In Vitro Dissolution and *In Vivo* Absorption of Nitrofurantoin from Deoxycholic Acid Coprecipitates

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Abstract □ The *in vitro* dissolution and *in vivo* absorption characteristics of various nitrofurantoin and nitrofurantoin–deoxycholic acid preparations were studied. *In vitro* particulate dissolution studies compared the dissolution of a 1:5 molar ratio nitrofurantoin–deoxycholic acid coprecipitate to that of a 1:5 physical mixture of nitrofurantoin and deoxycholic acid, precipitated nitrofurantoin, and pure nitrofurantoin. In pH 7.4 buffer, the dissolution rate of the coprecipitate system was approximately six times greater than the dissolution rate of the 1:5 physical mixture. However, no statistical differences could be shown among the dissolution rates of the 1:5 physical mixture, the pure nitrofurantoin, and the precipitated form of nitrofurantoin. In pH 1.2 buffer solution, the 1:5 coprecipitate showed a faster initial dissolution rate than the pure nitrofurantoin but became slower than the pure compound after 35 min. The *in vivo* absorption of the 1:5 coprecipitate, the 1:5 physical mixture, and pure nitrofurantoin, as determined by urinary excretion of unchanged nitrofurantoin, was carried out in four subjects in a crossover study. The 1:5 nitrofurantoin–deoxycholic acid coprecipitate showed significant increases in both the initial urinary excretion and the total cumulative amount of unchanged nitrofurantoin excreted when compared to either the 1:5 physical mixture or the pure nitrofurantoin. The study demonstrated the potential usefulness of drug–bile acid coprecipitate systems in increasing the *in vivo* absorption of dissolution rate-limited drugs.

Keyphrases □ Nitrofurantoin dissolution and absorption—deoxycholic acid coprecipitates, compared to nitrofurantoin alone and mixtures with deoxycholic acid □ Dissolution, nitrofurantoin–deoxycholic acid coprecipitates—compared to nitrofurantoin alone and mixtures with deoxycholic acid □ Absorption, nitrofurantoin–deoxycholic acid coprecipitates—compared to nitrofurantoin alone and mixtures with deoxycholic acid □ Bile acid–drug coprecipitate systems (nitrofurantoin–deoxycholic acid)—effect on absorption of dissolution rate-limited drugs □ Drug–bile acid coprecipitate systems (nitrofurantoin–deoxycholic acid)—effect on absorption of dissolution rate-limited drugs

Since Sekiguchi and Obi (1) first reported the principle of using solid solutions and eutectic mixtures of drugs and inert carriers (*e.g.*, urea and succinic acid) to enhance the rate of dissolution and oral absorption of poorly water-soluble drugs, reports dealing with the *in vitro* dissolution characteristics of these systems have appeared in the literature (2, 3). More recently, reports using other inert carriers such as polyethylene glycol (4) and polyvinylpyrrolidone (5, 6) to form solid dispersions of insoluble drugs have been made.

A previous article (7) reported that the increased dissolution rate noted for bile acid–reserpine coprecipitate systems was due most likely to a reduction in the particle size of reserpine, which occurred during the preparation of the coprecipitates. As a result, the *in vivo* blepharoptotic activity of reserpine was promoted. It was natural, therefore, to apply this approach to a drug whose dissolution is known to be particle-size dependent and whose rate of absorption and bioavailability have been shown to be influenced by the particle size of the drug. Such studies are unique in that a naturally occurring physiological material is used to prepare such solid dispersion or coprecipitate systems.

Nitrofurantoin, 1-[(5-nitrofurfurylidene)amino]hydantoin, is such a drug, since the available data (8, 9) show that the absorption and excretion of nitrofurantoin in man and the dog are more efficient when microcrystalline drug is administered than when the same dose of macrocrystalline material is given. Consequently, this drug appears to be suitable for study as a coprecipitate of a bile acid. We wish to report studies of the *in vitro* dissolution and *in vivo* absorption characteristics of several nitrofurantoin and nitrofurantoin–deoxycholic acid systems; deoxycholic acid was the agent with which nitrofurantoin was coprecipitated.

EXPERIMENTAL

Materials—Nitrofurantoin[1] was prepared from an aqueous solution of sodium nitrofurantoin by slowly acidifying the solution with hydrochloric acid until the free acid form of the drug precipitated from the system. The precipitate was washed with several portions of deionized water and was dried to constant weight at 60° in a vacuum oven. Deoxycholic acid[2], hyamine 10X monohydrate[3], *N,N*-dimethylformamide[4], absolute methanol[5], acetone[5], and all other chemicals were of reagent grade and used as received.

Preparation of Coprecipitate Systems—Coprecipitates of nitrofurantoin and deoxycholic acid, in a 1:5 molar ratio, were prepared by dissolving simultaneously the constituents in a minimum quantity of acetone and subsequently removing the solvent *in vacuo*. The coprecipitates were then dried *in vacuo* to constant weight. Precipitated nitrofurantoin was prepared by treating pure nitrofurantoin in a similar manner. A physical mixture composed of a 1:5 molar ratio of nitrofurantoin and deoxycholic acid was also prepared by mechanically mixing the two substances in a mortar and pestle. Unless otherwise specified, 40–50-mesh particles of the test systems were employed in *in vitro* dissolution rate and *in vivo* absorption experiments. The chemical uniformity of all dispersions was confirmed by assaying for nitrofurantoin (see *Assay Procedures*).

Dissolution Studies—The dissolution characteristics of 40–50-mesh particles of nitrofurantoin in the form of a 1:5 coprecipitate and a physical mixture with deoxycholic acid, nitrofurantoin alone, and precipitated nitrofurantoin were studied in a Clark-Lubs pH 7.4 phosphate buffer system. In all cases, the amount used contained 25 mg. of nitrofurantoin. The studies were carried out under sink conditions using 400 ml. of buffer in a 500-ml., three-necked, round-bottom flask maintained at 37° in a constant-temperature water bath. A three-bladed polyethylene propeller was immersed into the dissolution medium to a depth of 23 mm., and the stirring speed was maintained at 150 r.p.m. by a constant-speed stirring apparatus[6]. Five-milliliter samples were taken for analysis at specified time periods and replaced with fresh solvent. The effect of particle size on the dissolution behavior of nitrofurantoin was determined by studying the dissolution of 40–50-mesh (297–420-

[1] Supplied as sodium nitrofurantoin by Eaton Laboratories, Norwich Pharmacal Co., Norwich, N. Y.
[2] Nutritional Biochemical Corp., Cleveland, Ohio.
[3] Rohm and Haas, Philadelphia, Pa.
[4] Reagent grade, Fisher Chemical Co., Medford, Mass.
[5] Reagent grade, Allied Chemical Co., Morristown, N. J.
[6] Standard Servodyne power drive system, Cole-Parmer Instrument Co., Chicago, Ill.

Table I—*In Vitro* Dissolution Rates of Nitrofurantoin Systems in pH 7.4 Buffer at 37°

System	Mesh Size Range[a]	Dissolution Rate Constant[b], min.$^{-1}$ × 10^2
Nitrofurantoin	100–120 (125–149)	14.4 (14.4; 14.4)
Nitrofurantoin	70–80 (177–210)	9.15 (9.63; 8.66)
Nitrofurantoin	40–50 (297–420)	3.55 (3.43; 3.66)
Precipitated nitrofurantoin	40–50 (297–420)	3.36 (3.06; 3.66)
1:5 Mixture of nitrofurantoin–deoxycholic acid	40–50 (297–420)	3.20 (3.06; 3.34)
1:5 Coprecipitate of nitrofurantoin–deoxycholic acid	40–50 (297–420)	17.6 (17.0; 18.1)

[a] Particle-size range in microns in parentheses. [b] Mean of duplicate runs; individual runs shown in parentheses.

μ), 70–80-mesh (177–210-μ), and 100–120-mesh (125–149-μ) particles of nitrofurantoin at pH 7.4. The dissolution of 40–50-mesh particles of nitrofurantoin and the 1:5 coprecipitate was also studied in the presence of a pH 1.2, 0.1 *M* HCl buffer. All dissolution media contained 0.005% polysorbate 80[7] to ensure proper wetting of the various nitrofurantoin systems (10).

Absorption of Nitrofurantoin in Man—The absorption characteristics of nitrofurantoin from the test systems were evaluated in four healthy, adult male subjects using the urinary excretion method (8). The subjects were fasted overnight (*i.e.*, for not less than 8 hr.) and, on arising, voided their bladders of overnight urine. They then consumed a light standard breakfast consisting of 240 ml. (8 oz.) of milk and 30 g. (1 oz.) of breakfast cereal to minimize the possibility of drug-induced GI upset. One hour later, urine blanks were collected. Subsequently, a single dose of 100 mg. of nitrofurantoin in the form of a 1:5 coprecipitate, 1:5 physical mixture, or nitrofurantoin alone was orally administered to the subjects as a suspension of 40–50-mesh particles in 150 ml. of distilled water. All subjects were allowed free access to fluids following drug administration.

Each subject received all test systems, using a completely balanced crossover design and allowing at least a 1-week interval between each preparation. Urine samples were collected at hourly intervals for the first 8 hr. and then at convenient periods for 24 hr. after drug administration. The pH of each urine specimen was measured, and an aliquot was stored in 60-ml. (2-oz.) amber glass bottles at 4° until assayed for drug content. The amount of drug excreted in the urine at each time period was determined spectrophotometrically (see *Assay Procedures*) and appropriately corrected for blank urine values.

Assay Procedures—Nitrofurantoin was assayed spectrophotometrically using a spectrophotometer[8] at 383 nm. for the pH 7.4 dissolution studies and at 369 nm. for the pH 1.2 dissolution studies.

The urine samples were assayed spectrophotometrically at 397 nm. using the method of Conklin and Hollifield (11), which is specific for unchanged nitrofurantoin in urine. Deoxycholic acid was shown not to interfere with this assay. All samples containing nitrofurantoin were protected from light at all times.

RESULTS AND DISCUSSION

Dissolution Rate Studies—Dissolution was found to follow first-order kinetics. Semilogarithmic plots of percent drug undissolved *versus* time had excellent linearity, the correlation coefficient being 0.98 or greater in all cases. The dissolution rate constants obtained (Table I) are the means of duplicate runs on each system. It is obvious that the dissolution rate of nitrofurantoin at pH 7.4 is essentially the same as for nitrofurantoin alone, when precipitated, and when present as a 1:5 mixture with deoxycholic acid. However, there is almost a sixfold increase in the dissolution rate of nitrofurantoin when present in the 1:5 deoxycholic acid coprecipitate system.

These data permit the exclusion of certain factors as being responsible for the enhanced dissolution rate of nitrofurantoin from the coprecipitate system. Thus, since the precipitated form of nitrofurantoin does not dissolve more rapidly than the pure, nonprecipitated form, the enhanced dissolution of the coprecipitate is not due to the formation of a more soluble solvate or polymorph during its preparation. Additionally, bulk effects due to the presence of deoxycholic acid in solution are not responsible for the enhanced rate observed, since there is no significant difference between nitrofurantoin alone and when in the 1:5 mixture with deoxycholic acid. Therefore, factors such as complex formation, micelle formation, and surface tension lowering are not responsible for the enhanced nitrofurantoin dissolution from the coprecipitate system presented in Table I.

The various drug systems were also studied at pH 1.2 to simulate gastric pH conditions. As seen in Fig. 1, nitrofurantoin in the coprecipitate system dissolves at a rate faster than the pure drug during the first 30 min. Thereafter, the pure drug continues to dissolve at a steady rate, while the nitrofurantoin in the coprecipitate system shows a decreased rate with respect to its initial dissolution rate. Thus, the $T_{50\%}$ for nitrofurantoin in the coprecipitate is approximately twice that for the pure nitrofurantoin alone. Such behavior may be due to the poor solubility of deoxycholic acid at this acid pH. This would slow down the rate of dissolution of the bile acid matrix which, in turn, would retard the dissolution of nitrofurantoin. The enhanced dissolution of nitrofurantoin seen initially may be due to dissolution of the drug from the surface of the coprecipitated particles. As nitrofurantoin dissolves from the surface, the poor dissolution properties of deoxycholic acid at pH 1.2 leads to a decrease in the rate of formation of new surfaces in which the drug appears. Since the drug remains embedded inside the coprecipitate particle for a longer period of time before erosion exposes it, dissolution of nitrofurantoin is slowed.

To demonstrate that the dissolution rate of nitrofurantoin is affected by particle size, dissolution runs were carried out at pH 7.4 using three different size fractions. The results (Table I) show that as particle size decreases the rate of dissolution increases. The significance of this effect in terms of the *in vivo* absorption of the various nitrofurantoin systems is discussed in the following sections.

Absorption Studies—McGilveray *et al.* (12) demonstrated that a relationship exists in man between the blood levels of nitrofurantoin and its rate of urinary excretion. Hence, it is possible to determine the rate and extent of absorption of this drug by measuring the rate of appearance of unchanged drug in the urine. Individual data for the four subjects are presented in Table II.

Nitrofurantoin is a weakly acidic drug (pKa 7.2) so its urinary excretion rate in man can be significantly affected by variations in urinary pH (13). Since, in the present investigation, the absorption characteristics of nitrofurantoin from the three test systems were assessed by the urinary excretion rate method, it was important to monitor the pH of all urine specimens. In this connection, the mean pH (±*SD*) of the urine specimens over the experimental time

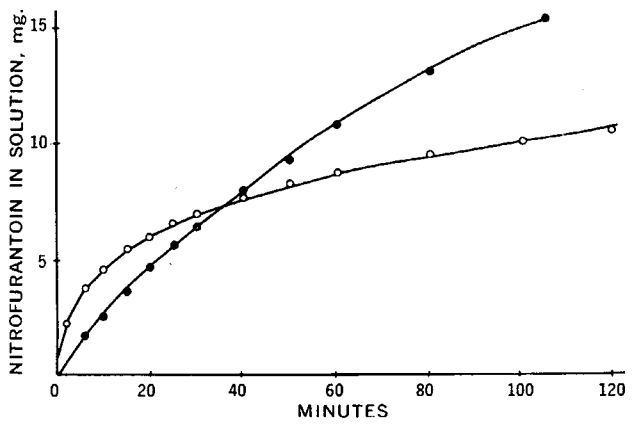

Figure 1—*Dissolution of nitrofurantoin* (●) *and a 1:5 molar ratio coprecipitate of nitrofurantoin deoxycholic acid* (○) *in pH 1.2 HCl buffer at 37°.*

[7] Tween 80.
[8] Beckman DB-G.

period was 5.77 (±0.52), 5.80 (±0.49), and 5.72 (±0.47) following the oral administration to the four subjects of nitrofurantoin alone, as a 1:5 physical mixture with deoxycholic acid, and as a 1:5 coprecipitate with deoxycholic acid, respectively. The similarity of these values for all test systems indicates that the slight variation in urinary pH would not affect the interpretation of results of the *in vivo* absorption studies. This is supported by the fact that the elimination rate constant ($hr.^{-1}$ $\pm SD$) for the drug, determined from the least-squares slope of the terminal portion of a plot of the logarithm of the excretion rate *versus* time, was found to be independent of the system used, *i.e.*, for the drug alone, 1.14 (±0.27); as a physical mixture with deoxycholic acid, 1.14 (±0.25); and as a coprecipitate with deoxycholic acid, 1.15 (±0.26).

The average amount of unchanged nitrofurantoin excreted by the four subjects during the experimental time intervals for each nitrofurantoin test system is summarized in Table III, and plots of the cumulative amount of drug excreted *versus* time are shown in Fig. 2. Figure 2 reveals that all of the plots tend to reach a plateau between 6 and 8 hr. after drug administration, indicating that the excretion of nitrofurantoin is essentially over by 8 hr. and that the cumulative amount of nitrofurantoin excreted in the urine in 24 hr. is a valid estimate of the extent of absorption or availability of the drug from the test preparations.

An examination of the excretion data presented in Table III indicates that nitrofurantoin from the coprecipitate material was excreted in the urine, and therefore absorbed, at both a faster rate and to a greater extent than either the drug alone or the 1:5 physical mixture. Approximately 2.5–4.5 times as much nitrofurantoin was excreted from the coprecipitate system during the first 3 hr. of the study as compared with the other two systems. Overall, the 24-hr. excretion of unchanged drug was increased between 50 and 80% for the coprecipitate system. Analysis of variance of the treatment averages shows that there are significant differences at the 99% level of confidence during the first 3 hr. postadministration of the three systems. There is also a significant difference for the cumulative amount excreted between 0 and 24 hr. No significant differences in excretion rate were found during the intermediate time periods. Analysis by paired comparison of the test systems verifies that there are no statistical differences at any time interval between the amounts excreted following administration of pure nitrofurantoin and the 1:5 physical mixture of nitrofurantoin and deoxycholic acid. The similarity between the percent of the dose of drug excreted in 24 hr. from the nitrofurantoin–deoxycholic acid coprecipitate (approximately 28%) and the value of 33% obtained by Reckendorf *et al.* (14), following the intravenous administration of 180 mg. of drug to 16 patients, suggests that nitrofurantoin is nearly maximally absorbed from the coprecipitate system.

Table IV lists the time of occurrence of the peak excretion rate for the various nitrofurantoin systems administered orally to each individual subject, and it illustrates that the drug was absorbed more rapidly from the nitrofurantoin coprecipitate than from the other two test systems. The average time of peak excretion was 1.6 hr. when the coprecipitate was administered, while the average peak excretion time was 3.6 hr. following the oral administration of the drug alone or as a physical mixture with deoxycholic acid. Paul *et al.* (8) reported values of 4.9–3.6 hr. for the time of occurrence of the peak excretion rate for nitrofurantoin administered to human subjects in various particle-size fractions of the pure drug (*i.e.*, 50–60 to 200–400 mesh and 10 μ). The coprecipitate used in the present study gave an earlier peak excretion rate than the micronized (10 μ) drug studied by Paul *et al.* Also, none of the subjects in the present studies gave any evidence of nausea or GI distress.

A comparison of the dissolution and absorption rates of nitrofurantoin, as the pure compound and as a 1:5 molar ratio physical mixture with deoxycholic acid, shows them to be almost identical. This observation eliminates the possibility that deoxycholic acid functions in the coprecipitate to increase the bulk solubility of nitrofurantoin in the fluids of the GI tract or to increase its rate of dissolution by lowering the interfacial tension between the hydrophobic drug and these biological fluids. In addition, the potential influence of deoxycholic acid on such physiological processes as gastric emptying, GI motility, and GI membrane permeability can be ruled out, since it is reasonable to assume that these changes would be the same for both the physical mixture and the coprecipitate.

The similarity of the *in vitro* dissolution rates of pure and precipitated nitrofurantoin at pH 7.4 (Table I) precludes the possibility

Table II—Amount of Unchanged Nitrofurantoin Excreted in Urine following a Single Dose of 100 mg. Nitrofurantoin in the Form of Three Different 40–50-Mesh Dosage Systems

Time Interval, hr.	Subject Number	Nitrofurantoin	1:5 Mixture of Nitrofurantoin–Deoxycholic Acid	1:5 Coprecipitate of Nitrofurantoin–Deoxycholic Acid
0	1	0.0 (5.97)[a]	0.0 (5.72)	0.0 (5.25)
	2	0.0 (5.60)	0.0 (6.40)	0.0 (6.00)
	3	0.0 (5.30)	0.0 (5.15)	0.0 (5.35)
	4	0.0 (5.40)	0.0 (5.20)	0.0 (5.30)
0–1	1	0.25 (5.20)	0.49 (5.65)	1.49 (5.30)
	2	1.03 (6.15)	0.72 (6.30)	1.73 (6.00)
	3	0.36 (5.35)	0.58 (5.85)	2.36 (5.40)
	4	0.06 (5.40)	0.52 (5.30)	2.10 (5.35)
1–2	1	1.19 (5.65)	2.48 (6.50)	6.13 (5.20)
	2	2.15 (6.60)	2.10 (6.20)	12.93 (6.70)
	3	2.52 (5.70)	2.51 (6.20)	12.92 (5.75)
	4	2.29 (5.40)	1.58 (5.25)	4.91 (5.25)
2–3	1	2.36 (5.37)	1.53 (5.95)	6.51 (5.20)
	2	4.66 (6.70)	3.27 (6.70)	8.41 (6.70)
	3	5.94 (6.30)	4.16 (6.80)	9.18 (6.10)
	4	2.46 (5.20)	2.61 (5.40)	4.88 (5.10)
3–4	1	2.96 (5.80)	2.30 (5.40)	1.24 (5.25)
	2	2.68 (6.40)	3.45 (6.50)	8.02 (6.40)
	3	4.67 (6.30)	5.18 (6.85)	6.18 (5.90)
	4	2.42 (5.15)	2.42 (5.50)	3.22 (5.10)
4–5	1	2.76 (5.60)	2.38 (6.25)	0.08 (5.78)
	2	4.51 (6.35)	2.04 (5.80)	4.59 (6.00)
	3	2.74 (5.90)	5.25 (6.15)	1.28 (6.10)
	4	2.51 (5.25)	2.18 (5.40)	3.97 (5.10)
5–6	1	0.88 (5.80)	1.31 (5.85)	0.22 (6.20)
	2	2.97 (7.35)	1.13 (6.20)	2.59 (6.10)
	3	0.76[b] (—)[c]	3.63 (5.50)	0.38 (5.50)
	4	0.46 (6.00)	0.81 (5.20)	2.71 (5.15)
6–7	1	0.23 (5.90)	0.90 (5.28)	0.18 (6.20)
	2	1.83 (7.35)	0.69 (5.60)	0.40 (6.10)
	3	0.48 (6.15)	2.61 (5.50)	0.18 (6.15)
	4	0.77 (5.80)	0.72 (5.30)	0.59 (5.20)
7–8	1	0.20 (5.70)	0.27 (5.75)	0.25 (6.28)
	2	0.13 (6.80)	1.34 (5.70)	0.23 (5.70)
	3	0.00 (6.00)	0.63 (6.05)	0.19 (6.45)
	4	0.09 (5.30)	0.48 (5.15)	0.71 (5.30)
0–24	1	11.29	12.43	18.86
	2	19.97	24.20	38.86
	3	17.56	25.65	33.11
	4	10.39	11.67	23.14

[a] Urine pH values. [b] Estimated graphically from cumulative excretion curve since no 6-hr. sample was taken. [c] No sample was taken.

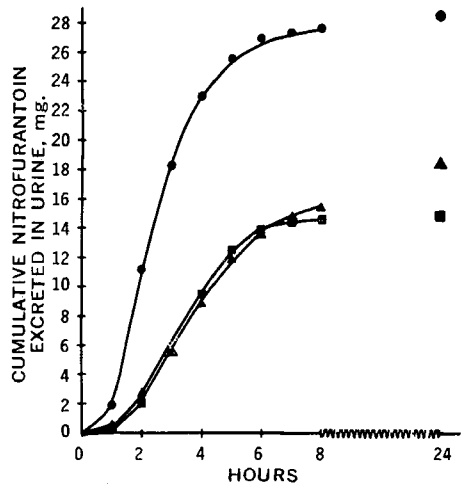

Figure 2—*Mean cumulative amount of nitrofurantoin excreted in the urine following oral administration of 100-mg. doses of nitrofurantoin. Key:* ●, *nitrofurantoin as a 1:5 molar ratio coprecipitate with deoxycholic acid;* ▲, *nitrofurantoin as a 1:5 molar ratio mixture with deoxycholic acid; and* ■, *nitrofurantoin alone.*

Table III—Average Amount of Unchanged Nitrofurantoin Excreted in Urine for Various 40–50-Mesh Nitrofurantoin Systems

Time Interval, hr.	Amount of Nitrofurantoin Excreted, mg.[a] Nitrofurantoin	1:5 Mixture	1:5 Coprecipitate	Differences among Systems, Average from ANOVA	Paired Comparison by Paired *t* Test: Nitrofurantoin *versus* Coprecipitate	Mixture *versus* Coprecipitate	Mixture *versus* Nitrofurantoin
0–1	0.43 (0.21)	0.58 (0.05)	1.92 (0.19)	Significant ($0.001 < p < 0.005$)	Significant ($0.01 < p < 0.02$)	Significant ($0.001 < p < 0.01$)	n.s. ($p \gg 0.10$)
1–2	2.04 (0.29)	2.16 (0.22)	9.22 (2.51)	Significant ($0.005 < p < 0.010$)	Significant ($0.02 < p < 0.05$)	Significant ($0.02 < p < 0.05$)	n.s. ($p \gg 0.10$)
2–3	3.10 (0.96)	2.89 (0.56)	7.24 (0.96)	Significant ($0.001 < p < 0.005$)	Significant ($0.02 < p < 0.05$)	Significant ($0.001 < p < 0.01$)	n.s. ($p \gg 0.10$)
3–4	3.94 (0.76)	3.34 (0.67)	4.67 (1.51)	n.s. ($p > 0.25$)	n.s. ($p > 0.10$)	n.s. ($p > 0.10$)	n.s. ($p > 0.10$)
4–5	3.13 (0.47)	2.96 (0.77)	2.48 (1.08)	n.s. ($p > 0.25$)	n.s. ($p > 0.10$)	n.s. ($p > 0.10$)	n.s. ($p > 0.10$)
5–6	1.23 (0.58)	1.72 (0.64)	1.47 (0.68)	n.s. ($p > 0.25$)	n.s. ($p > 0.10$)	n.s. ($p > 0.10$)	n.s. ($p > 0.10$)
6–7	0.69 (0.40)	1.23 (0.46)	0.33 (0.10)	n.s. ($p > 0.25$)	n.s. ($p > 0.10$)	n.s. ($p > 0.10$)	n.s. ($p > 0.10$)
7–8	0.11 (0.03)	0.68 (0.23)	0.35 (0.12)	n.s. ($0.10 < p < 0.25$)	n.s. ($p > 0.10$)	n.s. ($p > 0.10$)	n.s. ($0.05 < p < 0.10$)
Total amount excreted, 0–24 hr.	14.80 (2.35)	18.48 (3.73)	28.49 (4.57)	Significant ($0.001 < p < 0.005$)	Significant ($0.01 < p < 0.02$)	Significant ($0.01 < p < 0.02$)	n.s. ($p > 0.10$)

[a] Amount reported as mean of four subjects. Standard errors are in parentheses.

of the formation of a drug–solvate during the preparation of the coprecipitate system. However, two plausible explanations do exist. First, the two components of the coprecipitate system are probably more intimately associated with one another than they are in the physical mixture. As a result, only in the case of the coprecipitate can the concentration of deoxycholic acid in the diffusion layer surrounding the dissolving particles increase to such an extent so as to influence the solubility and/or wetting of nitrofurantoin in this region and, hence, increase its rate of dissolution and absorption. The second, more probable, explanation involves an examination of the procedure used to prepare the coprecipitate system. Initially both drug and bile acid are in solution. As the solvent system is stripped from the solution, a supersaturated solution is formed. This is apparent since the total quantity of material is still in solution even though the quantity of solvent has been reduced about 10-fold from the initial quantity necessary to effect solution of the drug and bile acid. Finally, the supersaturated solution loses enough solvent so that a very rapid precipitation of solute occurs. Such a rapid crystallization is commonly known to cause the formation of very fine particles, and herein seems to lie the effectiveness of the coprecipitate system. The smaller particles of drug evolved during precipitation are retained by the matrix of bile acid formed around it. When the coprecipitate is administered orally, the bile acid component readily goes into solution in the fluid of the small intestine because of its ability to dissociate under these pH conditions and/or be solubilized by endogenous conjugated bile salts and other physiological surfactants. Both the reduction in the particle size of nitrofurantoin and the ability of deoxycholic acid to be solubilized readily in the small intestine most likely contribute to the enhanced dissolution and absorption of the drug.

The present investigation has shown that the drug–bile acid coprecipitate system can be employed to potentiate the absorption characteristics of a drug that possesses a dissolution rate-limited absorption mechanism, such as nitrofurantoin. This approach may be applicable to other drugs whose absorption is also dissolution rate limited.

Table IV—Time (Hours) of Occurrence of Peak Excretion Rate

Subject Number	Nitrofurantoin	1:5 Mixture	1:5 Coprecipitate
1	4.0	3.5	1.5
2	3.5	3.5	2.0
3	2.5	4.5	1.5
4	4.5	3.0	1.5
Mean	3.6	3.6	1.6
SD	0.9	0.6	0.3

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