Effect of Aging on Hydrocortisone–Polyethylene Glycol 4000 and Hydrocortisone–Polyvinylpyrrolidone Dispersions

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Abstract □ Dispersions containing 40% hydrocortisone were prepared by the solvent method in polyethylene glycol 4000. Dispersions in polyvinylpyrrolidone were prepared by slow evaporation of solvent (type A) and by fast evaporation of solvent (type B). These dispersions were stored at 25°C for 30 d. Plots of time required for 50% ($t_{50\%}$) and 70% ($t_{70\%}$) of the hydrocortisone dispersion to dissolve (beaker method) *versus* time were obtained. Hydrocortisone–polyethylene glycol showed no apparent significant change in either dissolution rate, X-ray spectra, or scanning electron micrographs. Type A dispersions showed an increase in dissolution rate up to 8 d. Type B dispersions showed an initial decrease followed by an increase in dissolution rate. The initial decrease in dissolution rate of type B dispersions is due to hydrocortisone crystallizing out of the polyvinylpyrrolidone matrix. The increased dissolution for both types of polyvinylpyrrolidone dispersions was not expected and is explained by an increased proportion of the high-energy amorphous component, based on X-ray spectra. Other possibilities such as the presence of polymorphic forms of hydrocortisone and/or reduction in particle aggregation could not be discounted.

Keyphrases □ Hydrocortisone– dispersions with polyethylene glycol 4000 and polyvinylpyrrolidone, effect of aging □ Aging–effect on dispersions, hydrocortisone–polyethylene glycol 4000, hydrocortisone–polyvinylpyrrolidone.

Incorporation of water-soluble carriers with poorly soluble drugs, to increase the dissolution rate of the latter, has been widely studied and extensively reviewed (1, 2). Polyethylene glycol (3–5) and polyvinylpyrrolidone (6–8) have been popular choices as inert carriers for dispersions prepared by solvent or coprecipitation methods.

The effect of aging on solid dispersion systems has not been reported extensively. Aspirin was reported to undergo faster degradation in solid dispersions (9), whereas dissolution profiles for dicumarol–polyethylene glycol tablets did not change appreciably after 1 year of storage (3). Changes in dissolution profiles of other solid dispersions have not been reported. The corticosteroids continue to be of interest due to their poor water solubility and unpredictable dissolution rates (4–7, 10, 11). The present investigation reports the dissolution characteristics of hydrocortisone–polyvinylpyrrolidone dispersions stored at 25°C for 30 d.

EXPERIMENTAL SECTION

Materials—Micronized hydrocortisone[1], polyethylene glycol 4000[2], and polyvinylpyrrolidone[3] (average mol. wt. 30,000–40,000) were used. All other reagents and solvents were of analytical grade.

Sample Preparation and Storage—The solid dispersions of hydrocortisone in polyethylene glycol were prepared by the solvent method (1, 4). Hydrocortisone and varying quantities of carrier were accurately weighed and dissolved in 20 mL of 96% ethanol. The solvent was evaporated under a stream of nitrogen. The resultant solid dispersions were then dried under reduced pressure at 37°C over silica gel for 1 d. The hardened mass was powered and 85/235-mesh (sieve size) particles were used.

The solid dispersions of hydrocortisone–polyvinylpyrrolidone were prepared using the same technique. During an earlier investigation (6) it was found that the rate of evaporation of the solvent had an effect on dispersions. Dispersions were prepared by slow evaporation (type A) and by rapid evaporation (type B) of solvent. All samples were prepared in duplicate and stored in amber bottles in a desiccator over silica gel at 25°C.

Dissolution Studies—Approximately 50 mg of the solid dispersion was introduced directly on the surface of 500 mL of distilled water in a 1-L beaker at 25 ± 0.1°C and stirred at 100 rpm. The dissolution was followed by withdrawing 4-mL samples with a glass syringe fitted with a filter[4] (0.45 μm) to exclude particles. Hydrocortisone was assayed spectrophotometrically at 247.5 nm. Corrections were made for any absorption due to the carrier. The slope of the Beer's law plot was 0.0454 mg^{-1} (SEM = 0.0316, r = 0.9997).

The $t_{50\%}$ and $t_{70\%}$ values were obtained from plots of percent hydrocortisone dissolved *versus* time. All plots were obtained in duplicate. The results were analyzed for significance using the SPSS program for a one-way ANOVA with interval testing and a two-tailed t test.

X-ray Diffraction Studies—Dispersions were spread on glass slides as a thin layer with a small amount of petroleum jelly. CuK radiation was used. Diffraction patterns[5] were obtained by scanning at 1°/min in terms of the 2θ angle.

Thin-Layer Chromatography Studies—Silica gel-coated plates[6] were spotted with solutions containing 10 mg of dispersions in 5 mL of 95% ethanol. The plates were chromatographed using a two-dimensional method. The solvent system used was acetone–benzene (50:50, v/v) followed by dichloroethane–methanol–water (92:8:0.5, v/v/v). The plates were developed with tetrazolium blue (0.05%) and sodium hydroxide (8%) in methanol.

Scanning Electron Microscope Studies—Scanning electron micrographs were obtained from powdered dispersions mounted on stumps with double-sided cellophane tape and coated with gold.

RESULTS AND DISCUSSION

All dispersions contained 40% hydrocortisone; this selection was based on the results of an earlier study (6). At 40% concentration, hydrocortisone–polyvinylpyrrolidone dispersions showed the following changes in dissolution rate. Plots of time required for 50% and 70% of the hydrocortisone in the dispersion to dissolve *versus* percent hydrocortisone yielded zero slopes for dispersions with <40% hydrocortisone and positive slopes for dispersions with >40% hydrocortisone; dispersions with >40% hydrocortisone also exhibited an increased crystalline structure as evidenced by X-ray diffraction spectra (6). A limited study of the effect of aging on 40% hydrocortisone dispersions was therefore undertaken.

Effects of Storage for 30 d on Hydrocortisone–Polyethylene Glycol 4000 Dispersions—The dispersions were white. Thin-layer chromatography detected no decomposition during this study.

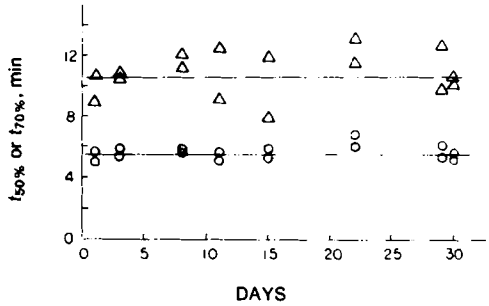

Figure 1—*Plot of* $t_{70\%}$ (△) *and* $t_{50\%}$ (○) *for hydrocortisone in hydrocortisone–polyethylene glycol 4000 dispersions* versus *time.*

[1] Hoechst, Frankfurt, Federal Republic of Germany.
[2] Union Carbide, England.
[3] May and Baker, England.
[4] Millipore Corp., Bedford, Mass.
[5] Phillips X-ray diffractometer; Phillips, Eindhoven, The Netherlands.
[6] Kieselguhr G; Analtech, Newark, Del.

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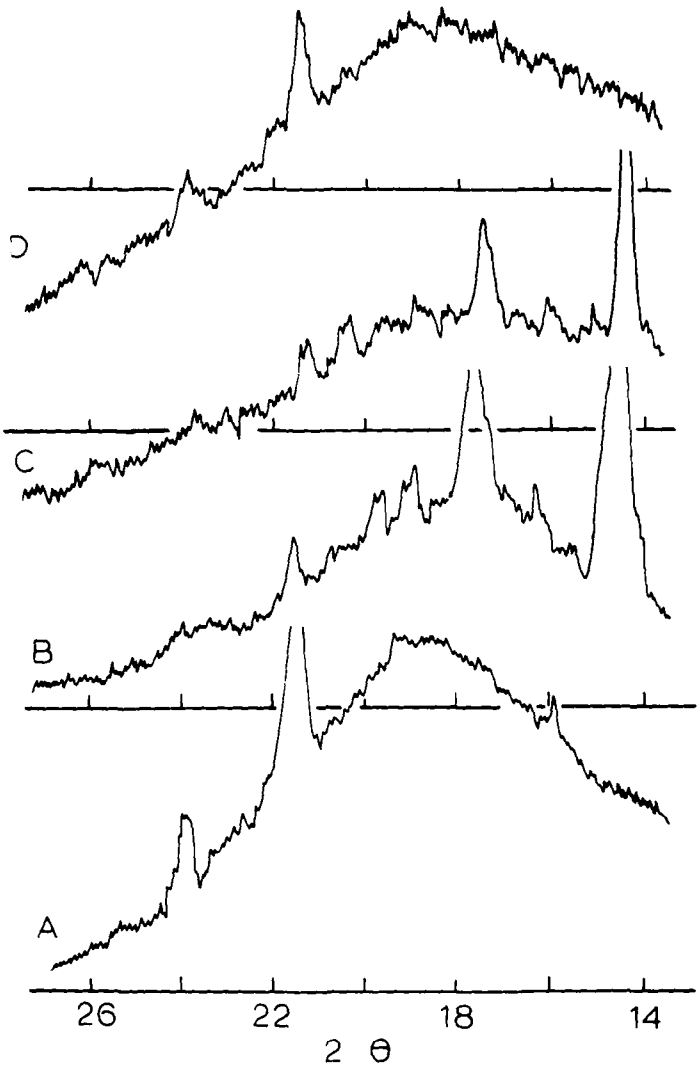

Figure 2—*X-ray diffraction spectra of polyvinylpyrrolidone (A), hydrocortisone (B), hydrocortisone-polyvinylpyrrolidone (type A) dispersion on day 2 (C), and hydrocortisone-polyvinylpyrrolidone (type B) dispersion on day 3 (D).*

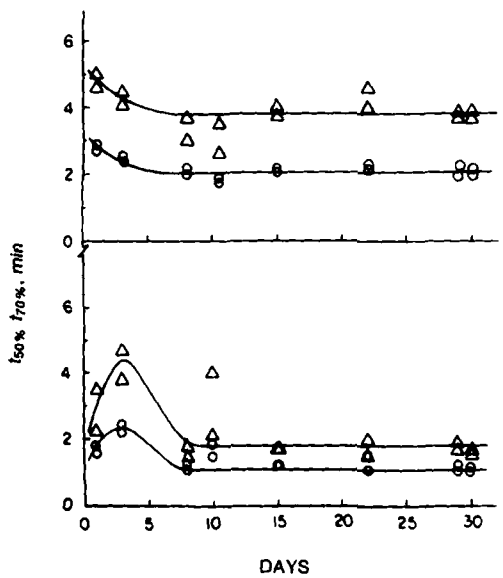

Figure 3—*Plot of* $t_{70\%}$ (△) *and* $t_{50\%}$ (○) *for hydrocortisone-polyvinylpyrrolidone dispersions* versus *time. Dispersions were prepared by the solvent method using a slow rate (upper curve, type A) and a fast rate (lower curve, type B) of evaporation.*

Figure 1 shows a plot of $t_{50\%}$ and $t_{70\%}$ (time required, respectively, for 50% and 70% of the hydrocortisone in the dispersion to dissolve) *versus* time. A one-way ANOVA with interval testing yielded a significant difference between $t_{50\%}$ and $t_{70\%}$ ($p = 0.07$); the two-tailed t test yielded $p < 0.001$. There does not appear to be any change in the dissolution of hydrocortisone over the 30-d storage period. These results are consistent with an earlier study of other polyethylene glycol dispersions (3).

X-ray diffraction spectra showed slight variations in peak heights at different days. These spectra also showed a slight increase in the scattering hump of the dispersions; however, no apparent trend was discernible over the period of this study. Thus, minor changes in X-ray diffraction spectra are not considered significant with respect to the observed dissolution rates. The scanning electron micrographs also did not show any apparent change in these dispersions.

X-ray Diffraction of Polyvinylpyrrolidone and Hydrocortisone—Polyvinylpyrrolidone, a high-molecular-weight polymer, is known to exist in a glass state and to have a relatively high glass-transition temperature of 175°C (12). Physically this polymer is a yellowish, transparent, brittle, glass solid, but the X-ray diffraction pattern (Fig. 2) shows that it is not completely amorphous. Weak diffraction peaks show a degree of order; the ordered portion seems small and the major portion of the solid seems amorphous. This is evident by the presence of the large diffused scattering hump in the spectrum. The diffuse reflection at 18°(2θ) corresponds to a spacing of approximately 0.5 nm, possibly the distance between the polymer chains.

Hydrocortisone is a crystalline compound. A small scattering hump (Fig. 2) is also evident in the diffraction patterns of hydrocortisone and may indicate the presence of a small amount of amorphous hydrocortisone. Such scattering may be caused by the small size of the hydrocortisone crystals.

Effects of Storage for 30 d on Hydrocortisone-Polyvinylpyrrolidone Dispersions—Figure 3 shows plots of $t_{50\%}$ and $t_{70\%}$ *versus* time for type A and B dispersions. For type A dispersions results of a one-way ANOVA with interval testing yielded $p = 0.01$; the two-tailed t test yielded $p < 0.001$. For type B dispersions the first four values in a one-way ANOVA with interval testing resulted in $p = 0.08$; two-tailed t test yielded $p = 0.002$. The last four values in a one-way ANOVA with interval testing resulted in $p = 0.02$; the two-tailed t test yielded $p < 0.001$. For the type A dispersions, $t_{50\%}$ and $t_{70\%}$ initially declined over 10 d and then became constant, indicating an increased dissolution rate in the first 10 d. The type B dispersions show ~50% decrease in dissolution rate in the first 3 d and then a steady increase until about day 10 before leveling off. No attempt was made to develop any mathematical relationship between variables.

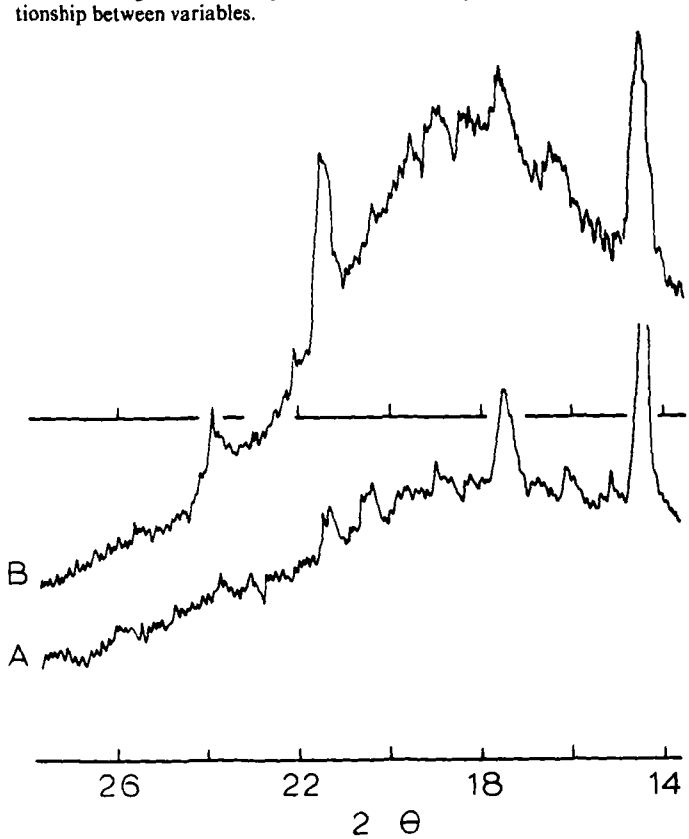

Figure 4—*X-ray diffraction spectra of hydrocortisone-polyvinylpyrrolidone type A dispersions stored at 25°C. Key: (A) after 1 d; (B) after 30 d.*

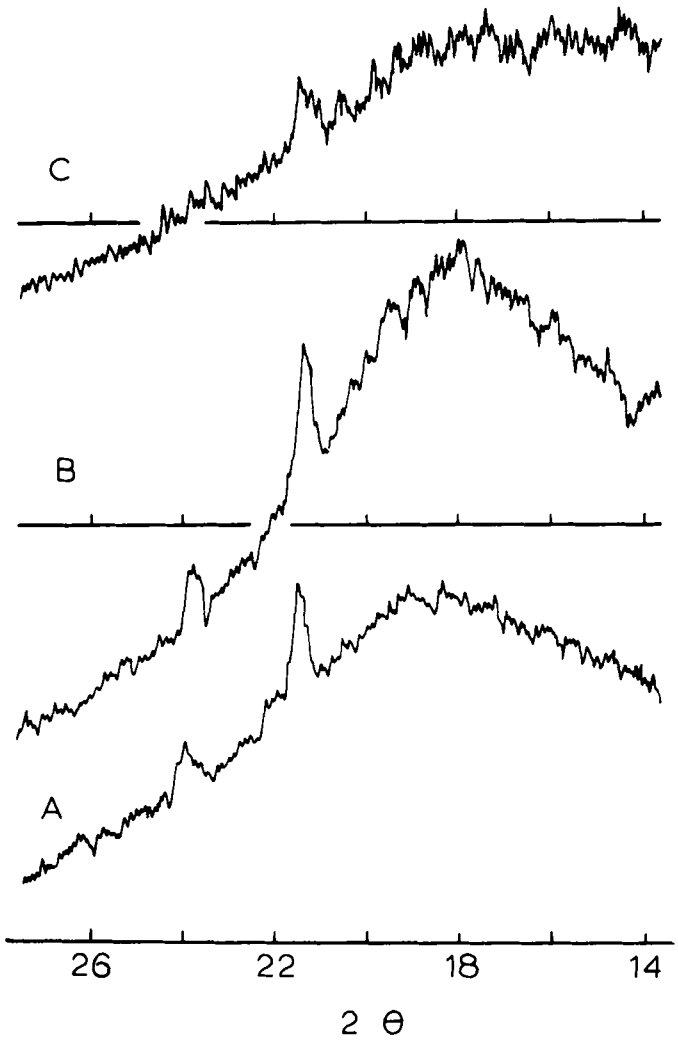

Figure 5—*X-ray diffraction spectra of hydrocortisone-polyvinylpyrrolidone type B dispersions stored at 25°C. Key: (A) after 2 d; (B) after 14 d; (C) after 30 d.*

Figure 2 shows X-ray diffraction spectra for hydrocortisone-polyvinylpyrrolidone dispersions. The X-ray diffraction pattern for type A shows the crystalline structure of hydrocortisone. Type B dispersions show an absence of crystalline structure. Type A dispersions would be expected to show decreased dissolution rates compared with type B. This was observed (Fig. 3) and is consistent with an earlier interpretation (4, 6). However, it is interesting to note that the degree of crystallinity and the resultant modification in dissolution are dependent on the rate of evaporation of solvent during the preparation of these dispersions.

These dispersions are considered to be glassy suspensions of hydrocortisone in polyvinylpyrrolidone. Since such systems are in a metastable state, they may undergo aging transformations yielding stable forms. The rate of the transformations vary with materials and storage conditions. Iopanoic acid and chloramphenicol palmitate were reported to crystallize from a polyvinylpyrrolidone glass solution (1). The initial decrease in the dissolution for type B dispersions (Fig. 3) could be readily explained in terms of hydrocortisone crystallizing out of the polyvinylpyrrolidone matrix.

The increased dissolution rate after an early decrease for type B dispersions and the increased dissolution rate for type A dispersions were unexpected. Figures 4 and 5 show changes in X-ray diffraction spectra for type A and type B dispersions, respectively. Both types of dispersions show increased scattering humps in X-ray diffraction spectra, indicating an increased proportion of an amorphous component. The amorphous forms are high-energy forms and generally possess higher solubility, explaining the increased dissolution. Other possibilities such as the presence of polymorphic form of hydrocortisone in polyvinylpyrrolidone matrix, reduction of particle aggregation, *etc.*, should not be discounted.

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