6-H), 6.77 (m, 1, indole-7-H), 6.93 (m, 1, indole-4-H), and 7.65 (*AB*q, 4, benzoyl ArH) ppm; pKa 4.11.

Anal.—Calc. for $C_{21}H_{20}N_2O_5$: C, 66.30; H, 5.30; N, 7.37. Found: C, 66.25; H, 5.38; N, 7.31.

1-(m-Acetamidobenzoyl)-5-methoxy-2-methyl-3-indolylacetic Acid (V)—Compound V was prepared in 77.8% yield from VII*b* and acetic anhydride by Method A. Recrystallized from benzene–chloroform, the product had a melting point of 135°; IR (KBr): 3440 (NH), 1710 (CO_2H), 1670 (C=O, secondary amide), and 1650 (C=O, tertiary amide) cm^{-1}; NMR (60 MHz) (dimethyl sulfoxide-d_6): δ 2.07 (s, 3, $COCH_3$), 2.25 (s, 3, indole-CH_3), 3.67 (s, 2, CH_2CO_2H), 3.80 (s, 3, CH_3O), 6.63–7.13 (m, 3, indole-H), and 7.33–7.97 (m, 4, benzoyl ArH) ppm.

Anal.—Calc. for $C_{21}H_{20}N_2O_5$: C, 66.30; H, 5.30; N, 7.37. Found: C, 65.80; H, 5.34; N, 7.29.

Reactivity of II and IV toward L-Tryptophan—L-Tryptophan was shaken at 37° for 24 hr with an equimolar quantity of II or IV in 67 m*M* phosphate buffer (pH 7.4). TLC revealed no products of reaction between either II or IV and L-tryptophan.

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Rectal Absorption of Nitrofurantoin

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Abstract □ The absorption in humans of nitrofurantoin from seven suppository bases was studied using urinary excretion measurements. Rectal absorption was poorer than GI absorption. The administration of 400 mg of nitrofurantoin in a polyethylene glycol–polysorbate 80 suppository base and in a polyethylene glycol–silica suppository base provided an adequate urinary concentration of nitrofurantoin. Persons who cannot tolerate orally administered nitrofurantoin due to gastric upset could receive nitrofurantoin therapy rectally.

Keyphrases □ Nitrofurantoin—rectal absorption, effect of various suppository bases, humans □ Absorption, rectal—nitrofurantoin, effect of various suppository bases, humans □ Antibacterials, urinary—nitrofurantoin, rectal absorption, effect of various suppository bases, humans

Nitrofurantoin is an antibacterial agent used widely in the treatment of urinary tract infections (1). Between 30 and 50% of an oral or intravenous dose can be recovered intact from the urine (2). The efficacy of nitrofurantoin depends on attaining an adequate concentration of drug in the urine.

Patients receiving nitrofurantoin may exhibit emesis and be deprived of an effective medication. Macrocrystals of nitrofurantoin improved GI tolerance without interfering with clinical efficacy (3). An optimal average crystal size of 150 mesh (80–200-mesh size fraction) reduced the incidence of emesis while still permitting ample urinary excretion for efficacy (4). The larger crystals dissolved more slowly than the smaller crystals and, since dissolution is the rate-limiting step for slightly soluble drugs, nitrofurantoin absorption was slower.

The purpose of this study was to investigate the rectal absorption of nitrofurantoin and to determine if nitrofurantoin could be administered in a suppository to per-

Table I—Formulas for Suppositories Containing 400 mg of Nitrofurantoin

Formula	Ingredient	Amount, g
B	Theobroma oil[a]	1.40
K	Lecithin and dried whey[b]	0.50
	Theobroma oil	1.00
D	Polyoxyethylene 4 sorbitan monostearate[c]	1.57
	Glyceryl monolaurate[d]	0.17
B-7	Polyethylene glycol 1540[e]	0.70
	Polyethylene glycol 6000	0.97
	Polyethylene glycol 400	0.42
C	Polyethylene glycol 1540	0.66
	Polyethylene glycol 6000	0.92
	Polyethylene glycol 400	0.40
	Sodium bicarbonate	0.14
L	Polyethylene glycol 1540	0.66
	Polyethylene glycol 6000	0.92
	Polyethylene glycol 400	0.40
	Colloidal silica[f]	
T	Polyethylene glycol 1540	0.66
	Polyethylene glycol 6000	0.92
	Polyethylene glycol 400	0.40
	Polysorbate 80[g]	0.20

[a] Hershey's. [b] Leciflow, Kraftco Corp. [c] Tween 61, ICI United States Inc. [d] Aldo MLD, Glyco Chemicals. [e] Carbowax, Union Carbide Chemicals. [f] Cab-O-Sil, G.L. Cabot Corp. [g] Tween 80, ICI United States Inc.

sons who otherwise would be deprived of nitrofurantoin therapy because of GI intolerance.

EXPERIMENTAL

Dosage Forms—Nitrofurantoin[1] was classified by a sonic sifter[2], and the 230–325-mesh size fraction (53 μm) was used throughout the experiment. Two hundred milligrams of nitrofurantoin without excipients was placed in a No. 2 gelatin capsule.

The formulations for the suppositories are given in Table I. The suppositories were prepared by the cold compress method[3] when feasible; suppositories containing polyethylene glycols were prepared by the fusion method. For Formula L, the powder to be incorporated into the suppository base was prepared by dissolving the nitrofurantoin in alcohol, suspending the silica in the liquid, and evaporating the solvent in a stream of air. The solid, which consisted of 20% silica and 80% nitrofurantoin, was then passed through a 100-mesh screen (5).

The percent of nitrofurantoin dissolved from the dosage form was determined using the USP disintegration apparatus. The dosage form was placed in the apparatus and held in a single glass cylinder by means of plastic tubing bent in the upper end of the cylinder to prevent the escape of the dosage form. The disintegration apparatus operated in 16 liters of distilled water at 37° contained in a 30 × 30-cm cylindrical jar. Samples were removed by a pipet fitted with a sintered-glass filter. The samples were analyzed, and the percent dissolved at each interval of time was calculated (Fig. 1).

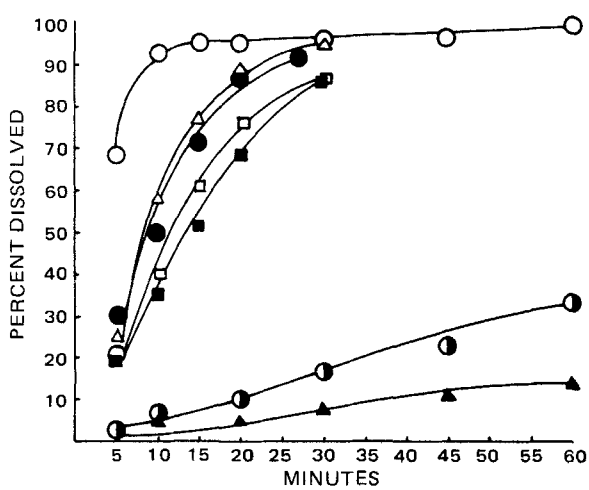

Figure 1—*Dissolution profiles in 16 liters of water at 37° of 400 mg of nitrofurantoin from several dosage forms. Key: ○, gelatin capsule; △, polyethylene glycol–sodium bicarbonate; ●, polyethylene glycol; □, polyethylene glycol–polysorbate 80; ■, polyethylene glycol–silica; ◑, lecithin and dried whey; and ▲, theobroma oil.*

[1] Sigma lot 43C-1550.
[2] Allen-Bradley.
[3] Apfelbaum machine.

Table II—Dosage Forms Administered to Subjects

Subject	Dosage
EP	400 mg po; 400 mg in five suppository bases (T, L, C, B, and D); 65 mg po
RW	400 mg po; 400 mg in two suppository bases (T and B-7)
SB	400 mg po; 400 mg in two suppository bases (T and B-7)
MS	400 mg po; 400 mg in two suppository bases (T and B)
SK	400 mg po; 400 mg in two suppository bases (K and B)
KS	400 mg po; 400 mg in two suppository bases (L and B-7)
TI	400 mg po; 400 mg in two suppository bases (L and B)

Analytical Method—The analysis of the urine samples was carried out by the method of Conklin and Hollifield (6) on the day of collection. To protect the nitrofurantoin from light, amber glassware was used.

Protocol—Seven healthy male human subjects, 25–51 years old and 62–77 kg, were studied. Four hundred milligrams of nitrofurantoin in gelatin capsules was administered orally after arising and voiding the bladder. Subjects were ambulatory and ingested food as desired. It was recommended that a minimum of 150 ml of water be ingested hourly.

Urine samples were collected at 1-hr intervals for 14 hr. Volumes were measured, and aliquots were retained in amber vials for analysis. The pH of the urine was determined at the time of each sample collection and ranged from 5 to 7.5. No attempt was made to control the urinary pH.

After 1 week, a suppository containing the same dose of nitrofurantoin was administered rectally, and the urine samples were collected according to the protocol. All suppositories were identified by code, and the drug was not identified for the subjects. After another week, a suppository containing the same dose of nitrofurantoin in a different suppository base was administered rectally, and the urine samples were collected according to the protocol. Each subject served as his control in the comparison of the urinary excretion of the drug from the oral and rectal administrations. Subjects received nitrofurantoin according to the schedule of dosage forms given in Table II.

RESULTS AND DISCUSSION

For the seven subjects, the fraction of the 400-mg oral dose of nitrofurantoin recovered in the urine in 24 hr ranged from 0.22 to 0.54, with

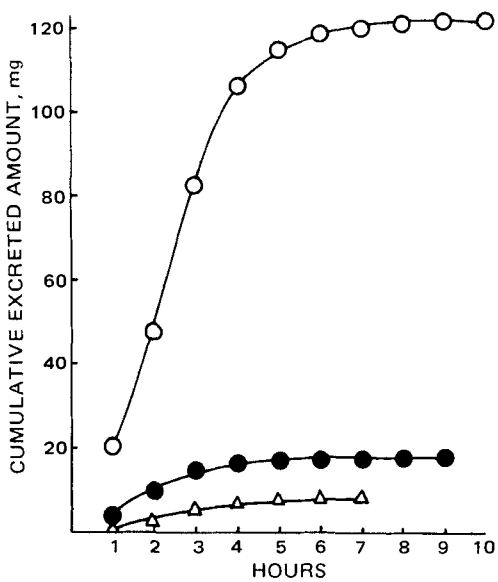

Figure 2—*Cumulative amount of nitrofurantoin excreted in the urine after oral and rectal administrations as a function of time. Key: ○, 400 mg po in a capsule; ●, 65 mg po in a capsule; and △, 400 mg rectally in theobroma oil.*

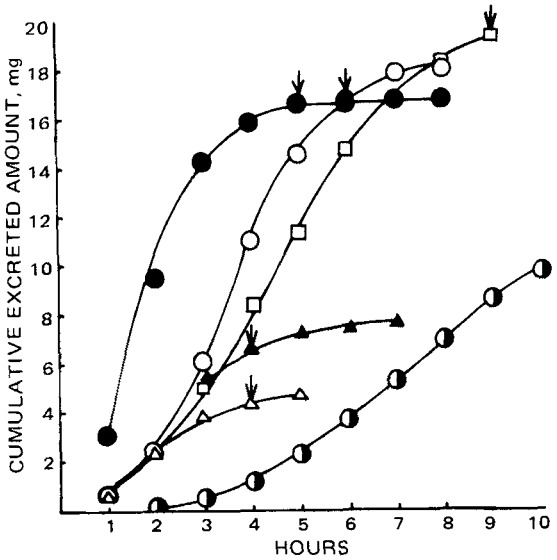

Figure 3—*Cumulative amount of nitrofurantoin excreted in the urine of Subject EP after oral and rectal administrations as a function of time. Key: ↓, latest urine sample having a concentration exceeding 1:100,000; ●, 65 mg po in a capsule; ○, polyethylene glycol–polysorbate 80; □, polyethylene glycol–silica; △, polyethylene glycol–sodium bicarbonate; ▲, theobroma oil; and ◑, sorbitan monostearate–glyceryl monolaurate.*

an average of 0.39. Nitrofurantoin is bacteriostatic in concentrations as low as 1:100,000–1:200,000 (7). A nitrofurantoin concentration of approximately 30 μg/ml (1:40,000) reportedly will eradicate at least 90% of the strains of *Escherichia coli* (8). In the seven subjects studied, the concentration of nitrofurantoin exceeded 1:40,000 for 7–9 hr, with an average of 8.6 hr, after a single oral administration of 400 mg of nitrofurantoin.

Nitrofurantoin frequently causes nausea and/or emesis. In this study, the administration of a single oral 400-mg dose of nitrofurantoin caused gastric upset in four of eight subjects (one subject withdrew). Rectal administration of 400 mg of nitrofurantoin provided poor absorption (Fig. 2); however, even though the fraction of the dose recovered in the urine was 0.02, the concentration of the nitrofurantoin in the urine exceeded 1:100,000 for 4 hr after insertion of the suppository. This result suggested that the administration of a large dose (400 mg) in a suitable suppository base might provide an adequate bacteriostatic concentration in the urine without gastric upset from three or four daily insertions.

In the preliminary stage, five suppository bases were used to administer 400 mg of nitrofurantoin rectally to Subject EP. The cumulative amount excreted and the concentration in the urine were compared to the amount

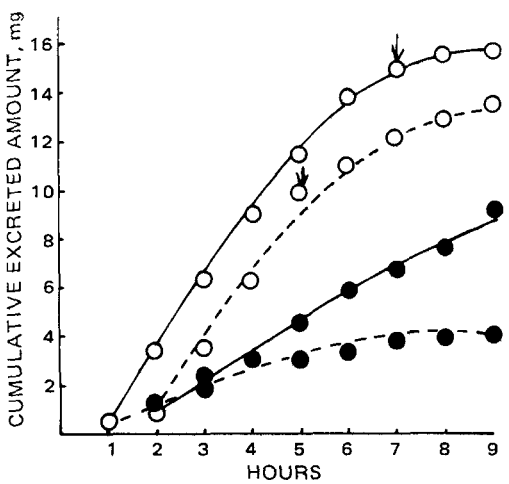

Figure 4—*Comparison of effect of suppository formulation on cumulative amount of nitrofurantoin excreted. Key: ↓, latest urine sample having a concentration exceeding 1:100,000; ○, polyethylene glycol–polysorbate 80; ●, polyethylene glycol; —, Subject RW; and - - -, Subject SB.*

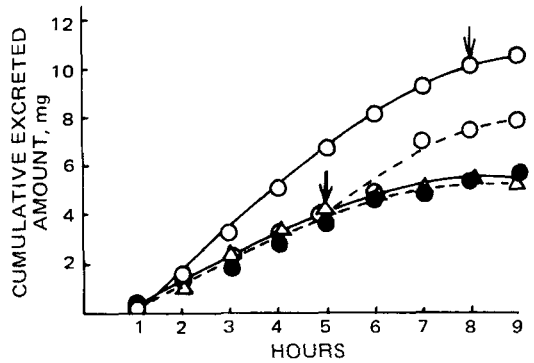

Figure 5—*Comparison of effect of suppository formulation on cumulative amount of nitrofurantoin excreted. Key: ↓, latest urine sample having a concentration exceeding 1:100,000; ○, polyethylene glycol–silica; ●, polyethylene glycol; △, theobroma oil; —, Subject KS; and - - -, Subject TI.*

and concentration after the administration of 65 mg of nitrofurantoin orally (Fig. 3). Formulas B, C, and D were unsatisfactory. Formulas L and T provided approximately 5% recovery of the administered dose in the urine, with the maximum amount released in the 4th hr of urine collection. The concentration of nitrofurantoin in the urine was 1:32,000 in the 6-hr collection with the polyethylene glycol–polysorbate 80 base (Formula T) and 1:34,000 in the 9-hr collection with the polyethylene glycol–silica base (Formula L).

For Subjects RW and SB 9 hr after administration, 1.7 and 3.3 times as much nitrofurantoin were eliminated in the urine from Formula T as from the polyethylene glycol base (Formula B-7) (Fig. 4), respectively. The amount of nitrofurantoin absorbed from the polyethylene glycol base was not sufficient to provide a bacteriostatic concentration. The amount of nitrofurantoin absorbed from the polyethylene glycol–polysorbate 80 base provided a concentration exceeding 1:100,000 until at least the 5th hr after insertion in Subjects EP, RW, and SB.

The volume of fluid in the rectum is only several milliliters. As a consequence of the limited fluid and the very slight solubility of nitrofurantoin, only a small part of the 400 mg administered rectally is dissolved. Thus, the apparently poor rectal absorption of nitrofurantoin is probably due to the severe restrictions on dissolution of the drug from the suppository base. The addition of a surface-active agent to a dosage form containing a hydrophobic drug often increases dissolution (9–12). With Formula T, polysorbate 80 reduced interfacial tension and thereby promoted wetting and/or deaggregation of nitrofurantoin.

For Subject KS 9 hr after administration, 1.8 times as much nitrofurantoin was eliminated in the urine from the polyethylene glycol–silica base (Formula L) as from the polyethylene glycol base (Formula B-7) (Fig. 5). With the latter, the concentration of nitrofurantoin in the urine exceeded 1:40,000 for only 1 hr. The concentration exceeded 1:40,000 for 6 hr after the insertion of a polyethylene glycol–silica base suppository. A similar elimination pattern is shown in Fig. 3. For Subject TI 9 hr after administration, 1.5 times as much nitrofurantoin was eliminated in the urine from Formula L as from the theobroma oil base (Formula B) suppository (Fig. 5).

If a hydrophobic drug is dispersed by means of a volatile organic solvent onto the surface of fumed silicon dioxide and then the mixture is dried, the resulting small size of the drug and the concomitant increase in surface area greatly increase the surface available for contact with the dissolution medium. Thus, adsorbents facilitate the dissolution process of relatively insoluble drugs (5).

In Subject MS, the amount of nitrofurantoin eliminated in the urine

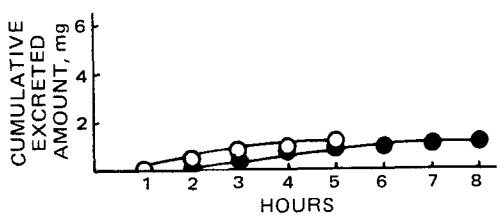

Figure 6—*Comparison of effect of suppository formulation on cumulative amount of nitrofurantoin excreted in Subject MS. Key: ○, polyethylene glycol–polysorbate 80; and ●, theobroma oil.*

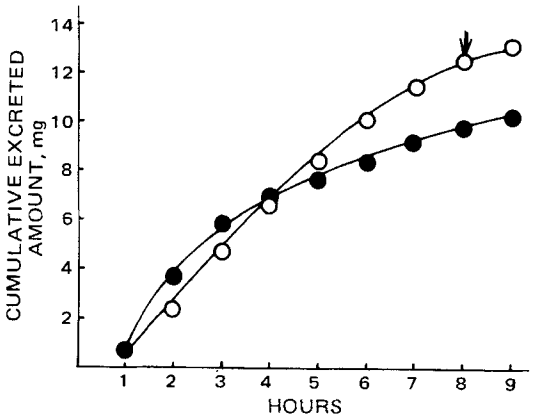

Figure 7—*Comparison of effect of suppository formulation of cumulative amount of nitrofurantoin excreted in Subject SK. Key: ○, lecithin and dried whey product; and ●, theobroma oil.*

from Formula T was greater than that from Formula B (Fig. 6); however, in this subject, both bases provided an adequate bacteriostatic concentration in the urine.

The amount of nitrofurantoin released from Formula D (Fig. 3) was so small that further investigation was not attempted.

Formula K provided a slightly greater amount of nitrofurantoin in the urine than the theobroma oil base suppository (Fig. 7). The dissolution profile of the theobroma oil base suppository suggested poor bioavailability, which was confirmed by *in vivo* data. In water at body temperature, the nitrofurantoin–theobroma oil suppository melted and formed a tacky mass from which the nitrofurantoin was slowly dissolved. With the limited fluid in the rectum, dissolution of the nitrofurantoin from the tacky mass was a very slow process. By mixing a lecithin and dried whey product with theobroma oil, it was hoped that the surface activity of the lecithin and the water solubility of the whey might enhance nitrofurantoin release. In measuring the dissolution profile, it was noticed that the mass was not tacky and that the release was slightly faster. Similarly, in the *in vivo* test, the amount of nitrofurantoin eliminated in the urine was slightly greater than that from the theobroma oil base.

SUMMARY

The usual adult dose of nitrofurantoin is 50–100 mg four times a day. If doses of nitrofurantoin several times the usual oral dose are administered with the same frequency rectally, adequate concentration of nitrofurantoin in the urine is attained. In this preliminary investigation, 400 mg of nitrofurantoin administered in a polyethylene glycol–polysorbate 80 suppository base and in a polyethylene glycol–silica suppository base provided an adequate concentration in the urine. Persons who exhibit nausea and emesis after oral administration of nitrofurantoin possibly could receive nitrofurantoin therapy by the rectal route.

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Electronic Absorption Spectra and Protolytic Equilibria of Doxorubicin: Direct Spectrophotometric Determination of Microconstants

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Abstract □ The ground- and excited-state dissociation constants and the electronic absorption and fluorescence spectra of doxorubicin were investigated by spectrophotometry. A general method for the direct calculation of individual microscopic dissociation constants was derived using the spectrophotometric data obtained. It was concluded that the protonated amino sugar group is slightly more acidic than the phenolic group. The spectrophotometric data were analyzed, and the macro- and microconstants for the various equilibria are reported.

Keyphrases □ Doxorubicin—electronic absorption and fluorescence spectrophotometric determination of dissociation constants and protolytic equilibria □ Spectrophotometry, electronic absorption and fluorescence—determination, doxorubicin dissociation constants and protolytic equilibria □ Dissociation constants—doxorubicin, electronic absorption and fluorescence spectrophotometric determination □ Protolytic equilibria—doxorubicin, electronic absorption and fluorescence spectrophotometric determination □ Antineoplastic agents—doxorubicin, electronic absorption and fluorescence spectrophotometric determination of dissociation constants and protolytic equilibria

Molecules containing a quinone moiety have been widely employed in trace analysis, dye manufacturing, and metal–ligand binding. In pharmaceutical applications, molecules such as the naphthoquinones (1) and the anthraquinones have shown promise as antifungal and antibacterial agents. Of more recent importance is the use of