Effect of Sodium Lauryl Sulfate in Dissolution Media on Dissolution of Hard Gelatin Capsule Shells

Fang Zhao,[1,2] Vyacheslav Malayev,[1] Venkatramana Rao,[1] and Munir Hussain[1]

Received June 3, 2003; accepted September 28, 2003

Purpose. Sodium lauryl sulfate (SLS) is a commonly used surfactant in dissolution media for poorly water soluble drugs. However, it has occasionally been observed that SLS negatively impacts the dissolution of drug products formulated in gelatin capsules. This study investigated the effect of SLS on the dissolution of hard gelatin capsule shells.

Methods. The USP paddle method was used with online UV monitoring at 214 nm (peptide bond). Empty size #0 capsule shells were held to the bottom of the dissolution vessel by magnetic three-prong sinkers.

Results. SLS significantly slowed down the dissolution of gelatin shells at pH < 5. Visually, the gelatin shells transformed into some less-soluble precipitate under these conditions. This precipitate was found to contain a higher sulfur content than the gelatin control sample by elemental analysis, indicating that SLS is part of the precipitate. Additionally, the slowdown of capsule shell dissolution was shown to be dependent on the SLS concentration and the ionic strength of the media.

Conclusions. SLS interacts with gelatin to form a less-soluble precipitate at pH < 5. The use of SLS in dissolution media at acidic pH should be carefully evaluated for gelatin capsule products.

KEY WORDS: capsule; dissolution media; gelatin; surfactant.

INTRODUCTION

Synthetic surfactants have widely been used in recent years for dissolution testing of poorly water soluble drug products. A number of studies have demonstrated that these surfactants can mimic, to some extent, the naturally occurring surfactants and micellar media in the gastrointestinal tract (1,2). Among common surfactants, sodium lauryl sulfate (SLS) is the most frequently used due to its excellent solubilization capacity, low cost, and the ease of use as a solid.

Formulated hard gelatin capsule dosage forms are commonly used for oral administration. Previous studies have shown that the presence of SLS in the dissolution media may slow down the dissolution of capsule formulations and increase the variability among capsules (3,4). However, this phenomenon has not been well-characterized or reported in the pharmaceutical literature. Typically, only the dissolution of the active ingredient is monitored and reported. What actually happens to the capsule shell is often overlooked or limited to visual observation. The current work is focused on the effect of SLS on the dissolution of the hard gelatin capsule shells in commonly used dissolution media. The study findings should be helpful in dissolution method development for poorly water soluble drug products. The conclusions also may be applicable to capsule formulations containing a significant amount of SLS as an excipient.

MATERIALS AND METHODS

Materials

Size #0 gray opaque hard gelatin capsule shells were obtained from Capsugel (Morris Plains, NJ, USA). These capsules were prepared from a mixture of type A and type B gelatin, and the exact ratio was not disclosed by Capsugel. Magnetic three-prong sinkers were purchased from Vankel (Cary, NC, USA). Sodium lauryl sulfate (>99% pure) and polysorbate 80 were purchased from EM Science (Gibbstown, NJ, USA). Type A and type B gelatin powders were purchased from Sigma (St. Louis, MO, USA); type A was from porcine skin (ca. 175 bloom), and type B was from bovine skin (ca. 225 bloom). All other chemicals used were at least ACS reagent grade.

Dissolution Method

A Distek dissolution system (Model 2100A; North Brunswick, NJ, USA) with the USP apparatus 2 (paddle) was used for the dissolution studies of the hard gelatin capsule shells. All experiments were conducted at 50 rpm in 500-ml media maintained at 37°C. HCl (0.001–0.1 N), sodium acetate buffer (50 mM), and sodium phosphate buffer (50 mM), with or without SLS, were used as the dissolution media to cover the pH range of 1–7. The dissolution media containing SLS were freshly prepared and used within 4 h of preparation. The magnetic three-prong sinker was used to hold the empty capsule shell at bottom of the vessel. This type of sinker has been demonstrated to exert less interference to the dissolution of capsules than coil sinkers (4,5). Sample analysis was carried out by an automated online UV system (Agilent Model 8453; Palo Alto, CA, USA) at a wavelength of 214 nm (peptide bond).

Elemental Analysis

The sample for elemental analysis was prepared as follows. A 30% w/w gelatin solution (type A or type B) in water was prepared at 65°C. The solution was poured into a ½-in. die and cooled to room temperature (RT). The gel was pushed out of the die and added to 0.01 N HCl with 1% SLS at 37°C. After 10 min of stirring, the precipitate was isolated and washed with cold water followed by drying under the ambient conditions. The dried sample was submitted for elemental analysis (C, H, N, and S). The starting material was also submitted as a control.

Surface Tension Measurement

A Krüss K-10 surface tensiometer (Charlotte, NC, USA) equipped with a Wilhelmy Plate was used to measure the surface tension as a function of SLS concentration in 0.1 N HCl at room temperature. Due to the presence of surface active impurity, the critical micelle concentration (CMC) of

[1] Biopharmaceutics R&D, Pharmaceutical Research Institute, Bristol-Myers Squibb Company, One Squibb Drive, P. O. Box 191, New Brunswick, NJ 08903.

[2] To whom correspondence should be addressed. (e-mail: fang.zhao@bms.com)

0724-8741/04/0100-0144/0

SLS in 0.1 N HCl was estimated to be the concentration at which the lowest surface tension value was obtained (6). CMC of SLS in water was also determined to validate the methodology; the experimental value (data not included) was found to be in good agreement with the value reported in literature.

RESULTS

Effect of SLS and pH

Dissolution of hard gelatin capsule shells was performed in media at pH 1–7 in the presence or absence of 1% (w/v; units used throughout) SLS, and the dissolution profiles are shown in Fig. 1. It should be mentioned that in the absence of SLS, dissolution rate of gelatin is known to decrease slightly as pH increases from 1 to 7. This is due to the inherent pH-solubility behavior of gelatin, which has an isoelectric point around pH 5–8 (7). In the presence of 1% SLS, the dissolution of gelatin shells slowed down significantly in the low pH media as shown in Figs. 1 a–d. Visually, the undissolved gelatin shell was observed to become like "stringy cheese," which took much longer time to dissolve. This unknown structure of gelatin is termed 'unknown precipitate' in the following text. As the pH increased, the formation of this unknown precipitate in the presence of SLS became less pronounced. At pH > 5 (Figs. 1 e–f), there was essentially no difference between the dissolution profiles obtained from the media with or without SLS.

It was noticed that the pH of 0.01 N and 0.001 N dissolution media increased by ca. 0.5 pH unit upon the addition of 1% SLS. To eliminate any potential interference due to this pH difference, the experiments were repeated in phosphate buffers at pH 2.1 and 3.1. As shown in Fig. 2, the results from the buffered systems were similar to those obtained from the unbuffered systems shown in Figs. 1 b and c.

Effect of SLS Concentration

The 0.1 N HCl system was chosen to study the effect of SLS concentration on the dissolution of gelatin capsule shells. The concentration of SLS commonly used in dissolution media ranges from 0.1–3% (1,2). Surface tension as a function of

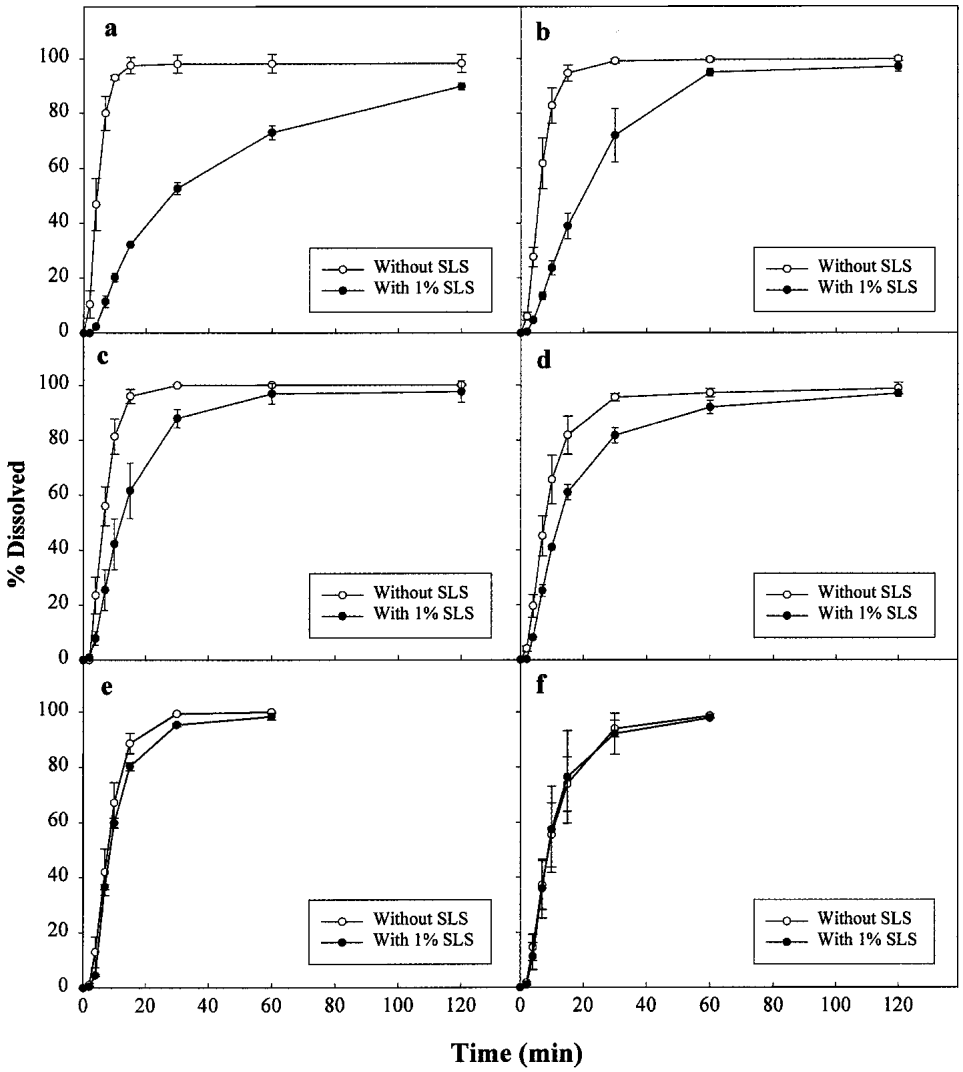

Fig. 1. Effect of 1% SLS on the dissolution of hard gelatin capsule shells at 37°C in (a) 0.1 N HCl, (b) 0.01 N HCl, (c) 0.001 N HCl, (d) 50 mM sodium acetate buffer pH 4.0, (e) 50 mM sodium acetate buffer pH 5.5, and (f) 50 mM sodium phosphate buffer pH 6.8. Data represent mean ± SD (n = 3).

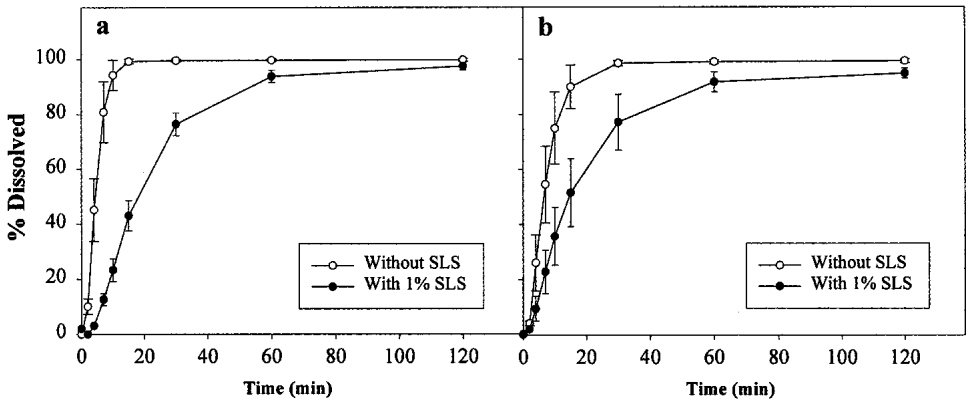

Fig. 2. Effect of 1% SLS on the dissolution of hard gelatin capsule shells at 37°C in (a) 50 mM sodium phosphate buffer pH 2.1 and (b) 50 mM sodium phosphate buffer pH 3.1. Data represent mean ± SD (n = 3).

SLS concentration in 0.1 N HCl was first measured to determine the critical micelle concentration (CMC), and it was estimated to be 0.03%. Therefore, the typical range of 0.1–3% SLS used in the dissolution media is well above the CMC of SLS in 0.1 N HCl. The dissolution of gelatin capsule shells as a function of SLS concentration between 0.1–3% was then performed in 0.1 N HCl. The dissolution profiles are presented in Figs. 3 a and b. At <1% SLS, the dissolution rate decreased as the SLS concentration increased, with the most significant change at >0.25%. When the SLS concentration increased to above 1%, interestingly the dissolution did not slow down any further.

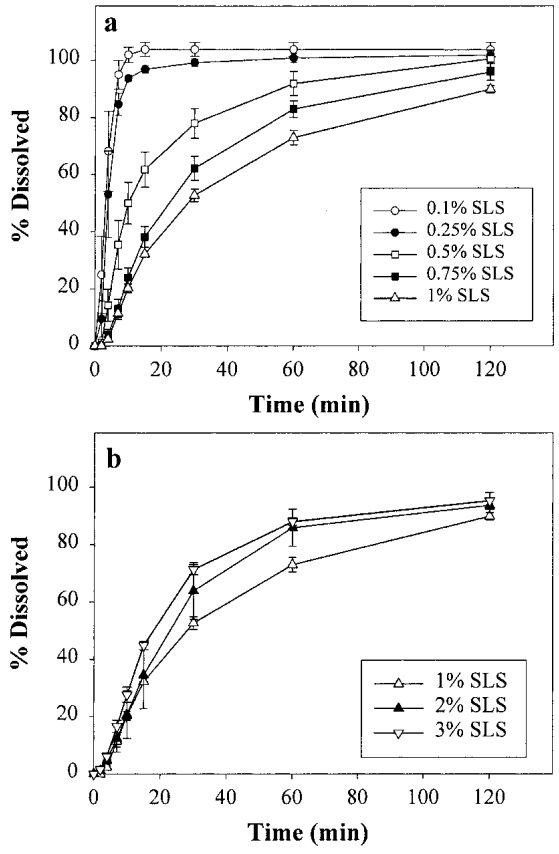

Fig. 3. Dissolution profiles of hard gelatin capsule shells at 37°C in 0.1 N HCl with (a) 0.1–1% SLS and (b) 1–3% SLS. Data represent mean ± SD (n = 3).

Characterization of the Unknown Precipitate

It was speculated that the unknown precipitate observed in the above dissolution experiments might be formed through some interactions between SLS and gelatin. Elemental analysis of the precipitate was conducted to confirm this hypothesis. The unknown precipitate was reproduced in larger quantities using gelatin powder (both type A and type B) as described in the "Materials and Methods" section. The elemental analysis results are summarized in Table I. In comparison to the control starting material, there was an increase in the sulfur content for the unknown precipitate obtained from either type of gelatin. This suggests that the unknown precipitate contained bound SLS. Due to the heterogeneous composition of gelatin, it is not possible to determine the precise molar ratio of SLS:gelatin in the precipitate.

Effect of Ionic Strength

To understand the nature of the interaction between SLS and gelatin, the dissolution experiment in 0.01 N HCl with 1% SLS was repeated with additional 0.1 M NaCl. A control experiment without SLS was also conducted. The results are illustrated in Fig. 4. In comparison to the profile in Fig. 1b, the capsule dissolution slowdown caused by SLS was more pronounced with the increased ionic strength. In the absence of SLS, the addition of NaCl did not affect the dissolution of the capsule shell.

Table I. Elemental Analysis Results of the Unknown Precipitate and the Starting Material

Element	Gelatin A (%)	Unknown from gelatin A (%)	Gelatin B (%)	Unknown from gelatin B (%)
C	44.24	48.92	42.96	48.30
H	6.70	7.18	6.45	7.55
N	16.49	13.64	15.48	13.55
S	1.01	2.75	0.47	2.59

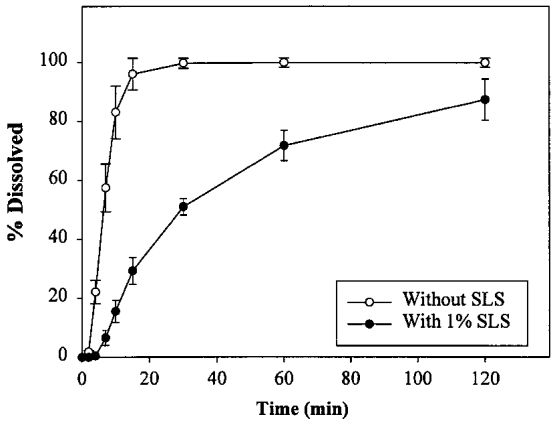

Fig. 4. Effect of increased ionic strength (0.1 M NaCl) on the dissolution of hard gelatin capsule shells at 37°C in 0.01 N HCl with or without 1% SLS. Data represent mean ± SD (n = 3).

Polysorbate 80 vs. SLS

Polysorbate 80 is a commonly used non-ionic surfactant. The dissolution of the hard gelatin capsule shells was conducted in 0.01 N HCl with 0.1% polysorbate 80 (>CMC) for comparison with the SLS-containing media. As shown in Fig. 5, polysorbate 80 did not cause any slowdown of the capsule dissolution, and it appeared to accelerate slightly the dissolution.

DISCUSSION

Gelatin is a heterogeneous protein mixture of partially hydrolyzed animal collagen. Type A is obtained from acid hydrolysis, and type B is obtained from alkaline hydrolysis. The hard gelatin capsule shells used in this study are made from a mixture of type A and type B gelatin. Gelatin contains most of the essential amino acids, including the basic amino acids that are capable of potential salt formation with SLS. The typical molecular weight range of gelatin is 15–250 kDa, and the isoelectric point is around pH 5–8 (7). Therefore, the overall net charge of gelatin at pH < 5 is positive. Studies have demonstrated that in the gel state, gelatin retains some of the secondary and tertiary structures of collagen and that the gel rigidity decreases at pH < 4 and > 10 (7). It can be assumed that the gelatin conformation stability is directly correlated to its rigidity and thus a function of the pH as well.

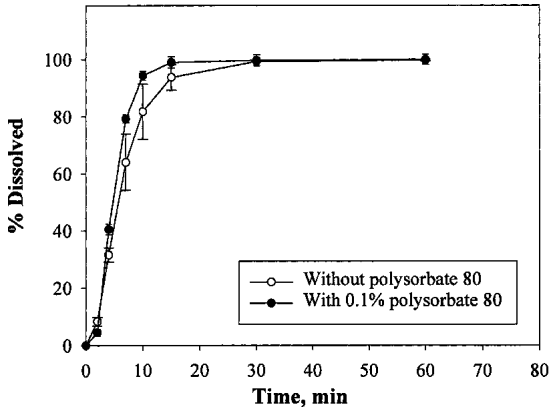

Fig. 5. Effect of 0.1% polysorbate 80 on the dissolution of hard gelatin capsule shells in 0.01 N HCl. Data represent mean ± SD (n = 3).

SLS is a well-known protein solubilizer and denaturant, and it is frequently used in protein purification and analysis. The denaturation (unfolding) process of protein molecules exposes the hydrophobic regions to the aqueous solvent environment, which sometimes leads to protein aggregation and precipitation through hydrophobic interactions. It has been reported that the susceptibility of a protein to SLS-induced denaturation depends on the charge state and the conformation stability of the protein (8).

The slowdown of gelatin capsule shell dissolution reported in this work appears to be an outcome of the physicochemical properties of gelatin as a function of pH and the denaturing effect of SLS. At low pH, the conformation of the gelatin is probably less stable, and its overall net charge becomes more positive as discussed above. These changes could render the gelatin molecules more prone to SLS-induced denaturation and precipitation. Moreover, SLS appears to bind to gelatin in the precipitation process as supported by the elemental analysis results and the effect of SLS concentration.

In theory, SLS can interact with gelatin through ionic charge–charge interactions and/or hydrophobic interactions. Typically, ionic interactions, as present in salts, would be impaired by increased ionic strength in the media. On the other hand, hydrophobic interactions are usually enhanced when ionic strength is increased. The fact that the additional 0.1 M NaCl in 0.01 N HCl with 1% SLS led to a further decrease in gelatin dissolution rate suggests that SLS binds to gelatin through predominantly hydrophobic interactions. Thus, the SLS-induced precipitation of gelatin at low pH may be due to the decreased conformation stability of gelatin rather than the increased positive net charge.

The SLS-induced gelatin precipitation is dependent on the SLS concentration as demonstrated in the 0.1 N HCl system. The typical range of 0.1% to 3% SLS used in dissolution media is well above the CMC of SLS in 0.1 N HCl, and therefore, the surface tension is constant. The decrease in capsule dissolution rate as a function of SLS concentration is attributed solely to the increased SLS:gelatin ratio. The interaction between SLS and gelatin leading to precipitation appears to be saturated at around 1% SLS, above which the solubilization effect of SLS becomes significant.

Outside the protein literature, similar observations have been reported on the interactions between SLS with cationic polymers (9,10). The solution pH and the SLS:polymer ratio were found to be the most important factors leading to the formation of different complexes: soluble complex, gummy rubbery precipitate, and redispersible solid. The complexation process in these systems was ascribed to both hydrophobic interactions and charge–charge interactions.

In comparison to these polymers, gelatin is a heterogeneous amphiphilic polymer system with a range of complex conformation structures. In addition, this work focuses on a kinetic dissolution event rather than an equilibrium state in solution, which makes it more challenging to interpret the data and to elucidate the mechanism. The goal of this study is to demonstrate the effect of SLS in media on the dissolution of hard gelatin capsule shells. Further understanding of the mechanism of SLS–gelatin interactions at the molecular level will require equilibrium studies, perhaps with a simplified model peptide/protein resembling gelatin.

CONCLUSIONS

SLS in dissolution media caused a slowdown of the dissolution of hard gelatin capsule shells at pH < 5 due to the formation of a less-soluble precipitate of gelatin. This gelatin precipitate contained bound SLS through hydrophobic interactions. Because SLS is typically added to dissolution media to improve the dissolution of poorly water soluble drugs, the slowdown of gelatin capsule shell dissolution can potentially counteract this effect. Other surfactants, such as polysorbate 80, should be investigated as an alternative to SLS in dissolution method development of gelatin capsule products if a low pH is required. The interaction between SLS and gelatin at acidic pH may also present a problem for SLS-containing gelatin capsule formulations, not only for *in vitro* dissolution testing but also during *in vivo* dissolution in the acidic stomach environment. The magnitude of the problem, however, will probably depend on the amount of SLS used, the intrinsic dissolution behavior of the active ingredient, and other formulation parameters.

ACKNOWLEDGMENTS

The authors acknowledge Drs. Sherif Badawy, Joseph Bogardus, Miriam Franchini, and Robert Lipper for their helpful discussion and input.

REFERENCES

1. V. Shah, J. Konecny, R. Everett, B. McCullough, A. Noorizadeh, and J. Skelly. In vitro dissolution profile of water-insoluble drug dosage forms in the presence of surfactants. *Pharm. Res.* **6**:612–618 (1989).
2. C. Noory, N. Tran, L. Ouderkirk, and V. Shah. Steps for development of a dissolution test for sparingly water-soluble drug products. *American Pharmaceutical Review* **4**:16–18 (2002).
3. Y. Wu, S. Betigeri, G. Derbin, M. Franchini, M. Paborji, and F. Zhao. Dissolution studies of capsule formulations: the effects of fill weight, sinker type, surfactant, and capsule shell type. *AAPS PharmSci.* **3**(3) (2001). http://www.aapspharmsci.org/.
4. Y. Wu, F. Zhao, and M. Paborji. Effect of fill weight, capsule shells, and sinker design on the dissolution behavior of capsule formulations of a weak acid drug candidate BMS-309403. *Pharm. Dev. Tech.* **8**:379–383 (2003).
5. R. Soltero, J. Hoover, T. Jones, and M. Standish. Effects of sinker shapes on dissolution profiles. *J. Pharm. Sci.* **78**:35–39 (1989).
6. J. Crison, N. Weiner, and G. Amidon. Dissolution media for *in vitro* testing of water-insoluble drugs: effect of surfactant purity and electrolyte on *in vitro* dissolution of carbamazepine in aqueous solutions of sodium lauryl sulfate. *J. Pharm. Sci.* **86**:384–388 (1997).
7. R. Jones. Gelatin: physical and chemical properties. In K Ridgway (ed.), *Hard Capsules—Development and Technology*. The Pharmaceutical Press, London, 1987, pp. 31–48.
8. C. Nelson. The binding of detergents to proteins. I. The maximum amount of dodecyl sulfate bound to proteins and the resistance to binding of several proteins. *J. Biol. Chem.* **246**:3895–3901 (1971).
9. E. Goddard, T. Phillips, and R. Hannan. Water soluble polymer-surfactant interaction—Part 1. *J. Soc. Cosmet. Chem.* **26**:461–475 (1975).
10. D. Jon and D. Chang. Interactions between an amine function polymer and an anionic surfactant. *J. Soc. Cosmet. Chem.* **41**:213–225 (1990).