Stability of Hydrocortisone in Polyethylene Glycol Ointment Base

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Abstract □ The degradation of 1% hydrocortisone in polyethylene glycol ointment USP was investigated. The stability tests were conducted on two different batches of ointments at 23, 45, and 60° for about 4 months. Decomposition occurred at the C-17 side chain as assayed by the blue tetrazolium reaction, as well as in ring A as determined by UV spectroscopy. The decomposition of the C-17 side chain was much faster (average half-life of 186 days at 60°) as compared with ring A (average half-life of 505 days at 60°). Decomposition of the C-17 chain appeared to be first order but was zero order for ring A. The energy of activation was determined to be 9.7 kcal/mole. Based on these studies, the shelflife for a 1% hydrocortisone ointment in polyethylene glycol base is suggested to be about 6 months. The shelflife may be extended to about 9 months with the addition of a 5% excess of the active ingredient at the time of manufacture.

Keyphrases □ Hydrocortisone ointment—stability, shelflife, polyethylene glycol base □ Polyethylene glycol base—stability, shelflife of hydrocortisone ointment □ Ointment, hydrocortisone—stability, shelflife, polyethylene glycol base

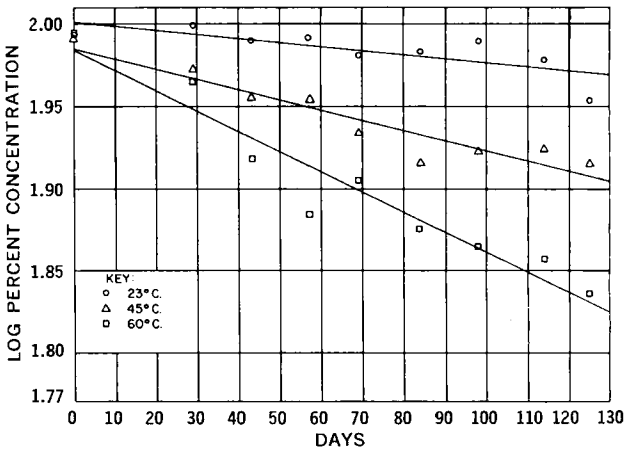


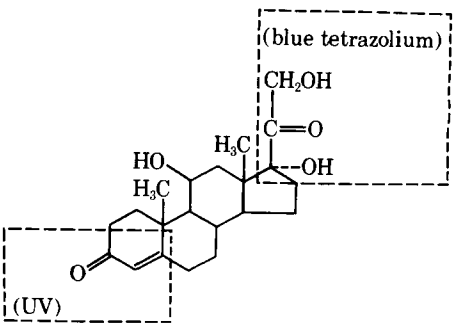
Figure 1—*First-order kinetic plot of hydrocortisone (Sample 1) at various temperatures, showing decomposition of the C-17 side chain.*

A study in this laboratory evaluated the diffusion of hydrocortisone from a series of commercially available bases[1], water, and polyethylene glycol. The maximum quantity of hydrocortisone diffused from the polyethylene glycol ointment base (1). It appears that no company is marketing hydrocortisone ointment in a polyethylene glycol base, and this may be due to the instability of hydrocortisone in such a base. Degradation of the C-17 dihydroxyacetone side chain of certain corticosteroids has been studied under various conditions for many years. A base-catalyzed anaerobic degradation of cortisone was reported (2). Deoxycorticosterone acetate and 21-acetoxypregn-5-en-3β-ol-20-one were converted by ethanolic potassium hydroxide in the presence of air to the corresponding ethianic acids (3); similar results using 6β,21-diacetoxypregn-4-ene-3,20-dione also were found (4).

These conversions were confirmed (5) by investigations into the kinetics of the base-catalyzed degradation of prednisolone, which suggested that it was a complex reaction resulting from at least three parallel pseudo-first-order reactions. The degradation of hydrocortisone hemisuccinate at 70° was studied over a narrow pH range and found to be a first-order, consecutive reaction (6).

The stability of cortisone and hydrocortisone was investigated (7) using UV spectrophotometry and phenylhydrazine methods to detect alterations in ring A and blue tetrazolium to detect deterioration of the C-17 side chain; both cortisone and hydrocortisone were stable and underwent no change on heating at 100° for 1 hr or at 130° for 2 hr. The stability of cortisone and hydrocortisone at various pH values was also studied; heating these steroids at pH 9 caused only slight decomposition (7).

Various factors influencing the stability of corticosteroids in aqueous suspensions and solutions were investigated (8), and the effects of some solid buffering agents on the stability of prednisolone were determined. Corticosteroids similar to prednisolone should not be exposed to materials capable of producing an elevated pH during formulation according to this report (8). Some factors influencing the rate of disappearance of prednisolone from aqueous solution were investigated, and decomposition was found to be markedly accelerated by contaminants in the buffer reagents, with the evidence strongly indicating that the contaminants were trace metals (9). A mix-



Scheme I

[1] Acid Mantel, Dome Laboratories, West Haven, Conn.; Aquaphor, Duke Laboratories, S. Norwalk, Conn.; cold cream, The Upjohn Co., Kalamazoo, Mich.; HEB, Barnes-Hind Pharmaceuticals Inc., Sunnyvale, Calif.; hydrophilic petrolatum, Emerson Laboratories, Dallas, Tex.; petrolatum, McKesson Laboratories, Bridgeport, Conn.; and vanishing cream, Neobase, Burroughs Wellcome and Co., Triangle Park, N.C.

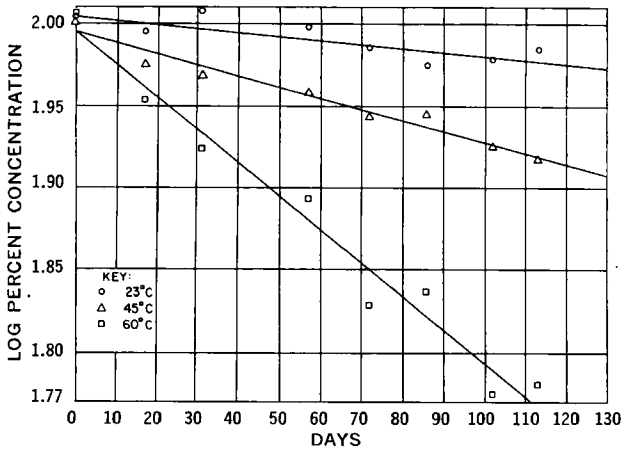


Figure 2—*First-order kinetic plot of hydrocortisone (Sample 2) at various temperatures, showing decomposition of the C-17 side chain.*

ture with a pH of <3.5 or >8.0 promoted the hydrolysis of hydrocortisone sodium succinate (10).

The stability of prednisolone in an organic medium containing 50% camphor, 25% *m*-cresyl acetate, and 25% *p*-chlorophenol was studied (11). This medium containing 1% prednisolone has been used as a pulp-capping agent to reduce thermal sensitivity in dental restorations. Due to the slightly acidic nature of the vehicle, a shelflife of 2–5 years was predicted for this product (11). Prednisolone in anhydrous form was observed to be stable in liquid paraffin but not in water (12).

The purpose of this study was to investigate the stability of hydrocortisone in a polyethylene glycol base.

EXPERIMENTAL[2]

Chemicals and Reagents—All chemicals and reagents were USP, NF, or ACS grade except for the 10% tetramethylammonium hydroxide solution[3]. All were used without further purification.

Ointment Preparation—Two separate batches of ointments were prepared by mechanically incorporating 1% hydrocortisone into polyethylene glycol ointment USP (1) using the trituration method.

Assay Procedures—After the initial assay, each ointment was divided into three parts and stored at 23 ± 2, 45 ± 2, and 60 ± 2°.

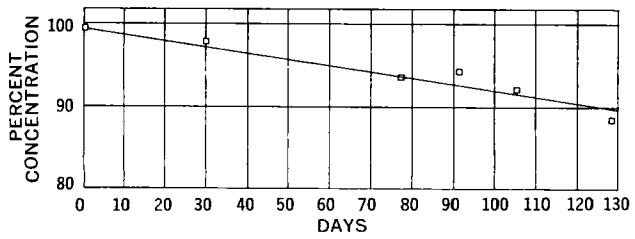


Figure 3—*Zero-order kinetic plot of hydrocortisone (Sample 1) at 60°, showing decomposition of ring A.*

[2] Ointment samples were incubated in ovens manufactured by National *Appliance Co., model 320,* serial FSR-6. A Beckman DB-GT grating spectrophotometer was used to measure all absorbance values at 247 nm. A Bausch & Lomb Spectronic 20 was used to measure all absorbance values at 525 nm. A Beckman IR-8 spectrophotometer was used for all IR determinations.

[3] Eastman Kodak.

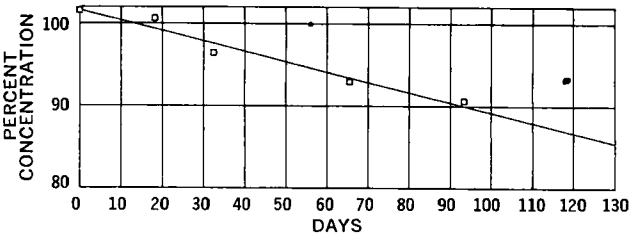


Figure 4—*Zero-order kinetic plot of hydrocortisone (Sample 2) at 60°, showing decomposition of ring A.*

At specified intervals, samples were taken and assayed. The ointment bases (without hydrocortisone) were assayed at the same time. To follow the decomposition of hydrocortisone, two methods of assay were used.

Blue Tetrazolium Assay Method for Detection of Degradation of C-17 Side Chain (Scheme I)—All blue tetrazolium assays were performed using the USP XVII (13) method for total steroids.

UV Spectrophotometric Method for Alterations in Ring A (Scheme I)—For the standard solution, weigh exactly 100.0 mg hydrocortisone USP and dissolve in sufficient ethanol to make 100.0 ml. Dilute 2.0 ml of this solution to 100.0 ml with distilled water.

For the assay preparation, dissolve exactly 200.0 mg of each ointment in enough distilled water to make 100.0 ml of the solution.

For the assay procedure, concomitantly determine the absorbances of the standard and assay solutions at 247 nm (the wavelength of maximum absorbance) in a suitable spectrophotometer, using distilled water as the blank.

Calculations—For both methods of assay, results were calculated by comparing absorbance readings of the samples with the standard reading. The assay results were treated theoretically and are presented in Figs. 1–5.

THEORETICAL

The order of reactions was determined graphically (Figs. 1–4). Before plotting, the regression analysis was conducted on the data to determine the best possible order of reaction.

The UV data (decomposition of ring A) at 23 and 45° were not treated graphically since the samples were satisfactory (loss of potency was less than 10%).

The energy of activation (E_a) on data from the blue tetrazolium assay was determined using the Arrhenius equation (Eq. 1):

$$\log \frac{K_2}{K_1} = \frac{E_a}{2.303R} \frac{(T_2 - T_1)}{T_2 T_1} \qquad \text{(Eq. 1)}$$

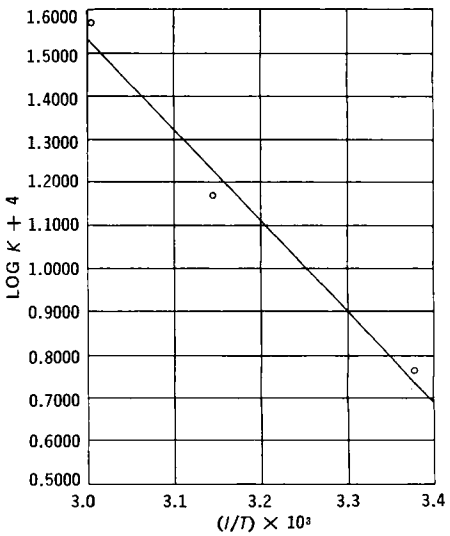
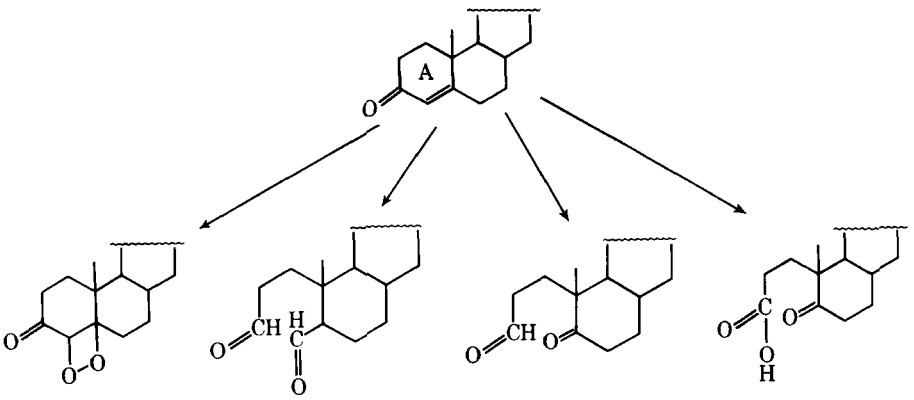


Figure 5—*Arrhenius plot of hydrocortisone using average* K *values from Samples 1 and 2 (see Figs. 1 and 2).*



Scheme II

The average K values (decomposition of C-17 side chain) for Samples 1 and 2 were used for the Arrhenius plot (Fig. 5). For the best line, the method of least squares was used. The energy of activation was determined to be 9.7 kcal/mole.

The average K value at room temperature (Figs. 1 and 2) was used to estimate the stability of the ointment under "shelf conditions" using Eq. 2:

$$t = \frac{2.303}{K} \log \frac{c_i}{c_t} \qquad \text{(Eq. 2)}$$

where t is time in days, c_i is the initial concentration, and c_t is the concentration at time t.

When substituting the data from the blue tetrazolium assay (decomposition of C-17 side chain) at 23° (average K = 5.78×10^{-4}/day) and using 100 and 90% for c_i and c_t, respectively, the expiration date is approximately 182 days. By increasing c_i to 105% (*i.e.*, by adding 5% excess), the shelflife is approximately 267 days or about 9 months.

DISCUSSION

Alterations in the hydrocortisone molecule apparently occurred at both ring A and the C-17 side chain (Figs. 1–4). The degradation of the dihydroxyacetone moiety was greater and of greater concern in stability studies. The degradation of the C-17 side chain has been extensively investigated and was well documented previously.

The degradation of the C-17 side chain appears to be first order. Although slow (the average half-life was 505 days at 60° *versus* 186 days using the blue tetrazolium assay), alterations in ring A were noticed (Figs. 3 and 4). The order of reaction for the degradation of ring A appears to be zero (see *Theoretical* and Figs. 3 and 4). To determine the scheme of degradation of ring A, the samples were inspected by IR spectroscopy. Except for the area between 1500 and 2000 cm^{-1}, the field was overshadowed by the base vehicle. A consistent trend was a progressive increase in absorption at 1715 cm^{-1} and diminution at 1635 cm^{-1} as samples were viewed from 23 to 45 to 60°. One possibility for the degradation of ring A is shown in Scheme II.

The activation energy of hydrocortisone was determined to be about 9.7 kcal/mole (see *Theoretical*).

Finally, the shelflife of the ointment at room temperature appears to be about 6 months (see *Theoretical*). Nevertheless, by adding an excess of 5% at the time of manufacture, hydrocortisone ointment, if prepared in polyethylene glycol ointment USP, should be reasonably stable for about 9 months. This length of time hardly justifies manufacture on a commercial basis considering the combined lag times involved in warehousing and shipping from the manufacturer through a wholesaler to a dispensing pharmacy and, ultimately, to the patient.

Although it has a limited shelflife, conditions at some hospitals and pharmacies may justify the manufacture of this product for their own use.

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