International Journal of Pharmaceutics, 58 (1990) 221–227
Elsevier

IJP 01985

Comparison of tolbutamide β-cyclodextrin inclusion compounds and solid dispersions

Physicochemical characteristics and dissolution studies

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(Received 7 July 1989)
(Accepted 20 August 1989)

Key words: Tolbutamide; β-cyclodextrin; Complexation; Solid dispersion; Poly(ethylene glycol); Physicochemical characteristics; Dissolution

Summary

Tolbutamide was found to form an inclusion complex with β-cyclodextrin. An equilibrium phase solubility diagram was obtained for the tolbutamide–β-cyclodextrin system in water. The solubility of tolbutamide increased on addition of β-cyclodextrin, displaying a Bs-type phase diagram. A stability constant of 2.101×10^3 M^{-2} was calculated. The insoluble complex obtained thereby had a stoichiometry of 1 : 2 (tolbutamide : β-cyclodextrin). Comparison of the complex was carried out with PEG 6000 solid dispersions, prepared by either the comelting or coprecipitation method, using X-ray diffraction, infrared spectrophotometry and differential thermal analysis. Dissolution profiles in a pH 2 medium, of tolbutamide, comelt, coprecipitate and inclusion complex demonstrated a faster dissolution rate of the inclusion complex compared to solid dispersions and tolbutamide alone. After 20 min the amount of drug released was around 19% for the powdered free drug, 33% for the coprecipitate, 38% for the comelt and 100% for the inclusion complex.

Introduction

Tolbutamide, a sulphonylurea compound, employed as an oral hypoglycemic agent, is practically insoluble in water. Its dissolution is considered to be the rate-limiting process for the absorption (Miralles et al., 1982). Solid dispersions of tolbutamide in water-soluble carriers such as urea, PEG 6000, PEG 4000, PEG 20 000, dextrose and mannitol, alone or combined in various proportions have been studied and reported with a view to increasing the dissolution rate (Miralles et al., 1982; McGinity et al., 1984; Alonso et al., 1988). Since the first description of a solid dispersion in order to increase the dissolution and oral absorption of poorly water-soluble drugs by Seikiguchi and co-workers (1961), the tremendous amount of research carried out in this field has led only to a very limited range of patented products on the world market. More recently, complexation with cyclodextrins has been extensively applied to im-

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prove the solubility, stability and bioavailability of various drugs (Saenger, 1980; Uekama, 1981; Nakai et al., 1984). Tolbutamide was included in β-cyclodextrin and turned out to penetrate their relatively hydrophobic cavities, leading to an increase in solubility of the drug (Uekama et al., 1978; Ueda and Nagai, 1981; Takeuchi et al., 1987). The present study was carried out to verify, using tolbutamide as a drug model, that the properties of a cyclodextrin-drug complex were at least similar to those obtained with solid dispersions of the same drug. Therefore, the aim of this work was to compare the physicochemical characteristics as well as the dissolution profiles of tolbutamide–β-cyclodextrin complexes and fresh solid dispersions prepared by either the comelt or coprecipitate method.

Materials and Methods

Materials

Tolbutamide (m.p. 127 °C) (Sigma, S. Louis, MO), polyethylene glycol 6000 (m.p. 55–62 °C) (Merck, Hohenbrunn, F.R.G.), and β-cyclodextrin (Aldrich, Steinheim, F.R.G.) were used as received. All other reagents and solvents were of analytical grade.

Phase solubility studies

Phase solubility studies were performed according to the method reported by Higuchi and Connors (1965). 20 mg tolbutamide were weighed out into 30-ml flasks. A constant volume of 20 ml distilled water was added to each container. Then successively increasing portions of β-cyclodextrin (0.001–0.028 M) were added to these vessels which were closed and brought to solubility equilibrium at room temperature, with stirring, over a period of 2 weeks. After attainment of equilibrium, the contents of the flasks were filtered through a Millipore membrane (HA 0.45 μm). The tolbutamide concentration in the filtered solutions was determined from the absorbance at 226 nm using a Perkin-Elmer UV-Visible spectrophotometer.

Sample preparation

Preparation of tolbutamide comelt. Tolbutamide and PEG 6000 (1 : 2) were melted together according to a previously published method (McGinity et al., 1984) by first heating the PEG 6000 in an aluminium dish over an oil bath at 80 °C. The drug was then dissolved in the molten carrier and stirred to obtain a homogeneous dispersion. Flash cooling of the dispersion by immersion in a bath of dry ice and acetone was employed. Indeed, it has been shown that rapid cooling gives rise to faster dissolution rates (McGinity et al., 1984). The dispersion was then dried under vacuum at room temperature for 24 h.

Preparation of tolbutamide coprecipitate. A mixture of tolbutamide and PEG 6000 (1 : 2) was dissolved in a sufficient volume of chloroform, and evaporation was carried out in vacuo at 25 °C (Alonso et al., 1988). The hardened mass was removed from the container and dried under vacuum at room temperature for 24 h.

Preparation of solid complex. Tolbutamide (1 g) and β-cyclodextrin (15.89 g) in 1000 ml distilled water were gently stirred at room temperature for 2 weeks. These amounts were calculated from the descending portion of the phase solubility diagram at the point shown by the arrow in fig. 1. At that point, no solid drug existed and the solubility of β-cyclodextrin was not exceeded (Chow and Karara, 1986). The complex, which precipitated as a white powder, was filtered off, washed with a small amount of distilled water, and then dried under vacuum at room temperature for 24 h.

Each sample of comelt, coprecipitate and solid complexes, all of which were dried, was then passed through a 28-mesh screen, and the 28–48-mesh fraction was retained for the dissolution study as well as X-ray diffraction, infrared spectrophotometry and differential scanning calorimetry investigations.

X-ray diffraction

X-ray diffraction patterns were obtained by scanning at 2°/min through the 2θ angle on a Rigaku diffractometer, using Co-Kα radiation.

IR spectrophotometry

A Unicam SP 1000 infrared spectrophotometer was used. The measurements were performed in KBr disks.

Differential thermal analysis (DTA) and thermogravimetric analysis (TGA)

Differential thermal and thermogravimetric analyses were carried out at a scanning rate of $1.7\,^{\circ}C\ min^{-1}$ on an electronic balance (Setaram Ugine Eyraud B70) equipped with a system combining temperature measurement, weighing and working under a self-generated atmosphere. The experiments were performed with 200 mg samples in platinum holders.

Dissolution studies

Drug dissolution tests were performed according to the USP XXIth Edition method with the apparatus 2. For each sample, 900 ml of pH 2 buffer (French Pharmacopoeia, 1987) were stirred at 75 rpm and maintained at $37 \pm 0.5\,^{\circ}C$. An amount of each sample equivalent to 100 mg tolbutamide was added to the medium after equilibrium temperature was reached. 2-ml samples were withdrawn at various time intervals and filtered through a 0.22 μm filter. The volume in the vessel was replaced with pure pH 2 buffer after each sampling. The concentration of tolbutamide dissolved in the medium was determined spectrophotometrically at 226 nm.

Results and Discussion

Determination of the complex stoichiometry

The phase solubility studies led to the data plotted in Fig. 1 which is a typical Bs phase solubility diagram (Higuchi and Connors, 1965). The stoichiometry of the complex which precipitated in the solution may be calculated from the plateau region. The amount of cyclodextrin is equal to that entering into the complex during this interval, and the corresponding amount of tolbutamide being included in the complex is equal to that which appears as free undissolved tolbutamide at point A. Therefore, the tolbutamide content of complex formed in the plateau region is equal to

$$3.698 \times 10^{-3}\mathrm{M} - 0.696 \times 10^{-3}\mathrm{M} = 3.002 \times 10^{-3}\mathrm{M};$$

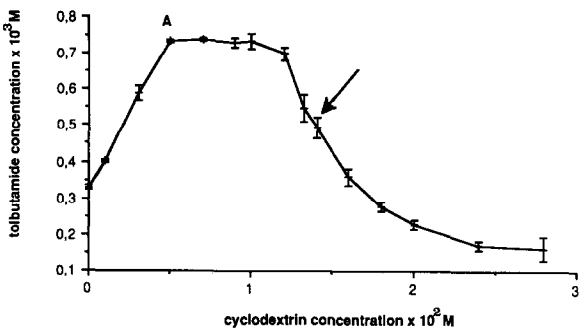

Fig. 1. Phase solubility diagram of tolbutamide–β-cyclodextrin system in distilled water at room temperature. Arrow: indicates experimental conditions for the preparation of the solid complex. Each point is the average of three measurements.

the β-cyclodextrin content of complex in the same region is equal to

$$1.1 \times 10^{-2}\mathrm{M} - 0.5 \times 10^{-2}\mathrm{M} = 0.6 \times 10^{-2}\mathrm{M};$$

and the stoichiometric ratio tolbutamide : β-cyclodextrin is then

$$3.002 \times 10^{-3}\mathrm{M}/0.6 \times 10^{-2}\mathrm{M} = 1:2;$$

indicating that the complex has the formula S_1L_2 which confirms the results of Gandhi and Karara (1988), but contrasts with those of Uekama et al. (1978). This difference might be explained by the fact that our method for preparation of the inclusion complex is very similar to that of Gandhi and Karara, while the preparative procedure employed is not described in the latter work.

The stability constant may be estimated from the descending portion of the curve. The equilibrium constant is expressed (Duchêne, 1987):

$$K_{1:2} = \frac{\mathrm{SB}}{(\mathrm{SX} - \mathrm{SB})(\mathrm{LX} - 2\mathrm{SB})^2}$$

where SB is the molar solubility of the complex, and SX and LX denote the total molar concentrations of the substrate (tolbutamide) and ligand (β-cyclodextrin), respectively, at any given point on the descending portion of the phase solubility diagram:

$$K_{1:2} = 2.101 \times 10^3\ \mathrm{M}^{-2}$$

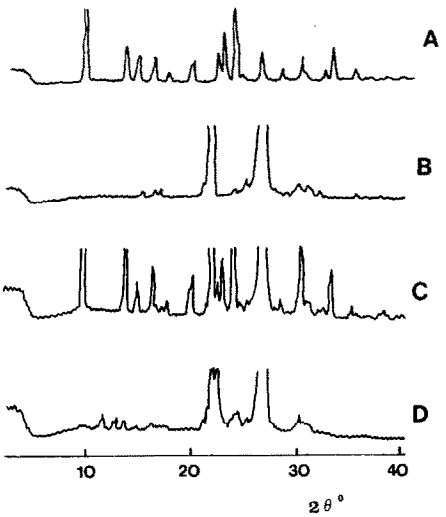

Fig. 2. X-ray diffraction patterns obtained for tolbutamide (A), PEG 6000 (B), tolbutamide-PEG 6000 coprecipitate (C), tolbutamide-PEG 6000 comelt (D).

This high stability constant indicates a good adjustment of the guest molecule inside the cavity of the host molecule as demonstrated by Seo et al. (1983) in the case of complexation of spironolactone by the α-, β- and γ-cyclodextrins.

X-ray diffraction patterns

The X-ray diffraction patterns of tolbutamide, polyethylene glycol 6000, and tolbutamide-PEG 6000 solid dispersion prepared by either the solvent method (coprecipitate) or the melt method (comelt) are shown in Fig. 2. Comparison of these patterns suggested that the coprecipitate pattern is simply due to the combination of each component, i.e. tolbutamide and PEG 6000. Therefore, it appears that no drug degradation or new drug compound occurred during the preparation process. In the X-ray diffraction pattern of the solid dispersion prepared by the melt method, the peaks are less numerous and correspond exactly to those of the carrier. The peaks concerning tolbutamide are no longer present, which tends to suggest the possibility of the formation of a true molecular dispersion of tolbutamide within the PEG matrix (McGinity et al., 1984).

The X-ray diffraction patterns of tolbutamide, β-cyclodextrin and tolbutamide–β-cyclodextrin complexes freshly prepared or 4 months old, are shown in Fig. 3. These patterns of the complexes appeared to differ with regard to superposition of the tolbutamide and β-cyclodextrin patterns. Such results confirm the formation of a new solid form which has a diffuse diffraction pattern with fewer and broader peaks, suggesting the complexation of the drug inside the cavity of the cyclodextrin as demonstrated by Uekama and co-workers (1979) in the case of acetohexamide with β-cyclodextrin.

After storage of the tolbutamide–β-cyclodextrin complex at room temperature for 4 months, no difference in pattern was found with respect to the fresh complex. This observation indicates a good stability of the complex for a duration of at least 4 months.

Infrared spectra

The IR spectra of the coprecipitate, comelt, and inclusion complex generally appeared to be the consequence of the superposition of those of the pure compounds, i.e. tolbutamide and the host molecule. The bands of tolbutamide are in all cases covered by those of the host molecule. Fig. 4 features the IR spectra of tolbutamide, β-cyclodextrin, tolbutamide-PEG 6000 coprecipitate and comelt, tolbutamide–β-cyclodextrin inclusion

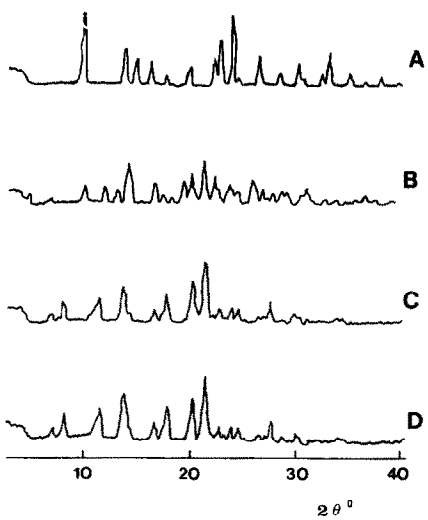

Fig. 3. X-ray diffraction patterns obtained for tolbutamide (A), β-cyclodextrin (B), tolbutamide–β-cyclodextrin complex at zero time (C), tolbutamide–β-cyclodextrin after 4 months (D).

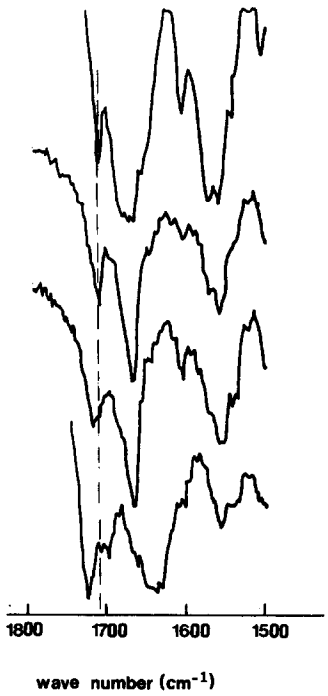

Fig. 4. IR spectra of tolbutamide (A), β-cyclodextrin (B), tolbutamide-PEG 6000 coprecipitate and comelt (C), tolbutamide–β-cyclodextrin inclusion complex (D) in the carbonyl stretching region.

complex, in the carbonyl stretching region. We observed that the carbonyl stretching at 1710 cm^{-1} for the drug and the coprecipitate is shifted to a higher wave number, i.e. 1715 cm^{-1} in the comelt, and 1725 cm^{-1} together with a broadening of the band in the inclusion complex. The formation of hydrogen bonds between tolbutamide and the host molecule as well as the dissociation of intermolecular hydrogen bonds between two molecules of tolbutamide may account for such shifts. The restriction on bending and increased stretching vibration in the β-cyclodextrin cavity are probably responsible for the broadening of the band, as stated by Gandhi and co-workers (1988).

Differential thermal analysis

The differential thermal analysis thermograms of tolbutamide, PEG 6000, comelt and of coprecipitate are presented in Fig. 5. Tolbutamide displays two endothermal peaks, one at 42 °C and the major one at 132 °C with decomposition at

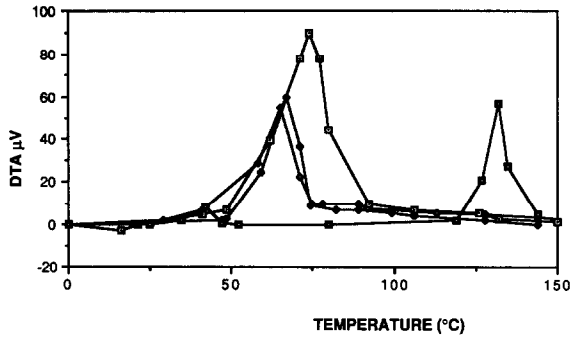

Fig. 5. DTA thermograms of tolbutamide (■), PEG 6000 (□), tolbutamide-PEG 6000 comelt (◆) and tolbutamide-PEG 6000 coprecipitate (◆).

around 140 °C. PEG 6000 shows a single peak at 74 °C. The same thermograms with endothermal peaks at about 65 °C were obtained with the two types of solid dispersions. The endothermal peak at 65 °C is apparently due to PEG 6000, since its height corresponds to approx. 2/3 of that of the PEG 6000 peak, for an amount of 200 mg for each sample, and since we know that the comelt and the coprecipitate contain 2/3 of PEG 6000 and 1/3 of tolbutamide. These results suggest that the tolbutamide peaks have disappeared, PEG 6000, which is slightly shifted, being the only remaining peak. Fig. 6 presents the DTA thermograms of tolbutamide, β-cyclodextrin, and the inclusion complex tolbutamide–β-cyclodextrin. β-Cyclodextrin has an endotherm stretching between 50 and 125 °C probably due to the dehydration of β-cyclodextrin. The thermogram of the inclusion

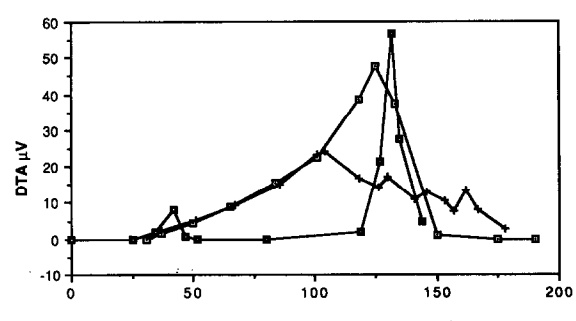

Fig. 6. DTA thermograms of tolbutamide (■), β-cyclodextrin (□) and tolbutamide–β-cyclodextrin inclusion complex (+).

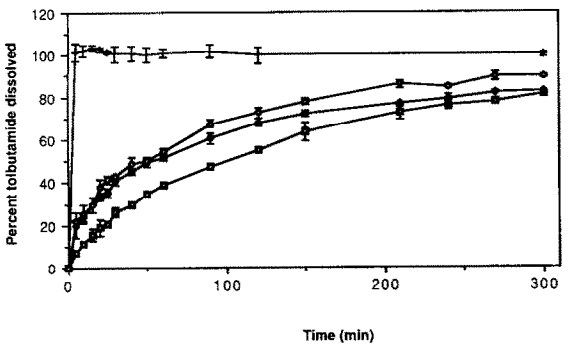

Fig. 7. Dissolution profiles of tolbutamide (■), tolbutamide-PEG 6000 coprecipitate (◆), tolbutamide-PEG 6000 comelt (◇) and tolbutamide–β-cyclodextrin complex (+) in pH 2 buffer at 37 °C. Each point is the average of three measurements.

complex shows a broad endothermal band between 50 and 163 °C due to the dehydration of the complex (Mazzi et al., 1988) and a melting point at about 190 °C. The interaction of tolbutamide with β-cyclodextrin is accompanied by the almost complete disappearance of the endothermal peak of tolbutamide, which confirms that an inclusion complex has been formed (Mura et al., 1988). The thermogravimetric analysis makes it clear that there is no variation in mass for tolbutamide, PEG 6000, comelt and coprecipitate. β-Cyclodextrin lost 134 (±1) mg/g and the complex 92 (±1) mg/g. The mass change may be correlated to the loss of water from these compounds (Mazzi et al., 1988). Therefore, the peaks seen on the thermograms are believed to correspond to the phenomenon of dehydration.

Dissolution profiles of tolbutamide alone and from its coprecipitate, comelt and inclusion complex

The dissolution profiles of tolbutamide alone and tolbutamide-PEG 6000 solid dispersions and inclusion complex are presented in Fig. 7. The dissolution profiles confirm the previous findings that the incorporation of tolbutamide into water-soluble carrier significantly enhanced the dissolution rates of the drug when compared with the free drug. After 20 min the amount of drug dissolved was around 19% for the powdered free drug, 33% for the coprecipitate, 38% for the comelt and 100% for the inclusion complex. Thus, it can be seen from these profiles that the increase in dissolution rate of tolbutamide was more significant with β-cyclodextrin than when PEG 6000 was used as the carrier. After 20 min we observed that the solubility of tolbutamide was 5.5-fold greater, due to the formation of a complex with β-cyclodextrin whereas the increase was only 2-fold for the solid dispersion. We have also proved that the results obtained with the melt method are more satisfactory compared to the solvent method.

Conclusion

The complexation or solid dispersion of tolbutamide leads to a new entity when compared to the physicochemical as well as the dissolution properties of the free drug. The very rapid in vitro dissolution rate of tolbutamide should decrease the influence of this parameter on the initial steps of absorption and thereby could increase the bioavailability of the drug. These preliminary results confirm the interesting possibility of using the complexation of tolbutamide with cyclodextrins as compared with solid dispersions which have often been presented as one of the most promising ways of enhancing drug solubility during the last 20 years.

The next step therefore is to determine whether, after incorporation in conventional drug dosage forms and upon ageing, these complexes can retain the same properties.

The two latter aspects combined with in vivo studies in rabbits are now underway in our laboratory and should help to confirm that most of the problems (especially that of stability) met with solid dispersions can be overcome by the cyclodextrin approach.

Acknowledgements

The authors are grateful to Drs. Yvon and Villieras for performing the DTA and TGA analyses and their helpful discussions have been appreciated. We also wish to thank Dr. Aubry for X-ray diffraction studies. The assistance of Ms.

Berthin in the preparation of this manuscript is greatly acknowledged.

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