Adsorption–Dissolution Relationship in Sulfamethazine–Benzoic Acid System

R. N. NASIPURI and SALEH A. H. KHALIL▲

Abstract □ Both the equilibrium solubility and dissolution rate of sulfamethazine were remarkably inhibited in the presence of benzoic acid. The effect was dependent on the concentrations of both the benzoic acid and sulfamethazine in the system. The inhibition of sulfamethazine dissolution was synchronous with the adsorption of benzoic acid on the sulfonamide particles. As low as 5 mg.% polyvinylpyrrolidone prevented the adsorption of benzoic acid on sulfamethazine and, consequently, the suppressive effect of benzoic acid on sulfamethazine dissolution was no longer shown.

Keyphrases □ Sulfamethazine–benzoic acid—adsorption–dissolution relationship, effect of polyvinylpyrrolidone □ Benzoic acid–sulfamethazine—adsorption–dissolution relationship, effect of polyvinylpyrrolidone □ Polyvinylpyrrolidone—effect on adsorption–dissolution relationship in sulfamethazine–benzoic acid system □ Dissolution—sulfamethazine in benzoic acid, effect of polyvinylpyrrolidone

During a study on the adsorption of benzoic acid on sulfamethazine particles, it was observed that in certain systems the equilibrium solubility of the sulfonamide was significantly decreased, sometimes reaching only about 6% of its solubility in water. The present article examines the effect of benzoic acid on the equilibrium solubility and dissolution rate of sulfamethazine and compares the dissolution results with the data of benzoic acid adsorption on the sulfonamide particles. The effect of polyvinylpyrrolidone on both adsorption and dissolution in the system is discussed.

EXPERIMENTAL

Materials—Sulfamethazine, BP grade[1], was used; the powder had a mean volume-surface diameter of 32.6 μ. Benzoic acid was of BP quality[2], and polyvinylpyrrolidone was a sample having an average molecular weight of 40,000[3]. Methylcellulose 20 and sodium carboxymethylcellulose of 50 and 100 viscosity grades[3] were used.

Methods—*Adsorption Isotherm*—The procedure described by Bean and Dempsey (1) was followed at 24 ± 0.2°.

Determination of Dissolution Rate—This was determined at 24 ± 0.2° in an oscillating water bath at a speed of 18 ± 2 strokes/min. After the specified time, the contents of the flask were filtered through a sintered-glass funnel[4]. The concentrations of both benzoic acid and sulfamethazine were determined in the filtrate spectrophotometrically by applying the equations of Tinker and McBay (2) for two-component systems. Measurements were made using a spectrophotometer[5] at 230 and 300 nm. (in 0.05 *N* HCl). The validity of the equations used were tested by assaying known mixtures of sulfamethazine and benzoic acid. The percentage errors were ±1.9% for sulfamethazine and ±2.3% for benzoic acid.

Elution Procedure—The suspension left after the adsorption experiment was filtered through a sintered-glass funnel[4], and the precipitate was digested in water (double the volume used in the adsorption experiment). The procedure described under *Determination of Dissolution Rate* was then followed.

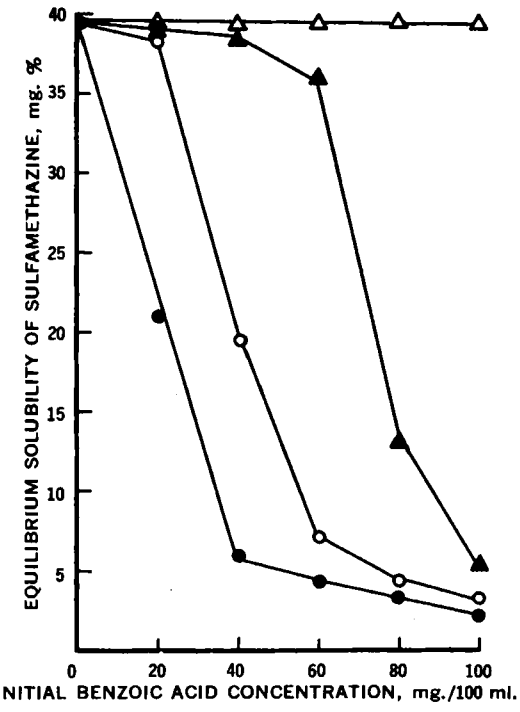

Figure 1—*Effect of benzoic acid on the equilibrium solubility of sulfamethazine. The concentrations of sulfamethazine in the system (g./100 ml.) were: (●) 0.06; (○) 0.1; (▲) 0.2; and (△) 0.3, 0.4, 4, and 10.*

RESULTS AND DISCUSSION

Figures 1 and 2 show, at different initial benzoic acid concentrations, the effect of benzoic acid on the equilibrium solubility of sulfamethazine and its adsorption on the sulfonamide particles. Within the concentration range of benzoic acid used, the equilibrium solubility of sulfamethazine showed a pronounced decrease; the effect was dependent on the concentrations of both benzoic acid and sulfamethazine in the system (Fig. 1). At and above 0.3 g./100 ml., sulfamethazine suffered no significant change in its equilibrium solubility; below 0.3 g./100 ml., a remarkable decrease occurred, reaching about 2.5 mg.% compared with 39.6 mg.% in water.

The decrease in sulfamethazine solubility in the presence of benzoic acid can be attributed to the adsorption of the acid on the sulfonamide particles. The data of benzoic acid adsorption are plotted in Fig. 2. The relationship between the amount of benzoic acid adsorbed per millimole sulfamethazine and the equilibrium

[1] Sulfadimidine, Imperial Chemical Industries, England.
[2] British Drug Houses, England.
[3] Plasdone k 29-32, GAF Corp., New York, N. Y.
[4] Jena 39 G3.
[5] Unicam SP 500.

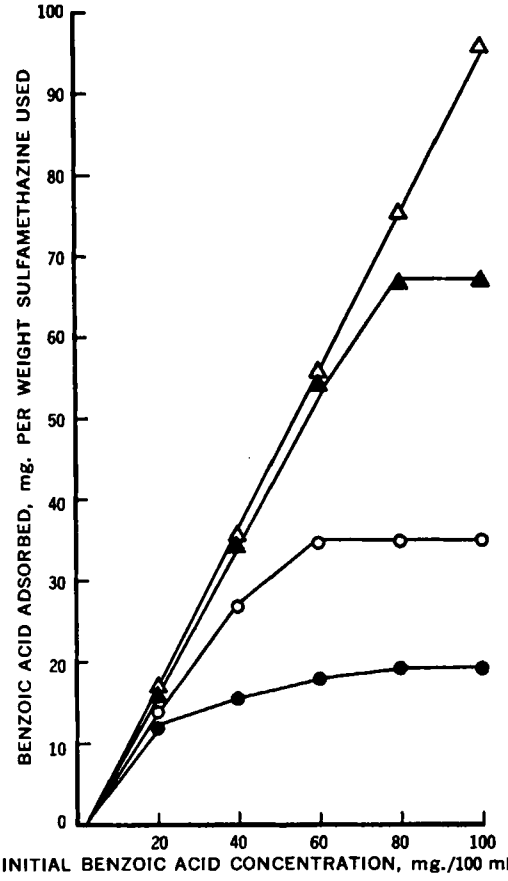

Figure 2—*Adsorption of benzoic acid on sulfamethazine. The concentrations of sulfamethazine in the system (g./100 ml.) were:* (●) *0.06;* (○) *0.1;* (▲) *0.2; and* (△) *0.3, 0.4, 4, and 10.*

solubility of the sulfonamide is shown in Table I. At a constant initial concentration of benzoic acid, the amounts of benzoic acid adsorbed per millimole sulfamethazine were 0.75, 0.77, and 0.76 mmole for systems containing 2.16, 3.60, and 7.20 mmoles sulfamethazine, respectively. These data may suggest that the sulfonamide particles were "saturated" by benzoic acid, as shown by the plateau regions in Fig. 2. As a result, the equilibrium solubility of sulfamethazine showed a pronounced decrease (Table I). At higher sulfamethazine concentrations, the amount of benzoic acid adsorbed showed a gradual decrease and the sulfonamide solubility exhibited an insignificant change (Table I).

The relationship between adsorption of benzoic acid and its effect on sulfamethazine dissolution, both during an adsorption run and an elution experiment, is shown in Fig. 3. After 30 min. of equilibration, the amount of benzoic acid adsorbed per 0.2 g. sulfamethazine was 66.6 mg. In this system the equilibrium solubility of

Table I—Data of Benzoic Acid Adsorption on Sulfamethazine and Its Effect on the Equilibrium Solubility of the Sulfonamide[a]

Sulfamethazine Concentration, mmoles/l.	Benzoic Acid Adsorbed, mmole/mmole Sulfamethazine	Equilibrium Solubility of Sulfamethazine, mmoles/l.[b]
2.16	0.75	0.076
3.60	0.77	0.083
7.20	0.76	0.173
10.80	0.72	1.400
14.40	0.54	1.442
36.00	0.22	1.417
72.00	0.11	1.457
144.00	0.054	1.424
360.00	0.022	1.421

[a] Initial concentration of benzoic acid = 8.18 moles/l. [b] Equilibrium solubility of sulfamethazine in water (pH 5.6) at 24° = 1.424 mmoles/l.

Table II—Effect of Polyvinylpyrrolidone on the Adsorption–Dissolution Relationship in the Sulfamethazine–Benzoic Acid System[a]

Initial Benzoic Acid Concentration, mg. %	Concentration of Polyvinylpyrrolidone, mg. %			
	Benzoic Acid —Adsorbed, mg.—		Sulfamethazine —Solubility, mg. %—	
	0	5	0	5
0	—	—	39.2	40.1
20	15.2	0.0	38.8	39.9
40	34.6	0.0	38.2	40.4
60	54.6	0.1	36.1	40.2
80	65.8	0.1	13.0	39.8
100	66.1	0.2	4.8	39.9

[a] Sulfamethazine concentration = 0.2 g.%.

sulfamethazine dropped from 39.2 to 4.8 mg.%. In the elution experiment, partial desorption of benzoic acid occurred since only about 10% of the amount originally adsorbed was eluted (Fig. 3B). Nevertheless, this seemed to have produced enough unoccupied sites on the sulfonamide particles as the result of partial desorption of benzoic acid, which could be claimed to be responsible for the increase in sulfamethazine dissolution during the elution experiment (Fig. 3A).

The role of polyvinylpyrrolidone in suppressing the adsorption of benzoic acid by sulfamethazine particles is shown in Table II. The incorporation of 5 mg.% of the polymer in the systems studied resulted in almost complete inhibition of benzoic acid adsorption. This was also reflected in the solubility of sulfamethazine, where no significant change was observed (Table II). It is suggested that polyvinylpyrrolidone, being a protective colloid, would be concentrated at the surface of sulfamethazine particles, thus "insulating" or "shielding" the surface. The work of Simonelli *et al.* (3) showed that polyvinylpyrrolidone inhibited the crystal growth of sulfathiazole due to the transport of the polymer molecules from the bulk to the crystal surfaces. Moriguchi and Kaneniwa (4) showed also that polyvinylpyrrolidone was preferentially adsorbed on talc, thus competing for the adsorption of cyanocobalamin on talc. The inhibition of sulfamethazine dissolution by benzoic acid reported in the present

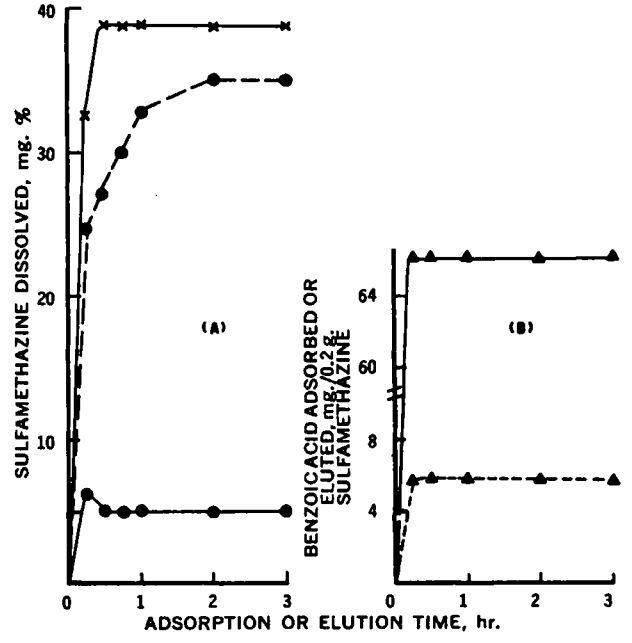

Figure 3—*(A) Effect of benzoic acid on the dissolution rate of sulfamethazine* (●—●) *during an adsorption experiment and* (●- - -●) *during an elution experiment;* (X—X) *is sulfamethazine dissolution in water. (B) Adsorption of benzoic acid on sulfamethazine and its elution. Key:* ▲—▲, *adsorption data; and* ▲- - -▲, *elution data. Sulfamethazine concentration = 0.2 g./100 ml.; initial benzoic acid concentration = 100 mg./100 ml.*

work is analogous to the work of Piccolo and Tawashi (5), who found that at low concentrations of some dyes, inhibition occurred to single crystal dissolution of a number of drugs.

SUMMARY AND CONCLUSIONS

In the presence of benzoic acid, both the dissolution rate and equilibrium solubility of sulfamethazine were suppressed. The phenomenon was attributed to the adsorption of benzoic acid on the sulfonamide particles. The inhibition of sulfamethazine dissolution was only shown when the sulfonamide particles were saturated by benzoic acid. Due to the protective effect of polyvinylpyrrolidone, as low as 5 mg.% of the polymer prevented the adsorption of benzoic acid and, consequently, its suppressive effect on sulfamethazine dissolution.

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Identification of a Rearranged Degradation Product from Carbamazepine-10,11-epoxide

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Abstract □ Carbamazepine-10,11-epoxide, a metabolite of carbamazepine found in human urine, undergoes a rearrangement and degradation to 9-acridinecarboxaldehyde during GLC.

Keyphrases □ Carbamazepine-10,11-epoxide—identification of GLC degradation product as 9-acridinecarboxaldehyde □ 9-Acridinecarboxaldehyde—identified as carbamazepine-10,11-epoxide GLC rearrangement product, synthesis, physical-chemical properties

In previous papers (1, 2), it was reported that carbamazepine-10,11-epoxide was found in human urine as a metabolite of carbamazepine. The epoxide was isolated and identified; however, at the same time it was mentioned that subjection of this compound to GLC resulted in a degradation to another material. This paper reports the isolation, identification, and alternative preparation of the degradation product.

EXPERIMENTAL[1]

Carbamazepine-10,11-epoxide—The synthesis described previously (1) was altered to give better, consistent yields for pharmaceutical requirements.

A solution of carbamazepine (50 g., 0.21 mole) and *m*-chloroperbenzoic acid (47.4 g., 0.27 mole) in 2 l. of ethylene chloride was heated under reflux with irradiation by a sun lamp (200 w.) for 3 hr. After cooling and washing with dilute aqueous sodium sulfite solution and with 5% aqueous sodium bicarbonate, the organic phase was dried and evaporated. The residue was taken up in boiling benzene and cooled, and the precipitate collected. The crude product was recrystallized from ethanol to give carbamazepine-10,11-epoxide as pale-yellow needles (16 g., 30%), m.p. 205–207° dec. [lit. (1) m.p. 190–195°]; IR (mineral oil mull): 3500–3100 (NH_2), 1675 (C=O, urea), 865 (C—O, epoxide), 752 (CH out-of-plane bending) $cm.^{-1}$; NMR (acetone–dimethyl sulfoxide, 2:1): 4.38 (s, 2H, —HCO— epoxide), 5.34 (broad s, 2H, $CONH_2$), and 7.7–7.1 (m, 8H, ArH).

9-Methylacridine—Diphenylamine, acetic anhydride, and anhydrous zinc chloride were heated together at 190° for 5 hr. according to Porai-Koshits and Khaskhazov (3). Separation and crystallization from hexane gave pure 9-methylacridine, m.p. 116–118° [lit. (4) m.p. 117–118°]; IR (mineral oil mull): 1150 (CH in-plane bending) and 755 (CH out-of-plane bending) $cm.^{-1}$.

9-Acridinecarboxaldehyde—This was prepared according to Tsuge *et al.* (5). 9-Methylacridine (0.40 g., 2.07 mmoles), *p*-nitroso-*N*,*N*-diethylaniline (0.55 g., 3.72 mmoles), and concentrated hydrochloric acid (0.1 ml.) were heated together under reflux for 2 hr. The resulting red-brown material, m.p. 235–237° dec., was hydrolyzed with 10% aqueous hydrochloric acid to yield 9-acridinecarboxaldehyde as yellow needles (0.1 g., 21%), m.p. 145–146° (ethanol), [lit. (6) m.p. 147°]; IR (mineral oil mull): 1680 (C=O, aldehyde), 1150 and 1040 (CH in-plane bending), and 870 and 745 (CH out-of-plane bending) $cm.^{-1}$; NMR ($CDCl_3$): 8.8–7.2 (m, 8H, ArH) and 11.38 (s, 1H, CHO).

RESULTS AND DISCUSSION

A clean, single-component gas chromatogram resulted from an ethanol solution of carbamazepine-10,11-epoxide. The mass spectrum (Fig. 1) obtained by hookup to the GLC showed a molecular ion at *m/e* 207 (100%) and a fragmentation to give *m/e* 179 (90%) corresponding to a loss of 28 atomic mass units (CO). This transition was confirmed by the presence of a metastable ion. Also present were ions at *m/e* 152 (15%) and 151 (17%) corresponding

[1] Melting points were determined with a Büchi capillary apparatus and are uncorrected. IR spectra were obtained on a Perkin-Elmer 157 spectrophotometer as mineral oil mulls or as liquid films. NMR spectra were determined with a Varian A60 or XL100/15 spectrometer using tetramethylsilane as an internal reference. Mass spectra were obtained on an LKB 9000 instrument operating under the previously described conditions (1). GLC was carried out on a Carlo Erba Fractovap G1 chromatograph using a 2-m. OV-17 column operating at 220° and an injection port temperature of 250°.