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SOLID DISPERSIONS: COMPARISON OF PREPARED MELTS AND COPRECIPITATES OF DIAZEPAM AND POLYOXYETHYLENE GLYCOL 4000

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Gastro-intestinal absorption and bioavailability of hydrophobic active ingredients are usually limited by their poor solubility and low dissolution rate.

With a view to improving these different parameters,a great deal of research work has been carried out to present the active ingredients in solid dispersion form.

The most widely used definition of solid dispersions is that put forward by Chiou and Reigelmans in 1971 (1). They are dispersions, in the particle or molecular state,of one or more very slightly soluble active ingredients in one or more water-soluble inert excipients.

Solid dispersions can be obtained by three main procedures: by melting, by using solvents, or by a combined process including melting and solvents.

Sekiguchi and Obi first used the melting method in 1961 (8). It consisted of melting the physical mixture of the active ingredient and the water-soluble excipient by agitation,and then,by cooling,causing rapid solidification of the liquid obtained. This product is then crushed and calibrated. This is the melt.

The advantage of this method is its simplicity and its economy. However,it has the drawback of possible decomposition or evaporation of the constituents during melting at high temperatures.

The solvent method was used for the first time by Tachibana and Nakamura in 1965 (9). This consisted of dissolving the active ingredient and the excipient in an organic solvent which was then evaporated. The product obtained is crushed and calibrated. This is the coprecipitate.

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This method does not involve the risk of decomposition or evaporation of the component products by heat. However a certain number of drawbacks subsist: the choice of the solvent, the difficulty of its complete elimination and,finally, the high cost of the process.

We thought it would be interesting to compare these two techniques: melt and coprecipitate. We chose diazepam for this investigation, which is a psychotropic benzodiazepin exhibiting absorption irregularities (2) which are no doubt related to its poor solubility. After a compatibility test between diazepam and various combination products in the form of melts or coprecipitates, we selected polyoxyethylene glycol 4000 (5) as excipient.

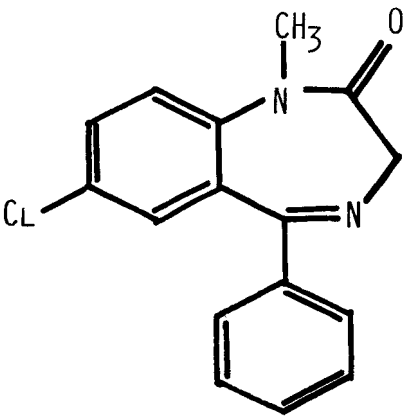
In fact,in 50/50 melt form, diazepam cannot be used with mannitol, sorbitol, galactose or citric acid,since this results in coloured products in which either the excipient or the diazepam is degraded. Neither can diazepam be used easily with glucose or urea due to poor miscibility with galactose. Used with PEG 4000,the melted product is a transparent liquid which takes on a homogeneous appearance on cooling.

1 EXPERIMENTAL

1.1 RAW MATERIALS

1.1.1 Diazepam

This is 7-chloro-1-methyl- 5- phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one.



It is a yellowish-white crystalline powder. Its melting point is between 130 and 133 °C. No thermal degradation appears before 160 °C. It is poorly soluble in water, but soluble in ethanol, methanol,chloroform, ether,acetone and propylene glycol.

1.1.2 Polyoxyethylene glycol 4000

This is a water-soluble polymer in solid form. Its melting point is 53 °C and it remains stable up to 135 °C. It is very soluble in methanol, ethanol, and chloroform.

1.1.3 Solvents

Methanol and ethanol were used as solvents in this investigation.

1.2 PRODUCTS INVESTIGATED

Figure 1 shows phase diagrams prepared using differential scanning calorimetry (DSC) carried out on mixtures of diazepam and PEG 4000 (in variable proportions), and taken from previous investigations (3,5,6).

We demonstrated the existence of a eutectic corresponding to the proportion diazepam 17 %/PEG 4000 83 % melting at 52 °C. On the

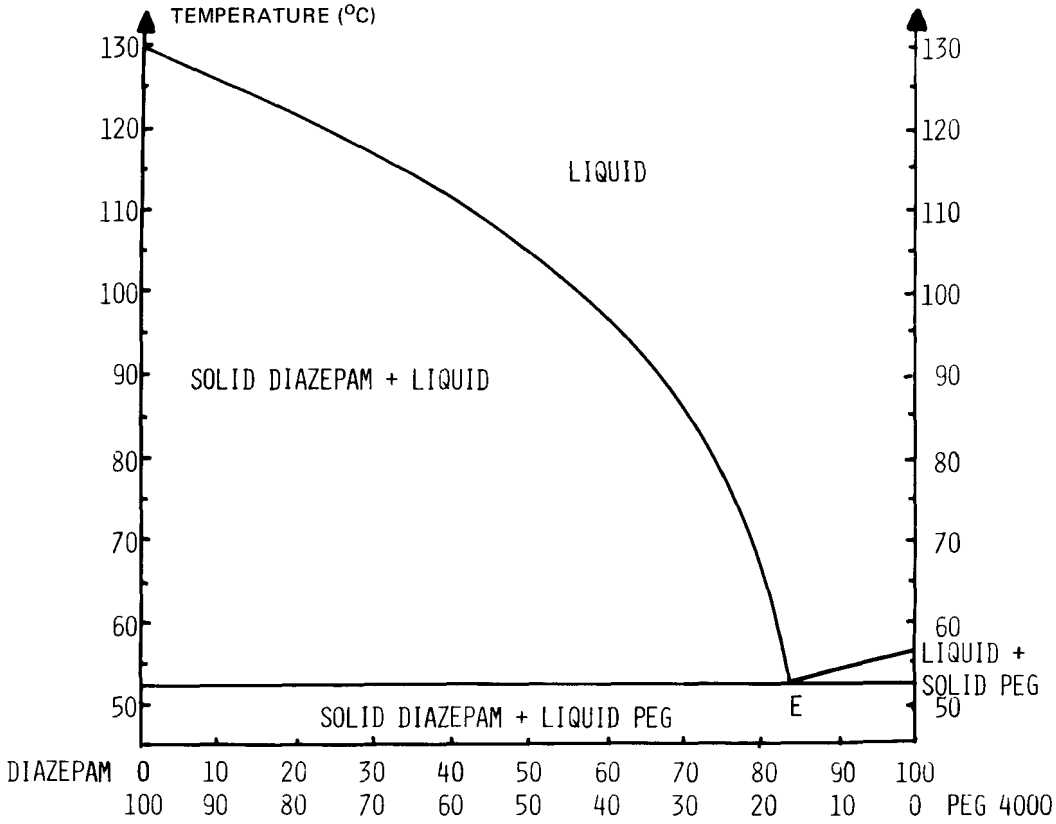


Figure 1. Phase diagram of mixtures of diazepam and PEG 4000

other hand it was not possible to confirm the existence of a solid solution.

These investigations pointed out that the higher the proportion of PEG 4000 in the melt (90 and 95%), the greater the dissolution rate of the diazepam. The melt corresponding to the composition of the eutectic did not exhibit any particular properties.

These results therefore led us to choose the proportion diazepam 10%/ PEG 4000 90% for the investigation presented here.

During this current work, the products which were particularly studied are first diazepam (basic product,product melted and recrystallized, product dissolved in methanol or ethanol and recrystallized), and secondly the combinations diazepam/PEG 4000 (physical mixture,melt,coprecipitates obtained either in methanol or ethanol).

1.3 PREPARATION OF DIAZEPAM/PEG 4000 COMBINATIONS

1.3.1 Physical mixture

A mortar was used to obtain the mixture of diazepam and PEG 4000. The mixture was then put through a 200 µm mesh sieve.

1.3.2 Melt

10 g of the physical mixture were placed in a crystallizer and allowed to melt in a silicone oil bath placed on a heating plate. This plate was regulated so that a temperature of 130 °C was reached in 20 minutes. At the moment of melting the mixture was stirred using a glass agitator. As soon as a homogeneous liquid was obtained, it was poured on to a cold porcelain surface and kept for 48 hours at 37 °C. The product was then recovered,crushed and put through a 200 µm mesh sieve.

1.3.3 Coprecipitate

10 g of the physical mixture of diazepam/PEG 4000, obtained as above, were dissolved in a minute quantity of solvent(methanol or ethanol) then placed in the flask of a rotary evaporator. Evaporation was carried out under vacuum in a bain-marie at 40 °C. When a pasty mass was obtained,this was recovered and total elimination of the remaining solvent achieved by stoving at 40 °C, the product being kept at this temperature to constant weight. The sold mass obtained was crushed and sieved as above.

1.4 DESCRIPTION OF TESTS

The tests carried out on the products obtained from the various treatments and combinations included thin layer chromatography,in order to check the non-alteration of the diazepam, and also determination of the solubility and dissolution rate of diazepam.

A storage test was also performed on the coprecipitates and the melt.

1.4.1 Thin layer chromatography

Chromatographs of diazepam were carried out on silica gel plate 60 F-254 (Merck).

The products to be studied were dissolved in methylene chloride using 10 mg (diazepam) or 20 mg (diazepam/PEG 4000 combinations) per cm^3. The deposits on the plate were 10 mm^3.

The migration solvent was made up of a 50/50 mixture of heptane and ethyl acetate. Solvent migration lasted 20 minutes.

After drying, development was carried out by ultraviolet.

1.4.2 Solubility

Dertermination of solubility in water was carried out at ambient temperature. To do this, 20 mg of diazepam were placed in 20 cm^3 of distilled water and continuously agitated for 48 hours using a vibrating plate. The solutions were filtered on N° 4 sintered glass. 1 cm^3 of the filtrate was taken up and 0.1 N sulphuric acid added to bring up to 20 cm^3. Final determination was carried out by ultraviolet absorption at 242 nm.

1.4.3 Dissolution rate

The dissolution rate was determined using a technique similar to the beaker method of Levy and Hayes (7).

A test sample of about 10 mg of diazepam was placed in a beaker containing 500cm^3 of distilled water kept at 37 °C. A propeller turning at 21 rad/s ensured agitation. Samples were taken at specific time intervals over a period of two hours, and these samples were replaced by equal volumes of distilled water. Determinations were carried out in the same conditions as above.

1.4.4 Storage

The following conditions were imposed for storage: four months at 4 and 37 °C for the melt, and five months at ambient temperature for the coprecipitates. After checking the non-alteration of the diazepam by ultraviolet spectrometry and thin layer chromatography, the dissolution rate of the diazepam was determined in the same conditions as for the previous test.

2 RESULTS AND DISCUSSION

2.1 EFFECT OF THE DIFFERENT TREATMENTS

2.1.1 Stability of diazepam

The chromatograms shown in Figure 2 indicate that neither melting nor dissolution in methanol or ethanol, followed by recrystallization, caused any degradation of the diazepam.

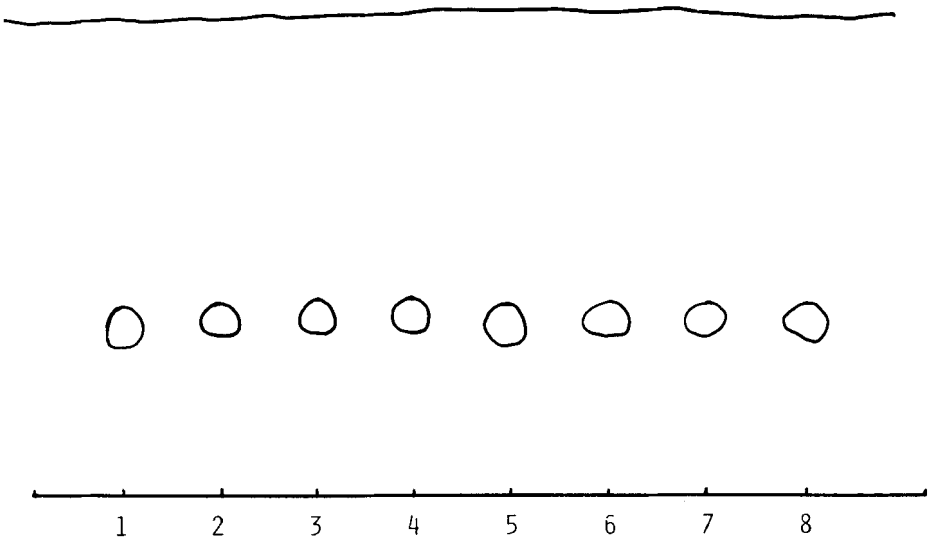


Figure 2. Chromatograms of : diazepam (1), melted diazepam (2), diazepam recrystallized in ethanol (3), diazepam recrystallized in methanol (4), physical mixture (5), melt (6), coprecipitate in ethanol (7), coprecipitated in methanol (8).

Table 1
Solubility of diazepam
Effect of recrystallization in methanol or ethanol

product	solubility in mg . 10^3 cm^{-3}
diazepam	46 ±0.7
diazepam/methanol	43.5 ±0.7
diazepam/ethanol	50 ±1.4

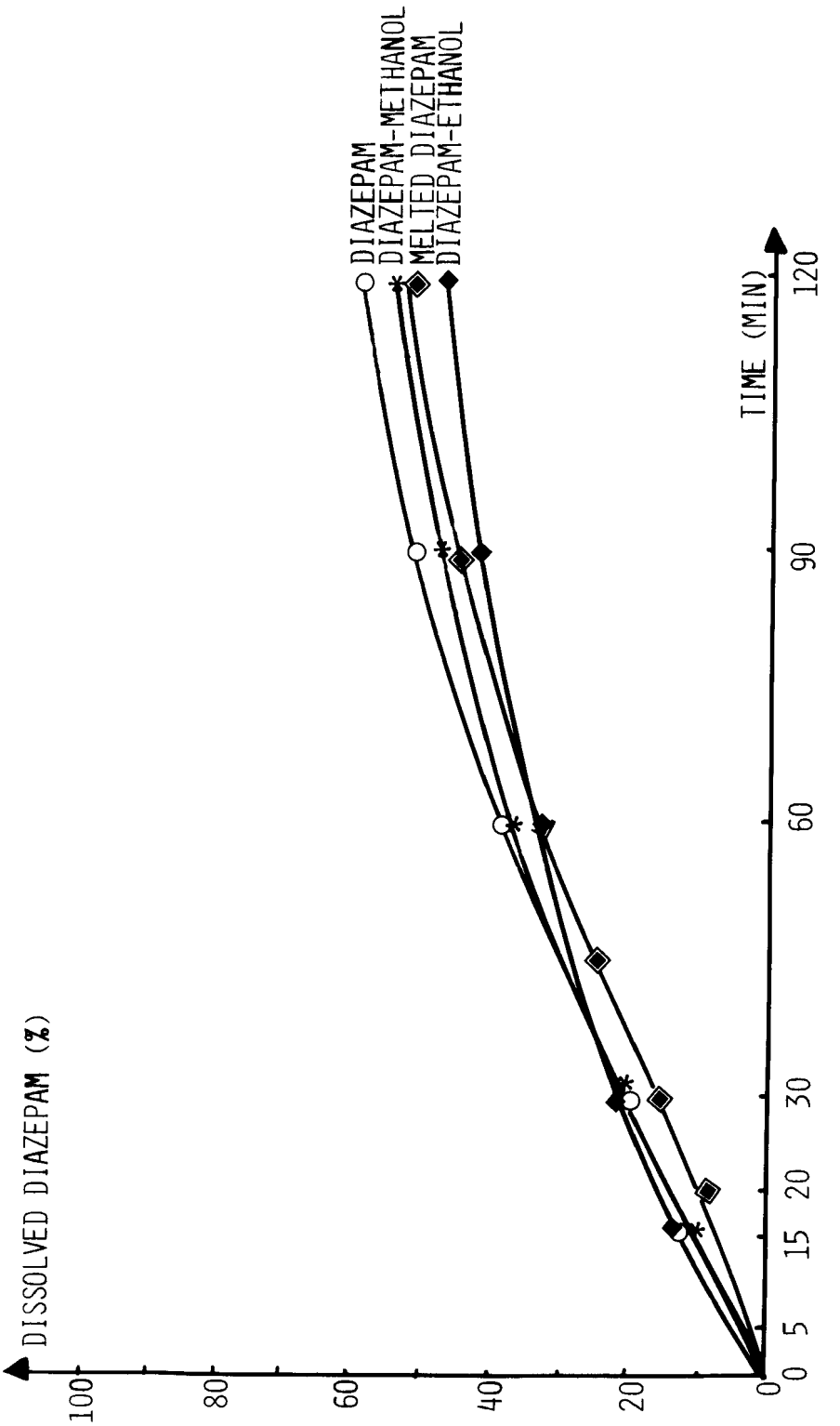


Figure 3. Dissolution of diazepam, effect of the differents treatments

2.1.2 Solubility

As can be seen from Table 1, dissolution in methanol or ethanol, followed by recrystallization of the diazepam, caused no significant alteration in its solubility, which remained between 43.5 and 50 mg . 10^3 cm^{-3}.

2.1.3 Dissolution rate

Regardless of the treatment undergone by the diazepam (melting or recrystallization), its dissolution rate remained about the same, or underwent a slight reduction (Figure 3): after 30 minutes the amounts dissolved were between 15 and 20 %, and after 90 minutes between 40 and 50 %. The variations were not important.

2.2. EFFECT OF COMBINATION WITH PEG 4000

2.2.1 Stability of the diazepam

The chromatographs shown in Figure 2 indicate that the combination of PEG 4000 and diazepam did not cause any degradation of the diazepam, whether this be in the physical mixture, or in the form of the melt or the coprecipitate.

2.2.2 Solubility

As can be seen from Table 2, the combination of PEG 4000 with diazepam had no serious effect on the solubility of this product; there was just a slight increase in the case of the solid dispersions (melt or coprecipitates).

Table 2

Solubility of diazepam
Effect of combination with PEG 4000 (diazepam 10 % / PEG 4000 90 %)

Product	solubility in mg . 10^3 cm^{-3}
diazepam	46 ±0.7
physical mixture	47 ±0.6
melt	53 ±1.5
methanol coprecipitate	56 ±0
ethanol coprecipitate	55 ±0.2

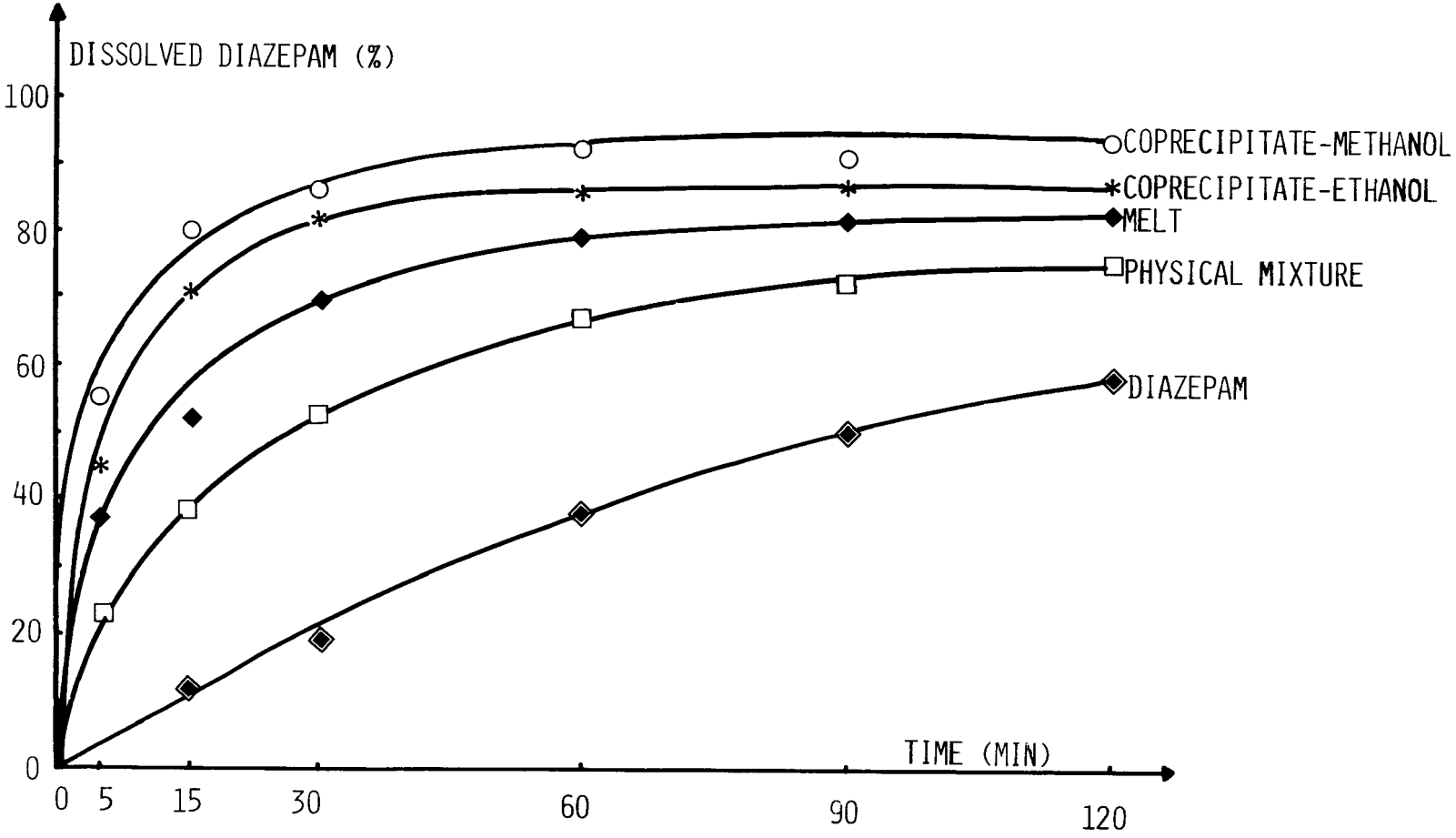


Figure 4. Dissolution of diazepam, effect of combination with PEG 4000

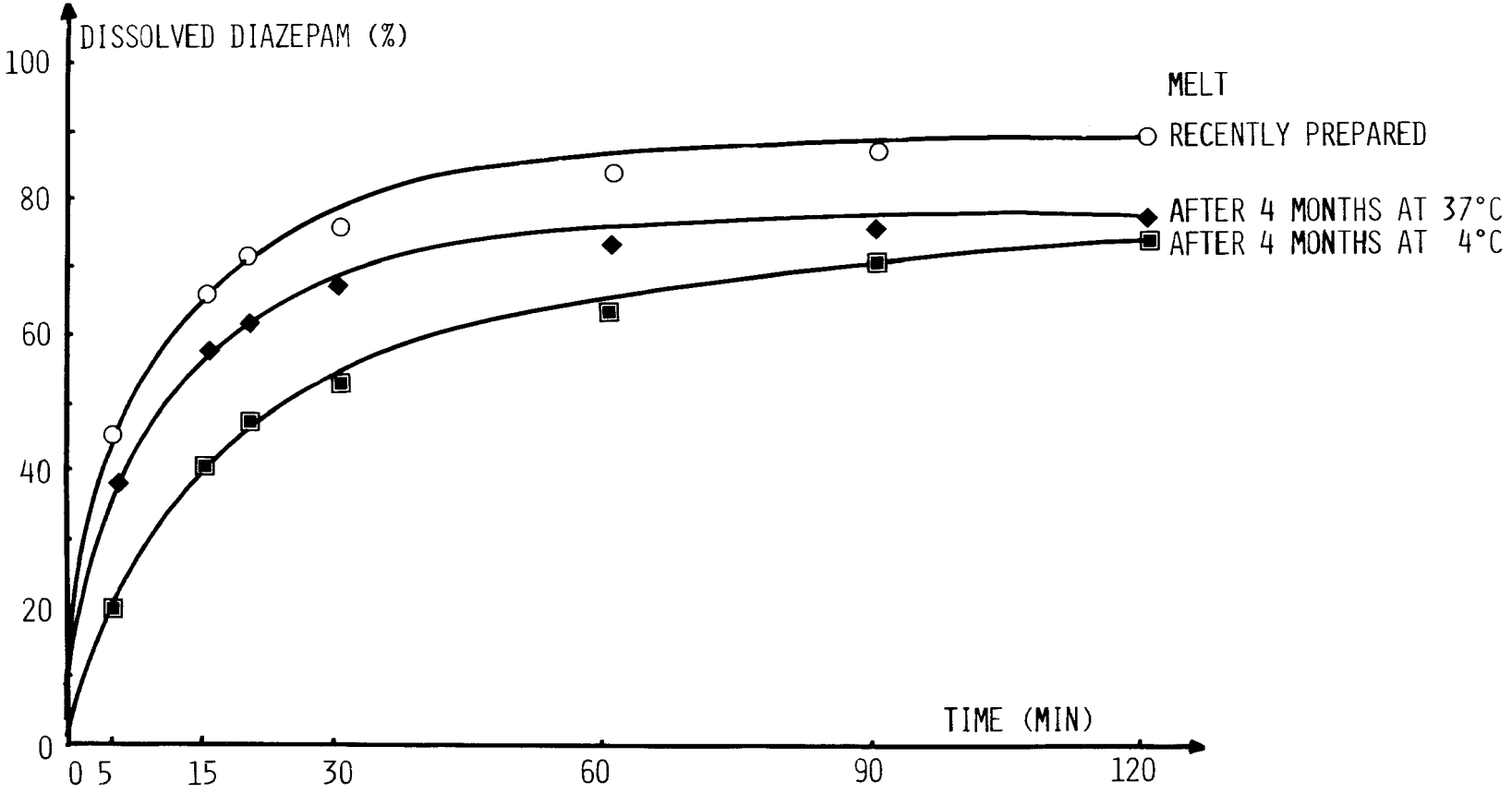


Figure 5. Dissolution of diazepam, effect of storage of melts

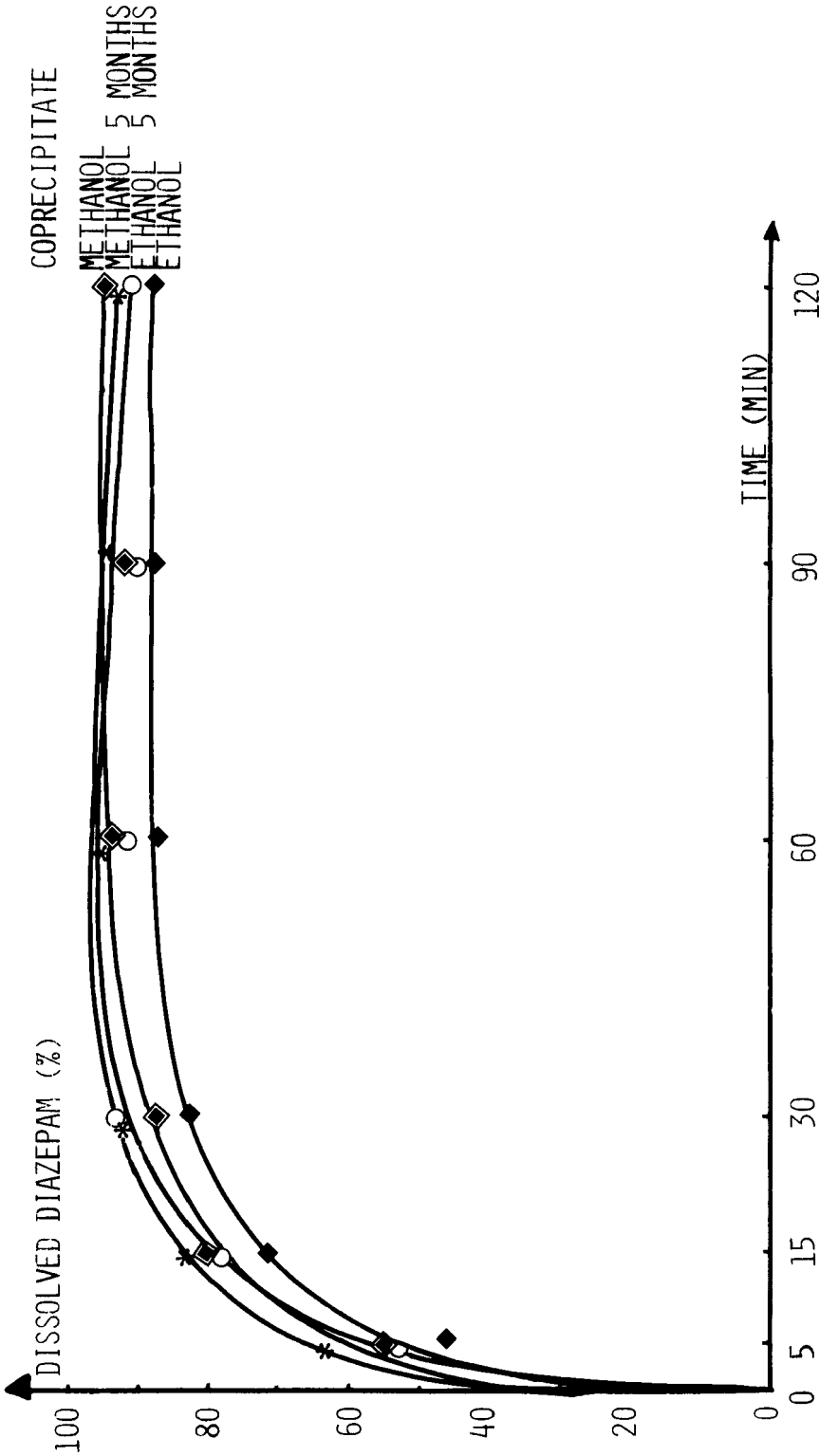


Figure 6. Dissolution of diazepam, effect of storage of coprecipitates.

2.2.3 Dissolution rate

In every case PEG 4000 increased the dissolution rate of diazepam (Figure 4) This situation was much more obvious for the solid dispersions than for the physical mixture. Also, among the solid dispersions, the coprecipitates (especially that obtained in methanol) dissolved somewhat more quickly than the melt. After 30 minutes, in fact, whilst only 19 % of diazepam had dissolved with regard to the pure product, the figure reached 52 % for the physical mixture 70 % for the melt, 82 % for the ethanol coprecipitate,and 86 % for the methanol coprecipitate.

The effect of PEG 4000 was therefore due not only to the improved "wetting"of diazepam, but also to a "finer" dispersion, indeed a dispersion approaching the molecular state, of the diazepam in the PEG 4000.

2.3 STORAGE OF SOLID DISPERSIONS

Although storage conditions were not the same for the melt (four months at 4 and 37 °C) and for the coprecipitates(five months at ambient temperature), it is surprising to note that the results are completely different for these two types of product.

In the case of melt, whatever its storage temperature, there was a reduction in the dissolution rate of the diazepam. This phenomenon was however less obvious at 37 °C than at 4 °C (Figure 5)

In the case of the coprecipitates stored at ambient temperature, no reduction in the dissolution rate was observed (Figure 6).

These results need to be extended over a greater temperature range and for longer periods. They do not in fact agree with the results of Ford and Rubinstein (4) who found that the storage of melts of indomethacin and PEG 6000 was better at 4 °C than at 35 °C, but also that in the latter case a stabilization of the product set in after several days in storage.

CONCLUSION

The work which has just been presented dealt with the preparation of solid dispersions of diazepam in polyoxyethylene glycol 4000, and particularly with the comparison of the products obtained, either by comelting, or by coprecipitation in methanol or ethanol.

The following points should be borne in mind.

The different treatments undergone by the diazepam during the preparation of the solid dispersions (melting or dissolution, followed by recrystallization) did not themselves cause either degradation of the diazepam, or any alterations to solubility or the dissolution rate.

The combination of diazepam with polyoxyethylene glycol 4000 caused, in every case, an increase in the dissolution rate of

diazepam. This increase was much more obvious for the solid dispersions than for the physical mixture,and especially for the coprecipitates, notably that prepared in methanol.

The storage of products obtained by comelting appears delicate, the dissolution rate decreasing with time. In the case of the coprecipitates, storage appears to be easier.

REFERENCES

(1) W.L. Chiou and S. Riegelmans,
Pharmaceutical applications of solid dispersion systems,
J. Pharm.Sci., 60, 1281-1302 (1971).

(2) J.T. Carstensen, S.E. Kenneth Jr., F. Maddrell, J.B. Johnson and H.N. Newmark,
Thermodynamic and kinetic aspects of parenteral benzodiazepins,
Bull.Parent. Drug Assoc., 25, N4,193-202 (1971).

(3) D. Duchêne,S.Henry,B. Legendre,C. Souleau and F. Puisieux,
Solid dispersions,
Acta Pharm.Suec., 18, 103-104 (1981),

(4) J.F. Ford and M.H. Rubinstein,
Ageing of indomethacin-polyethylene glycol 6000 solid dispersions,
Pharm. Acta Helv., 54, 353-358 (1979).

(5) S. Henry,
Dispersions solides de diazépam: étude thermodynamique, structurale et galénique,
Thèse de 3ème Cycle de Pharmacie, N° 38, Université de Paris-Sud (1982).

(6) S. Henry,B. Legendre, C. Souleau, F. Puisieux and D. Duchêne,
Dispersions solides: étude des cofondus à base de diazépam et de polyoxyéthylène glycol 4000,
Pharm.Acta Helv. (to appear).

(7) G. Levy and B.A. Hayes,
Physicochemical basis of polyvinylpyrrolidone and other binding agents in tablet formulation,
Drug Standards,26, 170-175 (1958).

(8) K. Sekiguchi and N. Obi,
Studies on absorption of eutectic mixtures. I A comparison of the behavior of eutectic mixture of sulfathiazole and that of ordinary sulfathiazole in man
Chem. Pharm. Bull., 9, 866-872 (1961).

(9) T. Tachibana and A. Nakamura,
β-carotene-PVP coprecipitates
Kolloid 2 Polym., 203, 130-133 (1965).