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THE EFFECT OF SOME FORMULATION ADJUNCTS ON THE STABILITY OF HYDROCORTISONE

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ABSTRACT

The stability of hydrocortisone in aqueous solutions containing (v/v) either 20% ethyl alcohol, 50% glycerin or 50% propylene glycol with or without other excipients was investigated. The study was conducted at higher temperatures (50° or 60°) and for some solutions at room temperature also. The effect of four antioxidants (ascorbic acid, L-cysteine hydrochloride monohydrate, propyl gallate, and sodium bisulfite), two surface active agents (polysorbate 80, and sodium lauryl sufate) and a thickening agent (hydroxypropyl methylcellulose) were also investigated.

At a higher temperature (60°) propylene glycol proved to be better than glycerin for the stability of hydrocortisone. None of the antioxidants improved the stability. Cysteine hydrochloride and sodium lauryl sulfate had an adverse effect on the stability of hydrocortisone. Propylene glycol and polysorbate 80 may be

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used for the preparation of stable hydrocortisone solutions provided that the pH is acidic (3.5).

BACKGROUND

Hydrocortisone (I) is widely used in topical dosage forms such as creams, lotions, and ointments. Many different types of vehicles are being used by the pharmaceutical manufacturers to incorporate hydrocortisone. Some of them may be using antioxidants and surfactants to improve the stability of I. Comprehensive studies on these commercial products are trade secrets, therefore, very little information is available in the literature.

The available literature on the stability of I and other similar corticosteroids was reviewed by the author[1]. Some previous studies may not be accurate because of the lack of a stability-indicating assay method. The effect of surfactants on the stability of drugs has been reported[2].

The purpose of this study was to determine the effect of some antioxidants (ascorbic acid, cysteine hydrochloride, and sodium bisulfite), glycerin, propylene glycol, two surfactants (sodium lauryl sulfate, and polysorbate 80) and a thickening agent (hydroxypropyl methylcellulose) on the stability of hydrocortisone. The study was conducted using stability-indicating assay methods [1,3] by high-perofrmance liquid chromatography (HPLC).

MATERIALS AND METHODS

Chemicals and Reagents: All chemicals and reagents were U.S.P., N.F. or ACS grade and used without further purification. Ascorbic acid[4], L-cysteine hydrochloride monohydrate[5], sodium lauryl sufate[6],

hydroxypropyl methycellulose[7], plysorbate 80[8], and propyl gallate[8]. were used as received.

Apparatus: The same as reported previously[3] except that a multiple wavelength detector[9] which was set at 254 nm (sensitivity 0.04) was used. Two columns as reported previously [1,3] were used. The column from reference 3 was used only for solution 4 (see Table 1) due to interference from propyl gallate in the assay procedure. All other solutions were assayed using previously reported method[1].

Chromatographic Conditions: For all solutions except 4, the solvent was 0.02 M KH_2PO_4 with 20% (v/v) of methanol in water. Flow rate was 2.0 ml/min and chart speed was 30.5 cm/hr. The temperature was ambient and the detector was set as 254 nm. The column was semipolar, consisted of monomolecular layer of cyanopropylsilane permanently bonded to silica (30 cm x 4 i.d.). For solution 4, the column was nonpolar, consisted of monomolecular layer of octadecyltrichlorosilane permanently bonded to silica (30 cm x 4 mm i.d.). The solvent was 0.01 M KH_2PO_4 with 50% (v/v) methanol in water. Flow rate was 1.6 ml/min and the rest of the conditions were the same as described above.

Preparation of Assay Solutions: All of the solutions studied are listed in Table 1 with their methods of preparations. After zero-day assays, solutions 1 to 8 were divided into two equal parts. One part was stored at room temperature (24°) and the other part either at 60° (solutions 1-4) or at 50° (solutions 5-8). Solutions 9-12 were not divided and stored only at 50°. Before analysis, all solutions were allowed to cool to room temperature, and an

appropriate volume was diluted with water to a concentration of 20.0 μg/ml of hydrocortisone.

Standard Solutions: Standard solutions were prepared fresh at the time of analysis by diluting a stock solution of hydrocortisone in ethyl alcohol (1.0 mg/ml). Water was used for dilution to obtain a solution containing 20 μg/ml of I. The stock solution in ethyl alcohol was stable for at least 18 months.

Assay Procedure: The assay procedure was the same as reported previously[3] except that peak heights were used to calculate the results. Preliminary investigations indicated that peak heights in addition to peak areas were related to the concentrations of hydrocortisone (range tested 0.2-0.5 μg). The results are presented in Tables 2-3 and Figures 1-2.

RESULTS AND DISCUSSION

The results indicate (Tables 2 and 3) that the effect of antioxidants, ascorbic acid, cysteine hydrochloride, propyl gallate, and sodium bisulfite on the stability of hydrocortisone is negligible. In all of the solutions containing antioxidant(s), results were about the same (within experimental errors) as those for solutions without them except that cysteine hydrochloride appeared to have an adverse effect on the stability of hydrocortisone (Table 3, solution 6 and Figure 3C). This was especially true after 335 days of storage at 50°. The chromatogram (Figure 3C) had additional peaks from products of decomposition as compared with others in Figure 3.

It is well known[10] that cysteine oxidizes to cystine according to Scheme I.

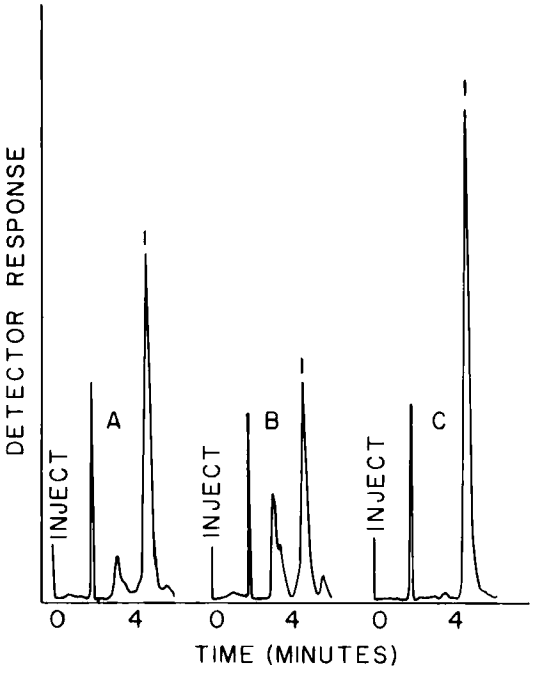


FIGURE 1

Sample chromatograms. Peak 1 is from hydrocortisone and all others from its decomposition products. Chromatogram A is from a standard solution of I. Chromatograms B and C are from 21 days old solutions of I (storage temperature 60°) in 50% propylene glycol and 50% glycerin, respectively.

It appears that the oxygen of air oxidized cysteine to cystine and further to some other unidentified products. The oxidation of cysteine was confirmed by mixing 5.0 ml of the appropriate solution (water for blank) with 0.5 ml of sodium nitroferricyanide solution (0.5% in approximately 0.1N HCl in water) and then adding 1.0 ml of approximately 1N NaOH solution in water. On testing the freshly made solution identical to 6 and 8 (Table 1) a red color (due to cysteine) was obtained. Others (solutions 5 and 7) gave a yellow color (same as for the blank). On substituting cystine for

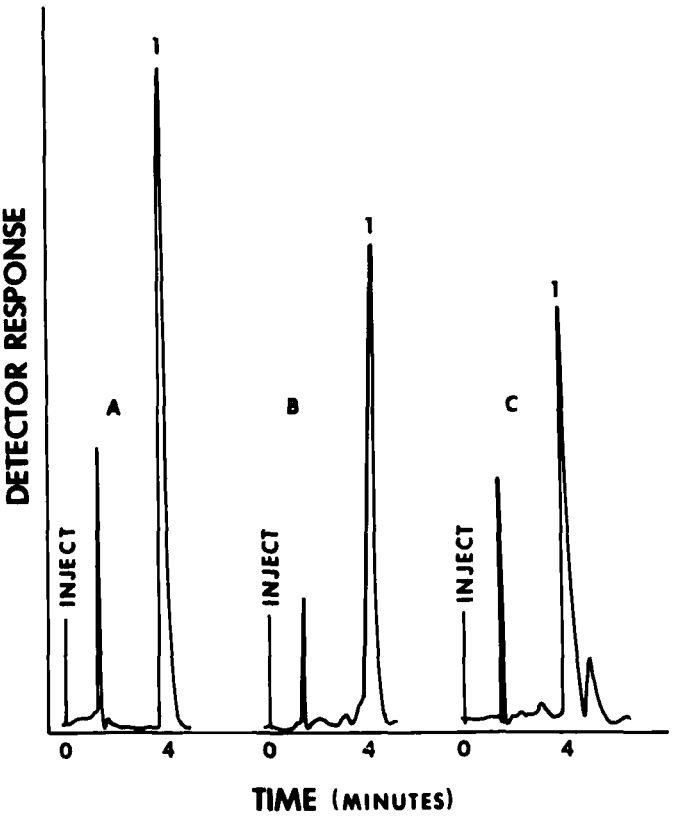


FIGURE 2

Sample chromatograms. A to C are from solutions 10, 11, and 12 (see Table 1), respectively, after 91 days of storage at 50°. Peak 1 is from hydrocortisone and all others are from the decomposition products.

cysteine in a fresh solution identical to 6, the color was also yellow. The test developed is very sensitive. The test was repeated on 405 days old solutions 5 to 8 (of both temperatures), all gave a yellow color. The yellow color was darker only for two solutions (6 and 8) which were stored at 50°. The dark yellow color may be an indication of further decomposition of cysteine. Since the reacting color obtained from solutions 6 and 8 when

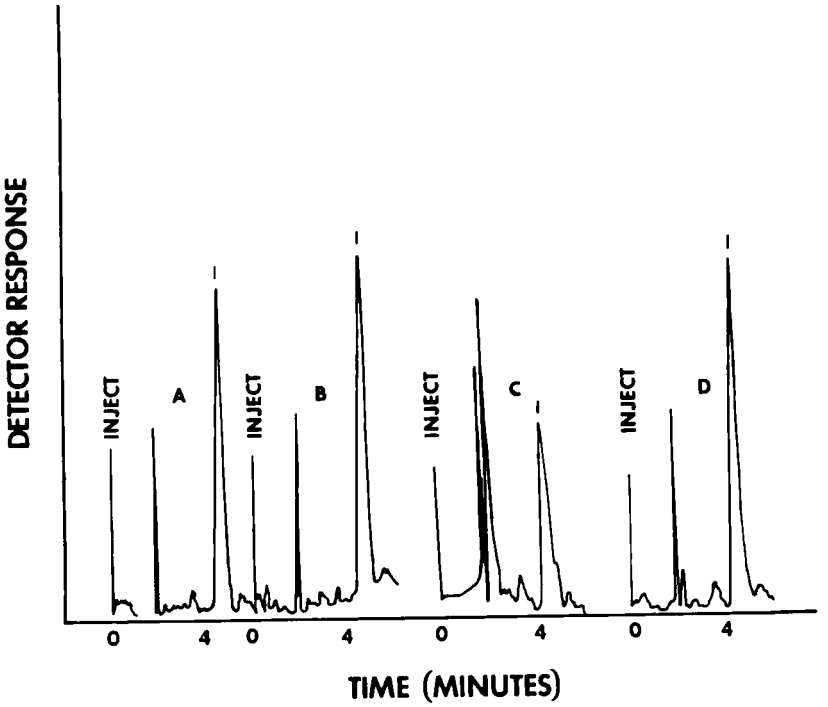
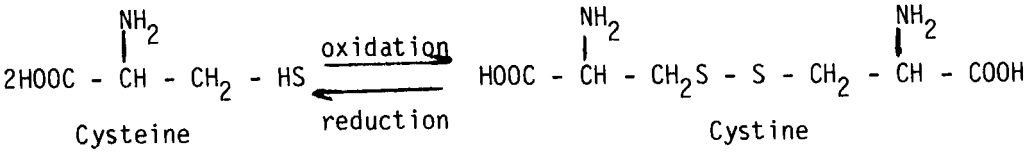


FIGURE 3

Sample Chromatograms. The chromatograms A to D are from solutions 5, 7, 6, and 8 (see Table 1) respectively after 335 days of storage at 50°. Peak 1 is from hydrocortisone. All others from the decomposition products.



Scheme I

TABLE 1

List of Solutions Studied

Solution #	Concentration of I (mg/ml)	Other Ingredients	Method of Preparation
1	0.5	Glycerin 50% by Volume	Solutions 1-4 were prepared by dissolving I in glycerin or propylene glycol with the aid of gentle heat, then bringing to volume with an aqueous phosphate buffer (0.1 M containing KH_2PO_4 and H_3PO_4) of pH 3.5.
2	0.5	Propylene Glycol 50% by volume	
3	0.5	As in #2 and 0.1% of Ascorbic Acid	
4	0.5	As in #2 and 0.02% of Propyl Gallate	
5	0.5	As in #2	Solutions 5-8 were prepared using the above method except that no heat was used to dissolve hydrocortisone. Hydrocortisone dissolved in propylene glycol in about two hours.
6	0.5	As in #2 and 0.02% of Cysteine Hydrochloride Monohydrate	
7	0.5	As in #2 and 0.05% of Sodium Bisulfite	
8	0.5	As in #2 and Both Cysteine Hydrochloride (0.02%) and Sodium Bisulfite (0.05%)	
9	0.2	Ethyl Alcohol 20% by Volume	Solutions 9-12 were prepared by mixing 0.1% alcoholic solution of hydrocortisone with water. The additional ingredient in each solution was dissolved in water before mixing with the alcoholic solution of I.
10	0.2	As in #9 and 0.5% of Hydroxypropyl Methycellulose	
11	0.2	As in #9 and 0.5% of Sodium Lauryl Sulfate	
12	0.2	As in #9 and 0.5% of Polysorbate 80 by Volume	

stored at room temperature was the same as of the blank, therefore, the decomposition of cysteine at room temperature did not appear to have proceeded as far as at higher temperature (for 405 days assay results see Tables 2 and 3).

The adverse effect of cysteine at a higher temperature seems to be due to these products of decomposition. Moreover, since cysteine did not exert an adverse effect until after 203 days (solution 6, Table 3), it could not have been its direct effect.

However, the oxidation of I by decomposition products of cysteine was prevented in solution 8 (Table 3 and Figure 3D) by sodium bisulfite, an antioxidant. A similar scheme explaining the effect of sodium metabisulfite on epinephrine has already been reported[11].

Furthermore, the dark yellow reaction color obtained at a higher temperature could not have been from the products of decomposition of I. If so, the reaction color should have been the same for solution 5 which has decomposed as much as solution 8. Of course neither sodium bisulfite nor its combination with cysteine improve the stability of hydrocortisone.

The solutions containing ascorbic acid (Tables 2 and 3, solution 3) had discolored both at 60° and at room temperature. Apparently, ascorbic acid got oxidized as confirmed by iodiometric assay method. The change in the potency of hydrocortisone was about the same as for the solution without ascorbic acid (Tables 2 and 3, solution 2). It can be assumed that hydrocortisone is not susceptible to oxidation from oxygen of the air in buffered solutions (pH 3.5).

TABLE 2

Assay Results of Samples Stored at Room Temperature

Solution # (See Table 1)	Results After (Days) Based on 100% at Zero Day 109	224	356
1	96.2	95.9	93.9
2	96.4	96.1	96.2
3	96.1[a]	--	95.8
4	96.3	--	95.7

	88	203	335	405
5	99.4	100.0	99.5	98.2
6	99.6	99.8	99.8	97.1
7	99.8	100.0	99.8	97.3
8	98.2	100.0	99.5	97.1

[a]Sample had discolored to a light yellow color in less than 40 days. This was determined to be due to oxidation of Vitamin C.

Both at 60° and at room temperature, propylene glycol (50% by volume) proved to be a better vehicle (Tables 2 and 3) than glycerin (50% by volume). The percent of decomposition in 21 days at 60° was 44.5% for the solution containing glycerin and only 29.5% for the solution containing propylene glycol. This is probably due to the difference in the polarities of the solvents since hydrocortisone is known to be more stable in nonpolar solvents. The dielectric constants of glycerin and propylene glycol are 43 and 32 respectively, at 20°.

TABLE 3

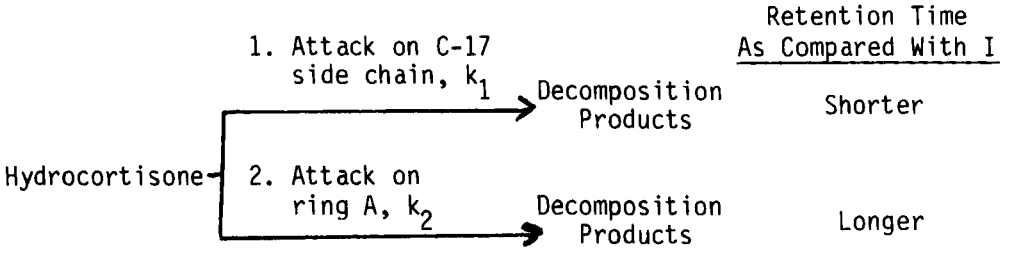
Assay Results of Samples Stored at High Temperatures[a]

Solution # (See Table 1)	Results After (Days) Based on 100% at Zero Day			
	21	Storage Temperature 60°		
1	55.5	After these readings, studies at 60° were discontinued due to very fast decomposition of hydrocortisone.		
2	70.5			
3	72.8[b]			
4	70.5			
	88	203	335	405
		Storage Temperature 50°		
5	85.8	68.8	49.1	41.9
6	84.9	61.1	25.9	19.7
7	84.1	68.9	49.6	42.8
8	84.4	71.4	49.9	41.1
	91	219		
9	67.3[c]	33.8		
10	68.8[c]	34.2		
11	40.4[c]	15.1		
12	89.7[c]	78.1		

[a]Solutions 1-4 were stored at 60°; all others at 50°.
[b]Sample had discolored to a light yellow color due to oxidation of vitamin C.
[c]pH values of solutions 9-11 were 6.6 and 3.4 for solution 12.

The decomposition products in the solution containing propylene glycol and glycerin at a higher temperature (60°) gave additional peaks both before and after the hydrocortisone peak. In 21 days, the decomposition products in solutions containing glycerin or propylene glycol had similar peaks (Figure 1). The peak heights (before and after the hydrocortisone peak) from the decomposition products in the solution containing glycerin varied (Figure 1C) from peak heights of solution in propylene glycol (Figure 1B). The peak (after the hydrocortisone peak) was much higher for the solution containing glycerin versus the solution containing propylene glycol. This indicates that the rates of the two parallel paths (see below) of decomposition reported earlier[1] are different for glycerin and propylene glycol, which is not unusual.

Sodium lauryl sulfate appears to have an adverse effect on the stability of hydrocortisone (Table 3, solution 11). The adverse effect of sodium lauryl sulfate (an anionic type surfactant) is not understandable since it is reported[2] to have a stabilizing effect on esters susceptible to base catalysis. Apparently, this is not true for nonesters such as hydrocortisone.



Scheme II (For further details, see Ref. 1)

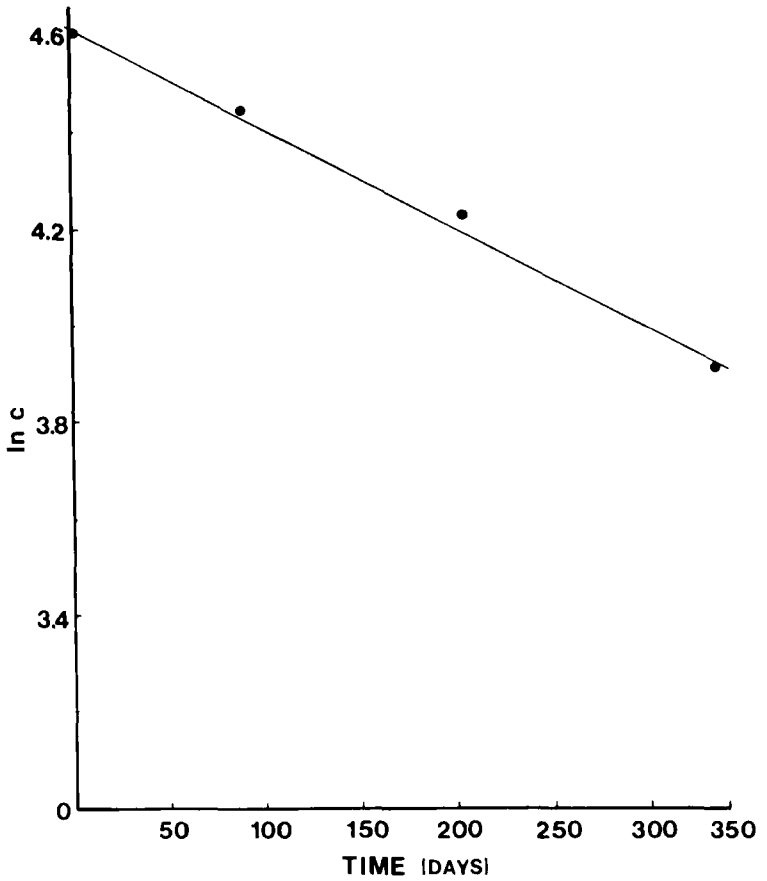


FIGURE 4

First-order plot of ln C versus time when solution number 5 (see Table 1) was stored at 50°.

Polysorbate 80 had a stabilizing effect on hydrocortisone (Figure 2 and solution 12 in Table 3). This effect is probably due to a change in the pH of the solution. The final pH value of solutions 9-11 was 6.6 versus 3.4 for the solution containing polysorbate 80. The effect of pH on the stability of hydrocortisone was reported earlier by the author[1]. The actual mechanism of action of polysorbate 80 was not investigated further.

Extensive studies on the kinetics of corticosteroids have already been reported. The literature was reviewed in an earlier report by the author[1]. Hydrocortisone decomposes according to first order (two parallel routes according to Scheme II). In the present investigations, the decomposition of I at room temperature was almost nil, hence, mathematical treatment was not possible. At 50°, data for solution 5 (see Table 1) was plotted (Figure 4) and K value was determined to be approximately 0.00215 day^{-1}. Although Figure 4 was drawn before 405 days data was obtained, the 405 days result using the above K value (0.00215 day^{-1}) was in agreement and would also fit on straight line of Figure 4.

For solution 6, 335 days data did not fit on the straight line. This is probably due to a faster rate of decomposition due to an adverse effect of cysteine hydrochloride or its products of decomposition on the reaction after 203 days of storage.

Assuming first order reaction, the K value for solution containing polysorbate 80 whose pH was 3.4 (similar to solutions containing propylene glycol) was approximately 0.001082 day^{-1}. This was calculated using the two available potencies (Table 3) of 89.7 and 78.1 percent after 91 and 219 days of storage at 50°.

Briefly, it can be stated that hydrocortisone is very stable at room temperature in an aqueous buffered solution (pH 3.5) containing 50% by volume of propylene glycol without the presence of antioxidant(s). If required, polysorbate 80 may be added as a surface active agent without an adverse effect on the stability of hydrocortisone.

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