the three currently commercially available capsule dosage forms of doxycycline hyclate and to compare their bioavailability profiles with those obtained from oral administration of an equivalent amount of doxycycline hyclate in solution form or an equivalent dose of doxycycline base in suspension form. Through the use of serial serum determinations and cumulative urinary excretion data collected in a single-dose study of crossover design, *in vivo* parameters were compared.

No statistically significant differences among the three capsule products were found, and the products were judged to be bioequivalent. This finding corroborates one other study (6) which concluded bioequivalency between two of the three brands employed in this study. When these same capsules were compared to the oral solution and suspension, differences were found in one prepeak mean serum level. *In vitro* dissolution tests were conducted on the three capsule products; time for 50% dissolution showed rank-order correlation with corresponding absorption rate constants.

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# Stability of Aspirin in Liquid and Semisolid Bases V: Polyglycerol Esters


**C. W. WHITWORTH [x] and A. F. ASKER**



**Abstract** □ The stability of aspirin in decaglycerol tetraoleate, decaglycerol octaoleate, and decaglycerol decaoleate was studied at 4, 26, and 45°. Degradation of aspirin in these polyglycerol esters was temperature dependent. Aspirin demonstrated the greatest stability in decaglycerol octaoleate and the lowest stability in decaglycerol tetraoleate at all temperatures studied. The hydroxyl value and the viscosity of the polyglycerol ester appeared to influence the stability of aspirin.



**Keyphrases** □ Aspirin—solubility and stability in polyglycerol esters, effect of temperature, hydroxyl value, viscosity □ Polyglycerol esters—as solvents for aspirin, stability, effect of temperature, hydroxyl value, viscosity □ Stability—aspirin in decaglycerol tetraoleate, decaglycerol octaoleate, and decaglycerol decaoleate


In previous reports (1–4), the stability of aspirin in various liquid and semisolid bases was investigated. The decomposition of aspirin in polyethylene glycols was due, at least in part, to a transesterification reaction between aspirin and polyethylene glycols (5). Blocking free hydroxyl groups on the polyethylene glycols retarded the decomposition of aspirin (1).

Polyglycerol esters are synthetic products and may be hydrophilic or lipophilic, depending on the number of hydroxyl groups that are reacted with the fatty acids and/or oils in question (6). The consistency of these esters varies from waxy solids and semisolids to liquids (6). Feeding studies (7) indicated that such esters are completely nontoxic and are degraded fully by the body to yield glycerol and the fatty acid. The Food and Drug Administration approved the use of polyglycerol esters ranging from 2 to 30 moles of glycerin and placed no limits on the amounts for use (6).

Decaglycerol tetraoleate, decaglycerol octaoleate, and decaglycerol decaoleate are liquid at room temperature and possess viscosity values of 6000–8000,

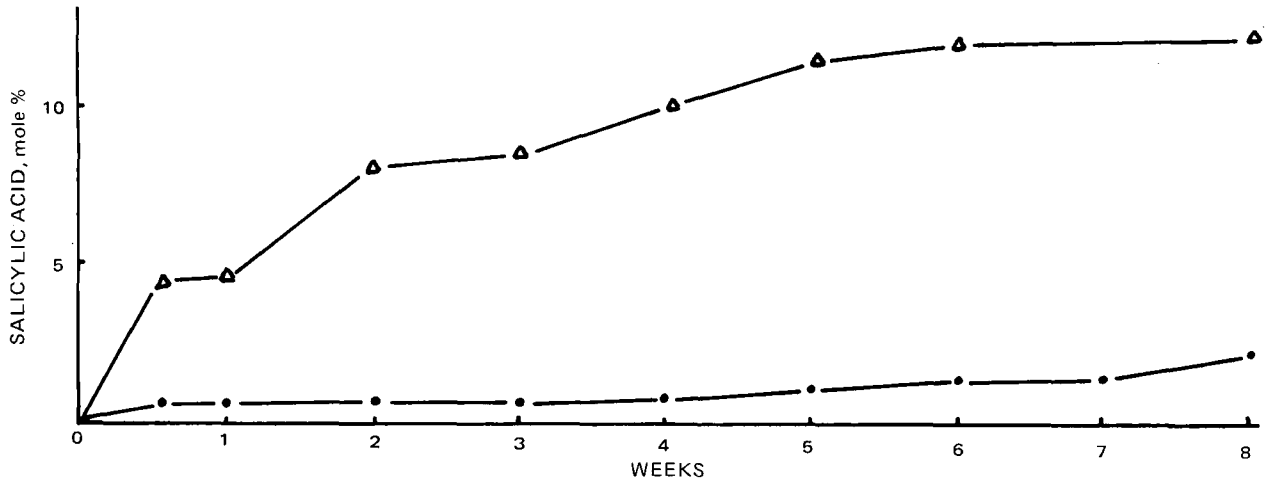


**Figure 1**—*Appearance of salicylic acid* versus *time for aspirin suspensions in polyglycerol esters at 4°. Key: △, decaglycerol tetraoleate; and ●, decaglycerol decaoleate.*

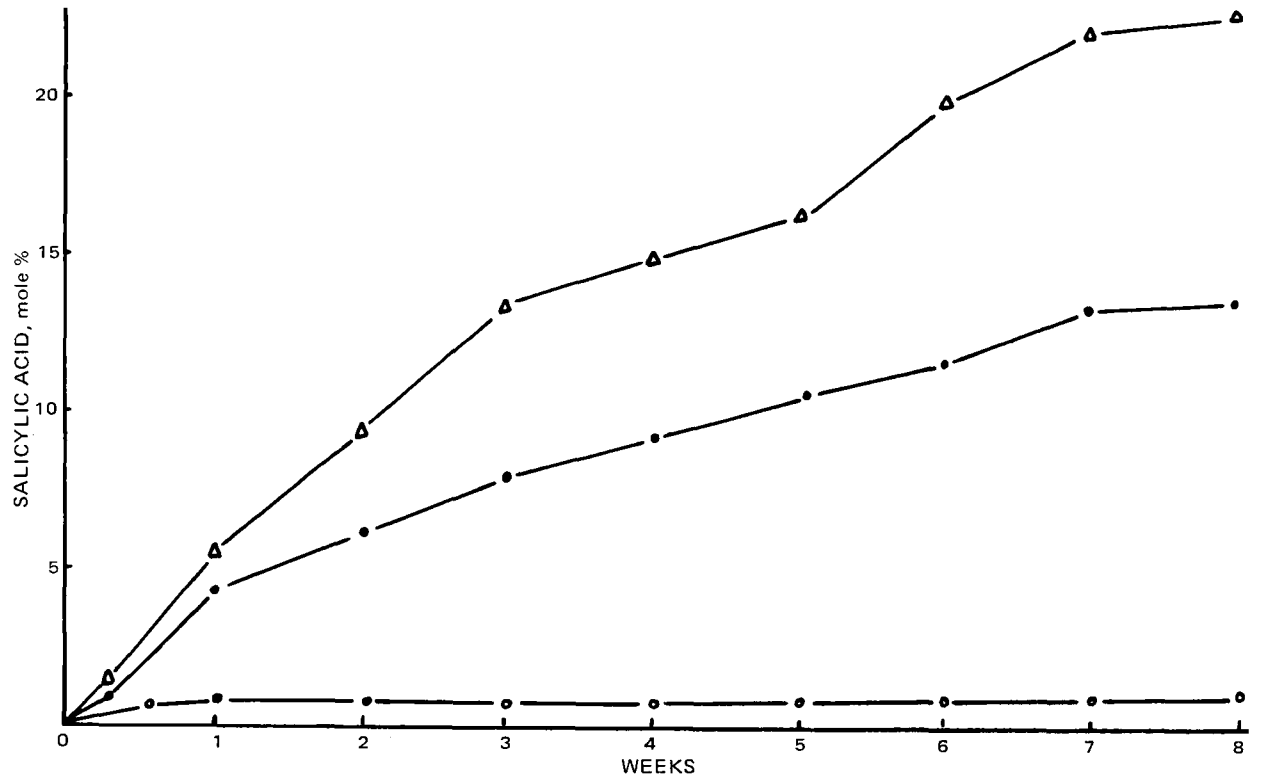


**Figure 2**—*Appearance of salicylic acid* versus *time for aspirin suspensions in polyglycerol esters at 26°. Key: △, decaglycerol tetraoleate; ●, decaglycerol decaoleate; and ○, decaglycerol octaoleate.*

800, and 400 cps, respectively (8). The hydroxyl values of these esters are 210–250 for the tetraoleate, 70–90 for the octaoleate, and 25–50 for the decaoleate (6, 8). The moisture content of these esters runs about 10%. The solubility of aspirin in the vehicles was determined and found to be 2.76, 2.19, and 2.01 mg/100 mg of vehicle for the tetraoleate, octaoleate, and decaoleate, respectively.

## EXPERIMENTAL

**Materials**—Aspirin[1] USP and salicylic acid[1] were used as received. The polyglycerol esters[2] were supplied by the manufacturer. Chloroform[3] was spectrograde.

**Sample Preparation**—The samples were prepared by suspending 0.3 g of aspirin in 9.7 g of the polyglycerol ester contained in airtight amber glass vials with screw caps. The suspensions were stored at 4, 26, and 45°.

**Analytical Method**—UV spectrophotometric analysis, as reported by Tinker and McBay (9), was employed to measure aspirin and salicylic acid. Samples were taken at specific intervals and dissolved in 100 ml of chloroform containing 1% acetic acid. A further appropriate dilution was made, and the absorbance of the dilution was read[4] at 280 nm for aspirin and at 310 nm for salicylic acid.

[1] Merck and Co., Rahway, N.J.

[2] PVO International Inc., Boonton, N.J.
[3] J. T. Baker Chemical Co., Phillipsburg, N.J.
[4] Cary model 118 spectrophotometer.

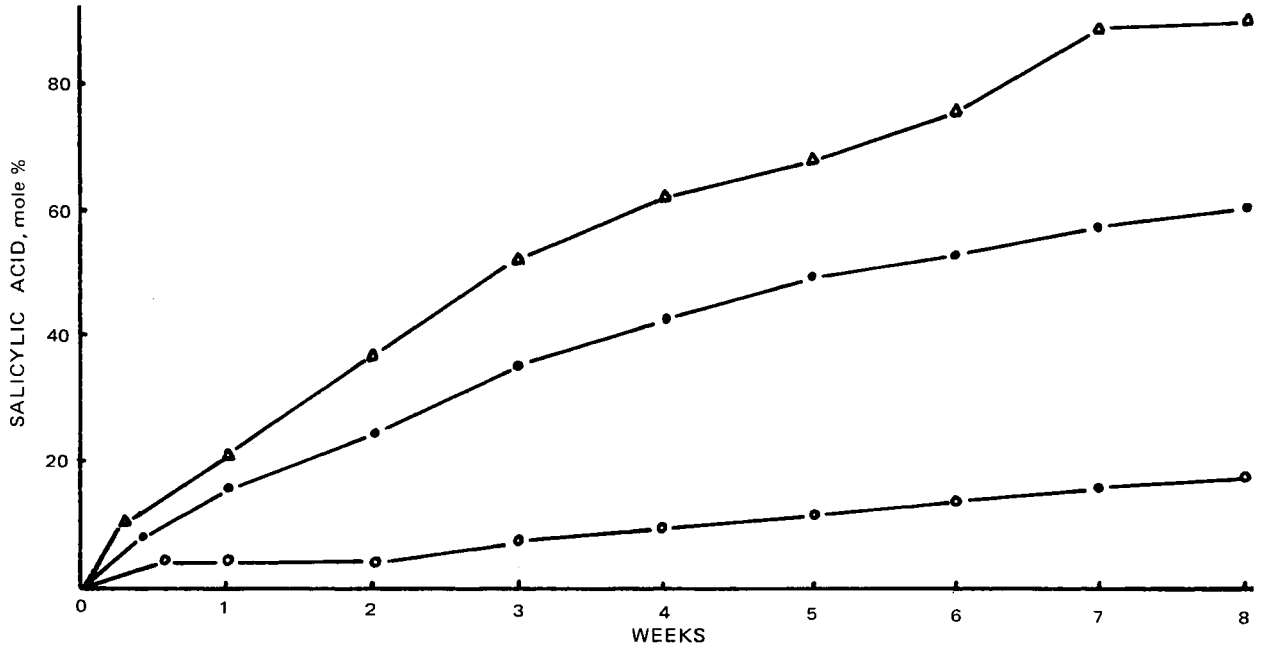


**Figure 3**—*Appearance of salicylic acid* versus *time for aspirin suspensions in polyglycerol esters at 45°. Key:* △, *decaglycerol tetraoleate;* ●, *decaglycerol decaoleate; and* ○, *decaglycerol octaoleate.*

Standard curves were prepared for aspirin and salicylic acid at these wavelengths. The quantification of aspirin and salicylic acid was based on the standard method of simultaneous spectrophotometric determinations.

**Solubility Determination**—The solubility of aspirin in each liquid was determined at 26° by adding 1 g of drug to 5 ml of vehicle and mixing with a mechanical stirrer for 24 hr. The mixture was then transferred to a test tube and centrifuged at 5000 rpm for 30 min. Three drops of the supernate were transferred to a 10-ml volumetric flask and accurately weighed.

The sample was dissolved by adding a 1% solution of acetic acid in chloroform, and the absorbance of a diluted sample of this solution was read at 280 and 310 nm. Three samples were used in each determination. The concentration of aspirin was determined by the standard method of simultaneous spectrophotometric determinations.

## RESULTS AND DISCUSSION

The overall profiles of aspirin degradation in decaglycerol tetraoleate, decaglycerol octaoleate, and decaglycerol decaoleate at 4, 26, and 45° are shown in Figs. 1–3. Aspirin demonstrated the least stability in decaglycerol tetraoleate at all temperatures studied. Decaglycerol tetraoleate had the highest hydroxyl value (210–250) of the polyglycerol esters studied.

A previous publication (5) reported that the decomposition of aspirin in polyethylene glycols was due, at least in part, to a transesterification reaction and that the blocking of free hydroxyl groups retarded aspirin decomposition (1). Therefore, it appears that the lowest stability of aspirin in decaglycerol tetraoleate could be due to the highest hydroxyl value possessed by this vehicle. Moreover, decaglycerol tetraoleate is dispersible in water, while the octaoleate and the decaoleate are immiscible (6). Therefore, water that might have contaminated the aspirin powder or the decaglycerol tetraoleate during sample preparation would be distributed throughout the vehicle to react with aspirin particles.

Aspirin in decaglycerol octaoleate showed no detectable decomposition at 4°, about 1% at 26°, and 18% at 45° after 8 weeks. Although decaglycerol octaoleate has a higher hydroxyl value than that of decaglycerol decaoleate, aspirin was more stable in the former vehicle. This finding could be explained on the basis that the degradation-enhancing effect due to the higher hydroxyl value would be outweighed by the stabilizing effect due to the higher viscosity possessed by decaglycerol octaoleate. This higher viscosity would hinder diffusion of any moisture that might have contaminated the aspirin powder during sample preparation and, therefore, retard the degradation reaction. The solubility of aspirin in the vehicles was very similar for all three liquids and does not explain the differences in stability.

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