Dissolution Behavior of a Poorly Water Soluble Compound in the Presence of Tween 80

Linna R. Chen,[1] James A. Wesley,[1,2] Shobha Bhattachar,[1] Bienvenido Ruiz,[1] Korey Bahash,[1] and Suresh R. Babu[1]

Received January 15, 2003; accepted February 3, 2003

Purpose. To investigate the mechanism by which Tween 80 impedes the dissolution of CI-1041, a poorly water-soluble compound in its free form.

Methods. Bulk powder and intrinsic dissolution (ID) of CI-1041 in 0.1 N HCl with various concentrations of Tween 80 were conducted. The residual solids of the dissolution experiments were characterized. The surface tension and the critical micellar concentration (CMC) of Tween 80 in 0.1 N HCl were determined.

Results. CI-1041 underwent solvent mediated conversion to its chloride salt (CS) in 0.1 N HCl. The coating of the CS on the surface of the CI-1041 pellet decreased the ID rate 20 to 30 fold. When the Tween 80 concentration in 0.1 N HCl was below 0.5 mg/ml, the CS formation rate increased with increasing Tween 80 concentration. Above 0.5 mg/ml of Tween 80 in 0.1 N HCl, opposite trend was observed. The change in trend at 0.5 mg/ml Tween 80 coincided approximately with the CMC of Tween 80 in 0.1 N HCL.

Conclusions. The authors propose the following mechanism mediated by Tween 80. Below CMC, reduced surface tension caused by addition of Tween 80 increases the rate of nucleation of insoluble CS, causing the formation of CS on the surface of the CI-1041 free form. This, in turn, decreases the dissolution rate by decreasing the release of compound into solution. Above CMC, the effect of reduced surface tension on the CS nucleation and therefore its formation may be negated by other factors, such as an increase in viscosity or adsorption of surfactant on the crystal surface.

KEY WORDS: nucleation; surface tension; dissolution; phase transformation; CI-1041.

INTRODUCTION

For an orally administered drug to be bioavailable, it needs to be first dissolved in the gastrointestinal (GI) fluid and subsequently absorbed into the blood stream through the GI mucosa. Frequently, dissolution is the rate-limiting step in the absorption of drugs with moderate to poor solubility. To enhance the rate of drug dissolution, for the purpose of enhancing drug bioavailability, surfactants are commonly incorporated into solid dosage forms. Surfactants enhance dissolution by (a) lowering the surface tension, which aids in displacing the air phase with the advancing liquid phase at the solid drug surface and effectively increase the surface area available for dissolution (1), or by (b) increasing drug solubility above the critical micellar concentration (CMC).

Tween 80 is a surfactant commonly used in solid oral dosage forms. Tween 80 was included in the CI-1041 capsule formulation because poor powder wettability was suspected to be the cause of slower dissolution rate for formulations containing milled drug compared to that containing unmilled drug. Tween 80 however, was found to decrease the rate and the extent of capsule dissolution in 0.1 N HCl.

CI-1041 (PD196860, 6-[[2-[4-[4-fluorophenyl) methyl]-1-piperidinyl]ethyl]sulfinyl]-2(3H)-benzoxazolone, Fig. 1), a subtype selective (NR1/NR2B) N-methyl-D-aspartate (NMDA) antagonist, was developed as an oral adjunct to levodopa and carbidopa for the treatment of idiopathic Parkinson's disease by Pfizer Global Research and Development (New York, NY, USA). It is a nonhygroscopic crystalline solid containing the racemic mixture of the free form. CI-1041 has an intrinsic solubility of 0.003 mg/ml, log P of 2.62 and experimental pKa of 7.7. CI-1041 is ionized at pH 1 and the solubility of the base was measured to be greater than 18.6 mg/ml. The exact solubility of the base was not determined at pH 1 because of the fast conversion to its CS. The solubilities of CI-1041 are: >18.6 mg/ml in 0.1 N HCl, 2.3 mg/ml in pH 4.0 sodium acetate buffer, 0.002 mg/ml in pH 7.4 sodium phosphate buffer, 0.094 mg/ml in pH 10.0 sodium borate buffer, and 30.3 mg/ml in 0.1 N NaOH. The solubility of CI-1041 in 0.1 N HCl was approximately determined because the drug precipitated out of solution very quickly. The solubility profile of CI-1041 dictates that fairly complete drug dissolution in the stomach is required to achieve good absorption. Beyond the stomach, CI-1041 is expected to be poorly soluble in the small and large intestines and therefore less likely to dissolve and be made available for absorption.

This research aims to investigate the mechanism by which Tween 80 affects CI-1041 dissolution in 0.1N HCl. This will aid in the development of a CI-1041 formulation of good bioavailability. In addition, because Tween 80 is commonly used in oral solid formulations, the understanding of the interaction between Tween 80 and CI-1041 will guide formulation development of chemically similar compounds.

MATERIALS AND METHODS

Materials

CI-1041 (>98% pure) was received as a highly crystalline powder and milled to achieve particle sizes of less than 20 μm. Tween 80 was purchased from Croda (Parsippany, NJ, USA). HCl (analytical grade) was purchased from either Mallinckrodt (Paris, KY, USA) or VWR (West Chester, PA, USA). Deionized and distilled water was purchased from Ricca Chemical Company (Arlington, TX, USA).

Capsule Dissolution

Dissolution of capsules containing 0 and 3% w/w Tween 80 was carried out using USP Apparatus 2 (Distek, Model 2100) (2) in 900 ml of 0.1 N HCl at 37°C. Paddle speed was maintained at 50 rpm. Capsules were prepared by mixing Tween 80 with a pre-blend of CI-1041, microcrystalline cellulose, lactose, croscarmellose sodium, magnesium stearate, and silicon dioxide. The dissolution media was pumped through a 0.1 cm flow cell using a peristaltic pump (Hewlett Packard, Model 8902A) and analyzed at $\lambda = 250$ nm at time

[1] Pharmaceutical Sciences, Pfizer Global Research and Development, Ann Arbor Laboratories, Ann Arbor, Michigan 48105.

[2] To whom correspondence should be addressed. (e-mail: James.Wesley@Pfizer.com)

0724-8741/03/0500-0797/0 © 2003 Plenum Publishing Corporation

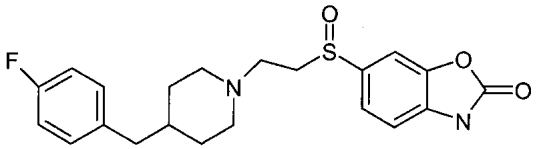

Fig. 1. Molecular structure of CI-1041.

intervals of 15 min using a UV-Vis spectrophotometer (Hewlett Packard, Model G1103A). Data analysis was carried out using UV/Vis ChemStation software package (Hewlett Packard, Version 4.0).

Bulk Drug Powder Dissolution

Bulk CI-1041 powder dissolution in 0.1 N HCl containing 0 or 1 mg/ml Tween 80 was conducted at ambient temperature (23°C). CI-1041 powder (500 mg) was suspended in 20 ml of the dissolution medium while stirring was applied using a magnetic stir bar. The concentration of drug in the solution phase was monitored as a function of time. At each sampling point, 0.5 ml of the suspension was withdrawn, filtered through 0.45 μm Nylon filter, diluted appropriately and assayed using a UV/Vis spectrophotometer at $\lambda = 250$ nm. The solid phase remaining after 60 min of dissolution was characterized by powder X-ray diffraction (PXRD), Fourier transform infrared spectroscopy (FTIR), and elemental analysis.

Intrinsic Dissolution

The intrinsic dissolution of CI-1041 in 0.1 N HCl containing 0 to 2 mg/ml of Tween 80 was conducted at 37°C. Circular drug pellets ($d = 1.1$ cm) were made by compressing 200 mg drug powder in a stainless steel die using a hydraulic press (Carver, Model 3912) at a pressure of 1000 psi and a dwell time of 60 s. The pellet, while inside the die, was centered and leveled with a bubble leveler at the bottom of a 1-Liter dissolution vessel (Distek, Model 2100). The pellet surface that was flushed against the surface of the die faced upwards. The opposite surface was sealed from the dissolution medium with Para film. The distance between the bottom surface of the paddle to the top surface of the pellet was fixed at 3.8 cm. With the paddle stirring at 50 rpm, 900 ml of the dissolution medium that was preconditioned to 37°C was poured carefully into the dissolution vessel at the start of the experiment. The dissolution media was continuously circulated through a flow cell using a peristaltic pump (Hewlett Packard, model 8902A) and analyzed every 30 s using UV-Vis spectrophotometry (Hewlett Packard, Model G1103A) at $\lambda = 250$ nm. The data were analyzed using the kinetic module of the UV/Vis ChemStation software package (Hewlett Packard, Version 4.0).

Surface Tension Measurement

The surface tension of 0.1 N HCl solution containing various concentrations of Tween 80 was measured using a Cenco DuNouy tensiometer (Fisher Scientific, Model 20). The solution was preconditioned to 37°C. The critical micellar concentration (CMC) was determined as the concentration above which no further decrease in surface tension was observed.

Physical Characterization

Powder X-Ray Diffraction (PXRD)

The powder X-ray diffraction patterns of solids were obtained using a powder X-ray diffractometer (Rigaku, Model RAD-3C). The samples were ground slightly using an agate mortar and packed into a 0.2 cm deep quartz cell. The conditions of measurement were as follows: Cu target, graphite monochromator, 40 kV, 40 mA, step size 0.12° 2-theta, scan rate of 5° 2-theta/min over 3°–50° 2-theta range.

Fourier Transform Infrared Spectroscopy (FTIR)

Approximately 0.5 to 1 mg of drug sample was mixed with 200 mg of KBr (Aldrich Chemical, FTIR grade) and compressed into a pellet at 2000 psi for 30 s. The IR spectra were recorded using a FTIR spectrophotometer (Nicolet, Model Protégé 460).

Elemental Analysis

Elemental analyses of the solid phases were conducted by Quantitative Technologies (Whitehouse, NJ, USA). Carbon, hydrogen, and nitrogen contents were determined using a CHN elemental analyzer (Perkin Elmer, Model 2400). Chlorine and sulfur contents were also determined by titration.

RESULTS AND DISCUSSION

The dissolution results of CI-1041 200-mg strength capsules in 0.1 N HCl at 37°C are given in Fig. 2. Tween 80 was shown to have an overall impedance effect on the rate and extent of CI-1041 capsule dissolution. At the end of the 120 min dissolution experiment, the extent of dissolution was smaller (82.3%) for capsules that contained Tween 80 compared to those containing no Tween 80 (96.5%). Student *t* test analysis (3) reveals that the amount of CI-1041 dissolved at 45, 60, 90, and 120 min was statistically different ($p < 0.05$) for formulations containing 0% and 3% Tween 80. Additionally, during the course of the experiment, the dissolution media gradually turned slightly milky. This suggests the possibility of

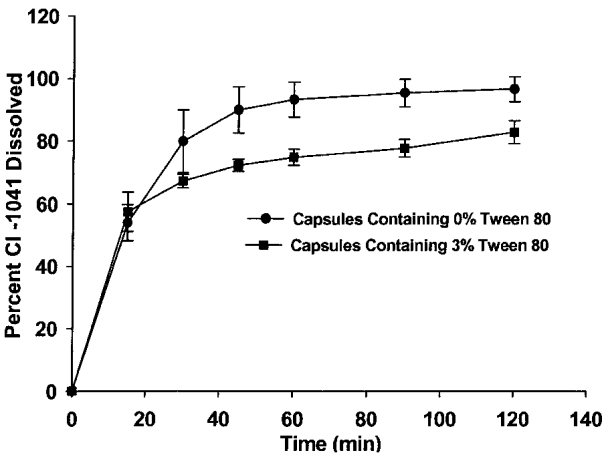

Fig. 2. Dissolution of CI-1041 200-mg strength capsules containing 0 and 3% w/w Tween 80 in 0.1 N HCl at 37°C (n = 3).

a new solid phase formation. However, the process is faster for capsules containing Tween 80.

One possible explanation for this observed impedance effect is that Tween 80 facilitates the solvent mediated transformation of CI-1041 to a less soluble solid phase during dissolution. CI-1041, a weak base, can ionize and potentially precipitate, as CS due to the presence of chloride ions in the dissolution medium. The CS salt is less soluble in 0.1 N HCl than the free form. Phase transformation to a less soluble solid phase on the surface of the original solid phase during dissolution has been reported to impede the solid dosage form dissolution and affect drug bioavailability (4). Dissolution is the net result of solubilzation of the original solid phase and the formation of a less soluble solid phase. The faster the formation of the less soluble solid phase, the slower the overall dissolution rate. In cases where the less soluble solid phase forms on the surface of the original solid phase, the dissolution rate decreases to approach that of the less soluble solid phase as the surface CS coverage increases. Tween 80 may have increased the rate of CS formation by increasing the nucleation rate of chloride salt. Classic nucleation theory predicts that crystal nucleation increases with decreasing interfacial tension (5,6).

We therefore proposed the following hypotheses regarding the effect of Tween 80 on CI-1041 dissolution: (1) In 0.1 N HCl, CI-1041 ionizes and undergoes a solvent mediated phase transformation to form its less soluble CS, and (2) Tween 80 increases the rate of CS nucleation by decreasing the interfacial tension, thereby increasing the formation of CS and decreasing the rate of capsule dissolution.

To test the first hypothesis, bulk dissolution in 0.1 N HCl containing 0 and 1 mg/ml Tween 80 was performed. The formation of CS was confirmed by characterizing the residual solid using PXRD, FTIR, and elemental analysis.

The concentration-time profiles of bulk CI-1041 powder dissolution in 0.1 N HCl are given in Fig. 3. In the absence of Tween 80, CI-1041 concentration rises rapidly to a maximum of 18.6 mg/ml at 2 min, then decreased rapidly to 5.3 mg/ml at 10 min, and eventually leveled to 2 mg/ml at 60 min, representing the solubility limit of the CS. In the presence of Tween 80, similar drug concentration-time profile is observed, and the drug concentration also reaches its maximum of 18.6 mg/ml at 2 min. The drop in drug concentration after reaching its maximum, however, is faster when Tween 80 is present. No change in the UV/Vis spectrum was observed during dissolution. Stability studies showed CI-1041 to be stable in 0.1 N HCl during the course of this experiment. Therefore, the drop in CI-1041 concentration cannot be explained by chemical degradation. Possible pH change, caused by solubilizing, 18.6 mg/ml of drug is also not great enough to cause a drastic decrease in drug solubility and cannot account for such a steep drop in drug concentration.

Physical characterization of the residual solids from the bulk dissolution showed that CI-1041 forms CS in 0.1 N HCl in the presence or absence of Tween 80. The PXRD patterns and the FTIR spectra are given in Figs. 4, and 5 respectively. The PXRD shows that the residual solids from both dissolution media are identical and are different from the starting physical state of CI-1041. The IR peaks are assigned based on published literature on related molecules (7,8). The greatest differences between the residual solids from bulk dissolution and the starting CI-1041 are observed in the C-N stretch region between 1200 and 1300 cm^{-1}. The residual solids exhibit three sharp peaks while the starting CI-1041 exhibits two sharp peaks. These peaks are assigned to the C-N bond in the piperidine ring. The restricted motion of the cyclic C-N bond causes its IR peaks to be sharp. IR absorption changes in this region support the premise that salt or complex formation occur near the piperidine amino group. This is also supported by elemental analysis, which shows a 1:1 CI-1041 to HCl stoichiometry for the residual solids formed in the presence and absence of Tween 80.

To test the second hypothesis that Tween 80 increases the rate of CS nucleation by decreasing the interfacial tension, the intrinsic dissolution of CI-1041 in 0.1 N HCl was performed. The rate of CS formation was determined from the intrinsic dissolution profile and plotted as a function of Tween 80 concentration. When solvent mediated solid phase transformation occurs, the new solid phase forms on the surface of the original solid, and the intrinsic dissolution rate changes gradually from that of the original solid phase to that of the new solid phase (9–11). The rate of the CI-1041 CS formation

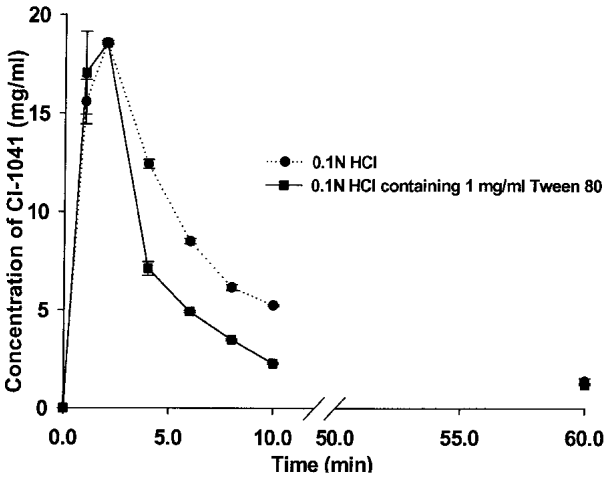

Fig. 3. Bulk Dissolution of CI-1041 in 0.1 N HCl at 23°C in the presence and absence of Tween 80 (n = 3).

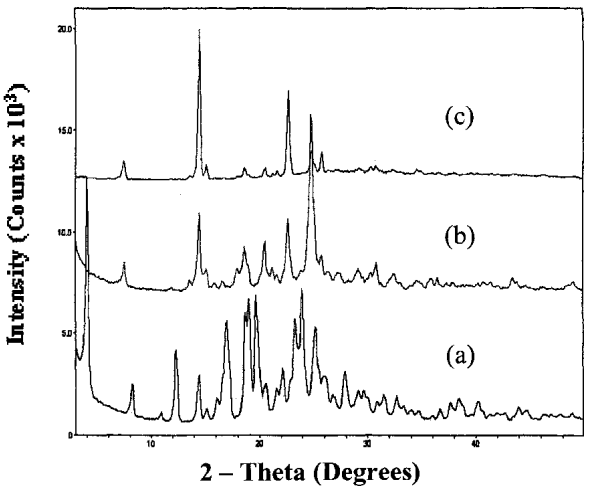

Fig. 4. Powder X-ray diffraction patterns of (a) CI-1041 free form, (b) residual solids from bulk dissolution in 0.1 N HCl, and (c) residual solids from 0.1 N HCl with 1 mg/ml Tween 80.

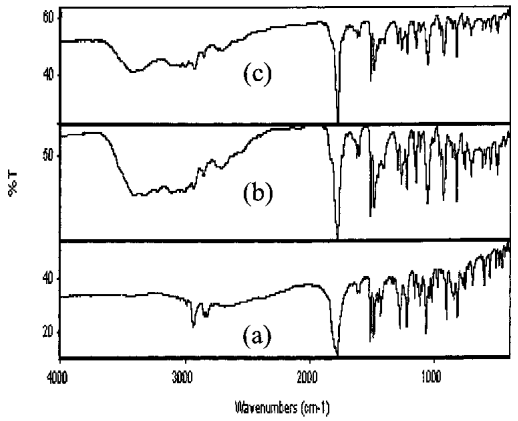

Fig. 5. Fourier transform infrared spectra of (a) CI-1041 free form, (b) residual solids from bulk dissolution in 0.1 N HCl, and from (c) 0.1 N HCl with 1mg/ml Tween 80.

(conversion rate) can be estimated from the intercept of the extrapolations from the two linear regions of the intrinsic dissolution rate profile (Fig. 6). Because concentration of drug in solution is high and the authors observed rapid rate of crystal growth once nucleation occurs, for ease of computation, the rate of CS nucleation was assumed to approximate the rate of CS formation.

Example intrinsic dissolution profiles are given in Fig. 6. The CI-1041 free base intrinsic dissolution profile exhibits two linear segments for all concentrations of Tween 80. The slope of the initial linear segment is steeper than the final linear segment of the dissolution profile. Visual examination of the dissolution pellet showed no chipping and that the constant dissolution surface area of the pellet were approximately maintained. The drug pellet left in the sample holder at the end of the dissolution experiment was characterized by PXRD, and FTIR and showed the formation CI-1041 CS on the surface of the free base. This *in situ* conversion from CI-1041 free base to its CS during dissolution is substantiated by the fact that the intrinsic dissolution rate of the CS is similar to the final intrinsic dissolution rate of the free base as also illustrated in Fig. 6.

The plot of the time required for the formation of the CS on the pellet surface (conversion time), which approximates the time required for nucleation according to our assumption, is given in Fig. 7. The time required for the CI-1041 to convert to its CS during ID ranged from 6–15 min. This time is fast enough to have a significant effect on the dissolution of the capsule formulation. The conversion time, and therefore the nucleation time, statistically decreased ($p < 0.05$) when comparing the 0 mg/ml and 0.5 mg/ml Tween 80 concentrations and then statistically increased ($p < 0.05$) when comparing the 0.5 mg/ml and 2 mg/ml Tween 80 concentrations. Statistical analysis was performed using the Students *t* test (3). The nonparametric Wilcoxon Rank-Sum test (12) statistical analysis was also performed to allow for potential non-normal distribution of the data and a sample size of 3–6. This treatment of the data again demonstrated a statistical difference ($p < 0.05$) between the 0 mg/ml and 0.5 mg/ml Tween 80 concentrations and between 0.5 mg/ml and 2.0 mg/ml Tween 80 concentrations ($p < 0.05$). Therefore, the trend of decreasing conversion time as the Tween 80 concentration is increased to 0.5 mg/ml and the trend of increasing conversion time at Tween 80 concentrations above 0.5 mg/ml is shown to be statistically significant. As noted in Fig. 7, a minimum conversion time or nucleation time was observed at the Tween 80 concentration of 0.5 mg/ml. This minimum, corresponding to a maximum in the rate of nucleation and conversion to CS, coincides approximately with the critical micelle concentration (CMC) of Tween 80, 0.3 mg/ml, determined using surface tension measurements (Fig. 8). This supports our second hypothesis. Because surface tension reduces with increasing surfactant concentration up to the CMC, it is plausible that the maximum nucleation rate occurs at around CMC. Others have also shown that surface active agents can increase nucleation rate by decreasing surface tension up to the CMC (13,14). The increase in conversion time >0.5 mg/ml Tween 80 concentration may be explained by other effects, such as decreased nucleation and crystallization rates resulting from an increase in viscosity (15) or decreased crystallization rate due to adsorption of Tween 80 on the crystal surface (16).

CONCLUSIONS

CI-1041 was found to undergo solvent mediated transformation to its CS during dissolution in 0.1 N HCl. The CS is

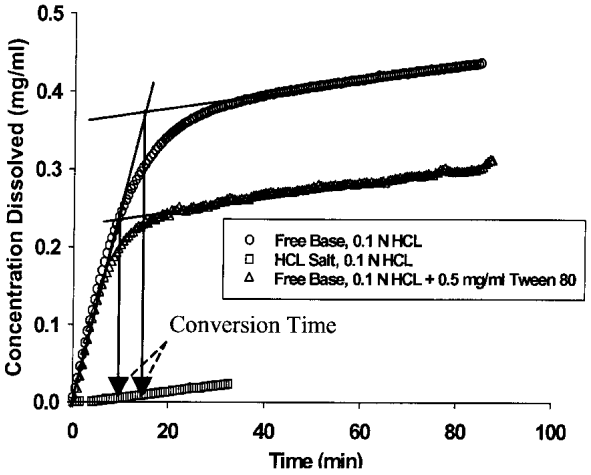

Fig. 6. Representative intrinsic dissolution profiles of CI-1041 and its chloride salt in 0.1 N HCl.

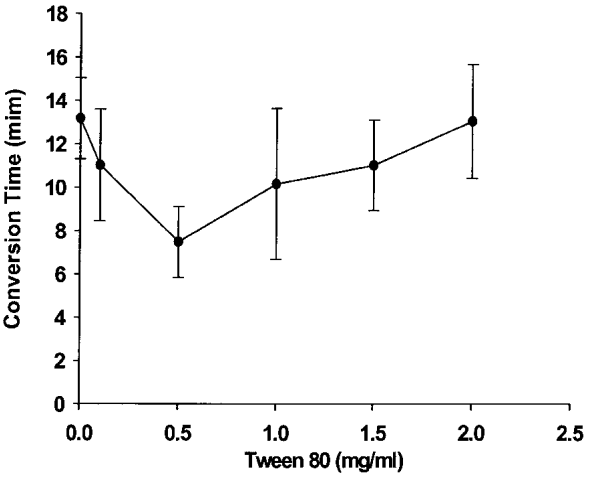

Fig. 7. Plot of time required to convert CI-1041 free form to chloride salt, in 0.1 N HCl at 37°C, as a function of Tween 80 concentration (n = 3–6).

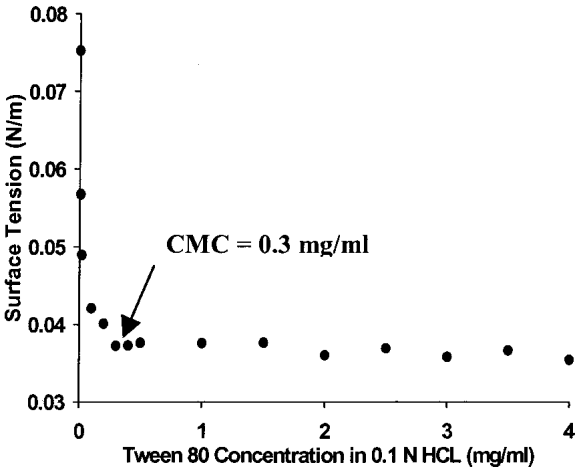

Fig. 8. Surface tension of 0.1 N HCl as a function of Tween 80 concentration at 37°C, determined using an Ostwald viscometer. The critical micellar concentration was determined to be 0.3 mg/ml, above which no further decrease in surface tension was observed.

less soluble in 0.1 N HCl than the starting free form because of the common ion effect. Tween 80 was found to facilitate this transformation to the less soluble CS and have a negative effect on the CI-1041 dissolution. Intrinsic dissolution in 0.1 N HCl shows at low concentrations of Tween 80 (<0.5 mg/ml), the rate of conversion to the CS increases with increasing Tween 80 concentration. This trend is reversed at Tween 80 concentration >0.5 mg/ml. The CMC of Tween 80, determined from surface tension measurements, coincides approximately with the Tween 80 concentration of 0.5 mg/ml, at which the maximum rate of CS formation and therefore nucleation occurs. This suggests that the mechanism by which Tween 80 impedes CI-1041 dissolution below CMC is through reducing surface tension and increasing CS nucleation and thus increased rate of formation of the less soluble CS. Above CMC, other opposing effects such as increases in viscosity and adsorption of surfactant on the crystal surface may have negated the effect of decreasing surface tension on the rate of CS formation.

ACKNOWLEDGMENTS

The authors thank Julie Spence, Helen Shi, and Harvey Qu for valuable assistance.

REFERENCES

1. A. Martin, J. Swarbrick, and A. Cammarata. *Physical Pharmacy, Physical Chemical Principles in the Pharmaceutical Sciences,* Lea & Febiger, Philadelphia, Pennsylvania, 1983 pp. 463–466.
2. United States Pharmacopeia (26). United States Pharmacopeial Convention Inc., Rockville, Maryland, 2003.
3. M. L. Samuels. *Statistics for the Life Sciences*, Dellen Publishing Company, San Francisco, California, 1989 pp. 190–258
4. Y. Kobayashi, S. Ito, S. Itai, and K. Yamamoto. Physicochemical properties and bioavailability of carbamazepine polymorphs and dihydrate. *Int. J. Pharm.* **193**:137–146 (2000).
5. N. Rodriguez–Hornedo and D. Murphy. Significance of Controlling Crystallization Mechanisms and Kinetics in Pharmaceutical Systems. *J. Pharm. Sci.* **88**:651–660 (1999).
6. J. W. Mullin. *Crystallization,* Butter Worth–Heinemann, Oxford, 1993.
7. D. Lin–Vein, N. B. Colthup, W. G. Fateley, and J. G. Grasselli. *The Handbook of Infrared and Raman Characteristic Frequencies of Organic Molecules*, Academic Press, New York, 1991.
8. R. M. Silverstein, G. C. Bassler, and T. C. Morrill. *Spectrometric Identification of Organic Compounds*, John Wiley & Sons, New York, 1991.
9. J. H. de Smidt, J. G. Fokkens, H. Grisjseels, and D. J. A. Crommelin. Dissolution of theophylline monohydrate and anhydrous theophylline in buffer solutions. *J. Pharm. Sci.* **75**:497–501 (1986).
10. N. Rodriguez–Hornedo, D. Lechuga–Ballesteros, and H. J. Wu. Phase transition and heterogeneous/epitaxial nucleation of hydrate and anhydrous theophylline crystals. *Int. J. Pharm.* **85**:149–162 (1992).
11. R. Khankari, L. Chen, and D. J. W. Grant. Physical characterization of nedocromil sodium hydrates. *J. Pharm. Sci.* **87**:1052–1061 (1998).
12. R. A. Johnson and G. K. Bhattacharyya. *Statistics: Principles and Methods*, John Wiley and Sons, New York, 1996.
13. N. I. Ivanova, A. F. Putilin, and E. D. Shchukin. The effect of nonionic surfactant on nucleation kinetics of new phase. *Colloid J.* **58**:578–580 (1996).
14. N. S. Kreshchanovskii, V. I. Prosvirin, and R. P. Zaletaeva. Influence of nitrogen on the surface tension and crystallization of austenitic steels. *Liteinoe Proizvodstvo* **1**:23–24 (1954).
15. H. Oosterhof, R. M. Geertman, G. J. Witkamp, and G. M. van Rosmalen. The growth of sodium nitrate from mixtures of water and isopropoxyethanol. *J. Crys. Growth* **198**:754–759 (1999).
16. S. Luhtala. Effect of sodium lauryl sulphate and polysorbate 80 on crystal growth and aqueous solubility of carbamazepine. *Acta Pharm. Nord.* **4**:85–90 (1992).