was then crystallized from 15 ml of isopropyl alcohol to yield 5 g (89%) of white plates, mp 117–119°.

Ethyl 2-Methoxyiminoalkyl Trithiocarbonates—Into a 100-ml round-bottom flask was placed 4 g (0.025 mole) of sodium ethyl trithiocarbonate in 20 ml of acetone, and 5.7 g (0.025 mole) of the *O*-methyl ether of ω-bromoacetophenone oxime in 10 ml of acetone was added with stirring. A white solid precipitate formed immediately and the solution became warm. The addition of 80 ml of water caused an oil to separate while the original precipitate went into solution. The oil was extracted with 15-ml portions of ether, and the extracts were combined and dried over anhydrous sodium sulfate. The ether was removed by distillation, and the remaining oil was distilled under reduced pressure.

Ethyl *S*-(2-Methoxyimino) Alkyl Dithiocarbonates—Into a round-bottom flask was placed 3.65 g (0.025 mole) of sodium *O*-methyl dithiocarbonate in 20 ml of acetone. To the stirred solution was added 5.7 g (0.025 mole) of the *O*- ethyl ether of ω-bromoacetophenone oxime in 10 ml of acetone. A white solid precipitate formed immediately and the solution became warm. When 80 ml of water was added, an oil separated while the original precipitate went into solution. The oil was then extracted with three 15-ml portions of ether. The extracts were combined and dried over anhydrous sodium sulfate. The ether was removed by distillation, and the remaining oil was distilled under reduced pressure.

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ACKNOWLEDGMENTS AND ADDRESSES

Received January 21, 1974, from the *Department of Medicinal Chemistry, College of Pharmacy, University of Illinois at the Medical Center, Chicago, IL 60612*

Accepted for publication May 13, 1974.

Abstracted in part from dissertations submitted by S. Chu and N. L. Hines to the University of Illinois in partial fulfillment of the Doctor of Philosophy degree requirements.

Supported in part by U.S. Public Health Service Research Grant RH 00293, National Center for Radiological Health.

ˣ To whom inquiries should be directed.

Suppression of Benzoic Acid Adsorption on Sulfamethazine by Polyvinylpyrrolidone: Effect of Contact Time

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

Abstract □ The suppressive effect of polyvinylpyrrolidone on benzoic acid adsorption by sulfamethazine was found to be time dependent. First-order plots showed that benzoic acid apparently diffused from the bulk to the sulfonamide surface through the polymeric "protective" film; therefore, the effect was dependent on the polymer–sulfonamide ratio. An increase in the polymer concentration slowed down the rate of benzoic acid migration. This effect cannot be attributable solely to an increase in bulk viscosity since nonpolymeric viscosity-imparting agents, *e.g.*, glycerol and syrup, did not appreciably inhibit adsorption.

Keyphrases □ Benzoic acid—suppression of adsorption on sulfamethazine by polyvinylpyrrolidone, effect of contact time □ Sulfamethazine—adsorption of benzoic acid, suppression by polyvinylpyrrolidone, effect of contact time □ Polyvinylpyrrolidone—suppression of benzoic acid adsorption on sulfamethazine, effect of contact time □ Adsorption—benzoic acid on sulfamethazine, suppression by polyvinylpyrrolidone, effect of contact time

Protective colloids have been used to inhibit some surface phenomena such as crystal growth and adsorption of solutes onto solid surfaces. Polyvinylpyrrolidone appears to be exceptionally effective for these purposes. For example, the polymer was effective in suppressing the crystal growth of sulfathiazole (1) and inhibiting the interconversion of two forms of sulfaline (sulfamethoxypyrazine) (2). The suppressive effect of polyvinylpyrrolidone on cyanocobalamin adsorption by talc was reported (3). Recently, the authors found that, in the presence of as little as 5 mg % of this polymer, benzoic acid adsorption on sulfamethazine was completely inhibited (4, 5).

Table I—Lag Period (in Hours)[a] at Various Sulfamethazine–Polyvinylpyrrolidone Concentrations

Polyvinylpyrrolidone Concentration, g %	Sulfamethazine Concentration, g %				
	0.1	0.4	1	4	10
0.02	2	1	1	1	1
0.04	4	2	2	2	1
0.10	8	6	4	4	2
0.20	10	10	6	4	4
0.50	20	12	8	6	4
1.00	24	16	12	8	8

[a] Average of four runs (±0.2 hr).

The effect of time on the suppressive effect of protective polymers has received little attention. The present report concerns the effect of contact time on the suppressive role of polyvinylpyrrolidone on benzoic acid adsorption by sulfamethazine.

EXPERIMENTAL

Materials—Sulfamethazine[1], BP grade, was used; the powder had a mean volume–surface diameter of 32.6 μm. Benzoic acid[2] was of BP quality and the polyvinylpyrrolidone[3] sample had an av-

[1] Sulfadimidine, Imperial Chemical Industries Ltd., Cheshire, England.
[2] British Drug Houses Ltd., Poole, England.
[3] Plasdone K 29–32, GAF Corp., New York, N.Y.

Table II—Effect of Various Sulfamethazine and Polyvinylpyrrolidone Concentrations on Rate Constant K of Benzoic Acid Adsorption

Sulfamethazine Concentration, g %[a]	Polymer–Sulfonamide Ratio[a]	$K \times 10^2$, hr^{-1}	Polyvinylpyrrolidone Concentration, g %[b]	Polymer–Sulfonamide Ratio[b]	$K \times 10^2$, hr^{-1}
0.1	1.40×10^{-3}	2.20	0.02	0.14×10^{-4}	9.79
0.4	0.34×10^{-3}	5.46	0.04	0.28×10^{-4}	8.66
1.0	0.14×10^{-3}	6.45	0.10	0.70×10^{-4}	5.60
4.0	0.34×10^{-4}	8.36	0.20	0.14×10^{-3}	3.80
10.0	0.14×10^{-4}	9.79	0.50	0.35×10^{-3}	3.65
—	—	—	1.00	0.70×10^{-3}	3.20
—	—	—	2.00	1.40×10^{-3}	0.75

[a] At a constant polyvinylpyrrolidone concentration of 0.02 g %; the average molecular weight of the polymer was taken as 40,000. [b] At a constant sulfamethazine concentration of 10 g %.

erage molecular weight of 40,000. Glycerol[2] and tragacanth[2] were of BP grade and the syrup was prepared according to the BP.

Methods—The adsorption experiments and the determination of benzoic acid were carried out as previously reported (4). Equilibrium dialysis experiments[4] were performed at 24 ± 0.2° following the procedure described previously (4).

The effect of contact time on the adsorption of benzoic acid in the sulfamethazine–polyvinylpyrrolidone system was studied by equilibrating the system at 24 ± 0.2° in an oscillating water bath. Samples were withdrawn at various intervals and filtered through a sintered-glass funnel[5], and the benzoic acid that remained unadsorbed was determined.

RESULTS AND DISCUSSION

First-order plots (Figs. 1 and 2) show a gradual decrease in the percentage of unadsorbed benzoic acid in systems containing varying concentrations of sulfamethazine and polyvinylpyrrolidone. This decrease suggests that benzoic acid was gradually adsorbed by the sulfonamide (4, 5) or possibly complexed with the polymer. In all systems studied, the percentage of "free" benzoic acid was unchanged in the 1st hr. This "lag period" varied from 1 to 24 hr, depending on the composition of the system (Table I).

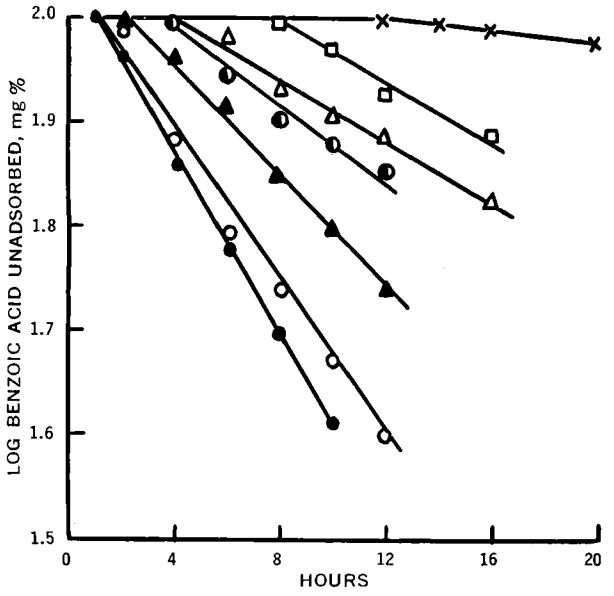

Figure 1—*Effect of time on the suppressive effect of varying concentrations of polyvinylpyrrolidone on benzoic acid adsorption by sulfamethazine. The concentrations of polyvinylpyrrolidone (g %) were: ●, 0.02; ○, 0.04; ▲, 0.10; ◐, 0.20; △, 0.5; □, 1.0; and ×, 2.0. The concentration of sulfamethazine in the system was 10 g %.*

[4] Visking tubing, The Scientific Instrument Centre Ltd., London, England.
[5] Jena 39 G.3.

At a constant sulfamethazine concentration (10% w/w), an increase in the polyvinypyrrolidone concentration resulted in an increase in the protective effect, as evidenced from the changes in the slopes of the linear plots of Fig. 1 and the values of the rate constant, K (Table II). The lag period was also extended from 1 to 24 hr for systems containing 0.02 and 2 g % polyvinylpyrrolidone, respectively. Increasing the sulfonamide content at a constant polymer concentration (0.02 g %) produced a relatively minor reduction of the lag period from 2 to 1 hr, but the slopes of the linear plots (Fig. 2) and the computed K values (Table II) suggest a decrease in the protective effect. The latter seemed to be affected by the molecular ratio of polyvinylpyrrolidone to sulfamethazine. Generally, a decrease in this ratio resulted in an increase in the values of the rate constant; as the ratio increased, the values of K decreased (Table II).

Since the majority of protective colloids are viscosity-imparting agents, their protective effect on the adsorption process may be attributed to: *(a)* the formation of a protective film at the adsorbent surface, *(b)* decreased diffusion of the adsorbate due to an increase in the bulk viscosity and environmental viscosity around the particle, and/or *(c)* possible interaction between the polymer and the adsorbate.

Polyvinylpyrrolidone has been reported to exert its protective effect by being preferentially adsorbed at the solid surface (1, 3).

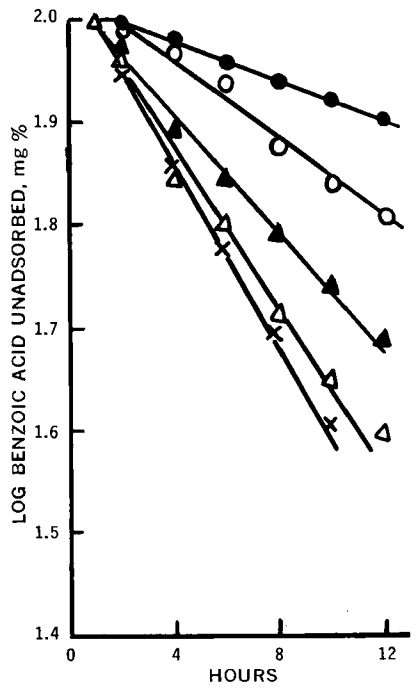

Figure 2—*Effect of time on the suppressive effect of polyvinylpyrrolidone on benzoic acid adsorption by sulfamethazine. The concentrations of sulfamethazine (g %) were: ●, 0.1; ○, 0.4; ▲, 1.0; △, 4.0; and ×, 10. The concentration of polyvinylpyrrolidone in the system was 0.02 g %.*

Table III—Comparative Suppressive Effects of Polyvinylpyrrolidone, Glycerol, Syrup BP, and Compound Tragacanth Powder BP on Benzoic Acid Adsorption by Sulfamethazine[a] (Contact Time of 1 hr)

	Polyvinylpyrrolidone		Glycerol		Syrup		Compound Tragacanth Powder	
Concentration, g %	0.02	2.0	10	50	10	50	2	4
Relative viscosity, η_{rel}[b]	1.03	1.27	1.49	4.65	1.42	3.19	4.01	12.21
Benzoic acid unadsorbed, mg %	99.9	100	7.6	11.9	6.9	8.9	27.2	45.9

[a] Initial benzoic acid concentration of 0.1 g %; initial sulfamethazine concentration of 4 g %. [b] Using an Ostwald viscometer at 24 ± 0.2°.

However, its effect on increasing the viscosity cannot be ruled out. To test this point, the effect of two nonpolymeric viscosity-imparting agents (glycerol and syrup BP) on benzoic acid adsorption by sulfamethazine was examined. The data obtained (Table III) were compared with the effect produced by two polymeric materials (compound tragacanth powder BP and polyvinylpyrrolidone). Although the relative viscosities of both glycerol and syrup (each at a concentration of 10 and 50% w/w) are higher than that of the highest polyvinylpyrrolidone concentration used, the protective effect of the former agents was negligible. The percentages of benzoic acid unadsorbed were about 12 and 9 (mg %) in systems containing 50 % (w/w) of glycerol and syrup, respectively. In the presence of polyvinylpyrrolidone, not more than 0.1 mg % benzoic acid was adsorbed in systems containing 0.02 g % of the polymer. Compound tragacanth powder had an intermediate protective effect (Table III). It can then be concluded that the suppressive role of polyvinylpyrrolidone cannot be attributed to an increase in bulk viscosity.

Dialysis experiments designed to test the possible interaction between benzoic acid and polyvinylpyrrolidone revealed that, in accordance with the data of Higuchi and Kuramoto (6), a negligible interaction occurred at a polymer concentration below 0.1 g %. When the polymer concentration was increased, a gradual increase in the interaction between benzoic acid (0.1 g %) and polyvinylpyrrolidone occurred, but this amounted to about 5% at a polymer concentration of 1%. This cannot solely account for the observed suppression in the adsorption.

In conclusion, the suppressive effect of protective polymers, *e.g.*, polyvinylpyrrolidone, on adsorption should be assessed taking into consideration the effect of time. In some instances, an increase in contact time may result in a reduction of the protective action of the polymer due to the transfer of the adsorbate from the bulk to the adsorbent surface.

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ACKNOWLEDGMENTS AND ADDRESSES

Received March 11, 1974, from the *Department of Pharmaceutics, Faculty of Pharmacy, University of Ife, Ile-Ife, Nigeria,* and the *University of Alexandria, Egypt.*

Accepted for publication June 11, 1974.

[x] To whom inquiries should be directed. Present address: Department of Pharmacy and Pharmacology, Faculty of Medicine and Pharmacy, University of Benin, Benin City, Nigeria.

Stability of Aspirin in Liquid and Semisolid Bases IV: Polyethylene Glycol 400 Diacetate and Triethylene Glycol Diacetate

C. W. WHITWORTH[x] and A. F. ASKER

Abstract □ The stability of aspirin in polyethylene glycol 400 diacetate and triethylene glycol diacetate was studied at 4, 26, and 45°. Degradation of aspirin in these vehicles was temperature dependent and appeared to follow a first-order rate. The results supported a previous conclusion of enhanced stability of aspirin in the substituted derivatives of polyethylene glycols.

Keyphrases □ Aspirin—stability in liquid and semisolid bases, polyethylene glycol 400 diacetate and triethylene glycol diacetate □ Polyethylene glycol 400 diacetate—stability of aspirin at three temperatures □ Triethylene glycol diacetate—stability of aspirin at three temperatures □ Stability—aspirin in polyethylene glycol 400 diacetate and triethylene glycol diacetate

A previous paper (1) on the decomposition of aspirin in polyethylene glycols provided data showing that degradation was due, at least in part, to a transesterification reaction between aspirin and polyethylene glycols. Blocking free hydroxy groups on the polyethylene glycols retarded the decomposition of aspirin (2). The purpose of this work was to study the degradation of aspirin in commercial substituted derivatives of polyethylene glycol, polyethylene glycol 400 diacetate and triethylene glycol diacetate.