Stability of Aspirin in Liquid and Semisolid Bases III: Effect of Citric and Tartaric Acids on Decomposition in a Polyethylene Glycol Base

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

Abstract □ The decomposition of aspirin in a polyethylene glycol base was inhibited by citric and tartaric acids at 45, 26, and 4°. Even in the presence of added water, citric acid tended to slow the decomposition process while several other additives failed to influence it.

Keyphrases □ Aspirin, stability in liquid and semisolid bases—effect of citric and tartaric acids on decomposition in polyethylene glycol base □ Suppositories—inhibition of aspirin decomposition by citric and tartaric acids, polyethylene glycol base □ Polyethylene glycol—aspirin stability, inhibition of decomposition by citric and tartaric acids □ Degradation, aspirin—inhibition by citric and tartaric acids in polyethylene glycol-type suppository

Aspirin decomposes rapidly when incorporated into a polyethylene glycol suppository base. The process was found to be partly due to transesterification (1) and is greatly temperature dependent.

Mixtures of polyethylene glycols have been used extensively as suppository bases for several years (2). These mixtures have desirable characteristics as bases since they do not require refrigeration, provided the incorporated drugs are stable at room temperature. Aspirin is less stable in these polyethylene glycol bases than in cocoa butter, which has to be refrigerated to prevent melting. The purpose of this study was to stablize aspirin in a polyethylene glycol suppository base using additives while retaining the essential characteristics of the base. Of the several additives tested, citric and tartaric acids proved promising. Less effective substances included calcium gluconate, colloidal silica, and acetic acid.

EXPERIMENTAL

Reagents—The basic polyethylene glycol formula into which aspirin and additives were incorporated was as follows: polyethylene glycol 400[1], 24.8%; polyethylene glycol 1540[1], 30.4%; polyethylene glycol 6000[1], 40.0%; and polysorbate 60[2], 4.8%.

The different concentrations of citric acid[3] and tartaric acid[3] were based on the weight of the suppository vehicle. The ingredients were melted at 55° with stirring, and aspirin[4] equal to 12% of the base-additive mixture was stirred into the melted mixture. The mixture was poured with stirring into suppository molds and permitted to congeal. Each batch was divided into three portions for storage at 45, 26, and 4°.

Analytical Method—Assays were performed at short intervals at the beginning of the study and at greater intervals as the rate of degradation slowed.

Each suppository was dissolved in 100 ml. of chloroform containing 1% acetic acid. A 1:50 dilution was made, and the absorbance was read at 278 nm. for aspirin and at 308 nm. for salicylic acid on a spectrophotometer[5]. The moles of each were determined from a standard curve, and the mole percent (percent decomposition) of salicylic acid was calculated.

RESULTS AND DISCUSSION

The results with all concentrations of citric and tartaric acids were somewhat similar. Figure 1 shows the decomposition of aspirin at 45, 26, and 4° in the polyethylene glycol suppository base when no additive was used. As in numerous other studies (3), the decomposition of aspirin was highly temperature dependent. The decomposition was approximately 26% in 28 days at 45°, about 18% in 80 days at 26°, and approximately 3% in 100 days at 4°. Refrigeration of aspirin suppositories utilizing a polyethylene glycol base is a necessity.

Figure 2 shows the decomposition of aspirin in the polyethylene glycol base in the presence of 1% citric acid. The decomposition was inhibited particularly at 26 and 4°. At 45°, the decomposition reached about 23% at 28 days; at 26°, it was around 11% after 102 days; and at 4°, it reached just over 2% in 110 days.

An increase in citric acid concentration to 5% resulted in a further decrease in the decomposition rate at 26 and 4°, but no change was noted at 45°. The decomposition at 26° reached about 8% in 100 days, while at 4° it was only about 1%.

There was little or no improvement in the stability of aspirin with 10% citric acid compared to the 5% concentration. Citric acid at the 10% level inhibited the decomposition of aspirin even in the presence of 5% added water. The rate of decomposition was greater than that shown without water but less than that of the control.

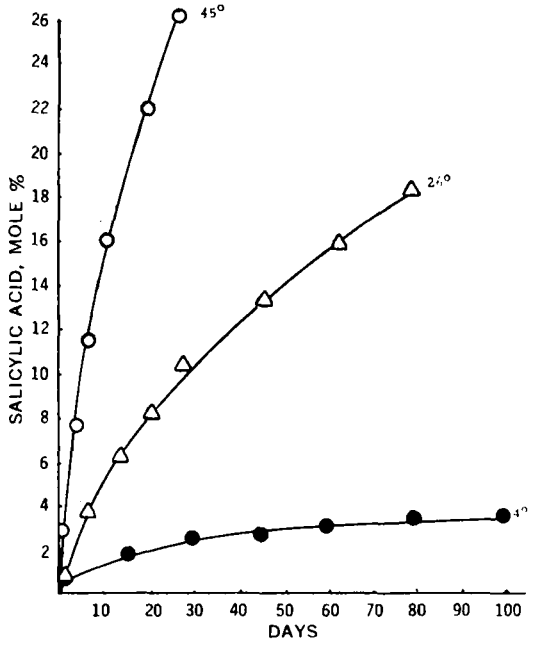

Figure 1—*Mole percent decomposition of aspirin with time in a polyethylene glycol base.*

[1] Union Carbide.
[2] Atlas Chemicals.
[3] J. T. Baker Chemical Co.
[4] Merck and Co.
[5] Beckman DU.

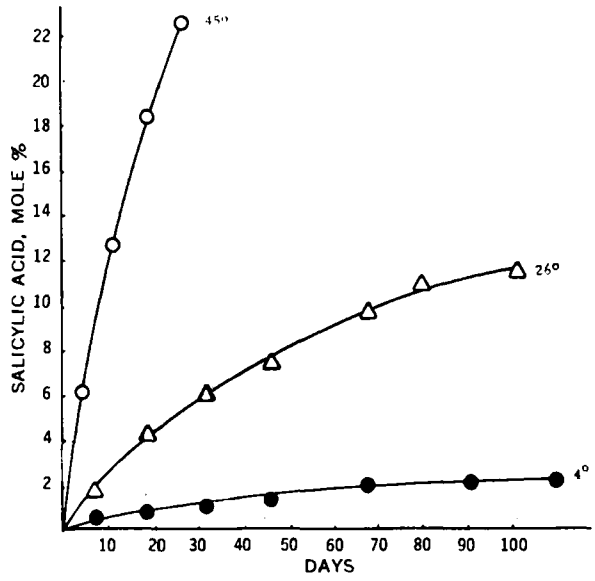

Figure 2—*Mole percent decomposition of aspirin with time in a polyethylene glycol base containing 1% citric acid.*

The effect of 10% tartaric acid on aspirin decomposition in this base was studied for a limited period, and the results were similar to those obtained with 5 and 10% citric acid for a comparable time. The percent decomposition at 26° was slightly lower with tartaric acid, but little difference was noted between these similar acids at 45 and 4°.

CONCLUSIONS

Certain substances can be added to a polyethylene glycol-type aspirin suppository mixture without appreciably changing its properties. Of the several additives studied, citric and tartaric acids inhibited decomposition. A 5% concentration of citric acid appeared to be the optimum concentration necessary to hinder decomposition. The importance of refrigeration at 4° on decomposition of aspirin in polyethylene glycol was evident.

REFERENCES

(1) H. W. Jun, C. W. Whitworth, and L. A. Luzzi, *J. Pharm. Sci.*, **61**, 1160(1972).

(2) A. F. Cacchillo and W. H. Hassler, *J. Amer. Pharm. Ass., Sci. Ed.*, **43**, 683(1954).

(3) C. A. Kelly, *J. Pharm. Sci.*, **59**, 1053(1970).

ACKNOWLEDGMENTS AND ADDRESSES

Received March 26, 1973, from the *School of Pharmacy, University of Georgia, Athens, GA 30602*

Accepted for publication May 30, 1973.

▲ To whom inquiries should be directed.

Biological Activity of Pentobarbital Metabolites

H. D. CHRISTENSEN▲, L. BARNETT, and F. I. CARROLL

Abstract □ The (1′*S*,3′*R*)-, (1′*S*,3′*S*)-, (1′*R*,3′*R*)-, and (1′*R*,3′*S*)-5-ethyl-5-(3′-hydroxy-1′-methylbutyl)barbituric acid metabolites of pentobarbital are relatively inactive and, therefore, cannot account for the differences in potency found between *R*(+)- and *S*(−)-pentobarbital. The (1′*S*,3′*R*)- and (1′*S*,3′*S*)-hydroxypentobarbital metabolites have very weak sedative activity when administered to CF-1 mice intravenously at an AD_{90} anesthetic dose of *RS*-pentobarbital.

Keyphrases □ Pentobarbital metabolites—anesthetic and behavioral activity in mice □ Barbituric acid metabolites, pentobarbital—anesthetic and behavioral activity in mice □ Anesthetic activity—pentobarbital metabolites, mice

The diastereoisomeric pairs of 5-ethyl-5-(3′-hydroxy-1′-methylbutyl)barbituric acid were first shown by Maynert and Dawson (1) to be biotransformation products of pentobarbital. More recently, the four optical isomers of 3′-hydroxypentobarbital were isolated in this laboratory from metabolism studies of optically pure *R*(+)- and *S*(−)-pentobarbital (2, 3). *R*(+)-Pentobarbital is metabolized to approximately equal amounts of the two hydroxylated metabolites in contrast to (*S*)-pentobarbital in which the ratio is 9:1. The *S*(−)-isomer is more toxic and potent as an anesthetic agent in mice than is the *R*(+)-isomer or the racemate (4). Maynert and Dawson (1) reported that the diastereoisomeric metabolites were inactive. Dickert *et al.* (5) found that (1′*RS*,3′*SR*)-3′-hydroxypentobarbital, prepared by synthetic methods, had very weak anticonvulsant activity and no anesthetic properties. Pharmacological differences in the enantiomers of pentobarbital and the respective ratios of their 3′-hydroxy enantiomers indicated the desirability of determining if some 3′-hydroxypentobarbital isomers were active and contributing to the differences in the activity of the pentobarbital stereoisomers.

EXPERIMENTAL

The structure and absolute stereochemical assignment of *R*- and *S*-pentobarbital as well as the four optically active 3′-hydroxypentobarbital metabolites were reported previously (6–9). The optical rotations and melting-point values for pentobarbital stereoisomers are: (*RS*), m.p. 129–130°; (*R*), $[\alpha]_D$ +13.1°, m.p. 121–122°; and (*S*), $[\alpha]_D$ −13.2°, m.p. 121–122°. For 3′-hydroxypentobarbital the values are: (1′*RS*,3′*RS*), m.p. 145–147°; (1′*RS*,3′*SR*), m.p. 191–192°; (1′*R*,3′*R*), $[\alpha]_D$ +12.8°, m.p. 170–176°; (1′*R*,3′*S*), $[\alpha]_D$ +30.5°, m.p. 202–205°; (1′*S*,3′*S*), $[\alpha]_D$ −15.3°, m.p. 181–183°; and (1′*S*,3′*R*), $[\alpha]_D$ −31.5°, m.p. 208–210°.

Biological activity was assessed by administering each epimer at the AD_{90} anesthetic dose of *RS*-pentobarbital to 10 CF-1 male mice.