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A comparative biopharmaceutical study of fresh and ageing tolbutamide–polyethyleneglycols solid dispersions

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Summary

Solid dispersions of tolbutamide with polyethylene glycol (PEG) 6000 and 20,000 were prepared by the solvent method. The identification of these systems by differential scanning calorimetry and X-ray diffraction suggested the formation of a crystalline mixture of drug and carrier. These dispersions were stored at a temperature of 25 °C for 1 year and no significant change was found in either the dissolution properties, the X-ray spectra, or the DSC thermograms. The statistical analysis of the plasma glucose levels obtained from the animal studies indicates no significant differences ($P > 0.05$) between the area under the glycaemia curve and the maximum decrease of glycaemia obtained when freshly or aged (after 6, 9 or 12 months) solid dispersions were administered.

Introduction

The incorporation of poorly soluble drugs into water-soluble carrier in order to increase the dissolution rate has been widely studied and extensively reviewed (Chiou and Riegelman, 1971; Ford, 1986). The most commonly used carriers are long-chain polymers such as polyethylene glycols (PEG). These hydrophilic carriers have been shown to increase the dissolution rate of several drugs, particularly oral hypoglycaemic drugs, for example, tolbutamide (Said et al., 1974; Kaur and Grant, 1979; Kassem et al., 1980; Kaur et al., 1980; Miralles et al., 1982; Mc Ginity et al., 1984).

One aspect of solid dispersion that has received little attention is the therapeutic efficacy of the dispersed drug. Theoretically if the dissolution rate is enhanced, the oral absorption rate should be increased provided that the absorption process is dissolution rate-limited. Although the relationship between the hypoglycaemic response and the plasma levels of the drug is not well defined, the influence of the in vitro dissolution rates of oral hypoglycaemic drugs on the decrease of the glucose level in the blood has been reported: increases in in vitro dissolution rate were reflected in increases in rate of decline of blood sugar level for tolbutamide dosage forms (Nelson et al., 1962). Moreover, it has been postulated that a considerable quantity of the drug (tolbutamide) must be accumulated before it actually shows a therapeutic response (Balant, 1981): that is the reason why we chose to analyse the glucose levels rather than the

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tolbutamide levels in order to establish the solid dispersions significance in vivo.

In previous reports the physicochemical properties of solid dispersions have been examined; however, the effect of ageing on these parameters has not been extensively studied. Furthermore the influence of the stability problems on the therapeutic response has not been thoroughly investigated. For the present work solid dispersions of tolbutamide with PEG 6000 and PEG 20,000 were prepared by the solvent method and the main purpose has been the evaluation of the in vivo efficacy of these systems (based on the plasma glucose levels using a commercial powder as the reference) as well as their activities when stored at 25 °C for 1 year.

Materials and Methods

Materials

Polyethylene glycol 6000 (m.p. 56 °C) (Merck, Spain), polyethylene glycol 20,000 (m.p. 65 °C) (Merck, Spain), and tolbutamide (m.p. 127 °C) (Hoechst, Spain) were used. All the other reagents and solvents were of analytical grade.

Sample preparation and storage

The solid dispersions were prepared by the solvent method. Mixtures of various compositions of the drug and PEG were dissolved into chloroform, and evaporation was carried out in vacuo at 25 °C. The hardened mass was powdered and sifted twice between 125 and 250 meshes. Then all the samples were stored in a desiccator over silicagel at 25 °C. At suitable time intervals, samples were examined with a view to determining physicochemical properties, the dissolution rates and the in vivo behaviour.

X-Ray diffraction studies

Diffraction patterns were obtained by scanning at 1 °/min through the 2θ angle on a Siemens D 500 diffractometer (Siemens, Spain), using Cu-K_α radiation.

Differential scanning calorimetry (DSC)

For the differential scanning calorimetry study, the sample weight was approximately 5 mg and the scanning rate was 2 °C/min. The analysis was run on a Perkin-Elmer DSC-Z calorimeter (Perkin-Elmer, Spain).

Dissolution studies

The dissolution assays of tolbutamide alone and tolbutamide coprecipitates were carried out at different time intervals during the storage (0, 2, 4, 6 and 12 months). A solution of 0.1 N HCl at 37 °C was used as the dissolution fluid and a continuous circulating system of this fluid was maintained during each experience (2 h). The percentages of dissolved tolbutamide were calculated by means of a method previously described (Llabres et al., 1978). The concentration of tolbutamide dissolved in the medium was determined spectrophotometrically. The amounts of dissolved tolbutamide after 20 and 120 min corresponding approximately to the dissolution of 50% and 100% of tolbutamide respectively, were the parameters used for the statistical analysis.

Studies of pharmacological activity

The in vivo studies were carried out in order to determine the glycaemic levels after the oral administration of a dose of 100 mg/kg tolbutamide (commercial powder and solid dispersions). The animal species were rabbits (New Zealand breed). For each formulation, blood samples were taken from 6 rabbits at the following time intervals: 0, 1, 2, 3, 4, 6 and 8 h. Two parameters were analysed statistically after 0, 6, 9 and 12 months ageing: first the time of the lowest glycaemic level and second the area under the curve (AUC) that is the coefficient of the glycaemic variation versus time (0–8 h).

Results and Discussion

The thermograms of the tolbutamide solid dispersions with PEG 6000 and PEG 20,000 displayed similar characteristics (Figs. 1, 2). Bulk PEG 6000 shows a double melting endotherm (thermograms not shown); similar results on DSC of PEG 6000 (Ford, 1984) suggested that the double melting endotherms were due to the presence of either two molecular weight fractions or

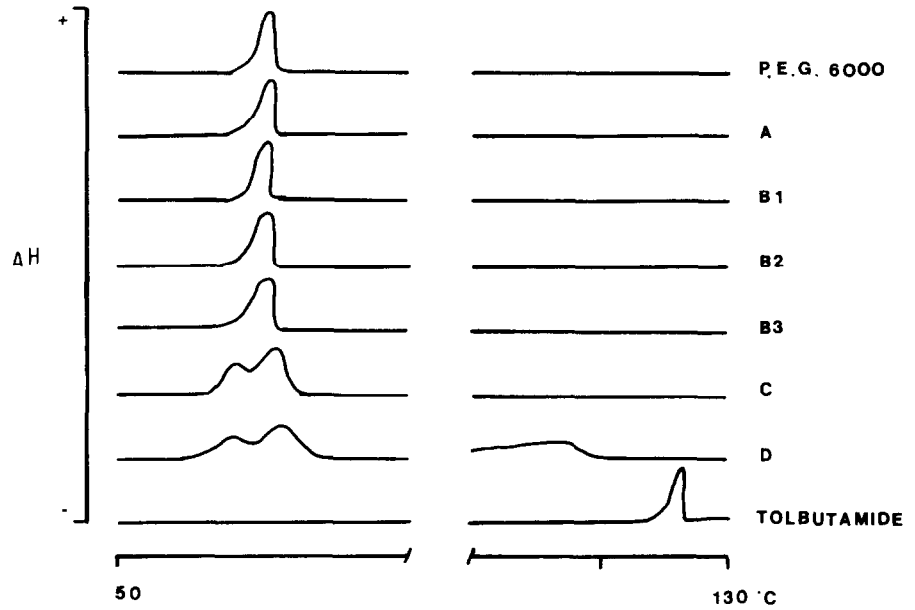

Fig. 1. Thermograms of the tolbutamide–PEG 6000 solid dispersions A and B1, respectively, 10% and 20% tolbutamide at 0 time; B2 and B3, 20% tolbutamide after, respectively, 6 and 12 months; C, 30% tolbutamide; D, 50% tolbutamide.

two PEG configurations. Following the coprecipitation process (PEG previously dissolved with chloroform) the thermogram of PEG 6000 showed only one melting endotherm (Fig. 1).

Incorporation, by coprecipitation, of tolbutamide into the glycols up to 20% (w/w) resulted in a single endotherm peak and no significant changes were observed, which suggests that tolbutamide is

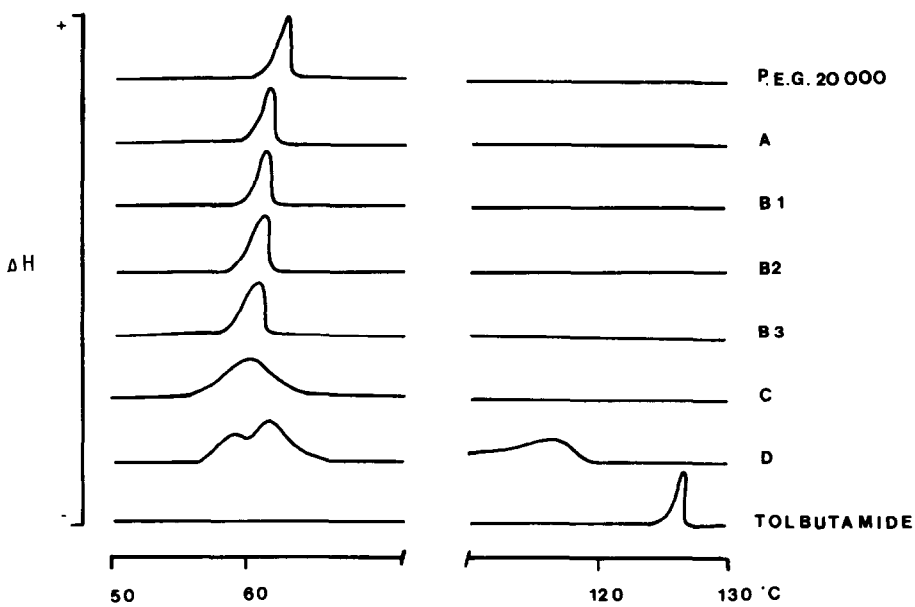

Fig. 2. Thermograms of the tolbutamide–PEG 20,000 solid dispersions (see legend in Fig. 1).

dissolved in the melted PEG. After increasing the tolbutamide level, a broadening of the peak as well as inflections on the trailing edges of the endotherms were observed. Finally, the thermograms for the highest percentages of drug exhibited two transitions that corresponded to the fusion of the excipient and the drug, respectively; these results correspond to previous observations made for tolbutamide–PEG 2000 systems (Kaur et al., 1980). It can be inferred that the solubility of tolbutamide in melt PEG is particularly high which increases substantially the molecular weight of the polymer and in the same way the heat of fusion. In addition, tolbutamide can exist in up to 4 polymorphic forms but the only tolbutamide form used under the conditions of the present work was the commercial powder which melted at a temperature of 127 °C (form III) (Al-Saieq et al., 1982).

Considering such results, the solid dispersions with both a single endotherm effect and the tolbutamide level of 20% (w/w) has been chosen for the stability studies. After 6 and 12 months, no important changes appeared, except for a slight, gradual broadening of the peak, probably caused by the precipitation of some drug molecules dispersed initially in the PEG matrix (Abdallah et al., 1986). Although the presence of solid solution is not obvious in the DSC pattern, a molecular dispersion of tolbutamide is conceivable to a slight extent, given the structure of the polymer (Ford, 1980).

A comparison of the powder X-ray diffraction patterns of tolbutamide and tolbutamide–PEG solid dispersions (Figs. 3, 4) suggested that no degradation or new compound formation had occurred (no additional new diffraction lines), and that the dispersion is present as a physical mixture of the drug and the carrier. The lower intensity of the tolbutamide peaks was probably due to changes in the preferred orientation of drug crystals rather than to any alteration in the physicochemical properties of the material (McGinity et al., 1984).

Moreover, X-ray diffraction spectra obtained at different time intervals showed a slight increase in the tolbutamide peak heights during storage, which may be attributed to an increase either in the

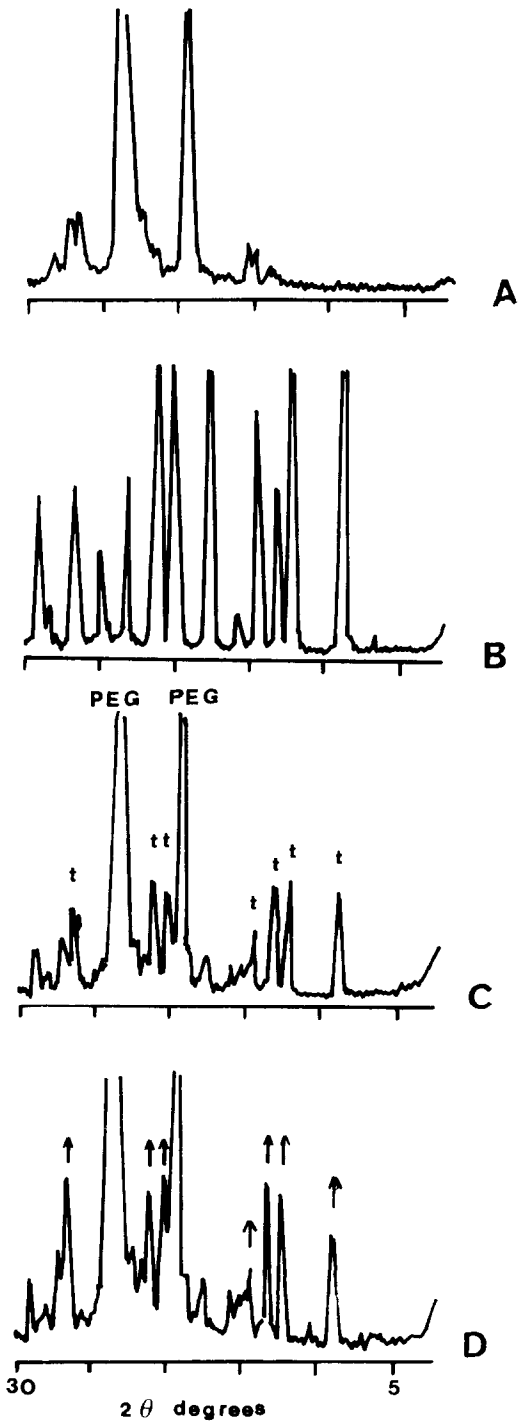

Fig. 3. X-Ray diffraction patterns obtained for the tolbutamide–PEG 6000 system. A: PEG 6000; B: tolbutamide; C: solid dispersion at 0 time; D: solid dispersion after 12 months.

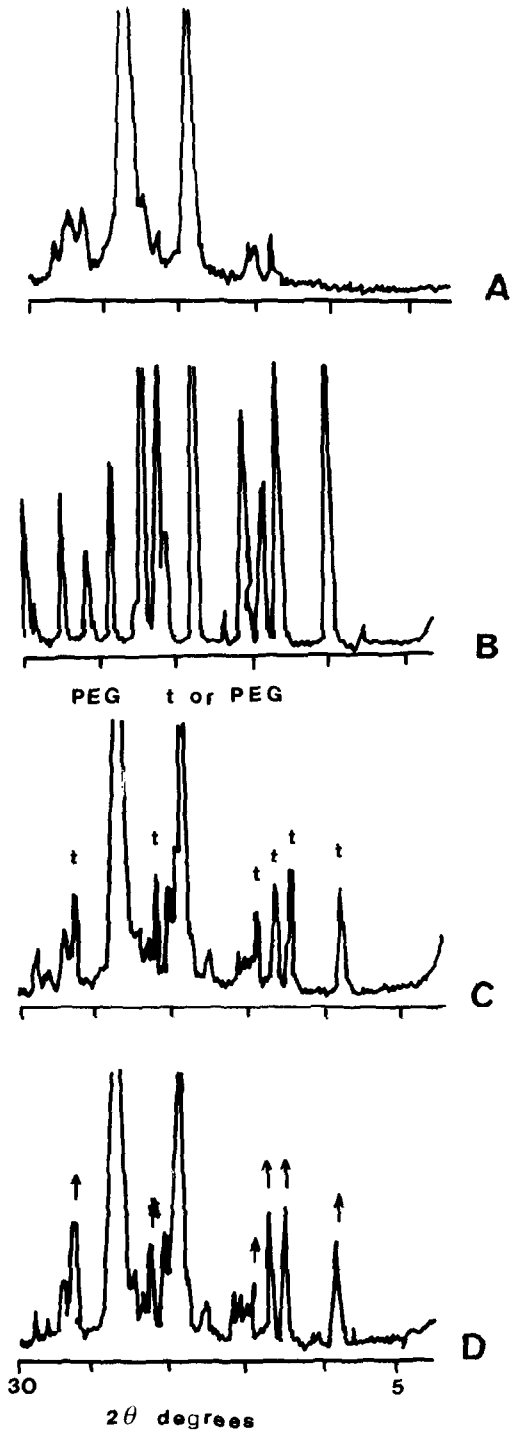

Fig. 4. X-Ray diffraction patterns obtained for the tolbutamide–PEG 20,000 system. A: PEG 20,000; B: tolbutamide; C: solid dispersion at 0 time; D: solid dispersion after 12 months.

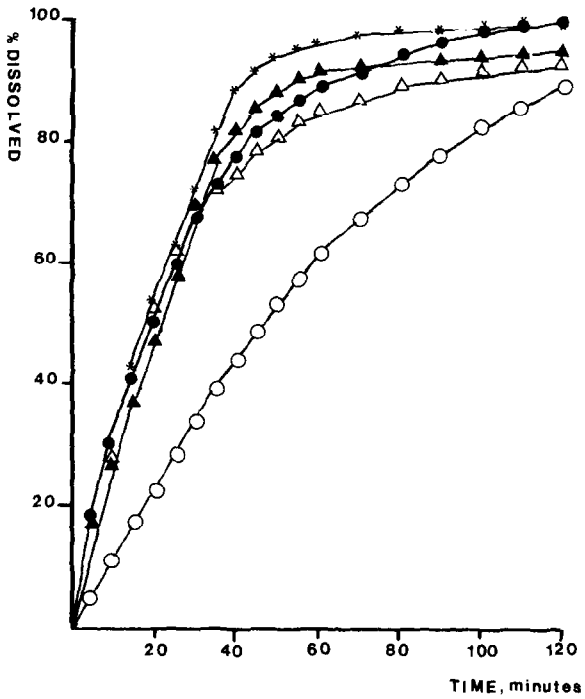

Fig. 5. Percentages of tolbutamide dissolved versus time. tolbutamide (○), tolbutamide–PEG 6000 solid dispersion at 0 time (●) and after 12 months (*), tolbutamide–PEG 20,000 solid dispersion at 0 time (▲) and after 12 months (△). Each point is the average of 4 samples.

degree of crystallinity or in the size of the tolbutamide particles.

The dissolution profiles found for the tolbutamide alone and the tolbutamide coprecipitates are shown in Fig. 5. These results confirm the previous findings that the incorporation of tolbutamide in PEG solid dispersions significantly enhanced the dissolution rates (Kassem et al., 1980; Miralles et al., 1982). It is obvious that the storage at 25 °C for 1 year did not appear to have any marked effect on the dissolution profiles. Moreover, the two-way ANOVA yielded no significant differences between the dissolved amount either after 20 min ($P > 0.05$) or after 120 min ($P = 0.05$–0.025) for the different ageing times (Tables 1 and 2). So if any change in the physicochemical properties had occurred, it could not possibly be significant enough to modify the dissolution kinetics of the drug. This stability study for the long-term has not frequently been referred

TABLE 1

Percentages of dissolved tolbutamide after 20 min

Time (months)	Tolbutamide	Tolbutamide –PEC 6000	Tolbutamide –PEG 20000
0	23.00 ± 1.88	50.48 ± 5.83	49.31 ± 1.07
2	–	56.48 ± 2.26	51.46 ± 1.27
4	–	55.40 ± 5.83	56.49 ± 1.27
6	–	55.97 ± 1.23	57.39 ± 1.33
12	–	52.07 ± 2.27	54.26 ± 2.37

Values are mean ± σ; $n = 4$

to as yet (Ford and Rubinstein, 1979; Bogdanova et al., 1983). For the analysis of the therapeutical efficiency of tolbutamide–PEG solid dispersions, and the possibility of an alteration in the drug activity during the storage, glycaemia levels in rabbits were determined after the oral administration of tolbutamide alone and as a solid dispersion. The lowest glycaemia levels were observed after 8 or 2 h when tolbutamide alone or as a solid dispersion were administered, respectively, as seen in Fig. 6. Similar results were found when glybornuride solid dispersions were used (Vila-Jato et al., 1986). The area under the curve reflecting the variations of the glycaemia levels versus time (0–8 h) and the percentages of glucose variation are presented in Tables 3 and 4, respectively, for both the solid dispersions and the commercial powder. No significant differences ($P > 0.05$) either in the AUC or in the variation of the glucose levels after 2 h for the different-age solid dispersions were detected (Tables 3, 4). On the contrary, the statistical analysis of the two latter parameters between the different solid dispersions

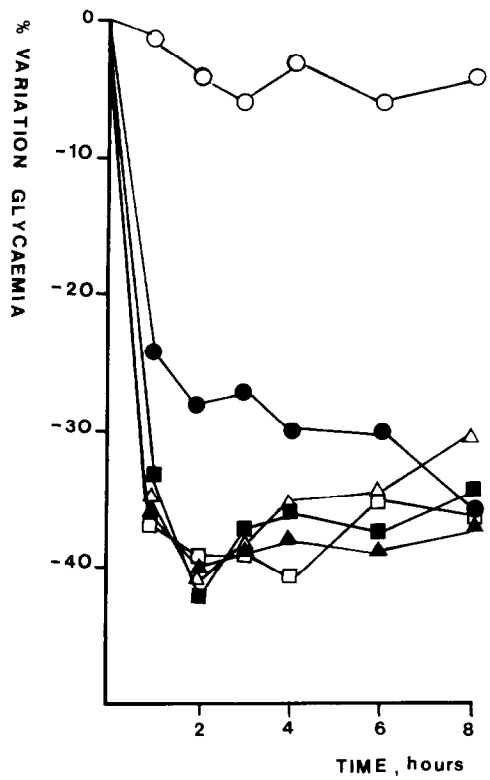

Fig. 6. Coefficient of variation of glycaemia in rabbits after administration of 100 mg/kg of tolbutamide (●), tolbutamide–PEG 6000 solid dispersion at 0 time (■) and after 12 months (□), tolbutamide–PEG 20,000 solid dispersion at 0 time (▲) and after 12 months (△). Control animals (○). Each point is the average of 6 samples.

systems (PEG 6000 and PEG 20,000) and the tolbutamide powder is considerably different ($P > 0.01$), confirming the dissolution results and the importance of the dissolution process in the pre-

TABLE 2

Percentages of dissolved tolbutamide after 120 min

Time (months)	Tolbutamide	Tolbutamide –PEG 6000	Tolbutamide –PEG 20000
0	89.23 ± 3.18	98.25 ± 1.76	94.97 ± 1.13
2	–	99.60 ± 0.18	96.67 ± 2.07
4	–	94.64 ± 4.99	93.20 ± 3.92
6	–	96.47 ± 3.01	98.42 ± 0.93
12	–	99.39 ± 0.22	93.66 ± 1.13

Values are mean ± σ; $n = 4$

TABLE 3

AUC (% of glycaemia variation × h) for the different dosage forms after oral administration in rabbits

Time (months)	Tolbutamide	Tolbutamide –PEG 6000	Tolbutamide –PEG 20000
0	251.88 + 56.42	251.50 + 30.70	261.50 + 33.36
6	–	279.70 + 70.45	267.00 + 20.66
9	–	311.16 + 25.58	276.50 + 37.78
12	–	283.00 + 46.75	263.00 + 51.41

Values are mean ± σ; $n = 6$.

TABLE 4

Percentages of glucose variation 2 h after oral administration of the different dosage forms in rabbits

Time (months)	Tolbutamide	Tolbutamide -PEG 6000	Tolbutamide -PEG 20000
0	25.00 ± 7.37	38.83 ± 5.74	38.00 ± 2.77
6	–	38.83 ± 6.38	40.67 ± 7.18
9	–	45.67 ± 7.67	39.33 ± 5.73
12	–	39.33 ± 5.18	41.67 ± 7.18

Value are mean ± σ; $n = 6$.

absorption steps in vivo. By using the tolbutamide–PEG coprecipitate, a larger and faster therapeutic response is obtained. Therefore the coprecipitate dosage form has improved the tolbutamide bioavailability. One of the most important problems with solid dispersions is the evolution during storage (Vila-Jato and Alonso, 1986); we have found that the improvement of the therapeutic activity was not altered by the storage. The two PEG coprecipitates displayed similar characteristics. Moreover, the slight change in the physicochemical properties did not change the coprecipitates' behaviour in vivo. Thus, the system can be considered as stable for at least one year.

The results presented in this work have shown that tolbutamide solid dispersions with PEG increase not only its absorption rate but also the total amount absorbed. Therefore the efficacy of the hypoglycaemic agent dispersed in the PEG matrices has been established. The stability of solid dispersions is the major problem for their development and few systems have been marketed so far: this work has shown the stability of the tolbutamide PEG coprecipitates but should be confirmed by long-term stability studies.

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