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Effect of pH-Sodium Lauryl Sulfate Combination on Solubilization of PG-300995 (an Anti-HIV Agent): A Technical Note

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INTRODUCTION

Solubilization in surfactant solutions above the critical micelle concentration (CMC) offers one approach to the formulation of poorly soluble drugs in solution form.[1] Weakly acidic and basic drugs may be brought into solution by the solubilizing action of surfactants.[2] In aqueous solutions, micelles consist of surfactant monomers that are oriented such that their nonpolar regions are in maximum contact with each other, and their polar regions are in maximum contact with water. Solutes get incorporated into various regions of the micelles depending upon their polarity.

The solubility of a solute is equal to its aqueous solubility at all surfactant concentrations below its CMC. It increases linearly with surfactant concentrations above the CMC.

The general equation for micellar solubilization is as follows:

$$S_{TOT} = S_W + \kappa C_{MIC}, \quad (1)$$

where S_{TOT} is the total molar solubility of the solute, S_W is the water solubility of the solute, κ is the molar solubilization capacity of the surfactant, and C_{MIC} is the molar concentration of the micellar surfactant (ie, the total surfactant concentration minus the CMC).[3]

In combination with surfactants, pH control can be used to enhance the solubility of ionizable solutes. Li et al[4] showed that the general equation for solubilization of a weak base by pH and a surfactant is as follows:

$$S_{TOT} = S_U + S_U (H^+/K_a) + \kappa_u C_{MIC} + (H^+/K_a) + \kappa_i C_{MIC} \quad (1)$$

where κ_u and κ_i represent the solubilization capacities for the un-ionized and ionized forms of the solute, respectively, and S_U represents the solubility of the un-ionized solute. Often, $\kappa_u >> \kappa_i$, and the only effect of the surfactant is to solubilize the un-ionized solute. For example, in the case of surfactants with the same charge as the solute, κ_i is near zero, and the combined slope κ is nearly identical to the slope for the un-ionized solute κ_u.

However, for a base at a pH value where (H^+/K_a) $\kappa_i >> \kappa_u$, micellar solubilization of the ionized species dominates (Equation 2). Therefore, even though the ionized species is less efficiently solubilized than the neutral species, the former can be solubilized to a greater extent because there is more of it in the nonmicellar phase.[4] In the case of ionic surfactants, oppositely charged solutes can be preferentially solubilized over uncharged or similarly charged solutes. While this is often the case, there can be instances where the oppositely charged solute and surfactant species result in formation of an insoluble salt. Such salt formation results in desolubilization of the solute, a phenomenon not normally observed in a routine surfactant solubility profile. One of the very few observations reported in literature is the insolubility of an estolate salt of erythromycin propionate in acidic media.[5]

In this study, an anionic surfactant sodium lauryl sulfate (SLS, CMC = 8.3 mM)[1] was used in combination with buffers (pH 2.0 and pH 7.0) to increase the solubility of PG-300995 (Figure 1), which has a basic pK_a of ~4.5 and an intrinsic aqueous solubility of 51 μg/mL.

MATERIALS AND METHODS

PG-300995 was provided by Procter and Gamble Co (Cincinnati, OH). SLS was purchased from Sigma Chemical Co (St Louis, MO). Trifloroacetic acid and glycine were purchased from Aldrich Chemical Co (Milwaukee, WI). All other reagents used were high-performance liquid chromatography (HPLC) grade.

Buffers in the pH range 1.0 to 3.0 were prepared with 0.1M glycine and 0.1M HCl. Phosphate buffer at pH 7.0 was pre-

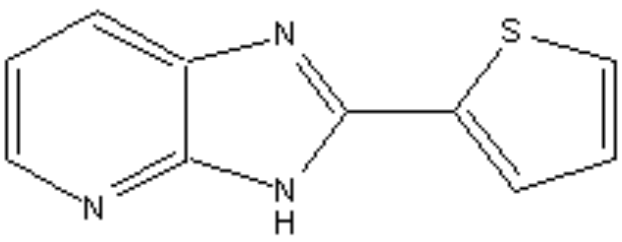

Figure 1. PG-300995 (2-[2-thiophenyl]-4-azabenzimidazole).

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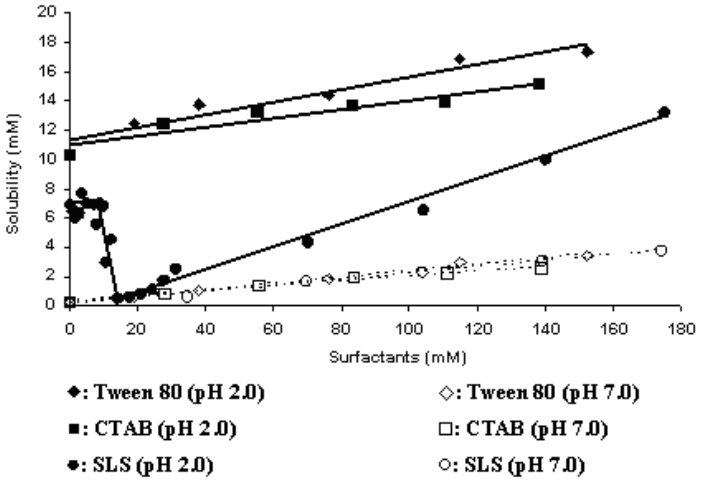

Figure 2. Solubility profiles for surfactants at pH 2.0 and pH 7.0.

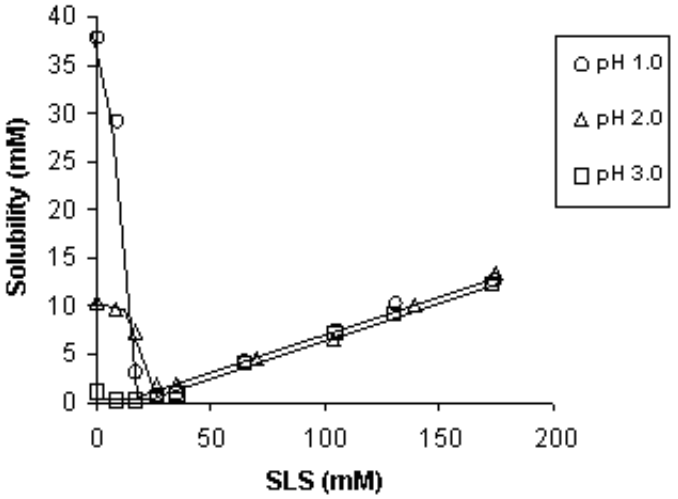

Figure 3. Solubility profile of PG-300995 with SLS at pH 1.0, 2.0, and 3.0.

pared with 0.01N KH_2PO_4 and 0.01N K_2HPO_4. An excess amount of PG-300995 was added to duplicate vials containing 2-mL mixtures of buffer at pH 2.0 and pH 7.0 with SLS at different concentrations. The sample vials were rotated for 3 days on an end-to-end Labquake rotator (Barnstead Thermolyne, Sparks, NV), and the pH of the solutions was measured and readjusted if required. The samples were then rotated for 2 additional days, filtered, and analyzed. A similar procedure was performed at pH 1.0 and 3.0. The HPLC assay included a 250 × 4.6 mm pinnacle octadecyl silica (ODS) amine column with a particle size of 5 μm. The mobile phase was composed of 82% trifloroacetic acid (0.1% in water) and 18% acetonitrile. A flow rate of 1.0 mL/min was maintained, and the effluent was detected at a wavelength of 320 nm using an Agilent 1100 G1315B Diode Array detector (Agilent Technologies Inc., Wilmington, DE) (A.J., Y.R., and S.H.Y., unpublished data, 2004).

Results and Discussion

The solubility profiles of PG-300995 in SLS at pH 2.0 and pH 7.0 are shown in Figure 2. For reference, similar profiles for 2 other surfactants (Tween 80 and Cetyl trimethylammonium bromide (CTAB) were obtained and are shown in Figure 2.

At pH 7.0, SLS is comparable with the other 2 surfactants in terms of solubilization capacities (κ). At pH 2.0, Tween 80 (neutral) and CTAB (cationic) showed normal solubility profiles. However, a desolubilization was observed at pH 2.0 at SLS concentrations below 15 mM. This desolubilization is due to the formation of an insoluble estolate (lauryl sulfate) salt of the drug. At very low SLS concentrations, the solubility of the drug remains constant at its intrinsic solubility at pH 2.0. Once the product of the concentrations of the ionized drug and SLS exceeds the solubility product, precipitation of the estolate salt occurs and drug solubility decreases. This desolubilization, appearing as a negative slope in Figure 2, continues until the CMC of SLS is reached. At concentrations above the CMC, micellization of SLS is responsible for the solubilization of the estolate salt and any ionized free drug present, as indicated by the ascending portion of the solubility curve.

In order to study the effect of pH on this desolubilization, additional solubility profiles for PG-300995 with SLS were generated at pH 1.0 and pH 3.0 (Figure 3).

As seen in Figure 3, there is a consistent decrease in drug solubility with increasing SLS concentration at each pH. Also, desolubilization decreases with an increase in pH from 1.0 to 3.0. At pH 1.0, the drug is completely cationic and readily forms an insoluble salt with the largely anionic SLS (pK_a ~0). As the pH increases, ionization of the drug decreases resulting in reduced salt formation and less pronounced desolubilization. Once SLS reaches a concentration where micellization is extensive, all 3 curves overlap and show similar positive slopes.

The bimodal solubilization curve obtained with SLS at low pH values can be explained by the schematic plot in Figure 4. The solubility of the un-ionized free drug (D_u) and the un-ionized drug partitioned into micelles (D_u^M) is low at all pH values and increases slightly with an increase in SLS concentration. However, the solubility of the ionized free drug (D_i) decreases at low SLS concentrations owing to the formation of an insoluble estolate salt (D_{salt}). This decrease in solubility results in the descending portion of the bimodal total solubility curve (D_{tot}). As the concentration of SLS increases, the enhanced micellization favors the uptake of the estolate salt and the ionized drug (D_i^M) into the micelles, thereby increasing the total solubility. This increase in solubility is responsible for the ascending linear portion of the bimodal total solubility curve. As the pH is increased, there is less ionized drug and thus less salt formation.

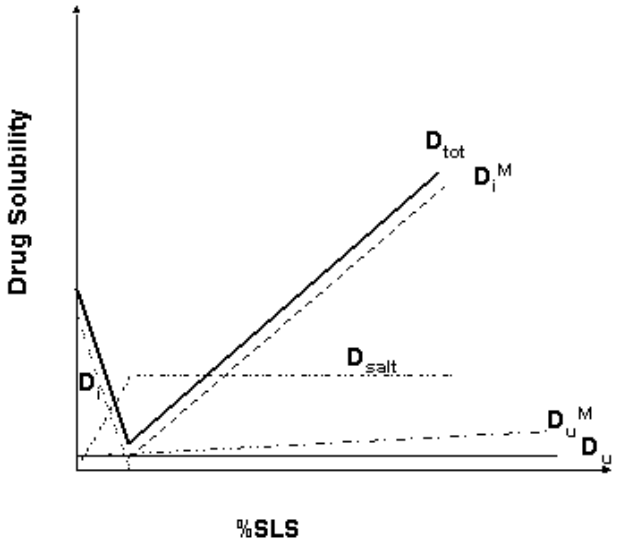

Figure 4. Solubility profile of ionized and un-ionized forms of PG-300995 with SLS at low pH values.

CONCLUSION

Solubilization of PG-300995 has been achieved using SLS at low pH. However, at a pH where both the solute and surfactant are ionized, desolubilization can occur owing to the formation of an insoluble estolate salt. This salt can be solubilized by higher concentrations of SLS.

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