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Solubilization of valsartan by aqueous glycerol, polyethylene glycol and micellar solutions

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Received May 30, 2005, accepted June 6, 2005

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Pharmazie 61: 322–324 (2006)

To increase the solubility of valsartan in aqueous solutions was considered of interest. This study therefore investigated the solubilization of valsartan by cosolvency and micellization. Of the solubilization agents used, sodium lauryl sulfate was found to be the most effective. The increase in solubility at the maximum concentration studied was in the following order: sodium lauryl sulfate > polysorbate-80 > polyethylene glycol 400 > glycerol. The effect of propylene glycol on the solubility of valsartan in a 2% w/v polysorbate-80 solution was also investigated and was found that propylene glycol decreased the solubilizing power of polysorbate-80 at the concentrations studied.

1. Introduction

In continuation of studies on the enhancement of aqueous solubility of valsartan, we have investigated the effects of glycerol, polyethylene glycol 400 (PEG 400), polysorbate-80 (Tween 80) and sodium lauryl sulfate on the solubility of valsartan. Furthermore, the effect of incorporation of propylene glycol into a 2% w/v of polysorbate-80 solution on valsartan solubility was also studied. A previous report (Mbah 2005) has shown that propylene glycol-water cosolvent system increased the aqueous solubility of the drug. Cosolvency and micellization have been employed in several studies to increase drug solubility (Alkhamis et al. 2003; Li and Zhao 2003; Khalil et al. 2000; Alvarez-Nunez and Yalkowsky 1998). The increase in solubiliy of drugs with low aqueous solubility by these techniques have allowed these medicinal agents to be formulated into pharmaceutical liquid dosage forms (Martin et al. 1973). Valsartan, a non-peptide AII type 1 receptor antagonist used in the treatment of hypertension presently has a solid dosage form (tablets) as the only pharmaceutical formulation. Nevertheless, the potential of formulating it into liquid dosage forms exists if sufficient aqueous solubilty could be achieved through cosolvency, micellization or a combination of both techniques. In this context, the study examines the influence of glycerol, polyethylene glycol 400, polysorbate-80 and sodium lauryl sulfate on the solubility of valsartan.

2. Investigation, results and discussion

The effect of polyethylene glycol (PEG 400) on the solubility of valsartan is illustrated in Fig. 1, in which the experimental total solubility is plotted against the concentration of polyethylene glycol 400. The graph shows an exponential increase in valsartan solubility with increasing cosolvent concentration. The graph also shows that at a concentration of 50% w/v at 25 °C the solubility of valsartan was 750.0 mg/100 ml, representing a 12-fold increase.

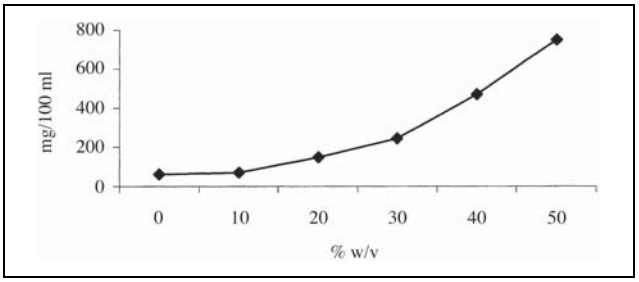

Fig. 1: Plot of valsartan solubility versus polyethylene glycol 400 concentration

The results are presented in Table 1. Unlike PEG 400, glycerol showed a neglible increase in solubilty. For instance, at a cosolvent concentration of 40% w/v and 50% w/v the solubility of the drug was 74.8 mg/100 ml (1.2-fold increase) and 81.9 mg/100 ml (1.3-fold increase) respectively. The difference in solubilizing power of glycerol and PEG 400 is due to the fact that PEG 400 is less polar than glycerol, making it possible for hydrogen bonding interactions in water molecules to be effectively disrupted. This in turn limits the ability of PEG 400-water system to squeeze out valsartan molecules. In Fig. 2, the experimental total solubility is plotted against the concentration of

Table 1: Effect of polyethylene glycol 400 on valsartan solubilty and thermodynamic parameter for valsartan in the cosolvent system

Cosolvent concentration (% w/v)	Polyethylene glycol 400	
	Solubility (mg/100 ml)	ΔG (J/mol) (25 °C)
0.0	61.3	
10	70.1	− 328.7
20	149.1	−2198.3
30	244.2	−3420.9
40	469.9	−5042.9
50	750.0	−6201.5

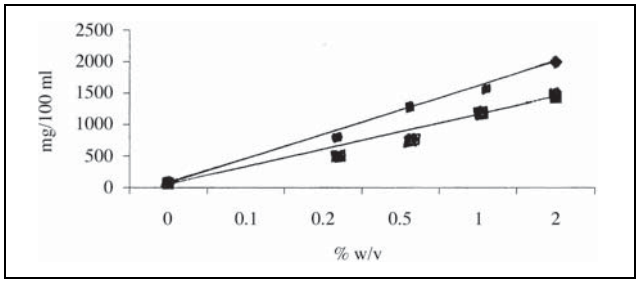

Fig. 2: Plot of valsartan solubility versus surfactant concentration
Polysorbate-80 ■——■——■ Sodium lauryl sulfate ■——■——■

Table 2: Solubilization of valsartan by micellar solutions and thermodynamic parameters for valsartan in the solutions

Surfactant conc. (% w/v)	Polysorbate-80		Sodium lauryl sulfate	
	Solubility (mg/100 ml)	ΔG (J/mol) (25 °C)	Solubility (mg/100 ml)	ΔG (J/mol) (25 °C)
0.0	61.3		61.3	
0.2	367.5	−44433.8	117.1	−1599.6
0.5	656.4	−5871.1	369.5	−4447.2
1.0	1140.3	−7239.8	868.8	−6565.9
2.0	1996.0	−8627.2	1432.6	−7805.7
4.0	1853.1	−8443.1	2692.8	−9369.2

polysorbate-80 (Tween 80) and sodium lauryl sulfate. The graphs show a linear relationship between the drug aqueous solubilty and the surfactant concentration for both surfactants. It is also observed from the graphs that polysorbate-80 produced a more solubilizing effect than sodium lauryl sulfate at increasing surfactant concentration. Considering a concentration of 2% w/v, the solubility of valsartan was 1996.0 mg/100 ml (32.6-fold increase) for polysorbate-80 compared to 1432.6 mg/100 ml found in the case of sodium lauryl sulfate (23.4-fold increase). However at surfactant concentration of 4% w/v, the solubilizing power of sodium lauryl sulfate was found to be higher than that of polysorbate-80. For example, the solubility for the drug at this concentration was found to be 1853.1 mg/100 ml (30.2-fold increase) and 2692.8 mg/100 ml (43.9-fold increase) for polysorbate-80 and sodium lauryl sulfate, respectively. The effect of sodium lauryl sulfate at this concentration is probably a pH effect (pH 10.08) on valsartan, a weak acid, resulting in a significant contribution to the total aqueous solubility by ionized species of valsartan in the micelle. Ionized forms of drugs though more polar than its unionized counterpart have been reported to significantly contribute to the total drug solubility (Li et al. 1999).

The incorporation of propylene glycol into 2% w/v polysorbate-80 resulted in a decrease in the solubilization power of the surfactant solution. For example, at concentration levels of 20% w/v and 30% w/v of propylene glycol, the aqueous solubility of valsartan was observed to be 1837.1 mg/100 ml and 1716.5 mg/100 ml, respectively. The study has envisaged a synergistic effect of propylene glycol and polysorbate-80 on valsartan solubility. However the result agrees with those of an earlier study that reported a decrease in aqueous solubility of ibuprofen following the addition of propylene glycol or ethanol to cyclodextrin aqueous solution of ibuprofen (Loftsson et al. 1993). The decrease in solubility could be explained by assuming that the small-sized nonpolar hydrocarbon portions of propylene glycol had more affinity for the interiors of micelles of the surfactant (which are much less polar than water) than the bulky nonpolar portions of valsartan. The relationship between the total valsartan solubility (S_{tot}) in a micellar solution and surfactant concentration can be described by the equation:

$$S_{tot} = S_w + kS_wC \quad \text{(Zhao et al. 1999)}$$

where S_w is drug solubility in water, C is the concentration of micellar surfactant (i.e. the total surfactant concentration minus the critical micellar concentration) and k is the micellar partition coefficient. When the critical micelle concentration (cmc) is small, C can be approximated to the total surfactant concentration. The free energy change for the different systems was calculated from the thermodynamic relationship (Feldman and Gibaldi 1967): $\Delta G = -2.303\ RT \log S_x/S_w$, where S_x and S_w are molar solubilities of valsartan in cosolvent system or surfactant solution and water respectively. The negative values of the free energy change are indicative of the spontaneity of the process.

The study indicates that the aqueous solubility of valsartan has been enhanced by polyethylene glycol 400 while glycerol showed little or no effect on the solubility. It also shows that the surfactants studied exhibited a significant increase in the drug solubility at a concentration level of 2% w/v, sufficiently enough to provide the potential of valsartan formulation into pharmaceutical liquid dosage form. Valsartan is a good candidate for such a formulation because of its stability in aqueous solution. It is also very stable in acidic or basic solution. With toxicity potentials of surfactant in consideration, polysorbate-80 is considered the surfactant of choice because a previous report has shown that it is non-toxic and has been used to a significant extent in parenteral formulations: 0.01–10%, e.g. 10% amiodarone injection (Powell et al. 1998) and other pharmaceutical liquid dosage forms in clinical use. No synergistic effect but rather a decrease in valsartan solubility was observed following the incorporation of propylene glycol into a 2% w/v polysorbate −80 solution. This observation is of interest because propylene glycol is often used as cosolvent in oral liquid preparations.

Finally, the study suggests that valsartan can be formulated into a pharmaceutical liquid dosage form containing 2% w/v of polysorbate-80 as a solubilizer.

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, LC Organizer injector, Kratos spectroflow 783 detector and 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

The stock solution of valsartan (100.0 μg/ml) and internal standard (400 μg/ml) were prepared in methanol. Aliquots (10.0–50.0 μg/ml) of the standard stock solution were pipetted into a 10 ml volumetric flask. A 1 ml aliquot of the internal standard (benzoic acid) was added to each flask and diluted to volume with methanol.

3.5. Solubility determination

It was determined by placing an excess of valsartan (100–500 mg) in 15 ml of water, cosolvent and surfactant solutions. The solutions were shaken or magnetically stirred at 25 °C for 24 h. After equilibration the supernatant was filtered and injected into the chromatograph after the addition of the internal standard. The valsartan concentration was calculated from the calibration graph.

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