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ACID-BASE EQUILIBRIA AND SOLUBILITY OF VERAPAMIL

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ABSTRACT

The intrinsic solubility – S_0 (only the neutral form is present in the solution) and pH-dependent solubility - S (heterogeneous system of neutral and ionized forms) of verapamil were determined spectrophotometrically. Based on solubility data pK_a value 9.15 of verapamil was indirectly obtained.

INTRODUCTION

Verapamil belongs to a class of calcium channel blockers applied in the treatment of cardiac arrhythmias, angina pectoris and hypertension. Because to the presence of single ionizable group, aliphatic tertiary amine, verapamil represents a weak base (Figure 1) and exhibits pH-dependent aqueous solubility [1].

In solutions of weak electrolytes there is an equilibrium between molecular and ionized forms with different physico-chemical properties. The most important physico-chemical parameters that affect the liberation and the absorption processes of drugs are solubility and pK_a value. Comprehensive understanding of these parameters is necessary for the development of novel drug delivery systems, improvement of existing pharmaceutical formulations, andfor the choice of the optimal experimental conditions in drug analysis[2].

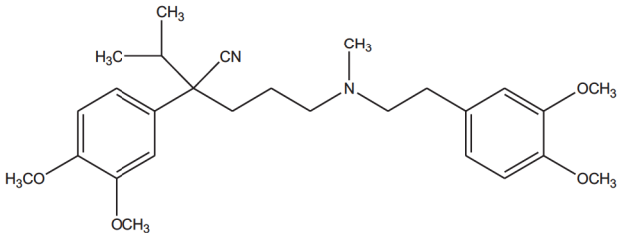

Figure 1. Chemical structure of verapamil.

EXPERIMENTAL

Spectrophotometric measurements were carried out on the UV-Vis spectrophotometer Cintra 20 (GBC, Australia). Automatic titrator 798 MPT

Titrino (Metrohm, Switzerland) with a combined electrode LL unitrode Pt 1000 (Metrohm, Switzerland) was used for potentiometric measurements. Verapamil hydrochloride was kindly donated from Medicines and Medical Devices Agency of Serbia (Belgrade, Serbia). All solutions were prepared in double distilled water. Standard solutions of HCl and carbonate-free NaOH were standardized potentiometrically.

Saturated solutions of verapamil (pH 7.8 to 12) were prepared by treating verapamil hydrochloride(0.25 mg/mL)in 0.1 mol/L NaCl solutionwith 0.1mol/L NaOH. Suspensions were thermostated at 25°C with occasional stirring for 24 h, thenfiltered through 0.22 μm membrane filter. After a specified dilution of the filtrate, concentration of verapamil was determined spectrophotometrically at 230 nm.

RESULTS AND DISCUSSION

From the chemical point of view verapamil represents the monoprotic base and its molecular form is poorly soluble in water. In a saturated aqueous solution of verapamil between the solid phase (B_s) and a solution the following equilibria is established:

$$B_s \rightleftarrows B \qquad K_{s0} = S_0 = [B] \tag{1}$$

$$B_s + H^+ \rightleftarrows BH^+ \quad K_{s1} = \frac{[BH^+]}{[H^+]} \tag{2}$$

where S_0 is the intrinsic solubility (solubility of molecular form) of verapamil.

The total solubility (S) of verapamil is equal to the sum of the concentrations of the molecular form (B) and of the protonated form (BH^+):

$$S = [B] + [BH^+] \tag{3}$$

Combining equations (1) – (3) gives the equation:

$$S = S_0 + K_{s1}[H^+] \tag{4}$$

where the constant K_{s1} can be replaced by relation that connects verapamil acidity constant (K_a) and constants in a heterogeneous system:

$$K_a = \frac{[B][H^+]}{[BH^+]} = \frac{K_{s0}}{K_{s1}} \tag{5}$$

to give the following equation:

$$\underbrace{S}_{y} = S_0 + \frac{S_0}{K_a}\underbrace{[H^+]}_{x} \tag{6}$$

Equation (6) represents linear dependence of the total solubility (S) on $[H^+]$. Based on pairs S-$[H^+]$it is possible to determine the intrinsic solubility (S_0) and the K_a value.For very poorly soluble compound, such as verapamil, theordinate intercept (S_0) is often within a statistical error. Reliable results

for $S_0$of verapamil can be obtained by determining the solubility at pH>(pK_a + 2), Table 1.

Table 1. The intrinsic verapamil solubilityat 25°C.

pH	S_0 (mol/L)
11.5	4.24×10^{-5}
11.7	2.60×10^{-5}
11.9	4.23×10^{-5}
12.0	6.20×10^{-5}
12.2	5.26×10^{-5}
Average	4.51×10^{-5}

Table 2. pH–dependent verapamil solubility at 25°C.

pH	S (mol/L)
8.41	2.22×10^{-4}
8.62	1.46×10^{-4}
8.84	8.76×10^{-5}
8.88	7.06×10^{-5}
9.09	5.57×10^{-5}

Tables 1 and 2 show the results of determination of the intrinsic solubility (S_0)and a pH-dependent solubility of verapamil.Figure 2 shows linear dependence of verapamil solubility (S) on [H^+] in a pH interval from 8.41 to 9.09.

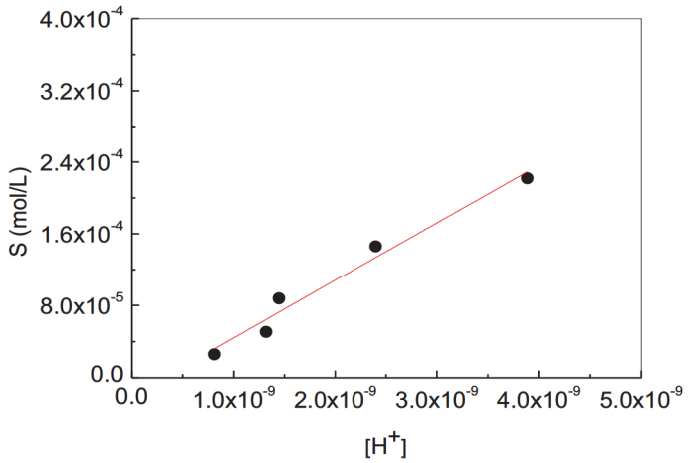

Figure 2. Linear dependence of verapamil solubility (S) on [H^+], eq. (6).

Based on the slope of the curve on Figure 2 (6.40×10^4) and the intrinsic solubility ($S_0 = 4.51\times10^{-5}$), acidity constant of verapamil $K_a=7.05\times10^{-10}$(pK_a 9.15) has been obtained.

The most frequently applied methods for the determination of ionization constants in aqueous solution, potentiometric and spectrophotometric, arenot applicable in the case of verapamil. Potentiometry could not be applied due to the low solubility of verapamil, and spectrophotometry due to very small differences in the absorption spectra of molecular and ionized

forms (Figure 3).The few published datashow that the pK_a value of verapamil (8.63, 8.72, 9.07) is determined exclusively by using a cosolvent system [3].

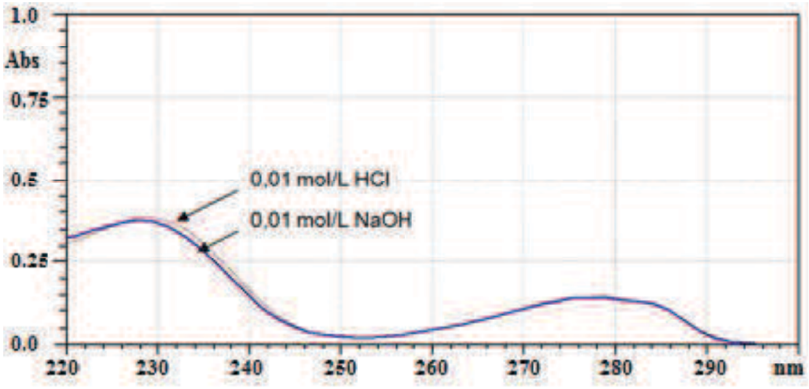

Figure 3.UV spectra of verapamil in 0.01 mol/L HCl (ionized form) and 0.01 mol/L NaOH (molecular form).

CONCLUSION

The intrinsic solubility and pH-dependent solubility of verapamil are determined. Based on the solubility data the pK_a value of the verapamil is indirectly determined. Obtained data are of great importance for the improvement of analytical procedures, pharmaceutical formulations, and evaluation of the pharmacological behavior of verapamil.

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