Study on the Solubilization of Sparfloxacin by Aqueous Cosolvent and Micellar Solutions

Mbah, C. J. and Eneasato, C. M.
Faculty of Pharmaceutical Sciences, University of Nigeria, Nsukka, Enugu State, Nigeria.

Corresponding author: Mbah, C. J. Faculty of Pharmaceutical Sciences, University of Nigeria, Nsukka, Enugu State, Nigeria. **Email:** cjmbah123@yahoo.com

Abstract

The effect of ethanol, glycerol, propylene glycol, polysorbate-80 and sodium lauryl sulfate on the aqueous solubility of sparfloxacin was studied. It was found that all these substances increase the aqueous solubility of the drug. Of the solubilizing agents used, sodium lauryl sulfate was observed to be the most effective. The increase was in the following order: sodium lauryl sulfate > polysorbate-80 > propylene glycol > glycerol.

Introduction

Alteration of solute or solvent is the major approach for increasing aqueous drug solubility. Solvent alteration is the most effective means of producing a thermodynamically stable increase in solubility (Yalkowsky, 1999). Sparfloxacin,5-Amino-1-cyclopropyl-7-(cis-3,5-dimethyl-1-piperazinyl)-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid is a difluoroquinolone antibacterial agent belonging to the third generation quinolones, Clinically, it is very effective in the treatment of streptococci infections. Its mechanism of action involves the inhibition of DNA synthesis by promoting cleavage of bacterial DNA in the DNA-enzyme complexes of DNA gyrase and type iv topoisomerase, resulting in rapid bacterial death (Hooper 1999). The water solubility is very limited. With such low aqueous solubility, the purpose of the study was to investigate how cosolvents and surfactants might enhance the drug's aqueous solubility. Numerous studies (Zhao *et al* 1999; Alkhamis *et al* 2003; Mbah 2006) have reported the effect of cosolvency and micellization on the solubility of slightly soluble drugs. Reports have also shown that these techniques have resulted in the formulation of drugs with limited water solubility into various liquid and parenteral dosage forms (Varia *et al* 1991; Powell *et al* 1998; Khalil *et al* 2000). It is against this background, that the present study explores the enhancement of aqueous solubility of sparfloxacin by ethanol, glycerol, propylene glycol, polysorbate-80 and sodium lauryl sulfate while envisaging the potentials of being formulated into pharmaceutical liquid dosage forms.

Materials and Methods

Materials and apparatus: Sparfloxacin (International PVT Ltd, India), and all other 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 sparfloxacin (20 μg/ml) was prepared in methanol. Aliquots (2- 10 μg/ml) of the standard stock solution were pipetted into a 10 ml volumetric flask and diluted to volume with methanol.

Solubility determination: The solubility was determined by placing excess of sparfloxacin (200 mg) in flasks containing 10 ml of water, cosolvent and surfactant solutions respectively. The flasks were stoppered and shaken at 25 ° C for 24 h. After equilibration, the supernatant was filtered and the absorbance taken after dilution at a maximum wavelength of 305 nm. The sparfloxacin concentration was calculated from the calibration graph.

Results and Discussion

The calibration curve of sparfloxacin was linear in the concentration range of 2 – 10 μg/ml. Absorbance versus concentration relationship is described by regression equation: A = 0.0534C+0.0129 (r =0.9982). The effect of ethanol, glycerol and propylene glycol on the aqueous solubility of sparfloxacin is shown in Fig. 1.

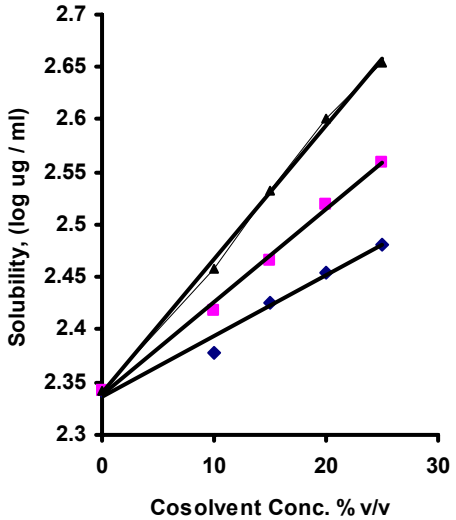

Fig: 1: Plot of log aqueous solubility (μg/ml) of sparfloxacin versus concentration of the cosolvent. The upper graph (▲--▲) is the ethanol-water system; middle graph (□----□) is propylene glycol-water system; lower graph (○----○) is glycerol-water system

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

Cosolvent Conc., %v/v	Solubility (mg/ml)			Δ G (J/mol) (25 ° C)		
	Ethanol	Glycerol	Propylene glycol	Ethanol	Glycerol	Propylene glycol
0.0	0.220	0.220	0.220	-	-	-
10	0.287	0.239	0.262	-659.0	-203.3	-433.1
15	0.341	0.267	0.292	-1083.0	-479.0	-700.8
20	0.399	0.285	0.330	-1475.7	-644.7	-1005.9
25	0.451	0.303	0.363	-1781.5	-801.8	-1238.3

Table 2: Effect of micellar solutions on the aqueous solubility of sparfloxacin

Surfactant Conc. (% w/v)	Polysorbate-80		Sodium lauryl sulfate	
	Solubility (mg/ml)	ΔG (J/mol) (25 ° C)	Solubility (mg/ml)	ΔG(J/mol) (25 ° C)
0.00	0.220	-	0.220	
0.20	0.292	-697.3	0.702	-2877.0
0.40	0.317	-1202.3	1.146	-4090.8
1.0	0.390	-1406.8	2.815	-6316.9
2.0	0.817	-3253.1	4.921	-7701.3

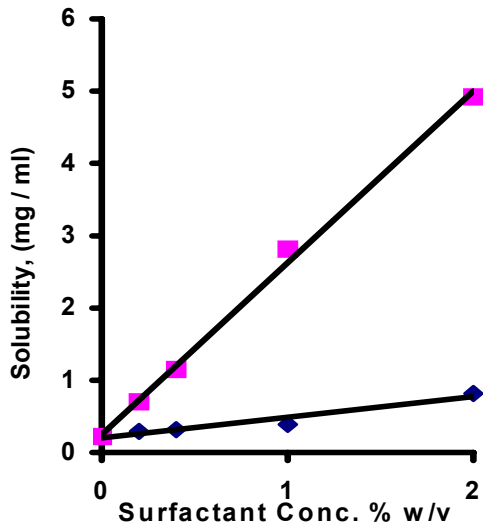

Fig. 2: Plot of aqueous solubility (mg/ml) of sparfloxacin versus concentration of surfactant. The upper graph (□----□) is sodium lauryl sulfate; lower graph (▫-----▫) is polysorbate-80

The graph indicates an exponential increase in sparfloxacin solubility with increasing cosolvent concentration. For instance, at a concentration level of 25 % v/v, solubility of sparfloxacin was 451.4 µg/ml (2-fold increase), 362.6 µg/ml (1.6-fold increase) and 303.9 µg/ml (1.4-fold increase) for ethanol, propylene glycol and glycerol respectively. The difference in solubilizing power of the cosolvents might be due to the disruption of hydrogen bonding interactions in water molecules as well as a decrease in the dielectric constant of the cosolvent system. The dielectric constant was calculated using this equation, $\varepsilon_c = \varepsilon_{ws} f_{ws} + \varepsilon_{ss} f_{ss}$, 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 relationship between the total sparfloxacin solubility (S_{tot}) in cosolvent system and cosolvent concentration can be described by: $\log S_{tot} = \log S_w + \delta C$, where S_w is drug solubility in water, C is the concentration of the cosolvent and δ is the solubilizing power. The free energy change (Δ G) for different system was calculated from the thermodynamic relationship (Feldman and Gibaldi 1967), $\Delta G = -2.303RT \log S_c / S_w$, where S_c / S_w = ratio of the molar solubility of sparfloxacin in cosolvent to that of water. The negative values of the free energy change indicate the spontaneity of the process. The results are presented in Table 1. In Fig. 2, the experimental total solubility is plotted against the surfactant concentration. The graph shows a linear relationship between the drug aqueous solubility and the surfactant concentration for both surfactants. It was also found from the graphs that sodium lauryl sulfate produced a more solubilizing effect than polysorbate-80. For example, considering a concentration level of 2 % w/v, the solubility of sparfloxacin was 4921.3 µg/ml (22.4-fold increase) for sodium lauryl sulfite compared to 817.4 µg/ml polysorbate-80 (3.7 fold increase). In addition to its surfactant properties, the effect of sodium lauryl sulfate on sparfloxacin solubility could probably be a pH effect resulting in sufficient increase in the drug's total aqueous solubility by ionized species of sparfloxacin in the micelle. The relationship between the total sparfloxacin solubility (S_{tot}) in a micellar solution (Table 2) and surfactant concentration is given by : $S_{tot} = S_w + kS_w C$, where S_w is the drug solubility in water, C is the concentration of surfactant (i.e. total surfactant concentration minus the critical micelle 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 as previously described. Once again, the negative values of the free energy show the spontaneity of the process.

Conclusion: The study shows that the aqueous solubility of sparfloxacin has been slightly enhanced by the cosolvent systems investigated. It was also found that the surfactants were better solubilizing agents than the cosolvents. Sodium lauryl sulfate produced very significant enhancement of sparfloxacin aqueous solubility than polysorbate-80. Finally, the study suggests that (i) cosolvency is not a good method for modifying aqueous solubility of sparfloxacin, (ii) although micellar solution of sodium lauryl sulfate at 2 % w/v produced very significant increase in aqueous solubility of sparfloxacin, its enhancement is not sufficient enough to solubilize the minimum therapeutic dosage strength of the drug necessary for it to be formulated into any liquid dosage form, (iii) toxicity effect might limit the use of higher concentrations of sodium lauryl sulfate in an attempt to obtain the aqueous solubility that could solubilize the minimum therapeutic dosage strength.

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