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Research Article

Solubilization and Wetting Effects of Bile Salts on the Dissolution of Steroids

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The ability of sodium taurocholate to increase the initial dissolution rate of five steroids was studied in terms of effects on solubility, wetting, and diffusion coefficient. For all compounds, wetting effects predominated over solubilization effects at bile salt concentrations representative of the fasted state. For hydrocortisone, triamcinolone, betamethasone, and dexamethasone, this trend also continued at the higher bile salt concentrations typical of the fed state. Bile salts solubilized these compounds by a factor of two or less, and diffusivity changes were negligible at bile salt concentrations up to 30 m*M*. For the more lipophilic danazol, the wetting effects were small and of importance only at premicellar levels of bile salt. At higher concentrations, the increase in solubility was the predominant factor. Incorporation into micelles appeared to decrease the diffusivity slightly, but this was important only at bile salts concentrations of 15 m*M* or higher. In conclusion, it appears that even within a series of structurally related compounds the mechanism by which bile salts mediate increases in dissolution rate can differ considerably.

KEY WORDS: steroids; dissolution rate; solubility; wetting; diffusivity; bile salts; sodium taurocholate.

INTRODUCTION

The ability of sodium taurocholate to increase the initial dissolution rate of five steroids was studied in terms of its effects on solubility, wetting and diffusion coefficient. A Noyes–Whitney (1) type of expression can be used to describe the initial rate of powder dissolution,

$$DR = dC/dt = (AC_sD)/(Vh)$$

where DR, the dissolution rate, is a function of the surface area available for dissolution, A, the saturation solubility of the compound, C_s, the diffusion coefficient of the compound, D, the volume of the dissolution media, V, and the boundary layer thickness, h. The addition of bile salts in the dissolution medium can be expected to alter C_s via solubilization and surface area A via wetting effects. Minor changes in diffusivity may also occur when a large percentage of the drug is associated with the micelles.

The contribution of solubilization by bile salts to the dissolution rate of drugs has been studied extensively (2–10). However, there are very few studies that have addressed the question of the degree to which the enhancement of the dissolution rate is due to wetting of the powder by bile salts. Furthermore, very little work has been done to determine the relative importance of solubilization vs wetting. Miyazaki *et al.* (11,12) proposed that the dissolution rate enhancement by bile salts of indomethacin was due mostly to solubilization, while for phenylbutazone the effect was due mostly to wetting. Similarly, Weintraub (13) found that the increase in the dissolution rate of salicylamide at physiological bile salt concentrations could not be explained by solubility results alone.

In order to elucidate the mechanism by which the dissolution of steroids is improved by bile salts, the factors that can contribute to the increase in the rate of powder dissolution must be examined separately. Dissolution enhancement via increases in the surface area available for dissolution is related to the ability of the liquid to wet the powder surface. It has been shown that the ability of a liquid to improve the wetting of hydrophobic powders is dependent on the contact angle and the structure of the powder aggregates (14). Of these two factors, only the contact angle can be readily characterized as a function of bile salt concentration. The degree of solubilization by bile salts micelles can be determined by measuring solubilities at several bile salt concentrations. Finally, the effect on diffusivity can be determined by studying the rate of dissolution by the rotating disk method as a function of speed of rotation in the presence and absence of bile salt micelles. These experiments also provide a means of determining whether the mechanism of the dissolution kinetics is diffusion-convection or reaction controlled. In an effort to separate solubilization from wetting contributions to dissolution rate, each of the above-mentioned parameters was

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compared to the rate of dissolution determined both in USP apparatus and by the rotating disk method.

MATERIALS AND METHODS

Hydrocortisone was purchased from Sigma Chemical Co. (St. Louis, MO). Betamethasone and dexamethasone were donated by The Upjohn Co. (Kalamazoo, MI). Danazol and triamcinolone were donated by the Sterling-Winthrop Research Institute (Rensselaer, NY) and Lederle Laboratories (Pearl River, NY), respectively. Table I summarizes the physicochemical properties and the surface areas of the compounds studied.

Sodium taurocholate was purchased from Sigma Chemical Co. (St. Louis, MO). The concentrations of taurocholate used were based on physiological bile salt concentrations in the fasted and fed state (15–20). The CMC of sodium taurocholate was determined by surface tension experiments to be 3 m*M* at 37°C and 0.1 ionic strength.

Dissolution Experiments

Powder Dissolution Experiments

The USP paddle method (Vanderkamp 600 dissolution tester, Van-kel Industries, Edison, NJ) was used to determine the dissolution rate of powdered drug at 100 rpm and 37°C. The volume of the test medium was 400 ml. For each compound, one lot was used for all dissolution studies in order to circumvent batch-to-batch variation effects on the specific surface area of the sample. The surface area of each drug was measured by adsorption of krypton at Micromeritics Inc. (Norcross, GA). Results are presented in Table I. To determine the rate of dissolution, samples were withdrawn at specific intervals over a period ranging from 30 min (hydrocortisone in 30 m*M* NaTC) to 4 hr (danazol in bile salt-free solution) and immediately replaced by an equal volume of dissolution medium kept at the same temperature. The samples were then filtered through a 0.4-μm-pore size polycarbonate membrane (Nuclepore Co., Pleasanton, CA), diluted if necessary, and assayed by UV spectroscopy or HPLC.

In order to compensate for the previously removed samples, a cumulative correction was made using the following formula (21):

$$C_n = C_{n\text{meas}} + (V_s/V_d)\, C_{s\text{meas}}$$

where C_n is the expected concentration of the nth sample if previous samples had not been removed, $C_{n\text{meas}}$ is the measured concentration, $C_{s\text{meas}}$ is the concentration in the previous sample, V_s is the sample volume, and V_d is the dissolution medium volume. The data were processed using a Macintosh SE program.

Dissolution rates were calculated from the linear portion of the concentration-vs-time plot. The regression analysis was performed by STATWORKS Macintosh software. Whenever feasible, the concentrations used for the analysis were kept below 20% of the solubility of the drug in the corresponding medium in order for the sink conditions assumption to be valid (22,23). This was not always possible, however, due to the low aqueous solubility of the drug and/or to the large increase in available surface area at high bile salt concentrations.

Table I. Physicochemical* Properties and Surface Areas of Steroids Studied

Compound	S_{aq} (M)[a]	logP[a]	logP[c]	m.p. (°C)[d]	area (m^2/g)[e]
hydrocortisone	1.08×10^{-3}	1.60	1.50	219	3.88 ± 0.04
dexamethasone	2.58×10^{-4}	1.83	1.95	270	5.39 ± 0.03
triamcinolone	2.07×10^{-4}	1.03	1.02	270	1.88 ± 0.01
betamethasone	1.71×10^{-4}	1.94	2.01	233	1.16 ± 0.03
danazol	1.80×10^{-6}[b]	4.53[b]		225	1.65 ± 0.02

[a] Tomida (1978) (37).
[b] Determined experimentally.
[c] Caron (1984) (36).
[d] Merck Index.
[e] Micromeritics (Norcross, Georgia).
* All partition coefficients are for partitioning between octanol and water.

Rotating Disk Dissolution Experiments

Dissolution rates were also determined by the rotating disk method (24) for each of the compounds at the same levels of sodium taurocholate used for the powder dissolution studies. The rotating disk apparatus consisted of a water-jacketed beaker maintained at 37°C with a constant water bath (Thermomix 1441, B. Braun, West Germany) and a stainless-steel Wood's die supported by a plexiglass holder with a shaft attached to an overhead synchronous motor of variable speed (Cole Palmer Instrument Co., Chicago, IL), which was calibrated with a digital tachometer (Cole Palmer Instrument Co., Chicago, IL). The jacketed beaker contained the dissolution medium (200 ml) in which the stainless-steel die supporting the disk was immersed. For all the compounds studied, a rotational speed of 200 rpm was used to determine the effect of increasing taurocholate concentration on the rate of dissolution. The disks were compressed in a Carver Press (Summit, NJ) and had a diameter of either 1 or 1.27 cm. Sample analysis was by flowthrough UV (Perkin Elmer Lambda 3, Norwalk, CT) for hydrocortisone and triamcinolone, while for betamethasone, dexamethasone, and danazol, HPLC assay was required.

Dissolution rates by the rotating disk method were calculated from the slope of the concentration-vs-time plot. The regression analysis was performed by Statworks Macintosh software. The sink conditions assumption was valid throughout each experiment since the concentrations measured were always below 20% of the drug's solubility in the corresponding medium. For compounds that required manual sampling, a cumulative correction was made for the removed samples as previously described.

For each compound, rates of dissolution by the rotating disk method were studied not only as a function of NaTC concentration but also as a function of speed of rotation. For the rotating disk method, the transport coefficient has been calculated to be (24)

$$k_t = 0.62\, \phi^{1/2}\, D^{2/3}\, \nu^{-1/6}$$

where ϕ is the speed of rotation, D is the diffusion coefficient

and v is the kinematic viscosity. k_r, and therefore the diffusion coefficient D, can be determined experimentally from the slope of the concentration-vs-time plot. Also, the linearity of the plot of the observed rate constant vs the square root of the square root of the speed of rotation would indicate that a transport- rather than a reaction-controlled mechanism was operative. The rotating disk dissolution rate of each compound was studied as a function of speed of rotation in a 30 mM NaTC solution. The same experiments were performed in a 0.1 N NaCl solution which served as the control. A break in the line at higher rotational speeds would indicate a change of mechanism, from diffusion-controlled for lower rpm to reaction-controlled at higher rpm values (25).

Solubility Studies

Screw-cap vials containing excess solid together with 20 ml of the corresponding bile salt solution were shaken on an orbital rotating mixer (Adam's Nutator, Becton Dickinson, Parsippany, NJ) in an oven maintained at 37°C (Thelco Precision, Precision Scientific Co., Chicago, IL). Samples were taken at 4, 8, 24, and 48 hr, filtered through 0.4-μm polycarbonate membranes (Nuclepore, Pleasanton, CA), diluted with an appropriate diluent (usually mobile phase or dissolution medium), and analyzed either by UV spectroscopy or by HPLC.

Contact Angle Studies

Advancing angles were measured using the sessile drop technique (26). The contact angles of the drugs were determined by a method similar to the one used by Zografi *et al.* (27). A constant-volume (2- to 3-μl) drop of the test liquid was added on the surface of compacts (Carver Press, Summit, NJ) of the compounds by means of a micrometer syringe (Rame-Hart Inc., Mountain Lakes, NJ). Angles measured from both sides were compared to determine that the drop was symmetrical. For danazol, the drop was recorded with a videocamera, digitalizing each frame and storing the data in a Macintosh Plus computer. For the other compounds a Rame-Hart goniometer (Rame-Hart Inc., Mountain Lakes, NJ) was used to determine the contact angles. Contact angles were measured on at least three disks for each compound.

HPLC Assay

For danazol, a Partisil 10 ODS 10-μm column, 250 mm in length and 4.6 mm in internal diameter (Whatman Inc., Clifton, NJ), was used in conjunction with a mobile phase consisting of 30% water, 30% methanol, 40% acetonitrile. A flow rate of 1 ml/min (Spectroflow 400, Kratos Analytical, Ramsey, NJ) resulted in an 8-min retention time. The absorbance was measured at 280 nm (Spectroflow 773 Absorbance Detector, Kratos Analytical, Ramsey, NJ). For the other steroids a mobile phase consisting of 45% water and 55% methanol was used. At a flow rate of 1.2 ml/min, the retention times for triamcinolone, betamethasone, and dexamethasone were 5, 7, and 8 min, respectively. The absorbance was measured at 242 nm. A constant volume (10 μl) of each sample was injected into the column via an automatic sampler (AN-728 autosampler, Anspec, Ann Arbor, MI) and injector (two-position electric valve actuator, Valco Instruments Co. Inc., Houston, TX). The signal was recorded and analyzed by a chromatointegrator (Model D-2000, Hitachi, Ltd., Tokyo). The method of external standards was used to convert the measured peak heights to concentration units. Several standard solutions were assayed during the course of each run, employing concentrations similar to the concentration of the unknown. Calibration curves for standard solutions had excellent correlation coefficients in all cases (R^2 values of 0.99 were typical).

UV Assay

The maximum wavelengths and absorptivities (ml/mg/cm) of betamethasone, dexamethasone, hydrocortisone, and triamcinolone were determined in the presence and absence of sodium taurocholate by a Perkin–Elmer Lambda 7 spectrophotometer (Perkin–Elmer, Norwalk, CT). The test media were prepared the same way as in the dissolution experiments. The Beer–Lambert law was closely obeyed for each compound at all bile salt levels (R^2 values of 0.999 were typical). The introduction of bile salt in the solution did not affect either the wavelengths or the absorptivities of the compounds.

RESULTS

Transport vs Reaction Control of Dissolution

For the test media used, the initial dissolution rate for the rotating disk of each compound increased linearly as a function of the square root of the rotational speed. The regression line passed through the origin, the y intercept not being significantly different from zero, indicating that in the presence of sodium taurocholate micelles, the dissolution rate constant for all the compounds studied was diffusion-controlled. A typical example is given in Fig. 1 for danazol in the 30 mM NaTC test medium.

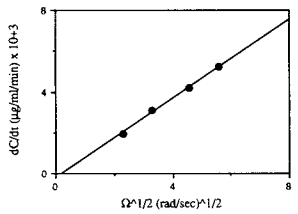

Fig. 1. Effect of rotational speed on the dissolution rate of danazol in 30 mM sodium taurocholate solution in the rotating disk apparatus ($y = -0.227 + 0.973x$, $r^2 = 0.997$).

Diffusivity Studies

Table II summarizes the diffusion coefficients of each compound in the 0.1 N NaCl and the 30 mM NaTC solution. No significant change in diffusivity was observed between the two levels of bile salt except in the case of danazol, for which the diffusivity decreased from 2.7×10^{-6} cm^2/sec for the 0.1 N NaCl solution to 1.67×10^{-6} cm^2/sec in the 30 mM NaTC solution. These results can be explained if we consider that the apparent diffusion coefficient in a micellar me-

dium, D_{app}, is a function of both the diffusion coefficient of free drug, D_{free}, and the diffusion coefficient of the drug associated with the micelles, D_{mic} (28,29):

$$D_{app} = p\,D_{mic} + (1 - p)\,D_{free}$$

where p is the fraction solubilized and $(1 - p)$ the fraction of the free drug. For compounds other than danazol, the extent of association with micelles was too small for there to be a significant effect on the diffusivity.

For danazol in a 30 m*M* sodium taurocholate solution, the calculated value of p is 0.976, indicating that most of the drug is associated with micelles and that the apparent diffusivity in the micellar bile salt solution will be driven by the micellar term. D_{mic} in the chenodeoxycholate/cholesterol system was previously determined to be 1.6 to 2.1 $\times$ 10^{-6} cm^2/sec (30). Assuming that the taurocholate/danazol system is behaving similarly, and taking into account the fact that danazol and cholesterol are of the same molecular size, D_{app} for danazol in 30 m*M* sodium taurocholate solution is calculated to be 1.6 to 2.1 $\times$ 10^{-6} cm^2/sec. This value is very similar to the D_{mic} and to the experimental value as determined by the rotating disk experiments (Table II).

Hydrocortisone

The effects of NaTC on the initial rate of dissolution in both the rotating disk and the powder dissolution apparatus are shown in Fig. 2. As the NaTC concentration increased there was a dramatic increase in the dissolution rate of hydrocortisone powder. The increase occurred above the CMC of NaTC. Below the CMC there was little effect, with dissolution rate at a minimum level. For the rotating disk dissolution the increase in dissolution rate was much less dramatic, indicating that the effect was mediated via different mechanisms in the two types of experiment. The solubility of hydrocortisone at various concentrations of NaTC is given in Table III. For low taurocholate concentrations (below the CMC) there was no increase in the solubility. For concentrations higher than the CMC the solubility increased linearly with the bile salt concentration. Comparing the solubility profile with the initial rate of dissolution obtained by the rotating disk method, it is obvious that the rotating disk behavior mirrors the solubility profile, indicating that the increase in the dissolution rate in the rotating disk experiments was due primarily to the increase in solubility. On the other hand, comparison of the solubility profile with powder dissolution results indicated that the dramatic increase in powder dissolution rate could not be explained by solubility effects alone and suggested that these differences might be attributable to wetting effects. The contact angle decreased with decreasing NaTC concentration (Fig. 3) until it reached

Table II. Diffusion Coefficients (cm^2/sec) $\times$ 10^{+6} of the Steroids Studied in 0.1 N NaCl and 30 mM NaTC Solution

compound	0.1 N NaCl	30 mM NaTC
hydrocortisone	4.73	4.36
triamcinolone	3.42	3.88
dexamethasone	6.03	ND
betamethasone	3.05	3.44
danazol	2.70	1.67

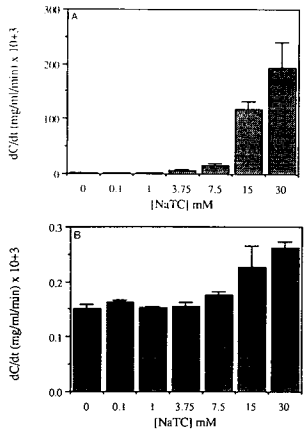

Fig. 2. Initial dissolution rate of hydrocortisone (A) powder dissolution in USP apparatus and (B) dissolution from a rotating disk, at several concentrations of sodium taurocholate.

a minimum at approximately 36°. The decrease in contact angle was well correlated with the increase in the initial powder dissolution rate (after normalizing for solubility by taking the quotient of the initial dissolution rate and the solubility at the given bile salt concentration). Increases in the dissolution rate due to wetting only occurred after the contact angle was reduced to a value of about 40°, corresponding to a NaTC concentration of about 7 m*M*. As the contact angle decreased the normalized dissolution rate increased, asymptoting toward a constant value as the contact angle approached a minimum value. The wetting process approached completion as the contact angle approached a minimum value, which in the case of hydrocortisone occurred between 15 and 30 m*M* NaTC. Finally, the diffusion coefficient in 0 m*M* was not found to be significantly different from the coefficient in 30 m*M* NaTC (Table II), suggesting that changes in diffusivity were not important in determining the dissolution rate of hydrocortisone over the range of NaTC concentrations studied.

Dexamethasone

The effects of sodium taurocholate on the initial rate of dissolution both by the USP apparatus and the rotating disk method are given in Fig. 4. As the bile salt concentration increased the rate of powder dissolution increased. This was true even for concentrations of taurocholate below the CMC, for which there was a small but definite increase in the rate of dissolution. The largest increase seemed to occur for concentrations near the CMC, while at high bile salt concentrations the rate of dissolution approached a maximum

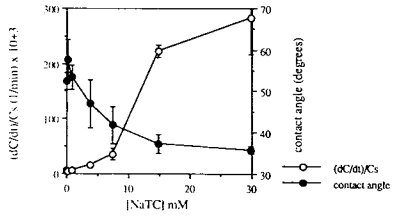

Fig. 3. Simultaneous plot of initial powder dissolution rate for hydrocortisone (normalized for solubility at the given bile salt concentration) and contact angle, as a function of sodium taurocholate concentration.

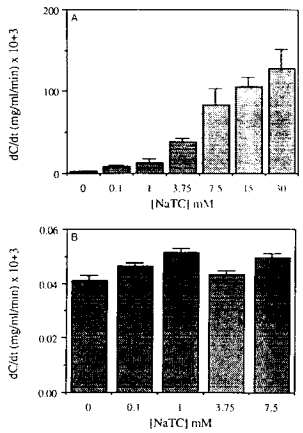

Fig. 4. Initial dissolution rate of dexamethasone (A) powder dissolution in USP apparatus and (B) dissolution from a rotating disk, at several concentrations of sodium taurocholate.

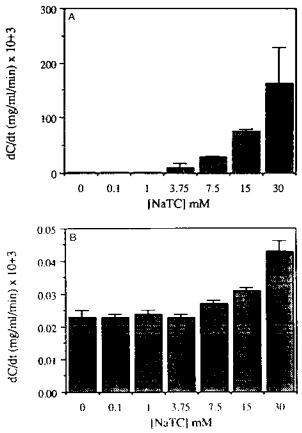

Fig. 6. Initial dissolution rate of betamethasone (A) powder dissolution in USP apparatus and (B) dissolution from a rotating disk, at several concentrations of sodium taurocholate.

value. For the rotating disk experiment, the dissolution rates for the two high bile salt concentrations are not included in the graph because the disks kept "capping off" during the experiment resulting in inconsistent and unreliable results. This behavior was observed only in the case of dexamethasone. For the concentrations studied, there was no increase in rotating disk dissolution as the bile salt concentration increased, suggesting lack of solubilization by the bile salt. Solubility studies (Table III) indicated that at concentrations below or near the CMC, no trend in solubility with taurocholate concentration was observed, consistent with the rotating disk results. At concentrations higher than the CMC, there was some increase in the solubility, but the degree of solubilization by the bile salts was small, especially at physiologically relevant levels of bile salts (the solubility in 15 m*M* NaTC was greater than solubility in 0.1 *N* NaCl by less than a factor of 1.5). To establish that the bile salts improve the wetting of dexamethasone, its contact angle was studied as a function of sodium taurocholate concentration (Fig. 5). For dexamethasone, contact angle decreased as a function of contact angle concentration until it reached a minimum at approximately 40°, corresponding to a NaTC concentration of 7.5 m*M*. The decrease in contact angle was very well correlated with the increase in the initial powder dissolution rate normalized for solubility. As the contact angle decreased the normalized dissolution rate increased, reaching a plateau with no further increase after the contact angle reached its minimum value (Fig. 5). Diffusivity of dexamethasone could not be measured at 30 m*M* NaTC because the disks kept capping off into the dissolution medium.

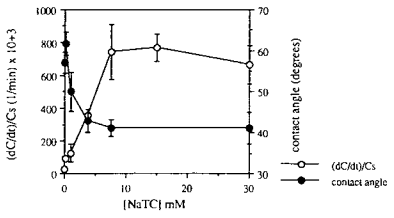

Fig. 5. Simultaneous plot of initial powder dissolution rate for dexamethasone (normalized for solubility at the given bile salt concentration) and contact angle, as a function of sodium taurocholate concentration.

Betamethasone

The effects of sodium taurocholate on the initial rate of dissolution both by the USP apparatus and the rotating disk method are given in Fig. 6. For concentrations below the CMC only a slight increase in powder dissolution was observed. For concentrations near to or higher than the CMC there was a significant increase in the dissolution rate. On the other hand, for the rotating disk dissolution, as the concentration of sodium taurocholate increased, there was only a modest increase in the dissolution rate even for concentrations well above the CMC. At taurocholate concentrations below the CMC there was no increase in the solubility. For concentrations higher than the CMC there was an increase in solubility similar to that observed for dexamethasone and hydrocortisone, a factor of only about 2 between 0 and 30 m*M* NaTC. These results suggest that the pronounced influence of bile salt concentration on the dissolution rate in the powder dissolution experiments may be attributable to wetting effects. For betamethasone, contact angle decreased as a function of NaTC concentration until it reached a minimum at approximately 45°, corresponding to a concentration of 15 m*M* NaTC. As for dexamethasone and hydrocortisone, the decrease in contact angle was very well correlated (Fig. 7) with the increase in the initial powder dissolution rate normalized for solubility. Likewise, when the contact angle reached a minimum value, there was no further increase in the normalized dissolution rate. For betamethasone, there was no significant difference between the diffusivity at 0 vs 30 m*M* NaTC.

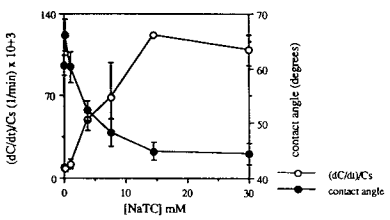

Fig. 7. Simultaneous plot of initial powder dissolution rate for betamethasone (normalized for solubility at the given bile salt concentration) and contact angle, as a function of sodium taurocholate concentration.

Table III. Solubility of Steroids at Various Concentrations of Sodium Taurocholate, at 37° and 0.1 Ionic Strength

[NaTC] mM	betamethasone mg/ml (± std. dev.)	danazol micg/ml (± std. dev.)	dexamethasone mg/ml (± std. dev.)	hydrocortisone mg/ml (± std. dev.)	triamcinolone mg/ml (± std. dev.)
0	0.063 ± 0.002	0.523 ± 0.041	0.092 ± 0.002	0.326 ± 0.006	0.168 ± 0.007
0.1	0.064 ± 0.001	0.661 ± 0.008	0.104 ± 0.001	0.312 ± 0.001	0.160 ± 0.002
1	0.063 ± 0.001	0.733 ± 0.930	0.104 ± 0.002	0.346 ± 0.008	0.142 ± 0.002
3.75	0.069 ± 0.003	0.789 ± 0.021	0.109 ± 0.002	0.377 ± 0.004	0.144 ± 0.002
7.5	0.069 ± 0.001	1.115 ± 0.055	0.114 ± 0.002	0.425 ± 0.001	0.151 ± 0.005
15	0.086 ± 0.002	6.103 ± 0.233	0.137 ± 0.003	0.528 ± 0.004	0.165 ± 0.009
30	0.118 ± 0.005	21.692 ± 0.521	0.193 ± 0.005	0.683 ± 0.006	0.204 ± 0.012

Triamcinolone

The effects of sodium taurocholate on the initial rate of dissolution by both the USP apparatus and the rotating disk method are given in Fig. 8. There was a dramatic increase in powder dissolution as the bile salt concentration increases. In contrast, for the rotating disk method there was almost no increase in the dissolution rate even for concentrations above the CMC. As for the previous three compounds, the rotating disk results followed the solubility behavior, which indicated that the degree of solubilization by bile salt micelles was insignificant for triamcinolone (Table III). Comparison of solubilities with powder dissolution behavior as a function of NaTC concentration indicated that the dramatic increase in powder dissolution could not be explained by solubility effects and suggested that wetting effects are of greater importance in the dissolution of triamcinolone powder. To establish that NaTC could improve the wetting of triamcinolone, the contact angle of compressed tablets of triamcinolone was studied as a function of sodium taurocholate concentration (Fig. 9). As for hydrocortisone, contact angle decreases as a function of bile salt concentration until it reaches a minimum, in this case approximately 36°. The NaTC concentration range over which the contact angle decrease was observed was narrower for triamcinolone than for hydrocortisone. The contact angle first dropped below 40° at a NaTC concentration of about 1 m*M* and reached the minimum value by 7.5 m*M* NaTC. Likewise, the increase in dissolution rate started to occur only for NaTC concentrations higher than 1 m*M*. The degree of dissolution enhancement was greater over the 1 to 7.5 m*M* range for triamcinolone than for the other compounds studied. Also in contrast to the behavior of the other steroids, the normalized dissolution rate continued to increase substantially even after the minimum contact angle was reached. This behavior suggested that complete wetting was not achieved even for the high bile salt concentrations, despite the fact that the contact angle had been reduced to its minimum value. Finally, as in the case of hydrocortisone, no significant differences were observed between the diffusion coefficient at 0 and that at 30 m*M* NaTC.

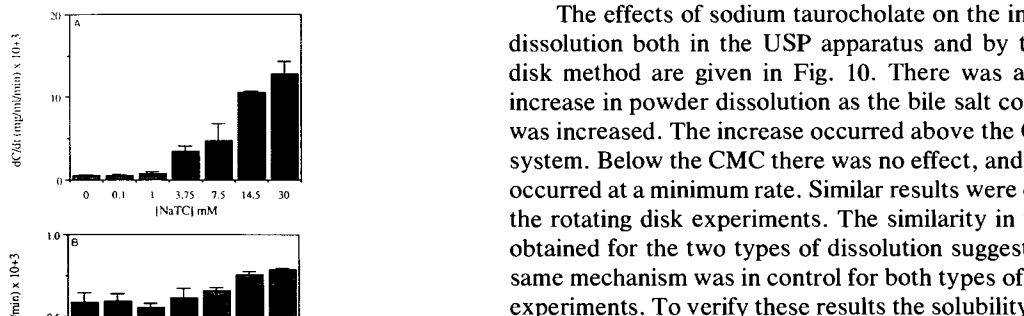

Fig. 8. Initial dissolution rate of triamcinolone (A) powder dissolution in USP apparatus and (B) dissolution from a rotating disk, at several concentrations of sodium taurocholate.

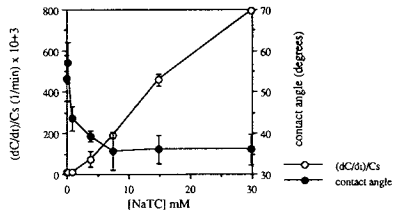

Fig. 9. Simultaneous plot of initial powder dissolution rate for triamcinolone (normalized for solubility at the given bile salt concentration) and contact angle, as a function of sodium taurocholate concentration.

Danazol

The effects of sodium taurocholate on the initial rate of dissolution both in the USP apparatus and by the rotating disk method are given in Fig. 10. There was a significant increase in powder dissolution as the bile salt concentration was increased. The increase occurred above the CMC of the system. Below the CMC there was no effect, and dissolution occurred at a minimum rate. Similar results were observed in the rotating disk experiments. The similarity in the profiles obtained for the two types of dissolution suggested that the same mechanism was in control for both types of dissolution experiments. To verify these results the solubility of danazol was studied as a function of NaTC concentration (Table III). For low taurocholate concentrations, below the CMC, there was very little increase in solubility. For concentrations higher than the CMC there was a large increase in solubility, with solubility increasing linearly as a function of bile salt concentration. Comparing the solubility profile with the initial rate profiles obtained both by the powder dissolution and

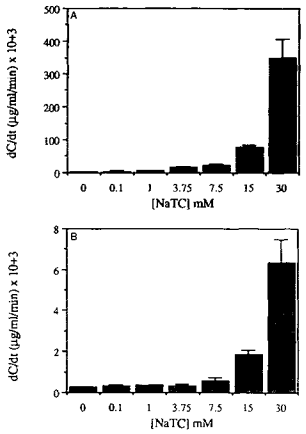

Fig. 10. Initial dissolution rate of danazol (A) powder dissolution in USP apparatus and (B) dissolution from a rotating disk, at several concentrations of sodium taurocholate.

the rotating disk, it is obvious that for danazol both the powder dissolution and the rotating disk mirrored the solubility behavior. Differences between the powder dissolution and the solubility behavior were observed only for concentrations less than 4 m*M*. For danazol, contact angle decreased as a function of contact angle concentration until it reached a minimum at approximately 34° (Fig. 11). The decrease in contact angle was very well correlated with the increase in the powder dissolution normalized with solubility. As the contact angle decreased, the normalized dissolution increased, reaching a plateau when the contact angle reached its minimum value. For danazol, complete wetting was achieved by a concentration of 4 m*M* NaTC, above which wetting effects did not contribute further to dissolution enhancement. This concentration range of wetting effects was considerably lower than that of the other compounds, for which contact angle continued to decrease until a concentration of 7.5 to 15 m*M* or higher was reached. Finally, for danazol the diffusivity at 30 m*M* NaTC was one-third lower than in the absence of bile salt (Table II).

DISCUSSION

The increases observed in powder dissolution when sodium taurocholate is added to the dissolution medium at concentrations of up to 30 m*M* could be explained by a combination of changes in solubility, wetting efficiency, and diffusivity for each of the compounds studied. Wetting effects were predominant for triamcinolone and hydrocortisone but made an almost negligible contribution to the overall increase in dissolution rate observed for danazol. Solubilization appeared to be of primary importance only in the case of danazol, which has the lowest aqueous solubility and the highest partition coefficient of the steroids studied. Sodium taurocholate appeared to have only limited ability to solubilize the other steroids studied. The apparent diffusivity of all the compounds remained unaffected by the presence of NaTC micelles, except in the case of danazol, the diffusion coefficient of which decreased by one-third between 0 and 30 m*M* NaTC. The combined diffusivity and solubilization results suggest that of the compounds studied, only danazol is associated with bile salt micelles to a significant extent.

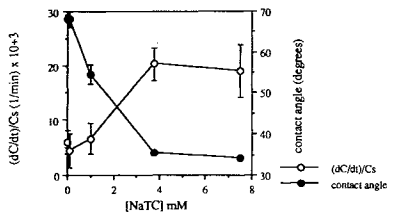

Fig. 11. Simultaneous plot of initial powder dissolution rate for danazol (normalized for solubility at the given bile salt concentration) and contact angle, as a function of sodium taurocholate concentration.

Powder vs Rotating Disk Dissolution

For all the compounds studied, changes in the rotating disk dissolution as the concentration of sodium taurocholate increased could be completely accounted for by solubility and diffusivity changes. For example, if one normalizes the rotating disk dissolution rate by the solubility and plots the normalized dissolution rate as a function of sodium taurocholate, one obtains a horizontal line in each case, indicating that solubilization processes account for all the dissolution effects seen in the rotating disk apparatus. Only for danazol was there a small decrease in the normalized dissolution rate at the two high bile salt concentrations. This decrease was attributed to the decrease in the diffusion coefficient since, at a high bile salt concentration, most of the drug is associated with micelles. If diffusivity changes are taken into account, differences in the rotating disk dissolution rate are completely accounted for. Examples of rotating disk dissolution plots, normalized for solubility, are given for danazol and betamethasone in Fig. 12. The other compounds behaved similarly to betamethasone.

On the other hand, the powder dissolution rate behavior was quite different from the rotating disk behavior for all the compounds studied except danazol (Figs. 2, 4, 6, and 8), suggesting that dissolution was mediated via different mechanisms in the two type of experiments. Differences other than changes due to solubility and diffusivity effects were attributed to wetting effects. Danazol was the only com-

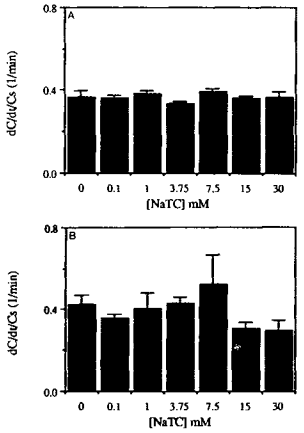

Fig. 12. Rotating disk dissolution rate of betamethasone (A) and danazol (B) normalized for solubility as a function of sodium taurocholate concentration.

pound for which the two type of experiments had very similar profiles (Fig. 10). Solubilization appears to be the major factor in the bile salt enhancement of danazol dissolution.

Wetting Effects

The importance of wetting contribution to powder dissolution has long been recognized. In early studies, Finholt and Solvang (31) showed that the effect of various concentrations of polysorbate 80 on the rate of dissolution of phenacetin powder was due only to a small extent to its solubilizing power, but it was caused mainly by its ability to decrease the interfacial tension between the drug substance and the dissolution medium. Samyn and Jung (32) also pointed out that the presence of the hydrophobic ingredient magnesium stearate in a powder capsule formulation reduced the rate of dissolution medium penetration in the powder mass. Dissolution was therefore slowed due to the limited area of contact between the powder mass and the fluid. In more recent studies, Lippold and Ohm (33) showed that the quotients of the effective surface area and the hydrodynamic boundary layer, as calculated from the initial dissolution rate of pharmaceutical powders in propanol/water mixtures, were correlated with the contact angles of the drugs and the corresponding solvent mixtures.

In the present study contact angle was used as a measure of the ability of the fluid to wet the powders. However, as several investigators have already shown (14,34,35), the wetting of powders is complicated by the fact the hydrophobic powders agglomerate when they come in contact with water creating porous aggregates with entrapped air which prevent immersion of the powder in the liquid ("floating"). The ability of a liquid to wet such a system will depend upon its ability to penetrate into the pores and displace the entrapped air. Wetting of a pore involves having the appropriate miniscus curvature to allow the capillarity to drive the liquid in. As Yang and Zografi (34) pointed out, pore shape and size as well as the physical properties of the liquid–solid system are important features of liquid penetration in nonuniform shape pores. Heertjes and Witvoet (14) studied liquid penetration in the case of a nonuniform size capillary. They showed that in order to remove air from the capillary and for wetting of the pore to occur, the contact angle of the liquid should be decreased to a value sufficiently low to ensure that the force causing liquid penetration will be able to overcome the one resisting it. This minimum contact angle value depends not only on the surface properties of the solid–liquid system but also on the structure of the aggregate (pore size and shape).

Keeping these limitations in mind, contact angle behavior was examined relative to increases in powder dissolution rate above those due to solubility changes. Contact angle behavior was shown to correlate well with these changes, except in the case of triamcinolone. Triamcinolone is the least hydrophobic of the compounds studied in terms of the octanol/water partition coefficient. As previously mentioned, the contact angle measurements were made on compacts and therefore measure only the ability of the surfactant to adsorb at the solid/liquid interface. These effects relate mostly to the hydrophobicity of the compound. The experiments do not test for the ability of the surfactant to displace air from the aggregates. For triamcinolone, the aggregate behavior is likely to be as important, if not more so, as its hydrophobicity, providing a possible explanation for the poor ability of the contact angle experiments to predict the observed changes in its powder dissolution rate with bile salt concentration.

Wetting vs Solubilization by Bile Salts

The relative importance of the contributions of solubilization and wetting by bile salts to the dissolution rate of hydrophobic powders has been the subject of several other studies. Weintraub and Gibaldi (13) showed that the dissolution of salicylamide in 10 m*M* glycocholate solution could not be explained by solubility results alone. It was proposed that powder dissolution rate enhancement at physiological bile salts concentrations is due not only to increases in solubility but also to improved wetting of the powder aggregates. The authors further hypothesized that the wetting effects resulted from the decrease in the interfacial tension because of adsorption of surfactant at the liquid/air and solid/air interfaces. Miyazaki *et al.* (11,12) studied powder dissolution of indomethacin and phenylbutazone in the presence of 2 m*M* (below the CMC) and 40 m*M* (above the CMC) sodium deoxycholate, cholate, and taurocholate. Comparison with solubility behavior suggested that solubilization effects dominated for indomethacin, while for phenylbutazone the dissolution is mediated via wetting effects. The authors suggested that this was consistent with the values of the contact angle of the drugs with water, which were observed to be 28 and 90° for indomethacin and phenylbutazone, respectively. However, the value for indomethacin is quite different from the value of 61° measured by Zografi and Tam (27). In our studies, the contact angle in the absence of bile salt ranged from 52° for hydrocortisone to 68° for danazol, suggesting that the change from wetting to solubilization predominance may occur over a fairly narrow range of contact angle values. None of the previous studies determined contact angles as a function of bile salt concentration to support the importance of wetting effects. The range of NaTC concentrations over which contact angle decreased appeared to correlate well with the concentration range over which wetting effects were influential to the dissolution rate, except in the case of triamcinolone. This range varied considerably between the compounds studied, even though they have fairly similar contact angles in the absence of bile salts (e.g., 52° for hydrocortisone with wetting related improvement up to 30 m*M* vs 57° for dexamethasone with effects up to 7.5 m*M*).

Fasted vs Fed State

Finally, we were interested in determining whether solubilization or wetting was the prominent mechanism in the fasted vs the fed state. Over the bile salt concentration range typical of the fasted state, the major contribution to improvement in dissolution rate was always wetting. In the fed-state case, the means via which dissolution changes were mediated was very much dependent on the properties of the compound. For triamcinolone, hydrocortisone, dexamethasone, and betamethasone, wetting was the primary factor in enhancing dissolution rate in the bile salt concentration range

typical of the fed state. In the case of danazol, most of the dissolution enhancement was achieved at fed-state levels, and the enhancement appeared to be related primarily to solubilization.

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