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NOTES

Stability of Aspirin in Liquid and Semisolid Bases I: Substituted and Nonsubstituted Polyethylene Glycols

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Abstract □ The stability of aspirin in methoxypolyethylene glycol, polyethylene glycol acetate, or a mixture of polyethylene glycols was studied at three temperatures. Degradation proceeded to the highest extent in a mixture of polyethylene glycols and to a lesser extent in methoxypolyethylene glycol. Degradation in polyethylene glycol acetate for 30 days at 45° was insignificant. The data confirm that decomposition of aspirin in polyethylene glycol is due primarily to a transesterification reaction.

Keyphrases □ Aspirin—stability in liquid and semisolid bases, polyethylene glycols □ Polyethylene glycols—stability of aspirin, liquid and semisolid bases □ Stability, aspirin—in polyethylene glycols, liquid and semisolid bases

In a previous paper (1) on the decomposition of aspirin in polyethylene glycols, these laboratories provided data showing that degradation was due at least in part to a transesterification reaction between aspirin and the polyethylene glycols. This conclusion was reached when it was found that acetic acid was not among the degradation products when a mixture of aspirin and polyethylene glycols was stored at different temperatures. Further evidence of a transesterification reaction was the degradation of aspirin in various polyethylene glycols in the apparent absence of moisture and the resultant appearance of acetylated polyethylene glycol. Both the absence of acetic acid and the presence of acetylated polyethylene glycol were established using NMR techniques (1).

The implications of these findings are far reaching and, more specifically, may be applied to cases where polyethylene glycols may be desirable as a vehicle (either liquid, semisolid, or solid) for aspirin preparation. This being the case then, the next logical step was to establish the stability of aspirin when the transesterification pathway is inhibited. It was thought that inhibition of the transesterification mechanism could be brought about by reducing the number of sites available for this reaction, namely, by blocking free hydroxyl groups on the polyethylene glycols.

Methoxypolyethylene glycol has the formula CH_3—O—CH_2—$(CH_2$—O—$CH_2)_nCH_2OH$, which has a methoxy radical at one terminal and only one remaining hydroxyl group that may enter into the reaction. Acetylation of polyethylene glycol also reduces the number of hydroxyl groups and likewise was expected to retard the decomposition of aspirin.

EXPERIMENTAL

Materials—Aspirin USP[1] and polyethylene glycols[2] 400, 1540, and 6000 were used as received. Chloroform[3] was spectroscopic grade. Monosubstituted methoxypolyethylene glycol 550[4] was purchased, and polyethylene glycol 400 acetate was prepared in these laboratories.

Analytical Method—UV spectrophotometric techniques[5] were employed to measure aspirin and salicylic acid (2). Samples were taken at specific time intervals, dissolved in 1% acetic acid–chloroform, and read at 278 nm. for aspirin and 308 nm. for salicylic acid after appropriate dilutions. Standard curves were prepared for aspirin and salicylic acid. A correction factor was obtained to account for the overlapping of absorbance at absorption maxima of each drug. The quantification was based on the standard method of simultaneous spectrophotometric determinations (3).

Procedure—The samples were prepared by the incorporation of 12% of aspirin in methoxypolyethylene glycol 550, polyethylene glycol 400 acetate, and a mixture of polyethylene glycols [polyethylene glycol 400–1540–6000 (27:31:42)] at the melting points of the individual bases. Preparations were kept in airtight amber containers and stored in a desiccator at 4, 26, and 45°. At various time intervals a weighed amount (2.5 g.) of samples was dissolved in 1% acetic acid–chloroform. Spectrophotometric readings were taken immediately after dilutions for aspirin and salicylic acid.

[1] Merck & Co., Inc., Rahway, N. J.
[2] Matheson, Coleman and Bell, Norwood, Ohio.
[3] J. T. Baker Chemical Co., Phillipsburg, N. J.
[4] Union Carbide, New York, N. Y.
[5] Beckman DU spectrophotometer.

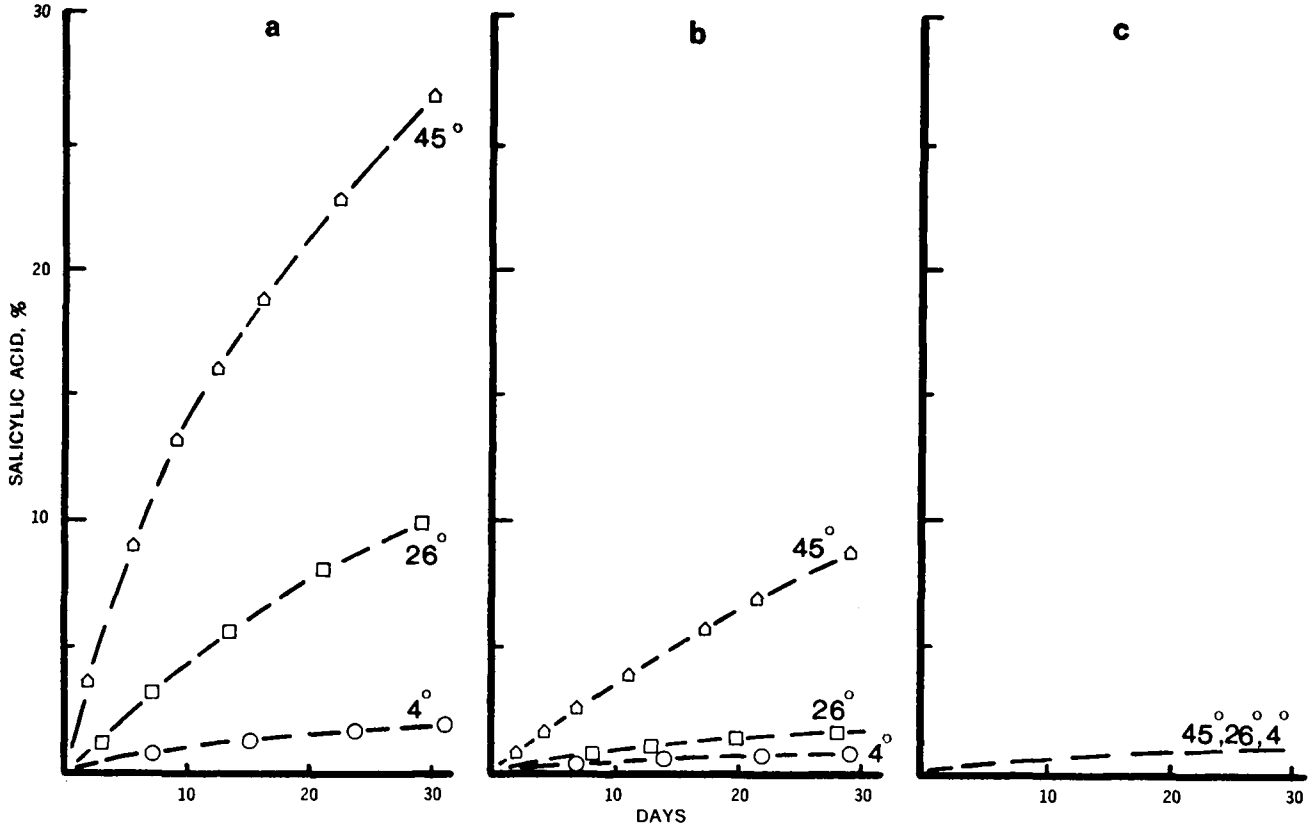

Figure 1—*Rate of appearance of salicylic acid* versus *time in a mixture of polyethylene glycols (a), in methoxypolyethylene glycol 550 (b), and in polyethylene glycol 400 acetate (c) at three temperatures.*

Acetylation of Polyethylene Glycol 400—Polyethylene glycol 400 acetate was prepared by refluxing a mixture of polyethylene glycol 400 and acetic anhydride (1:12 w/w ratio) at 139° for 4 hr. (4). Unreacted acetic anhydride and by-product were removed by vacuum evaporation.

RESULTS AND DISCUSSION

Earlier results (1) showed that degradation of aspirin in polyethylene glycols was due at least in part to transesterification (5). The present report deals with the comparison of the stability of aspirin in formulations of unsubstituted and substituted polyethylene glycols. The objectives were to investigate the possibility of blocking the transesterification route of degradation and to determine the effects on the stability of aspirin when this route is at least partially inhibited.

Table I shows the amount of aspirin remaining in three different formulations at three storage temperatures for 30 days. The percent as aspirin remaining varied widely at the three temperatures when unsubstituted polyethylene glycol was used as the base. The stability of aspirin was enhanced considerably when the monosubstituted glycol (Fig. 1b) was used. The acetylated glycol, prepared in these laboratories, was considerably more effective in preserving the stability of aspirin than the monosubstituted methoxyglycol.

Table I—Percent of Aspirin Remaining after 30 Days of Storage at Three Temperatures

Temperature	Mixture of Polyethylene Glycols (Unsubsituted)	Methoxy-polyethylene Glycol 550	Polyethylene Glycol 400 Acetate
4°	98.3	99.5	99.0
26°	90.0	98.5	99.0
45°	73.5	91.3	99.0

Figure 1 shows the overall profiles of degradation of aspirin in the three preparations at 4, 26, and 45° as indicated by the rate of the appearance of salicylic acid. A significant difference in the rate of formation of salicylic acid was seen between the substituted and unsubstituted glycols.

As shown in Fig. 1c, the stability of aspirin in the acetylated base was not temperature dependent during the 30 days of the test. From these results, it may be concluded that a transesterification reaction between aspirin and the polyethylene glycols is the predominating route for the degradation of aspirin in these bases. Speculation, at this stage, strongly favors the possibility of formulating stable preparations of aspirin in substituted polyethylene glycol bases.

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