF ESTER PRO-DRUGS OF PROPRANOLOL.

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Summary

The pK_a values, solubilities and partition coefficients of a series of O-n-acyl propranolol pro-drugs have been estimated. The direct measurement of solubilities is limited by the instability of the esters and pK_a values are difficult to estimate by potentiometric titration due to low solubilities. Titrations in a range of aqueous methanolic solutions provide an estimate of the pK_a while titration under non-logarithmic conditions, when excess, undissolved base is present in the system, allows the determination of solubility.

Keywords

Partition, pK_a, potentiometric titration, pro-drugs, propranolol, solubility.

INTRODUCTION

A series of O-n-acyl pro-drugs of propranolol, designed to study the interaction with ion-exchange resins for controlled release purposes, has been described.[1] The

physico-chemical and kinetic properties of these compounds are important in determining the loading and release properties of the ion-exchange resinates and the generation of drug from its precursor. Moreover, these parameters have been shown to influence formulation variables, activity and pharmacokinetic profiles.[2-5] In this communication we report the pK_a, solubility and partition properties of the propranolol derivatives. Due to the low solubility and instability of the bases, pK_a values were obtained by titration in mixed solvents and solubilities were estimated by potentiometric titration under non-logarithmic conditions.

EXPERIMENTAL

Apparatus

The determination of pK_a values was undertaken using an system previously described.[6] This was based upon a Radiometer TTA60 titration assembly with hydrogen-ion concentrations measured with a Radiometer PHM64 pH meter, with a three decimal digit display of pH, using a combined glass-electrode with a silver-silver chloride reference system. Values for pK_a and associated statistics were obtained from both logarithmic and non-logarithmic titration data by means of the BASIC program PKA implemented on an IBM-PC microcomputer. Partition coefficients and solubilities were measured using a shaking-flask method.[7,8] Hplc analyses were undertaken using the system reported earlier,[1] with the mobile phases consisting of aqueous acetonitrile (65%), adjusted to pH=2.8 with orthophosphoric acid, containing diethylamine (0.1-0.2%) as moderator. Differential scanning calorimetry was undertaken with a Perkin-Elmer DSC-4 instrument using the Thermal Analysis Data Station (TADS) for data collection, handling and presentation.

Methods

Potentiometric titrations using both logarithmic[9] and non-logarithmic methods[10] were used. For non-logarithmic titration propranolol HCl solutions (5.4 mM, 25 cm^3) were placed in the titration cell, held at 37°C, and 1M NaOH, in 10µL aliquots, was added during the titration (end-point

0.135 cm³). The aqueous solubility of the free base was determined in 0.01M NaOH. O-n-acyl esters (25 cm³, 10 mg) were similarly titrated with 0.1M NaOH at 25°C. The titration solution was not allowed to exceed pH=9.0 and the titration time was limited to 10 minutes to minimise stability problems. Normal potentiometric titration (logarithmic) was used to determine the pK_a values of propranolol HCl and the O-acetyl, n-propanoyl, n-butanoyl, n-valeroyl, n-hexanoyl and pivaloyl esters at 25°C. Solutions of the hydrochlorides were prepared in methanol (800 mg in 100 cm³) and aliquots (5 cm³, 40 mg) were diluted to 25 cm³ with water or aqueous methanol and were added to the titration cell. Methanol concentrations of 20-80% (propranolol and acetyl and n-propanoyl esters), 40-80% (n-butanoyl and n-valeroyl esters) and 50-90% (n-hexanoyl and pivaloyl esters) were used. Solutions were titrated with 0.1M NaOH at 25°C with rapid addition of the titrant to minimise degradation. Numerical analysis was restricted to data points collected below pH=9.0 so that competing degradation did not influence values. The effect of surfactant on the pKa values of O-acetylpropranolol were also examined using the logarithmic method by titrating aqueous solutions (25 cm³, 1.184 mM) in dodecyltrimethylammonium bromide (0.02M) or in sodium lauryl sulphate (0.02M).

Partition experiments were performed under various pH conditions using McIlvaine buffer solutions adjusted to an ionic strength of 0.5M with potassium chloride.[11] Mutually-saturated octanol and buffer phases were prepared and the distribution of the O-n-acyl propranolols, dissolved in octanol (10 cm³, 2.96 mM), into aqueous buffers (100 cm³) was determined by ultraviolet spectroscopy at 290 nm. Degradation of the esters limited the pH range to acid conditions and monitoring by means of hplc was used to confirm the stability of the pro-drugs. Propranolol HCl (50 cm³, 6.76 mM) in octanol-saturated buffer was also partitioned into octanol (50 cm³) at 37°C alone and in the presence of sodium hexanesulphonate as ion-pairing agent (0-10mM).

The solubility of propranolol free base was determined by direct solubility in 0.01M NaOH[3,12] in the presence of excess solid while those of the O-n-acyl esters were obtained from the non-logarithmic potentiometric titration data. The solubility of N,O-diacetylpropranolol was measured in propylene glycol (0-40%) in McIlvaine buffer (pH=7.5, μ=0.5M) again in the presence of excess solid. Assays in this case were performed by hplc using a mobile phase comprising aqueous acetonitrile (65%) with diethylamine (0.1%) as moderator and ethyl paraben added as internal standard.

Samples for thermal analysis were accurately weighed (1-4 mg) into an aluminium pan, covered with an aluminium lid and crimped into position. The pan was placed in the DSC oven together with a blank, prepared in exactly the same way but without the sample. The sample and blank were continuously purged with nitrogen gas at a flow rate of 25 $cm^3 min^{-1}$ (1.4 kg cm^{-2}) and thermograms were recorded over a temperature range of 40-220°C with a programmed heating rate of 10°C min^{-1}. Temperature calibration was made with an indium standard (onset temperature 156.6°C).

RESULTS AND DISCUSSION

DSC analysis of the hydrochlorides of the O-n-acyl prodrugs of propranolol described here showed normal melting profiles (Figure 1). These derivatives, however, undergo both hydrolysis and rearrangement reactions, particularly under alkaline conditions.[13] They are too unstable for normal equilibrium solubility determinations and the low aqueous solubility of the free base limits the application of titrimetric methods to determine pK_a values. To overcome these problems potentiometric titrations in mixed solvents and during precipitation have been used. Results with propranolol are also reported to confirm the methodology. The dissociation constants (K_a) of weak acids or bases may be obtained by potentiometric titration with strong bases or

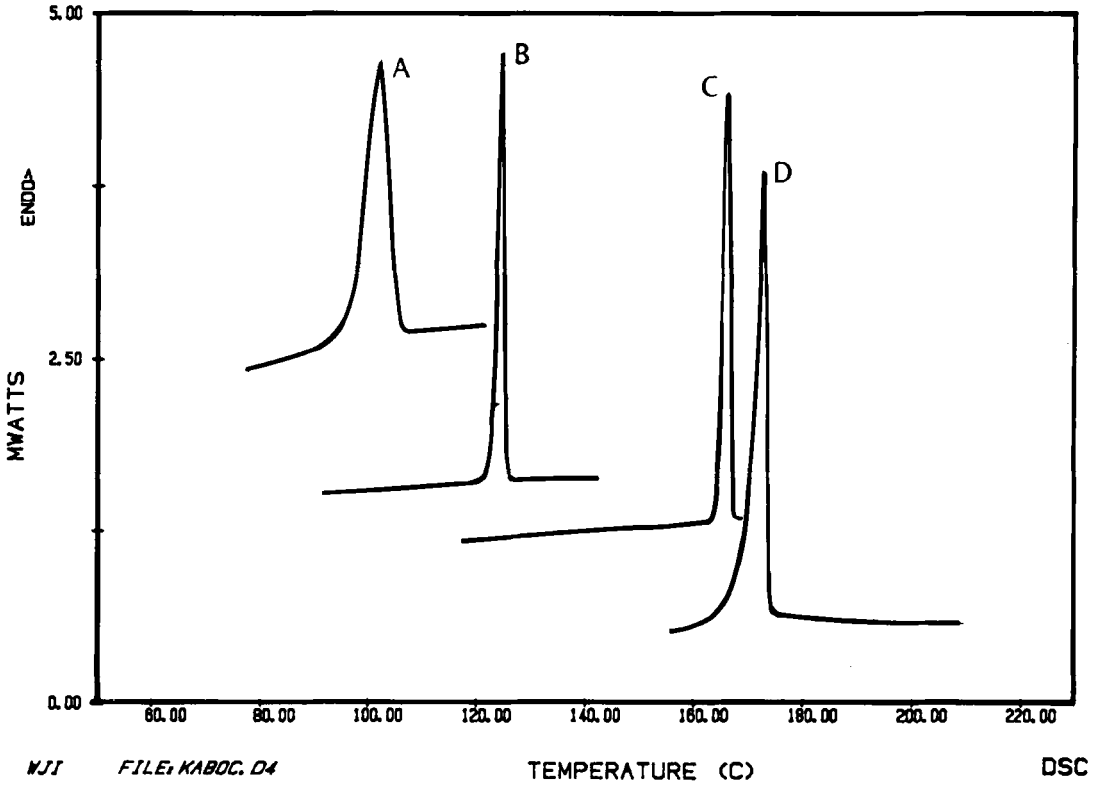

Figure 1. DSC curves of O-n-acyl propranolol hydrochlorides. (Components are: A, O-n-octanoyl; B, O-n-hexanoyl; C, propranolol; D, O-acetyl; hydrochlorides)

acids using the precise form of the Henderson-Hasselbalch relationship:[6,9]

$$K_a = [H_3O^+] \cdot \frac{b+[H_3O^+]-[OH^-]}{a-[H_3O^+]+[OH^-]} \cdot \frac{f[H_3O^+]f[B]}{f[BH^+]} \qquad (1)$$

where a and b represent the stoichiometric concentrations of conjugate acid and base during the titration; f represent the activity coefficients of the various species and are often assumed to be unity when dilute solutions are involved. This system assumes that the species remain in solution throughout the titration. When a less soluble species is produced during the titration, such as an amine from an amine salt,

precipitation of the poorly-soluble base may occur. After this point, the concentration of the conjugate base (b) in solution is constant and equal to the saturated solubility B_{sol}. This substitution into Equation 1 leads to:

$$Z' = [A_o] - \frac{[H_3O^+]}{K_a}.([B_{sol}]+[H_3O^+]-[OH^-]).\frac{f[H_3O^+]f[B]}{f[BH^+]} \quad (2)$$

where $Z' = [M^+]+[H_3O^+]-[OH^-]$, [Ao] is the initial concentration of the base salt and $[M^+]$ is the concentration, in the titration cell, of strong alkali added during the titration. This may be converted into volume of titrant added using:

$$[M^+] = \frac{m.\Sigma V_a}{V_c+\Sigma V_a} \quad (3)$$

where m is the molarity of the titrant, ΣV_a is the cumulative volume of titrant added and V_c is the initial volume in the titration cell. When B_{sol} and $[M^+]$ are significantly larger than the ionic species term $([H_3O^+]-[OH^-])$, and if the titrant is reasonably concentrated, so that the cell volume change is negligible, Equation 2 simplifies to:

$$\frac{m.\Sigma V_a}{V_c} = [A_o] - \frac{[B_{sol}][H_3O^+]}{K_a} \quad (4)$$

and may be used manually in appropriate cases although the program PKA, used to estimate pKa values from both titration methods, uses the full equations.

Figure 2 shows the potentiometric titration profile for propranolol HCl at 37°C. This curve has two components. The initial portion, up to the addition of 0.07 cm^3 NaOH, reflects titration while complete solution is maintained (Equation 1) and the later part of the curve shows the effect of precipitation. The discontinuity at 0.07 cm^3 involves the establishment of equilibrium with the solid phase of propranolol base and data from 0.08 cm^3 follow Equation 2.

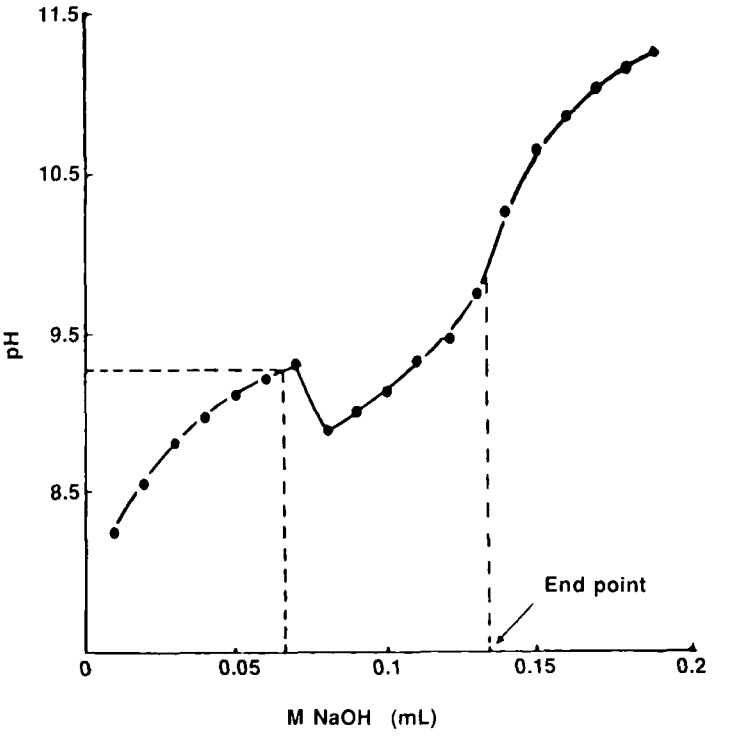

Figure 2. Potentiometric titration of propranolol HCl showing logarithmic (up to 0.07 cm^3 NaOH) and non-logarithmic (from 0.08 cm^3 NaOH) regions.

This behaviour allows the solubility of propranolol to be estimated from a single potentiometric titration. Analysis of the data before precipitation provides a value for the pK_a of 9.33 (±0.03, 95% error limits), a result in agreement with a quick estimation of this parameter taken as the pH at the half-neutralisation point.

The later data, calculated according to Equation 2 and using the K_a value from the earlier part of the curve, provide a value for the solubility of propranolol base under these conditions of 771 μM. To estimate the error involved the solubility of propranolol was determined by two alternative methods. The variation in the solubility of bases with pH is governed by the expression:

$$S_o = S_i \cdot \left[\frac{K_a + [H_3O^+]}{[H_3O^+]} \right] \qquad (5)$$

Table 1. pK_a values of O-n-acyl propranolols in aqueous methanol at 25°C.

Ester	Methanol (%)						
	20	40	50	60	70	80	90
Propranolol	9.35	9.16	9.09	9.00	8.92	8.85	
Acetyl	8.37	8.23	8.13	8.04	7.99	7.92	
n-Propanoyl	8.38	8.24	8.17	8.11	8.02	7.93	
n-Butanoyl		8.25	8.19	8.09	8.00	7.95	
n-Valeroyl		8.24	8.20	8.10	8.01	7.92	
n-Hexanoyl			8.12	8.03	7.95	7.85	7.79
Pivaloyl			8.34	8.27	8.18	8.11	8.03

where S_o and S_i are the observed and intrinsic solubilities of the base such that $B_{sol}=S_i$. The intrinsic solubility estimated by this procedure from the slope of the $(K_a+[H_3O^+])/[H_3O^+]$ against S_o plot was 813 μM. Direct solubility measurements after equilibration in 0.01M NaOH yielded a value of 803 μM. The use of the non-logarithmic titration method to determine solubility involves an underestimate, probably due to equilibration kinetics during the titration. The error involved,however, is in the order of 5%, and can probably be tolerated for many purposes.

To apply this method to the determination of the solubilities of the ester pro-drugs it is also necessary to find an independent measurement of the pK_a values in water. Solubility precludes direct potentiometric titration but mixed solvents allow suitable concentrations to be obtained. Values in aqueous methanol are shown in Table 1.

Some workers have shown that extrapolation of such plots may generate hockey-stick plots which provide a poor estimate of aqueous pK_a values.[9,14,15] In such cases a reciprocal dielectric constant plot may be useful.[16] In the present case, it appears that these data do provide a usable estimate of pK_a (Table 2) with a value for propranolol found as 9.51 compared to values of 9.45[17] and 9.5[18] reported previously.

Table 2. pK_a and solubility estimates for O-n-acyl propranolols from logarithmic and non-logarithmic potentiometric titrations.

Ester	Estimated aqueous pK_a	Estimated aqueous solubility (μM)
Propranolol	9.51	771.0
Acetyl	8.52	680.5
n-Propanoyl	8.54	170.0
n-Butanoyl	8.57	52.76
n-Valeroyl	8.59	15.25
n-Hexanoyl	8.53	5.4
Pivaloyl	8.71	8.44

Additionally, the pK_a values of all esters are in reasonable agreement with each other despite the significant differences in extrapolation due to variations in solubility. The presence of surfactants may significantly alter pK_a estimates.[19-22] The value for O-acetylpropranolol, for example, is depressed to 7.66 in the presence of 0.02M dodecyltrimethylammonium chloride while elevation to 10.18 is observed in the presence of 0.02M sodium lauryl sulphate.

These data, together with the non-logarithmic titration of the esters after precipitation, provide estimates of the solubility which are recorded in Table 2. The solubilities may be related to the carbon number in the alkyl side-chain (n) by the equation: $-\log(S_o) = 1.9015n + 5.10$ ($r=0.999$).

The variation in the partition coefficient of a base with pH is modelled by the equation:[7]

$$P_{app}.\left[\frac{K_a+[H_3O^+]}{[H_3O^+]}\right] = P_i + P_u.\left[\frac{K_a}{[H_3O^+]}\right] \qquad (6)$$

where P_{app} is the measured partition coefficient and P_i and P_u are the true partition coefficients of the ionised and unionised forms of the base. Linear plots of $K_a/[H_3O^+]$ against $P_{app}.(K_a+[H_3O^+])/[H_3O^+]$ provide P_u as the slope and

Table 3. Apparent partition coefficients for propranolol dependent upon pH.

pH:	6.50	6.82	7.29	7.70	8.09
Papp:	3.30	6.38	15.10	33.54	78.00

Table 4. True partition coefficients [$\log_{10}(P_u)$] of O-n-acyl propranolol pro-drugs.

Ester	Partition coefficient $\log_{10}(P_u)$
Propranolol	3.260
Acetyl	4.505
n-Propanoyl	4.991
n-Butanoyl	5.560
n-Valeroyl	6.300
n-Hexanoyl	6.850
n-Octanoyl	7.870
Pivaloyl	6.440

P_i as the intercept. Data for propranolol are recorded in Table 3. and yield values of P_u=1820 and P_i=2 (r=0.9999). Agreement with reported values is satisfactory.[18,23]

The measured pK_a values (Table 2) and the apparent partition coefficients of the O-n-acyl pro-drugs similarly lead to estimates of the true partition coefficient. In theses instances, the partition of the protonated form was very small and could be approximated to zero. Values are recorded in Table 4.

$\log_{10}(P_u)$ is also modelled by the carbon number of the alkyl side-chain by: $\log_{10}(P_u) = 0.576n + 3.9$ (r=0.998). Partition coefficients, in combination with melting points, have also been used to predict aqueous solubilities.[26] The equation: $\log(S_w) = 1.05 - \log(P_u) - 0.01mpt$ predicts the water solubility of propranolol (mpt, 96°C) quite well giving

Table 5. Effect of sodium hexanesulphonate on the partition coefficient of propranolol at pH=6.5 at 37°C.

Sodium Hexane sulphonate (mM):	0	2	4	6	8	10
P_{app}	3.15	5.50	8.30	10.80	13.70	16.60

Table 6. Effect of propylene glycol on the aqueous solubility of N,O-diacetylpropranolol in pH=7.4 buffer at 37°C.

PG (%)	0	5	10	15	20	25	30	35	40
Solubility (μM)	14	20	29	35	44	61	93	125	181

a value of 812 μM. An analogous approach also allows some prediction of the aqueous solubilities of the ester pro-drugs. In this instance, however, a high correlation with partition alone is observed: $\log_{10}(S_w)=0.731-0.888\log_{10}(P_u)$ (r=0.995) and melting behaviour cannot be included in the multiple regression analysis.

The presence of surfactant and ion-pairing systems may affect the measured values considerably. Table 5 displays the influence of sodium hexanesulphonate (SHS) on the P_{app} of propranolol at pH=6.5 which follows the linear relationship: $P_{app} = 1.348[SHS] + 2.936$ (r=0.9994).

In contrast to the O-n-acyl pro-drugs, the solubility and partition properties of N,O-diacetylpropranol and similar structures are not influenced by the pH of the medium. To control solubility in this and related cases, cosolvents may be necessary and an enhanced solubility was obtained through the addition of propylene glycol (Table 6). This enhancement follows the simple relationship: $\log(S_f) = \log(S_w) + af$ where S_f is the solubility of the solute in the binary solvent, S_w is the water solubility, f is the volume fraction of the co-solvent and a is a constant characteristic of the system

Table 7. Effect of propylene glycol (PG) on the pH of aqueous mixtures of pH 7.4 buffer at 25°C.

PG (%):	0	5	10	15	20	25	30	35	40
pH :	7.4	7.47	7.54	7.59	7.67	7.74	7.80	7.88	7.96

under study.[24,25] The constants for this system were evaluated as: $\log(S_f) = 1.15 + 0.027f$ (r=0.997).

Although the ionisation does not influence solubility in this instance, the cosolvent exerts a significant effect on pH (Table 7) and this effect must be considered when weak electrolytes or unstable species are used.

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