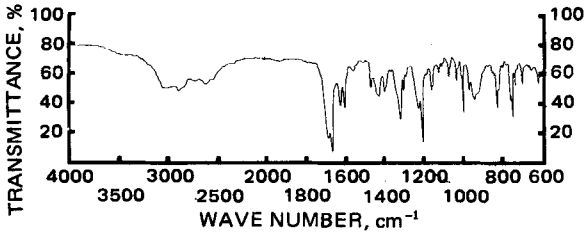

Figure 2—*IR spectrum of itanoxone*

The exchangeable acid proton appeared faintly in dimethyl sulfoxide-d_6, but a very marked singlet was obtained in pyridine-d_5 at 9.9 ppm.

Mass Spectroscopy—The molecular peak was observed at *m/z* 300, corresponding to the molecular mass of the product. The most characteristic fragments of I gave a series of peaks at *m/z* 302, 300, 277, 255, 217, 215, 152, and 76. The peak at *m/z* 302 corresponded to the chlorine 37 isotope. The isotopic peaks at p + 2 were also observed in the various fragments containing chlorine.

Fragmentation is shown in Scheme II. The $C_{12}H_8$ ion (*m/z* 152) (18, 19) was followed by the series of ions at *m/z* 151, 150, 126, 76, 75, 74, and 63. The relative intensities of these ions in the spectrum of I were very close to those in the Cornu–Massot catalog (20) for diphenylene and acenaphthene. This result indicates that the ion obtained after the removal of C=O and the chlorine atom rearranges to give a radical ion with a structure close to diphenylene or acenaphthene.

REFERENCES

(1) "International General Designation," *Chron. Org. Mond. Santé*, **33** (3), list 41-8 (1975).

(2) H. Cousse, G. Mouzin, J. P. Rieu, and A. Delhon (to P. Fabre S. A.), French pat. 2,300,551 (1975).

(3) A. Bizzi, M. T. Tacconi, E. Veneroni, and M. Cini, "7th International Congress of Pharmacology," Paris, France, 1978.

(4) A. Delhon, J. P. Tarayre, H. Lauressergues, and S. Casadio, "International Conference on Atherosclerosis," Milan, Italy, Nov. 1975.

(5) J. Lubetzki and A. Mose, "International Conference on Atherosclerosis," Milan, Italy, Nov. 1975.

(6) F. Mazoyer (to P. Fabre S.A.), U.S. pat. 105,420 (1979).

(7) J. P. Rieu, G. Mouzin, H. Cousse, and A. Boucherle, *J. Pharm. Sci.*, **69**, 49 (1980).

(8) H. Cousse, P. Hascoet, G. Mouzin, and J. P. Rieu, French pat. 79.245.82 (1979).

(9) H. Cousse, G. Mouzin, and J. P. Rieu, (to P. Fabre S.A.), French pat. 2,265,409 (1974) and U.S. pat. 4,058,558 (1977).

(10) H. Cousse, G. Mouzin, and J. P. Rieu, Swiss pat. 595,322 (1975).

(11) P. Pascal, "Traité de Chimie Minérale, Masson et Cie," Paris, France, 1932.

(12) C. Hansch, R. M. Muir, T. Fujita, P. P. Maloney, F. Geiger, and M. Streich, *J. Am. Chem. Soc.*, **85**, 2817, (1963).

(13) T. Fujita, J. Iwasa, and C. Hansch, *ibid.*, **86**, 5175, (1964).

(14) R. Roques, H. Cousse, G. Mouzin, *Acta Crystallogr.*, in press.

(15) R. Gaboriaud, J. C. Halle, and P. Letellier, *Bull. Soc. Chim. Fr.*, **1976**, 1093.

(16) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed., Methuen, London, England, 1966.

(17) M. L. Martin and G. L. Martin, "Manual of Nuclear Magnetic Resonance," Azoulay, Paris, France, 1971.

(18) F. W. McLafferty, "Interpretation of Mass Spectra," 2nd ed., Benjamin, Mass., 1973.

(19) S. Safe, *Org. Mass Spectrom.*, **5**, 1221 (1971).

(20) A. Cornu and R. Massot, "Compilation of Mass Spectral Data," Heyden and Son, 1966.

Effect of Docusate Sodium on Drug Release from a Controlled-Release Dosage Form

WALTER G. CHAMBLISS, ROBERT W. CLEARY, RICHARD FISCHER, ALAN B. JONES, PAUL SKIERKOWSKI, W. NICHOLES, and ARTHUR H. KIBBE ˣ

Received December 22, 1980, from the *Department of Pharmaceutics, University of Mississippi, University, MS 38677.* Accepted for publication April 1, 1981.

Abstract □ This study was designed to determine the effect of a clinically used surfactant, docusate sodium, on the release of chlorpheniramine from a controlled-release dosage form (encapsulated coated pellets). *In vivo* treatments consisted of the controlled-release capsule alone or with 200 mg of docusate sodium. Plasma chlorpheniramine levels were determined, and the *AUC* was calculated. No significant difference in *AUC* values was observed between the two treatments. At a concentration below the CMC, docusate sodium enhanced the *in vitro* drug release rate. The surfactant exerted a greater effect on the release of the first one-third of the drug contained in nonwax-coated pellets. At the CMC, 0.02% (w/v), docusate sodium rapidly entrapped chlorpheniramine in micelles. The overall enhanced dissolution rate *in vivo* may have been offset by micellar drug entrapment.

Keyphrases □ Docusate sodium—effect on drug release from a controlled-release dosage form □ Controlled-release formulations—effect of docusate sodium on drug release □ Surfactants—effect on drug release of controlled-release dosage forms

Most long-acting oral dosage forms utilize a physical barrier to decrease the rate of drug release into the GI tract. The wax coating on the pellets of a controlled-release capsule serves as this barrier (1).

Disintegration of the wax coat is thought to be controlled by the penetration of moisture through pores (2). The pH of the medium reportedly does not affect disintegration (3) although surface tension is thought to be important. The surface tension of intestinal fluid is less than gastric fluid due to bile salts in the intestines. This lowered surface tension may lead to the release of more drug into the intestinal fluids (2). The effect of lowered surface tension in the GI tract on the release of drug from wax-coated pellets has not been reported.

BACKGROUND

Numerous studies have been performed to determine the effect of surfactants on drug absorption, mainly with surfactants that promote oral absorption of a poorly absorbed drug. The exact mechanism by which docusate sodium and other surfactants enhance drug absorption is unknown. The most popular theory has been that surfactants directly alter membrane permeability of the GI tract (4–14). Although the mechanism of this "hyperabsorptive state" is unknown, most investigators believe that the surfactant disrupts the integrity of the epithelial membrane in a reversible fashion (4–11). The removal of proteins (12, 13) and phos-

0022-3549/81/1100-1248$01.00/0

Table I—Accumulative *AUC* (Micrograms Minutes per Milliliter) of Chlorpheniramine from Subjects Receiving 12 mg of Chlorpheniramine in a Controlled-Release Capsule with (Treatment B) or without (Treatment A) 200 mg of Docusate Sodium

	Subject 1			Subject 2		
	Treatment		Area	Treatment		Area
Min	A	B	Change	A	B	Change
40	8.79	5.79	−3.90	5.23	5.48	+0.25
80	18.10	13.13	−4.97	12.30	12.28	−0.02
160	37.10	26.60	−10.50	24.24	25.02	+0.78
240	54.79	40.59	−14.20	41.63	37.26	−4.37
480	107.48	88.24	−19.24	107.68	71.90	−35.78
	Subject 3			Subject 4		
	Treatment		Area	Treatment		Area
Min	A	B	Change	A	B	Change
40	6.36	8.07	+1.71	7.36	8.89	+1.53
80	13.03	19.32	+6.29	17.95	18.20	+0.25
160	25.40	37.69	+12.29	37.03	33.89	−3.13
240	38.16	57.00	+18.84	56.08	52.25	−3.83
480	69.54	105.08	+35.54	113.73	107.61	−6.12
	Subject 5			Subject 6		
	Treatment		Area	Treatment		Area
Min	A	B	Change	A	B	Change
40	9.27	7.14	−2.13	10.49	7.18	−3.31
80	19.28	19.22	−0.06	20.91	18.63	−2.28
160	42.24	41.76	−0.48	40.51	48.93	+8.42
240	64.28	63.05	−1.23	57.38	76.46	+19.08
480	118.70	131.47	+12.77	99.03	156.60	+57.57
	Subject 7					
	Treatment		Area			
Min	A	B	Change			
40	9.18	10.87	+1.69			
80	19.41	21.32	+1.91			
160	41.00	39.46	−1.54			
240	62.11	69.09	+6.98			
480	112.21	145.95	+33.74			

pholipids (13, 14) from the membrane by surfactants may alter permeability. "Plasticization" of the membrane by the action of surfactant molecules in the lipoidal epithelium has also been suggested as a possible mechanism for altered permeability (7).

Gouda and colleagues (4–8) determined that the effect of docusate sodium on drug absorption was concentration related. The critical micelle concentration (CMC) was closely related to the critical concentration for the enhancement of drug absorption. The CMC for docusate sodium was reported to be 0.02–0.03% (w/v) (15). Surfactants can trap drug molecules in micelles that form in surfactant concentrations above the CMC. Since micelles are thought to be too large to diffuse across the mucosal membrane, drugs trapped by micelles are not available for absorption (16).

EXPERIMENTAL

In Vivo—A 2 × 2 Latin square design was used to study the effect of coadministration of 200 mg of docusate sodium on the GI absorption of chlorpheniramine released from a controlled-release capsule[1]. Seven subjects were randomly assigned to two different groups. Study days were separated by 7 days to allow adequate drug clearance of the previous dose.

All subjects were adult males, 22–34 years of age, who were within 10% of their ideal body weight. Since the drugs were not administered on a milligram per killigram basis, only subjects weighing 72–80 kg were used. In addition, all subjects had prestudy test results within the normal laboratory limits.

Subjects fasted for 12 hr prior to drug administration and were allowed water *ad. libitum*. Blood samples were drawn through a 21-gauge heparin lock inserted into a vein on the dorsal side of the forearm. Treatment A consisted of 12 mg of chlorpheniramine in controlled-release capsule dosage form[1]. Treatment B consisted of the chlorpheniramine capsule and two 100-mg docusate sodium capsules[2]. Drugs were ingested with 240 ml of water. Blood samples (7.5 ml) were drawn at 0, 10, 20, 40, 80, 160, 240, 360, and 480 min. Plasma was immediately separated and kept frozen until assayed.

Assay Procedure—The procedure of Chiou *et al.* (17) was modified and used for the assay of chlorpheniramine in plasma. Samples were analyzed by a high-performance liquid chromatograph[3] equipped with a reversed-phase column[4] and a UV detector set at 264 nm[5]. The mobile phase consisted of 20% acetonitrile in phosphate buffer (0.075 *M* monobasic ammonium phosphate in 0.016 *M* phosphoric acid). Chlorpheniramine and the internal standard, brompheniramine, had average retention times of 9.64 and 12.75 min, respectively, at a flow rate of 1 ml/min.

Aliquots (200 μl) of the plasma samples were added to 5-ml centrifuge tubes containing 10 μl of brompheniramine solution (3.67 μg of brompheniramine free base/ml of 0.5% phosphoric acid). Then 200 μl of 60% methanol in 0.2 *M* sodium acetate buffer was added, followed by vortexing for 10 sec. The samples were centrifuged at 400×*g* for 10 min.

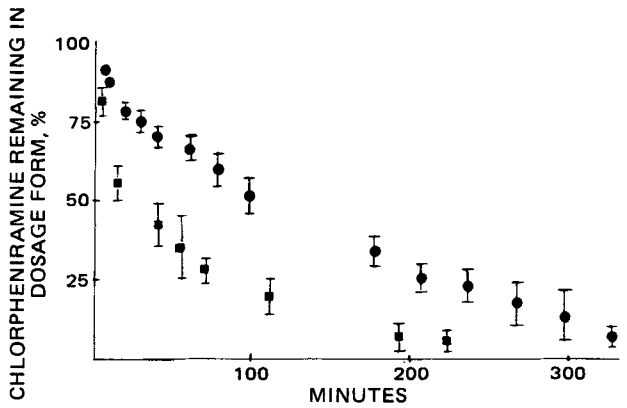

Figure 1—*Linear* in vitro *dissolution profile of 12 mg of chlorpheniramine released from the controlled-release dosage form into 0.1* N *HCl containing 0.01% (w/v) docusate sodium (Group II, ■) or no docusate sodium (Group I, ●).*

[1] Teldrin Spansule, 12 mg, Lot X566573, Smith Kline & French.
[2] Colace capsules, 100 mg, lot MJN73, Mead Johnson.
[3] Varian model 4200.
[4] μBondapak C_{18}, Waters Associates.
[5] Tracor model 970.

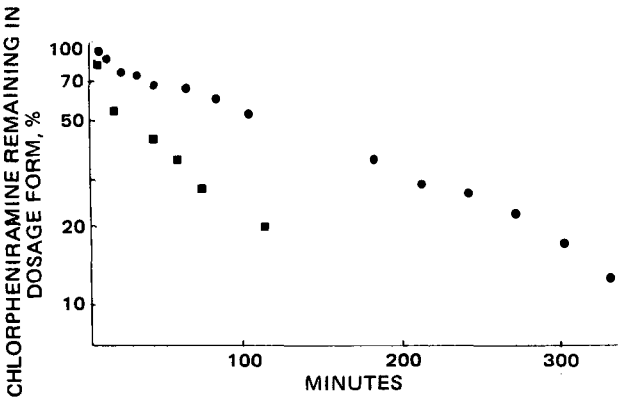

Figure 2—*Semilogarithmic* in vitro *dissolution profile of 12 mg of chlorpheniramine released from the controlled-release dosage form into 0.1* N *HCl containing 0.01% (w/v) docusate sodium (Group II, ■) or no docusate (Group I, ●).*

Duplicate 20-μl injections of the supernate were analyzed by high-performance liquid chromatography (HPLC).

The ratio of the area units of the chlorpheniramine peak to the area units of the brompheniramine peak was used to determine the plasma chlorpheniramine concentration from the standard curve. Linearity (r = 0.992) on the standard curve was observed from 0.0088 mg to 0.352 mg/ml of pooled plasma.

In Vitro—A USP rotating-basket dissolution apparatus[6] was used for all dissolution studies. The controlled-release capsule was placed into the 40-mesh rotating basket and lowered into 500 ml of 0.1 *N* HCl (Group I, no docusate sodium; Group II, 0.01% (w/v) docusate sodium). The dissolution medium was maintained at 37 ± 0.2°. The basket was lowered to a position 2 cm from the bottom of the vessel and rotated at 100 rpm. Aliquots of 3.0 ml were removed from the point midway between the cylindrical edge of the basket and the wall of the vessel.

Samples from Group I were immediately transferred to a cell and analyzed for chlorpheniramine by UV spectroscopy[7] at 264 nm. Samples from Group I were drawn at 0, 5, 10, 20, 30, 40, 60, 80, 100, 180, 210, 240, 270, 300, 330, 360, 390, 420, 450, 540, and 720 min. Samples from Group II were transferred to a 5-ml centrifuge tube and centrifuged at 400×*g* for 10 min. Centrifugation was necessary because the surfactant solubilized the wax, resulting in an opaque suspension. The supernate was transferred to a cell and analyzed at 264 nm. Sampling times for Group II were 0, 5, 15, 40, 55, 70, 110, 190, 220, 250, 280, 355, 540, and 720 min. All samples were returned to the dissolution medium, but samples from Group II were first remixed with centrifuged material.

Micellar Entrapment Study—A single study was performed to determine the effect of surfactant concentration on chlorpheniramine availability. Chlorpheniramine powder USP (12 mg) was added to the dissolution vessel which contained 500 ml of 0.1 *N* HCl and either 0.01 or 0.02% (w/v) of docusate sodium. The solutions were agitated by the rotation of the dissolution basket at 100 rpm. Aliquots of 3.0 ml were removed at 0, 1, 3, 4, 6, 9, and 11 min. The samples were immediately transferred to a cell and the amount of free chlorpheniramine was determined by UV detection at 264 nm.

RESULTS AND DISCUSSION

In Vivo—The plasma concentrations for each subject were plotted *versus* time, and the areas under the curves (*AUC*) were calculated by the trapezoidal rule. Table I shows the *AUC* for each subject at 40, 80, 160, 240, and 480 min. The mean *AUC* and the standard deviations are given in Table II. A t test (p = 0.1) revealed no significant difference between the mean *AUC* obtained after administration of Treatments A (no docusate sodium) or B (200 mg of docusate sodium) at each time period. A paired t test was performed on the mean change in area from Treatment A to B for each time. No significant difference was observed at p = 0.1.

***In Vitro* Dissolution**—Figures 1 and 2 contain graphs of the percent of total drug remaining in the dosage form *versus* time on linear and semilogarithmic graph paper, respectively. Each data point represents the average of four trials. As shown in Fig. 2, the drug was released in a first-order process in both groups. The data (percent remaining *versus* time) were analyzed by the NONLIN subroutine of the AUTOAN computer program (18) to determine if the dissolution profile was best described by a mono- or polyexponential equation. The data from both groups were best described by a biexponential equation.

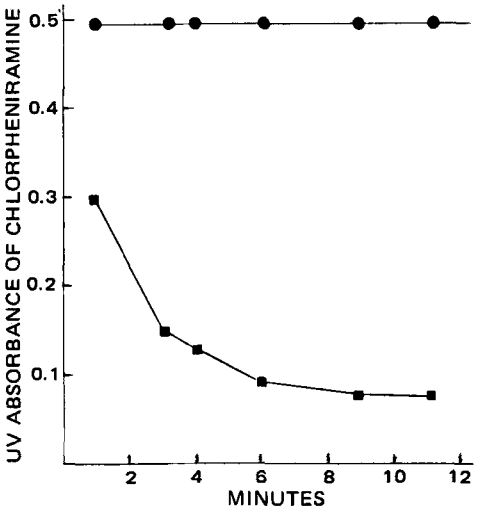

Figure 3—*Micellar entrapment of chlorpheniramine in 0.1* N *HCl containing 0.01% (●) or 0.02% (■) w/v of docusate sodium.*

The results of the analysis are shown in Table III. As expected, the initial dissolution rate constants, k_1, from both groups were greater than the corresponding terminal rate constants, k_2. The first phase of drug release provides the loading dose at a rapid rate. The second rate constant, k_2, is associated with the slower rate at which the maintenance dose is released.

The overall effect that docusate sodium had on drug release from the controlled-release capsule may be observed by comparing the dissolution rate constants calculated for each group. Both initial and terminal rates of drug release were increased by the surfactant. The initial rate constant, k_1, was tripled (from 1.25×10^{-2} to 3.92×10^{-2} min^{-1}) in the presence of the surfactant. The terminal rate constant, k_2, was doubled (from 5.85×10^{-3} to 1.19×10^{-2} min^{-1}) by the surfactant. The ratio of k_1 to k_2 was increased by the surfactant from a value of 2.14 to 3.29. This finding suggests that the surfactant exerted a greater effect on the initial drug release than on the release of the maintenance dose.

One-third of chlorpheniramine contained in the controlled-release capsule was in nonwax-coated pellets, with the remainder of the drug contained in pellets coated with varying thicknesses of wax. Table IV contains the dissolution data divided into two segments, which roughly correspond to the amounts of drug contained in these two types of pellets. The times given in Table IV were determined from regression analysis of the dissolution data using the biexponential equations described in Table III. A value of 95% released was chosen for the last group due to the difficulty of accurately determining the time at which 100% of the drug had been released from the dosage form.

The ΔT values in Table IV represent the time required for chlorpheniramine to be released from each pellet group. The ΔT value for the first one-third of the drug was simply the time required for 33.33% to be released from the dosage form. The ΔT value for the release of drug from wax-coated pellets (33.33–95%) was determined by subtracting ΔT for the first one-third from the total time required to release 95% of the drug. The surfactant decreased the required release time from both pellet groups. However, as shown by the ratio of ΔT from Group I to ΔT from Group II in Table IV, the surfactant had a greater effect on the amount

Table II—Mean *AUC* (Micrograms Minutes per Milliliter) ± *SD* from Subjects Receiving 12 mg of Chlorpheniramine in a Controlled-Release Capsule with (Treatment B) or without (Treatment A) 200 mg of Docusate Sodium

Minutes	Treatment A	Treatment B	Mean Area Change
40	8.10 ± 1.85	7.62 ± 1.87	−0.48 ± 2.30
80	17.28 ± 3.31	17.44 ± 3.39	+0.16 ± 3.49
160	35.36 ± 7.46	36.19 ± 8.45	+0.83 ± 7.53
240	53.49 ± 9.92	56.53 ± 14.38	+3.04 ± 12.52
480	104.05 ± 16.41	115.26 ± 30.78	+11.21 ± 33.38

[6] Erweka type DT.
[7] Varian Techtron 635.

Table III—Results of Regression Analysis Used to Determine Lines of Best Fit from Dissolution Data

Group[a]	Time Interval, min	r	y-Intercept, %	k_1, min^{-1}	k_2, min^{-1}
I	0–20	0.995	98.82	1.25×10^{-2}	—
I	30–390	0.995	95.67	—	5.85×10^{-3}
II	0–15	0.999	100.27	3.92×10^{-2}	—
II	15–190	0.995	67.35	—	1.19×10^{-2}

[a] Group I = 12 mg of chlorpheniramine released from a controlled-release capsule into 0.1 *N* HCl, and Group II = 12 mg of chlorpheniramine released from a controlled-release capsule into 0.1 *N* HCl containing 0.01% (w/v) docusate sodium.

Table IV—Time Required for a Fixed Amount of Chlorpheniramine to be Released from the Controlled-Release Capsule

Percent Released	Group I[a] Time, min	Group I[a] ΔT[c], min	Group II[b] Time, min	Group II[b] ΔT, min	Ratio, $\Delta T_I/\Delta T_{II}$
33.33	64.22	64.22	10.62	10.62	6.05
95.00	502.10	437.88	218.07	207.47	2.11

[a] Dissolution of 12 mg of chlorpheniramine released from the controlled-release capsule into 0.1 *N* HCl. [b] Dissolution of 12 mg of chlorpheniramine released from the controlled-release capsule into 0.1 *N* HCl containing 0.01% (w/v) docusate sodium. [c] Amount of time required for chlorpheniramine to be released from each pellet group.

of time required for the first one-third of the drug to be released. This ratio decreased from 6.05 for the nonwax-coated pellet group to 2.11 for the wax-coated pellet group.

Figure 3 shows the results of the micellar entrapment study. Below the CMC, the amount of free chlorpheniramine in solution was not altered. However, in 0.1 *N* HCl containing 0.02% (w/v) docusate sodium, the amount of free chlorpheniramine decreased rapidly over a short time. This finding demonstrated that the micelles formed in the surfactant solution at the CMC apparently have a high affinity for the chlorpheniramine molecules. Drugs trapped in surfactant micelles must be released from the micelle before crossing the mucosal membrane. Therefore, micellar entrapment *in vivo* could delay or decrease drug absorption. The concentration of docusate sodium that was in contact with the controlled-release capsule in the *in vivo* study probably exceeded the CMC.

CONCLUSIONS

The availability of chlorpheniramine maleate from a controlled-release capsule was not significantly altered *in vivo* by the coadministration of 200 mg of docusate sodium. No significant difference in the *AUC* at 40, 80, 160, 240, and 480 min was observed between the administration of the capsule alone or with docusate sodium.

Docusate sodium enhanced the *in vitro* rate of chlorpheniramine release from the dosage form. The initial drug release rate tripled and the release of the remainder of the drug doubled in the presence of the surfactant. Micelles formed in the dissolution medium at the CMC of docusate sodium were shown to bind rapidly to chlorpheniramine.

There are several possible explanations as to why the enhanced drug release rate was not observed *in vivo*. The surfactant concentration *in vivo* may have exceeded the CMC of docusate sodium. Although the drug release rate may have been enhanced, micellar entrapment of the drug molecules may have occurred. Drug molecules trapped by surfactant micelles are generally considered to be too large to be absorbed from the GI tract. The overall effect of the surfactant on drug release from the dosage form may have been negated by micellar entrapment. The surfactant also was observed to exert its major effect *in vitro* on the release of the loading dose. The nonwax-coated pellets in the controlled-release capsule are designed for the rapid release of the loading dose *in vivo*. Rapid therapeutic blood levels of chlorpheniramine were obtained in this study both in the presence and absence of the surfactant. Initial therapeutic levels of the drug were obtained so fast that any enhancement of initial drug release due to surfactant was not discernible.

The effect of docusate sodium on the absorption of a solution of chlorpheniramine maleate is not known. Investigation of this effect would show whether micellar entrapment of the drug by 200 mg of docusate sodium occurs *in vivo*. Additional insights into the *in vivo* effects of the surfactant on drug release from the dosage form would be gained by decreasing the amount of surfactant administered to the subjects. The effect of premicellar concentrations of the surfactant could be observed.

Although the *in vivo* study showed no significant difference in the *AUC* after administration of the controlled-release capsule alone or with the surfactant, generalizations should not be made. The effect of a surfactant on drug absorption is highly dependent on the drug being studied. Surfactants have been shown to increase, decrease, or have no effect on the absorption of a drug already released from the dosage form. Other drugs contained in similar long-acting oral dosage forms may show marked changes in drug absorption when exposed *in vivo* to a surfactant.

REFERENCES

(1) J. Lazarus and J. Cooper, *J. Pharm. Sci.*, **50,** 722 (1961).

(2) M. Robinson, in "The Theory and Practice of Industrial Pharmacy," 2nd ed., L. Lachman, H. A. Lieberman, and J. L. Lieberman, Eds., Lea & Febiger, Philadelphia, Pa., 1976, p. 449.

(3) E. Parrot, in "Prescription Pharmacy," 2nd ed., J. Sprowls, Ed., Lippincott, Philadelphia, Pa., 1970, p. 153.

(4) M. W. Gouda, *Can J. Pharm. Sci.*, **9,** 37 (1974).

(5) M. W. Gouda, S. Malik, and D. Canaham, *J. Pharm. Sci.*, **64,** 987 (1975).

(6) M. W. Gouda, S. Malik, and S. Khalil, *Can. J. Pharm. Sci.*, **10,** 24 (1975).

(7) M. W. Gouda, N. Khalafallah, and S. Khalil, *J. Pharm. Sci.*, **64,** 991 (1975).

(8) M. W. Gouda, S. Gamal, A. Ebian, and S. Khalil, *Can. J. Pharm. Sci.*, **13,** 16 (1978).

(9) G. Levy and J. A. Anello, *J. Pharm. Sci.*, **57,** 101 (1968).

(10) W. Davis, R. Pfeiffer, and J. Quay, *ibid.*, **59,** 960 (1970).

(11) G. Levy, in "Prescription Pharmacy," J. Sprowls, Ed., Lippincott, Philadelphia, Pa., 1970, p. 73.

(12) S. Feldman and M. Reinhard, *J. Pharm. Sci.*, **65,** 1460 (1976).

(13) S. Feldman, M. Reinhard, and C. Wilson, *ibid.*, **62,** 1961 (1973).

(14) A. Mattocks and S. Penzotti, *ibid.*, **61,** 475 (1972).

(15) P. Mukerjee and K. Mysels, in "Critical Micelle Concentrations of Aqueous Surfactant Systems," U.S. Department of Commerce–National Bureau of Standards, Washington, D.C. 1971, p. 136.

(16) M. Gibaldi, in "The Theory and Practice of Industrial Pharmacy," 2nd ed., L. Lachman, H. A. Lieberman, and J. L. Kanig, Eds., Lea & Febiger, Philadelphia, Pa., 1976, p. 108.

(17) W. Chiou, N. Athanika, G. Peng, R. Nation, and S. Huang, *J. Chromatogr.*, **162,** 367 (1979).

(18) "Decision-Making Pharmacokinetic Computer Program," Publication Distribution Service, University of Michigan, Ann Arbor, Mich., 1974.

ACKNOWLEDGMENTS

Supported by the Research Institute of Pharmaceutical Sciences.