Comparison of the Mechanism of Dissolution of Hydrocortisone in Simple and Mixed Micelle Systems

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Received April 3, 1992; accepted December 15, 1992

Lecithin, a major phospholipid component of human bile, is instrumental in the formation of mixed micelles *in vivo*, with implications for the dissolution and absorption of poorly soluble compounds administered orally. Hydrocortisone, a poorly aqueous soluble drug ($S_{aq} = 1.08 \times 10^{-3}$ *M*), was chosen to compare the rate and mechanism of dissolution in a NaTC/lecithin (mixed micelle) system with its NaTC-only (simple micelle) counterpart. Surface tension, solubility studies, contact angles, rotating disk dissolution rates, and powder dissolution rates were compared for hydrocortisone between solutions containing NaTC/lecithin (4:1) and NaTC-only under conditions representative of the small intestine (0–30 m*M* NaTC, pH 5.5, 0.1 *M* NaCl). At all concentrations, the solubility of hydrocortisone in NaTC/lecithin was slightly higher (up to twofold) than in the corresponding NaTC-only solutions. At low NaTC concentrations, initial powder dissolution rates were faster in the NaTC/lecithin solutions than in corresponding NaTC-only solutions. In contrast, at high NaTC concentrations, initial powder dissolution rates in the NaTC-only solutions were faster. Results indicated that in the NaTC-only system wetting effects predominated for dissolution, while in the NaTC/lecithin system, the dissolution rate of hydrocortisone was enhanced mainly via solubilization.

KEY WORDS: hydrocortisone; bile salts; sodium taurocholate; lecithin; micelles; dissolution rate; solubility; contact angles; wetting.

INTRODUCTION

A common explanation for improvements in the absorption of poorly soluble drugs taken with food is that their dissolution is enhanced by the presence of bile (1). Bile salt surfactants, along with other components of biliary secretion including phospholipids, cholesterol, triglycerides, pigments, and ions, interact not only with each other, but also with dietary components such as fatty acids and triglycerides to modify drug bioavailability.

Using indomethacin and phenylbutazone as model compounds, Miyazaki *et al.* (2,3) attempted to discern the mechanism by which simple bile salt systems enhance the dissolution of poorly soluble drugs. Results suggested that phenylbutazone dissolution in simple bile salt solutions was augmented mostly by improving wetting, while indomethacin dissolution was improved mainly via micellar solubilization. Recently, Bakatselou *et al.* (4)[3] investigated the mechanism by which the powder dissolution rate of five steroids, including hydrocortisone, was improved in sodium taurocholate (NaTC) solutions. Wetting, diffusivity, and solubilization were studied over a range of NaTC concentrations representative of fasted (near 5 m*M* NaTC) and fed states (near 15 m*M* NaTC) in the human gut (5). Like the Miyazaki studies, data indicated that the mechanism by which dissolution was enhanced varied between compounds. Dissolution of danazol, a highly lipophilic steroid (log p = 4.5) (4), was predominantly facilitated by solubilization. In contrast, improvement in the dissolution of hydrocortisone and other moderately lipophilic steroids was mediated mainly via wetting effects.

The current study focuses on the ability of lecithin to modify the mechanism of dissolution of hydrocortisone in the presence of NaTC. After the bile acids, the most abundant group of organic compounds in human bile is the phospholipids, of which lecithin (phosphatidylcholine) is the major component (6). Phospholipids are required for the formation of mixed micelles, which act as solubilizing vehicles for nonswelling amphiphiles such as long chain fatty acids, and cholesterol. Mixed micelles are required to keep cholesterol in solution in bile (7) and are necessary for the absorption of both cholesterol and the fat-soluble vitamins (8). It is, therefore, important to investigate the combined effects of bile salts and lecithin on the dissolution of poorly soluble drugs.

The ratio of lecithin to total bile salt varies with bile output in healthy human subjects (9). At low output, the bile salt/lecithin ratio is approximately 2.5:1, while at high output, the ratio increases to 5:1. Hence, an intermediate value of 4:1 was selected to represent usual conditions in the intestine. The bile salt chosen was NaTC, a prevalent bile salt in the small intestine (5). Because NaTC has a pK_a near 2 (10), this assures its complete ionization at pH 5.5, the pH of the test system. Therefore, variations in bile salt solubility, degree of bile salt ionization, or micelle aggregation number, which might otherwise arise from minor experimental variations in pH,[3] are avoided. Hydrocortisone was selected as the model compound due to its low aqueous solubility, 1.08×10^{-3} *M* (4), which may contribute to its incomplete bioavailability upon oral administration (11).

MATERIALS AND METHODS

Hydrocortisone and NaTC were purchased from Sigma Chemical Co. (St. Louis, MO). To circumvent modifications in powder dissolution rates due to particle size variation, Lot 38F-0863 was used exclusively in NaTC-only studies, while Lot 118F-0818 was used exclusively in NaTC/lecithin studies. Surface areas for Lots 38F-0863 and 118F-0818 were 3.88 ± 0.04 and 2.772 ± 0.002 m^2/g, respectively, as measured by two-point BET analysis (Micromeritics, Norcross, GA). L-α-Egg lecithin (99% pure) in chloroform was purchased from Avanti Polar Lipids (Pelham, AL). Upon arrival

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[3] Except for the surface tension studies, NaTC-only results have been published previously (4). They are presented again in Table I, and in some of the figures, to facilitate comparison of the behavior of hydrocortisone in the two types of surfactant media.

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and monthly, lecithin purity was monitored by thin-layer chromotography (13). Prior to experimental use, excess solvent was blown off in a rotary evaporation apparatus (Rotavapor-R, Brinkman Instruments, Westbury, NY). Headspaces of partially used lecithin vials were replaced with helium before re-storing at −10°C. Test media were adjusted to pH 5.5 with NaOH or HCl, to reflect duodenal pH in the fed state (14). Ionic strength was adjusted to 0.1 *M* with NaCl (Mallinckrodt, Paris, KY).

Surface Tensions

Surface tensions were determined for NaTC-only and NaTC/lecithin solutions both in the absence of hydrocortisone and after saturating with hydrocortisone. Surface tension was measured (n = 5, ~25°C) using a Rosano surface tensiometer (Roller-Smith) with a Wilhelmy plate apparatus (15). Since bile salt micelles form over a concentration range, CMCs were determined as the intersection of the two linear portions of the surface tension-versus-taurocholate concentration curves (16) (0.0–3.0 and 7.43–29.73 m*M* for NaTC only, 0–0.1 and 3.0–6.0 m*M* for NaTC/lecithin).

Solubility, Contact Angles, Rotating Disk, and Powder Dissolution

These procedures have been previously described (4). In NaTC/lecithin, solubilities (n = 3) were monitored for 48 hr, with equilibrium attained between 4 and 12 hr. Initial rotating disk dissolution rate (IRDDR) was studied as a function of both concentration (200 rpm) and rotational speed in NaTC/lecithin medium. To maximize the possibility of detecting reaction-controlled dissolution, experiments were conducted in concentrated solutions (i.e., 15 m*M* NaTC/lecithin) (17), at speeds ranging from 50 to 300 rpm. At least three experiments were performed at each concentration and rotational speed. For powder dissolution studies in NaTC/lecithin solutions, n = 6 at each bile salt concentration.

Calculation of Diffusion Coefficients

Higuchi (18) used a film model to describe diffusion limited dissolution in a surfactant system. The equilibrium expression for the reaction between the free drug and surfactant may be written

$$nD + \text{surfactant} \longleftrightarrow \text{surfactant} - nD$$

where D represents the drug in the system and $n \geq 1$. If equilibrium is assumed to be rapidly established in the boundary layer, the diffusion coefficient in the Levich equation can be replaced by the experimentally measured diffusion coefficient, D_{exp}. The diffusion coefficient of micellar associated drug, D_{mic}, may be calculated from Eq. (1), where C_s is the saturation solubility of the drug in surfactant solution, C_0 is the aqueous solubility of the drug, C_{mic} is the solubility of the drug in the micelles ($C_s - C_0$), and D_0 is the diffusion coefficient of the drug in water.

$$D_{exp} = \frac{(D_{mic}C_{mic}) + (D_0C_0)}{C_s} \quad (1)$$

Analytical Methods

Samples were analyzed by ultraviolet (UV) spectroscopy (Perkin Elmer Lambda 7, Danbury, CT) at the wavelength of maximum absorption, λ_{max}. For hydrocortisone in the NaTC/lecithin solutions, λ_{max} was determined to be 248 nm, a shift of 1 nm from 247 nm, the λ_{max} in NaTC-only solutions. Molar absorptivities were linear over the range of concentrations obtained, indicating compliance with the Beer–Lambert law.

RESULTS AND DISCUSSION

Critical Micelle Concentration (CMC), Solubilization Effects

In the presence of lecithin, the CMC of the NaTC dropped from 4.7 to 0.25 m*M* NaTC (~25°C; NaTC/lecithin ratio, 4:1; 0.1 *M* NaCl). According to Carey and Small (18), this can be expected due to the "more effective solubilization capacity of the mixed micelle." Direct comparison to other literature values is difficult, as CMC is dependent on experimental parameters, including the type of bile salt used, pH, temperature, and counterion concentration. Bakatselou *et al.* (4) obtained a CMC of 3.3 m*M* for NaTC in lecithin-free solutions at 37°C using a Wilhelmy apparatus, while Carey and Small reported CMCs of 4.0 m*M* NaTC (0.15 *M* NaCl, 37°C) for NaTC only and 0.77 m*M* NaTC at a 5.7:1 NaTC/lecithin ratio (0.15 *M* NaCl, 37°C) using a spectral shift technique (18).

Upon saturation with hydrocortisone, the CMC of NaTC in the presence of lecithin decreased further, to 0.18 m*M* (T = 27.352, $P < 0.0001$; Fig. 1), implying some interaction between hydrocortisone and NaTC/lecithin micelles.

In NaTC-only solutions (Table I), the solubility of hydrocortisone improved modestly with increasing NaTC concentration (C_s = 0.01[TC] + 0.35; r^2 = 0.99), at levels above the CMC (7.44–30 m*M* NaTC). Similarly, in mixed micelle solutions, hydrocortisone solubility increased linearly with taurocholate concentration above the CMCR (3.72–15 m*M* NaTC; C_s = 0.02[TC] + 0.35; r^2 = 0.99). A t test comparing the slopes of supra-CMC solubilities plotted versus taurocholate concentration for NaTC/lecithin and NaTC-only systems indicated different slopes (T = 6.197, $P < 0.010$). Overall, NaTC solubilized hydrocortisone to a

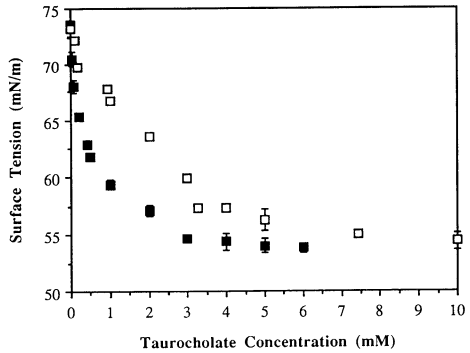

Fig. 1. Surface tension of (□) NaTC-only solutions and (■) NaTC/lecithin (4:1) solutions with taurocholate concentration in the presence of saturated hydrocortisone from 0 to 30 m*M* NaTC.

Table I. Solubility and Initial Rates of Hydrocortisone Dissolution in Rotating Disk and Powder Dissolution Apparatuses, in NaTC Media with and Without Lecithin (Bile Salt/Lecithin Ratio, 4:1)

			Initial dissolution rate (mg/mL/min) × 10^3			
	Solubility (mg/mL)		Rotating disk		Powder	
[NaTC], m*M*	NaTC only (SD)[a]	NaTC/lecithin (SD)[b]	NaTC only (SD)[a]	NaTC/lecithin (SD)[b]	NaTC only (SD)[a]	NaTC/lecithin (SD)[b]
0	0.326 (0.006)	0.325 (0.011)	0.151 (0.008)	0.184 (0.006)	1.8 (0.4)	3.2 (0.4)
0.093	0.312 (0.001)	0.449 (0.006)	0.163 (0.004)	0.198 (0.0001)	1.1 (0.3)	5.6 (0.2)
0.18	ND[c]	0.415 (0.021)	ND	ND	ND	ND
0.93	0.346 (0.008)	0.418 (0.001)	0.153 (0.003)	0.174 (0.005)	2.0 (0.4)	9.3 (3.0)
3.72	0.377 (0.004)	0.413 (0.031)	0.155 (0.007)	0.235 (0.022)	5.9 (1.1)	6.7 (1.4)
7.44	0.425 (0.001)	0.503 (0.043)	0.176 (0.007)	0.230 (0.004)	15.2 (4.3)	6.7 (1.2)
15	0.528 (0.004)	0.629 (0.075)	0.227 (0.037)	0.301 (0.0001)	117.7 (6.3)	8.5 (1.4)
30	0.683 (0.006)	ND	0.261 (0.013)	ND	193.5 (46.0)	ND

[a] Lot 38F-0863; surface area = 3.88 ± 0.04 m^2/g (Micromeritics, Norcross, GA).
[b] Lot 118F-0818, surface area = 2.772 ± 0.002 m^2/g (Micromeritics, Norcross, GA).
[c] Not determined.

modest extent over the physiological concentration range. This effect was enhanced by the presence of lecithin.

Rotating Disk Studies as a Function of Rotational Speed

For hydrocortisone in NaTC/lecithin solutions, the initial rotating disk dissolution rate (IRDDR) increased linearly with the square root of rotational speed (Fig. 2). Least-squares regression analysis indicated a linear relationship (r^2 = 0.99), with an intercept not significantly different from zero (P = 0.116), suggesting a convection–diffusion-controlled dissolution process (19). Bakatselou *et al.* (4) determined that the dissolution of hydrocortisone was also convection-diffusion rate limited in NaTC-only solutions.

Using the film model, D_{mic} for hydrocortisone in NaTC/lecithin micelles was calculated to be 1.38 × 10^{-6} cm^2/sec, corresponding to a micellar radius of 24 Å. This was slower than the diffusion coefficient of 4.36 × 10^{-6} cm^2/sec (4) obtained in a 30 m*M* NaTC-only solution, corresponding to a radius of 7 Å. The diffusivity of hydrocortisone was slower in the presence of lecithin, as expected, on the basis of larger aggregation numbers for mixed micelles, and was comparable to literature values of similar systems (12,20). Although NaTC/lecithin mixed micelles traverse the boundary layer at a slower rate than small NaTC-only micelles, the number of drug molecules per micelle may be higher in the presence of lecithin. If there is an increase in the payload, each mixed micelle will be able to deliver a greater number of drug molecules than its NaTC-only counterpart across the diffusion layer per unit of time. The balance between payload and diffusivity effects can be ascertained by comparing the ratio of the rotating disk dissolution rates with the ratio of solubilities between NaTC-only and NaTC/lecithin systems at supramicellar concentrations. Over the concentration range 0.93 to 15 m*M*, the solubility ratio averaged 1.17 (range, 1.10–1.21), whereas the ratio of rotating disk dissolution rates averaged 1.38 (range, 1.31–1.52). These results suggest that the NaTC/lecithin mixed micelles carried a greater payload than their NaTC-only counterparts, which outweighed the decrease in diffusivity caused by their larger size.

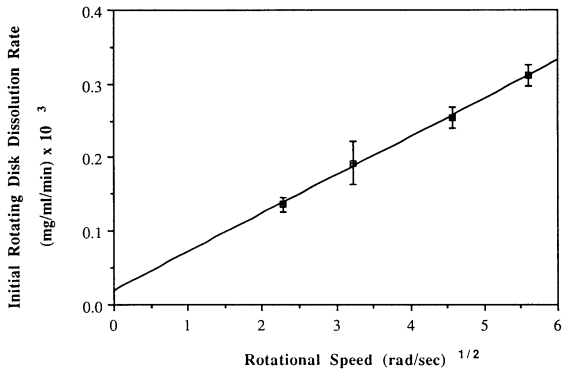

Fig. 2. Effect of rotational speed on the dissolution rate of hydrocortisone in 15 m*M* NaTC/lecithin (4:1) (y = 1.8801 × 10^{-2} + 5.226 × $10^{-2}x$; r^2 = 0.998).

Rotating Disk Studies as a Function of Concentration

Double-y plots comparing dimensionless solubilities ($C_s/C_{s,0}$) versus dimensionless initial rotating disk dissolution rates (IRDDR/IRRDR$_0$) are shown in Fig. 3a. For NaTC-only solutions, a plot of initial rotating disk dissolution rate normalized for solubility (IRDDR/C_s) versus NaTC

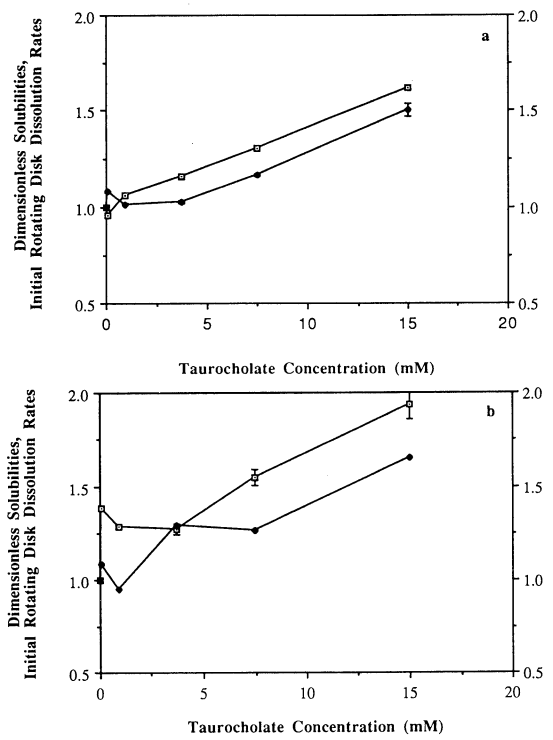

Fig. 3. (a) Double-y plot showing dimensionless solubility (□; $C_s/C_{s,0}$) and dimensionless initial rotating disk dissolution rate (◆; IRDDR/IRDDR$_0$) as a function of taurocholate concentration for the NaTC-only system. (b) Double-y plot showing dimensionless solubility (□; $C_s/C_{s,0}$) and dimensionless initial rotating disk dissolution rate (◆; IRDDR/IRDDR$_0$) as a function of taurocholate concentration for the NaTC/lecithin system.

concentration indicated that the slope of the best fit line was not significantly different from zero (F = 1.4862, P = 0.2898).

The addition of lecithin to bile salt solutions increased the IRDDR at all concentrations by a factor of 1.1–1.5. This minor enhancement in dissolution followed solubility enhancement over the same concentration range. Interestingly, IRDDRs at bile salt concentrations slightly above the respective CMCs of each system (e.g., 7.44 mM NaTC and 0.093 mM NaTC/lecithin) were similar.

Rotating disk rates also paralleled solubility data in NaTC/lecithin studies (Fig. 3b). When the initial rotating disk dissolution was normalized for solubility (IRDDR/C_s) and plotted versus NaTC concentration in the presence of lecithin, the slope was not significantly different from zero (F = 0.0006, P = 0.9817). In summary, the combined effect of solubilization and diffusivity completely accounted for IRDDR increases in hydrocortisone in both NaTC-only and NaTC/lecithin solutions.

Powder Dissolution Studies

In NaTC only, powder dissolution rates (Table I) improved 33-fold as bile salt concentrations increased from submicellar (3.72 mM) to supramicellar (30 mM) levels. Unlike solubility and initial rotating disk dissolution behavior for hydrocortisone in the NaTC-only system, dimensionless initial powder dissolution rates (IPDR/IPDR$_0$) fit an exponential function [y = 0.86 + $10^{(0.13x)}$; r^2 = 0.99] (Fig. 4a).

IPDR/IPDR$_0$ and $C_s/C_{s,0}$ of hydrocortisone plotted versus NaTC concentration for NaTC/lecithin solutions (Fig. 4b) produced regression lines with slopes that were not statistically different (T = 0.2392, $P > 0.800$). Likewise, slopes of regression lines fit through IRDDR/IRDDR$_0$ and IPDR/IPDR$_0$ versus NaTC concentration were not statistically different (T = 0.58219, $P > 0.800$).

After normalizing IPDR for solubility (IPDR/C_s) in the mixed NaTC/lecithin system, the slope of the regression line was not statistically different from zero (F = 0.0399, P = 0.8513). These results suggest that powder dissolution rates of hydrocortisone in NaTC/lecithin solutions were mediated mostly by improved solubilization.

Contact Angles, Wetting Effects

Wetting was the predominant mechanism by which powder dissolution rate increases were mediated in NaTC-only media (4), surpassing the effects of solubilization throughout the range 0–30 mM NaTC. Contact angle measurements showed that wetting continued to increase beyond the CMC (Fig. 5a). Increases in IPDR occurred only after the contact angle was reduced to a value near 45°, corresponding to a NaTC concentration near 7 mM. Above this concentration, both IPDR/C_s and contact angles exhibited asymptotic behavior, implying that complete wetting

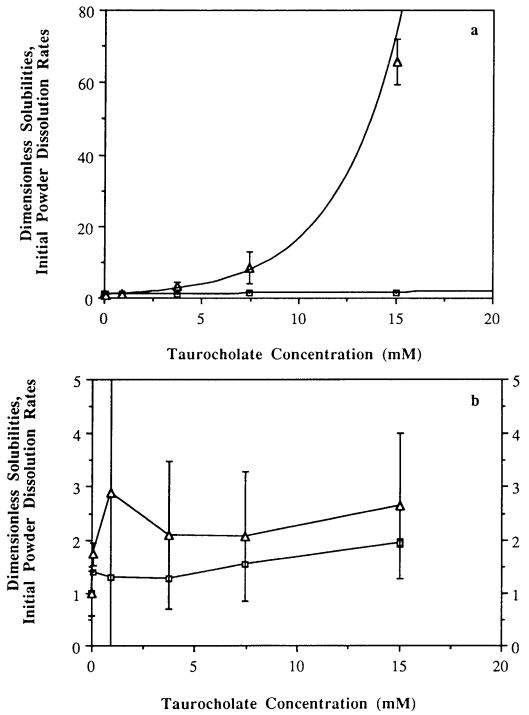

Fig. 4. (a) Double-y plot showing dimensionless solubility (□; $C_s/C_{s,0}$) and dimensionless initial powder dissolution rate [△; IPDR/IPDR$_0$; y = 0.86 + $10^{(0.13x)}$] as a function of taurocholate concentration for the NaTC-only system. (b) Double-y plot showing dimensionless solubility (□; $C_s/C_{s,0}$) and dimensionless initial powder dissolution rate (△; IPDR/IPDR$_0$) as a function of taurocholate concentration for the NaTC/lecithin system.

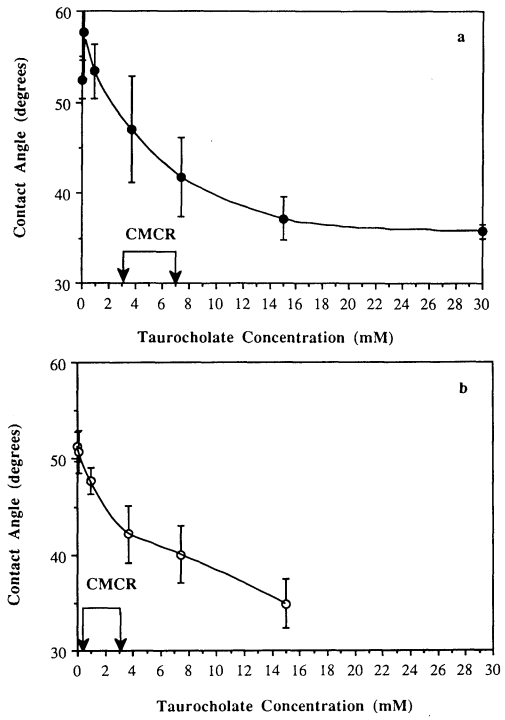

Fig. 5. (a) Contact angles measured using hydrocortisone compacts as a function of bile salt concentration in the NaTC-only solutions (adapted from Ref. 4). (b) Contact angle as a function of taurocholate concentration in the NaTC/lecithin system.

was achieved at a NaTC concentration somewhat above the CMC (4).

Contact angle measurements further suggested that wetting of hydrocortisone would be important when lecithin is added to the bile salt system (Fig. 5b). However, contact angle results overpredicted wetting contributions to the dissolution behavior of hydrocortisone powder. Wetting served, at most, a minor role in the dissolution rate of hydrocortisone powder in NaTC/lecithin solutions. Comparison of powder dissolution behavior in NaTC-only versus NaTC/lecithin systems indicated that lecithin strongly suppressed the ability of NaTC to wet the hydrocortisone powder.

Results suggest that contact angles do not provide an adequate model for correlating the wetting of powders by bile salt/lecithin systems. Contact angles on compacts measure the angle at the solid/liquid/air interface, a function of compound hydrophobicity and adsorbed vapor. The ability of surfactant media to displace air from aggregates, a function of pore geometry (21) which is not measured by the contact angle (22), may be the more important parameter with regard to the dissolution of powders.

Implications for Fasted- Versus Fed-State Behavior

Bile salt concentrations average 4–6 m*M* in the fasted state and about 10–20 m*M* in the fed state (5). IPDR in the simple bile salt system would suggest about a 20-fold increase in the dissolution rate of hydrocortisone between fasted and fed states. However, in the presence of physiologically relevant quantities of lecithin, differences in powder dissolution rates between taurocholate concentrations typical of fasted and fed states are very modest, and not expected to be of clinical significance in terms of the bioavailability of hydrocortisone.

The mechanism by which enhancement of dissolution is achieved appears to be greatly affected by the addition of lecithin to bile salt systems. These results highlight the need to determine dissolution rates in media which closely represent physiological conditions in order to predict whether a drug will have dissolution related differences in bioavailability between the fasted and fed states. An additional difference between fasted and fed states, which also merits further investigation, is that fatty acids and triglycerides are usually present in substantial quantities in the fed state.

ACKNOWLEDGMENTS

L.J.N. is an American Foundation for Pharmaceutical Education (AFPE) fellow. This research was also funded by an Upjohn Research Award.

The authors would like to thank George Zografi, of the University of Wisconsin, for sharing his time and expertise on the construction of the environmental chamber used in the contact angle studies.

These results were presented, in part, as a poster at the Sixth Annual AAPS Meeting and Exposition in Washington, DC, November 17–21, 1991.

NOMENCLATURE

NaTC	Sodium taurocholate
CMC	Critical micelle concentration, m*M*
CMCR	CMC range, m*M*
D_{exp}	Experimental diffusion coefficient, cm^2/sec
D_{mic}	Micellar diffusion coefficient, cm^2/sec
D_0	Aqueous diffusion coefficient, cm^2/sec
C_s	Saturation solubility, mg/mL
$C_{s,0}$	Solubility when [NaTC] = 0, mg/mL
$C_s/C_{s,0}$	Dimensionless solubility
C_0	Aqueous solubility, mg/mL
C_{mic}	Micellar solubility, mg/mL
IRDDR	Initial rotating disk dissolution rate, mg/mL/min
$IRDDR_0$	IRDDR when [NaTC] = 0, mg/mL/min
$IRDDR/IRDDR_0$	Dimensionless initial rotating disk dissolution rate
$IRDDR/C_s$	Initial rotating disk dissolution rate normalized for solubility, min^{-1}
IPDR	Initial powder dissolution rate, mg/mL/min
$IPDR_0$	IPDR when [NaTC] = 0, mg/mL/min
$IPDR/IPDR_0$	Dimensionless initial powder dissolution rate
$IPDR/C_s$	Initial powder dissolution rate normalized for solubility, min^{-1}

REFERENCES

1. M. Gibaldi and S. Feldman. Mechanism of surfactant effects on drug absorption. *J. Pharm. Sci.* 59:579–589 (1970).
2. S. Miyazaki, H. Inoue, T. Yamahira, and T. Nadai. Interactions of drugs with bile components. I. Effects of bile salts on the

dissolution behavior of indomethacin and phenylbutazone. *Chem. Pharm. Bull.* 27:2468–2472 (1979).
3. S. Miyazaki, T. Yamahira, Y. Morimoto, and T. Nadai. Micellar interaction of indomethacin and phenylbutazone with bile salts. *Int. J. Pharm.* 8:303–310 (1981).
4. V. Bakatselou, R. Oppenheim, and J. Dressman. Solubilization and wetting effects of bile salts on the dissolution of steroids. *Pharm. Res.* 8:1461–1469 (1991).
5. M. Rautureau, A. Bisalli, and J. Rambaud. Bile salts and lipids in aqueous intraluminal phase during the digestion of a standard meal in normal man. *Gastroenterol. Clin. Biol.* 5:417–425 (1981).
6. N. Weisbrodt. Bile production, secretion, and storage. In Johnson (eds.), *Gastrointestinal Physiology,* C. V. Mosby, St. Louis, MO, 1985, pp. 94–104.
7. B. Isaksson. On the dissolving power of lecithin and bile salts for cholesterol in human bladder bile. *Acta Soc. Med. Upsalein.* 50:296–306 (1953/1954).
8. W. Simmonds, A. Hofmann, and E. Theodor. Absorption of cholesterol from a micellar solution: Intestinal perfusion studies in man. *J. Clin. Invest.* 46:874–890 (1967).
9. T. Schersten. Formation of lithogenic bile in man. *Digestion* 9:540–553 (1973).
10. M. Carey and D. Small. Micelle formation by bile salts: Physical chemical and thermodynamic considerations. *Arch. Intern. Med.* 130:506–527 (1972).
11. H. Tomida, T. Yotsuyanagi, and K. Ikeda. Solubilization of steroid hormones by polyoxyethylene lauryl ether. *Chem. Pharm. Bull.* 26:2832–2837 (1978).
12. J. Dressman, G. Amidon, and D. Fleisher. Absorption potential: Estimating the fraction absorbed for orally administered compounds. *J. Pharm. Sci.* 74:588–589 (1985).
13. B. Fried and J. Sherma. *Chromatographic Science Series,* 1986, pp. 223–265.
14. J. Dressman, R. Berardi, L. Dermentzoglou, T. Russell, S. Schmaltz, J. Barnett, and K. Jarvenpaa. Upper gastrointestinal (GI) pH in young, healthy men and women. *Pharm. Res.* 7:756–761 (1990).
15. J. Padday. The measurement of surface tension. In Matijevic (ed.), *Surface and Colloid Science,* Wiley-Interscience, New York, 1969, pp. 124–131.
16. P. Mukerjee. Micellar properties of drugs: Micellar and nonmicellar patterns of self-association of hydrophobic solutes of different molecular structures—monomer fraction, availability, and misuses of micellar hypothesis. *J. Pharm. Sci.* 63:972–981 (1974).
17. J. Tao, E. Cussler, and D. Evans. Accelerating gallstone dissolution. *Proc. Natl. Acad. Sci.* 71:3917–3921 (1974).
18. W. Higuchi. Effects of interacting colloids on transport rates. *J. Pharm. Sci.* 53:532–535 (1964).
19. V. Levich. *Physicochemical Hydrodynamics,* Prentice-Hall. Englewood Cliffs, NJ, 1962.
20. F. Woodford. Enlargement of taurocholate micelles by added cholesterol and monoolein: Self-diffusion measurements. *J. Lipid Res.* 10:539–545 (1969).
21. P. Heertjes and W. Witvoet. Some aspects of the wetting of powders. *Powder Technol.* 3:339–343 (1969/1970).
22. Y. Yang and G. Zografi. Use of Washburn-Rideal equation for studying capillary flow in porous media. *J. Pharm. Sci.* 75:719–720 (1986).