to their ability to inhibit the oxidation of other substrates of the tricarboxylic acid cycle.

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Decomposition of Aspirin in Polyethylene Glycols

H. W. JUN▲, C. W. WHITWORTH, and L. A. LUZZI

Abstract □ Decomposition of aspirin in polyethylene glycols was studied at four temperatures. The decomposition proceeded as a pseudo-first-order reaction at these temperatures. Different molecular weights of polyethylene glycol did not affect the reaction rate. It is shown that decomposition of aspirin in polyethylene glycols is due to a transesterification reaction. The effect of temperature on decomposition rate was found to be significant, and an Arrhenius plot is shown.

Keyphrases □ Aspirin—decomposition in polyethylene glycols at various temperatures □ Polyethylene glycols—effect of temperature on aspirin decomposition □ Decomposition—aspirin in polyethylene glycols, effect of temperature

Decomposition of aspirin has been encountered in various pharmaceutical dosage forms (1, 2), notably in liquid dosage forms. Because of the use of aspirin in suppository bases in which polyethylene glycols may be incorporated, the rate of decomposition of aspirin in four polyethylene glycols with different molecular weights was studied at four temperatures.

Preliminary studies indicated that a significant amount of aspirin was decomposed in polyethylene glycol bases in the apparent absence of water. Although the rate of degradation of aspirin in polyethylene glycols was considerably decreased in the absence of water compared to that in the presence of added water, it was a significant factor when the shelflife of polyethylene glycol–aspirin products was involved.

This report shows that aspirin degrades in polyethylene glycols by transesterification in the absence of added water, and that the resultant products of this degradation are salicylic acid and acetylated polyethylene glycol.

EXPERIMENTAL

Materials—Aspirin USP[1] and polyethylene glycols[2] 400, 1540, 4000, and 6000 were used as received. Chloroform[3] was spectroscopic grade; all other chemicals were reagent grade.

Analytical Method—Spectrophotofluorometric analysis[4], as reported by Miles and Schenk (3), was employed to measure aspirin and salicylic acid. Uncorrected excitation and emission maxima for aspirin and salicylic acid were 280 and 350 nm. and 312 and 450 nm., respectively. Calibration curves were obtained by dissolving known amount of aspirin and/or salicylic acid in a 1% acetic acid–chloroform solution.

Procedure—Ten percent aspirin was incorporated in each polyethylene glycol base at elevated temperature. Preparations were kept in airtight amber containers and stored in a desiccator at tempera-

[1] Merck & Co., Inc., Rahway, N. J.
[2] Matheson, Coleman & Bell, Norwood, Ohio.
[3] J. T. Baker Chemical Co., Phillipsburg, N. J.
[4] The instrument used was the Aminco-Bowman spectrophotofluorometer with 150-w. xenon lamp.

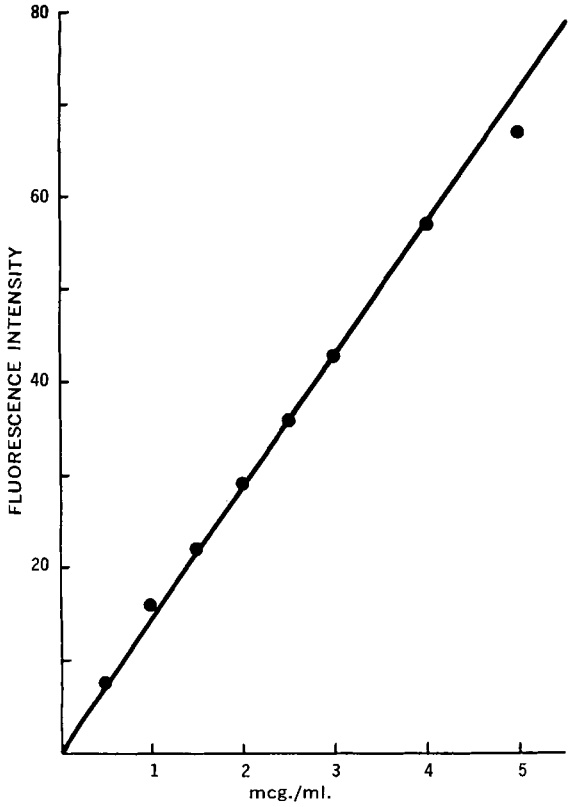

Figure 1—*Standard curve for salicylic acid in 1% acetic acid in chloroform.*

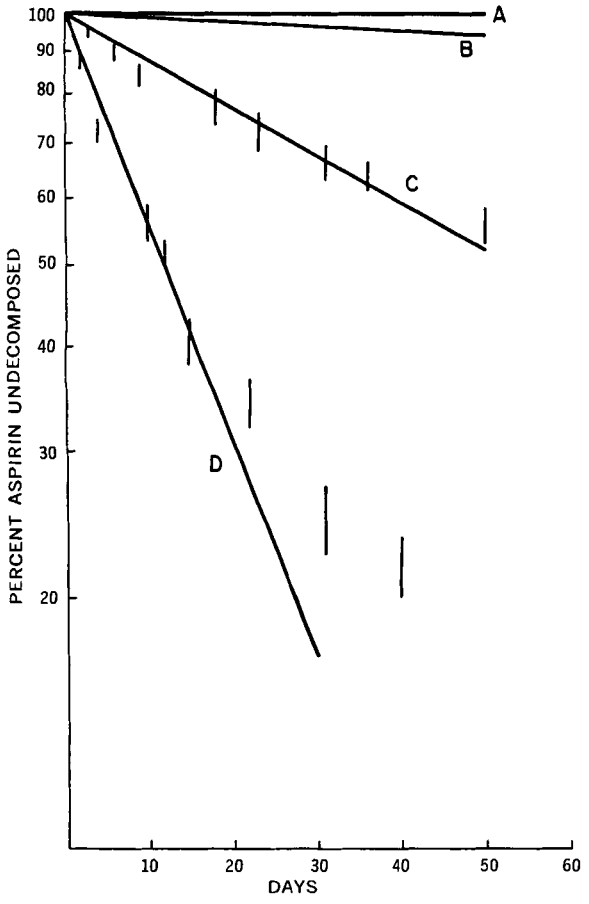

Figure 2—*Semilogarithmic plots of percentage of aspirin undecomposed in polyethylene glycols against time at four temperatures. Key: A, 4°; B, 27°; C, 45°; and D, 60°.*

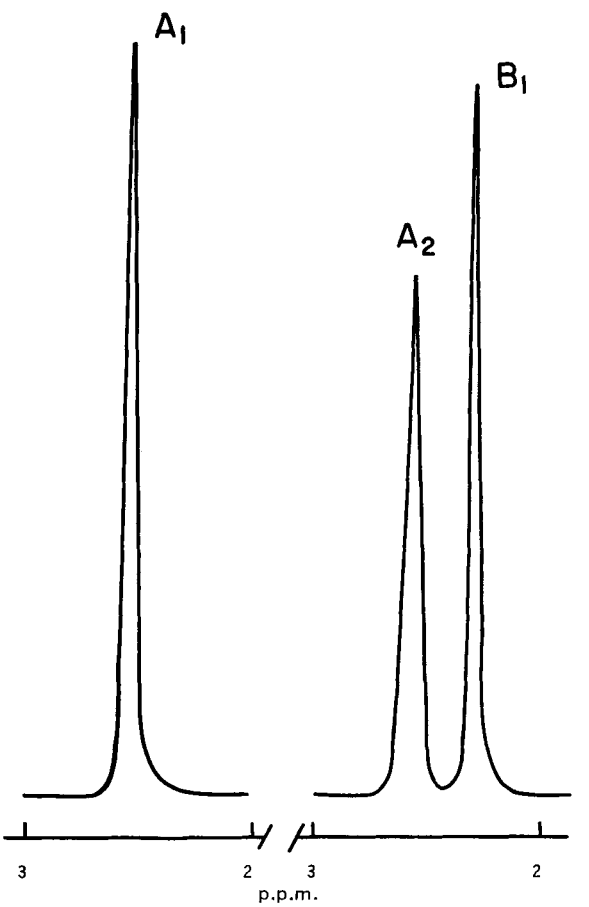

Figure 3—*NMR spectra of aspirin (A_1) in polyethylene glycol 400 and of aspirin peak (A_2) and decomposition product (B_1) after the sample was kept for 2 weeks at 45°.*

tures of 4, 27, 45, and 60°. At various time intervals, a weighed amount (3 g.) of sample was dissolved in 0.2 *N* HCl solution (10 ml.) and extracted with anhydrous diethyl ether (150 ml.). Ten microliters of ether extract was added to 2 ml. of a 1% acetic acid–chloroform mixture. Fluorescence intensity was measured for both aspirin and salicylic acid.

NMR Studies—NMR spectroscopy was used to identify aspirin, acetic acid, and esterified polyethylene glycol 400. Samples were diluted with equal quantities of deuterated dimethyl sulfoxide, and NMR spectra were examined.

Standard NMR spectra of aspirin and acetic acid in polyethylene glycol 400 and acetylated polyethylene glycol 400 were made and were compared to scans of mixtures of polyethylene glycol and aspirin at various degradation times.

Acetylization of Polyethylene Glycol 400—Acetylation was carried out by the dropwise addition of acetyl chloride to vigorously stirred polyethylene glycol 400 at 45°. The reaction mixture was vacuum purged for a sufficient time to remove any unreacted acetyl chloride and hydrogen chloride.

RESULTS AND DISCUSSION

Initial stability studies in these laboratories indicated that aspirin degrades in polyethylene glycols in the apparent absence of moisture. These results led to the current report of the decomposition of aspirin in polyethylene glycols. In this report, negative Karl Fischer results were taken to mean the absence of moisture in the polyethylene glycols used.

Figure 1 is a standard calibration curve obtained for the fluorescence of salicylic acid in a 1% acetic acid–chloroform mixture. For the concentration range shown, the line is linear and passes through the origin. It was found that there was no interference of salicylic acid fluorescence at the excitation and emission maxima in the presence of aspirin and that salicylic acid did not interfere with the

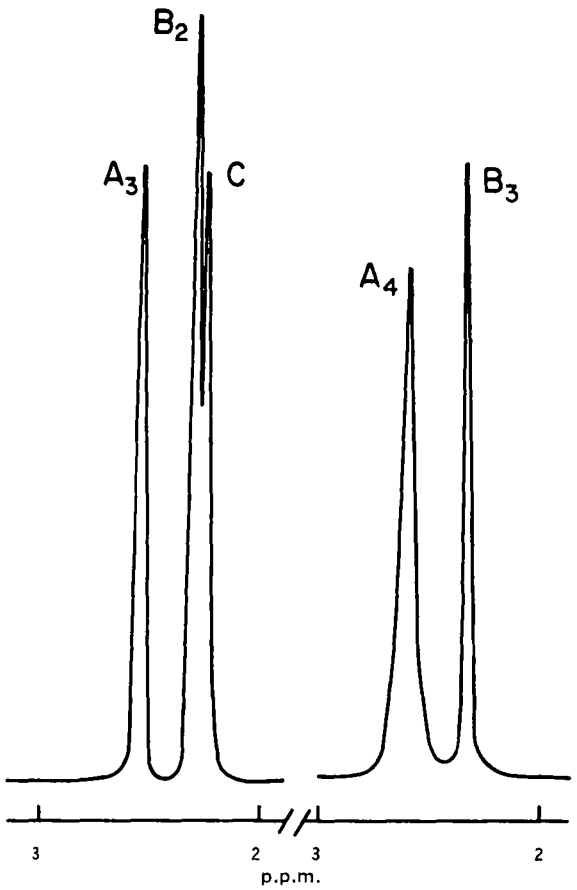

Figure 4—*NMR spectra of aspirin (A_3 and A_4), decomposition product (B_2), acetic acid (C) added to the sample, and acetylated polyethylene glycol 400 (B_3).*

emission maxima for aspirin. The technique is simple, sensitive, and reproducible and has the added advantage of allowing the determination of either salicylic acid or aspirin in the presence of the other.

Figure 2 shows the semilogarithmic plot of percentage of aspirin remaining in polyethylene glycols against time at four temperatures. The effect of temperature on the rate of decomposition of aspirin in polyethylene glycols is also shown. At all temperatures the decomposition reaction appeared to follow pseudo-first-order kinetics and the reaction was temperature dependent.

It may also be seen from Fig. 2 that vertical lines are used on curves C and D to indicate the range of aspirin remaining in polyethylene glycol 400, 1540, 4000, and 6000 at each time interval. The range is shown since no distinction or rank order of the effect on the degradation of aspirin by the various polyethylene glycols used could be found at any of the temperatures studied.

It was first thought that decomposition of aspirin in polyethylene glycols was due to a hydrolysis reaction in the presence of moisture. However, the apparent absence of moisture in polyethylene glycols led to studies to identify the decomposition products in the sample using NMR spectroscopy.

Figure 3 is an NMR spectrum of a freshly prepared aspirin–polyethylene glycol 400 mixture (peak A_1) and of the same mixture after 2 weeks at 45° (peaks A_2 and B_1). It may be seen in Fig. 3 that the methyl protons of aspirin (peak A_1) show a peak at 2.6 p.p.m. Peak A_1 of Fig. 3 occurs at the identical site of peak A_2. Peak B_2 is a new peak and is found at 2.3 p.p.m. Peak B_1 is apparently the result of the degradation of aspirin and/or of some change in the polyethylene glycol molecule.

The elucidation of peak B_1 in Fig. 3 is found in Fig. 4. Peaks A_3, B_2, and C of Fig. 4 were found from a mixture of aged aspirin–polyethylene glycol 400 and added acetic acid. Peak C (2.25 p.p.m.) is new and different from the peaks B_1 and B_2, while peaks A_3 and B_2 of Fig. 4 are identical to peaks A_2 and B_1 of Fig. 3. The comparison of Figs. 3 and 4 indicates that peak C is due to the methyl protons of acetic acid and that acetic acid is not a product of the degradation of aspirin in polyethylene glycol 400.

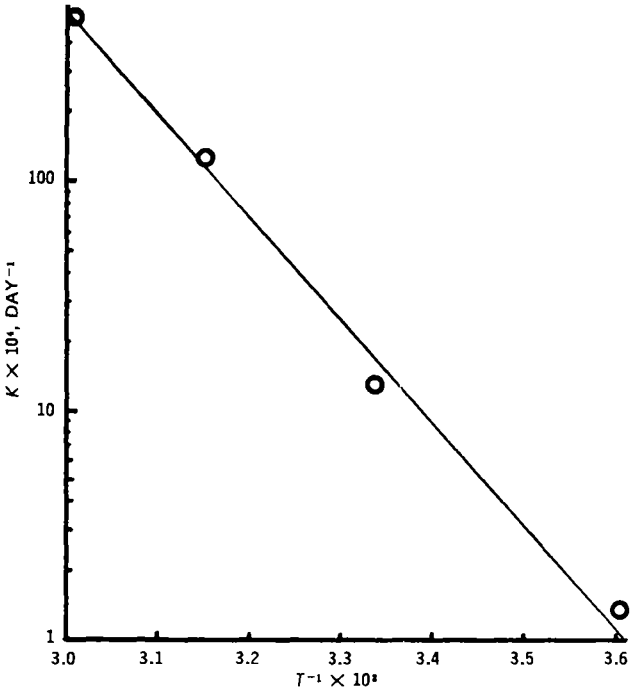

Figure 5—*Arrhenius plot showing the temperature dependency of transesterification at 4, 27, 45, and 60°.*

Since acetic acid was shown not to be a degradation product of the aspirin–polyethylene glycol 400 mixture, the possibility of transesterification (4) between aspirin and polyethylene glycol was examined. Salicylic acid has no protons which may be observed in this range and should not enter into this analysis.

Peaks A_4 and B_3 of Fig. 4 are a result of scanning a mixture of freshly prepared acetylated polyethylene glycol 400 and aspirin. It may be seen that these two peaks occur at the identical positions of peak A_2 and B_1 of Fig. 3. This establishes that one product of the decomposition of aspirin in polyethylene glycol 400 is acetylated polyethylene glycol 400.

Figure 5 is an Arrhenius plot showing the temperature dependency of the transesterification reaction of aspirin and polyethylene glycols. From the Arrhenius equation the energy of activation was calculated to be 20.1 kcal./mole for this reaction.

It has been shown that although aspirin may hydrolyze in moisture-laden polyethylene glycols, it also degrades by entering into a transesterification reaction between aspirin and polyethylene glycol in the apparent absence of moisture. This conclusion is a result of acetic acid not being found among the decomposition products and the establishment of acetylated polyethylene glycol as a product of decomposition.

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