methotrexate peak to give levels of actual methotrexate. As can be seen in Fig. 1, by 4 hr. the contribution of the nonmethotrexate component was very significant. Although the percentage of total label represented by the nonmethotrexate component increased with time, the actual concentration appeared to remain relatively constant.

Whether the nonmethotrexate component originates from metabolism of methotrexate by intestinal bacteria, by metabolism within the rat, from a trace contaminant in the purified ^{3}H-methotrexate solution for injection, or from a combination of these factors is unknown at this time.

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Inconsistencies in Rationale Underlying Official USP Dissolution Rate Specifications for Nitrofurantoin

Keyphrases ☐ Nitrofurantoin tablets and oral suspension—dissolution rate specifications with respect to compendial requirements ☐ Oral suspension, nitrofurantoin—dissolution rate specifications with respect to compendial requirements ☐ Dissolution rates, nitrofurantoin tablets and oral suspension—considerations with respect to compendial requirements

Sir:

Nitrofurantoin, 1-[(5-nitrofurfurylidene)amino] hydantoin, is an antibacterial agent used clinically to treat specific urinary tract infections. Physiocochemically, the drug is a weak acid (pKa 7.2) possessing relatively low aqueous solubility characteristics at pH values normally encountered in the various segments of the GI tract of man. As a result, it is not surprising that the drug displays a particle-size dependence in its dissolution rate (1) and rate and extent of absorption (bioavailability) in man (1–4).

USP XVIII (5) recognizes aqueous suspension and compressed tablet dosage forms of the drug, but only the monograph for nitrofurantoin tablets contains specifications for dissolution rate determinations. The requirement, contrary to that for other official drug tablet dosage forms, states that: "The time required for 60 percent of the labeled amount [50 or 100 mg.] of $C_8H_6N_4O_5$ in the Tablets to dissolve is not less than 1 hour, pH 7.2 phosphate buffer [900 ml.] being used as the *Dissolution Medium* and the basket being rotated at 100 r.p.m., and ...." Apparently, it is the intent of this unusual specification to ensure a *slow* rate of dissolution of nitrofurantoin from commercial tablet dosage forms in the GI fluids and thereby reduce both the maximum concentration of drug bathing the GI mucosa and present in the systemic circulation at any time. This, in turn, would presumably minimize the incidence of the major side effects of nitrofurantoin therapy in man, namely, locally (mucosal irritation) and/or systemically induced nausea and emesis (2, 6). Based on clinical observations of increased tolerance to capsules containing *macrosize* drug (80–200 mesh) as compared to tablets containing *microsize* (about 10 μ) drug (6), the rationale underlying the official dissolution rate specification for nitrofurantoin tablets appears, at first glance, to be sound, albeit totally arbitrary from a quantitative point of view. However, the requirement does not impose an upper dissolution rate limit and thus fails to ensure optimal bioavailability of nitrofurantoin from various brands of commercial tablets. Hence, the test does not reflect differences encountered in the *in vivo* absorption characteristics of nitrofurantoin from several different tablet formulations (7).

In addition, it appears quite inconsistent for the compendia, on the one hand, to be cognizant of the potential side effects of nitrofurantoin from tablet dosage forms but, on the other, not to provide for a dissolution rate specification for nitrofurantoin oral suspension USP. Apparently, it failed to recognize that the possible occurrence of adverse drug reactions from a suspension dosage form may be equal to, or even significantly greater than, that from a tablet dosage form. This conclusion can be readily appreciated from a consideration of basic biopharmaceutical principles (8)—*viz.*, that a relatively water-insoluble drug, administered orally in an aqueous suspension dosage form, generally dissolves, is absorbed, and, therefore, appears in the systemic circulation at a faster rate than can be normally achieved *via* administration of a compressed tablet dosage form.

While studying the rate of absorption and bioavailability of nitrofurantoin in man from different pharmaceutical dosage forms, the need arose to develop a *single* dissolution rate methodology applicable to both the official aqueous suspension and tablet dosage

Table I—*In Vitro* Dissolution Rates of Nitrofurantoin from Commercial Aqueous Suspension and Tablet Dosage Forms at 37°

Commercial Dosage Form	Mean Dissolution Half-Life, min.[a], at pH 7.20
Aqueous suspension	2.64 (±0.336)[b]
Compressed tablet	167 (±35.8)

[a] Determined from log-normal probability plots of dissolution rate data. Mean of five determinations. [b] Standard deviation in parenthesis.

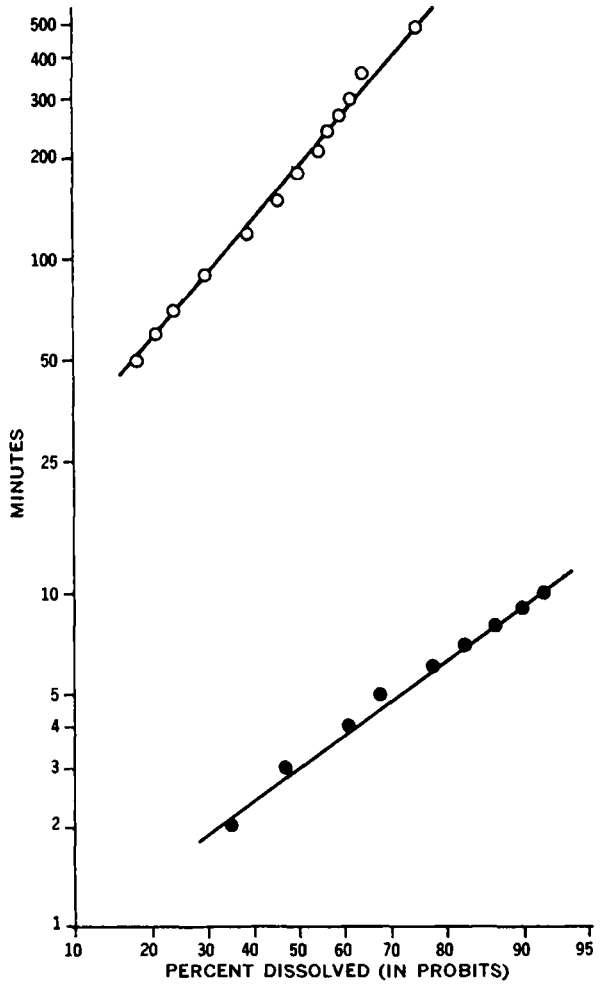

Figure 1—*Representative log-normal probability plots of dissolution rate data for nitrofurantoin from commercial dosage forms at 37° (pH 7.20). Key: —●—, aqueous suspension; and —○—, compressed tablet.*

forms. This precluded the use of the USP rotating-basket apparatus, since it was found to be inappropriate for dissolution rate studies performed with the official suspension dosage form. This preliminary communication presents some of our *in vitro* research experiences with the *stirrer-flask method*, which was demonstrated previously in our laboratories to be quite appropriate for suspension and tablet dosage forms of salicylamide (9) and provides correlation with *in vivo* absorption parameters in man (1, 9) and lower animals (10).

The apparatus employed to evaluate the dissolution behavior of nitrofurantoin from commercial aqueous suspension[1] (25 mg. microsize drug/5 ml.) and tablet[2] (100 mg. microsize drug/tablet) dosage forms was described elsewhere (9). At time zero, one tablet or a weight of suspension equivalent to 100 mg. of nitrofurantoin was added to 900 or 880 ml. of pH 7.20 phosphate buffer, which had been previously equilibrated to 37° under an agitation intensity of 200 r.p.m. Both the aqueous, gel-like suspension and tablet dosage forms were dense enough to sink immediately to the bottom of the 1-l., three-necked, round-bottom flask and occupy a central position, 5 cm. below the 70-mm. diameter Teflon stirring propeller. Periodically, 5-ml. samples were withdrawn from the flask, filtered, and assayed spectrophotometrically (1) for drug content. Following the removal of each sample, a 5-ml. quantity of fresh dissolution medium was added to the flask. All dissolution rate data were corrected appropriately for this dilution effect (11). The equilibrium solubility of nitrofurantoin at 37° was determined to be 272 mg./l. of pH 7.20 phosphate buffer. Five dissolution rate determinations were made with each dosage form.

Representative dissolution rate profiles of nitrofurantoin from the two different pharmaceutical dosage forms at pH 7.20 are depicted in Fig. 1 as log-normal probability plots of the dissolution data. The dissolution half-life (T_{50}) for each run was determined from such linear plots. An examination of the mean half-life data (Table I) reveals that the dissolution rate of nitrofurantoin from the commercial aqueous suspension is markedly faster (approximately 60-fold) than from the commercial tablet. These differences are consistent with the physical observation that unlike the aqueous suspension dosage form, which rapidly dispersed throughout the dissolution medium, the tablet dosage form displayed poor disintegration characteristics, produced relatively large granules, and maintained most of its shape during most of the dissolution run.

In light of the present findings, the rationale underlying the official dissolution rate specification for nitrofurantoin tablets appears quite arbitrary and inconsistent with the dissolution profile and potential toxicity of the official suspension dosage form.

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[1] Furadantin suspension, purchased on the open market.
[2] Furadantin tablets, purchased on the open market.