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A 3 year stability study of tolbutamide solid dispersions and β-cyclodextrin complex

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Abstract

The aim of this work was to compare the effect of aging on tolbutamide solid dispersions with PEG 6000 and tolbutamide-β-cyclodextrin inclusion complex stored at three temperatures for 3 years. The effect of aging was displayed by comparing the physicochemical characteristics followed by X-ray diffractometry, infrared spectrophotometry and differential thermal analysis as well as the dissolution profiles of these compounds. The results obtained showed that tolbutamide-PEG 6000 solid dispersions and tolbutamide-β-cyclodextrin inclusion complex were stable for the 3 years of the study.

Keywords: Tolbutamide; β-Cyclodextrin complex; Solid dispersion; Stability

The incorporation of poorly soluble drugs into water-soluble carriers in order to increase their solubility or their dissolution rate has been widely studied and extensively reviewed since the first description by Sekiguchi and Obi (1961). However, despite the vast amount of research conducted in this field with different technologies, carriers and drugs, there are few products on the market using the concept of solid dispersions. Indeed, the major problem of solid dispersions is still their long-term stability. More recently, complexation of poorly water-soluble drugs with cyclodextrins has led to renewed interest in this research field (Saenger, 1980; Uekama et al., 1981; Nakai et al., 1984).

Comparison of the effect of aging on solid dispersions and inclusion complex with the same drug for a long period of time has received little attention. Therefore, the present study was carried out in order to compare the stability of the three different dosage forms: comelt, coprecipitate and β-cyclodextrin complex using tolbutamide as a model drug. Thus, the effect of aging was demonstrated by comparing the physicochemical characteristics as well as the dissolution profiles of these compounds after storage at three temperatures for a period of 3 years.

Comelts, coprecipitates and solid complexes of tolbutamide were prepared according to previ-

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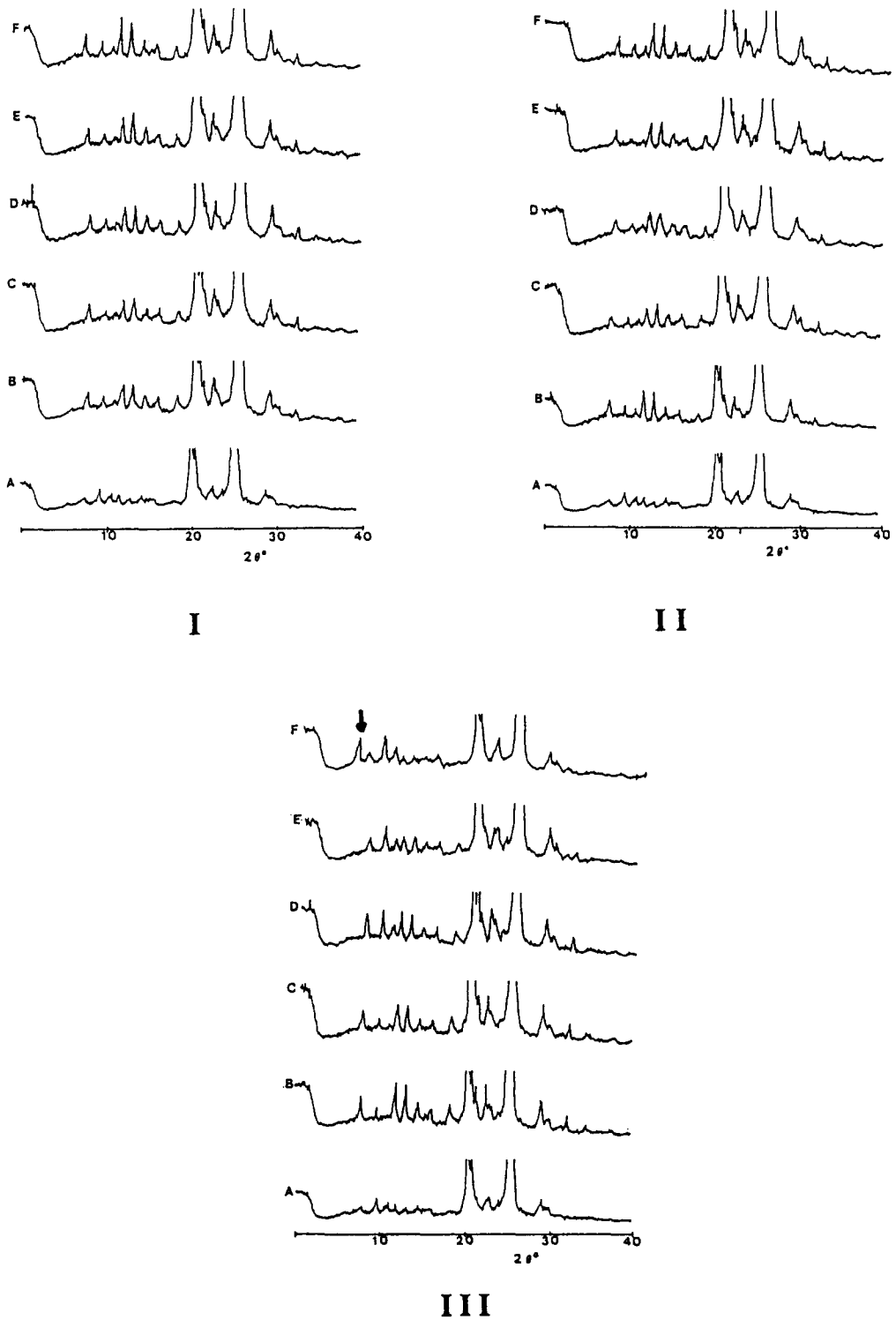

Fig. 1. X-ray diffraction patterns of tolbutamide-PEG 6000 comelt after aging: (I) at room temperature, (II) at 5°C, (III) at 37°C (A) Before storage, (*B*) 0.5 year storage, (C) 1 year storage, (D) 1.5 years storage, (E) 2 years storage, (F) 3 years storage.

ously described methods (McGinity et al., 1984; Alonso et al., 1988; Kedzierewicz et al., 1990). The three dosage forms were dried at room temperature under vacuum and the 28–48 mesh fraction was retained for stability studies. Samples of both solid dispersions and of the inclusion compound were stored under normal laboratory conditions at three temperatures: 5°C, room temperature (25 ± 3°C) and 37°C. They were examined at 0, 0.5, 1, 1.5, 2 and 3 years in the case of both coprecipitate and comelt. As for the inclusion complexes, they were only tested at 0, 1, 2 and 3 years. In order to characterize the physicochemical status of tolbutamide-PEG 6000 solid dispersions and the inclusion complex of tolbutamide-β-cyclodextrin, examinations by X-ray diffractometry, differential thermal analysis and infrared spectrophotometry as well as dissolution studies were carried out.

The X-ray diffraction patterns of tolbutamide-PEG 6000 solid dispersions prepared by the solvent method (coprecipitate) and stored at room temperature, 5°C and 37°C were simply due to the combination of each component, i.e., tolbutamide and PEG 6000. They reflect the fact that the drug is dispersed in the polymeric matrix. No drug degradation or new peaks were detectable after 3 years of storage at each temperature. However, although irrelevant, the peaks varied in intensity during the storage. These results confirm, but over a longer period of time, the previous findings of Alonso et al. (1988) for the same coprecipitate stored at room temperature for 1 year.

With solid dispersions prepared by the melt method (comelt), the peaks of the diffraction patterns correspond to those of the carrier, i.e., PEG 6000; the tolbutamide peaks are not visible (Fig. 1). We have already suggested the possibility of the formation of a true molecular dispersion of tolbutamide within the PEG matrix (Kedzierewicz et al., 1990). As early as after 6 months of storage and for each temperature, morphological changes can be detected. Two phenomena were observed: (i) an increase in the intensity of the peaks present at time 0 in the amorphous region $2\theta = 8–16°$; and (ii) new peaks at $2\theta = 18$ and 32°. Indeed, the peaks of tolbutamide which had completely disappeared at time 0 were again visible, although only slightly, in the amorphous region. This was attributed to an increase in crystallinity of the overall system as well as to the potential precipitation of tolbutamide crystals. Subsequently, there were no major modifications up to 3 years in the diffractograms at both room temperature and 5°C. However, on the diffractograms of the samples stored at 37°C for 3 years, a new peak appeared ($2\theta = 6°$). Since this new peak was not observed previously for both PEG 6000 and tolbutamide, it was concluded that it could reflect the appearance of a degradation product.

In the case of the tolbutamide-β-cyclodextrin solid complex, at time 0, the pattern is diffuse with broader and fewer peaks which correspond to the formation of a new solid form. We suggest that complexation of the drug takes place inside the cavity of the cyclodextrin. After 1, 2 and 3 years at room temperature, 5°C or 37°C, we observed that the peaks were exactly the same as at time 0 but were higher. Thus, X-ray studies showed that storage did not significantly affect the crystalline structure of the tolbutamide-β-cyclodextrin complex. Using a tolbutamide-β-

Table 1
Temperature of the four endothermal peaks of the tolbutamide-β-cyclodextrin complex at 0 time and stored during 3 years at room temperature, 5°C and 37°C

Time (years)	Temperature		
	5°C	Room temperature	37°C
0	106, 133, 147, 163	106, 133, 147, 163	106, 133, 147, 163
1	104, 130, 146, 163	107, 132, 143, 166	102, 131, 143, 166
2	109, 136, 148, 169	108, 122, 147, 169	97, 131, 147, 170
3	97, 125, 146, 171	108, 123, 146, 170	99, 136, 146, 171

cyclodextrin complex which was stored for 1 year at room temperature, Torres-Labandeira et al. (1991) did not observe variations in the diffractograms and also concluded that the system was stable.

Differential thermal analysis showed the same thermograms with the endothermal peaks of PEG 6000 at about 65°C with the two types of solid dispersions. Furthermore the tolbutamide peak disappeared. During the 3 years of the study, the temperature corresponding to the endothermal peaks changed only slightly with time. In addition, no other peaks were present. Thus, the DTA results confirm that the coprecipitate and comelt stored during 3 years at 5°C, room temperature and 37°C were very stable.

The DTA thermograms of tolbutamide-β-cyclodextrin inclusion complex display a broad endothermal band between 50 and 170°C during the 3 years of storage for the three temperatures. Table 1 summarises the temperatures of the four observed endothermal peaks due to the dehydration of the complex. This confirms the disappearance of the phenomenon of melting due to the tolbutamide which otherwise displays two endothermal peaks, one at 42°C and a major one at 132°C. However, the second endotherm (values between 132 and 136°C) could still reflect the presence of a few drug crystals in the preparation but the height of this endotherm is dramatically reduced in comparison with pure tolbutamide. Furthermore, this indicates that the drug stays mainly in an amorphous state during the 3 years of the study, thus confirming the X-ray results.

In all cases, during the 3 years of storage, no differences in IR spectra were found with respect to the fresh solid dispersions or complex.

Storage at room temperature and 5°C did not have any marked effect on the dissolution profiles for the tolbutamide-PEG 6000 coprecipitate. This observation confirms the results of Alonso et al. (1988) who studied the aging of a similar system at 25°C for 1 year. However, in the case of 37°C storage (Fig. 2), it was observed that the percentage of tolbutamide dissolved increased significantly with storage time. Generally, the increased dissolution rate of coprecipitates with time is rather infrequent. Nevertheless, it was previously

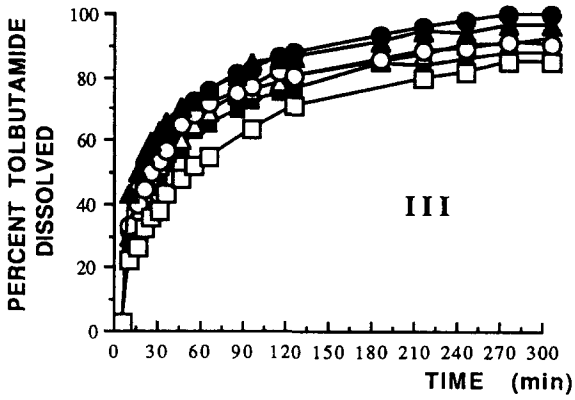

Fig. 2. Dissolution profiles of tolbutamide-PEG 6000 coprecipitate after storage at 37°C. (□) Fresh, (■) 0.5 year storage, (△) 1 year storage, (●) 1.5 years storage, (○) 2 years storage, (▲) 3 years storage.

observed by Hajratwala and Ho (1984) for hydrocortisone-PEG 4000 stored for 30 days at 25°C. As proposed by the latter authors, this phenomenon could be due to either the presence of a polymorphic form of tolbutamide in the PEG matrix or to the reduction of particle aggregation. Indeed, it has been shown that tolbutamide can display four polymorphic forms (Al-Saieq and Riley, 1981).

The dissolution profiles found for tolbutamide-PEG 6000 comelt indicate that at each temperature there is a slight, although not statistically different, decrease in the dissolution rate in comparison to the fresh preparation. This decrease in dissolution rate probably corresponds to the increase of crystallinity of tolbutamide observed as soon as after 6 months of storage. However, we can consider that the tolbutamide-PEG 6000 comelt is very stable even after 3 years of storage at either 5°C, room temperature or 37°C.

The dissolution profiles of the tolbutamide-β-cyclodextrin complex indicate that there is no difference in the dissolution rate after storage at 5°C, room temperature and 37°C.

In conclusion, this study has demonstrated that it is possible to prepare stable solid dispersions for a long period of time. For both the comelt and the coprecipitate, only slight modifications can be observed in the physicochemical characteristics of the systems as well as for the dissolu-

tion properties. This is in good agreement with previous studies also using tolbutamide as a model drug but for a shorter period of time. This observation could be related to tolbutamide which would be very stable in both systems, since many other drugs display, for example, a decrease in the dissolution properties upon aging (Sjökvist Saers et al., 1993). In the case of the inclusion compound, it is also very stable regardless of the temperature. It is therefore concluded that the three systems studied are potential candidates for further incorporation into dosage forms such as hard capsules or tablets.

References

Alonso, M.J., Maincent, P., Garcia-Arias, T. and Vila-Jato J.L., A comparative biopharmaceutical study of fresh and ageing tolbutamide-polyethyleneglycol solid dispersions. *Int. J. Pharm.*, 42 (1988) 27–33.

Al-Saieq, S.S. and Riley, G.S., Polymorphism in sulphonylurea hypoglycaemic agents: I Tolbutamide. *Pharm. Acta Helv.*, 56 (1981) 125–129.

Hajratwala, B.R. and Ho, D.S.S., Effect of aging on hydrocortisone-polyethylene glycol 4000 and hydrocortisone-polyvinylpyrrolidone dispersions. *J. Pharm. Sci.*, 73 (1984) 1539–1541.

Kedzierewicz, F., Hoffman, M, Maincent, P., Comparison of tolbutamide β-cyclodextrin inclusion compounds and solid dispersions: physicochemical characteristics and dissolution studies. *Int. J. Pharm.*, 58 (1990) 221–227.

McGinity, J.W., Maincent, P. and Steinfink, H., Crystallinity and dissolution rate of tolbutamide solid dispersions prepared by the melt method. *J. Pharm. Sci.*, 73 (1984) 1441–1444.

Nakai, Y., Yamamoto, K., Terada, K., Akimoto, K., The dispersed states of medicinal molecules in ground mixtures with α- or β-cyclodextrin. *Chem. Pharm. Bull.*, 32 (1984) 685–691.

Saenger, W., Cyclodextrin inclusion compounds in research and industry. *Angew. Chem. Int. Ed. Engl.*, 19 (1980) 344–362.

Sekiguchi, K. and Obi, N., Studies on absorption of eutectic mixture. A behaviour eutectic mixture of sulfathiazole and that of ordinary sulfathiazole in man. *Chem. Pharm. Bull.*, 9 (1961) 866–872.

Sjökvist Saers, E., Nyström, C. and Aldén, M., Physicochemical aspects of drug release. XVI. The effect of storage on drug dissolution from solid dispersions and the influence of cooling rate and incorporation of surfactant. *Int. J. Pharm.*, 90 (1993) 105–118.

Torres-Labandeira, J.J., Otero-Espinar, S., Anguiano-Igea, J., Blanco-Méndez, J. and Vila-Jato, J.L., Influence of storage on the biopharmaceutical properties of the tolbutamide/β-cyclodextrin inclusion complex. *S.T.P. Pharma. Sci.*, 5 (1991) 326–330.

Uekama, K., Hirayama, F., Wakuda, T. and Otagiri, M., Effects of cyclodextrins on the hydrolysis of prostacyclin and its methyl ester in aqueous solution. *Chem. Pharm. Bull.*, 29 (1981) 213–219.