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Physicochemical properties of valsartan and the effect of ethyl alcohol, propylene glycol and pH on its solubility

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The aqueous solubility and partition coefficient of valsartan were determined at room temperature. The effect of ethyl alcohol, propylene glycol and pH on its solubility was also investigated. It was found that both solvents increased the solubility of the drug in water. The solubilizing power of ethyl alcohol was found to be higher than that of propylene glycol. Valsartan solubility was also observed to increase at high pH values and its lipophilicity was demonstrated by the high positive value of the logarithm of partition coefficient.

1. Introduction

Valsartan, *N*-[*p*-(*o*-1*H*-tetrazol-5-ylphenyl)benzyl]-*N*-valeryl-L-valine, is a potent long-acting non-peptide AII type 1 receptor antagonist (Latif et al. 2001). Clinically, it is used in the treatment of hypertension. Its solubility in water is very limited. A number of reports have appeared in literature concerning the effect of cosolvents on the solubility of slightly soluble drugs. Varia et al. (1991) investigated the solubilization of tipredane (corticosteroid) by a cosolvent system consisting of polyethylene glycol 400, propylene glycol and water. Yalkowsky and Rubino (1985) showed that a propylene glycol-water mixture enhanced the solubility of poorly soluble drugs. Furthermore, it has been reported that hydroalcoholic mixtures have been employed as cosolvents for non-polar solutes (Breon 1970; Li et al. 1999). As cosolvency or pH adjustment enables slightly soluble drugs to be formulated into pharmaceutical liquid dosage forms (oral or topical), this work was undertaken to investigate the extent to which the aqueous solubility of valsartan could be enhanced by cosolvent systems or aqueous solutions of varying pH values. It is envisaged that formulation of valsartan into oral liquid dosage form could alleviate the potential difficulties experienced with solid dosage forms of valsartan by geriatric or other hypertensive patients. Hitherto, no such study on the physicochemical properties and solubilization of valsartan has been reported and in this paper, we report on the aqueous solubility, partition coefficient of valsartan and the effect of ethyl alcohol, propylene glycol and pH on its solubility.

2. Investigations, results and discussion

The calibration graph of valsartan was linear in the range of 9.40–46.9 μg/ml. Peak area ratio versus concentration relationship is described by regression equation $A = 0.0133 + 0.0775\ C$ ($R^2 = 0.9999$). The influence of ethyl alcohol, propylene glycol on the solubility of valsartan is illustrated in Fig. 1. The graph indicates that both solvents increased the solubility of valsartan and that this effect increases as the concentration is increased. Considering a concentration level of 30% v/v, solubility of valsartan was 236.8 mg/100 ml (a 4-fold increase) for ethyl alcohol compared to 159.9 mg/100 ml (about 3-fold increase) in the case of propylene glycol. The observed solubilization of valsartan in these solvent systems could be as a result of the nonpolar hydrocarbon region in the cosolvent reducing the ability of the aqueous system to squeeze out valsartan molecules. Furthermore, a decrease in the dielectric constant of the system could also explain the solubility enhancement. The dielectric constant was calculated using the following relationship, $\varepsilon_C = \varepsilon_{WS}\, f_{WS} + \varepsilon_{SS}\, f_{SS}$ where ε and f are the dielectric constant and volume fraction respectively; and the subscripts c, ws, ss represent values for the cosolvent, weaker solvent and stronger solvent respectively. The study also found that at 10% v/v or less, both solvent systems gave no increase in the solubility. The free energy change (ΔG) was calculated from the following thermodynamic relationship (Feldman and Gibaldi 1967), $\Delta G = -2.303\ RT \log S_C/S_W$ where S_C/S_W = ratio of the molar solubility of valsartan in cosolvent to that in water. The spontaneity of the process is indicated by the negative values of the free energy change obtained for the different systems. The results are summarized in Table 1. The effect of pH on the solubility of valsartan is given in Table 2. The results indicate that solubility increases at high pH values and at pH 10.06, a 2-fold increase in solubility was observed.

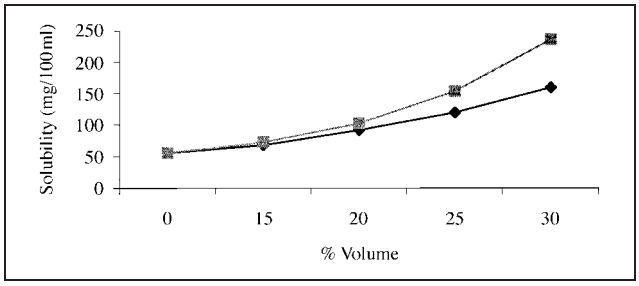

Fig. 1: Plot of solubility of valsartan versus percentage volume of the cosolvent
◆——◆ Propylene glycol ■——■ Ethyl alcohol

Table 1: Effect of ethyl alcohol, propylene glycol on the solubility of valsartan and the thermodynamic parameter of valsartan in both solutions

Cosolvent conc. (% v/v)	Ethyl alcohol		Propylene glycol	
	Solubility (mg/100 ml)	G (J/mol) (20 °C)	Solubility (mg/100 ml)	G (J/mol) (20 °C)
0	55.6	–	55.6	–
15	72.7	– 648.0	68.2	– 497.6
20	102.9	−1490.7	92.3	−1229.4
25	154.0	−2478.6	120.0	−1872.2
30	236.8	−3525.5	159.9	−2566.5

Table 2: Effect of pH on the solubility of valsartan

pH	Solubility (mg/100 ml)
2.30	12.3
3.10	25.2
4.07	56.6
5.40	53.9
6.12	59.4
7.02	62.8
8.36	71.0
9.18	71.6
10.06	100.0

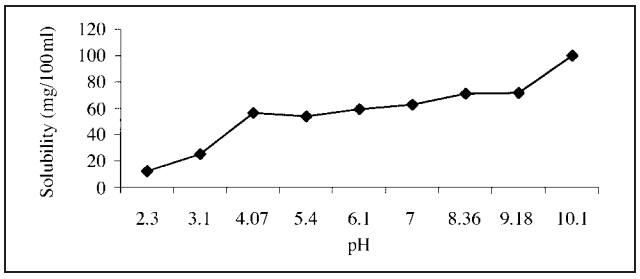

Fig. 2: Plot of solubility of valsartan versus pH

The increase in solubility could be as a result of an increase in the percentage of valsartan molecules ionzing at high pH values. A plot of the solubility of valsartan versus pH is shown in Fig. 2. The graph shows points of inflection at pH 4.07 and 8.36 respectively, suggesting that the pK α values of valsartan could be about 4 and 8. The partition coefficient (P) of valsartan was determined in 1-octanol-water system and found to be 22.2. The high positive value of log P confirms the lipophilic character of the drug and hence its biological activity.

Although the solubility of valsartan has been enhanced by the cosolvent systems and aqueous pH solutions studied, further increase in solubility is necessary if valsartan is to be formulated into pharmaceutical liquid dosage form. Hence further studies would require the incorporation of additives into the cosolvent systems with the aim of obtaining a more significant increase in valsartan solubility.

3. Experimental

3.1. Materials

Valsartan (Norvatis Pharmaceuticals), benzoic acid (Fisher Scientific) and all other solvents were of HPLC grade (Sigma-Aldrich).

3.2. Apparatus

All separations were carried out with Hitachi LC 6200 pump and LC Organizer injector, Kratos spectroflow 783 detector. A zorbax analytical column C18, 150 mm × 4.6 mm, 3.5 μm.

3.3. Chromatographic procedure

The mobile phase consisted of 1% aqueous acetic acid in methanol. The flow rate was 1 ml/min at room temperature. The injection volume was 10 μl and detection was effected at 254 nm.

3.4. Standard solution

Stock solutiion of valsartan (94.0 μg/ml) and internal standard (400 μg/ml) were prepared in methanol. Aliquots (9.40–46.9 μg/ml) of the standard stock solution were pipetted into a 100 ml volumetric flask. A 10 ml aliquot of the internal standard (benzoic acid) was added to each flask and diluted to volume with methanol.

3.5. Solubility determination

Solubility was determined by placing an excess of valsartan (100 mg) in 15 ml of water, cosolvent and aqueous solutions of varying pH respectively, under shaking at room temperature for 24 h. After equilibration the supernatant was filtered and the concentration of the filtrate was determined chromatographically by reference to the calibration graph of valsartan.

3.6. Partition coefficient

The apparent partition coefficient was determined in an 1-octanol-water system. The aqueous phase was distilled water and the organic phase was 1-octanol. To the aqueous solution (20 ml) containing 24 mg of valsartan was added 20 ml of 1-octanol and agitated at room temperature for 2 h to achieve complete equilibration. The aqueous phase was analysed by a chromatographic method for valsartan content and its concentration was calculated from a preconstructed calibration graph.

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