Solid Dispersions of Nitrofurantoin, Ethotoin, and Coumarin with Polyethylene Glycol 6000 and Their Coprecipitates with Povidone 25,000

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Abstract □ The influence of two linear polymers, polyethylene glycol 6000 and povidone 25,000, on the dissolution rate of three poorly soluble drugs, nitrofurantoin, ethotoin, and coumarin, was studied. Povidone 25,000 produced better drug solubilization than polyethylene glycol 6000 with the drug–polymer ratios studied, and an increase in the weight fraction of either polymer gave more rapid dissolution. TLC and IR studies ruled out any interaction between the drugs and polyethylene glycol 6000. IR spectrophotometry provided evidence that there was complex formation between nitrofurantoin and povidone 25,000, probably *via* hydrogen bonding.

Keyphrases □ Nitrofurantoin—solid dispersions with polyethylene glycol 6000, coprecipitates with povidone, effect on dissolution rate □ Ethotoin—solid dispersions with polyethylene glycol 6000, coprecipitates with povidone, effect on dissolution rate □ Coumarin—solid dispersions with polyethylene glycol 6000, coprecipitates with povidone, effect on dissolution rate □ Solid dispersions—nitrofurantoin, ethotoin, and coumarin with polyethylene glycol 6000, effect on dissolution rate □ Coprecipitates—nitrofurantoin, ethotoin, and coumarin with povidone, effect on dissolution rate □ Dissolution rates—nitrofurantoin, ethotoin, and coumarin, solid dispersions with polyethylene glycol 6000 and coprecipitates with povidone □ Polyethylene glycol 6000—solid dispersions with nitrofurantoin, ethotoin, and coumarin, effect on dissolution rates □ Povidone—coprecipitates with nitrofurantoin, ethotoin, and coumarin, effect on dissolution rates

The formation of solid dispersions or coprecipitates of relatively water-insoluble drugs with various pharmacologically inert carriers increases *in vitro* dissolution rates significantly (1–22). However, the use of linear polymeric materials, especially povidone, as carriers in coprecipitate systems has received limited attention (7, 13). In theory, an enhancement in the dissolution rate of a drug should facilitate its GI absorption rate if the absorption process is dissolution rate limited. The mechanism and advantages of increased dissolution rates of drugs coprecipitated in povidone were described (13, 16).

The mechanism underlying the influence of polyethylene glycols in enhancing the dissolution rate of drugs was the subject of intensive study by IR spectral analysis (16), X-ray diffraction (23), differential thermal analysis (24), microscopic examination (24), and TLC (16, 25). Each of these approaches for increasing the dissolution rate requires a unique type of drug molecule (26). The coprecipitation of reserpine with povidone markedly enhanced the absorption characteristics of this hydrophobic drug, and these *in vivo* increases were correlated quantitatively with *in vitro* dissolution rates (14, 17).

Recently, several reports (27, 28) confirmed the existence of a close correlation between *in vitro* dissolution and plasma digoxin levels. Therefore, dissolution experiments were carried out to reflect bioavailability. This study reports the influence of solid dispersions of polyethylene glycol 6000 (I) coprecipitates and physical mixtures of povidone 25,000 (II) on the dissolution rates of three poorly water-soluble drugs: nitrofurantoin, ethotoin, and coumarin.

EXPERIMENTAL

Materials—Nitrofurantoin[1], ethotoin[2], and coumarin[3] were pharmaceutical grade. Compounds I[4] and II[5] had average molecular weights of 6000 and 25,000, respectively. Chloroform, hydrochloric acid, and acetone were analytical reagent grade.

Test Preparation—Solid dispersions of nitrofurantoin, ethotoin, and coumarin in I were prepared by the fusion method. A weighed quantity of the drug was dissolved in a melted quantity of I over a thermostatically heated water bath and then spread in a thin layer on a glass slab. The resultant mixtures were cooled and solidified gradually at room temperature. The formed crust was scraped off, homogeneously mixed, and incubated at 45–50° for 6 hr. It was then pulverized in a mortar, and the 125–180-μm particles were collected.

The 1:2, 1:4, and 1:8 (w/w) drug–II coprecipitates were prepared by dissolving both components in chloroform and subsequently evaporating the organic solvent *in vacuo*. The residue was then dried to constant weight *in vacuo* and screened, and the drug–II weight ratio was confirmed analytically.

The 1:4 (w/w) nitrofurantoin, ethotoin, and coumarin physical mixtures with II were prepared by gently triturating appropriate quantities of each drug and II in a glass mortar. Pure drug possessing the same particle-size range served as a control.

Dissolution Rate Studies—The dissolution apparatus was similar to that employed by Levy and Hayes (29). A 400-ml beaker contained 200 ml of 0.1 *N* HCl as the dissolution medium. The dissolution medium was maintained at 37 ± 0.5° and agitated at 100 rpm with a polytef stirrer blade connected to a constant-speed stirring moter[6].

The test preparations were filled into capsules, each containing a quantity equivalent to 100 mg of drug. At frequent time intervals after the test preparation was added to the dissolution medium, a 2.0-ml sample was withdrawn, filtered, and replaced with 2.0 ml of fresh dissolution medium. The amount of the drug in solution at each time interval, appropriately corrected for this dilution effect (30), was determined spectrophotometrically[7] at 367, 257, and 276 nm for nitrofurantoin, ethotoin, and coumarin, respectively. Compounds I and II in the concentration present in the assay samples did not interfere with the determination of these drugs.

IR Spectral Analysis—A mineral oil mull of each sample was smeared as a thin film between two sodium chloride plates, and the IR spectrum[8] was recorded at the slow scanning speed.

TLC—TLC plates of 0.25-mm thickness were prepared using a slurry of silica gel G[9] (25 g) with 60 ml of water. The solvent systems were chloroform–diethylamine (90:10), benzene–acetone (90:10), and chloroform–acetone (90:10) for nitrofurantoin, coumarin, and ethotoin and their test preparations, respectively. Aliquots (10 μl) of 0.1% alcoholic solutions of each drug and its preparations were spotted on the TLC plates and developed. Nitrofurantoin, coumarin, and their preparations were detected by UV light, but the visualization of ethotoin and its preparations was by UV light after spraying with 2′,7′-dichlorofluorescein alcoholic solution.

[1] Eaton Laboratories, Norwich Pharmacal Co., Norwich, N.Y.
[2] Abbott.
[3] British Drug House Chemicals Ltd., Poole, England.
[4] Hoechst, West Germany.
[5] BASF, Ludwigshafen, West Germany.
[6] Citenco Ltd., England.
[7] Model DU-2, Beckman Instruments.
[8] IR-10, Beckman Instruments.
[9] E. Merck, Darmstadt, West Germany.

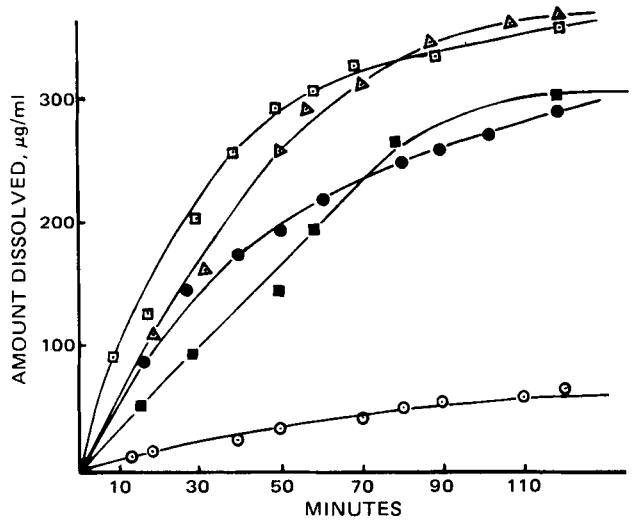

Figure 1—*Dissolution rates of coumarin from test preparations at 37°. Key: ○, pure coumarin; ●, 1:4 (w/w) solid dispersion; □, 1:10 (w/w) solid dispersion; ■, 1:4 (w/w) physical mixture; and △, 1:4 (w/w) coprecipitate.*

RESULTS AND DISCUSSION

Dissolution followed first-order kinetics. Semilogarithmic plots of the percent drug undissolved *versus* time were linear, the correlation coefficient being 0.98–0.99 in all cases. Figures 1–3 show that the dissolution rate of the solid dispersions of coumarin, ethotoin, and nitrofurantoin increased considerably. For capsules containing coumarin only, the release rate was slow and steady (Fig. 1). However, there was almost a sevenfold increase in the dissolution rate of coumarin when present in a 1:10 I solid dispersion system. Figures 2 and 3 show that there were fivefold and sevenfold increases in the dissolution rates of ethotoin and nitrofurantoin, respectively, in the 1:10 and 1:8 drug–I solid dispersion systems.

In addition, there was a progressive increase in the percentage release of the medicament corresponding to the increased weight fraction of I. The maximal release attained depends upon the weight fraction of the polymer (Figs. 1–3). Thus, maximum drug release was achieved after 45 and 60 min from the dispersion system of coumarin–I in ratios of 1:10 and 1:4, respectively. The plain capsules gave only 10% release after 120 min. Similar results were obtained for both ethotoin–I and nitrofurantoin–I dispersion systems. The demonstrated fairly fast *in vitro* release of the selected three compounds from dispersion systems suggests their high potential application for the formulation of most water-insoluble drugs. The bioavailability of such dosage forms as compared to the conventional forms, however, will be the subject of further study.

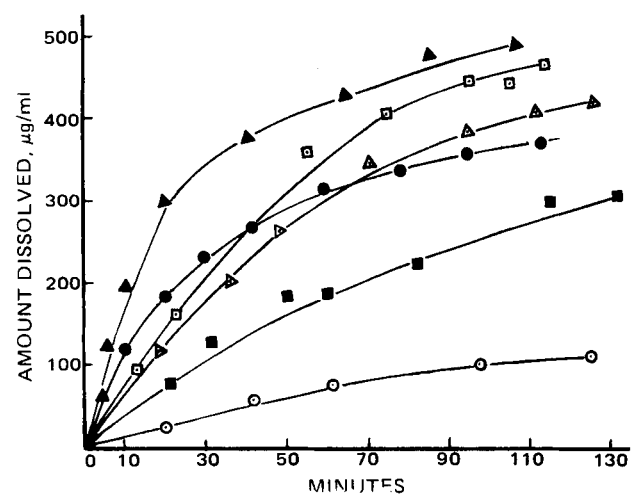

Figure 2—*Dissolution rates of ethotoin from test preparations at 37°. Key: ○, pure ethotoin; ●, 1:4 (w/w) solid dispersion; □, 1:10 (w/w) solid dispersion; ■, 1:4 (w/w) physical mixture; △, 1:4 (w/w) coprecipitate; and ▲, 1:8 (w/w) coprecipitate.*

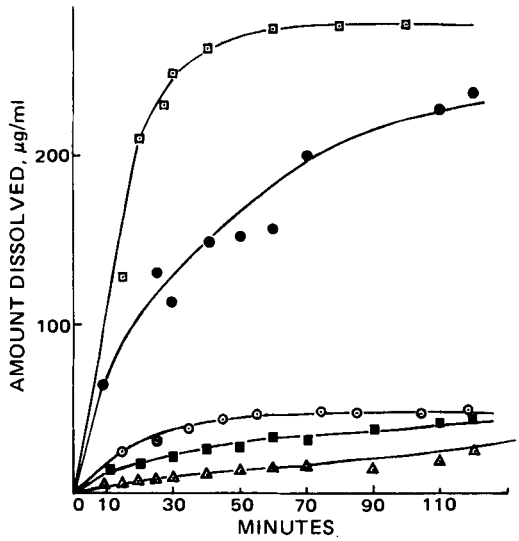

Figure 3—*Dissolution rates of nitrofurantoin from test preparations at 37°. Key: ○, pure nitrofurantoin; ●, 1:4 (w/w) solid dispersion; □, 1:8 (w/w) solid dispersion; ■, 1:4 (w/w) physical mixture; and △, 1:4 (w/w) coprecipitate.*

The dissolution rate profiles for 1:4 (w/w) physical mixtures and 1:4 (w/w) coprecipitates of coumarin, ethotoin, and nitrofurantoin are also shown in Figs. 1–3. At each time interval, marked differences existed between the amount of drug in solution from the coprecipitate and the other two preparations (Figs. 1 and 2). Surprisingly, the capsules prepared from nitrofurantoin–II as a 1:4 physical mixture and a 1:4 coprecipitate achieved dissolution rates essentially lower than pure nitrofurantoin alone (Fig. 3). From these data, it can be concluded that bulk effects due to the presence of II in solution are responsible for the decrease in the dissolution rate observed, since there was a significant difference between nitrofurantoin alone and when present in a 1:4 physical mixture and a 1:4 coprecipitate with II. Therefore, factors such as insoluble complex formation, chemisorption, micelle formation, and other surface phenomena are probably responsible for the decreased nitrofurantoin dissolution rate.

An increase in the weight fraction of II resulted in a corresponding increase in the ethotoin dissolution rate (Fig. 2). However, II induced better solubilization of ethotoin and coumarin than I with the drug–polymer ratios tested. If it is assumed that the dissolution rate from the powder surface is rate limited by the dissolution of the controlling I external layer, analogous to the controlling II layer in the high II weight fractions (13), then the dissolution rate of the drug from the same drug–I dispersion surface will be proportional to the drug–I ratio of the solid dispersion. In other words, the dissolution rate of the drug from a 1:4 solid dispersion will be almost twice as fast as from a 1:2 solid dispersion if the dissolution surface is the same. Other factors, such as the possible complexation between the drug and I or II and the conversion of the molecular dispersion to particulate aggregates of pure compounds, may also affect the dissolution.

Chromatographic Behavior—TLC showed that the drug–I solid dispersion was resolved into two separate spots of R_f (× 100) values of 52, 73, 3, and 78 for I, ethotoin, nitrofurantoin, and coumarin, respectively, which were identical to the pure components. The nitrofurantoin–II coprecipitate was not resolved into two separate spots as were coumarin–II and ethotoin–II coprecipitates. Therefore, TLC indicated the existence of complexation between nitrofurantoin and II, but there was no evidence of complexation between coumarin or ethotoin and II.

IR Spectra—The bands characteristic for each drug were unaffected in the drug–I systems, and the IR spectrum of the drug–I system was simply the summation of the spectra of the two components. There was no evidence of complexation between nitrofurantoin, ethotoin, or coumarin and I. On the other hand, the sharp band at 3300 cm^{-1}, due to the NH stretching vibration of nitrofurantoin, completely disappeared in the nitrofurantoin–II system. Other sharp bands at 680, 820, 975, 1100, and 1239 cm^{-1}, characteristic of nitrofurantoin, disappeared in the nitrofurantoin–II system.

In contrast, the band at 3300 cm^{-1}, due to the NH stretching vibration of ethotoin, was unaffected in the ethotoin–II system, and the IR spec-

trum of the ethotoin–II system was the summation of the spectra of the two components. Again there was no evidence of complexation between the two compounds. The formation of an insoluble complex between nitrofurantoin and II may explain the decrease in the dissolution rates from both the nitrofurantoin–II physical mixture and the coprecipitate.

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GLC Determination of Meperidinic and Normeperidinic Acids in Urine

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Abstract □ A GLC procedure for the determination of meperidinic and normeperidinic acids in human urine is described. After the extraction of any interfering meperidine or normeperidine, the urine samples are dried and the acids are reesterified using ethanol–sulfuric acid. The resulting meperidine and normeperidine are then extracted and quantified. With this method, the urinary excretion of these metabolites was followed in five subjects who received a single meperidine dose of 36 mg/m^2 im. This method represents an improvement over the previously described methods for meperidinic and normeperidinic acids and can be applied to clinical situations.

Keyphrases □ Meperidine metabolites—meperidinic and normeperidinic acids, GLC analyses, human urine □ GLC—analyses, meperidinic and normeperidinic acids in human urine □ Analgesics, narcotic—meperidine metabolites, GLC analyses in human urine

The pharmacokinetics of meperidine (I) were described previously (1), and its metabolites were identified (2). Unchanged meperidine was identified in the urine along with the *N*-demethylated metabolite normeperidine (II), meperidinic acid (III), normeperidinic acid (IV), and conjugated esters of these acids (Scheme I) (2). These initial studies were limited to high drug doses due to the limitations of the analytical colorimetric method.

The recent development of more sensitive GLC assays for meperidine in serum (3) and for meperidine and normeperidine in urine (4) permitted the study of the pharmacokinetics and metabolism of meperidine in humans using usual clinical doses (5). A sensitive method for the determination of urinary levels of meperidinic and normeperidinic acids has not been reported previously. This report describes a GLC technique for the analysis of these metabolites using small aliquots of urine samples.

EXPERIMENTAL

Ten milliliters of urine, 1 ml of 5 *N* NaOH, and 5 ml of chloroform were shaken for 10 min in a 50-ml glass-stoppered centrifuge tube. Then the tube was centrifuged, and 9 ml of the aqueous phase was transferred to a 50-ml round-bottom flask and evaporated to dryness by freeze drying. Absolute ethanol, 9 ml, and 1 ml of sulfuric acid were added to the residue, and the resulting mixture was refluxed for 3 hr.

After cooling, 1 ml of the reaction mixture was added to a 15-ml screw-capped centrifuge tube containing 2 ml of 2.5 *N* NaOH. Chloroform, 100 μl, containing an internal standard (lidocaine, 20 μg/ml), was added to the solution, and the resulting mixture was vortexed for 30 sec and centrifuged for 5 min. A 5-μl aliquot of the chloroform layer was then injected into the chromatograph[1].

The analysis was carried out using a hydrogen flame-ionization detector

[1] Perkin-Elmer model 3920.