Nitrofurantoin Solubility in Aqueous Urea Solutions

Keyphrases □ Nitrofurantoin—solubility in aqueous urea solutions □ Urea—solubility of nitrofurantoin in aqueous solutions □ Solubility—nitrofurantoin in aqueous urea solutions

To the Editor:

Nitrofurantoin, 1-[(5-nitrofurfurylidene)amino]-hydantoin, is an antibacterial agent used to treat urinary tract infections. The drug is a weak acid (pKa 7.2) possessing relatively low aqueous solubility characteristics. Solubilities in water at 37° have been reported to be 190 mg/liter in pH 7 distilled water (1) and 125 mg/liter in pH 4.8 water (2). Bates and coworkers[1] (3) reported the solubilities of nitrofurantoin in pH 1.12 and 7.2 aqueous systems to be 154 and 379 mg/liter, respectively.

Much higher solubilities, however, have been reported for nitrofurantoin in urine. Nitrofurantoin concentrations of 250–500 mg/liter were found after administering 200 mg of drug every 6 hr to an 80-kg patient (4) and urine concentrations of 200–400 mg/liter were reported (5). Maximum urine nitrofurantoin concentrations from 158 to 372 mg/liter were reported in nine normal individuals, each of whom received a 100-mg tablet every 4 hr (6).

Although urine concentrations that represent saturation or supersaturation are routinely attained after normal usage, there are no reported incidents of crystalluria associated with nitrofurantoin therapy. These facts suggest that the normal urine contents might have some effect on the solubility of nitrofurantoin in urine. We wish to report our preliminary findings concerning the effect of urea on the aqueous solubility of nitrofurantoin.

An excess amount of nitrofurantoin (approximately 50 mg) was added to 40 ml of the appropriate test solution (0.0–5% urea in distilled water) in a screw-capped bottle of 45-ml capacity. The tightly closed container was placed in a constant-temperature water bath at 30 or 37 ± 0.1° and rotated[2] for at least 24 hr. Preliminary experiments indicated that equilibrium was established within 12–18 hr. After equilibrium, the test solutions were subject to filtration[3] (0.45-μm pore size), and the filtrate was diluted with deionized distilled water to make a solution of proper concentration (40–100 mg/liter) for spectrophotometric assay using the method of Conklin and Hollifield (7). At least five experimental runs were made for each individual test medium.

Figure 1 shows the effect of urea on the solubility of nitrofurantoin at two temperatures. The addition of urea to aqueous media had the paradoxical effect of first promoting increased nitrofurantoin solubility up to a maximum concentration level and then causing decreased solubility at higher urea concentrations. The change was abrupt, and nitrofurantoin solubility decreased to levels considerably lower than nitrofurantoin solubility in plain distilled water. The nitrofurantoin solubility was dependent on temperature, and the amount of urea needed to bring about maximum nitrofurantoin solubility was greater at 37° (2.25%) than at 30° (2.0%). The findings that urea first increased the aqueous solubility of nitrofurantoin might explain in part the elevated solubilities of this drug in urine (5, 6). This explanation is supported by the fact that concentrations of urea in human urine are normally in the neighborhood of 2% (8, 9).

The effect of urea on the aqueous solubility of organic compounds has been widely studied. Urea has been shown to increase the water solubility of chloramphenicol (10, 11) and acetaminophen (12) and to decrease the solubility of sulfathiazole (13). The solubility of methylene blue was reported to be 30 times higher in 10 *M* urea solution than in water (14). A recent investigation found that 1–5 *M* urea increased the water solubility of methyl *p*-hydroxybenzoate (15).

The effects of urea and thiourea on the solubility of benzoic and salicylic acids have been studied (16, 17). Altwein *et al.* (17) concluded that the interaction of urea with salicylic acid was relatively complex but that increases in the solubility of hydroxybenzoic acids were due to formation of soluble complexes. Feldman and Gibaldi (18), however, concluded that the enhanced solubility of benzoic and salicylic acids in urea and alkylurea solutions did not involve complexation. They proposed that urea and alkylureas solubilized benzoic and salicylic acids by "breaking up" water clusters surrounding the nonpolar molecule, increasing the entropy of the system, and producing a "driving" force for the solubilization.

In studying the effect of urea on hydrocarbon solubility, Wetlaufer *et al.* (19) suggested several mechanisms to explain the increase of hydrocarbon solubility in aqueous urea solutions: *(a)* the solute is solely dissolved by the urea, *(b)* urea alters the structure of water so as to enhance solvation of the solute by water molecules, and *(c)* solute molecules were solvated both by urea and water molecules. The proposed mechanisms have usually been associated with increased solubility of compounds in relatively high urea concentrations (1–5 *M*), and it appears that there is no conclusive evidence to support any one mechanism whereby urea changes solubilities.

In the present study, because of the paradoxical behavior of the system (first an increase followed by a considerable decrease in nitrofurantoin solubility), a single explanation of the phenomenon is certainly

[1] T. R. Bates, School of Pharmacy, State University of New York at Buffalo, personal communication.
[2] Menhold rotating apparatus, Lester, Pa.
[3] Millipore.

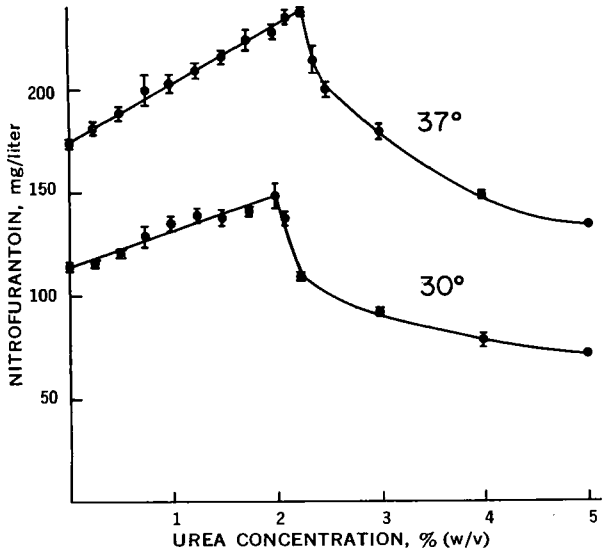

Figure 1—*Nitrofurantoin solubility in aqueous urea solutions at 30 and 37°. Bars mark off 1* SD *on either side of the average.*

not possible now. Preliminary spectral studies suggest some type of interaction between nitrofurantoin and urea molecules. This possible interaction may account for the increased solubility at low urea concentrations. The breakdown of water structure might account for the increase in solubility at lower urea concentrations; however, disruption of the water structure might not occur at the low urea concentrations used. The rapid decrease in nitrofurantoin solubility at higher urea concentrations may be due to a salting-out effect. However, the formation of an insoluble complex at higher urea concentrations might account for the abrupt decrease in solubility.

Further investigations are being conducted in these laboratories to determine the effect of urea and another urine component, creatinine, on nitrofurantoin solubility at various temperature and pH conditions and to elucidate the mechanism(s) of action of the solubilization phenomena.

(1) H. E. Paul and M. F. Paul, in "Experimental Chemotherapy," vol. II, R. J. Schnitzer and F. Hawking, Eds., Academic, New York, N.Y., 1964, p. 334.

(2) M. F. Paul, R. C. Bender, and E. G. Nohle, *Amer. J. Physiol.*, **197**, 580(1959).

(3) T. R. Bates, J. M. Young, C. M. Wu, and H. A. Rosenberg, *J. Pharm. Sci.*, **63**, 643(1974).

(4) W. A. Richards, E. Riss, E. H. Kass, and M. Finland, *AMA Arch. Intern. Med.*, **96**, 437(1955).

(5) E. H. Beutner, J. J. Petronio, H. E. Lind, H. M. Trafton, and M. Correia-Branco, in "Antibiotics Annual 1954–1955," H. Welch and F. Marti-Ibanez, Eds., Medica Encyclopedia Inc., New York, N.Y., 1955, p. 988.

(6) M. F. Paul, C. Harrington, R. C. Bender, E. Nohle, and M. J. Bryson, *Proc. Soc. Exp. Biol. Med.*, **125**, 941(1967).

(7) J. D. Conklin and R. D. Hollifield, *Clin. Chem.*, **11**, 925(1965).

(8) H. A. Harper, "Review of Physiological Chemistry," 14th ed., Lange Medical Publications, Los Altos, Calif., 1973, p. 398.

(9) A. White, P. H. Handler, and E. L. Smith, "Principle of Biochemistry," 3rd ed., McGraw-Hill, New York, N.Y., 1964, p. 737.

(10) K. Sekiguchi, N. Obi, and Y. Ueda, *Chem. Pharm. Bull.*, **12**, 134(1964).

(11) A. H. Goldberg, M. Gibaldi, J. L. Kanig, and M. Mayersohn, *J. Pharm. Sci.*, **55**, 581(1966).

(12) A. H. Goldberg, M. Gibaldi, and J. L. Kanig, *ibid.*, **55**, 482(1966).

(13) K. Sekiguchi and N. Obi, *Chem. Pharm. Bull.*, **9**, 866(1961).

(14) P. Mukerjee and A. K. Ghosh, *J. Phys. Chem.*, **67**, 193(1963).

(15) C. McDonald and E. Lindstrom, *J. Pharm. Pharmacol.*, **26**, 39(1974).

(16) S. Bolton, *J. Pharm. Sci.*, **52**, 1071(1963).

(17) D. M. Altwein, J. N. Delgado, and F. P. Cosgrove, *ibid.*, **54**, 603(1965).

(18) S. Feldman and M. Gibaldi, *ibid.*, **56**, 370(1967).

(19) D. B. Wetlaufer, S. K. Malik, L. Stoller, and R. L. Coffin, *J. Amer. Chem. Soc.*, **86**, 509(1964).

Donald E. Cadwallader ˣ
Hung Won Jun
Lian-Kaun Chen

Department of Pharmacy
School of Pharmacy
University of Georgia
Athens, GA 30602

Received December 20, 1974.
Accepted for publication February 2, 1975.
ˣ To whom inquiries should be directed.

Ambrosin, Tumor Inhibitory Agent from *Hymenoclea salsola* (Asteraceae)

Keyphrases □ Ambrosin—tumor inhibitory agent from *Hymenoclea salsola*, isolation and identification □ *Hymenoclea salsola* (Asteraceae)—isolation and identification of ambrosin, a tumor inhibitory agent □ Antitumor agents—isolation and identification of ambrosin from *Hymenoclea salsola*

To the Editor:

As a result of the continuing search for plants having tumor inhibitory constituents, it was found that the chloroform extract of the leaves and stems of *Hymenoclea salsola* Torr. and Gray (Asteraceae)[1] showed inhibitory activity toward the P-388 lymphocytic leukemia test system (3PS)[2].

One of the two major constituents of the chloroform extract was shown to be ambrosin, previously isolated from many plants of the Asteraceae family including *H. salsola* (1). Isolation was effected by column chromatography, recrystallization, and preparative TLC[3]. Identification was achieved by IR, NMR, mass spectrometry, elemental analysis, and comparison with an authentic specimen[4].

Ambrosin demonstrated activities of 180, 158, 130, and 132% test/control (T/C) at 35, 22, 14, and 9.6 mg/kg, respectively, in the 3PS system. Activity in

[1] Identification was confirmed by Dr. Robert E. Perdue, Medicinal Plant Resources Laboratory, Plant Genetics and Germ Plasm Institute, Beltsville, Md. A reference specimen was deposited in that herbarium. The plant was collected in California in December 1973.

[2] Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Bethesda, Md.

[3] In our plant extract, ambrosin crystallized as a 1:1 mixture with its 11,13-dihydro derivative, so preparative TLC was required to isolate pure ambrosin. Geissman and Toribio (1) detected none of the dihydro material in their plant extract.

[4] We are indebted to Professor Werner Herz, Florida State University, Tallahassee, Fla., for providing the authentic sample of ambrosin.