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Research Article

Solution-Mediated Phase Transformation of Haloperidol Mesylate in the Presence of Sodium Lauryl Sulfate

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Abstract. Forming a salt is a common way to increase the solubility of a poorly soluble compound. However, the solubility enhancement gained by salt formation may be lost due to solution-mediated phase transformation (SMPT) during dissolution. The SMPT of a salt can occur due to a supersaturated solution near the dissolving surface caused by pH or other solution conditions. In addition to changes in pH, surfactants are also known to affect SMPT. In this study, SMPT of a highly soluble salt, haloperidol mesylate, at pH 7 in the presence of a commonly used surfactant, sodium lauryl sulfate (SLS), was investigated. Dissolution experiments were performed using a flow-through dissolution apparatus with solutions containing various concentrations of SLS. Compacts of haloperidol mesylate were observed during dissolution in the flow-through apparatus using a stereomicroscope. Raman microscopy was used to characterize solids. The dissolution of haloperidol mesylate was significantly influenced by the addition of sodium lauryl sulfate. In conditions where SMPT was expected, the addition of SLS at low concentrations (0.1–0.2 mM) reduced the dissolution of haloperidol mesylate. In solutions containing concentrations of SLS above the critical micelle concentration (CMC) (10–15 mM), the dissolution of haloperidol mesylate increased compared to below the CMC. The solids recovered from solubility experiments of haloperidol mesylate indicated that haloperidol free base precipitated at all concentrations of SLS. Above 5 mM of SLS, Raman microscopy suggested a new form, perhaps the estolate salt. The addition of surfactant in solids that undergo solution-mediated phase transformation can add complexity to the dissolution profiles and conversion.

KEY WORDS: dissolution; Raman microscopy; salt forms; solution-mediated phase transformation; surfactant.

INTRODUCTION

Many approaches are used to increase the solubility of poorly soluble pharmaceutical compounds, including manipulation of the solid form of the drug, such as forming a salt, amorphous solid or cocrystal (1–3). These solid forms often result in supersaturated solutions of the drug during dissolution, which can lead to precipitation (4,5). Solution-mediated phase conversion of more soluble forms to lower solubility forms during dissolution is hypothesized to occur in three steps: (1) dissolution to create a supersaturated solution, (2) nucleation of less soluble phase, and (3) growth of that phase (5). The occlusion of the more soluble form often occurs by the growth of the less soluble phase on the dissolving surface, greatly reducing the enhanced dissolution rate one hoped to gain by forming a more soluble solid (6–8).

Pharmaceutical salts are prone to solution-mediated phase conversion during dissolution depending on the solubility and pH (9). The equilibrium form of an ionizable drug is defined by the pH solubility curve (10). For example, as the pH is raised, a soluble salt of a basic drug undergoes solution-mediated phase transformation to the free base. This has been shown for soluble salts of haloperidol (2,11). Solution-mediated phase transformation of haloperidol mesylate at pH 7 in 1–25 mM phosphate buffer resulted in occlusion of the dissolving surface by haloperidol free base (11). Li *et al.* have also investigated the solution-mediated phase transformation of haloperidol mesylate to the less soluble hydrochloride salt in 0.01 M hydrochloric acid with additional 0–0.15 M NaCl present. They found solution-mediated transformation of the mesylate salt to the chloride salt, in the presence, but not in the absence of additional NaCl because the K_{sp} of the less soluble chloride salt was exceeded (12). Thus, solution-mediated phase transformation of salts is dependent on not only the pH of the solution, but also solution conditions such as other counterions and buffer concentrations. The phenomenon of solution-mediated phase transformation of salts is significant to oral dosage form development, since the pH and solution conditions in the GI tract varies.

Surfactants generally improve dissolution of poorly soluble compounds, and therefore are used in many dissolution methods and oral dosage form formulations to aid in wetting and solubilization (13,14). Authors have described

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biorelevant dissolution media in which sodium lauryl sulfate and other additives are used (15,16). However, surfactants have also been shown to affect solution-mediated phase transformation (8,17). Surfactants are known to affect nucleation and crystal growth during the crystallization process, although no general trend is observed (18). The use of Tween 80 at 0–2 mg/ml in 0.1 M HCl was shown to enhance the solution-mediated phase transformation of a basic drug form (pK_a, 7.7) to its hydrochloride salt, decreasing its dissolution rate (17). Sodium lauryl sulfate, a commonly used surfactant, used at concentrations of 4.3–17.3 mM was also shown to increase the conversion from anhydrous carbamazepine to the dihydrate during dissolution (8). However, surfactants do not always enhance solution-mediated phase transformation. The use of dodecyl ammonium chloride, a cationic surfactant, was shown to inhibit the transformation of α to β glutamic acid presumably by disrupting the nucleation and growth processes (19). The use of surfactants to enhance the solubility and avoid solution-mediated phase transformation of cocrystals has been recently described (20). Therefore, solution-mediated phase transformation in the presence of surfactants is dependent on the surfactant, other solution conditions, and the solid being studied.

In this paper, we report the solution-mediated phase transformation of a highly soluble salt, haloperidol mesylate, at pH 7 in the presence of a commonly used surfactant, sodium lauryl sulfate (SLS). By understanding the dissolution and subsequent precipitation of soluble salts, we can gain insight into the time scale of these events *in vitro* and *in vivo*. Such studies would be useful in the solid form selection of poorly soluble drugs to assess the potential dissolution rate advantage of salt forms.

MATERIALS

Haloperidol was purchased from Sigma Chemical (St. Louis, MO). Haloperidol mesylate was prepared at GlaxoSmithKline (Durham, NC). Sodium phosphate monohydrate, sodium diphosphate heptahydrate, SLS, LC/MS grade acetonitrile and trifluoroacetic acid (99.5%) were obtained from Fisher Scientific (Pittsburgh, PA) and were used as received.

METHODS

Dissolution Using Flow Cell Apparatus

A dissolution flow cell was designed to study dissolution in a laminar flow environment with concurrent observation of the solid. The design of the dissolution flow cell has been described previously and shown in Fig. 1 (21). In this report, we use a 1×6 mm (H×W) channel with a circular drug compact having a surface area of 0.13 cm^2. Haloperidol mesylate was compressed into the flow cell insert of the dissolution flow cell using a 2-ton press at 500 lbs (ICL low ton press, Garfield, NJ) such that it was flush with the channel surface, so that the surface area for a poorly soluble material remained constant throughout the experiment. Experiments were performed at room temperature (20–22°C). Fluid was delivered to the flow cell by syringe pump (KD Scientific Syringe Pump, Holliston, MA) at 0.5 ml/min. Solids were

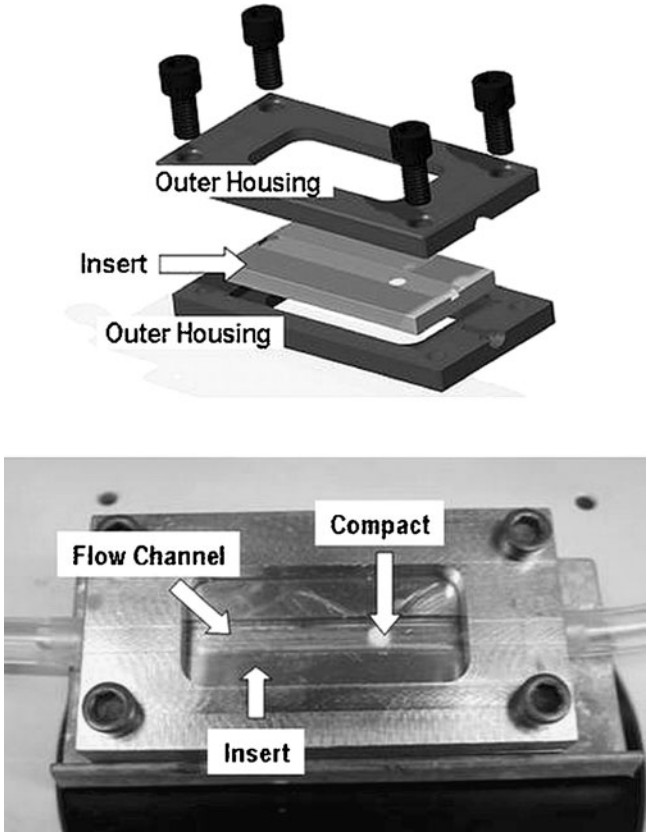

Fig. 1. Schematic and picture of the dissolution flow cell

observed during dissolution using a stereomicroscope (SZ61, Olympus, Center Valley, PA), and images were captured (Media Cybernetics Evolution Camera with Image Pro software, Bethesda, MD). Solutions of 5 mM phosphate buffer at pH 7 with various concentrations of SLS were used as dissolution media. The critical micelle concentration (CMC) of SLS in 5 mM phosphate buffer was reported to be 6 mM at 25°C (22). The concentrations of SLS studied were 0.1, 0.2 mM, (well below the CMC), 5 mM, (just below the CMC), and 10 mM, 15 mM (well above the CMC). The CMC close to the surface is expected to be lower than the bulk solution due to the dissolution of haloperidol mesylate (23).

HPLC

Concentration of the effluent from the dissolution flow cell was measured in fractions every 10 min by high-performance liquid chromatography (HPLC) (Thermo Finnigan HPLC, Waltham, MA). Samples were centrifuged at 6,000 rpm for 10 min using a mini centrifuge (Cole Parmer, Vernon Hills, IL) before HPLC analysis. The mobile phase was 45% acetonitrile and 55% 0.25% trifluoroacetic acid in water. The flow rate was 1 ml/min. A C8 column (Symmetry, Waters, Milford, MA) was used with detection at 254 nm.

Analysis of Solids

Compacts were examined immediately after dissolution using a Raman microscope (Ramascope Micro-Raman with a laser source of 100 mW 785 nm laser source at 30% power,

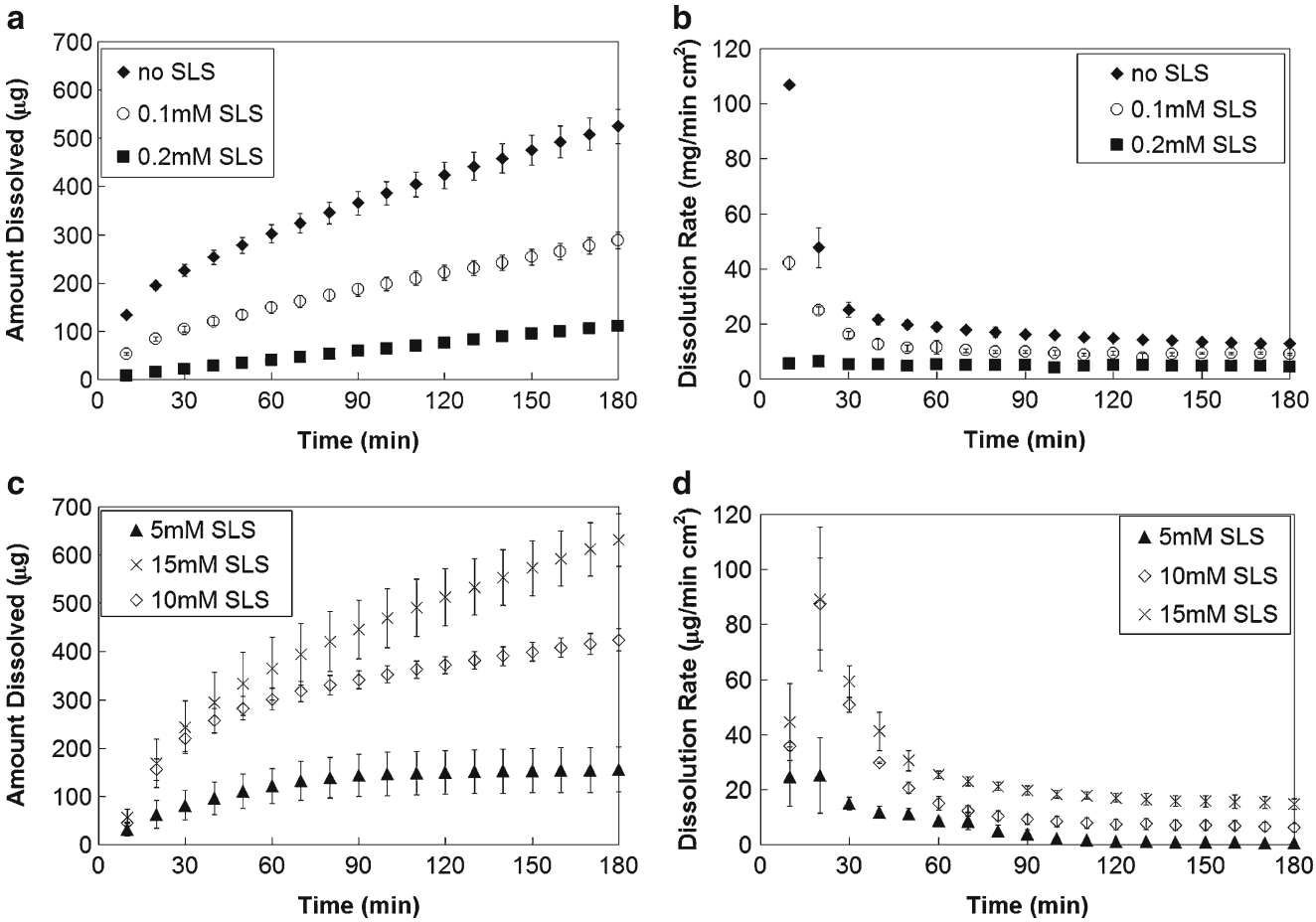

Fig. 2. Dissolution profiles of haloperidol mesylate in 5 mM phosphate buffer and various concentrations of sodium lauryl sulfate, pH 7 in the dissolution flow cell at 0.5 ml/min. **a** Cumulative amount *vs.* time: low concentrations of SLS. **b** Dissolution rate *vs.* time: low concentrations of SLS. **c** Cumulative amount *vs.* time: high concentrations of SLS. **d** Dissolution rate *vs.* time: high concentrations of SLS

Renishaw, Hoffman Estates, IL). A ×20 objective was utilized to scan solids and data collection was one scan with 60-s acquisition. The spectral resolution for the instrument in this configuration was 1 cm^{-1}. These data were found to be inconclusive. It could not be determined whether the spectra collected at the surface of the compact after dissolution were indicative of a new form of haloperidol or a combination of the spectra of the starting material and haloperidol free base. Therefore, powder samples of haloperidol mesylate (200 mg) were equilibrated overnight in amber scintillation vials at room temperature in 5 mM phosphate buffer and various concentrations of SLS (5 ml) before analysis to induce complete transformation. A polarized light microscope (Zeiss, Germany) with a ×10 objective was used to examine solids collected in the wake of the compact and in the tubing after dissolution. Images were digitally captured (CCD Iris, Sony, NY). In addition, an X-ray diffractometer (XDS 2000, Scintag, Inc., Sunnyvale, CA) with CuKa radiation at 45 kV, and 40 mA was used to evaluate solids of the sample at an interval of 0.02° and a scanning rate of 2°/min over a 2θ range of 5° to 50°.

Solubility Studies

Haloperidol mesylate (200 mg) was equilibrated overnight in amber scintillation vials at room temperature in 5 mM phosphate buffer and various concentrations of SLS (5 ml), as described above. As solids were added to solutions, the pH was titrated to pH 7 with 1 N NaOH before equilibration overnight. The pH of the slurries was measured before analysis. The concentrations of the supernatant were measured by HPLC. Due to the limited availability of material, determinations of haloperidol mesylate solubility were limited to two on different days (T=19°C for trial 1, T= 20°C for trial 2). The concentration of each solution was analyzed twice, 6 h apart, with no significant difference in the measurement.

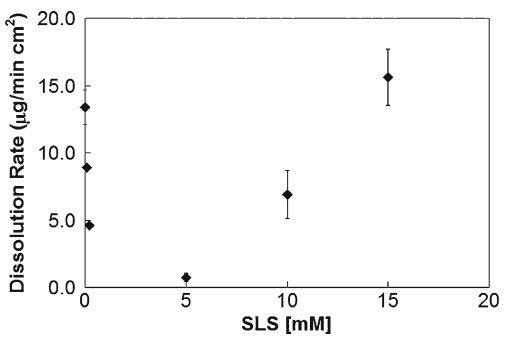

Fig. 3. Terminal dissolution rate of haloperidol mesylate in 5 mM phosphate buffer as a function of sodium lauryl sulfate concentration

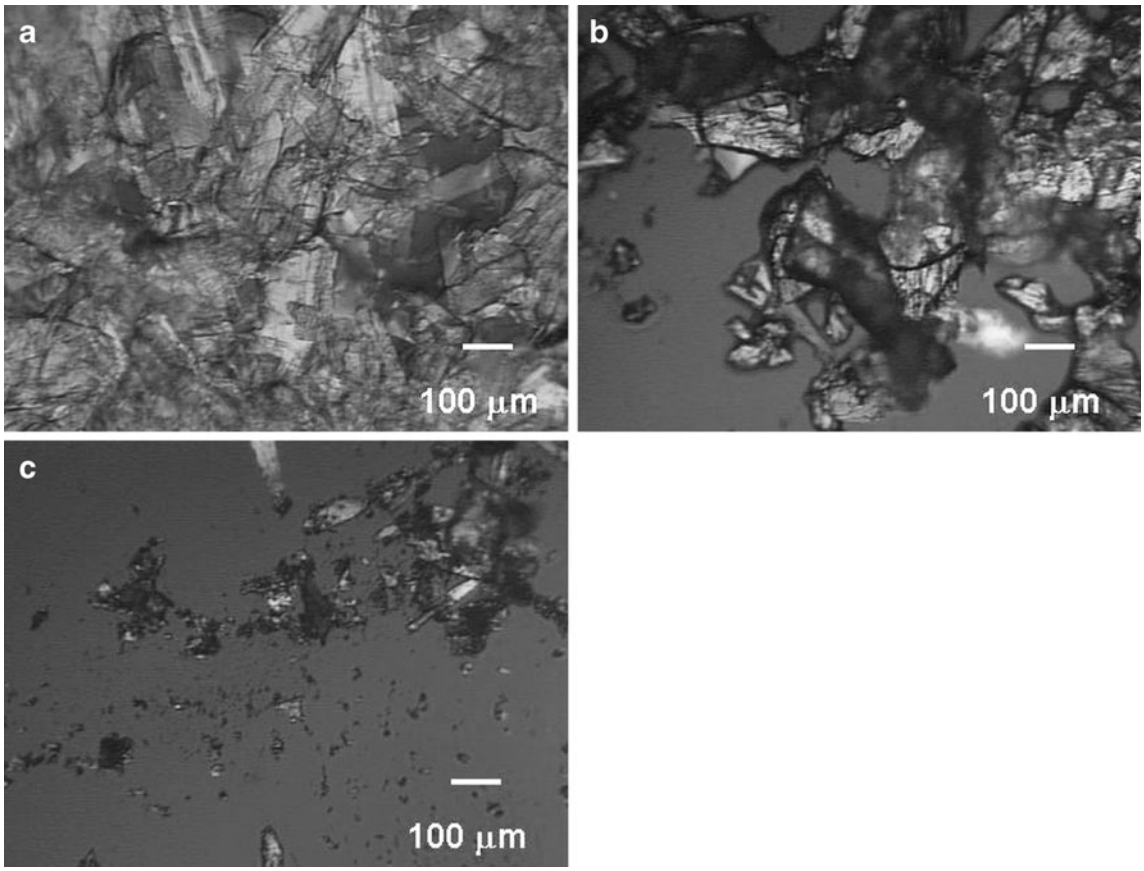

Fig. 4. Polarized light micrographs of solids recovered from the wake of the dissolving haloperidol mesylate compact in the channel after dissolution in 5 mM phosphate buffer. **a** No SLS, **b** 0.2 mM SLS, or **c** 15 mM SLS

RESULTS AND DISCUSSION

The dissolution of haloperidol mesylate in 5 mM phosphate buffer at pH 7 and a flow rate of 0.5 ml/min was influenced by the addition of SLS in a complex manner (Fig. 2). In the absence of SLS, the dissolution profile exhibited curvature which has been shown to be solution-mediated phase transformation from haloperidol mesylate to the lower solubility haloperidol free base form (11). The addition of low concentrations of SLS suppressed the dissolution of haloperidol mesylate. In 0.1 mM SLS, the amount dissolved *vs*. time curve exhibited curvature, which indicates a decrease in dissolution rate with time (Fig. 2a). The time course of the dissolution rate is more clearly seen in Fig. 2b. At 0.2 mM SLS, the dissolution rate was relatively constant throughout the experiment; however, it was greatly reduced compared to the initial dissolution rate of haloperidol mesylate without SLS. This is an indication that a conversion occurs very quickly at this concentration of SLS.

At 5 mM SLS the amount of haloperidol mesylate dissolved over the time course of the experiment was greater

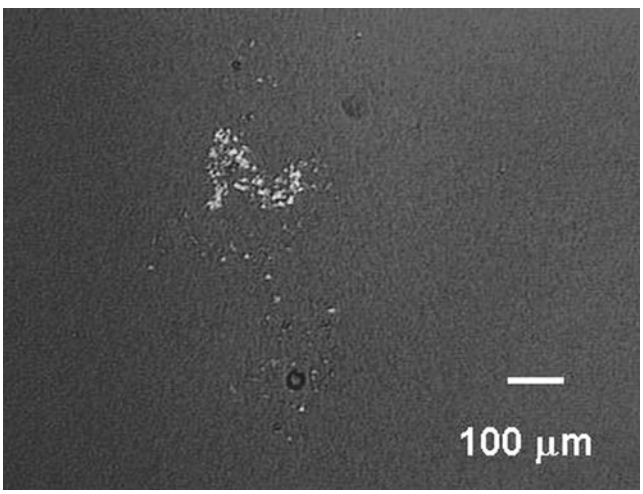

Fig. 5. Polarized light micrographs of solids recovered from the outlet tubing of the flow cell after dissolution of haloperidol mesylate dissolution in 5 mM phosphate buffer and 15 mM SLS

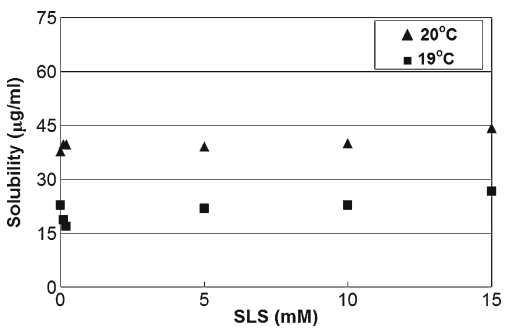

Fig. 6. Haloperidol mesylate solubility in 5 mM phosphate buffer and various concentrations of sodium lauryl sulfate (two determinations, not averaged values)

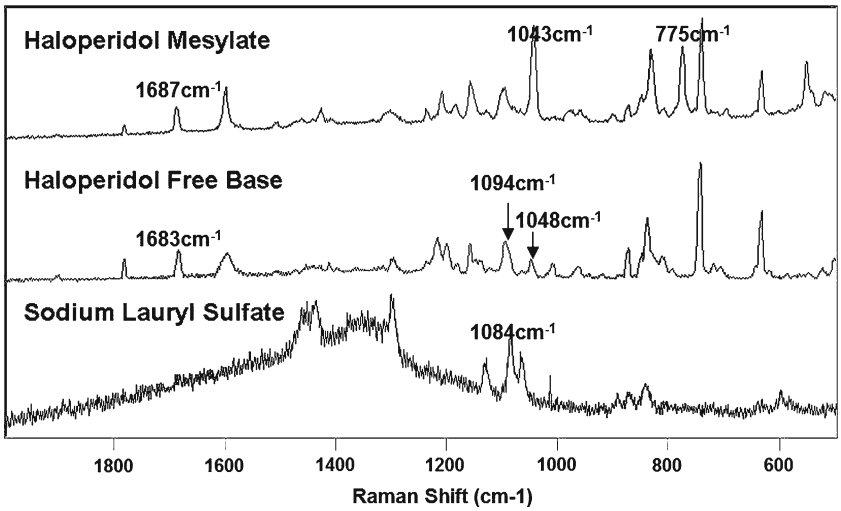

Fig. 7. Raman microscopy of haloperidol mesylate, haloperidol free base, and sodium lauryl sulfate before dissolution

than at 0.2 mM SLS; however, the dissolution rate was not constant throughout the experiment (Fig. 2c and d). The dissolution rate decreased with time from the start of the experiment to a very low terminal value, as indicated by the nearly flat portion of the amount dissolved *vs.* time curve from approximately 90 min until the end of the experiment. The terminal dissolution rate was not significantly different from the dissolution rate of haloperidol free base in 5 mM phosphate buffer (11). At 5 mM, SLS was close to the reported CMC value of 6 mM (22). As the concentration of SLS was increased beyond the CMC to 10 and 15 mM, the amount of dissolved haloperidol mesylate increased presumably due to increased micellar solubilization. The dissolution rate of haloperidol mesylate increased and then decreased with time at 10 and 15 mM SLS (Fig. 2d). This phenomenon was only observed in dissolution media containing SLS concentrations higher than the CMC. The terminal dissolution rate of haloperidol mesylate in each solution was calculated by averaging the dissolution rate values for the last hour of each dissolution experiment (Fig. 3). SLS did not have a monotonic effect on the terminal dissolution rate of haloperidol mesylate. At low concentrations of SLS, the terminal dissolution rate decreased with increasing SLS concentration. Close to the reported CMC of SLS of the bulk solution, 5 mM, the terminal dissolution rate reached a minimum. As the SLS concentration was increased above the CMC, 10 and 15 mM, the terminal dissolution rate increased again.

As the concentration of SLS was increased from 0 to 5 mM, there was an observed change in the nature of the precipitated crystals. The solid that precipitated on the channel wall in the wake of the compact was recovered and viewed under polarized light (Fig. 4). As seen at all SLS concentrations, this solid was found to be crystalline. At the lower concentrations of SLS, no particles were observed in the tubing. In contrast, many solid particles were visible in the outlet tubing during the dissolution of haloperidol mesylate in 5, 10, and 15 mM SLS. Under the polarized light microscope, the solids that had precipitated in the outlet tubing were

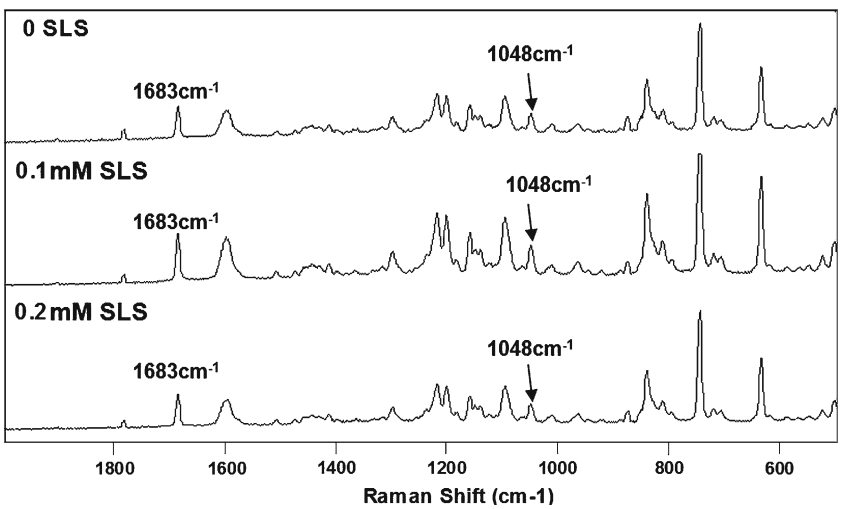

Fig. 8. Raman microscopy of solids recovered from solubility experiments of haloperidol mesylate in 5 mM phosphate buffer and 0, 0.1, 0.2 mM sodium lauryl sulfate

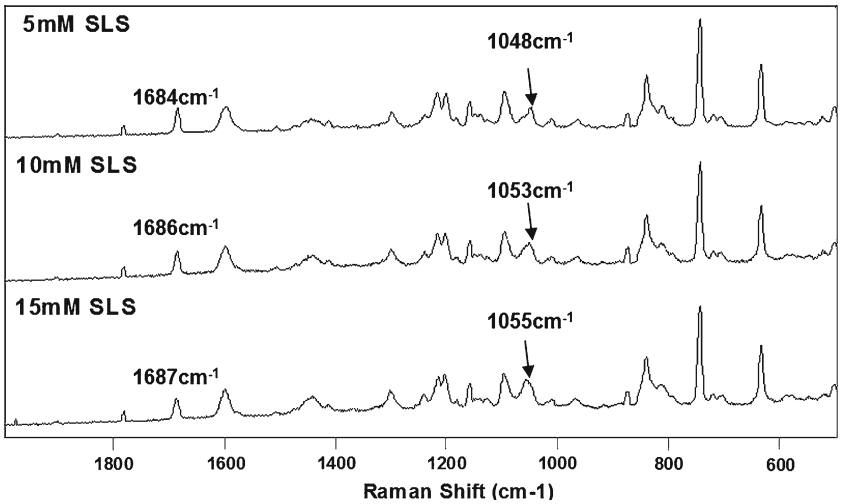

Fig. 9. Raman microscopy of solids recovered from solubility experiments of haloperidol mesylate in 5 mM phosphate buffer and 5, 10, 15 mM sodium lauryl sulfate

found to be crystalline, but of a much smaller particle size than the material recovered from the wake of the compact (Fig. 5).

Haloperidol mesylate compacts were recovered after exposure to the dissolution medium for 3 h and examined by Raman microscopy. The results were inconclusive due to the signal of the unexposed haloperidol mesylate from underneath the precipitated material. Therefore, excess haloperidol mesylate powder was equilibrated at room temperature overnight in 5 mM phosphate buffer and various concentrations of SLS to generate more solid sample for evaluation by Raman microscopy. SLS had no significant effect on the apparent solubility of haloperidol mesylate (Fig. 6)[1] which is inconsistent with the dissolution rate data (Fig. 2). Therefore, in this case the solubilities of haloperidol mesylate in the various media were not predictive of the dissolution profiles. The solids recovered after the solubility experiments showed that at low concentrations of SLS (0.1, 0.2, and 5 mM), haloperidol free base was the only solid form detected (Figs. 7 and 8). As the concentration of SLS was increased above 5 mM, shifts in the Raman spectra suggested another form was present in addition to haloperidol free base (Figs. 7 and 9). The ketone peak in the free base is found at 1,683 cm^{-1}, while the peak in the solids isolated from 10 and 15 mM SLS was shifted to 1,687 cm^{-1} which has been associated with the mesylate salt; however, the peak at 775 cm^{-1} is absent in these solids, indicating the mesylate salt was likely not present. A shift at approximately 1,055 cm^{-1} was observed in the Raman spectra, which did not appear in any of the starting materials (Fig. 7).

To further investigate the solids that precipitated during dissolution, both haloperidol mesylate powder and haloperidol free base powder were equilibrated in 5 mM phosphate buffer with 15 mM SLS at room temperature overnight. The solids were recovered and analyzed by X-ray diffraction (XRD) (Fig. 10). The X-ray patterns indicate that haloperidol free base was found in each sample that was recovered from these slurry experiments. The halo in the X-ray patterns also indicated that an amorphous solid had also precipitated. The solids recovered after equilibration of haloperidol mesylate powder also showed a diffraction peak at 8° 2θ. This peak was not observed in any known solid form of haloperidol. The solids recovered from both haloperidol mesylate and free base slurries were observed under the polarized light microscope (data not shown) and also found to contain amorphous and crystalline solids in agreement with XRD data. The species present at pH 7 could have been the haloperidol estolate salt. Various attempts were made to generate an estolate salt from solutions of haloperidol and lauric acid. These attempts did not result in a solid form that could be isolated for characterization, instead a gel-like solid and oily residue formed. However, others have reported estolate salt conversion in the presence of basic compounds (24).

Taking into consideration the dissolution and solids characterization, there are two plausible explanations for the decrease in the dissolution rates at low SLS concentrations (Fig. 2). It is known that nucleation is dependent on the interfacial tension between the supersaturated solution and the critical nuclei (18). As the SLS concentration was increased, the interfacial tension was reduced and could increase the nucleation and crystal growth. The interfacial tension was expected to be lowest at the CMC of SLS, therefore the highest rate of nucleation and crystal growth was expected at 5 mM SLS which is the concentration at which the lowest terminal dissolution rate is observed. We note, however, that although the lowest terminal dissolution rate is observed at 5 mM SLS, the fastest conversion to haloperidol free base was observed for 0.2 mM SLS. At this point, we cannot rule out the possibility that there is a concentration of SLS intermediate to 0.2 and 5 mM that will be a maximum for conversion rate and minimum for terminal dissolution rate. Another explanation for the decreased

[1] It was noted that the solubility determinations in each solution differed by approximately twofold, which appears to be a systematic error. During addition of the mesylate salt to the solutions, the pH was dramatically reduced, and titration to pH 7 was difficult due to the precipitation and reprecipitation of the free base form and salt form (or possibly other forms). Therefore, the two solubility trials were not averaged and shown as separate data points.

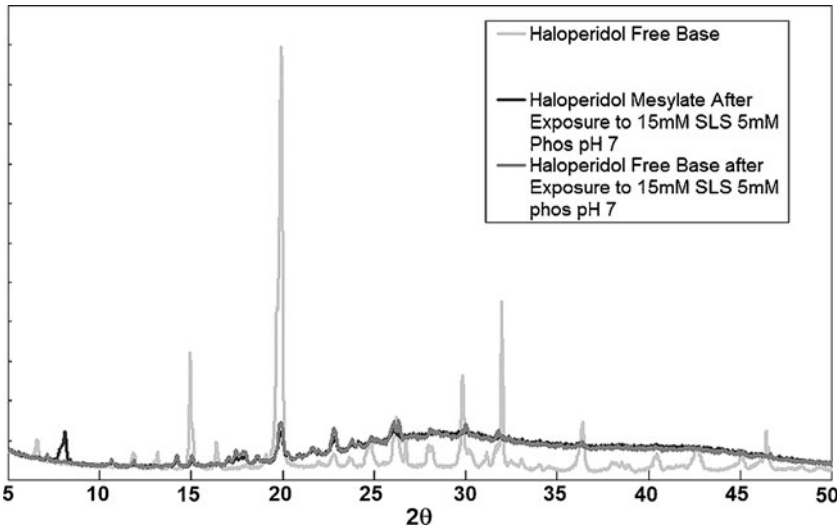

Fig. 10. XRD of haloperidol free base and solids recovered after haloperidol free base and haloperidol mesylate equilibration in 5 mM phosphate buffer and 15 mM sodium lauryl sulfate

dissolution in the presence of SLS concentrations below the CMC is an ionic interaction of the anionic laurate ion and the protonated haloperidol ion on the dissolving surface. If this were to occur, the tail of the laurate ion would be exposed to the aqueous solution, making the haloperidol surface more hydrophobic. Such interactions have been proposed by other authors (24,25).

SUMMARY AND CONCLUSIONS

The dissolution of a soluble salt, haloperidol mesylate, at pH 7 exhibited complex behavior as a function of the concentration of an ionic surfactant, sodium lauryl sulfate (SLS). The solution-mediated phase transformation to the free base was promoted by the addition of surfactant at low concentrations of SLS (0.1, 0.2, and 5 mM). In solutions containing concentrations of SLS above the CMC, the dissolution of haloperidol mesylate increased compared to below the CMC. The solubility measurements of haloperidol mesylate in 5 mM phosphate buffer and various concentrations of SLS were not found to be predictive of the dissolution profiles. The solids recovered from solubility experiments appeared to contain haloperidol free base at all concentrations of SLS. However, above 5 mM of SLS, Raman spectra indicated that an unidentified form of the drug was also present. On further investigation by XRD and PLM, the solid was determined to be partially amorphous. The haloperidol estolate salt was suspected but could not be confirmed.

In conclusion, the addition of a surfactant to the dissolution media can add complexity to dissolution profiles for solids that undergo solution-mediated phase transformation. The use of multiple surfactant concentrations can be helpful in obtaining a thorough understanding of the dissolution and precipitation behavior of soluble salt forms.

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