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Dissolution and Solubility Behavior of Fenofibrate in Sodium Lauryl Sulfate Solutions

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ABSTRACT The solubility of fenofibrate in pH 6.8 McIlvaine buffers containing varying concentrations of sodium lauryl sulfate was determined. The dissolution behavior of fenofibrate was also examined in the same solutions with rotating disk experiments. It was observed that the enhancement in intrinsic dissolution rate was approximately 500-fold and the enhancement in solubility was approximately 2000-fold in a pH 6.8 buffer containing 2% (w/v) sodium lauryl sulfate compared to that in buffer alone. The micellar solubilization equilibrium coefficient (k^*) was estimated from the solubility data and found to be 30884±213 L/mol. The diffusivity for the free solute, 7.15×10^{-6} cm^2/s, was calculated using Schroeder's additive molal volume estimates and Hayduk-Laurie correlation. The diffusivity of the drug-loaded micelle, estimated from the experimental solubility and dissolution data and the calculated value for free solute diffusivity, was 0.86×10^{-6} cm^2/s. Thus, the much lower enhancement in dissolution of fenofibrate compared to its enhancement in solubility in surfactant solutions appears to be consistent with the contribution to the total transport due to enhanced micellar solubilization as well as a large decrease (~8-fold) in the diffusivity of the drug-loaded micelle.

KEYWORDS Fenofibrate, Intrinsic dissolution rate, Micellar solubilization, Sodium lauryl sulfate

INTRODUCTION

Fenofibrate (isopropyl ester of 2-[4-(4-chloro-benzoyl) phenoxy]-2-methyl-propanoic acid) is a widely used hypolipidemic drug. Its pharmacological activity consists in reducing triglyceride and cholesterol concentration in plasma (Adkins & Faulds, 1997; Balfour et al., 1990; Genest et al., 2000; Guay, 1999; Kosoglou et al., 2004; Packard, 1998).

Solubility and permeability are the fundamental parameters controlling the rate and extent of drug absorption. Amidon and co-workers devised a Biopharmaceutics Classification System (BCS) that categorized drugs into four classes according to their solubility and permeability properties (Amidon et al.,

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1995). The objective of the BCS is to predict in vivo pharmacokinetic performance of drug products from measurements of permeability and solubility. Correlations or non-correlations with the in vivo process may be explained by evaluation of these parameters of a drug product (Wu & Benet, 2005). According to the BCS, fenofibrate is a Class II, low solubility, and high permeability drug.

It is well known that dissolution of a drug in vivo is affected by the environmental changes in the gastrointestinal tract such as pH, surfactant, ionic strength, buffer capacity, or viscosity (Dressman et al., 1998). A prerequisite for drug absorption and clinical success for all drugs given orally in a solid dosage form is its dissolution within the gastrointestinal tract, which in many cases can be the rate-limiting step in the in vivo overall absorption process (Remon et al., 1983).

It is generally accepted that the dissolution media are not completely representative of gastrointestinal (GI) conditions (Horter & Dressman, 1997), yet it is proposed in guidelines that a good method will employ a dissolution media that is physiologically meaningful or closely mimics in vivo conditions (Skelly et al., 1993).

The in vivo dissolution rate for many poorly water-soluble drugs is enhanced due to the presence of micelle forming surfactants in the intestinal fluid (del Estal et al., 1993). Aqueous micelle solutions are structurally "simple" and are often used as models for the more complex and metastable biological membranes as their interfaces are structurally similar (He et al., 1989).

The upper intestinal region in the fasted state has bile salt concentrations of ~5 mM (Tangerman et al., 1986). It is proposed that for low solubility neutral compounds, the concentration of solubilizing compounds in bile salts or in meals is the prime determinant of solubility and, hence, dissolution behavior (Galia et al., 1996).

It has been suggested that inclusion of surface active agents in dissolution media is important for poorly soluble compounds because lack of a surface tension lowering agent would result in poorer wetting and in vitro dissolution rates that are not representative of in vivo rates (Galia et al., 1999). The FDA has promoted the use of surfactants in media for conducting dissolution studies of poorly soluble compounds (Noory et al., 1999; Shah et al., 1995).

Wetting is an important factor in the dissolution process, both in vitro and in vivo (Gibaldi & Feldman, 1970; Luner et al., 1996). Veiga and Ahsan (2000) observed that the addition of SLS to the dissolution media enhances the dissolution efficiency of the poorly water-soluble drug, tolbutamide, by acting as a wetting agent (Luner & VanDer Kamp, 2001).

Surfactants often need to be used in the in vivo–in vitro correlations (IVIVC). Lake et al. (1999) found a favorable IVIVC of carbamazepine immediate release tablets with the parameters primary related to the absorption phase when a 1% w/v aqueous solution of SLS was used as the dissolution testing medium (Lake et al., 1999).

A variety of surfactants have been used to adjust the surface tension and solubilizing capacity of dissolution media (Abdou, 1989; Crison et al., 1996). The dissolution rate of poorly water-soluble drugs thus becomes a function of the solubilization of drug molecules into micelles, as well as the diffusivity of the drug-loaded micelles.

In this study, compressed rotating disks of fenofibrate with a constant surface area were used to investigate the effect of sodium lauryl sulfate (SLS) on the intrinsic dissolution rate (J) of this compound, an un-ionizable, water-insoluble drug. Also, the equilibrium solubility (S) of fenofibrate was determined in aqueous phosphate buffer solutions containing different concentrations of SLS.

MATERIALS AND METHODS

Chemicals

Fenofibrate and 99% pure SLS, were purchased from Sigma Chemical Company (St. Louis, MO, USA). Distilled, filtered water was used for all dissolution experiments.

Dissolution Experiments

The rotating disk method was used to determine the J of fenofibrate. Fenofibrate powder (200 mg) was compressed in a rotating disk die into non-disintegrating disks at 1000-pound pressure for 3 min in a hydraulic laboratory press (Fred S. Carver, Inc., Summit, NJ). The rotating disk die was constructed of stainless steel with a tablet radius of 0.55 cm. The stainless steel die was then screwed onto a Plexiglas shaft connected to an overhead synchronous motor (Cole-Palmer Scientific, Niles, IL). The dissolution experiments were

carried out in a water-jacketed beaker maintained at 37±1.0°C with a circulating water bath. The dissolution media consisted of McIlvaine buffer at pH value of 6.75, prepared by mixing appropriate quantities of 0.1 M citric acid and 0.2 M disodium hydrogen phosphate, and contained SLS as a pharmaceutical surfactant at concentrations of 0, 0.05, 0.5, 1.0, and 2.0% (w/v). All dissolution media were degassed prior to use and 200 mL of each medium was placed in the jacketed beaker. It was assumed that sink conditions were maintained throughout the entire experiment because of the low concentrations (less than 10% of the saturation solubility) measured in the dissolution cell. The dissolution medium was continuously circulated through ultraviolet (UV) spectrophotometer flow cells at 8 mL/min using a peristaltic pump (Masterflex, Cole-Palmer Instrument Co., Chicago, IL). The absorbance was recorded at predetermined intervals at 290 nm (Perkin-Elmer Lambda 3B UV/VIS Spectrophotometer, Oak Brook, IL). The rotating disk-dissolution experiments were conducted at 50, 100, and 200 rpm in triplicate. The intrinsic dissolution rates were estimated with the slope of the regression line ($0.9868 \leq r \geq 0.9996$) of the plot dissolved amount of fenofibrate (mg/cm^2), as a function of time (min), multiplied by the volume of the medium (200 ml), divided by the surface area of the compact disk (0.950 cm^2), using linear regression assuming zero intercept. Values of 0.007 cm^2/s and 0.0076 cm^2/s were used for the kinematics viscosity for aqueous phosphates buffer solution and all surfactant concentrations studied, respectively (Lee et al., 2005).

Solubility Determinations

The solubility of fenofibrate in different concentrations of surfactant was determined by placing excess of fenofibrate (the aqueous solubility of fenofibrate was determined using powder obtained after grinding and then sonicading the suspension for 1 h) in 20 mL scintillation amber vials containing solution, and gently agitating on an orbital shaker-water bath (LABLINE Instruments INC., Melrose Park, IL). After 72 h, so that the equilibrium could be achieved, the contents were filtered through a 0.45 μm filter (Acrodisc® 13 GHP, Gelman Laboratory, Ann Arbor, MI) and assayed. Fenofibrate concentrations in solutions with SLS concentrations highest to 0.5% w/v were measured at 290 nm with a Perkin Elmer-Lambda 3B UV/VIS spectrophotometer. Fenofibrate concentrations in aqueous or 0.05% w/v SLS solutions were assayed using high performance liquid chromatography (HPLC). The concentration of fenofibrate was calculated by reference to predetermined standard curves. All solubilities were measured in triplicate at 37±1°C and reported as the mean±the standard deviation of the mean.

HPLC Analysis

The chromatographic system consisted of a pump (model 501, Waters Associates, Milford, MA) operated at 1 mL/mi, a sample processor (WISP Model 712, Waters Associates, Milford, MA), a variable wavelength UV detector (Spectroflow 783 Absorbance detector, Kratos Analytical Instruments, Ramsy, NJ) set at 290 nm, and connected to an integrator (HP 3396 Series II, HP Company, Avondale, PA). The mobile phase consisted of a mixture of acetonitrile and 0.02 M phosphoric acid solution (70:30, v/v). The analytical column used was a LiChroCART® column (250 × 4 mm I.D.) packed with LiChrospher® 100 RP-18, 5 μm particle size (EM Science, Gibbstown, NJ) preceded by a LiChroCART® guard column (4 × 4 mm) of the same packing material. The retention time of fenofibrate under these conditions was ~5.7 min.

RESULTS AND DISCUSSION

Effect of SLS on Solubility and Dissolution

Figure 1 shows the enhanced solubility (total solubility divided by aqueous phosphate buffer

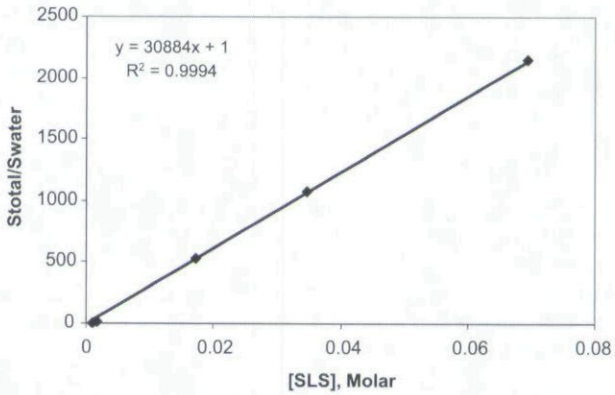

FIGURE 1 Fenofibrate Solubility Enhancement [S_{total} (Total Solubility)/S_{water} (Aqueous Solubility)] as a Function of the Surfactant Concentration.

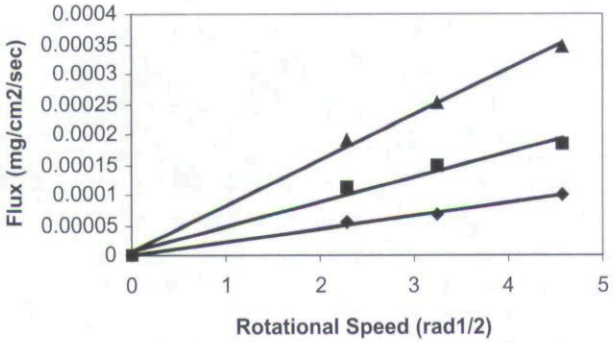

FIGURE 2 Flux of Fenofibrate at Different Concentrations of SLS as a Function of the Square Root of the Rotational Speed of the Disk (◆ 0.5% w/v SLS; ■ 1.0% w/v SLS; ▲ 2.0% w/v SLS).

solubility) of fenofibrate in different concentrations of SLS plotted as function of surfactant concentration.

Enhanced solubility was observed at surfactant concentrations $\geq 0.5\%$ (0.017 M), which is well above the critical micelle concentration (cmc) reported in the literature for pure SLS in water (approximately 0.008 M). In aqueous media, fenofibrate exhibits very poor solubility at 37°C (<0.0002912 mg/ml). A 2% w/v solution of SLS (0.069 M) increased the solubility of fenofibrate more than 2145-fold, indicating that the incorporation of fenofibrate into the micelle was significant.

The equilibrium coefficient, k^*, was determined by fitting the data to the following equation:

$$S_{\text{total}}/S_{\text{water}} = 1 + k * C_{m(b)} \qquad (1)$$

where S is the solubility and $C_{m(b)}$ is the molar concentration of SLS.

The equilibrium coefficient, k^*, was found by linear regression to be 30884±213 L/mol.

The Levich equation (Levich, 1962) describes the intrinsic dissolution or flux of a drug dissolving from a rotating disk for a diffusion-convection controlled dissolution process

$$Js = 0.62Ds^{2/3}\nu^{-1/6}C_s\omega^{1/2} \qquad (2)$$

where Js is the flux, Ds is the diffusion coefficient of the diffusing compound, ν is the kinematics viscosity,

TABLE 1 Diffusivity of Free Solute (D_s) and Effective Diffusivity of Free Solute and Drug-Loaded Micelle (D_{eff}) as Function of SLS Concentration ($\times 10^{-6}$ cm²/sec)

SLS, molar			
0.0	0.0173	0.0347	0.0693
7.15	1.02	0.97	0.83

TABLE 2 Intrinsic Dissolution Rate 200 rpm, Flux and Reaction Factor as a Function of SLS Concentration

SLS, molar	Flux, $J/\omega^{1/2}$ (mg/cm²/s) $\times 10^{-6}$
0	0.0153
0.0173	0.2187
0.0347	0.4290
0.0693	0.7724

ω is the angular velocity of rotation, and C_s is the initial concentration of the diffusing epecies.

For dissolution into surfactant solutions, substituting Ds with the effective diffusion coefficient (D_{eff}), which is a weighted average diffusivity of the free (Ds) and micelle-bound drug (D_{sm}), modifies Eq. 2 to

$$J_{\text{total}} = 0.62D_{\text{eff}}^{2/3}\nu^{-1/6}C_{\text{total}}\omega^{1/2} \qquad (3)$$

where J_{total} is the total flux.

Under conditions of constant diffusivity and area, a plot of the flux determined from the dissolution rate as a function of square root of angular velocity should yield a straight line, as can be seen in Fig. 2.

From the slope of the regression line of the Levich plot ($0.9867 \leq r \geq 0.999$), the effective diffusion coefficients were calculated (Table 1).

On the basis of the observed linear relationship and zero intercept, the dissolution was assumed to be diffusion controlled according to Eq. 2.

The dissolution rate of fenofibrate in aqueous phosphate buffer could not be measured due to its limited aqueous solubility. Therefore, a theoretical value of diffusivity for the free solute of 7.15×10^{-6} cm²/s was calculated from the estimated molal volume (Reid et al., 1977).

The reaction factor, which is taken as the total flux divided by the flux of fenofibrate in aqueous

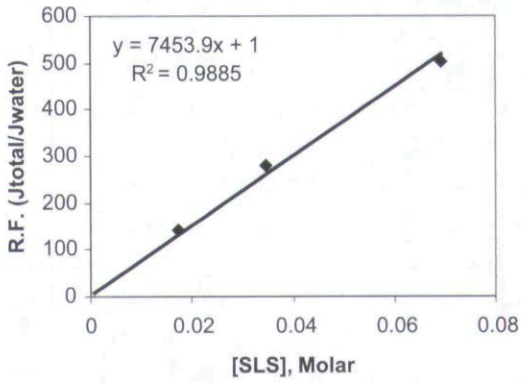

FIGURE 3 Reaction Factor for the Film Equilibrium Model as a Function of Surfactant Concentration.

TABLE 3 Effective and Micellar Diffusion Coefficients of Fenofibrate

Solubility ratio ($S_{2\%\ w/v\ SLS}/S_o$)	Dissolution ratio, 200 rpm ($J_{2\%\ w/v\ SLS}/Js$)	D_s diffusion coefficient in phosphate buffer, $\times 10^{-6}$ cm^2/s	D_{eff} effective diffusion coefficient in 2% w/v SLS, $\times 10^{-6}$ cm^2/s	D_{sm} micellar diffusion coefficient, $\times 10^{-6}$ cm^2/s
2144.712	504.41	7.15	0.83	0.85

phosphate buffer (Table 2), was plotted against the surfactant concentration in Fig. 3. From the slope of this plot, D_{sm} was calculated according to Eq. 4 and was found to be 0.85×10^{-6} cm^2/s.

$$\phi \text{R.F.} = 1 + \left(D_{sm}^{2/3} k * C_{m(b)}\right) \Big/ D^{2/3} \qquad (4)$$

Drug dissolution in micellar solutions is affected by two competing factors. The first factor is the solubilization effect due to the uptake of drug into the micelles, which enhances the solubility. The second factor is that the enhancement in the effective molecular size of the diffusing species reduces its overall apparent diffusivity. The relative values of the increased solubility and decreased diffusivity determine the magnitude of dissolution rate enhancement (Stella et al., 1998).

In the case of fenofibrate, the lack of corresponding increase in dissolution rate relative to its solubility accounts for a decrease in the diffusion coefficient of this drug (Table 3). The diffusion coefficient in micellar solution was almost ~8 times lower than of that of the fenofibrate in aqueous phosphate buffer. This decrease in diffusivity is due to the higher molecular weight of $[\text{Fenofibrate}]_{\text{micelle}}$ compared to that of the free solute (Gibaldi et al., 1970).

CONCLUSIONS

SLS significantly increased the solubility and dissolution rate of fenofibrate. The solubility enhancement in a 2% w/v SLS solution was ~2000 times higher than that of fenofibrate in aqueous phosphate buffer solution and, the enhancement in its intrinsic dissolution rate was ~500-fold. Thus, the much lower enhancement in dissolution of fenofibrate compared to its enhancement in solubility in surfactant solutions appears to be consistent with the contribution to the total transport due to enhanced micellar solubilization, as well as a large decrease (~8-fold) in the diffusivity of the drug-loaded micelle.

The in vivo dissolution rate for many poorly water-soluble drugs is enhanced due to the presence of micelle forming surfactants in the intestinal lumen. The dissolution of solid dosage forms is a complex process and involves multiple steps. Each step may be influenced to some degree by the mixture of surface active agents present in the media (Luner, 2000). Schott et al. suggested that release of drugs from tablets would be most influenced by surfactants through the mechanisms of wetting, micellar solubilization and deflocculation (Schott et al., 1982). Therefore, the dissolution results obtained in this study indicate that the addition of a surfactant agent such as SLS to the dissolution medium could be a suitable way to mimic the in vivo dissolution process to predict the oral absorption of the tested drug through an IVIVC.

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