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BIOPHARMACEUTICAL STUDY OF GLYBORNURIDE-POLYETHYLENE GLYCOL SYSTEMS

José L. VILA-JATO and Maria J. ALONSO
Departamento de Farmacia Galénica
Facultad de Farmacia
Santiago de Compostela (Spain)

ABSTRACT

Glybornuride is an oral hypoglucaemiant drug which exhibits a very low water solubility. Consequently,the solid dispersions of this drug with PEG 6,000; 10,000 and 20,000 have studied. According to the phase diagrams obtained, the following solid dispersions of glybornuride were prepared: at 30% with PEG 6,000 and 10,000 and 40% with PEG 20,000.Dissolution curves show that glybornuride dissolves faster as solid dispersion, particularly with PEG 6,000.

The administration of glybornuride as a solid dispersion into rabbits induced a faster decrease of glucaemia levels than a physical mixture with polyethylene-glycols.

INTRODUCTION

The increasing technological and biopharmaceutical importance of solid dispersions is witnessed by the amount of relevant review articles (1; 2). According to Hajratwala (3) the increased dissolution of the drugs in solid dispersions may be due to a solubilizing effect of the carrier (4), a

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reduction in particle size in the eutectics (5), a reduction in the aggregation of hydrophobic drugs (6), improved humectation (7) and solidification of the drug in a rapidly soluble metastable form (8).

Ford (9) has pointed out that for some drugs the molecular weight of the polyethylene-glycol employed may be of great importance: the dissolution rate of spironolactone and digoxin increases with the molecular weight of the polyethylene-glycol (10; 11) but decreases for drugs suchs as papaverine, sulfametoxydiazine and chlorothiazide (12; 13; 14). The method of preparing the solid dispersion may also affect the dissolution rate of the drug, as Henry et al. (15) have shown for diazepam and El-Gindy et al. (16) for nalidixic acid.

Drugs that have been studied in the form of solid dispersions include oral hypoglucaemiants, particularly tolbutamide and chlorpropamide (17; 18; 19; 20). The intent of the present study is the preparation and " in vitro " and " in vivo" evaluation of the solid dispersions of glybornuride, a very poorly hydrosoluble oral antidiabetic drug, with polyethylene-glycols of weights 6,000; 10,000 and 20,000.

MATERIALS AND METHODS

Preparation of solid dispersions-. Solid dispersions were prepared by dissolution of the components in chloroform, evaporation in vacuo at 25º C and sifting twice between 210-125 sieves. Differential Scanning Calorimetry was carried out in a Perkin-Elmer DSC-2 equipped with a Perkin-Elmer model 56 recorder.
Dissolution method-. Percentage of glybornuride dissolved were calculated using the apparatus and methods described by Llabres et al. (21). The concentration of dissolved glybornuride in the medium (0,1 N ClH) was determined spectrophotometrically at 228 nm using a double-beam spectrophotometer (Shimadzu UV 240).

RESULTS

From thermograms obtained by DSC (Figure 1) the phase diagrams shown in Figure 2 were constructed. The thermograms show a single endothermic peak when low percentages of glybornuride are used; however, when this percentage is increased, two peaks can be distinguished.These two peaks are evident at glybornuride concentration of 40% or higher when polyethylene-glycols 6,000 or 10,000 are used; in contrast, no doble peak are produced when polyethylene-glycol 20,000 are used at glybornuride concentration of 40%.

On the basis of these diagrams, which are similar to those obtained by Kaur el al (22) for tolbutamide with polyethylene-glycol 2,000 and by Vila et al. (23) for tolbutamide with polyethylene-glycol 6,000;10,000 and 20,000, the solid dispersion made with polyethylene-glycol 20,000 was prepared with 40% glybornuride and the polyethylene-glycols 6,000 and 10,000 solid dispersions with 30% glybornuride.

Table 1 list the mean percentages of undissolved glybornuride (four experiences) comparing glybornuride, solid dispersions and physical mixtures with the same composition as the dispersions. In Figure 3 the logarithms of the percentages of glybornuride undissolved are plotted against the time at which samples were taken from the dissolution apparatus. The equations of the straight lines fitted to the data are as follows:

Glybornuride $Y = 1.99 - 8.05.10^{-4} X$

Glybornuride-PEG 6,000

Physical mixture $Y = 1.99 - 9.24.10^{-4} X$

Solid Dispersion $Y = 2.00 - 17.65.10^{-4} X$

Glybornuride-PEG 10.000

Physical mixture $Y = 2.00 - 9.29.10^{-4} X$

Solid Dispersion $Y = 2.00 - 14.9.10^{-4} X$

Glybornuride-PEG 20,000

Physical mixture $Y = 2.00 - 9.12.10^{-4} X$

Solid Dispersion $Y = 2.00 - 13.4.10^{-4} X$

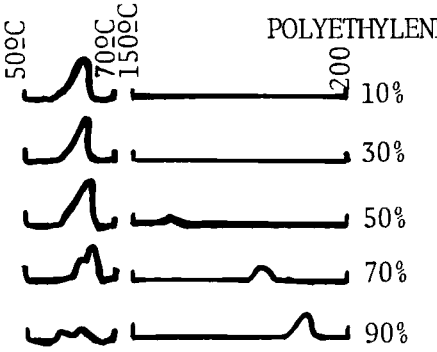

FIGURE 1

Thermograms of Glybornuride PEG solid dispersions.

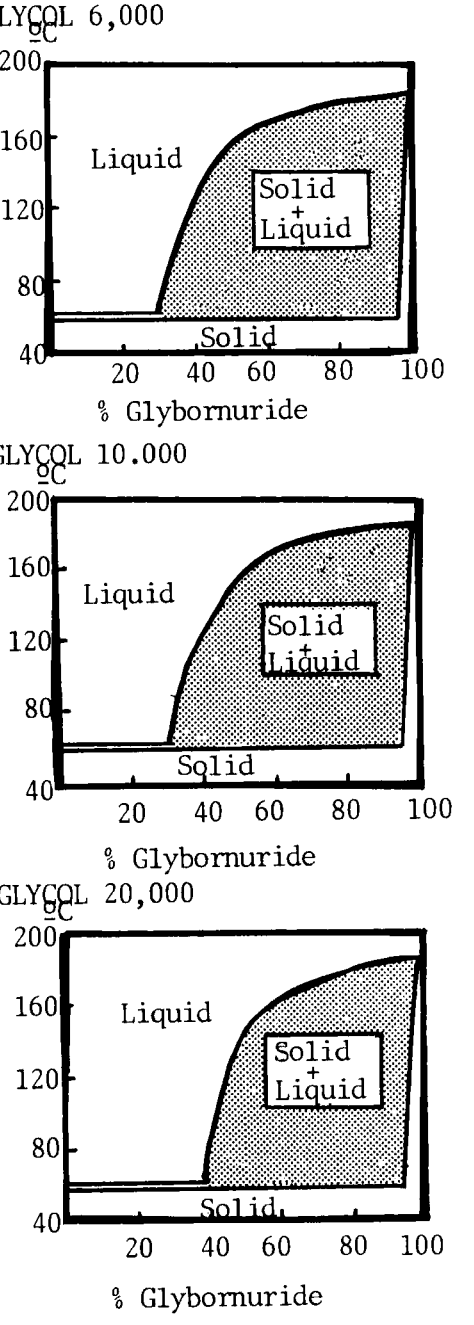

FIGURE 2

Phase Diagrams of solid dispersions of Glybornuride PEG.

TABLE 1
Mean percentages (± SD) of undissolved glybornuride (4 experiences)

Time Min.	Glybornuride	Physical Mixture			Solid Dispersion		
		6.000	10.000	20.000	6.000	10.000	20.000
10	97.66 (±1.71)	97.89 (±1.19)	97.90 (±1.07)	97.67 (±1.48)	96.02 (±1.48)	96.62 (±0.90)	96.97 (±1.25)
20	96.36 (±0.90)	95.83 (±1.19)	95.85 (±0.81)	95.89 (±1.29)	92.35 (±1.88)	93.37 (±0.86)	94.35 (±0.95)
30	94.57 (±0.90)	93.96 (±1.16)	93.74 (±1.47)	93.50 (±1.44)	87.80 (±1.79)	90.22 (±1.18)	91.17 (±1.46)
40	92.84 (±1.34)	91.84 (±1.40)	91.87 (±1.43)	91.94 (±1.58)	85.00 (±1.65)	87.18 (±1.29)	88.43 (±1.18)
50	91.12 (±1.39)	89.90 (±1.41)	89.94 (±1.41)	90.03 (±1.81)	81.63 (±1.07)	84.21 (±1.30)	85.69 (±1.33)
60	89.44 (±1.05)	88.00 (±1.02)	88.05 (±1.31)	88.16 (±0.98)	77.88 (±2.26)	81.40 (±1.37)	83.13 (±1.60)
80	86.18 (±1.24)	84.33 (±1.51)	85.08 (±1.25)	84.66 (±0.96)	72.29 (±1.74)	76.00 (±1.84)	78.16 (±1.13)
100	83.04 (±1.70)	80.82 (±1.60)	80.90 (±1.50)	81.06 (±1.65)	66.63 (±1.88)	70.96 (±1.67)	73.49 (±1.46)
120	80.00 (±1.16)	77.45 (±1.55)	77.54 (±1.07)	77.74 (±1.20)	59.15 (±2.60)	66.26 (±1.21)	69.10 (±2.03)
140	77.08 (±1.19)	74.22 (±1.47)	74.32 (±1.03)	74.53 (±1.73)	56.65 (±0.93)	61.87 (±1.27)	64.97 (±1.62)
160	74.25 (±1.91)	71.12 (±1.67)	71.24 (±0.89)	71.47 (±1.63)	52.23 (±1.68)	57.77 (±1.50)	61.10 (±1.61)
180	71.56 (±1.36)	68.13 (±1.86)	68.29 (±1.35)	68.53 (±1.40)	48.16 (±1.80)	53.94 (±0.89)	57.45 (±1.79)
200	68.94 (±1.58)	65.31 (±1.58)	65.37 (±2.07)	65.71 (±1.36)	44.40 (±1.99)	50.33 (±0.91)	54.01 (±1.65)
220	66.43 (±1.45)	63.09 (±1.89)	62.73 (±1.46)	63.00 (±1.41)	40.94 (±2.02)	47.02 (±0.89)	50.79 (±2.32)
240	64.50 (±0.90)	60.48 (±2.95)	60.13 (±2.17)	60.42 (±1.72)	37.75 (±2.15)	43.91 (±0.96)	47.75 (±1.89)
260	61.81 (±1.61)	57.48 (±1.59)	56.88 (±1.89)	57.93 (±1.99)	34.80 (±1.35)	41.25 (±1.49)	44.90 (±1.96)
280	59.42 (±1.83)	55.10 (±1.60)	55.24 (±1.89)	55.55 (±1.56)	32.09 (±1.34)	38.28 (±1.38)	42.22 (±2.00)
300	57.36 (±1.40)	52.79 (±1.66)	52.95 (±1.75)	53.25 (±2.11)	29.59 (±1.75)	35.74 (±1.60)	39.70 (±1.97)

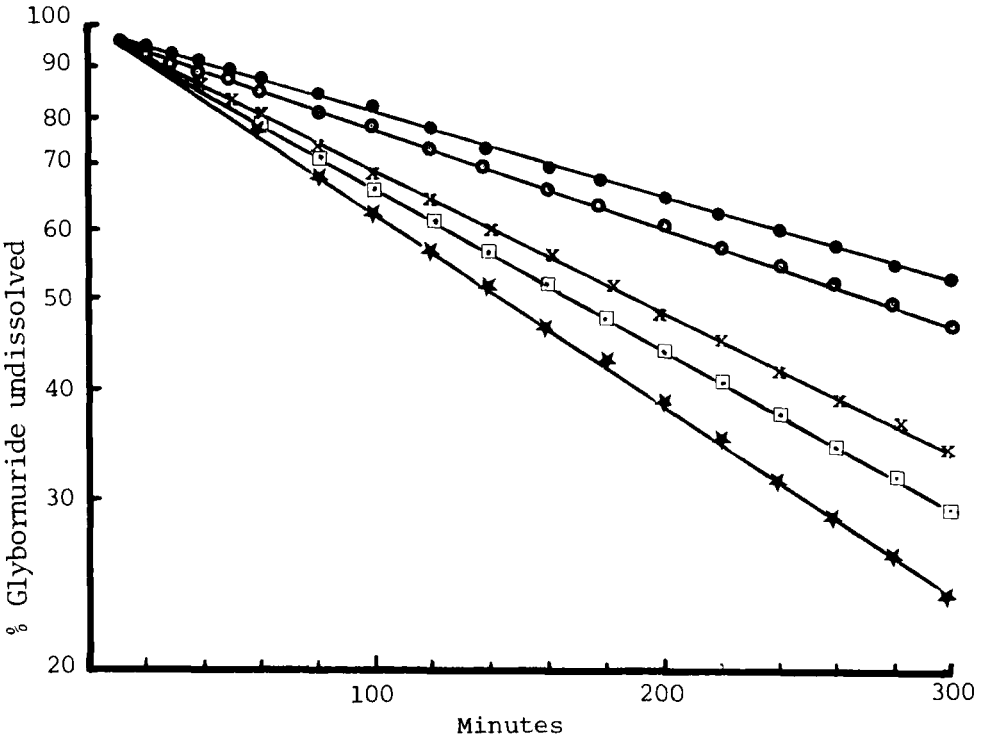

FIGURE 3-. Percentage of glybornuride undissolved vs time Glybornuride (●); Physical Mixtures (⊙); Solid Dispersions: PEG 6,000 (✱); PEG 10,000 (□) PEG 20,000 (x)

DISCUSSION

The results show in Table 1 are sufficient evidence that glybornuride dissolves faster when is incorporated in solid dispersions with the polyethylene-glycols studied. However, since the mere presence of polyethylene-glycol is known to affect the dissolution rate of certain drugs, the slopes of the glybornuride regression line and those of the three physical mixtures and solid dispersions were compared statistically using a t-test (24). The results, listed in Table 2, show that:

1-. Glybornuride dissolves more rapidly when physically mixed with polyethylene-glycols than when unmixed.

TABLE 2

Glybornuride vs Physical Mixtures	$S.E_{diff}$	$s^2_{r_{12}}$	t	
PEG 6.000	$7.05.10^{-5}$	$1.51.10^{-5}$	7.88	
PEG 10.000	$6.95.10^{-5}$	$1.50.10^{-5}$	8.32	
PEG 20.000	$6.71.10^{-5}$	$1.47.10^{-5}$	7.28	
Physical Mixtures				
PEG 6,000 vs PEG 10.000	$8.01.10^{-5}$	$1.61.10^{-5}$	0.31	N.S.
PEG 6.000 vs PEG 20.000	$7.76.10^{-5}$	$1.58.10^{-5}$	0.76	N.S.
PEG 10.000 vs PEG 20.000	$7.66.10^{-5}$	$1.47.10^{-5}$	1.15	N.S.
Solid Dispersions vs Physical Mixtures				
PEG 6.000	$1.25.10^{-4}$	$2.04.10^{-5}$	41.2	
PEG 10.000	$7.83.10^{-5}$	$1.59.10^{-5}$	35.28	
PEG 20.000	$1.03.10^{-4}$	$1.82.10^{-5}$	23.52	
Solid Dispersions				
PEG 6.000 vs PEG 10.000	$1.27.10^{-4}$	$2.03.10^{-5}$	13.54	
PEG 6.000 vs PEG 20.000	$7.48.10^{-5}$	$1.55.10^{-5}$	27.42	
PEG 10.000 vs PEG 20.000	$1.05.10^{-5}$	$1.84.10^{-5}$	8.15	

2-. There were no statistical significant differences between the dissolution rates of glybornuride in the three physical mixtures.
3-. Glybornuride dissolves more rapidly in the solid dispersions studied than in physical mixtures of the same composition.
4-. The dissolution rate of glybornuride in the solid dispersions decreases as the molecular weight of the polyethylene-glycol increases.

Although the polyethylene-glycols studied exhibited low interaction with glybornuride in the aquous phase as manifested by their low solubilizing capacity, yet they proved to be powerful carriers when used in solid dispersion systems. The mean 50% dissolution time, calculated from the regression straigh lines were: 361 minutes for the glybornuride, 327 minutes for the three physical mixtures and 170, 202 and 225 minutes for the polyethylene-glycol 6,000; 10,000 and 20,000 solid dispersions respectively.

According to the " in vitro " results an " in vivo " study was carried out to determine glucaemia levels after oral administration of 5 mg/Kg of glybornuride in solid dispersions and physical mixtures. Blood samples from six rabbits per treatment taken after: 0;1;2;3;4;6 and 8 hours yielded the mean glucaemia levels shown in Figure 4. The lowest glucaemia levels are recorded after four hours when glybornuride in physical mixture was used, but after only two hours when glybornuride was administered in solid dispersions, apparently because in the latter form it dissolved and was absorbed faster.

There are no significant statistical differences (ANOVA) between the coefficients of variation of glucaemia levels obtained at 2 hours for the three solid dispersions studied and there also are no statistical significant differences between the coefficients of variation of glucaemia levels obtained at 2 hours with solid dispersions and at for 4 hours with physical mixtures.

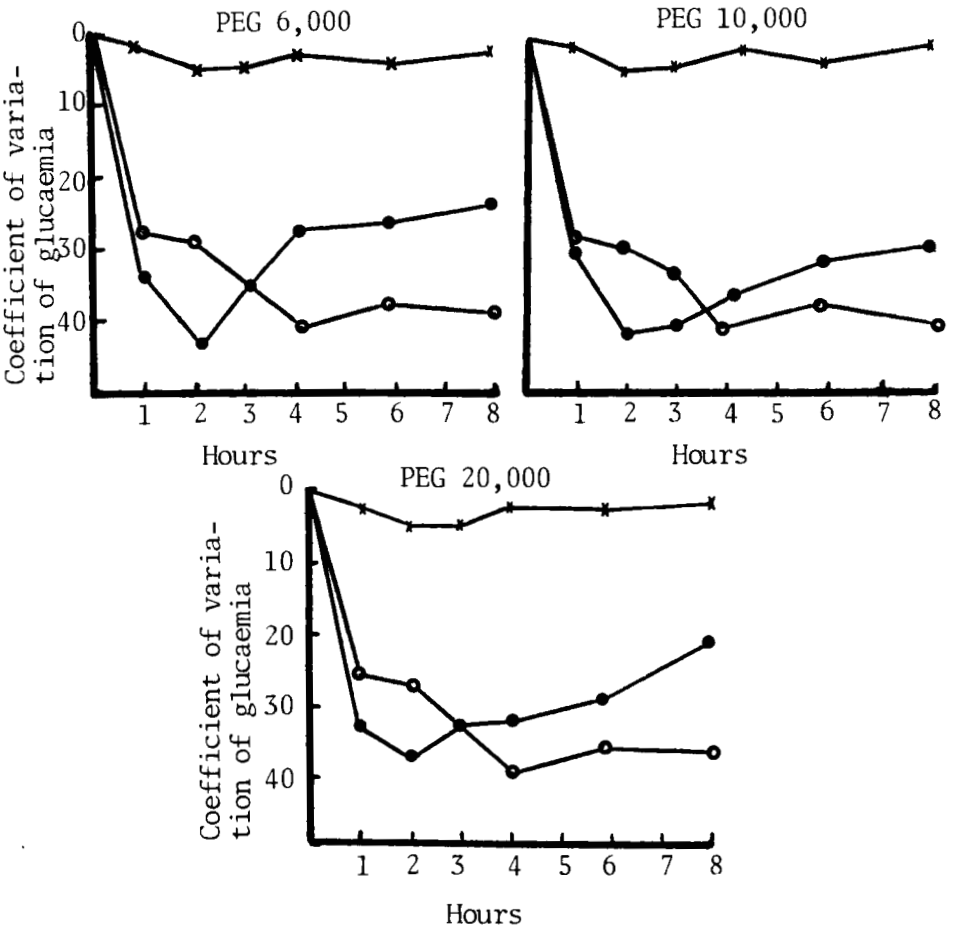

FIGURE 4-. Coefficients of variation of glucaemia in rabbits after administration of 5 mg/Kg of glybornuride (x) Basal glucaemia; (o) Physical Mixture and (•) Solid Dispersion.

On the other hand there are no statistical significant differences between the areas under the curves coefficient of variation of glucaemia levels-time (0 to 8 hours) corresponding to solid dispersions and physical mixtures. Therefore glybornuride in solid dispersion with polyethylene-glycols increase its absortion rate but not the total quantity absorbed

which agrees with the fact that glybornuride is well absorbed by the gastrointestinal tract (25).

To conclude, the solid dispersions of glybornuride with polyethylene-glycols 6,000; 10,000 and 20,000 can be used for the enhancement of the dissolution rate of glybornuride and produces a more rapid lowering in the glucaemia levels.

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