pH-Dependent Dissolution Rate of Nitrofurantoin from Commercial Suspensions, Tablets, and Capsules

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Abstract □ The dissolution rate of nitrofurantoin from commercial suspensions and tablets containing microcrystalline drug particles and from capsules containing macrocrystalline drug particles was determined at 37° in simulated gastric (pH 1.12) and intestinal (pH 7.20) fluids using the stirrer-flask method. As expected from solubility considerations alone, the dissolution rate of nitrofurantoin (pKa 7.2) from the suspension and capsule dosage forms at pH 7.20 was significantly faster than at pH 1.12. In contrast, the drug from the tablet dosage form dissolved in the pH 1.12 dissolution medium at a rate twice that observed at pH 7.20. This unusual pH effect could be explained satisfactorily on the basis of observed differences in the physical characteristics of the tablet when exposed to the two media. The pH 7.20 phosphate buffer medium suggested by USP XVIII was unable to discern inherent, particle-size-dependent differences in the rate of solution and the reported incidence of side effects of nitrofurantoin from the microcrystalline drug tablet and macrocrystalline drug capsule. The reported existence of a relationship between the dissolution rate of nitrofurantoin from these two dosage forms in simulated gastric fluid and their reported toxicities suggests that the official USP XVIII dissolution rate specification for products of this drug should be modified.

Keyphrases □ Nitrofurantoin—pH-dependent dissolution rate from commercial dosage forms □ Dissolution—nitrofurantoin from commercial dosage forms □ Bioavailability—pH-dependent dissolution rate of nitrofurantoin from commercial suspensions, tablets, and capsules

The dissolution rate (1), bioavailability in humans (1–4), and incidence of side effects (5) of the poorly soluble, weakly acidic antibacterial agent nitrofurantoin (pKa 7.2) are significantly affected by its particle size.

Presumably, in an attempt to ensure a minimal incidence of drug-induced side effects (nausea and emesis), the USP XVIII monograph for nitrofurantoin tablets (6) requires that 60% of the labeled amount of drug dissolve in pH 7.2 phosphate buffer in *not less* than 1 hr. Based on the lack of a dissolution rate specification for nitrofurantoin oral suspension USP, coupled with the markedly faster dissolution rate of microcrystalline nitrofurantoin from commercial suspension compared to commercial tablet dosage forms, the consistency underlying the official requirement of an unusually slow dissolution rate of nitrofurantoin from tablets has been questioned (7).

Table I—Effect of pH on the Dissolution Rate of Nitrofurantoin from Commercial Dosage Forms at 37°

Commercial Dosage Form	Mean Dissolution Rate Half-Life (T_{50})[a], min	
	pH 1.12	pH 7.20
Aqueous suspension[b]	12.5 (1.21)[c]	2.64 (0.336)
Compressed tablet[d]	77.9 (19.0)	167 (35.8)
Gelatin capsule[e]	212 (44.5)	160 (24.7)

[a] Determined from log-normal probability plots of individual dissolution rate data. Mean of five determinations. [b] Furadantin suspension containing microcrystalline (<10 μm) drug. [c] Standard deviation in parentheses. [d] Furadantin tablets containing microcrystalline (<10 μm) drug. [e] Macrodantin capsules containing macrocrystalline (80–200 mesh) drug.

Upon oral ingestion, nitrofurantoin dosage forms are exposed first to the highly acidic (pH 1–2) gastric fluid. As a result, the drug contained therein is afforded the opportunity to be released and dissolve in this region of the GI tract. The amount of nitrofurantoin capable of dissolving in this region would depend primarily on the residence time of the dosage form in the gastric pouch and on the release and dissolution rate of the drug from the dosage form.

To reduce the incidence of nitrofurantoin-induced nausea and emesis, all dosage forms of this drug are commonly prescribed with food and/or milk. A recent report (8), related to the effect of food on nitrofurantoin absorption in humans, indicated that the presence of food in the stomach appreciably delays gastric emptying. A marked enhancement in the bioavailability of both macro- and microcrystalline nitrofurantoin from commercial capsule and tablet dosage forms in nonfasting as compared to fasting subjects was also observed (8). These findings are consistent with the argument that a significant fraction of drug from both dosage forms dissolves in the stomach prior to being emptied into the duodenal region of the small intestine where absorption is optimal (9). Hence, to design the most appropriate dissolution rate specification for official and nonofficial dosage forms of nitrofurantoin, which could potentially correlate best with the absorption characteristics and toxicity of the drug from these products, it is important to examine their dissolution rate profiles under pH conditions simulating both gastric and intestinal fluids. The official USP dissolution rate test for tablet dosage forms of nitrofurantoin presently utilizes only a pH 7.2 phosphate buffer medium (simulated intestinal fluid). As a result, the specification does not consider the possibility that some physicochemical property (*e.g.*, solubility) of an "inert" ingredient(s) in a particular tablet formulation may be pH dependent and, thus, affect the release, dissolution, and absorption of the drug. This shortcoming may be partly responsible for the inability of the USP dissolution rate test to reflect the *in vivo* absorption characteristics of the drug from 19 different commercial tablet formulations (10).

The present investigation was designed to characterize the pH-dissolution rate behavior of nitrofuran-

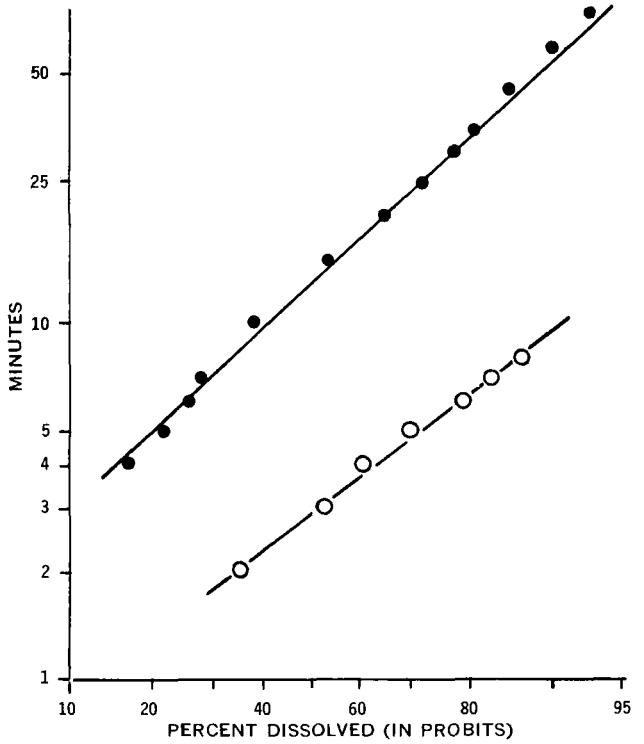

Figure 1—*Representative log-normal probability plots of dissolution rate data for nitrofurantoin from a commercial suspension at 37°. Key: ●, pH 1.12; and ○, pH 7.20.*

toin from official commercial suspension and tablet dosage forms containing microcrystalline drug, as well as from a nonofficial commercial capsule dosage form containing macrocrystalline drug.

EXPERIMENTAL

Materials—The commercial suspension of microcrystalline (<10 μm) nitrofurantoin[1], the compressed tablets of microcrystalline (<10 μm) nitrofurantoin[2], and the capsules of macrocrystalline (80–200 mesh) nitrofurantoin[3] employed in this investigation were purchased on the open market and were assayed for drug content prior to use. All other materials were reagent grade and were used as received.

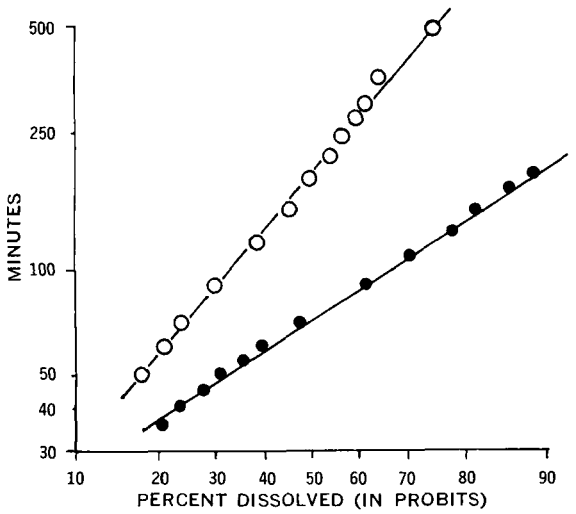

Figure 2—*Representative log-normal probability plots of dissolution rate data for nitrofurantoin from a commercial compressed tablet at 37°. Key: ●, pH 1.12; and ○, pH 7.20.*

Equilibrium Solubility Determinations—The equilibrium solubility of nitrofurantoin at 37° was determined in pH 1.12 hydrochloric acid and pH 7.20 phosphate buffer media. Excess quantities of nitrofurantoin were placed into 50-ml glass-stoppered flasks together with 25.0-ml portions of either buffer solution. The flasks were closed securely, protected from light, and shaken mechanically in a water bath maintained at 37 ± 0.25° until equilibrium was attained. The equilibrated samples were subjected to filtration[4] (0.45-μm pore size) at 37°, the filtrates were diluted and adjusted to pH 7.20 with phosphate buffer when necessary, and the concentration of drug in solution was determined spectrophotometrically at 383 nm (1).

Dissolution Rate Determinations—The dissolution apparatus consisted of a 1-liter, three-necked, round-bottom flask containing 880 (suspension studies) or 900 (tablet and capsule studies) ml of pH 1.12 hydrochloric acid or pH 7.20 phosphate buffer solution. The dissolution medium was maintained at 37 ± 0.25° and agitated at 200 rpm by means of a Teflon stir blade (70 mm diameter) connected to a constant-speed stirring mechanism[5].

At time zero, one tablet, one capsule, or a weight of suspension corresponding to 100 mg of nitrofurantoin was introduced into the dissolution medium. Periodically, 5-ml samples were withdrawn from the flask, filtered, adjusted to pH 7.20 when necessary, and assayed spectrophotometrically at 383 nm using a recording spectrophotometer[6]. Immediately following the removal of each sample, a 5-ml quantity of fresh dissolution medium was added to the flask. All dissolution data were corrected appropriately for this dilution effect (11).

Both the aqueous, gel-like suspension and tablet dosage forms were sufficiently dense to sink immediately to the bottom of the flask and occupy a central position, 5 cm below the stir blade. To accomplish this with the capsule dosage form, it was necessary to employ a specially constructed, nonmetal holding device. The device made minimal contact with the capsule dosage form and, thus, had an insignificant effect on the release characteristics of this dosage form.

Five dissolution rate determinations were made with each dosage form, and the data obtained were interpreted by the log-probit method suggested by Wagner (12).

RESULTS AND DISCUSSION

The equilibrium solubility of nitrofurantoin at 37° was determined to be 104 and 272 mg/liter under pH conditions simulating those of gastric (pH 1.12) and intestinal (pH 7.20) fluids, respectively.

Representative dissolution rate profiles of nitrofurantoin from the commercial aqueous suspension, tablet, and capsule dosage forms are depicted in Figs. 1–3, and the dissolution half-lives (T_{50}), determined from plots of this nature, are summarized in Table I. Inspection of the data reveals an interesting interrelationship among the pH of the dissolution medium, the solubility of the drug, the release and/or solubility characteristics of some "inert" component(s) of the dosage forms, and the resultant dissolution rate profile of the drug. The significantly slower dissolution rate of nitrofurantoin from either the aqueous suspension or capsule dosage form at pH 1.12 as compared to that at pH 7.20 is consistent with the pH-dependent solubility characteristics of the drug. In contrast, the drug from the tablet dosage form dissolved in the pH 1.12 dissolution medium at a rate approximately *twice* that observed at pH 7.20. This unusual pH effect is contrary to that expected based on drug solubility considerations alone, but it can be correlated satisfactorily with observed differences in the physical release characteristics of the tablet dosage form when exposed to acidic and slightly alkaline dissolution media. Unlike physical characteristics of the tablet at pH 1.12, when this dosage

[1] Furadantin suspension, 25 mg/5 ml, Eaton Laboratories, Control No. 700364.
[2] Furadantin tablets, 100 mg, Eaton Laboratories, Control No. 694673.
[3] Macrodantin capsules, 100 mg, Eaton Laboratories, Control No. 695242.
[4] Millipore.
[5] Servodyne laboratory stirrer, Cole-Parmer Instrument Co., Chicago, IL 60648
[6] Beckman DB-G, Beckman Instruments Inc., Fullerton, CA 92634

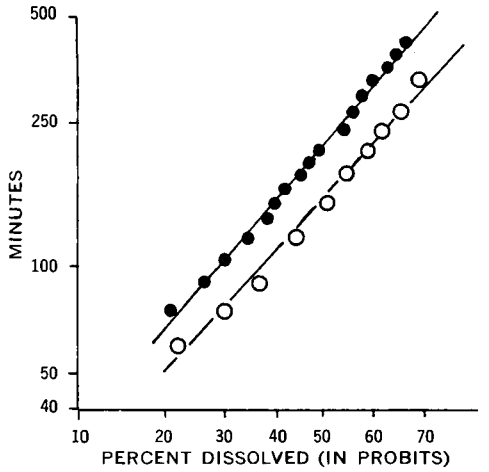

Figure 3—*Representative log-normal probability plots of dissolution rate data for nitrofurantoin from a commercial capsule at 37°. Key: ●, pH 1.12; and ○, pH 7.20.*

form was introduced into the pH 7.20 medium, it displayed poor disintegration properties, produced relatively large granules, and maintained most of its shape during the greater portion of the dissolution run.

Hailey and Glascock (5) demonstrated, in patients with known intolerance to nitrofurantoin, that the incidence of undesirable side effects is markedly reduced upon oral administration of a commercial capsule containing macrocrystalline drug particles[3] as compared to a commercial tablet containing microcrystalline drug particles[2]. In view of these findings, the lack of official recognition for this larger particle-size fraction of drug or its capsule dosage form seems surprising. When dissolution rate experiments were conducted at pH 7.2, the pH suggested by the USP (6), the dissolution rate of macrocrystalline nitrofurantoin from the commercial capsule was identical to that of microcrystalline drug from the tablet dosage form (Table I). These results are inconsistent with the anticipated slower dissolution rate of nitrofurantoin from the macrocrystalline drug capsule (1) and its lower toxicity (5). However, when the same two dosage forms were exposed to simulated gastric fluid (pH 1.12), an interrelationship was found to exist among the particle size of drug contained within the dosage form, its dissolution rate (Table I), and its reported toxicity (5).

The results of the present investigation provide evidence that the dissolution rate of nitrofurantoin from three different pharmaceutical dosage forms can be markedly affected by pH. The dissolution medium (pH 7.2 phosphate buffer) recommended by the USP (6) is unable to discern inherent, particle-size-dependent differences in the rate of solution and incidence of side effects of nitrofurantoin from commercial, microcrystalline drug tablet and macrocrystalline drug capsule dosage forms. The dissolution rate characteristics of nitrofurantoin from these two dosage forms in simulated gastric fluid (pH 1.12) and the existence of a relationship between these *in vitro* results and reported toxicity data suggest that the USP XVIII dissolution rate specification for nitrofurantoin products should be modified.

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COMMUNICATIONS

Effect of γ-Radiation on Intestinal Absorption of Sulfanilamide

Keyphrases □ Radiation, gamma—effect on intestinal absorption of sulfanilamide, rats □ Sulfanilamide—effect of γ-radiation on intestinal absorption, rats □ Absorption, intestinal—effect of γ-radiation on rate of sulfanilamide absorption, rats

To the Editor:

Following sublethal irradiation of the mammalian small intestine, cell division in the intestinal epithelium slows. The mass of the epithelium declines temporarily and then becomes abnormally large before the intestine appears histologically normal again (1). Since the barrier characteristics of the intestinal epithelium are thought to control the absorption of many orally administered drugs, exposure of the intestine to ionizing radiation could affect drug absorption.

Although the results of a number of studies on the influence of radiation on the intestinal absorption of vitamins, minerals, water, and nutrients have been reported (1, 2, and references cited therein), there is very little published information on the effects of ra-