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STABILITY AND DISSOLUTION RATES OF CORTICOSTEROIDS IN POLYETHYLENE GLYCOL SOLID DISPERSIONS

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ABSTRACT

A study has been made to examine the stability and dissolution rates of prednisolone, prednisone and hydrocortisone formulated as solid dispersions in polyethylene glycols. Of the five PEG samples used, three enhanced the chemical instability of the steroids; the effect being dependent on the PEG sample and storage conditions of the solid dispersions. Dissolution rates of the steroids were relatively fast from the solid dispersions and showed no significant changes upon storage. Using two methods of analysis (direct UV spectrophotometry and the USP blue tetrazolium method), it is concluded that the chemical instability of the

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steroids in some PEG samples was due to alterations in the dihydroxy acetone side chain. One of the decomposition products found appeared to be an acidic compound resulting from oxidation of the C_{17} side chain. The oxidation is presumably accelerated by a peroxide impurity in PEG samples.

INTRODUCTION

Polyethylene glycols (PEG) are employed in pharmacy for a number of purposes. They are used as solvents, water-soluble ointment and suppository bases, in tablets as lubricant and coating materials and as carriers for insoluble drugs. Solid dispersions using PEG 4000 and 6000 were used to increase the dissolution rates of cardiac glycosides and steroids including prednisolone acetate (1) and hydrocortisone (2). Being polymeric in nature, PEG samples were found to contain varying levels of ethylene oxide monomer as an impurity. Boon and Mace (3) determined the ethylene oxide contents in some batches of PEG. The analyses revealed that all the batches examined contained ethylene oxide from 0.01 to 0.2%. The loss of tripelennamine in PEG due to quaternization was associated with batches containing more than 0.1% ethylene oxide.

Since PEGs are polyethers, the presence of peroxides as impurities has been reported (4,5). The deterioration

of penicillin and bacitracin (6), chloramphenicol (7) and an experimental topical corticosteroid (8) was attributable to the presence of peroxides in PEG samples contained the above drugs. In one report (8), it was stated that the level of peroxide in the PEG samples was increased by ageing. A recent study (9) revealed that prednisone tablets, granulated with a batch of PEG 6000, exhibited poor chemical stability upon storage. The objective of the present work has been to study the chemical stability of three corticosteroids formulated as solid dispersions using five PEG samples obtained from various sources. The changes in the dissolution rates of the steroids from the aged formulations was also studied.

MATERIALS

Three batches of PEG 4000 and two batches of PEG 6000 were obtained from various sources. The pH values of 3% w/v solutions of the samples ranged from 5.6 to 6.1 and the melting points ranged from 60 to 70°C. Prednisone, prednisolone and hydrocortisone were of B.P. grade. Blue tetrazolium and tetramethylammonium hydroxide (as 25% solution) were of USP quality. Chloroform and ethanol were of A.R. grade.

METHODS

1. Gas Chromatographic Examination of PEG Samples -

A Pye Unicam PU 4500 GC fitted with flame ionization detectors was used. The conditions were: Injector temperature 150°, detector temperature 150°, column oven 130°, column: 1.5 m x 4 mm chromosorb 102, carrier gas: nitrogen 45 ml/min, recorder: PM 8251 chart speed 1 cm/sec. The PEG sample was dissolved in dichloromethane and quantitative comparison was made of the peak heights of the impurities obtained from the five samples.

2. Preparation of the Solid Dispersions - All the solid dispersions were prepared in a ratio of 1:99 (drug:PEG). Two methods were used:

(i) Solvent Method: A chloroformic solution of the drug and PEG was evaporated at room temperature under vacuum using a rotary evaporator. The residue was dried over phosphorus pentoxide for two days, pulverized and sieved. The fraction having particle diameter 100-125 microns was used for dissolution rate and stability testings.

(ii) Fusion Method: A blend of the drug and PEG was heated on a water bath till complete melting. The molten mass was stirred at room temperature till congealed. The product was dried over phosphorus pentoxide for two days and the mass was pulverized and sieved as under 'Solvent Method'.

3. Storage of the Formulations - The solid dispersions were kept in tightly closed amber glass bottles at either 22±1° or 40±0.2°. At suitable time intervals, samples were examined for their dissolution rates and assayed for drug contents by the two methods mentioned under 'Stability Testing'. At least duplicate runs were made for each sample and the results averaged.

4. Dissolution Rate Testing - A modified USP disintegration apparatus (10) was used for determination of dissolution rates. The dissolution medium consisted of 500 ml of water maintained at 37±0.1°. A sample of the solid dispersion, equivalent to 5 mg of the steroid, was spread over the center of the dissolution medium; the spreading was effected by the movement of the rotating glass spiral. At specified time intervals, a 5 ml-aliquot was withdrawn, filtered and assayed directly by UV spectrophotometry at the λ max of the drugs (244 - 248 nm). Contribution due to PEG was negligible.

5. Stability Testing - Two methods of analysis were used to monitor the stability of the steroids in the solid dispersions.

(i) Direct UV spectrophotometry: This was used to detect possible changes in the conjugated structure in Ring A of the steroid. The sample (0.1 g) was dissolved in ethanol (100 ml) and the absorbance was measured at the λ max of the steroid (240-244 nm).

(ii) The USP colorimetric blue tetrazolium method: This method enables the detection of decomposition in the dihydroxy acetone side chain at C_{17}. The presence of PEG in the sample did not interfere with the measurements. The sample was assayed following the USP procedure (11).

6. TLC Examination - Separation of the decomposition products in the solid dispersions was made by TLC using silica gel G 254F-coated plates. Two solvent systems were used; System I: Methylene chloride 100, dioxane 50 and water 50, System II: Chloroform:methanol 90:10. The location of the spots were revealed under the UV lamp. An artificially-decomposed prednisolone by 30 volume hydrogen peroxide (treated for 3 hr at 40°) was spotted for comparison.

7. Estimation of an Acidic Decomposition Product in the Solid Dispersions - One of the decomposition products obtained upon oxidation of prednisolone, is the corresponding etianic acid (12). To estimate its content in the solid dispersions, a procedure based on the work of Guttman and Meister (12) was followed. A weight of the sample (0.1 g) was dissolved in water (30 ml) containing sodium carbonate (0.5 g). Chloroform (3 x 10 ml) was used in the extraction and the combined chloroformic phase was washed with water and evaporated to dryness. The residue was dissolved in ethanol and assayed by the

blue tetrazolium method. The aqueous phase, containing the acidic decomposition product, was suitably diluted and assayed by direct UV spectrophotometry at 248 nm against a blank. In calculating the concentration of the acidic decomposition product, an absorptivity of 42 was assumed (12).

RESULTS AND DISCUSSION

Gas Chromatographic Examination of the PEG Samples - The GC examination of the PEG samples revealed three impurities eluting before the solvent; one major and two minor. Comparison at both high and low sensitivity levels showed no discernible difference between the impurities obtained from the five samples.

Stability Testing - Direct UV-spectrophotometric analysis of the solid dispersions before and after storage, revealed no apparent changes in the steroidal contents even after storage for 10 months at 40°. The absorbance values obtained were almost constant within ±5%. This suggests that no apparent changes have occurred to the conjugation of the carbonyl group at C_3 with the double bond between C_4 and C_5 of ring A of the steroids. Results of analysis of the steroidal contents using the blue tetrazolium method showed significant degradation of the drugs in the presence of three PEG samples: PEG 4000 A. PEG 4000 B and PEG 6000 B. No significant

degradation was detected in PEG 4000 C and PEG 6000 A. The possible site of decomposition of the three steroids, as detected by the blue tetrazolium method, is the dihydroxyacetone side chain at C_{17}.

Stability data obtained at 40°, fitted a first-order kinetic; a representative plot is shown in Figure 1 for prednisolone. Values of the rate constant (K) and half-lives for prednisolone, prednisone and hydrocortisone are shown in Table I. Storage of the solid dispersions at 22° also resulted in the degradation of the steroids in the PEG samples 4000 A, 4000 B and 6000 B. Again, no significant degradation was detected in the PEG samples 4000 C and 6000 A. Table II shows the percent steroids remaining after storage for 10 months.

The method of preparations of the solid dispersions appeared to have an insignificant effect on the stability of the steroids. This is shown from the values of (K) for the solid dispersions prepared by the solvent and fusion methods (Table I).

Dissolution Rate Testing

The results obtained in the present work confirm the earlier finding that the incorporation of steroids in PEG solid dispersions significantly enhanced the dissolution rates (2). Representative data are shown in Fig. 2. For prednisolone, the dissolution rates of the drug from the

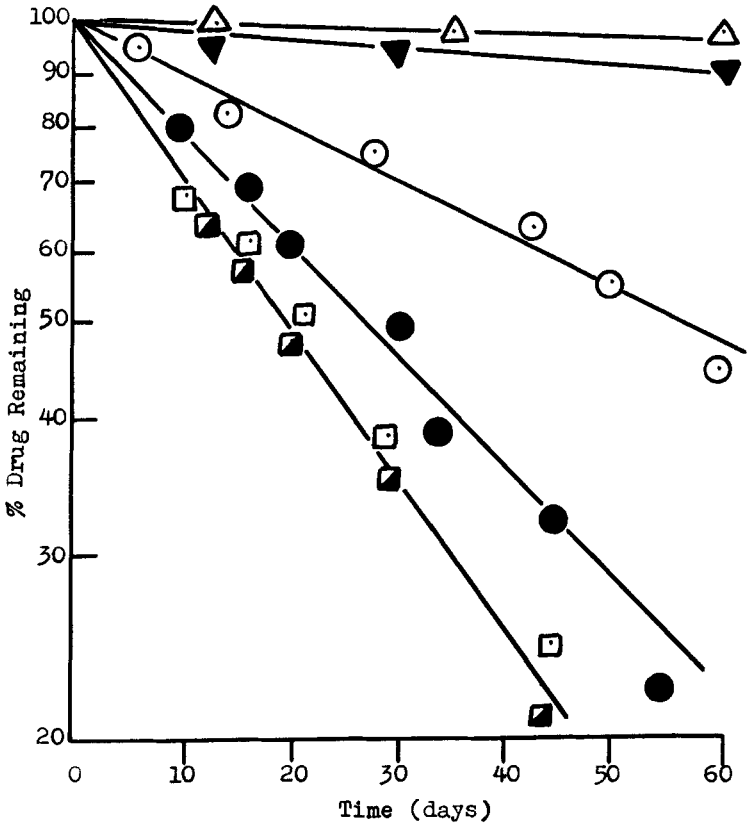

Figure 1.

A first-order plot showing the stability at 40±0.2 of prednisolone in solid dispersions prepared by various PEG samples and assayed by the blue tetrazolium method. PEG samples used (△) 4000C; (▼) 6000A; (⊙) 6000B; (●) 4000B; (⊡) 4000A, solvent method; (◪) 4000A, fusion method.

TABLE I

Values of the Rate Constant (K) and Times of 50% Decomposition ($t_{50\%}$) of the Steroids in PEG Solid Dispersions Prepared by Solvent (I) and Fusion (II) Methods. Storage Temperature: 40°±0.2, PEG Sample: 4000B

Steroid	K (day^{-1})		$t_{50\%}$ (days)	
	I	II	I	II
Prednisolone	0.0232	0.0241	29.9	28.8
Prednisone	0.0114	0.0118	61.0	58.7
Hydrocortisone	0.0144	0.0145	48.2	47.9

TABLE II

Stability of the Steroids in PEG Solid Dispersions Prepared by the Fusion Method Using Various PEG Samples. Storage Temperature: 22±1°.

Steroid	% Steroid Remaining After 10 months				
	4000A	4000B	4000C	6000A	6000B
Prednisolone	38.6	42.0	99.1	96.8	71.0
Prednisone	-	76.0	-	-	-
Hydrocortisone	-	69.1	-	-	-

PEG solid dispersions was independent of the PEG samples used (Fig. 2A). The dissolution rate profiles were almost similar for all the solid dispersions. Compared with the 'plain' steroid, the dissolution rates from the solid dispersions showed about 2.5 fold increase. Figure 2B compares the dissolution rates of the three steroids

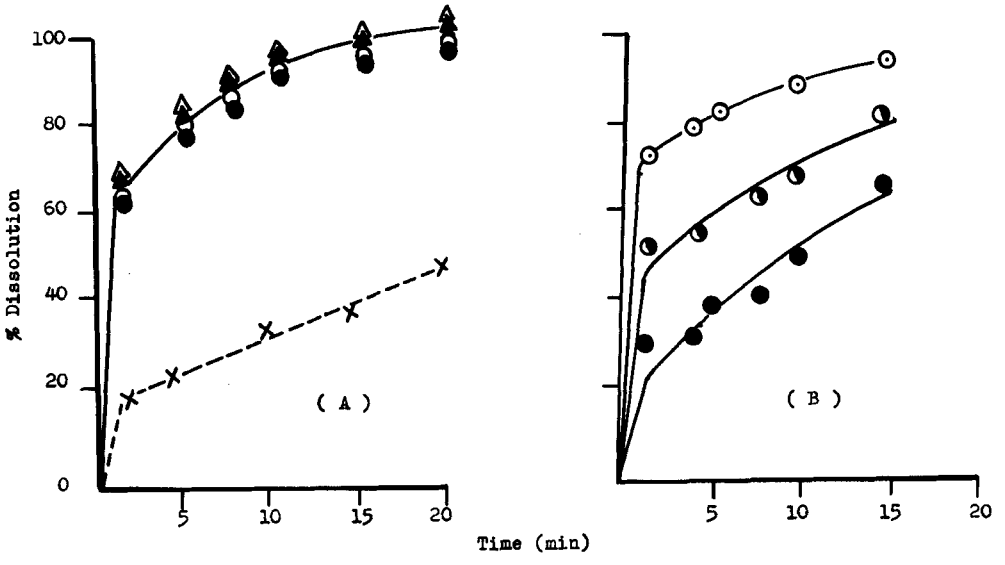

Figure 2.

(A) Effect of PEG sample on the dissolution rates of prednisolone from solid dispersions prepared by the solvent method.
PEG samples used (△) 6000A; (▲) 4000A;
(○) 4000C; (●) 4000B.
(X---X) prednisolone crystallized from chloroform.

(B) Dissolution rates of prednisolone (⊙), hydrocortisone (◑) and prednisone (●) from PEG solid dispersions prepared by the fusion method using PEG 4000B.

from PEG solid dispersions. The rates were dependent on the steroid incorporated and followed the sequence : prednisolone > hydrocortisone > prednisone. This order was the same for the solid dispersions prepared by either the solvent or fusion method.

Storage of the solid dispersions at 22° for 10 months did not produce any apparent change in dissolution rates. Also, the rates were independent of the percentages of steroid remaining. The latter finding may be explained in view of the non-selectivity of the UV-spectrophotometric method used since the decomposition products were found to absorb at the same wavelength. The results also suggest that the decomposition products had similar dissolution rates as the 'intact' steroid.

The three steroids examined possess at C_{17} the same dihydroxyacetone side chain. The latter, is the site of decomposition in the solid dispersions as monitored by the blue tetrazolium method. Nevertheless, significant variations in the extent of steroid decomposition and dissolution rates were observed. This may be attributed to the difference in the relative polarity of the tested steroids as reflected on their equilibrium aqueous solubilities. Prednisolone, with relatively the highest aqueous solubility of the three steroids (1:1300 at 20°) showed relatively, the fastest dissolution rates and poorest stability in the stored solid dispersions. Prednisone, which lacks the hydroxyl group in Ring C, is

practically insoluble in water at 20°. Therefore, relatively slower dissolution rates and lesser decomposition were obtained from the solid dispersions. Hydrocortisone, with an intermediate aqueous solubility (1:3700 at 20°) exhibited dissolution rates and stability data intermediate between prednisolone and prednisone.

TLC Examination

Direct TLC examination of prednisolone-stored solid dispersions of about 90% decomposition, revealed the presence of three spots. One was due to PEG on the starting line, the second corresponded to the 'intact' prednisolone (R_f= 0.40, system I and 0.55, system II) and the third corresponded to a decomposition product(R_f= 0.88, system I and 0.77 system II).

An artificially-decomposed prednisolone by 30 volume hydrogen peroxide (equilibrated at 40° for 3 hr) gave two spots (R_f= 0.41, and 0.88 using system I). The second spot had the same R_f value as that of the decomposition product obtained from the stored solid dispersion.

Estimation of an Acidic Decomposition Product in the Prednisolone-PEG Solid Dispersions

This was carried out following the procedure previously described under 'METHODS'. Two stored samples of prednisolone-PEG 4000B were examined;their percentages decomposition were 73.0 and 90.4 (for samples A and B,

respectively). The results obtained, after analysis of the aqueous alkaline phase and the chloroformic phase, enabled the calculation of the level of acidic product(s) in the sample. The results are summarized in Table III. The presence of non-acidic, chloroform-soluble decomposition product(s) was verified by TLC examination of the chloroformic phase after alkaline extraction. Using system II, two spots were obtained with R_f= 0.55 (intact prednisolone) and 0.61 (decomposition product).

The results obtained in the present work suggest that chemical instability may occur when corticosteroids with free dihydroxyacetone side chains are formulated in some PEG samples. The presence of certain levels of impurities in PEG appears to be responsible for the observed degradation. Gas chromatographic examination of the five PEG samples used in the present work, revealed no detectable difference in the level of the volatile impurities and therefore the observed decomposition of the steroids in only three PEG samples can not be attributed to ethylene oxide impurity.

TABLE III

Sample	% Prednisolone Remaining	% Acidic Product
A	27.0	45.3
B	9.6	40.4

Since one of the decomposition products of the steroids was an acidic compound, this suggests that oxidation of the side chain has taken place to give the corresponding etianic acid. A supporting evidence to this suggestion is given by the results of TLC examination of an artificially-decomposed prednisolone. One of the decomposition products obtained had the same R_f value as that obtained from the stored PEG-prednisolone solid dispersions. Oxidation of the side chain may have been accelerated by peroxide impurities found in the PEG samples.

CONCLUSIONS

1. Some PEG samples were found to contain trace impurities (including peroxides) that accelerated decomposition of corticosteroids possessing free dihydroxyacetone side chain.
2. No alterations occurred to the conjugation of Ring A of the steroids examined.
3. Solid dispersions of the steroids in PEG accelerated the dissolution rates of the drugs and no apparent changes in dissolution rate profiles were noted upon storage even in the decomposed samples as monitored by direct UV-spectrophotometry.
4. Care should be taken in formulating corticosteroids with PEG and rigid standards should be specified for trace impurities in PEG especially limits for peroxides.

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