



THE EFFECT OF pH CONTROL ON THE SOLUBILITY AND PARTITION COEFFICIENT OF TRANDOLAPRIL

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ABSTRACT

The objective of the present study was to investigate the effect of pH control on the aqueous solubility and partition coefficient of trandolapril respectively. The aqueous solubility was determined at 25 °C using pH values of 1.0, 2.0, 4.0, 5.0, 5.4, 5.8, 6.4, 8.0 and 9.0 respectively. The aqueous solubility of the drug was also studied at 35 °C and 45 °C respectively. The partition coefficient of trandolapril was determined at 25 °C between chloroform and aqueous buffer solutions using pH values of 2.0, 4.4, 5.0, 5.4, 5.8, 6.4, 7.4 and 9.0 respectively. The pH-solubility profile of trandolapril showed an intrinsic solubility of 3.524×10^{-2} mg/ml at $25 \pm 1^\circ\text{C}$. The pH-dependency of the apparent chloroform-water partition coefficient of trandolapril gave a partition coefficient of 58.88 for free trandolapril. The results of the study allowed the dissociation constant of the drug to be calculated. The physicochemical data obtained at alkaline pH (≥ 9.0) can be useful in the development of pharmaceutical liquid dosage forms of the drug.

KEYWORDS: Trandolapril, solubility, partition coefficient, pH control.

INTRODUCTION

Trandolapril (2S,3aR,7As)-1-[(2S)-2-[(1S)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]octahydro-1H-indole-2-carboxylic acid, is a potent nonsulphydryl angiotensin-converting enzyme inhibitor. It is used clinically to treat patients with congestive heart failure, hypertension and myocardial infarction^{1,2}. The drug has poor aqueous solubility and commercially exists only in pharmaceutical solid dosage forms (tablets or capsules). To aid in the development of a pharmaceutical liquid dosage form of trandolapril, its relevant physicochemical properties would be required. Previous reports³⁻⁶ have shown that optimization of these physicochemical properties have led to the development and formulation of pharmaceutical liquid dosage forms. A survey of the literature has revealed inadequate and incomplete information about the physicochemical characteristics of trandolapril under various pH and temperature conditions. The present investigation was aimed at determining some of the relevant physicochemical properties, namely aqueous solubility, partition coefficient under these conditions.

MATERIAL AND METHOD

Materials

Trandolapril (Abbot Laboratories, USA), chloroform and methanol (Fisher Scientific, USA). All other chemicals were of analytical grade. Ultraviolet/Visible spectrophotometer (UV 2102 PC Unico) was used to measure the absorbance readings. The pH measurement was performed with Orion pH meter, model 5A, 520 with combination glass electrode.

Standard solution

Stock solution of trandolapril (100 µg/ml) was prepared in methanol. Aliquots (10.0-50.0 µg/ml) of the standard stock solution were pipetted into a 10 ml volumetric flask, diluted to volume with methanol.

Determination of solubility

Excess trandolapril (20 -50 mg) was added to a 5 ml buffer solution or deionized water adjusted to pH values required with variable volumes of either hydrochloric acid or sodium hydroxide. The final pH was measured at the time of filtration. The shaking was done at $25 \pm 1^\circ\text{C}$ for 24 h. The supernatant was analyzed at a maximum wavelength of 210 nm spectrophotometrically.

Determination of partition coefficient

The partitioning of trandolapril between mutually pre-saturated chloroform and buffer solution (pH values 3-9) was determined at $25 \pm 1^\circ\text{C}$ using previously reported method⁷. The shaking was carried out for 2 h. The aqueous phase was analyzed by a spectrophotometric method for trandolapril content at a maximum wavelength of 210 nm and its concentration calculated from a pre-constructed graph. The partition coefficient of trandolapril was calculated using the following equation:

$$P = \frac{(C_1 - C_w)V_w}{C_w V_o} \text{ ----- 1}$$

where, P = partition coefficient, C_1 = total concentration of trandolapril, C_w = concentration of trandolapril in the aqueous phase, V_w = volume of the aqueous phase, V_o = volume of the organic phase.

Determination of pKa by UV spectrophotometry

The method described by Islam *et al.*⁸ was used in the determination. A stock solution of trandolapril (4.65×10^{-4} M) was prepared in methanol. Based on the UV spectra of the ionized and free (molecular) forms of trandolapril, an analytical wavelength of 210 nm was chosen. The pH of each solution (4.65×10^{-5} M) was adjusted with 0.1 M hydrochloric acid or 0.1 M sodium hydroxide or biphthalate buffer. The absorbance of the solution was recorded immediately after a stable pH reading was obtained. The determinations were carried out at $25 \pm 1^\circ\text{C}$.

RESULTS AND DISCUSSION

A correlation coefficient of 0.9997 was obtained from the regression analysis of the calibration curve of trandolapril. The solubility values of trandolapril at different pH values are listed in Table 1. The results show that the solubility of the drug in aqueous solution was very low in an acid medium. However, it was observed that significant increase in solubility occurred with increase in pH value probably due to the presence of ionizable groups in the drug. The total solubility (S_{tot}) of trandolapril can be described by the following equation:

$$S_{\text{tot}} = [\text{HA}] + [\text{A}^-] = [\text{HA}] + K_a[\text{HA}]/[\text{H}^+] \text{ ----- 2}$$

where, [HA] is the intrinsic solubility of the neutral or undissociated trandolapril. A value (3.524×10^{-2} mg/ml) of [HA] was obtained from the intercept of a plot of total molar solubility versus the reciprocal of hydrogen ion

concentration. The plot is shown in Figure 1. This value was found to be close to the aqueous solubility of the drug (3.293×10^{-2} mg/ml) obtained by direct measurement. The pH-solubility profile allowed the ionization constant of the drug to be calculated. The pK_a was obtained to be 5.81. The effect of temperature on the aqueous solubility of trandolapril was determined at $25 \pm 1^\circ \text{C}$. The classical van't Hoff type of plot ⁹ of the equilibrium solubility of the drug in water at different temperatures is shown in Figure 2. The plot shows good linear relationship. The regression equation describing the plot is:

$$\log S = -2552.5 / T + 4.4459 \text{ ----- 3.}$$

The equation could be used to calculate the solubility of trandolapril at arbitrary temperatures. The heat of solution ΔH (48.88 kJ/mol), was calculated from the slope of the plot: slope = $-\Delta H / 2.303 R$, where R is the gas constant. The positive value of ΔH indicates an increase in aqueous solubility of trandolapril. The free energy change (ΔG) at 35°C and 45°C respectively was calculated using a modified thermodynamic relationship ¹⁰:

$$\Delta G = 2.303 RT \log S_T / S_{T25^\circ \text{C}} \text{ ---- 4}$$

where $S_{T25^\circ \text{C}}$ is solubility at 25°C , and S_T is solubility any other temperature. Employing equation 5, the entropy change during solubilization was evaluated.

$$\Delta S = \Delta H - \Delta G / T \text{ ----- 5}$$

The results of the effect of temperature on solubility and thermodynamic parameters are shown in Table 2.

The pH-dependency of the partition coefficient of trandolapril was obtained using this equation:

$$1 / P_{\text{app}} = 1 / P_m - K_a / P_{\text{app}} [H^+] \text{ ----- 6}$$

where, P_{app} is the apparent (observed) partition coefficient of trandolapril, P_m is the partition coefficient of the free form and K_a is the ionization constant. From the plot using equation 6, a value of 3.388×10^{-7} for K_a ($pK_a = 6.47$) from the slope and a value of 58.88 for P_m from the intercept were found. The partition data at pH 4.40-5.82 were used to construct Figure 3, since sensitivity to pH in this region was high. To confirm the reliability of the solubility method and partition method respectively, in ionization constant determination, the ionization constant of trandolapril was determined by means of UV spectrophotometric method. The ionization constant was calculated using the following equation:

$$pK_a = \text{pH} - \log (A - A_a) / (A_b - A) \text{ ----- 7,}$$

where A is the absorbance of a solution at specific pH, A_a and A_b are absorbance at the same concentration in acid and alkaline solution respectively. The determined pK_a value was 5.50 ± 0.306 . The results are given in Table 3

CONCLUSION

The positive heat of solution showed that solubility increased with an increase in temperature. The negative values of the free energy change are indicative of the spontaneity of the process in each case. The positive values of the entropy indicate some degree of randomness during the solubilization process.

The entropy change was found not vary significantly at varying temperature. The solubility method was observed to be a more accurate and reliable method of determining the pK_a of trandolapril than partitioning method because its result correlated better with the spectrophotometric method result. Finally, the study suggests that the physicochemical data obtained at alkaline pH (≥ 9.0) can be optimized to develop and formulate pharmaceutical liquid dosage forms of trandolapril.

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Table 1: Solubility, Partition Coefficient of Trandolapril as a function of pH ($25 \pm 1^\circ \text{C}$)

pH	Solubility ($\pm$ SD $\mu\text{g/ml}$)	Partition Coefficient ($\pm$ SD)
1.02	11.17 ± 0.58	ND
2.03	21.31 ± 0.05	100.83 ± 0.71
4.02	32.73 ± 0.19	ND
4.41	ND	61.35 ± 0.61
5.01	41.53 ± 0.51	54.65 ± 0.31
5.42	52.68 ± 0.28	52.49 ± 0.37
5.81	70.06 ± 0.54	48.24 ± 0.47
6.42	93.89 ± 0.49	45.38 ± 0.44
7.41	ND	40.84 ± 0.26
8.02	147.13 ± 0.58	ND
9.04	205.98 ± 0.25	36.21 ± 0.53

ND = Not determined.

Table 2: Temperature Dependency of Solubility of Trandolapril

Temperature ($^\circ \text{C}$)	Molar Solubility	ΔH (kJ/mol)	ΔG (kJ)	ΔS (J/K/mol)
25	7.616×10^{-5}	48.88	-	-
35	1.503×10^{-4}	48.88	-11.64	196.23
45	2.467×10^{-4}	48.88	-19.73	215.75

Table 3: Dissociation Constant (pK_a) of Trandolapril Determined by UV Spectrophotometry

pH	Absorbance	pK_a
5.03	0.174	5.10
5.21	0.179	5.25
5.44	0.187	5.42
5.60	0.190	5.55
5.83	0.193	5.76
6.02	0.198	5.91
Mean $\pm$ SD		5.50 $\pm$ 0.306
0.10 M HCl	0.073	
0.10 NaOH	0.295	

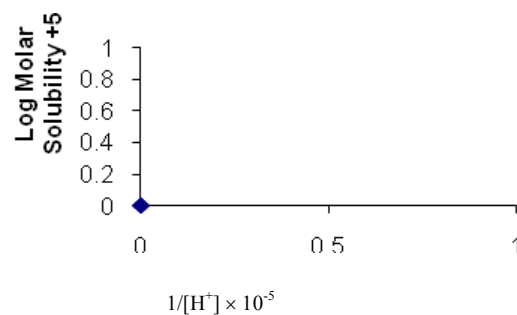


Figure 1: Plot of solubility versus the reciprocal of hydrogen ion concentration for trandolapril.

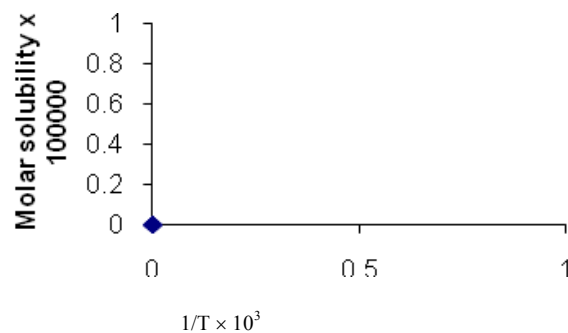


Figure 2: Plot of solubility versus the reciprocal of absolute temperature for trandolapril.

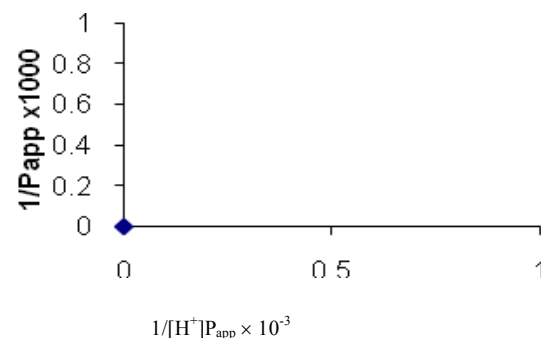


Figure 3: Plot of reciprocal of apparent partition coefficient versus reciprocal of product of hydrogen ion concentration and apparent partition coefficient for trandolapril.

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