

# Aspirin Stability in Substituted and Nonsubstituted Polyhydric Alcohols in Absence and Presence of Added Water

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**Abstract** □ The degradation of aspirin in methoxypolyethylene glycol 350, 550, and 5000 and unsubstituted polyethylene glycol 400 was studied at four temperatures. The rate of degradation was slower in methoxypolyethylene glycols than in unsubstituted polyethylene glycol. The data were then compared to those obtained in the presence of varying amounts of water added to the bases. The effect of water on the rate of degradation of aspirin was greater in methoxypolyethylene glycol than in polyethylene glycol. Slower degradation of aspirin in methoxypolyethylene glycol was due to the fact that the transesterification pathway is partly blocked in this base. A conclusion is made that the stability of aspirin in polyhydric alcohols may be achieved by blocking the free hydroxyl group in the molecules.

**Keyphrases** □ Aspirin stability—in substituted and nonsubstituted polyhydric alcohols, effect of added water □ Stability, aspirin—in substituted and nonsubstituted polyhydric alcohols, effect of added water □ Degradation, aspirin—in substituted and nonsubstituted polyhydric alcohols, effect of added water □ Methoxypolyethylene glycols—aspirin stability, effect of added water, degradation rates of aspirin

The degradation of aspirin in various pharmaceutical dosage forms has been generally considered to be due to a hydrolytic reaction in the presence of water. Edwards (1) and Garrett (2) extensively studied the hydrolysis of aspirin in aqueous solutions.

Recently, it was reported (3) that when aspirin was incorporated into polyethylene glycol suppository bases, it decomposed to the extent that the product could not meet stability standards. The mechanism responsible for degradation of aspirin in polyethylene glycol base was reported to be due in part to a transesterification reaction between acetyl groups of aspirin and hydroxyl groups in polyethylene glycols (4). Therefore, in the apparent absence of water, it was expected that degradation of aspirin would be less when incorporated in substituted polyethylene glycol than polyethylene glycol *per se*. This is because in substituted materials such as methoxypolyethylene glycol, the transesterification pathways are partly blocked. The purpose of this work was to study the degradation of aspirin in polyethylene glycol and in the substituted derivative, methoxypolyethylene glycol. The effects of added water on the degradation of aspirin in both bases were also studied.

## EXPERIMENTAL

**Materials**—Aspirin USP<sup>1</sup> and polyethylene glycol 400<sup>2</sup> were

**Table I**—Degradation of Aspirin in Polyethylene Glycol 400 as a Function of Added Water at Various Temperatures

Days	Aspirin Remaining, %					
	0% Water	0.5% Water	1% Water	3% Water	5% Water	10% Water
<b>At 4°</b>						
0	99.5	99.5	99.5	99.5	99.5	99.5
6	99.3	99.0	99.4	99.4	99.3	99.5
18	99.0	99.1	99.0	99.2	98.3	99.2
27	98.8	98.9	98.6	98.8	98.9	99.0
41	98.9	98.9	99.0	99.0	99.0	98.9
56	98.1	98.2	99.8	97.9	98.2	98.5
<b>At 24°</b>						
0	99.6	99.6	99.6	99.6	99.6	99.6
9	97.8	97.8	98.1	97.4	97.6	98.0
17	96.6	96.6	96.7	96.8	96.9	97.1
24	95.6	95.6	95.4	95.9	96.1	95.6
31	95.1	95.3	95.4	95.2	95.3	95.0
43	93.8	93.7	93.9	94.2	94.0	93.5
57	92.4	92.5	92.7	92.5	92.8	91.6
72	91.2	91.3	91.4	91.6	91.8	90.5
90	90.1	89.9	90.2	90.3	90.2	88.5
<b>At 36°</b>						
0	99.5	99.5	99.5	99.5	99.5	99.5
3	97.5	97.6	97.7	97.7	97.7	97.9
10	93.8	93.9	93.6	94.1	93.8	93.4
16	91.7	91.9	92.1	91.8	92.1	90.9
22	89.7	89.9	90.0	89.5	90.6	88.4
31	86.8	86.9	86.9	86.8	86.9	84.4
<b>At 45°</b>						
0	99.5	99.5	99.5	99.6	99.6	99.6
1	97.0	97.6	97.1	—	—	—
3	—	—	—	95.4	95.9	94.7
4	93.0	93.7	92.5	—	—	—
7	—	—	—	91.3	92.3	90.0
8	89.7	90.1	88.1	—	—	—
11	—	—	—	87.0	88.2	85.5
12	86.8	86.4	84.6	—	—	—
17	—	—	—	80.3	83.5	79.4
18	81.6	81.7	80.7	—	—	—
25	—	—	—	73.5	76.4	72.1
27	76.4	75.3	74.1	—	—	—
33	—	—	—	67.9	70.4	65.6
39	69.4	69.6	66.4	—	—	—
41	—	—	—	63.2	64.8	58.8
49	—	—	—	57.4	57.8	50.7

used as received. Monosubstituted methoxypolyethylene glycol 350, 550, and 5000 were supplied by the manufacturer<sup>3</sup>. Chloroform<sup>4</sup> was spectrograde.

**Sample Preparation**—The samples were prepared by incorporating 12% of aspirin by weight in methoxypolyethylene glycol 350, 550, and 5000 and in polyethylene glycol 400. When effects of water were studied, a predetermined amount of distilled water was added to the bases prior to incorporation of aspirin. Samples were kept in airtight containers and stored at 4, 24, 36, and 45°.

<sup>1</sup> Merck & Co., Rahway, N.J.

<sup>2</sup> Matheson, Coleman and Bell, Norwood, Ohio.

<sup>3</sup> Union Carbide, New York, N.Y.

<sup>4</sup> J. T. Baker Chemical Co., Phillipsburg, N.J.

**Table II—Degradation of Aspirin in Methoxypolyethylene Glycol 350 and in the Presence of Added Water at Various Temperatures**

Days	Aspirin Remaining, %					
	0% Water	0.5% Water	1% Water	3% Water	5% Water	10% Water
At 4°						
0	99.6	99.6	99.6	99.6	99.6	99.6
6	99.7	99.7	99.6	99.4	99.5	99.5
12	99.5	99.2	99.5	99.2	99.2	99.4
21	99.5	99.4	99.4	99.3	99.3	98.4
34	99.4	99.3	99.3	99.3	99.1	98.9
55	99.2	99.3	99.2	99.0	99.0	98.8
At 24°						
0	99.6	99.6	99.6	99.6	99.6	99.6
3	99.3	99.3	99.0	99.0	99.0	98.8
8	99.1	99.0	98.8	97.8	98.2	97.4
13	98.8	98.7	98.5	98.1	99.8	97.6
20	98.0	98.1	98.1	97.8	97.1	96.4
29	97.5	97.6	97.5	97.0	96.2	95.6
36	97.3	97.2	97.2	95.4	95.7	94.6
44	96.8	96.9	97.1	95.8	95.5	94.6
53	96.7	96.5	96.3	95.2	94.5	93.2
65	95.6	96.0	95.6	94.5	94.0	92.0
At 36°						
0	99.6	99.6	99.6	99.6	99.6	99.6
3	98.7	98.7	98.8	98.7	98.3	98.4
10	96.9	97.0	96.7	96.2	95.3	94.6
16	95.3	95.7	95.4	94.9	94.1	92.0
22	94.8	94.5	94.5	93.3	92.1	90.1
31	93.0	92.6	92.3	90.8	89.4	85.7
At 45°						
0	99.5	99.5	99.5	99.5	99.5	99.5
3	98.0	97.3	97.4	96.8	96.4	96.0
8	95.2	95.3	95.0	93.7	93.3	92.0
14	92.5	92.4	92.1	90.2	89.3	87.2
21	89.7	89.4	89.1	86.8	85.2	81.2
28	87.4	86.6	86.4	83.5	81.6	76.2
36	84.0	83.6	83.2	80.0	77.8	70.7
44	81.8	80.5	80.0	76.2	74.2	61.1
55	78.4	77.2	77.1	72.2	68.8	58.9

At various intervals, the samples were assayed.

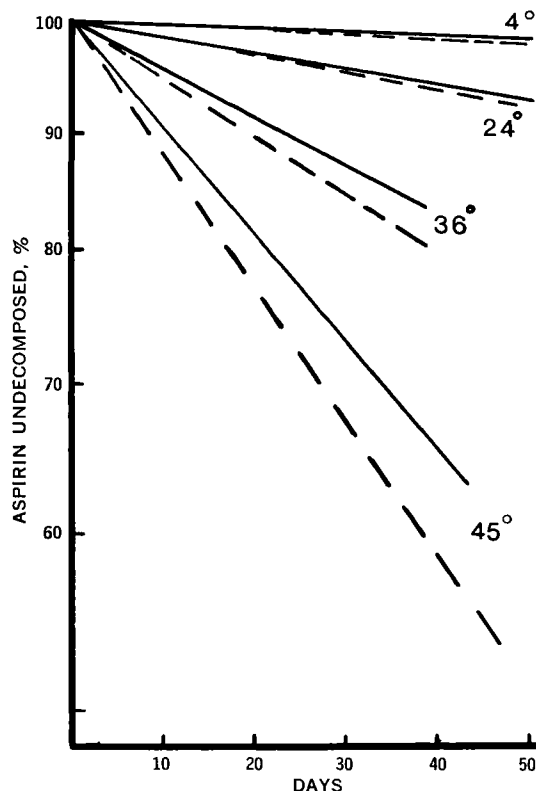
**Analytical Method**—UV spectrophotometric analysis, as reported by Tinker and McBay (5), was employed to measure aspirin and salicylic acid. Samples (approximately 2.4 g) were taken at specific intervals and dissolved in 100 ml chloroform containing 1% acetic acid. A further appropriate dilution was made, and the absorbance of the dilution was read<sup>5</sup> at 278 nm for aspirin and 308 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

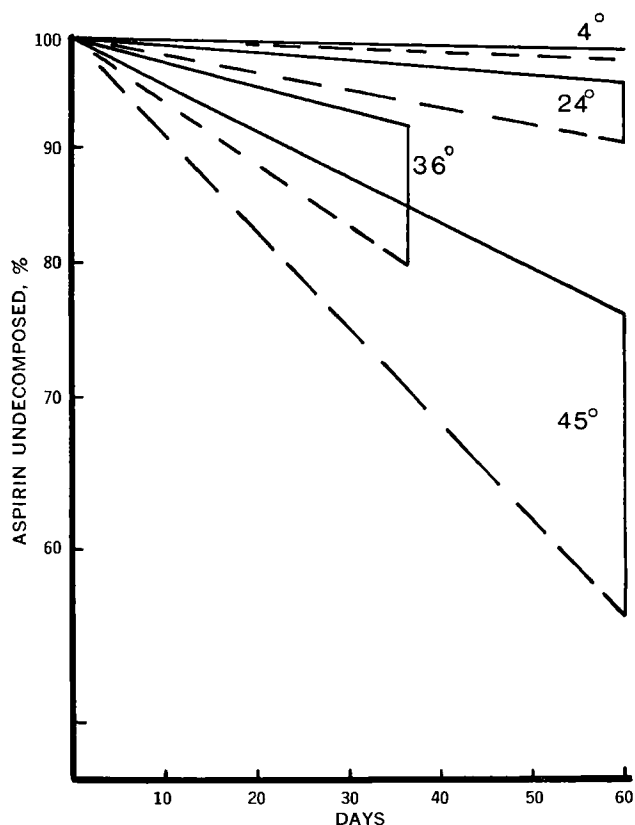
Aspirin undergoes degradation in polyethylene glycol at least in part *via* a transesterification reaction (4). In the presence of water, however, it was expected that the mechanism of degradation would probably be more complex. Tables I and II summarize the data obtained in the present study. Under all experimental conditions, the degradation of aspirin showed a temperature dependency.

In Fig. 1, the solid lines indicate the amount of aspirin remaining in polyethylene glycol 400 at four temperatures. The reaction appears to follow the first-order process. When samples were stored at 4°, the degradation was relatively slow. When varying amounts of water were added to the base, differences were observed in the rate of degradation. The dotted lines indicate the degradation of aspirin in the same base with 10% water added. The effect of water on the rate of degradation of aspirin in this base was generally small. At lower temperatures (4 and 24°), no significant effects were observed while the differences were some-

<sup>5</sup> Beckman DU spectrophotometer.



**Figure 1—Degradation of aspirin in polyethylene glycol 400 at four temperatures (solid lines). Dotted lines are for degradation of aspirin in the base in the presence of 10% water.**



**Figure 2—Degradation of aspirin in methoxypolyethylene glycol 350 at four temperatures (solid lines). Dotted lines are for degradation of aspirin in the base in the presence of 10% water.**

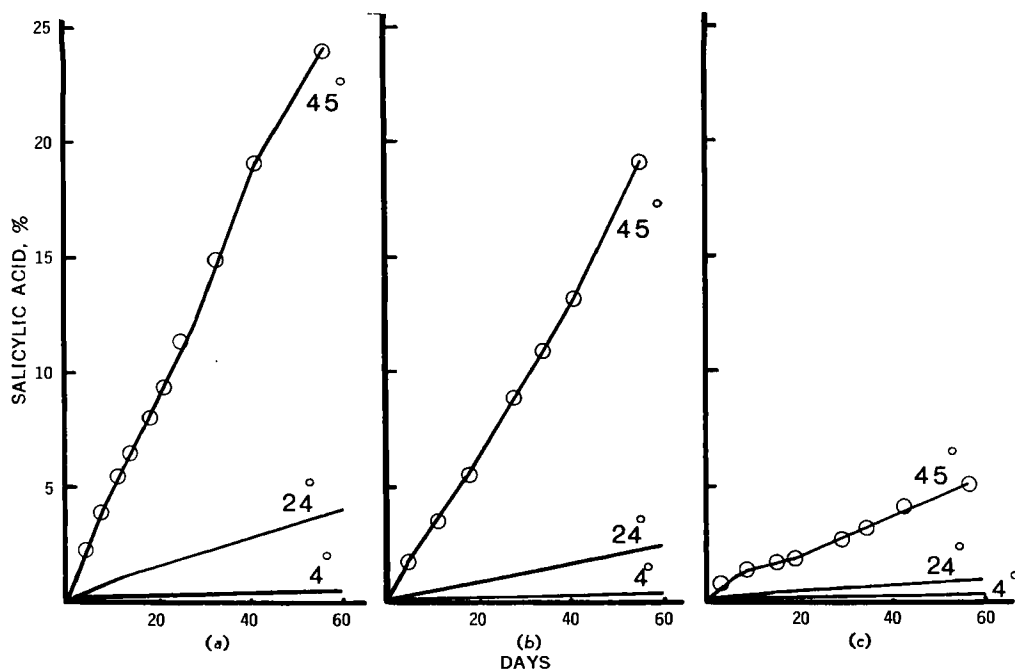


Figure 3—Degradation of aspirin in methoxypolyethylene glycol 350 (3a), 550 (3b), and 5000 (3c) at three temperatures.

what greater at higher temperatures. When smaller amounts of water (0.5–5%) were added to the base, the rates of degradation fell between the solid and dotted lines. A small effect of added water on the degradation of aspirin in polyethylene glycol suggests that aspirin molecules may be entrapped in polyethylene glycol in the presence of water, thus reducing a molecular contact between water and aspirin.

The greater effect of water on the degradation of aspirin in methoxypolyethylene glycol as compared to polyethylene glycol is probably due primarily to hydrolysis effects.

Figure 2 shows degradation of aspirin in methoxypolyethylene glycol 350 (solid lines) and in a mixture of methoxypolyethylene glycol 350 and water (dotted lines) at four temperatures. In methoxypolyethylene glycol, aspirin appeared to degrade more slowly than in unsubstituted polyethylene glycol (compare Figs. 1 and 2). After 31 days at 36°, aspirin decomposed about 13% in polyethylene glycol but only about 7% in methoxypolyethylene glycol. This is attributed to the fact that transesterification pathways were partly blocked in methoxypolyethylene glycol. When 10% water was added to the bases, however, the difference in the amount of aspirin decomposed in methoxypolyethylene glycol was considerably more pronounced than that in polyethylene glycol (compare Figs. 1 and 2). After 31 days at 36°, aspirin degraded 15% in polyethylene glycol and 14% in methoxypolyethylene glycol. The greater effect of water on degradation of aspirin in methoxypolyethylene glycol may be due to the fact that in methoxypolyethylene glycol a transesterification reaction was partly blocked and when water was added the unreacted aspirin became available for hydrolysis.

Figure 3 shows degradation of aspirin in methoxypolyethylene glycol 350, 550, and 5000 at three temperatures, as indicated by the rate of appearance of salicylic acid. In methoxypolyethylene glycol 350, aspirin degraded 25% in 50 days at 45° as compared to 19 and 5% in methoxypolyethylene glycol 550 and 5000, respectively. At lower temperatures, the differences have the same relationship. In higher molecular weight methoxypolyethylene glycols, fewer hydroxyl radicals per unit weight are available for the transesterification reaction. The finding supports the hypothesis that aspirin degrades in polyhydric alcohols at least in part via a transesterification reaction.

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