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

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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.

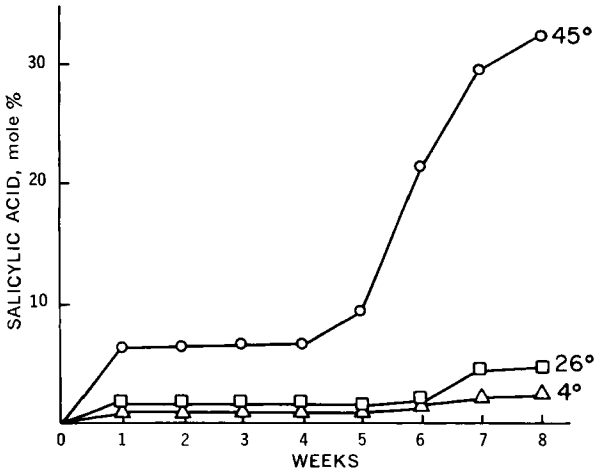

Figure 1—*Rate of appearance of salicylic acid* versus *time for a 5% solution of aspirin in polyethylene glycol 400 diacetate.*

EXPERIMENTAL

Materials—Aspirin USP[1] and salicylic acid[1] were used as received. Polyethylene glycol 400 diacetate[2] and triethylene glycol diacetate[2] were supplied by the manufacturer. Chloroform[3] was spectrograde.

Sample Preparation—The samples were prepared by dissolving the aspirin in either polyethylene glycol diacetate or triethylene glycol diacetate at room temperature to give solutions of 5 and 10% (w/v) of aspirin. Five milliliters of each solution was placed in airtight amber glass vials with screw caps and the solutions were stored at 4, 26, and 45°.

Analytical Method—UV spectrophotometric analysis, as reported by Tinker and McBay (3), was employed to measure aspirin and salicylic acid. Samples were taken at specific intervals and dissolved in 100 ml of chloroform containing 1% acetic acid. A further appropriate dilution was made, and the absorbance of the dilution was read[4] at 280 nm for aspirin and 310 nm for salicylic acid. At these wavelengths, standard curves were prepared for aspirin and salicylic acid. The quantification of aspirin and salicylic acid was based on the standard method of simultaneous spectrophotometric determinations.

RESULTS AND DISCUSSION

Aspirin undergoes degradation in polyethylene glycol at least in part *via* a transesterification reaction (1). The use of substituted derivatives of polyethylene glycols such as the acetylated glycol and the methoxyglycol was found to enhance the stability of aspirin (2).

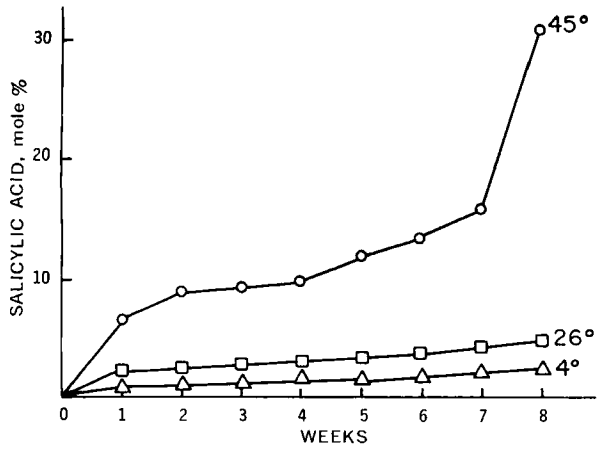

Figure 2—*Rate of appearance of salicylic acid* versus *time for a 10% solution of aspirin in polyethylene glycol 400 diacetate.*

[1] Merck & Co., Rahway, N.J.
[2] Union Carbide Corp., New York, N.Y.
[3] J. T. Baker Chemical Co., Phillipsburg, N.J.
[4] Cary model 118 spectrophotometer.

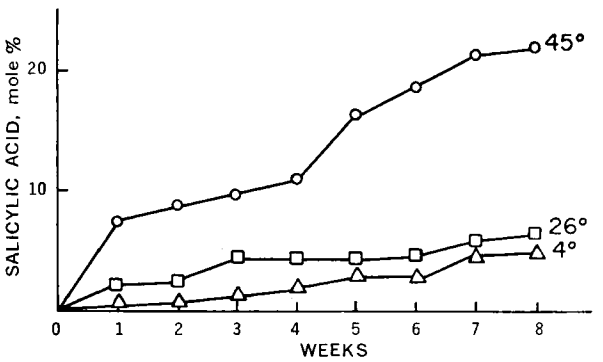

Figure 3—*Rate of appearance of salicylic acid* versus *time for a 5% solution of aspirin in triethylene glycol diacetate.*

Figures 1–4 show the overall profiles of aspirin degradation in the two vehicles studied at three temperatures as indicated by the rate of appearance of salicylic acid. It is evident from the figures that the decomposition of aspirin was temperature dependent.

Table I shows the amount of aspirin remaining in the two vehicles after storage for 8 weeks at three temperatures. A previous publication (4) reported that the decomposition of aspirin in polyethylene glycol 400 was such that the amounts of aspirin remaining after storage at 4 and 24° for 8 weeks were 98.1 and 92.4%, respectively. However, at 45°, the amount of aspirin remaining after 39 days was 69.4%. In the present study, the average amounts of aspirin remaining after 42 days of storage at 45° were 82.67% in polyethylene glycol 400 diacetate and 78.21% in triethylene glycol diacetate. The results indicate that the substituted derivatives of polyethylene glycols have a stabilizing effect on aspirin, thus supporting data published previously (2, 4, 5).

Figures 5 and 6 show apparent first-order degradation of aspirin at 45° in polyethylene glycol 400 diacetate and triethylene glycol diacetate, respectively. Almost identical degradation patterns and essentially the same slope were obtained regardless of the initial concentration of aspirin used, thus verifying first-order dependence of the reaction with respect to aspirin. The reaction velocity constants for the degradation of aspirin in polyethylene glycol 400 diacetate and triethylene glycol diacetate were 2.95/day and 85.27 $\times 10^{-2}$/day, respectively. The velocity constant for the degradation of aspirin in polyethylene glycol 400 diacetate was based on the data taken from the 5th to the 8th week of storage since the rate of degradation during the initial period of storage was relatively slow.

The method of least squares was used to obtain the curves of Figs. 5 and 6. Data for the decomposition of aspirin at 4 and 26° were not treated graphically in a similar fashion since the samples stored at these temperatures were satisfactory (degradation was

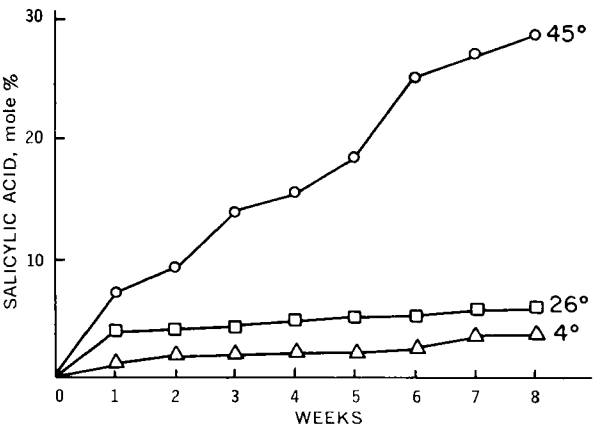

Figure 4—*Rate of appearance of salicylic acid* versus *time for a 10% solution of aspirin in triethylene glycol diacetate.*

Table I—Percent of Aspirin Remaining after 8 Weeks of Storage at Three Temperatures

Temperature	Polyethylene Glycol 400 Diacetate		Triethylene Glycol Diacetate	
	5%	10%	5%	10%
4°	98.65	97.80	95.38	96.50
26°	95.49	95.44	93.81	94.69
45°	67.77	69.00	77.19	72.06

less than 5% in the case of polyethylene glycol 400 diacetate and less that 7% in the case of triethylene glycol diacetate after storage for 8 weeks).

Tsakalotos and Horsch (6, 7) found that acetic acid increased the rate of decomposition of aspirin. Kelly (8) also indicated that hydrolysis of aspirin is catalyzed by the acetate ion, a considerably more powerful nucleophile than water. Therefore, it may be speculated that the higher rate of aspirin decomposition in polyethylene glycol 400 diacetate during the last 5–8 weeks might be due to the hydrolysis of this vehicle. This hydrolysis would result in the formation of the more polar polyethylene glycol 400 and acetic acid.

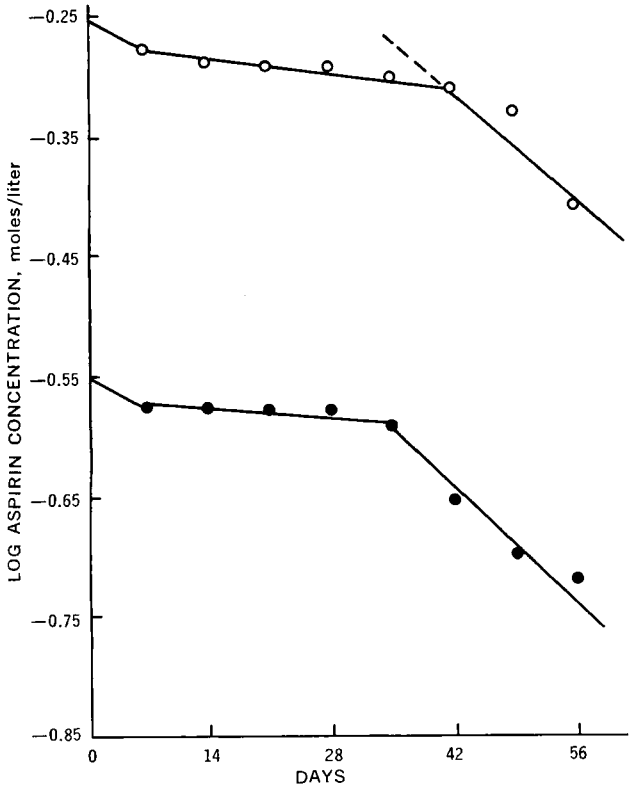

Figure 5—*First-order plot for the degradation of aspirin at 45° in polyethylene glycol 400 diacetate. Key: ○, 10% solution; and ●, 5% solution.*

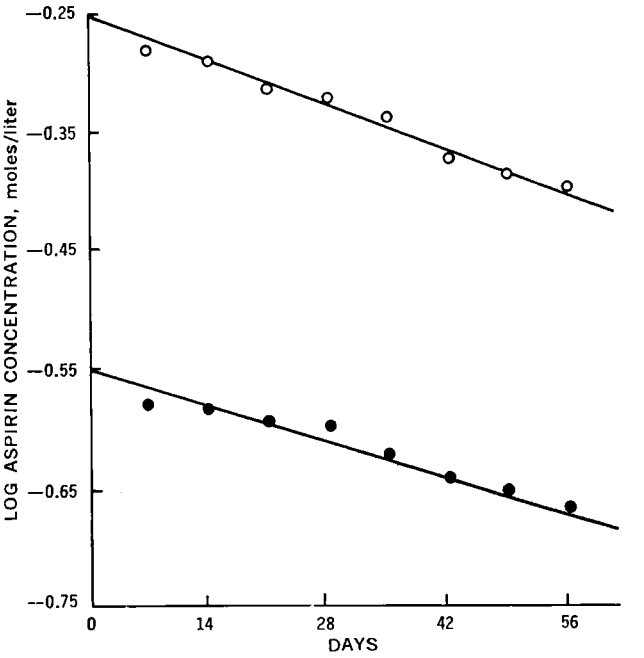

Figure 6—*First-order plot for the degradation of aspirin at 45° in triethylene glycol diacetate. Key: ○, 10% solution; and ●, 5% solution.*

These hydrolytic products are expected to enhance the decomposition of aspirin, especially in the presence of traces of moisture. This moisture could have contaminated the dry aspirin during preparation of the samples and then gradually diffused throughout the relatively viscous vehicle during storage at 45°.

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