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THE AGING OF SOLID DISPERSION OF GLYBORNURIDE IN POLYETHYLENGLYCOL 6000

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ABSTRACT

Glybornuride is an oral hypoglucaemiant whose solubility in water is considerably increased by solid dispersion in P.E.G. 6000. The present article reports the effect of storage at 25 º C on such dispersion. After 1 year slight alterations in DSC thermograms and X-Ray diffraction spectra are apparent and in studies of dissolution kinetics there is a significant reduction in the percentage of glybornuride dissolved after 6 and 12 months, but glucaemia levels in rabbits recorded after 6, 9 and 12 months do not differ significantly from those obtained with the freshly prepared dispersion.

INTRODUCTION

The extensive literature on solid dispersions, which has been reviewed on several occasions (1; 2; 3), reflects the growing technological and biopharmaceutical importance of this systems. Among the numerous drugs which have been studied in solid dispersion, attention has been paid to oral hypoglucaemiant drugs, especially tolbutamide and chlorpropamide (4; 5; 6; 7), and in a recent study of solid dispersions of glybornuride in P.E.G. 6000, P.E.G. 10000 and P.E.G. 20000 Vila-Jato et al (8)

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have observed a considerable increase in the drug´s dissolution rate, particularly with P.E.G. 6000. This increase in dissolution rate causes the maximum drop in glucaemia to be reached faster than when glybornuride alone is administered. The aim of the work reported in the present article was to study possible alterations in the dissolution kinetics of 30:70 solid dispersion of glybornuride in P.E.G. 6000 when stored for 12 months at 25ºC.

MATERIAL AND METHODS

Preparation of the solid dispersion-. The solid dispersion was prepared by dissolution of the components (glybornuride and P.E.G. 6000, 30:70) in chloroform, evaporation in vacuo at 25ºC and sifting twice between 210-125 sieves.

Dissolution method-. Percentages of glybornuride dissolved were calculated using the apparatus and method described by Llabres et al. (9). The concentration of glybornuride dissolved in the medium (0.1 N HCl) was determined spectrophotometrically at 228 nm using a Shimadzu UV-240 double-beam spectrophotometer.

Others-. Differential scanning calorimetry was carried out in a Perkin Elmer DSC-4 equipped with a Perkin Elmer 56 recorder, the sample size being approximately 5 mg and the scanning rate 5ºC/min. Powder X-Ray patterns were obtained in a Siemens D-500 diffractometer.

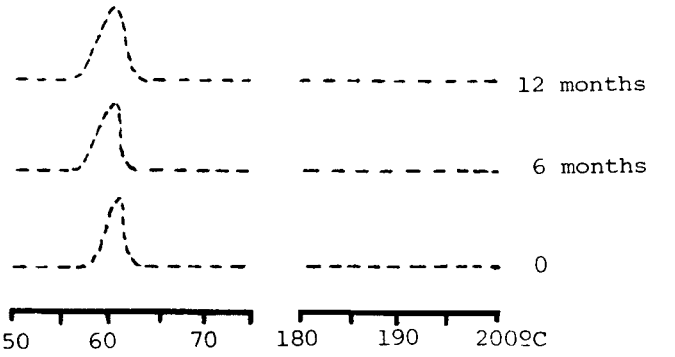

FIGURE 1-. Thermograms of Glybornuride-P.E.G. 6000 solid dispersion.

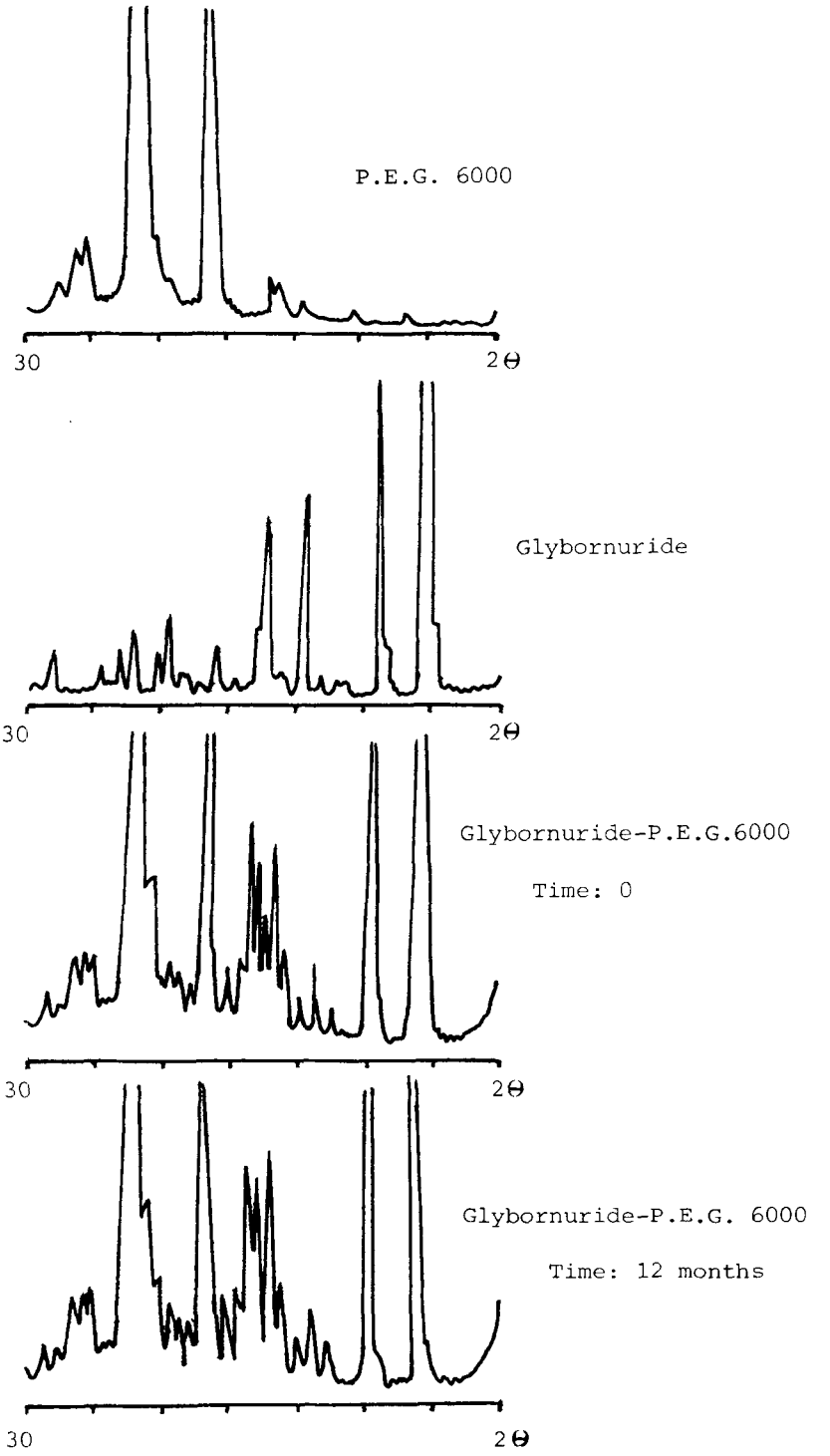

FIGURE 2-. X-Ray Diffraction Patterns

RESULTS AND DISCUSSION

Differential Scanning Calorimetry-. Figure 1 shows thermograms obtained immediately after preparation of the solid dispersion of glybornuride in P.E.G. 6000 and again 6 and 12 months later. No important changes are evident, the locations and shapes of the peaks being very similar, with just a slight progressive broadening of the peak corresponding to the melting of the solid dispersion after 6 and 12 months.

Powder X-Ray diffraction patterns-. Figure 2 shows the X-Ray diffraction espectra of the solid dispersion when freshly made and after 12 months´ storage, together with those of pure glybornuride and P.E.G. 6000. A year´s storage increases the intensity of the peaks characteristic of glybornuride, which would seem to reflect an increase either in the degree of crystallinity of the dispersion or in the size of the glybornuride particles.

Dissolution kinetics-. Figure 3 shows the dissolution kinetics of glybornuride alone and glybornuride solid dispersion in P.E.G. 6000 after 0, 2, 4, 6 and 12 months. The slope of the linear regression of time v.s. logarithm of the percentage of undissolved glybornuride falls appreciably after a year´s storage (Table 1), in consonance with which the percentage of glybornuride dissolved after 5 hours is also much lower after 12 months (Table 2)

Analysis of the variance of the results shown in Table 2 yields a value of $F = 77.23$ (5 and 18 df) which is significant at the $\alpha = 0.01$ level. It may therefore be concluded that with respect to the percentage of glybornuride dissolved after 5 hours there are significant differences among the six treatments. The least significant difference may be calculated as 2.83, so that a significant differences exists between glybornuride alone and the fresh solid dispersion. After 2 month´s storage the quantity of glybornuride dissolved from the solid dispersion after 5 hours falls slightly, but the results after 4 months are practically equal to those of the freshly prepared dispersion. After 6 months the percentage of glybornuride dissolved falls again, and a further drop is registered after 12 month´s storage.

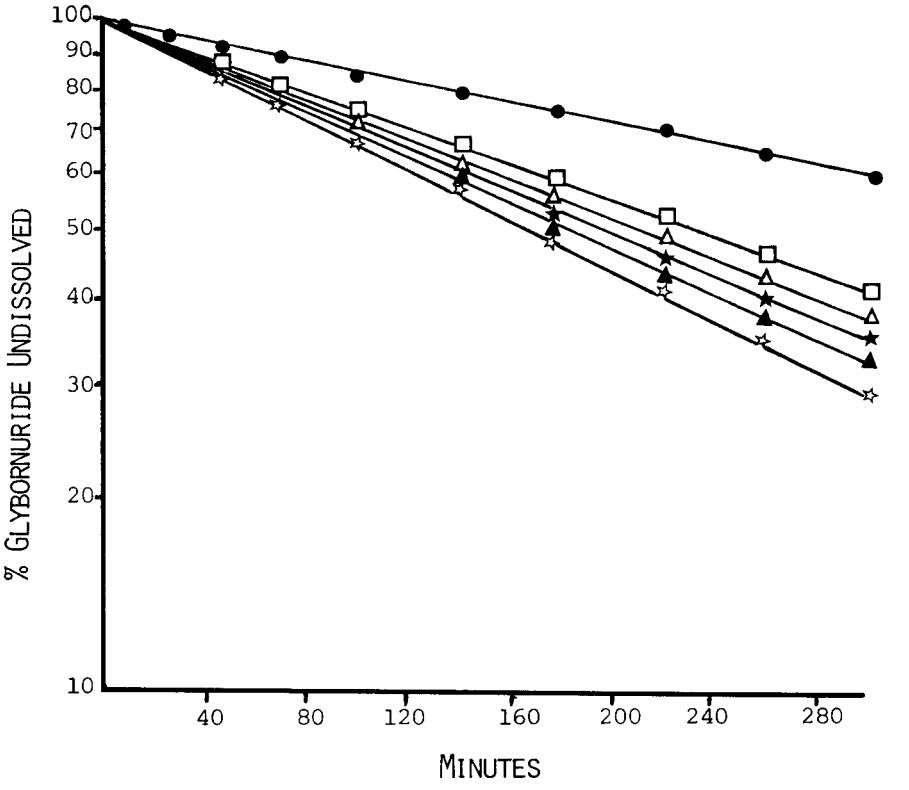

FIGURE 3-. Percentage of Glybornuride undissolved vs time Glybornuride (●); Glybornuride-P.E.G. 6000 solid dispersion 0 time (▲); 2 months (★); 4 months (☆); 6 months (Δ); 12 months (□)

TABLE 1

Slopes of the linear regression: time vs.logarithm of the percentage of glybornuride undissolved.

Formulation	Storage at 25ºC	Slope
Glybornuride-P.E.G. 6000	0	$16.84.10^{-4}$
	2 months	$15.03.10^{-4}$
	4 months	$17.46.10^{-4}$
	6 months	$13.81.10^{-4}$
	12 months	$12.72.10^{-4}$

TABLE 2

Percentages of glybornuride dissolved after 5 hours

Solid dispersion glybornuride-P.E.G. 6000					Glybornuride
0 m.	2 m.	4 m.	6 m.	12 m.	
70.38	63.69	74.16	61.66	59.67	40.61
74.64	67.77	74.98	64.38	60.53	38.95
66.16	65.63	68.66	63.38	56.79	43.17
69.62	66.88	68.39	63.17	58.12	44.11

The progressive fall in the percentage of glybornuride dissolved that takes place after 6 month´s storage may be explained by the well-known fact that the interface energy of solid dispersions tends to a minimum by reducing interface area and thereby increasing the size of the particles. El-Gamal et al. (10), who have observed this phenomenon in solid dispersions of phenylbutazone in P.E.G. 6000, state that the molecules of drug may diffuse through the polymer matrix to adhere to and enlarge existing particles. Henry et al (11) have observed that the storage of solid dispersions of diazepam in P.E.G. 4000 also causes a reduction in dissolution rate with respect to the freshly prepared dispersion.

The interpretation of the dissolution results after 2 and 4 months is more tricky. However, a likely explanation of the dispersion´s behaviour during the first 6 months of storage seems to be suggested by the findings of Ford et al. (12), who have observed the progress of microscopical structural changes in solid dispersions of indomethacin in P.E.G. 6000. According to these authors, the time normally required for the orientation of P.E.G. 6000 molecules is roughly a month, but the inclusion of indomethacin reduces the rate of crystallization so that up 2 months may be necessary for a stable structure to be attained by the solid dispersion. Similar structural modifications may well

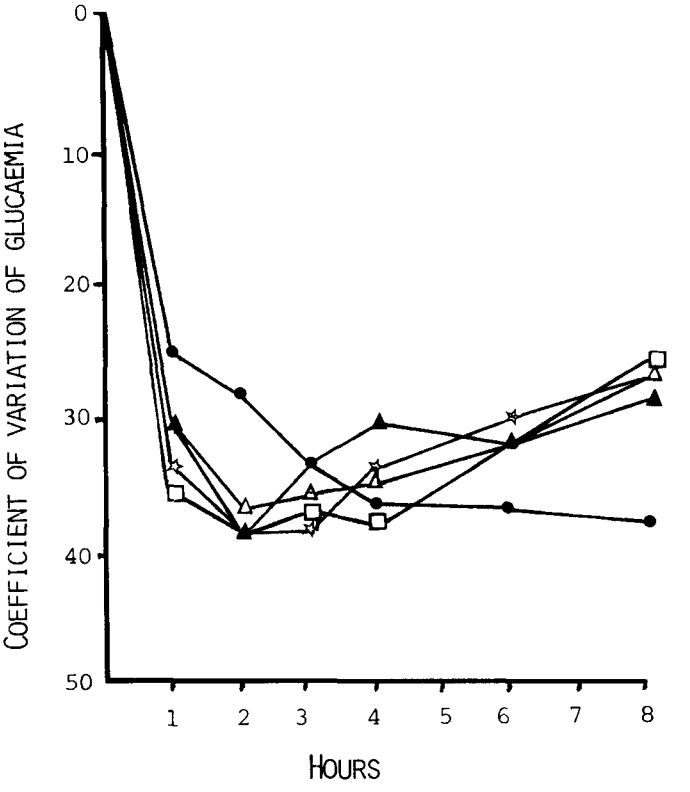

FIGURE 4-. Coefficient of variation of glucaemia in rabbits after administration of 5 mg/Kg of Glybornuride (●) and glybornuride-P.E.G. 6000 solid dispersion 0 time (▲); 6 months (Δ); 9 months (□) and 12 months (☆).

be responsible for the changes in the dissolution behaviour of solid dispersions of glybornuride in P.E.G. 6000.

In order to determine the degree to which the alterations in its dissolution kinetics during storage modify the drug activity as a hypoglucaemiant, rabbits were administered doses of 5 mg/Kg of glybornuride in solid dispersion and glucaemia levels were determined 1, 2, 3, 4, 6 and 8 hours after oral administration. No appreciable differences were observed among the responses to solid dispersions stored for different times (Figure 4),

which may probably be attributed to the observed fall in dissolution rate with storage time not being sufficient to alter the pharmacological response given the large interindividual variations encountered.

To sum up, it may be concluded that glybornuride undergoes a significant fall in dissolution rate when stored in solid dispersion in P.E.G. 6000 for longer than 6 months at 25ºC, but that these changes have not been shown significantly to influence the drug´s effect on glucaemia levels in rabbits.

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