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Effect of surfactants on the solubility and intrinsic dissolution rate of sparfloxacin

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The effect of surfactants on the solubility and intrinsic dissolution rate of sparfloxacin was investigated at room temperature. The surfactants used in the study were anionic sodium lauryl sulfate (SLS) and nonionic polysorbate 80 (Tween 80). Sodium lauryl sulfate showed very significant increase in solubility Tween 80 at the highest concentration studied. The intrinsic dissolution rates were determined compared to at the same surfactant concentrations used in the solubility study by rotating disk method. Diffusion coefficient (D) of sparfloxacin was evaluated to be 7.19×10^{-6} cm^2s^{-1} and the apparent mean diffusion coefficient for sparfloxacin-loaded micelle was estimated to 3.98×10^{-6} and 2.21×10^{-6} cm^2s^{-1} in Tween 80 and SLS respectively.

1. Introduction

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 used 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). Sparfloxacin is water-insoluble. The use of surfactants to improve the solubility of sparingly-soluble or water-insoluble drugs has been reported (Zhao et al. 1999; Alkhamis et al. 2003; Li and Zhao 2003). Intrinsic dissolution rate is the rate of dissolution of a pure pharmaceutical active substance under constant temperature, pH, agitation, surface area and ionic strength of the dissolution medium. It is a parameter that allows the screening of drugs and helps in understanding their solution behaviour under various biophysiological conditions. Various studies have reported the influence of surfactants on dissolution of pharmaceutical active ingredients (Crison et al. 1997; Chowdary and Manjula 2000; Jinno and Oh 2000; Balakrishnan et al. 2004; Park and Choi 2006). Surfactants are employed in dissolution studies because natural surfactants in the body aid in the dissolution and subsequent absorption of drugs with limited aqueous solubility. Due to this physiological relevance, their use in dissolution rate determinations over other mechanisms such as cosolvency, increasing the volume of dissolution medium or increasing the rate of agitation is increasing.

However, little or no information is available on the influence of surfactants on the intrinsic dissolution rate of sparfloxacin. This study therefore investigated the effect of micellization on the aqueous solubility and intrinsic dissolution rate of sparfloxacin.

2. Investigations, results and discussion

The influence of surfactants on the solubility of sparfloxacin is illustrated in Fig. 1, in which the experimental total solubility is plotted against the concentration of surfactant. A linear relationship between aqueous solubility and surfactant concentration was observed with each of the solubilization curves. It was also observed from the graph that sodium lauryl sulfate gave a better solubilizing effect than Tween 80. For instance, at the maximum concentration studied (1.5% w/v), the solubility of sparfloxacin was 3.81 mg/ml (17-fold increase) for SLS compared to 0.630 mg/ml found in the case of Tween 80 (3-fold increase). The results are presented in Table. In Figs. 2 and 3, the effect of surfactants on the intrinsic dissolution rate of sparfloxacin is shown, in which the cumulative amount of sparfloxacin dissolved per unit area is plotted against time. The linear curves that resulted have correlation coefficients higher than 0.990 in each case. The cumulative amount of drug that dissolved (Q_t) was calculated from Eq. (1) (Aronson 1993):

$$Q_t = V_m C_t + \sum_{i=0}^{t-1} V_s C_i \qquad (1)$$

where C_t is sparfloxacin concentration in the dissolution medium at each sampling time, C_i is the drug concentration of the i^{th} sample, and V_m and V_s are the volumes of the dissolution medium and the sample respectively. The intrinsic dissolution rate study results are summarized in the Table. The results show that dissolution into surfactant solutions was enhanced, but only about one-third and one and a third as much as solubility enhancement for SLS and Tween 80, respectively. For example, at a concentration level of 1.5%w/v (maximum concentration studied), a 5-fold increase in dissolution was observed with SLS while Tween 80 produced a 4-fold increase. In accordance with Noyes-Whitney relationship, under sink conditions and with

Table: Solubility and intrinsic dissolution rate of sparfloxacin in surfactant solutions at 25 °C

Percent surfactant	Polysorbate 80		Sodium lauryl sulfate	
	Solubility (mg/ml)[x]	Intrinsic dissolution rate (mg/cm^2/min)[x]	Solubility (mg/ml)[x] rate	Intrinsic dissolution (mg/cm^2/min)[x]
0.0	0.2200 ± 0.0094	0.2411 ± 0.0063	0.2200 ± 0.0094	0.2411 ± 0.0063
0.1	0.2305 ± 0.0064	0.2973 ± 0.0027	0.4870 ± 0.0074	0.4606 ± 0.0059
0.2	0.2915 ± 0.0063	0.3925 ± 0.0060	0.7024 ± 0.0086	0.5615 ± 0.0058
0.4	0.3174 ± 0.0076	0.4150 ± 0.0047	1.146 ± 0.0615	0.6181 ± 0.0015
1.0	0.3898 ± 0.0081	0.5322 ± 9.0066	2.815 ± 0.0669	0.7774 ± 0.0088
1.5	0.6295 ± 0.0050	0.8518 ± 0.0076	3.814 ± 0.0598	1.201 ± 0.0049

X: mean ± SD (n = 3)

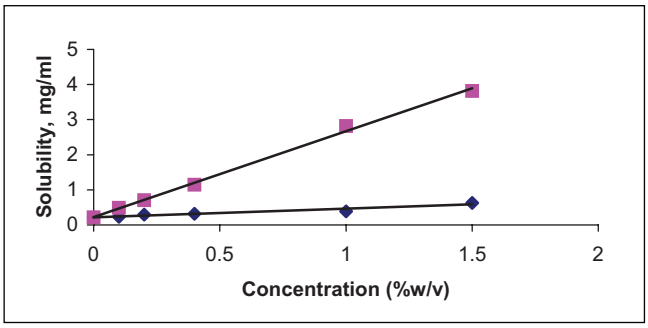

Fig. 1: Plot of aqueous solubility of sparfloxacin versus surfactant concentration. Key: (■) Sodium lauryl sulfate; (■) Tween 80

constant surface area, dissolution rate of sparfloxacin (d.r) may be described by Eq. 2:

$$d.r = KC_s \quad (2)$$

where K is a constant and C_s is the saturated solubility of sparfloxacin. In aqueous solution, K = D/h, where D is sparfloxacin diffusion coefficient and h is the effective diffusion layer thickness. If D and h are considered to be invariant when sparfloxacin is dissolved in surfactant solution, then the theoretical dissolution rate ratio can be calculated using Eq. 3:

$$R = \frac{C_{s*}}{C_s} \quad (3)$$

where R is the ratio of dissolution rate in surfactant to that in water, C_{s*} and C_s are sparfloxacin solubility in surfactant solution and its saturated solubility in water respectively. When the plot of theoretical dissolution rate ratios of sparfloxacin against surfactant concentration using Eq. 3 was compared with the plot

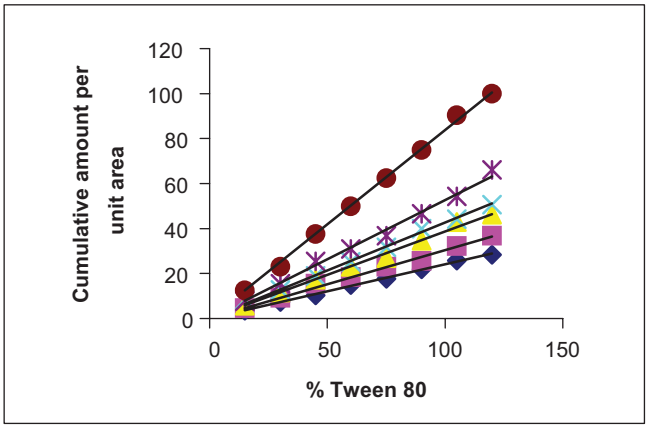

Fig. 2: Plot of cumulative amount of sparfloxacin dissolved per unit area versus tween 80 concentration. Key: (■) Distilled water; (■) 0.1% w/v; (▲) 0.2% w/v; (×) 0.4% w/v; (*) 1.0% w/v; (●) 1.5% w/v

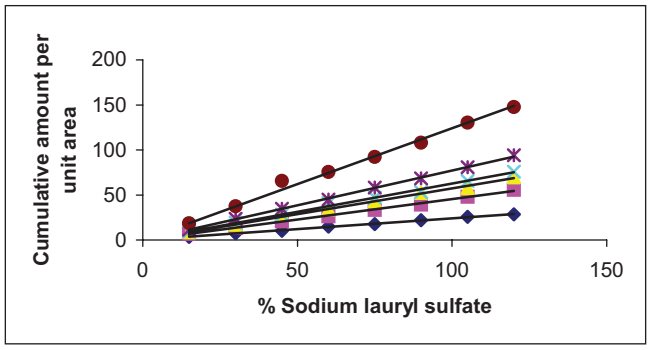

Fig. 3: Plot of cumulative amount of sparfloxacin dissolved per unit area versus sodium lauryl sulfate concentration. Key: (■) Distilled water; (■) 0.1% w/v; (▲) 0.2% w/v; (×) 0.4% w/v; (*) 1.0% w/v; (●) 1.5% w/v

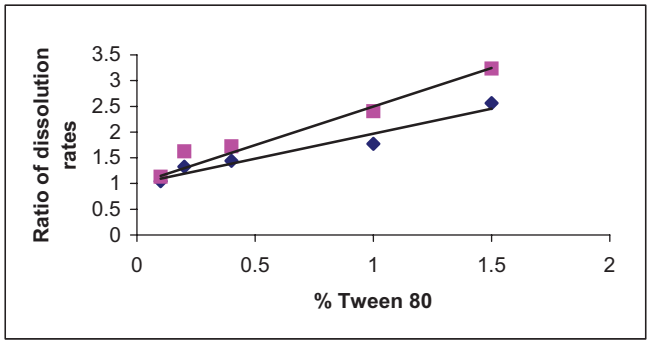

Fig. 4: Plot of dissolution rate ratio versus concentration of tween 80. Key: (■) Theoretical dissolution rate ratio); (■) Experimental dissolution rate ratio

obtained by plotting experimental dissolution rate ratios versus surfactant concentration, the curves (Figs. 4 and 5) indicate that Noyes-Whitney equation failed to predict dissolution behaviour of sparfloxacin in surfactant solution. The predicted curve did not fit the experimental data curve. Using the integrated form of

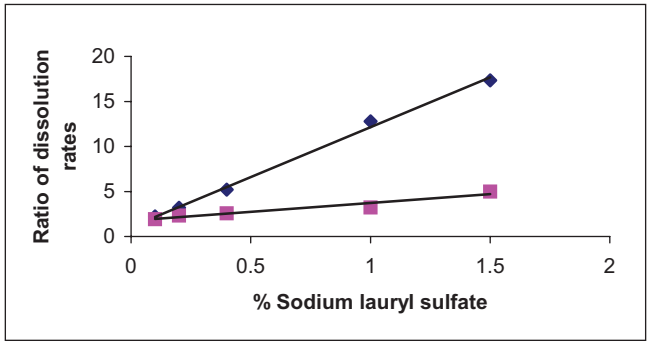

Fig. 5: Plot of dissolution rate ratio versus concentration sodium lauryl sulfate. Key: (■) Theoretical dissolution rate ratio; (■) Experimental dissolution rate ratio

Nernst equation (Eq. 4):

$$\log(C_s - C_t) = \frac{-AD \times t}{2.303Vh} + \log C_s \quad (4)$$

where, A is area of the dissolving surface of the solid, D is diffusion coefficient of solute in the solvent, V is volume of the solvent, h is thickness of Nernst diffusion layer, C_s is concentration of the saturated solution at that temperature, C_t is concentration of the solution at any time t, the slope of this straight line equation will be evaluated. Equating the slope obtained by plotting log (C_s – C_t) versus t, the values of D/h could be calculated. The diffusion coefficient (D) of sparfloxacin was calculated using Eq. (5) (Coulson and Richardson 1959):

$$D = \frac{7.7 \times 10^{-10} T}{(V^{1/3} - V_o^{1/3})\mu,} \quad (5)$$

where, D is diffusion coefficient in cm^2/s, T is temperature in degrees absolute, V is molar volume of solvent (8.0 for diffusion in water, Coulson and Richardson 1959), V_o is molar volume of solute as obtained from KOPPS Table of atomic volumes (Coulson and Richardson 1959), μ is viscosity in poises (absolute viscosity of water 25 ° C was taken as 0.85 centipoise, Perry and Chilton 1973). From the known values of the slope and the diffusion coefficient, the value of the thickness of the diffusion zone could be calculated. Also using the experimental R values, the appropriate solubilization data and D value (7.19×10^{-6} cm^2/s) of sparfloxacin, the apparent mean diffusion coefficient (D*) of 3.98×10^{-6} and 2.21×10^{-6} cm^2/s for sparfloxacin-loaded micelle of Tween 80 and SLS respectively, was estimated. The D* value was estimated using Eq. (6) (Higuichi 1964):

$$R = \frac{DC_s + D * C_{s*}}{DC_s} \quad (6)$$

where D* is diffusion coefficient of micelle-solubilized sparfloxacin, C_{s*} is solubility increase due to solubilization and C_s is saturated aqueous solubility of sparfloxacin.

In conclusion, the aqueous solubility of sparfloxacin was enhanced in surfactant solutions. Sodium lauryl sulfate produced greater aqueous solubility enhancement of sparfloxacin than Tween 80. The dissolution rate enhancement was greater in SLS solution than Tween 80 solution. The dissolution rate enhancement could be limited by the entrapment of sparfloxacin molecules in the micelles, which decreases the kinetic displacement of the molecules resulting in a decrease of the effective diffusion rate of the drug molecules. This phenomenon was found to be more applicable to SLS than Tween 80.

3. Experimental

3.1. 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.

3.2. Standard solution

Stock solution of sparfloxacin (20 (g/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.

3.3. Solubility measurement

The solubility study was carried out as previously reported (Mbah and Eneasato 2010). Excess of sparfloxacin (200 mg) was placed in flasks containing 10 ml of water 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.

3.4. Dissolution rate measurement

The Wood apparatus was used in the determination (Carstensen 1976). Sparfloxacin (300 mg) was placed in the 0.8 cm diameter die cavity. The punch was inserted into the cavity and compressed with the aid of a benchtop press for 4-5 min at 20 kg/cm^{-2}. The exposed smooth compact pellet (after the disconnection of the base plate from the die) and die were connected to the rest of the apparatus. The shaft of the apparatus was attached to a retort stand using a clamp. The die was then lowered into the dissolution vessel containing 500 ml of dissolution medium at 25 °C. The medium was magnetically stirred and at appropriate intervals, an aliquot was removed and replaced with equal volume of fresh dissolution medium. Analysis of the sample withdrawn was done spectrophotometrically at 305 nm. Intrinsic dissolution rates in $mg/cm^2/min$ were calculated from the slopes of cumulative amount dissolved per surface area against time. The results are shown in the Table.

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