ELSEVIER

International Journal of Pharmaceutics 123 (1995) 25–31

international journal of pharmaceutics

Influence of the preparation method of solid dispersions on their dissolution rate: study of triamterene-D-mannitol system

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Received 30 November 1994; accepted 18 January 1995

Abstract

In this paper, we illustrate the usefulness of spray-drying as a resourceful procedure for preparing solid dispersions. The study in the solid state of the triamterene-D-mannitol system from 10 to 40% w/w drug included scanning electron microscopy (SEM), X-ray diffraction (DRX) and differential scanning calorimetry (DSC). The main finding arising from the former studies was that a strong drug-carrier interaction existed in the systems prepared by spray-drying. In contrast, solid dispersions prepared by the melting carrier method showed only weak interactions between triamterene and D-mannitol. This observation helps to explain the much better dissolution rates obtained for the spray-dried outputs.

Keywords: Dissolution rate; D-Mannitol; DSC; Scanning electron microscopy; Solid dispersion; Spray-drying; Triamterene; X-ray diffraction

1. Introduction

Solid dispersions represent a useful pharmaceutical technique for increasing the dissolution, absorption and therapeutic efficacy of drugs in dosage forms. The term 'solid dispersion' refers to the dispersion of one or more active ingredients in an inert carrier or matrix in the solid state prepared by the melting, solvent or melting-solvent methods (Chiou and Riegelman, 1971).

In this study, the drug used was triamterene (2,4,7-triamino-6-phenylpteridine). It is a potassium-sparing diuretic that is practically insoluble in water and very slightly soluble in alcohol (Dittert et al., 1964). Because of its weak basicity ($pK_a = 6.2$), all attempts at forming more soluble salts have failed. Therefore, despite the fact that this drug has been well known for a considerable time, few investigations on improvement of its dissolution rate have been published. Based on all these reasons, triamterene appears to be a suitable drug for manufacturing as solid dispersions.

Several highly soluble substances can be used as carriers to accelerate the release of poorly hydrosoluble drugs. In our case, D-mannitol was

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SSDI 0378-5173(95)00026-7

selected as a vehicle in the preparation of solid dispersions of triamterene. It was chosen on the basis of its low toxicity, high aqueous solubility and physiological acceptance. It is a hexahydric alcohol isomer of sorbitol, white and odourless, crystalline powder, that possesses an exceptionally high thermal stability (melting point 165–167.0° C) and can be heated to 250° C without undergoing decomposition (Kanig, 1964).

Previous papers referring to triamterene-D-mannitol solid dispersions revealed the thermal behaviour of systems prepared by the melting carrier method (Ginés et al., 1994b) and the efficacy of this technique in improving the therapeutical properties of the drug (Arias et al., 1994a).

2. Objectives

The aim of this work was to check and to compare the results obtained through the preparation of solid dispersions by the melting carrier method (Arias et al., 1994a; Ginés et al., 1994b) with those obtained by the spray-drying technique (Arias et al., 1994b).

In order to establish the causes of the different in vitro release profiles for the spray-dried formulations, a complementary study was performed. This consisted of the physico-chemical characterization of the systems under study by spectroscopical techniques (X-ray diffraction), thermal analysis (DSC) and microscopical methods (SEM). Through such analysis we wished to elucidate the mechanisms responsible for the different behaviour of the dissolution rate recorded for these systems.

3. Materials and methods

3.1. Materials

Micronized triamterene was provided by Laboratories Miquel S.A. (Barcelona, Spain) and commercial D-mannitol of pharmaceutical grade was supplied by Acofar (Barcelona, Spain).

3.2. Methods

3.2.1. Preparation of the samples

Physical mixtures and solid dispersions were formulated in ratios from 5 to 40% w/w drug. Physical mixtures (particle size 50–200 μm) were prepared by simple intensive mixing (15 min) and solid dispersions by the melting carrier method and spray-drying technique.

3.2.1.1. Melting carrier method. Triamterene-D-mannitol solid dispersions were prepared by melting the carrier and adding the different ratios of triamterene. D-Mannitol was gradually heated to 165° C with constant stirring. When the carrier appeared completely melted, the drug was added. Once the resultant melt was homogeneous, the melted mixture was flash-cooled on ice water. After solidification the solid obtained was ground and sieved, the fraction between 50 and 200 μm being selected.

3.2.1.2. Spray-drying technique. Triamterene and D-mannitol were separately dissolved in 400 ml of 96% ethanol and 400 ml of purified water, respectively. Subsequently, the solutions were mixed for 20 min under sonication to produce a clear solution, which was subjected to spray-drying using a Büchi 190M Mini Spray-Dryer. The drying conditions were as follows: flow rate, 600 ml/h; inlet temperature, 115° C; outlet temperature, 71° C; air flow rate, 450 Nl/h. The final product was sieved and the 50–200 μm fraction was selected.

3.2.2. In vitro dissolution rate studies

The characteristics of triamterene dissolution from solid dispersions and physical mixtures were investigated adopting the USP XXII rotating basket apparatus (Turu Grau D-6), at stirring rates of 50 rpm and a temperature of 37° C. 1000 ml of USP XXII gastric medium without enzymes was utilized.

Amounts of solid dispersions and physical mixtures equivalent to 20 mg drug were packed into hard gelatin capsules, size 1. Then, the capsules were placed in the dissolution basket and at

appropriate intervals, samples of 3 ml were withdrawn and measured spectrophotometrically (Hitachi U-2000) at 357 nm. Dissolution behaviour was determined after three assays for each sample.

3.2.3. Physico-chemical characterization

3.2.3.1. Scanning electron microscopy (SEM). The morphology of the triamterene-D-mannitol systems prepared by the melting carrier or spray-drying methods was investigated by means of SEM equipment (Philips XL30).

3.2.3.2. X-ray diffraction (XRD) patterns. XRD patterns were obtained on a Siemens Kristalloflex D-500 diffractometer with Ni-filtered CuKα radiation at a goniometer speed of 1° (2θ)/min and a chart speed of 1 cm/min.

3.2.3.3. Differential scanning calorimetry (DSC). Samples of about 10 mg were accurately weighed ($\pm$0.1 mg) and encapsulated in flat-bottomed aluminum pans of 45 μl with crimped-on lids. The thermograms were recorded in air on a Mettler DSC instrument (model Mettler FP85), by heating from 100 to 400° C at 10° C/min.

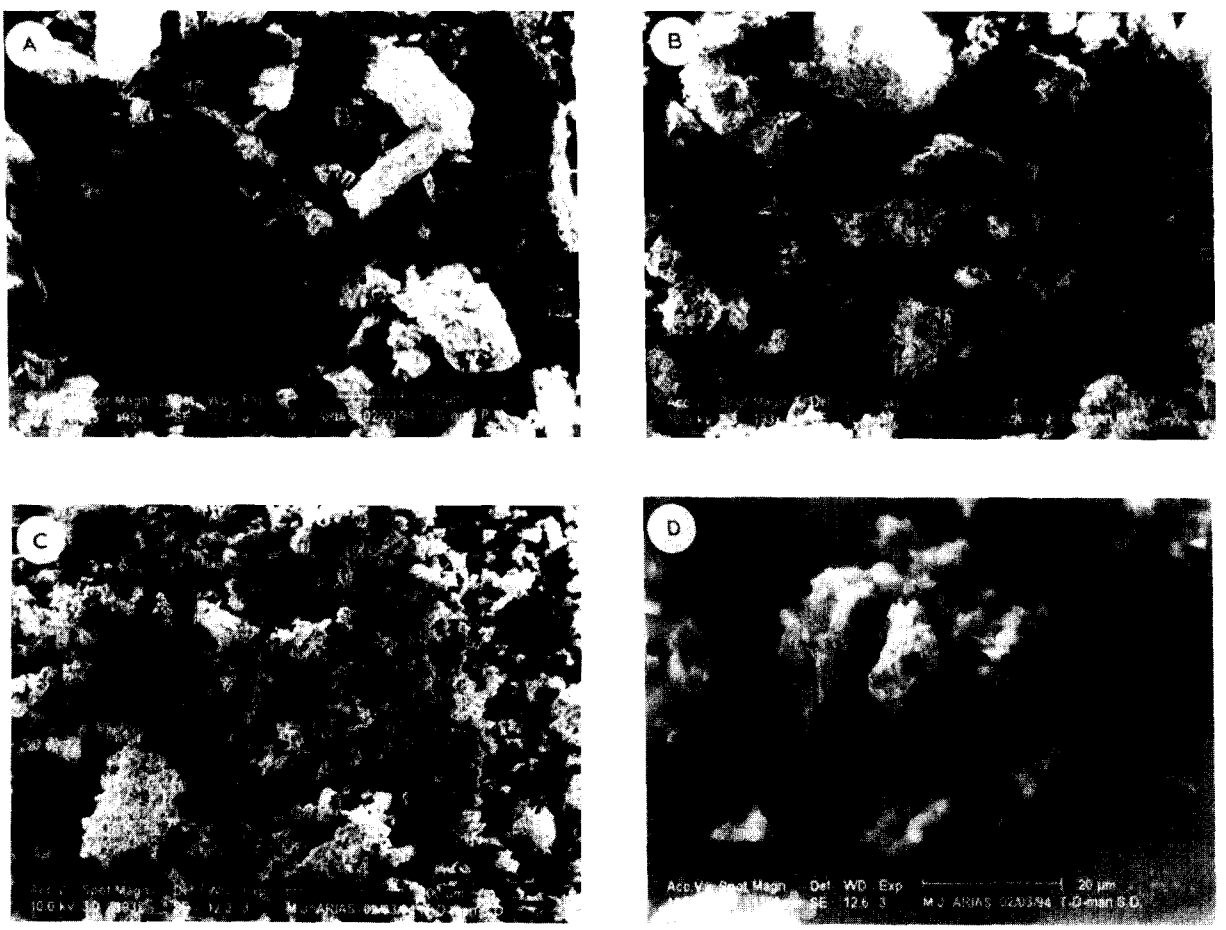

Fig. 1. SEM micrographs corresponding to the 10% w/w triamterene-D-mannitol binary system: (a) physical mixture (193 ×), (b) melting carrier solid dispersion (193 ×), (c) spray-dried solid dispersion (193 ×) and (d) spray-dried solid dispersion (1159 ×).

4. Results and discussion

4.1. Physico-chemical characterization

4.1.1. SEM

The magnification of the SEM micrographs (Fig. 1) was 193 × or 1159 ×. The first magnification was the optimum from the viewpoint of assessing the general morphology of the products.

The micrograph of the 10% w/w triamterene-D-mannitol physical mixture (Fig. 1a) displayed significant differences in the dimensions of the commercial components: triamterene particles appeared as small crystals (2–5 μm) of similar morphology and with a strong tendency to adhere onto the crystal surface of D-mannitol. This excipient appeared as large crystalline particles (25–100 μm) of rather irregular size. Moreover, the shape of the carrier arising promoted the adhesion of minor particles of the carrier and drug.

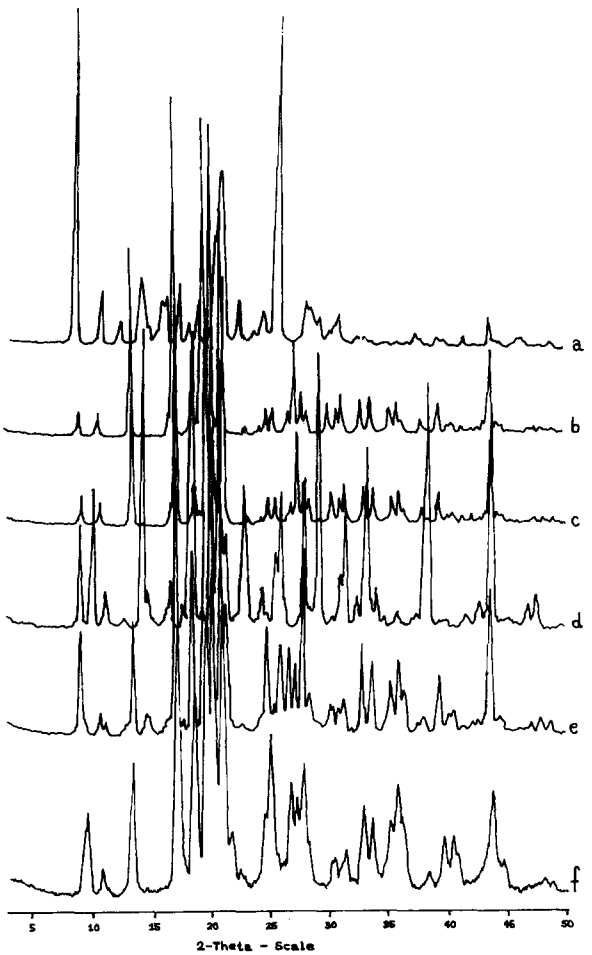

Fig. 2. X-ray diffraction patterns corresponding to: (a) triamterene, (b) commercial D-mannitol, (c) recrystallized D-mannitol from 195° C, (d) 10% w/w triamterene-D-mannitol melting carrier solid dispersion, (e) physical mixture and (f) spray-dried solid dispersion.

The micrograph of the 10% w/w triamterene-D-mannitol melting carrier solid dispersion (Fig. 1b) demonstrated crystalline particles of variable dimensions (50–100 μm) characterized by their uneven surface. Small crystals corresponding to microcrystalline triamterene can be seen on this surface.

The spray-dried solid dispersion of the same composition (Fig. 1c) revealed a product constituted of isodimensional and spherical, amorphous diminutive pieces with a strong tendency to self-agglomerate to create bulky masses of the same product.

Since the magnification of 193 × was not sufficient to study the morphology of the spray-dried product – the particle size being too small – we continued our analysis employing greater magnification of the image of one of these pieces. Fig. 1d represents the same spray-dried product at a magnification of 1159 ×. It is evident that each small particle was, at the same time, the result of the aggregation of a variable number of others of quite smaller dimensions (about 1 μm). The effect of our SEM observations on the dissolution behaviour of the drug is discussed later in this paper.

4.1.2. XRD patterns

Fig. 2 shows the X-ray diffractograms for triamterene, D-mannitol, D-mannitol recrystallized from 195° C and 10% w/w triamterene-D-mannitol binary systems. The diffraction spectra of the raw materials demonstrate the high purity of the commercial products, as compared with the JCPDS entries. Moreover, for D-mannitol, comparison with this data base allowed us to assign the original sample to the β form.

After melting of the carrier, the β form of D-mannitol crystallizes as a mixture of the α form (majority) and a low percentage of the β-form.

The new intense band that appeared at 23(2θ) in the X-ray diffractogram corresponding to D-mannitol recrystallized from 195° C supported this observation. This same band is present in the melting carrier solid dispersion, but not in the physical mixture.

Concerning the spray-dried preparation, the changes observed in the diffraction pattern are indicative of a strong interaction between the amine groups of the drug and the hydroxyl groups of the carrier (Ford, 1986). This interaction was previously proposed by us for the systems prepared by the melting carrier method (Ginés et al., 1994b).

4.1.3. DSC

The DSC traces of triamterene, D-mannitol and triamterene-D-mannitol binary systems are illustrated in Fig. 3. Both triamterene and D-mannitol gave rise to sharp melting endotherms at 342 and 183° C, respectively. In the case of D-mannitol, no apparent decomposition was recorded up to at least 320° C.

The DSC curves corresponding to 10% w/w triamterene-D-mannitol physical mixtures exhibited two melting endotherms in the zone between 320 and 350° C. The melting carrier solid dispersion showed similar endotherms in the same zone. These results are explained on the same basis as that of the previously described interaction. The minor differences recorded for these endotherms in the case of physical mixtures could be attributed to the fusion treatment for preparation of the melting carrier solid dispersions as compared with the physical mixtures. On the other hand, the slight difference recorded in temperature corresponding to fusion of D-mannitol in the case of the melting carrier solid dispersion (184.6° C) could be explained on the basis of the crystallization of D-mannitol from its original form (β form) to the α variety. This assumption is supported by the X-ray diffraction data (Fig. 2).

Finally, the spray-dried solid dispersion displayed a characteristic DSC profile, where D-mannitol was also found to exist as a mixture of α and β forms and where a new exotherm appeared at 316° C. This effect may be attributed to the crystallization of the partially amorphous

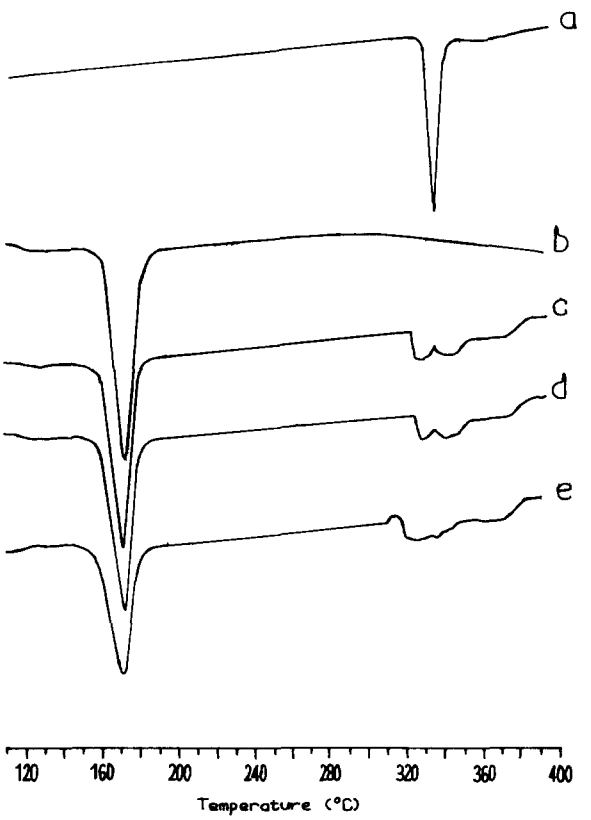

Fig. 3. DSC thermograms corresponding to 20% w/w triamterene-D-mannitol system: (a) triamterene, (b) D-mannitol, (c) physical mixture, (d) melting carrier solid dispersion and (e) spray-dried solid dispersion.

product. The following melting effects could be a consequence of the strong drug-carrier interaction occurring in this molecularly dispersed system.

4.2. In vitro dissolution rate studies

The shapes of the dissolution profiles were examined using the following parameters: the times employed in dissolving 20, 50 and 80% of the drug (T_{20}, T_{50} and T_{80}), the dissolution percentage over the first 30 min (DP_{30}) and the dissolution efficiency over the first 30 min (DE_{30}). Table 1 summarizes all these in vitro dissolution parameters for the systems under study.

4.2.1. Influence of the addition of D-mannitol

The presence of D-mannitol increases the solubility of triamterene from their physical mixtures

Table 1
In vitro dissolution parameters for the indicated systems

		T_{20}	T_{50}	T_{80}	DP_{30}	DE_{30}
	PD	41.2	–	–	17.8	9.8
5%	PM	25.0	56.1	–	25.0	14.2
	MCSD	14.5	27.2	35.6	65.0	21.7
	SDSD	5.9	14.6	25.0	90.0	41.6
10%	PM	21.3	59.6	–	29.7	15.9
	MCSD	16.6	24.5	34.1	57.5	20.9
	SDSD	11.1	21.8	32.4	75.0	33.5
20%	PM	35.9	–	–	65.0	8.9
	MCSD	21.5	35.4	41.8	43.1	17.2
	SDSD	13.4	30.0	54.9	50.0	21.4
40%	PM	27.8	57.2	–	22.5	9.5
	MCSD	24.9	41.8	–	28.9	11.3
	SDSD	17.3	38.4	–	38.9	15.8

PD, pure drug; PM, physical mixture; MCSD, melted carrier solid dispersion; SDSD, spray-dried solid dispersion.

(Ginés et al., 1993), and this solubilizing effect will increase the dissolution rate. Water structure formers such as D-mannitol cause increase in solubility and dissolution of triamterene: D-mannitol strengthens intermolecular hydrogen bonding in water, making the solvent more hydrophobic and thus favouring the dissolution of the drug.

4.2.2. Influence of the ratio (w/w) of drug in the formulation

The time required for 20, 50 and 80% of the total drug to dissolve increased with increase in the ratio (w/w) of triamterene. In samples with higher drug content, the dissolving surface may become depleted of D-mannitol with time, causing a subsequent reduction in concentration of D-mannitol in the diffusion layer, and hence, in its solubilizing effect. This will result in a decrease in dissolution rate and a more linear profile.

Moreover, and although dissolution is a function of particle size, since the method of preparing the melting carrier solid dispersions did not appreciably affect the particle size of triamterene, the enhancement in dissolution rate achieved for these systems may be interpreted only on the basis of the hydrophilic effect of the vehicle (analogously to the diazepam-PEG 6000 (Rabasco et al., 1991) and triamterene-urea systems (Ginés et al., 1994a)). This assumption readily explains the faster dissolution rate achieved for lower ratios (w/w) of drug.

4.2.3. Influence of the formulation as solid dispersions

Reduction in the time parameters in the dispersion systems, which were greater in magnitude than for the physical mixtures, preferentially occurred at low triamterene contents, and are also thought to be connected to the D-mannitol surface concentration effects. Furthermore, we postulate that during the preparation of solid dispersions, D-mannitol encircles the drug, decreasing the aggregation of drug particles and agglomeration. This allows ready dissolution for triamterene, since the water is able to make better contact with and to wet the drug particles.

4.2.4. Influence of the preparation of solid dispersions the by melting carrier or spray-drying technique

The examination of the spray-dried system allowed us to achieve a greater reduction in dissolution times, as corroborated by the in vitro dissolution parameters. While the melting carrier method yielded a crystalline powder, the spray-dried solid dispersions took on a porous and non-crystalline aspect. Thus, a complementary effect of partial amorphization was taken into account for explaining the dissolution behaviour of these samples. This assumption was supported by X-ray diffraction patterns and DSC profiles (Fig. 2 and 3).

An amorphous sample may be expected to have a rapid initial dissolution rate due to solution of the drug element. This behaviour is explained on the basis of the high energy state of the drug, a generally undefined term which can be interpreted as the prevention by D-mannitol of the drug losing the exothermic enthalpy of crystallization and reduced inhibiting crystal forces. Thus, in spray-dried D-mannitol-triamterene solid dispersions, the dissolution rate increases are due to the solubilizing effect of the carrier and, in addition to this effect, to a dissolution-promoting effect of a partially amorphous phase. Finally, the strong triamterene-D-mannitol interaction in the particular case of the spray-dried solid disper-

sions, signifying close contact between drug and carrier, can also be interpreted as a quite important reason for the decrease in dissolution time.

5. Conclusions

Our experiments have demonstrated that the original morphology and nature of the investigated materials changed advantageously during spray-drying (decrease in particle size and partial amorphization), thus improving the dissolution performance of the drug. Moreover this technique provides closer contact between the carrier and drug that, in our case, led to a significant triamterene-D-mannitol interaction.

References

Arias, M.J., Ginés, J.M., Moyano, J.R. and Rabasco, A.M., The application of solid dispersion technique with D-mannitol to the improvement in oral absorption of triamterene. *J. Drug Targeting*, 2 (1994a) 45–51.

Arias, M.J., Ginés, J.M., Rabasco, A.M., Veiga, M.D., Díaz, P. and López-Gil, M.T., Influence of elaboration method of solid dispersions in their dissolution rate: Study of triamterene-D-mannitol system. Abstract Book. *54th International FIP Congress*, Lisbon, 4–9 September, 1994b, p. 147.

Chiou, W.L. and Riegelman, S., Pharmaceutical applications of solid dispersion systems. *J. Pharm. Sci.*, 62 (1971) 1281–1302.

Dittert, L.W., Higuchi, T. and Reese, D.R., Phase solubility technique in studying the formation of complex salts triamterene. *J. Pharm. Sci.*, 53 (1964) 1325–1328.

Ford, J.L., The current status of solid dispersions. *Pharm. Acta Helv.*, 61 (1986) 69–88.

Ginés, J.M., Arias, M.J. and Rabasco, A.M., Elaboration and dissolution study of solid dispersions triamterene-D-mannitol. Summary of presentations. *Congressus Pharmaceuticus Hungaricus IX*, Budapest, 19–22 September, 1993, p. 85.

Ginés, J.M., Arias, M.J., Holgado, M.A., Fernández-Arévalo, M. and Rabasco, A.M., Dissolution rate study of fresh and aging triamterene-urea solid dispersions. *Drug Dev. Ind. Pharm.*, 20 (1994a) 2729–2740.

Ginés, J.M., Arias, M.J., Rabasco, A.M. and Sánchez-Soto, P.J., Thermal analysis of the system triamterene-D-mannitol. *J. Thermal Anal.*, 42 (1994b) 143–158.

Kanig, J.L., Properties of fused mannitol in compressed tablets. *J. Pharm. Sci.*, 53 (1964) 188–192.

Rabasco, A.M., Ginés, J.M., Fernández-Arévalo, M. and Holgado, M.A., Dissolution rate of diazepam from polyoxyethylene glycol 6000 solid dispersions. *Int. J. Pharm.*, 67 (1991) 201–205.