The Effect of Cosolvents and Surfactants on the Aqueous Solubility of Irbesartan

Mbah, C. J. and Eneasato, C. M.
Department of Pharmaceutical Chemistry, University of Nigeria, Nsukka, Enugu State, Nigeria.

Corresponding author: Mbah, C. J. Department of Pharmaceutical Chemistry, University of Nigeria, Nsukka, Enugu State, Nigeria.

Abstract

It was considered an interest to enhance the aqueous solubility of irbesartan. To accomplish this objective, the solubilization of irbesartan by cosolvency and micellization was investigated. It was found that all the cosolvents (ethanol, glycerol, propylene glycol) and surfactants (sodium lauryl sulfate, polysorbate-80) increased the solubility of irbesartan. Sodium lauryl sulfate was observed to be the most effective of the solubilizing agents used. The increase in aqueous solubility of irbesartan at the maximum concentration studied was in the following order: sodium lauryl sulfate > polysorbate-80 > ethanol > propylene glycol > glycerol.

Keywords: Cosolvents, Surfactants, Aqueous solubility, Irbesartan

Introduction

Irbesartan, 2-n –butyl-4-spirocyclopentane-1-[{(2'-tetrazol-5-yl)biphenyl-4-yl}methyl]-2-imidazol-5-one is a potent, long-acting nonpeptide A II receptor antagonist with a high specificity for the angiotensin type 1 subtype (Waber 2001; Gillis 1997).

Clinically, it is administered as tablets for the treatment of hypertension. Its mechanism of action offers irbesartan advantages in safety and tolerability over prior classes of drugs in the treatment of hypertension, diabetic neuropathy and heart failure (Cazaubon *et al.,*. 1993). Several reports have appeared in literature concerning the effects of cosolvents and surfactants 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. Other reports (Mbah 2006; Alkhamis *et al*. 2003; Li and Zhao, 2003; Alvarez-Nunez and Yalkowsky, 1998) have employed cosolvency and micellization to increase aqueous solubility of poor soluble drugs. These techniques of increasing the solubilities of drugs with low aqueous solubilities have allowed their formulation into pharmaceutical liquid and parenteral dosage forms (Khalil *et al*. 2000; Powell *et al*. 1998). Irbesartan presently has a solid dosage form (tablets) as the only pharmaceutical formulation. Nevertheless, the potential of formulating it into other dosage forms exists if sufficient aqueous solubility could be achieved through cosolvency, micellization or a combination of both techniques. In this context, the study examines the effect of ethanol, glycerol, propylene glycol, polysorbate-80 (tween 80) and sodium lauryl sulfate on the solubility of irbesartan.

Materials and Methods

Materials and apparatus: Irbesartan (Bristol-Meyers Squibb, USA) and all other reagents and solvents were of analytical grade (BDH). Ultraviolet/Visible spectrophotometer (UV 2102 PC Unico) was used to measure the absorbance readings.

Standard solution: The stock solution of irbesartan (20 µg/ml) was prepared in methanol. Aliquots (2-10 µg/ml) of the standard stock solution were pipetted into 10 ml volumetric flask and diluted to volume with methanol with which a standard Beer's plot was obtained.

Solubility determination: The solubility was determined by placing excess of irbesartan (200 mg) in flasks containing 10 ml of water, cosolvent and surfactant solutions respectively. The flasks were stoppered and shaken at 25 ^{o} C for 24 h. After equilibration, the supernatant was filtered and the absorbance taken after dilution at a maximum wavelength of 230 nm. The irbesartan concentration was calculated from the pre-constructed calibration curve.

Results and Discussion

The influence of ethanol, glycerol and propylene glycol on the solubility of irbesartan is shown in Fig. 1. The graph indicates that the solvents increased the aqueous solubility of irbesartan and that this effect increases as the concentration of the cosolvent is increased. Considering a concentration level of 25 % v/v for instance, solubility of irbesartan was 66.0 µg/ml (1.2-fold increase) for ethyl alcohol compared to 60.6 µg/ml (1.1-fold increase) and 59.0 µg/ml (1.1-fold increase) for propylene glycol and glycerol respectively. The observed solubilization of irbesartan 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 irbesartan molecules. Furthermore, a decrease in the dielectric constant of the mixture could also explain the slight increase in irbesartan solubility by the added cosolvents. The relationship between total irbesartan solubility (S_{tot}) in cosolvent system and the cosolvent concentration can be described by eq 1: $\log S_{tot} = \log S_w + \delta C$ – eq.1, where S_w is the drug solubility

Table 1: Effect of cosolvents on the aqueous solubility of irbesartan

Cosolvent conc. (%v/v)	Solubility (µg/ml)			ΔG (J/mol) (25 ° C)		
	Ethanol	Glycerol	Propylene glycol	Ethanol	Glycerol	Propylene glycol
0.0	55.26	55.26	55.26			
10	59.05	56.66	57.20	-162.5	-62.2	-85.8
15	61.50	57.37	58.40	-265.5	-93.2	-137.1
20	63.53	58.24	59.63	-345.6	-130.3	-189.1
25	65.96	59.03	60.57	-438.9	-163.9	-227.8

Table 2: Effect of surfactant solutions on the aqueous solubility of irbesartan

Surfactant conc.	Polysorbate-80		Sodium lauryl sulfate	
(% w/v)	Solubility (µg/ml)	ΔG (J/mol) (25 ° C)	Solubility (µg/ml)	ΔG (J/mol) (25 ° C)
0.00	55.26		55.26	
0.20	66.08	-443.4	169.33	-2775.3
0.40	75.18	-763.1	251.15	-3752.1
1.0	108.76	- 1678.1	501.45	-5465.6
2.0	179.02	-2913.2	1077.25	-7360.5

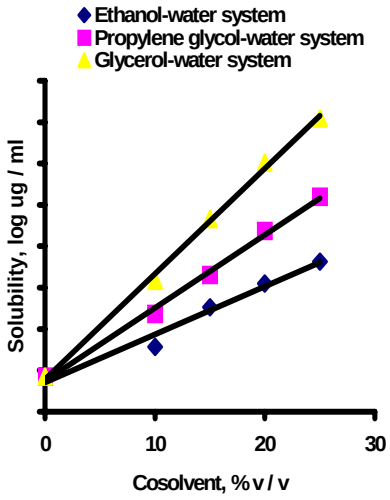

Fig. 1 : Plot of log aqueous solubility (µg/ml) of irbesartan versus concentration of the cosolvent.

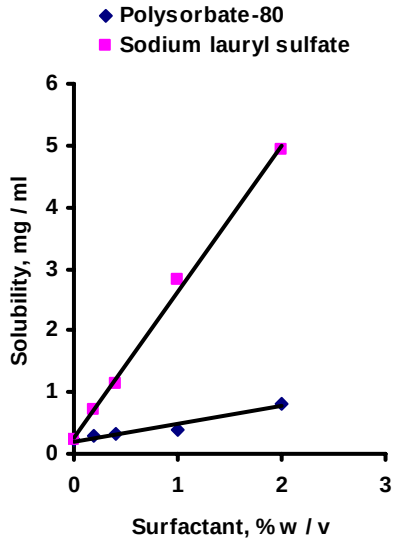

Fig. 2: Plot of aqueous solubility (µg/ml) of irbesartan versus concentration of surfactant.

in water, C is the concentration of the cosolvent and ð is the solubilizing factor. For a given cosolvent system, the solubilizing power gave a quantitative estimate of the ability of the stronger solvent to increase the solubility of irbesartan in the system. The free energy change (ΔG) for different system was calculated from the thermodynamic relationship (Feldman and Gibaldi, 1967), $\Delta G = -2.303\ RT \log S_c / S_w$ - eq. 2, where S_c / S_w is the ratio of molar solubility of irbesartan in cosolvent to that of water. The spontaneity of the process is indicated by the negative values of the free energy change obtained for different systems. The results are summarized in Table 1. The effect of surfactants on the solubility of irbesartan is given in Table 2. The results indicate that irbesartan solubility increased with increasing concentration of the surfactants. It was observed that sodium lauryl sulfate exhibited greater enhancing effect on irbesartan solubility than polysorbate-80. For instance, at a concentration level of 2 % w/v, the solubility of irbesartan was 1077.2 µg/ml (19.5-fold increase) for sodium layryl sulfate and 179.0 µg/ml (3.2-fold increase) for polysorbate-80. The effect of sodium lauryl sulfate on irbesartan solubility is probably a combination of surfactant and pH effects. The pH effect results from ionized species of irbesartan (a weak acid) in the micelle significantly contributing to the total aqueous solubility. Ionized forms of drugs though more polar than their unionized counterpart have been reported to significantly contribute to the total drug solubility (Li *et al.,* 1999). A plot of total solubility of irbesartan versus surfactant concentration is shown in Fig. 2. The graph shows a linear relationship between the drug aqueous solubility and the surfactant concentration for both surfactants. The relationship between total irbesartan solubility (S_{tot}) in a micellar solution and surfactant concentration is given by eq. 3: $S_{tot} = Sw + kS_wC$ – eq.3 where S_w is the drug solubility in water, k is the micellar partition coefficient and C is the concentration of the surfactant (i.e. total surfactant concentration minus the critical micelle concentration). 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 using equation 2. The negative values obtained for the free energy indicate the spontaneity of the process

Conclusion: The study indicates that cosolvency is not a good method of enhancing the aqueous solubility of irbesartan. Surfactants were found to be better solubilizing agents for irbesartan aqueous solubility than cosolvents. Sodium lauryl sulfate produced very significant increase in the solubility of irbesartan. However, the increase at the maximum concentration studied could not afford sufficient aqueous solubility of the drug to enable potential liquid formulation of the drug. Potential toxicity of the sodium lauryl sulfate limited the investigation at higher concentrations.

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