Stability of Aspirin in Liquid and Semisolid Bases II: Effect of Fatty Additives on Stability in a Polyethylene Glycol Base

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Abstract □ Aspirin decomposes rapidly when incorporated into mixtures of polyethylene glycols, but aspirin incorporated into fatty-type suppository bases is much more stable. Fats of vegetable origin were incorporated into a polyethylene glycol base in an attempt to inhibit the decomposition of aspirin in this type of mixture. The process is temperature dependent and refrigeration of the mixture greatly slows decomposition. Degradation was retarded at 26°, but little effect was noted at 4 and 45° within the time limits of this study.

Keyphrases □ Aspirin—effect of fatty additives on stability of polyethylene glycol base suppositories □ Fatty additives—effect on decomposition of aspirin in polyethylene glycol base suppositories □ Degradation—effect of fatty additives on aspirin stability in polyethylene glycol base suppositories □ Polyethylene glycol–aspirin formulations—effect of fatty additives on aspirin stability □ Additives, fatty—effect on aspirin stability in polyethylene glycol base suppositories

Aspirin has been found to degrade in polyethylene glycol mixtures. The process has been shown to be due in part to transesterification (1). The process is greatly temperature dependent, with refrigeration at 4° markedly slowing the rate of decomposition.

Aspirin is commercially available in suppository form in a cocoa butter base. Under refrigeration, these suppositories are sufficiently stable, although an expiration date is necessary. Aspirin is likewise much more stable in other fatty vehicles than in the polyethylene glycols. A product composed of distilled acetylated monoglycerides was tested as a vehicle for aspirin and found to inhibit greatly the degradation process (Fig. 1). It was then decided that fatty additives might have an inhibiting effect on aspirin decomposition in a polyethylene glycol base. The purpose of this study was to formulate a stable aspirin suppository using a polyethylene glycol base without altering the desirable characteristics of the base. A 10% concentration of additive was used in the study, and no compatibility problems were encountered with the formulation. Six different additives were utilized.

Polyethylene glycol mixtures serve as excellent suppository bases for some drugs (2). Their main advantages are water solubility, an innocuous nature, the ability to release a drug for absorption (3), and firmness at room temperature. Since the polyethylene glycols dissolve in the body secretions rather than melting, they do not require refrigeration with most drugs; in this respect, they have a great advantage over the fatty-type bases such as cocoa butter.

Unfortunately the polar and perhaps also the hygroscopic nature of these glycols tends to allow certain drugs such as aspirin to degrade when incorporated into this type of base.

One aspect of the study was to determine if packaging and storage procedures contributed significantly to the degradation process. Commercially, polyethylene glycol base suppositories are packaged unwrapped in jars and stored at room temperature until dispensed. In this project, the control batch of aspirin suppositories was divided into groups and some were wrapped in aluminum foil and stored both with and without a desiccant in the container. The degradation of these suppositories was compared with another batch stored without either wrapping or desiccant. There were no appreciable differences in the degradation curves for these batches. Throughout the study, however, a desiccant was present in all containers to reduce the effect of moisture on the decomposition process.

EXPERIMENTAL

Materials—The formula for the polyethylene glycol base used in the study was as follows:

polyethylene glycol 400[1]	24.8%
polyethylene glycol 1540[1]	30.4%
polyethylene glycol 6000[1]	40.0%
polysorbate 60[2]	4.8%

The additives used in the project were:

1. Hard butter containing lauric fats[3]. Free fatty acids, 0.1% max. Iodine value, 3 max. Used in confections and candies as coatings.
2. A coating butter made from domestic vegetable oils[4]. Free fatty acids, 0.1% max. Iodine value, 58–63. Used in confections and candies.
3. Hard butters obtained from lauric oils[5]. Free fatty acids, 0.05% max. Used in candies and confections.
4. Distilled, fully acetylated monoglycerides[6]. Acid value, 4. Iodine value, 44. Made from edible fats. Used in cosmetics as emulsifiers.
5. Oil expressed from roasted seeds of *Theobroma cacao*[7]. A mixture of glycerides. Iodine value, 35–43. Used as a suppository base.
6. Hydrogenated glycerides of fatty acids from palm oils[8]. Acid value, 1. Iodine value, 2. Used as suppository base.

Procedure—The additives were added in quantities equivalent to 10% of the amount of base used. The ingredients were then melted at 55° with stirring, and aspirin equal to 12% of the base–additive mixture was stirred into the melted mixture. The mixture was poured with stirring into suppository molds and allowed to congeal. The batch of suppositories was divided into three quantities for storage at the temperatures reported in this study. All suppositories were stored in airtight containers containing a desiccant.

Aspirin was added with stirring to the acetylated monoglyceride product in the same ratio as with all the other formulations and stored under similar conditions.

Analytical Method—Assays were performed at short intervals for the first part of the study, and the intervals gradually lengthened

[1] Union Carbide.
[2] Atlas Chemicals.
[3] Paramount H, Glidden-Durkee.
[4] Kaomel, Glidden-Durkee.
[5] Pinnacle 18, Humko Products.
[6] Myvacet 9-45, Eastman Chemicals.
[7] Theobroma oil USP, Fisher Scientific.
[8] Suppocire AM, A and S Corp.

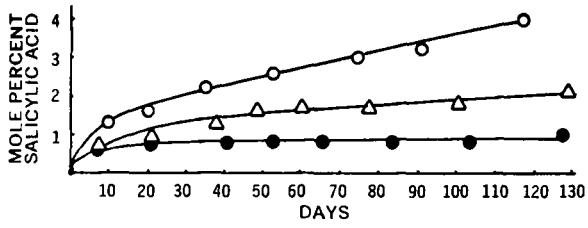

Figure 1—*Mole percent decomposition of aspirin with time in a vehicle composed of acetylated monoglycerides. Key: ○, 45°; △, 26°; and ●, 4°.*

as decomposition slowed down. When the percent decomposition reached 30–35%, assaying was discontinued. The assay procedure consisted of dissolving each suppository (approximately 2.4 g.) in 100 ml. of a solution of chloroform containing 1% acetic acid. A 1:50 dilution was made, and the absorbance of the dilution was read at 278 nm. for aspirin and 308 nm. for salicylic acid on a spectrophotometer[9]. From a standard curve the moles of each drug were determined and mole percent of salicylic acid (percent decomposition) was calculated.

RESULTS AND DISCUSSION

Figure 1 shows the degradation of aspirin in acetylated monoglycerides. The graphs are all plots of mole percent salicylic acid against time. The ordinates likewise represent mole percent decomposition of aspirin. Figure 2 represents the control, which was the polyethylene glycol mixture without additives. Since all additives yielded essentially identical results, only one curve at each temperature is shown in Fig. 3. For purposes of comparison, the control curves appear as broken lines in Fig. 3.

A comparison of Figs. 1 and 2 shows a drastic difference in the rate of decomposition of aspirin in a fatty-type vehicle compared to a polyethylene glycol base. In acetylated monoglycerides the decomposition after about 130 days at 45, 26, and 4° had reached

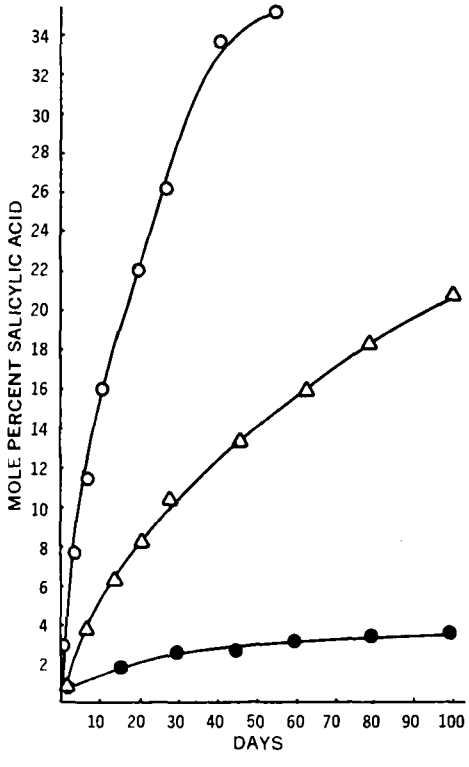

Figure 2—*Mole percent decomposition of aspirin with time in a polyethylene glycol base (control). Key: ○, 45°; △, 26°; and ●, 4°.*

[9] Beckman DU.

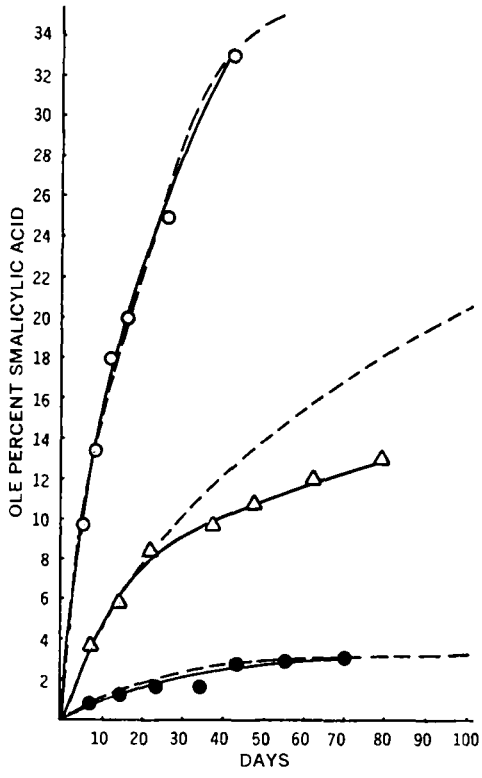

Figure 3—*Mole percent decomposition of aspirin with time in a polyethylene glycol base containing 10% acetylated monoglycerides. Broken lines represent control. Key: ○, 45°; △, 26°; and ●, 4°.*

only approximately 5, 2, and 1%, respectively; in the polyethylene glycol base, the decomposition was much greater.

The effect of temperature on aspirin degradation in many different types of vehicles is well documented. However, no study heretofore has dealt with aspirin stability in a polyethylene glycol-type suppository base. In practice, polyethylene glycol-type suppositories are stored at room temperature. This study shows this procedure should not be followed with aspirin.

As could be expected and as may be seen from Fig. 3, degradation was drastically inhibited in all the mixtures by reducing the temperature of storage. At 45°, both the control and the bases with additives reached the range of 30–35% decomposition in about 40–50 days, at which time sampling was discontinued. It is readily apparent that the fatty additives used in this study had no significant effect on aspirin degradation in the polyethylene glycol base at 45°. This is probably due to the rapid rate of the reaction at this temperature.

Figure 3 also shows that storage of suppositories at 26° drastically reduced the rate of decomposition of both the control and additive bases. For comparable time periods, the percent decomposition at 26° was less than half that at 45°. It may be seen that the additives had an inhibiting effect on aspirin degradation at this temperature. The difference in stability becomes apparent after about 20 days when the curves diverge.

Refrigeration of the suppositories at 4° reduced the decomposition of aspirin to less than 4% within the time limits of this study, for both the control and the additive bases. There was no apparent difference between the results from the control and the treated bases. It is possible that the additive would show an inhibiting effect on the degradation of aspirin after a much longer storage period.

The aims of this project were to study aspirin decomposition in polyethylene glycol mixtures and to devise means of stopping or reducing this degradation. As previously reported, the degradation is partly due to a transesterification mechanism (1).

It was felt that fatty additives might render a polyethylene glycol suppository base suitable as a vehicle for aspirin. From this study, it is concluded that while the fatty additives have an inhibiting effect at a room temperature of 26°, the percent of decomposition is still prohibitively high. Furthermore, the results showed temperature

effect to be much more pronounced than additive effect. Refrigeration dramatically slows the rate of decomposition.

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Synthesis of (±)-*trans*-11-Methylthio-1,2,3,4,6,7,12,12b-octahydrohydroxyindolo[2,3-*a*]quinolizine

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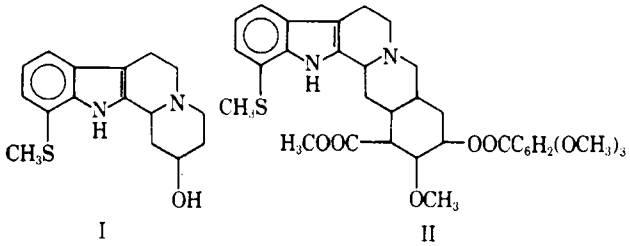
Abstract □ (±)-*trans*-11-Methylthio-1,2,3,4,6,7,12,12b-octahydrohydroxyindolo[2,3-*a*]quinolizine was synthesized as a cardiovascular agent. Biological evaluation of the title compound and several precursors (7-methylthiotryptamine formate, 7-methylthiotryptamine formamide, 8-methylthio-3,4-dihydro-β-carboline, *trans*-11-methylthio - 1,2,3,4,6,7,12,12b - octahydro - 2 - oxoindolo[2,3 - *a*] quinolizine) showed no activity.

Keyphrases □ (±)-*trans*-11-Methylthio-1,2,3,4,6,7,12,12b-octahydrohydroxyindolo[2,3-*a*]quinolizine—synthesis, pharmacological evaluation □ Thioindole derivatives—synthesis and pharmacological evaluation of (±)-*trans*-11-methylthio-1,2,3,4,6,7,12,12b-octahydrohydroxyindolo[2,3-*a*]quinolizine

The title compound, (±)-*trans*-11-methylthio-1,2,3,4,-6,7,12,12b - octahydrohydroxyindolo[2,3 - *a*]quinolizine (I), was prepared as an extension of the authors' interest in thioindole derivatives and the reported (1) activity of methiopidine (II). Unsubstituted octahydroindolo[2,3-*a*]-quinolizine has been synthesized (2) and reported to be a hypotensive agent. Synthesis (Scheme I) of I was achieved by first preparing 7-methylthiotryptamine through a sequence described by Abramovitch and Shapiro (3). Preparation of the phenylhydrazone (III) was carried out *via* the Japp-Klingemann reaction of S-methyl - 2 - aminobenzenethiol and 3 - carbethoxy - 2-piperidone. Cyclization of III into the β-carboline (IV) was smooth in hot acetic acid–hydrogen chloride gas. Hydrolysis of the β-carboline (IV) to the amino acid (V) was quantitative in 5% alcoholic potassium hydroxide. Decarboxylation to 7-methylthiotryptamine (VI) was accomplished with difficulty in refluxing 2 *N* hydrochloric acid–acetic acid. Synthesis of the octahydroindolo[2,3-*a*]quinolizine (X) followed a procedure described previously (4–6). Addition of ethyl acetate–90% formic acid (1:1) to an ethyl acetate solution of 7-methylthiotryptamine afforded the formate salt (VII) which, upon heating, was converted to the formyl derivative (VIII). The *N*-formyl derivative was treated under Bischler–Napieralski conditions to form the Schiff base (IX), which was converterted to the *trans*-indolo[2,3-*a*]-quinolizine (X) by warming with methyl vinyl ketone and a catalytic amount of ethanol saturated with hydrogen chloride gas. Assignment of the *trans*-configuration was based on the presence of a Bohlman band between 2700 and 2800 cm.$^{-1}$ (KBr) on the IR spectrum (7). Reduction of X with lithium aluminum hydride afforded the title compound, I.



I II

PHARMACOLOGICAL RESULTS

The compounds were tested[1] in a variety of *in vitro* and *in vivo* assays: antibacterial, antifungal, antiparasitic, and antiviral assays. In some cases they were checked for activities of potential interest in the cardiovascular and behavioral fields. A total of 114 individual bioassays was run.

The compounds were tested in chicks (8) for possible anticoccidal activity and for *in vitro* anthelmintic activity against larvae or eggs of trichostrongyle nematodes (9). Antiviral screening (10) was conducted at sample concentrations up to 400 mcg./ml. in cell cultures.

Activity was demonstrated only by Compound VII in any of the screening procedures. Compound VII was active in a concentration of 400 p.p.m. against the organism *Bacillus megaterium* (ATCC 7056). The compound was tested by the medicated agar dilution technique, in which the compound is added to the agar and the test organism is inoculated (about 3 × 10^5 cells) on the surface. The end-point is the level of compound that prevents emergence of visible growth. Since Compound VII was active against only a single organism, lower dose levels were not run.

EXPERIMENTAL[2]

7-Methylthiotryptamine Formate (VII)—To a vigorously stirred solution of 19.4 g. (0.094 mole) of crude VI (11) in ethyl acetate (100 ml.) was slowly added a solution of 1:1 ethyl acetate–90% formic

[1] In the Merck Sharp & Dohme Research Laboratories.

[2] All melting points were determined in open glass capillaries on a Thomas–Hoover apparatus and are corrected.