Dissolution of Ionizable Water-Insoluble Drugs: The Combined Effect of pH and Surfactant

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ABSTRACT: This study reports the results of the combined effect of pH and surfactant on the dissolution of piroxicam (PX), an ionizable water-insoluble drug in physiological pH. The intrinsic dissolution rate (Jtotal) of PX was measured in the pH range from 4.0 to 7.8 with 0%, 0.5%, and 2.0% sodium lauryl sulfate (SLS) using the rotating disk apparatus. Solubility (ctotal) was also measured in the same pH and SLS concentration ranges. A simple additive model including an ionization (PX « H+ + PX−) and two micellar solubilization equilibria (PX + micelle « [PX]micelle, PX− + micelle « [PX−]micelle) were considered in the convective diffusion reaction model. Jtotal and ctotal of PX increased with increasing pH and SLS concentration in an approximately additive manner. Nonlinear regression analysis showed that observed experimental data were well described with the proposed model (r2 = 0.86, P < 0.001 for Jtotal and r2 = 0.98, P < 0.001 for ctotal). The pKa value of 5.63 ± 0.02 estimated from ctotal agreed well with the reported value. The micellar solubilization equilibrium coefficient for the unionized drug was estimated to be 348 ± 77 L/mol, while the value for the ionized drug was nearly equal to zero. The diffusion coefficients of the species PX, PX−, and [PX]micelle were estimated from the experimental results as (0.93 ± 0.35) × 10−5, (1.4 ± 0.30) × 10−5, and (0.59 ± 0.21) × 10−5 cm²/s, respectively. The total flux enhancement is less than the total solubility enhancement due to the smaller diffusion coefficients of the micellar species. This model may be useful in predicting the dissolution of an ionizable water insoluble drug as a function of pH and surfactant and for establishing in vitro–in vivo correlations, IVIVC, for maintaining bioequivalence of drug products. © 2000 Wiley-Liss, Inc. and the American Pharmaceutical Association J Pharm Sci 89: 268–274, 2000

Key words: piroxicam; solubility; dissolution; rotating disk method; pKa; diffusivity

INTRODUCTION

A Biopharmaceutic Classification System (BCS) has been recently proposed for drug product bioequivalence requirements. Solubility and permeability, the key parameters in BCS, play impor-

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The effect of surfactant on the dissolution of a solid. Gibaldi et al.\textsuperscript{4,5} examined the influence of polyoxyethylene (23) lauryl ether on the dissolution of benzoic acid and salicylic acid by the rotating disk and the static disk method. Singh et al.\textsuperscript{6} investigated the influence of micelle–drug solubilization on the dissolution rate for the benzocaine–polysorbate 80 system under different hydrodynamic models. De Smidt et al.\textsuperscript{7–9} reported the effect of sodium lauryl sulfate on the dissolution of griseofulvin, a poorly soluble drug. On the other hand, Mooney et al.\textsuperscript{10,11} investigated the effect of pH on the solubility and dissolution of ionizable drugs based on a film model with total component material balances for reactive species, proposed by Olander.\textsuperscript{12} McNamara and Amidon\textsuperscript{13,14} developed a convective diffusion model that included the effects of ionization at the solid–liquid surface and irreversible reaction of the dissolved species in the hydrodynamic boundary layer. However, there is very little attention paid to the combined effect of pH and micellar solubilization.

The objective of this paper is to investigate the combined effect of pH and surfactant on the intrinsic dissolution rate of an ionizable water insoluble drug. Piroxicam (PX, Figure 1) was chosen as the model drug. The intrinsic dissolution and solubility of PX were measured in buffer solutions at various pH values and different concentrations of sodium lauryl sulfate (SLS) using the rotating disk dissolution method. A major question to be answered by these studies is whether additivity of pH and surfactant solubilization can account for the experimental results.

**THEORETICAL SECTION**

**Micelle Facilitated Dissolution Influenced by pH Model**

Both pH and surfactant often affect the dissolution of an ionizable water insoluble drug. Figure 2 illustrates a proposed model describing equilibria of PX in aqueous solution containing a surfactant.\textsuperscript{2} This scheme includes an ionization equilibrium and two solubilization equilibria. PX\textsuperscript{−}, [PX]\textsubscript{micelle} and [PX\textsuperscript{−}]\textsubscript{micellar} represent ionized drug, unionized drug in micelle, and ionized drug in the micelle, respectively. It is reported that PX can be ionized as a zwitterion which has two \( \text{pK}_\text{a} \) values (\( \text{pK}_\text{a1} = 1.86, \text{pK}_\text{a2} = 5.46 \) measured in DMSO–buffer 1:100).\textsuperscript{15} However, the \( \text{pK}_\text{a1} \) value is relatively low compared with the biological pH range of the small intestine. Therefore, PX was treated as a weak acid not an ampholyte in this paper. The equilibrium constant for the ionization is defined as follows:

\[
K_a = (c_{\text{PX}^-})[H^+]/c_{\text{PX}}
\]  (1)

where \([H^+]\) is hydrogen ion concentration, and \(c_{\text{PX}}\) and \(c_{\text{PX}^-}\) are the concentrations of unionized and ionized drugs, respectively. The following equilibria between free solute and micelle solubilized solute are assumed\textsuperscript{16–19}:

\[
k^* = c_{[\text{PX}]\text{micelle}}/(c_{\text{PX}}(c_m))
\]  (2)

\[
k^{**} = c_{[\text{PX}^-]\text{micellar}}/(c_{\text{PX}^-}(c_m))
\]  (3)

\[
c_m = c_{\text{surfactant}} - \text{cmc}
\]  (4)
where \( k^* \) and \( k^{**} \) are the equilibrium constants for micellar solubilization of unionized and ionized species, \( c_m \) is the concentration of surfactant/micelle which is equal to surfactant concentration \( (c_{\text{surfactant}}) \) minus critical micelle concentration \( (c_{\text{cmc}} = 0.008 \text{ M for SLS}) \). \( c_{[\text{PX}]_{\text{micelle}}} \) and \( c_{[\text{PX}^-]_{\text{micelle}}} \) are the concentrations of unionized and ionized drugs in the micelle, respectively.

**Total Solubility**

The combined effect of pH and surfactant on the solubility of weakly acidic and basic drugs was discussed by Rippie et al. The total solubility \( (c_{\text{total}}) \) of a weak acid in surfactant solution can be expressed as a sum of the solubility values of each species:

\[
c_{\text{total}} = c_{\text{PX}} + c_{\text{PX}^-} + c_{[\text{PX}]_{\text{micelle}}} + c_{[\text{PX}^-]_{\text{micelle}}} \tag{5}
\]

Substituting \( c_{\text{PX}^-} \), \( c_{[\text{PX}]_{\text{micelle}}} \) and \( c_{[\text{PX}^-]_{\text{micelle}}} \) in eq 5 using eqs 1, 2, and 3 gives eq 6:

\[
c_{\text{total}} = \left\{1 + K_a/[\text{H}^+] \right\} + (k^* + k^{**} K_d/[\text{H}^+] c_m) c_{\text{PX}} \tag{6}
\]

**Dissolution**

The general equation describing the mass transport in a fluid is:

\[
\frac{\partial c_i}{\partial t} = D_i \nabla^2 c_i - v \nabla c_i + R_i \tag{7}
\]

where \( D_i \), \( c_i \), and \( R_i \) are the diffusion coefficient, the molar concentration, and the rate of production per volume of species \( i \), \( v \) is the fluid velocity, and \( t \) is time. The terms on the right side of eq 7 represent the diffusive, convective, and reactive contributions to mass transfer, respectively. Assuming the instantaneous irreversible reactions at the solid–liquid surface, mass transfer in the rotating disk system at steady state can be simplified to:

\[
D_i \frac{d^2 c_i}{dz^2} - v \frac{dc_i}{dz} = 0 \tag{8}
\]

where \( v_z \) is the axial velocity of fluid toward the disk. Levich solved the equation to derive the flux of the solute from the rotating disk as:

\[
J = 0.62D_i v^{2/3} \omega^{1/6} c_{i0}^{1/2} \tag{9}
\]

where \( J \) is the flux, \( v \) is the kinematic viscosity, \( D_i \) is the diffusivity, \( c_{i0} \) is the concentration of species \( i \) at the disk surface, and \( \omega \) is the angular velocity of the disk. Equation 9 can be applied to the micelle-facilitated dissolution of an ionizable drug from the rotating disk to give:

\[
J_{\text{total}} = 0.62D_{\text{eff}} v^{2/3} \omega^{1/6} c_{\text{total}}^{1/2} \tag{10}
\]

where \( J_{\text{total}} \) is the total flux of the drug and \( D_{\text{eff}} \) is the effective diffusivity. The total dissolution rate \( (J_{\text{total}}) \) is expressed as:

\[
J_{\text{total}} = J_{\text{PX}} + J_{\text{PX}^-} + J_{[\text{PX}]_{\text{micelle}}} + J_{[\text{PX}^-]_{\text{micelle}}} \tag{11}
\]

The dissolution rates for the each species are as follows:

\[
J_{\text{PX}} = 0.62D_{\text{PX}} v^{2/3} \omega^{1/6} c_{\text{PX}} \tag{12}
\]

\[
J_{\text{PX}^-} = 0.62D_{\text{PX}^-} v^{2/3} \omega^{1/6} c_{\text{PX}^-} \tag{13}
\]

\[
J_{[\text{PX}]_{\text{micelle}}} = 0.62D_{[\text{PX}]_{\text{micelle}}} v^{2/3} \omega^{1/6} c_{[\text{PX}]_{\text{micelle}}} \tag{14}
\]

\[
J_{[\text{PX}^-]_{\text{micelle}}} = 0.62D_{[\text{PX}^-]_{\text{micelle}}} v^{2/3} \omega^{1/6} c_{[\text{PX}^-]_{\text{micelle}}} \tag{15}
\]

Substituting \( J_{\text{PX}}, J_{\text{PX}^-}, J_{[\text{PX}]_{\text{micelle}}}, \text{ and } J_{[\text{PX}^-]_{\text{micelle}}} \) in eq 11 with eqs 12, 13, 14, and 15 gives:

\[
J_{\text{total}} = 0.62v^{2/3} \omega^{1/6} c_{\text{PX}} (D_{\text{PX}}^{2/3} + D_{\text{PX}^-}^{2/3} K_a/\text{[H}^+] + D_{[\text{PX}]_{\text{micelle}}}^{2/3} k^* c_m + D_{[\text{PX}^-]_{\text{micelle}}}^{2/3} k^{**} K_d/[\text{H}^+] c_m) \tag{16}
\]

for the total flux.

The experimental data will be evaluated for agreement with eq 6 for solubility and eq 16 for dissolution.

**EXPERIMENTAL SECTION**

**Materials and Data Analysis**

Piroxicam (PX) and sodium lauryl sulfate (SLS, >99% purity) were purchased from Sigma Chemical Company (St. Louis, MO). Distilled, deionized, and filtered water was used for all experiments. A stainless steel rotating disk with a tablet radius of 0.55 cm was used for dissolution experiments. Model fitting and parameter estimations were performed with nonlinear regression analysis by SigmaPlot (SPSS Inc., Chicago, IL). The regression analysis for the dissolution data was weighted by reciprocal values of square of the standard deviation.
Dissolution Media
McIlvaine buffers were prepared at pH 4.0, 5.0, 6.0, 7.0, and 7.8 by mixing appropriate volumes of 0.1 M citric acid and 0.2 M disodium phosphate solutions. SLS was dissolved with the buffers at the concentration of 0.5, 1.0, and 2.0 w/v%. The media were deaerated by stirring under vacuum prior to use.

Dissolution Experiments
The intrinsic dissolution rates of PX were determined using the rotating disk method. PX powder (200 mg) was compressed to form a circular compact in the rotating disk die at 1,000 lbs for 10 min using a hydraulic press (Fred Carver, Inc., Summit, NJ). The die containing the compact was mounted onto a Plexiglass shaft attached to an overhead synchronous motor (Cole-Parmer Scientific, Niles, IL). The die was rotated at 50, 100, and 200 rpm. The rotational speed was calibrated with a digital tachometer (Cole-Parmer Scientific, Niles, IL). The single face of the compact was exposed to 150 mL of the dissolution medium in a jacketed beaker circulated with water heated at 37 ± 1°C using a water bath circulator (Isotemp Constant Temperature Circulator Model 8000, Fisher Scientific, Pittsburgh, PA). The dissolution media was continuously circulated through a flow cell using a peristaltic pump (Masterflex, Cole-Parmer Scientific, IL) in 8 mL/min. UV absorbance at 254 nm was recorded at 1- or 5-min intervals using a UV spectrophotometer (Perkin-Elmer, Lambda 3B). Dissolved amounts of PX were maintained less than 10% of the solubility over the entire experiments to ensure sink condition.

Solubility Experiments
An excess amount of PX powder (50–200 mg) was shaken in screw-capped vials containing 10 mL of buffers in an orbital shaker water bath (LAB-LINE Instruments, Inc., Melrose Park, IL) at 37°C. At suitable time intervals 0.8-mL samples were collected. The samples were filtered through 0.45 μm membrane filters and diluted with the appropriate amount of buffer. PX concentration in the samples was assayed by the HPLC method described in United States Pharmacopeia XXII.

RESULTS
Solubility–Time Profile
The dissolved amount of PX versus time profile indicates a maximal value of solubility shown in

Table I. Maximal Solubility (mg/mL) of Piroxicam at Different pH and SLS Concentrations

<table>
<thead>
<tr>
<th>pH</th>
<th>SLS Concentration (w/v %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.0</td>
<td>0.0320 0.178 0.265 0.497</td>
</tr>
<tr>
<td>5.0</td>
<td>0.0396 0.188 0.334 0.531</td>
</tr>
<tr>
<td>6.0</td>
<td>0.198 0.359 0.427 0.659</td>
</tr>
<tr>
<td>7.0</td>
<td>1.37 1.45 1.62 1.98</td>
</tr>
<tr>
<td>7.8</td>
<td>4.79 4.59 5.43 5.05</td>
</tr>
</tbody>
</table>
Intrinsic Dissolution Rate

Figure 4 shows typical results of the dissolution experiments. The intrinsic dissolution rates were calculated as a slope of the plot multiplied by the volume of media (150 mL) divided by the surface area of the compact (0.950 cm²) using linear regression assuming zero intercept. The obtained intrinsic dissolution rates are listed in Table II. The data are the average of triplicated values ± the standard deviation while the average of duplicated values were presented for cases in the presence of SLS at pH 7.0 and 7.8. Dissolution at pH 7.8 with 1.0% or 2.0% SLS was not measured due to rapid disintegration of the tablet.

Table II. Intrinsic Dissolution Rate \( (\frac{J}{\omega^{1/2}}; \times 10^4 \, \text{mg/cm}^2/\text{s}^{1/2}/\text{rad}^{1/2}) \) of Piroxicam at Different pH and SLS Concentrations

<table>
<thead>
<tr>
<th>pH</th>
<th>SLS concentration (w/v %)</th>
<th>0</th>
<th>0.5</th>
<th>1.0</th>
<th>2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.0</td>
<td>0.201 ± 0.009</td>
<td>0.892 ± 0.076</td>
<td>1.30 ± 0.15</td>
<td>2.12 ± 0.26</td>
<td></td>
</tr>
<tr>
<td>5.0</td>
<td>0.234 ± 0.019</td>
<td>0.837 ± 0.115</td>
<td>1.29 ± 0.19</td>
<td>2.04 ± 0.25</td>
<td></td>
</tr>
<tr>
<td>6.0</td>
<td>1.01 ± 0.04</td>
<td>1.74 ± 0.29</td>
<td>2.95 ± 0.16</td>
<td>3.09 ± 0.43</td>
<td></td>
</tr>
<tr>
<td>7.0</td>
<td>6.47 ± 0.41</td>
<td>10.8 ± 1.1</td>
<td>12.1 ± 0.3</td>
<td>11.8 ± 0.3</td>
<td></td>
</tr>
<tr>
<td>7.8</td>
<td>19.8 ± 1.3</td>
<td>33.7 ± 6.3</td>
<td>a</td>
<td>a</td>
<td></td>
</tr>
</tbody>
</table>

* Not measured due to disintegration of the disk.

DISCUSSION

Nonlinear Regression Analysis of Solubility

The total solubility increased with increasing pH and SLS concentration, as expected. The measured solubility values were fitted to eq 6 by nonlinear regression analysis. Figure 5 illustrates the fitted surface with the observed values as functions of pH and SLS concentration \( (r^2 = 0.98, \, P < 0.001) \). The \( pK_a \) value and the micellar solubilization equilibrium coefficients \( (k^* \) and \( k^{**} \) ) were estimated to be 5.63±0.02, 348±77 L/mol, and 0.0±1.5 L/mol, respectively. The estimated \( pK_a \) value agrees well with the reported \( pK_a \) value of 5.46 determined in DMSO/water (1:100) by a spectrophotometric method. The low \( k^{**} \) value indicates that the micellar solubilization of ionized drug is negligible.

Nonlinear Regression Analysis of Intrinsic Dissolution Rate

Similar to the solubility, the dissolution rate also increased with increasing pH and SLS concentration. These enhancements in dissolution are well agreed with corresponding solubility enhancement. The dissolution data were fitted to eq 16 with the \( pK_a \) and \( k^* \) fixed at the estimated values from nonlinear regression analysis of the solubility data. The \( k^{**} \) value was assumed to be zero based on the analysis of solubility data. Figure 6 shows the result of the nonlinear regression analysis for the normalized dissolution rate \( (\frac{J}{\omega^{1/2}}) \) as functions of pH and SLS concentration \( (r^2 = 0.86, \, P < 0.02) \). The fitted surface is similar to that of the total solubility. In the pH range lower than its \( pK_a \), a relatively large dissolution enhancement of up to 30-fold, was observed by the addition of SLS. In the pH range higher than its
pKₐ; however, a relatively small enhancement of up to 3-fold was observed. Since the pH in duodenum is around 5 and that in jejunum is 5–6 under fed state, the absorption of piroxicam can be increased by postprandial bile secretion. However, Ishizaki et al. reported that the extent of PX absorption in man was uninfluenced by food intake. This is probably due to potentially good absorption of PX due to its high jejunum permeability ($P_{eff} = (10.40 \pm 5.93) \times 10^{-4}$ cm/s in humans) and relatively low dose number ($D_0 = 11$). The estimated diffusivity values for species PX, PX⁻, and [PX]micelle were $(0.93 \pm 0.35) \times 10^{-5}$, $(1.42 \pm 0.30) \times 10^{-5}$, and $(0.59 \pm 0.21) \times 10^{-5}$ cm²/s, respectively. The diffusivity value of PX agrees well with a theoretical value of $0.86 \times 10^{-5}$ cm²/s calculated from the estimated molal volume. The diffusivity of [PX]micelle was 1.7 time lower than that of PX. This decrease in diffusivity is due to the higher molecular weight of [PX]micelle compared to that of the free solute. However, this ratio is lower than the ratio of 9.0 observed for the carbamazepine–SLS system. Thus for the PX–SLS system the enhancement in the dissolution rate is the result of the increase in total solubility due to the pH change and solubilization. These results suggest that the dissolution process in vivo, while more complicated due to the more complex and time-dependent environment, can be captured in vitro. However, when establishing an in vitro–in vivo correlation for a compound such as piroxicam, care must be taken when selecting the pH of the dissolution media and the hydrodynamics in the dissolution flask. For example, if the solubility of the drug in the dissolution media versus in vivo solubility is under-estimated, then the first derivative of the correlation between the fraction absorbed versus fraction dissolved will decrease with time. On the other hand, if the solubility of the drug in the dissolution media versus in vivo solubility is over-estimated, the first derivative of the correlation between the fraction absorbed versus fraction dissolved will increase with time. Thus, the time course of dissolution rates in vitro and in vivo will in general be different and some curvature in the IVIVC should be expected.

CONCLUSION

The dissolution rate and solubility of PX are well estimated by a simple additive model for the effect of pH and surfactant. The total solubility of PX is a sum of the values for the individual species PX, PX⁻, and [PX]micelle. The proposed model will be useful in predicting the dissolution and the solubility of an ionizable water-insoluble drug as functions of pH and surfactant. It also suggests that in vitro–in vivo correlations will in general show some curvature for BCS Class II drugs.

REFERENCES AND NOTES


