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Solid dispersion of ketoprofen in pellets

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Abstract

The formulation of ternary solid dispersions of ketoprofen with Macrogol and kollagen hydrolizate derivative as carriers was elaborated on the basis of the results of the experiments in which different methods of solid dispersion preparation (melting, solvent method, different cooling), different concentrations of drug/carriers and molecular weight of Macrogol were tested. The best solid dispersion consisted of: ketoprofen–Macrogol 6000-KLH_T (1 + 8.9 + 0.1) was chosen to formulate the pellets on the basis of the pharmaceutical availability of ketoprofen from solid dispersion and the physical chemical studies: thermomicroscopic, DSC and X-ray diffraction. The pellets were prepared by the extrusion and spheronization method. The mechanical properties of the pellets as well as ketoprofen released from pellets containing solid dispersion, in comparison with physical mixtures and the drug alone, were evaluated. The increase in the amount of released ketoprofen from solid dispersion pellets was 3.8-times greater than from the pellets containing the drug alone. The stability of solid dispersion pellets was satisfactory.

Keywords: Solid dispersion; Pellets; Ketoprofen; Macrogol 6000; Geliderm-tensid 3000 (KLHT)

1. Introduction

In order to ensure the optimum therapeutic effect of a drug it is necessary to prepare the proper dosage form for targeted and time release. The enhancement of the drug dosage form formulation is connected with the application of new auxiliary substances or with new technological possibilities.

Discovering a way to increase the solubility of poorly soluble drugs in order to improve their pharmaceutical and biological availability still remains one of the major technological problems. There are numerous ways of enhancing this process, of which the solid dispersion technique is more and more widely used and constantly improved (Margarit et al., 1994). Polyethylene glycols (Macrogol) of different molecular weights are frequently used as a carrier in the formulation of solid dispersion. The formulation of ternary solid dispersions which include surfactants shows an

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increase in drug dissolution. Sjökvist et al. (1992)prepared solid dispersion by incorporating sodium dodecylsulphate (SDS) in griseofulvin-PEG 3000 solid dispersion. Due to the incorporation of surfactant the dissolution rate of grisefulvin was faster than the dispersion without SDS. Griseofulvin was dissolved into the carrier/surfactant solid dispersion. Kollagen hydrolizate derivatives: Gelita Collage, Gelita Sol.D, Geliderm 3000 (KLH_T) as an additional carrier of binary solid dispersion in Macrogol had been previously tested (Jachowicz et al., 1997). Compared to many polymer enzymatically produced collagen hydrolysates lead to a rise in viscosity of aqueous solutions and lower the surface tension (Nürnberg, 1989; Nürnberg and Frieβ, 1992). Among the other derivatives *N*-cocoyl-protein condensate sodium salt (KLH_T) gave the best results (Maciejewska and Jachowicz, 1998). Its incorporation in Prednisolone–Macrogol binary solid dispersion influenced the dissolution rate of the drug. As a result, KLH_T was chosen to formulate the ternary solid dispersion of ketoprofen, a poorly water soluble drug. Its dissolution rate and bioavailability is relatively low. Following oral administration solubilized ketoprofen is absorbed rapidly and completely in different ways (Ahn et al., 1998; Mura et al., 1999). An attempt to enhance pharmaceutical availability of ketoprofen has already been made (Ahn et al., 1998).

The oral administration of conventional dosage forms of ketoprofen can cause serious systemic side effects and gastric irritation (Chi and Jun, 1991). Therefore, the pellets in the form of spherical granules with a diameter of 0.1–2 mm as a 'multiple unit' form of the drug are easier to assess than 'single unit' form tablets. As a drug delivery system the pellets ensure less irritation of the gastro-intestinal tract and a lower risk of side effects (Fekete et al., 1998; Nürnberg and Wunderlich, 1999).

The aim of the present study was the preparation of solid dispersion pellets containing ketoprofen. Therefore the binary and ternary solid dispersions of ketoprofen were formulated in different drug to carrier ratios by use of two different methods in order to choose the best formulation for the preparation of pellets. The properties of solid dispersions studied by differential scanning calorimetry (DSC), X-ray powder diffraction and microscopy, as well as dissolution profiles of ketoprofen from solid dispersions and pellets, were presented along with a discussion of the results obtained.

2. Materials and methods

2.1. Materials

Ketoprofen (Rhone–Poulenc, France), Macrogol 4000, 6000, 9000 (Fluka Chemie AG, Switzerland), Geliderm 3000, KLH_T (Deutsche Gelatine Fabriken Stoess AG, Eberbach, Germany), Microcrystaline cellulose-Avicel PH 101 (Lehmann & Voss, Hamburg, Germany), Lactose monohydrate 100M (Bufa B.V. Holland), ethanol 95% analitycal grade.

2.2. Procedure

The test samples: the solid dispersions and the physical mixture were prepared in the same w/w ratios, which were as follows: binary system: ketoprofen–Macrogol 6000 $1+1$, $1+9$; ketoprofen–Macrogol 4000 $1+9$; ketoprofen–Macrogol 9000 $1+9$; ternary system: ketoprofen–Macrogol 6000-KLH_T $1+8.9+0.1$.

2.3. Preparation of solid dispersions

Two different methods were used for the preparation of solid dispersions.

2.3.1. Melting method

An appropriate amount of ketoprofen and Macrogols were mixed and heated directly on a sand bath to 100°C. In the case of the ternary solid dispersions KLH_T was added at the end of the process. Two different cooling methods were used. One consisted of putting the melted mass at ambient temperature and continually stirring, the other used fast cooling on ice. After 24 h storage in a desiccator the solidified mass was pulverised in mortar and sieved to obtain the fraction 0.49–0.3 mm.

2.3.2. Solvent method

The samples were prepared by dissolving the mixture of the drug and Macrogol in ethanol 95%, followed by the evaporation of the solvent with a vacuum evaporator. The obtained solid mass was then pulverized and sieved to obtain the fraction 0.49–0.3 mm.

2.4. Preparation of pellets

Four kinds of pellets were prepared: containing the drug alone, physical mixture (ternary system), and solid dispersions: ternary system $1 + 8.9 + 0.1$ and binary system ketoprofen–Macrogol 6000 $(1 + 1)$. Preliminary tests were carried out to estimate a suitable proportion of microcrystalline cellulose to lactose and the wettability zone so that extrusion and spheronization could be made possible.

2.4.1. Pellets manufacture

The powder mass containing microcrystaline cellulose, lactose $(3 + 7)$ and ketoprofen as well as the solid dispersion or physical mixture were dry blended for 5 min. Water was gradually added and mixed (ca 26 g of water–100 g of dry mass of ternary system). The wet plastic mass was extruded immediately after granulation by passing the wet powdered mass between the rolls of a rotary cylinder extruder (GA65 Alexanderwerk, Germany). A granulating cylinder (diameter 70 mm, perforation 1.2 mm) and pressure cylinder (diameter 60 mm) were used at the roller rotation speed of 150 rpm. The spheronization of wet extrudate was performed in a spheronizer C.B. Caleva 120SPH for 10 min at 1000 rpm. Different spheronization time and rotation speed were established experimentally in order to obtain spherical pellets (controlled with a stereomicroscope). Preliminary experiments showed the influence of the rotation speed on the pellets shape. After the spheronization, pellets were dried at 30°C for 24 h. The ketoprofen content uniformity in the pellets was estimated spectrophotometrically.

2.5. Evaluation of pellets

The particle size distribution was evaluated by a standard sieving method using a mechanical sieve shaker. The size fraction 1.0–1.4 mm (62% of all pellets) was separated after 10 min of dry sieving. The breaking strength of the pellets was measured with Vanderkamp VK 200 apparatus. The friability was evaluated by agitating a sample of pellets with glass balls in a friabilator (Table 1).

2.6. Dissolution studies

Dissolution studies were carried out according to the Ph.Eur.3 rotating basket method (VanKel VK 700). A certain amount of powder samples (solid dispersions, physical mixtures) or pellets, equivalent to 50 mg of ketoprofen, was put into the basket in 1000 ml of water at 37°C. The basket rotation speed was 50 rpm. The samples of solution were removed at measured intervals, diluted and assayed spectrophotometrically. The amount of the drug dissolved after 0.5 h from different solid dispersion of ketoprofen with Macrogols is presented in Fig. 1. Fig. 2 shows dissolution profiles of ketoprofen from binary, ternary solid dispersion and physical mixture in comparison to ketoprofen alone. The amounts of ketoprofen dissolved after 0.5 h from solid dispersion with Macrogol 6000 prepared by the melting and solvent method are shown in Fig. 3. The profile of ketoprofen release from pellets containing solid dispersion, physical mixture and the drug alone is presented in Fig. 4. The dissolution test was carried out in triplicate.

Table 1
Physical properties of pellets with solid dispersion (S.D) and physical mixture (Ph.M.)

Pellets	Breaking strength (kg)	Friability (%)
Ketoprofen	0.90	0.3
S.D. (1+8.9+0.1)	0.70	1.0
Ph. M. (1+8.9+0.1)	0.60	1.1
S.D. (1+1)	0.63	0.9

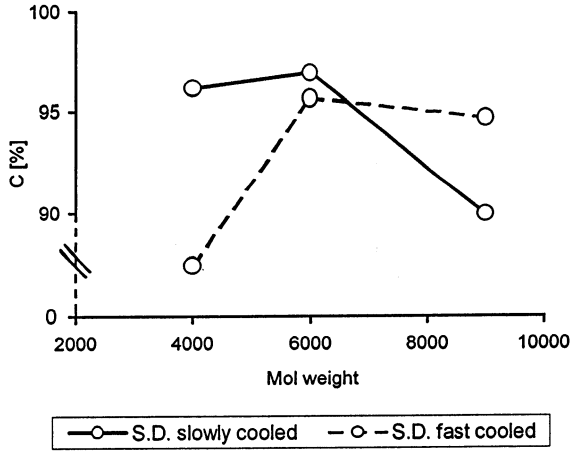

Fig. 1. Amount of ketoprofen dissolved from solid dispersions (S.D.) after 30 min versus mol weight of Macrogol.

2.7. Assaying procedure

Ketoprofen was assayed spectrophotometrically at $\lambda = 260$ nm Unicam B Helios spectrophotometer.

2.8. Differential scanning calorimetry

Differential scanning calorimetry (DSC) was used to characterize the thermal properties of ketoprofen, carriers and solid dispersion. DSC analysis was performed with PL-DSC instrument (Fa.Rheometric, Bensheim). Samples of approximately 2 mg were weighed, sealed in an alumunium pan and heated from 20 to 140°C (Fig. 5).

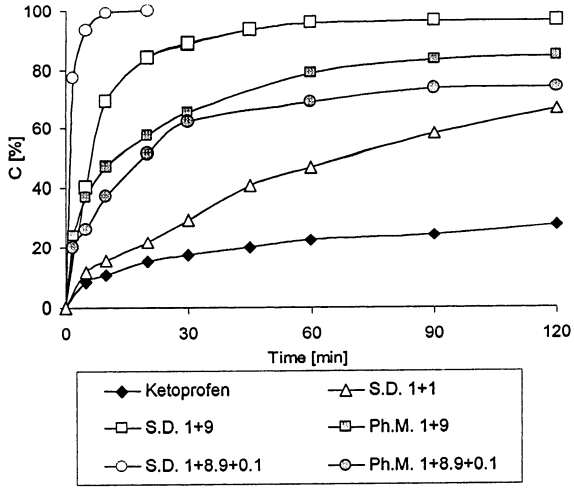

Fig. 2. Disssolution profiles of ketoprofen from solid dispersion (S.D.), physical mixture (Ph.M) and ketoprofen alone.

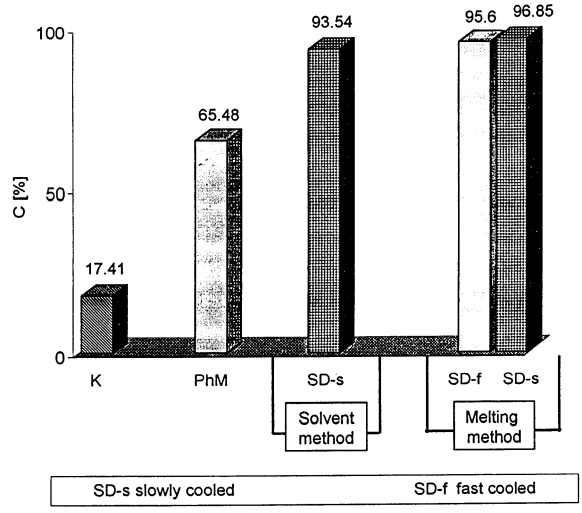

Fig. 3. Amount of ketoprofen dissolved after 30 min from solid dispersions (S.D.) prepared by melting and solvent method in comparison with physical mixture (Ph. M.) drug alone.

2.9. X-ray diffraction studies

X-ray diffraction patterns of the powdered samples of the drug, the carrier and the solid

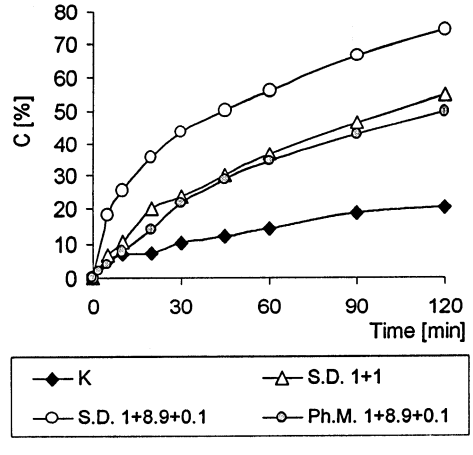

Fig. 4. Keptoprofen release profiles from pellets containing: solid dispersion (S.D.), physical mixture (Ph. M.) drug alone.

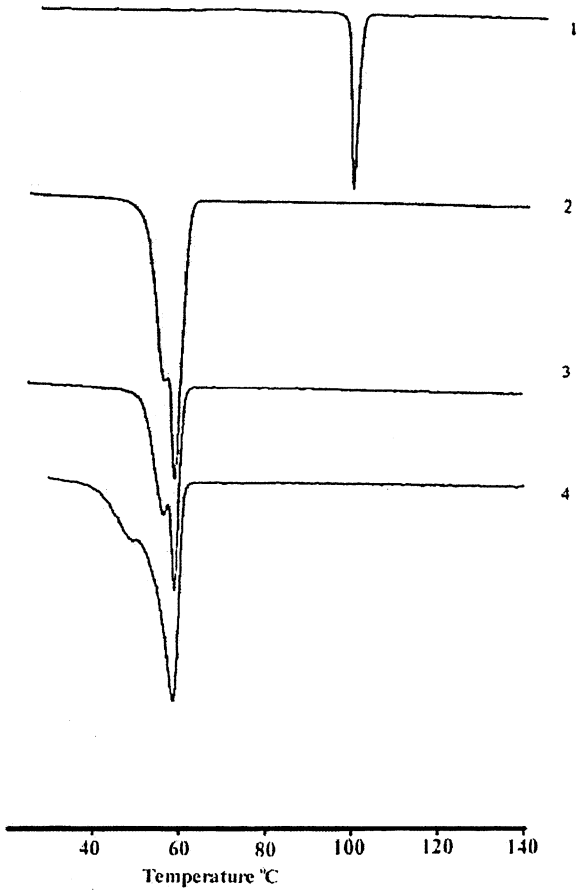

Fig. 5. Thermograms of (1) ketoprofen, (2) Macrogol 6000, (3) Macrogol 6000-KLH_T, (4) S.D. ketoprofen–Macrogol 6000-KLH_T.

dispersion were recorded using a Philips Röentgen powder diffractometer (Philips, Kassel), operated at 40 kV and 40 mA (Generator PW3040, Goniometer PW3050/10, X-ray tube PW3373) with monochromatic Cu–K_α ($\lambda = 1.5418$ A) radiation (Fig. 6).

2.10. Microscopy studies

Additional information on the thermal behaviour of the solid dispersions studied was obtained by visual identification with hot stage microscopy Boëtius (HMK 66/1258, Küstner Nachf. Dresden), (Table 2). The pellet shapes were examined with a stereomicroscope (STM Stereo Zoom PZO, Poland) at 40 × magnification.

2.11. Effect of aging

A characterization of pellets containing the ternary solid dispersion and drug alone was carried out after 0, 3, 6 months. After preparation, the pellets were kept in a Stability Test Chamber Sanyo (PSC-060.XHA.C) at a temperature of 25°C and a relative humidity of 60%. The amount of ketoprofen released from the pellets after 6 months of storage is presented in Table 3.

3. Results

A higher dissolution rate of ketoprofen was obtained when the drug was present in the form of solid dispersion, although the amount of the drug dissolved depended considerably on the concentration of carriers and molecular weight of Macrogol (Figs. 1 and 2).

The binary solid dispersions of ketoprofen in Macrogol of different molecular weights were tested in preliminary experiments aimed at choosing a suitable carrier, in order to formulate the ternary systems. Solid dispersion with Macrogol 6000 proved to give the best results. The study showed that the amount of the dissolved drug from solid dispersion with Macrogol 4000 and Macrogol 6000 was the same (96.1 and 96.85%, respectively), whereas when Macrogol 9000 was used the amount was approximately 90% (Fig. 1).

The dissolution profiles of ketoprofen varied depending on the ratio of ketoprofen to Macrogol (Fig. 2). After 2 h of the dissolution process the amount of ketoprofen dissolved from solid dispersion 1 + 9 was twice that from solid dispersion 1 + 1, and approximately 5 times greater than

Table 2
The melting points of the samples

Samples	Melting point (°C)
Ketoprofen	95
S.D. Macrogol 4000	57–68
S.D. Macrogol 6000	59–65
S.D. Macrogol 9000	63–65, 88
Ph.M. Macrogol 6000	59–60, 92
S.D. (1+8.9+1)	55

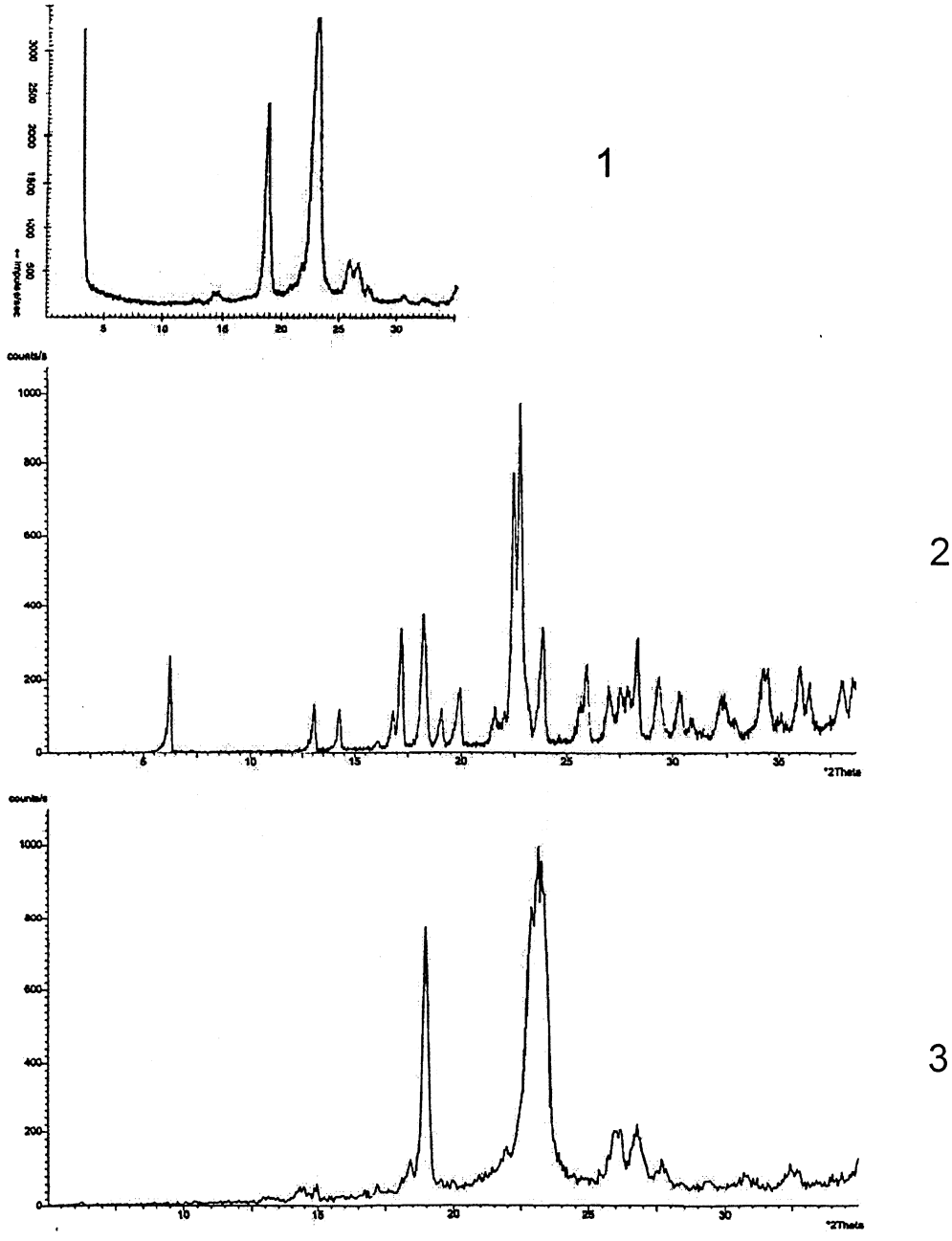

Fig. 6. X-ray diffractograms.

Table 3
Amount of ketoprofen released (%) from pellets freshly prepared (1) and after 6 months storage (2)

Time (min)	Ketoprofen				Solid dispersion			
	1		2		1		2	
	(%)	$S_{rel\ (\%)}$	(%)	$S_{rel\ (\%)}$	(%)	$S_{rel\ (\%)}$	(%)	$S_{rel\ (\%)}$
2	4.50	4.02	2.30	5.32	13.62	2.75	14.61	4.15
5	4.94	2.50	2.90	3.20	18.16	2.01	19.74	3.90
10	6.88	0.80	4.16	2.55	25.54	1.80	26.43	3.10
20	7.31	0.75	6.83	2.40	36.65	2.10	36.25	2.05
30	10.05	0.42	8.74	1.90	43.69	1.40	43.46	1.80
45	12.10	0.68	11.09	0.70	50.20	1.70	50.06	1.60
60	14.20	0.70	13.46	0.60	56.11	1.10	56.75	0.70
90	18.60	0.60	16.20	0.65	66.46	1.05	67.41	0.85
120	20.30	0.90	20.04	0.42	74.71	0.60	74.52	0.40

from the drug alone. The amount of ketoprofen dissolved from physical mixtures was smaller than the one obtained from solid dispersion 1 + 9, however the solubilizing effect of Macrogol 6000 on the dissolution of ketoprofen is considerable. The difference between the amount of ketoprofen dissolved from solid dispersion and physical mixture after 2 h of dissolution is about 12% (Fig. 2).

The two different methods (melting and solvent) used in the preparation of solid dispersions with Macrogol 6000 had practically no influence on the dissolution rate of ketoprofen. The only difference in the amount of the drug dissolved after 0.5 h of dissolution was negligible: 96.85 and 93.54%, respectively (Fig. 3). Both kinds of solid dispersion differ in their physical properties. Difficulty with the pulverization of samples obtained by the solvent evaporation was due to their plastic properties. The problem was not observed during the pulverization of the solid dispersion prepared by the melting method and fast-cooling on ice. In the case of Macrogol 6000, the fast cooling of the solid dispersion influenced the dissolution rate only to a very small extent (Fig. 1). When Macrogol 4000 or 9000 were used as carriers, greater differences were observed. The amount of dissolved ketoprofen from fast cooling solid dispersion with Macrogol 9000 after 0.5 h of dissolution was greater (94.6%) than from the solid dispersion cooled slowly at ambient temperature (89.95%). The opposite results were obtained in the case of Macrogol 4000. The slow cooling of solid dispersions resulted in a greater amount of dissolved ketoprofen – 96.1%, in comparison with fast cooling solid dispersion – 87.4%. These results can be explained by the different viscosities of the melted samples. Gines et al. (1996) noted that fast cooling conditions of oxazepam-Macrogol produce the simultaneous formation of several crystalization nuclei. However the growth rate of the crystals in the solidification of the melt is also dependent on the crystalization temperature.

The observation of the behaviour of samples during the heating process with hot stage microscopy supplies additional information (Table 2). The particles of solid dispersion in Macrogol 4000 began to melt at a temperature of 57°C, and small crystals of ketoprofen were observed inside melted droplets of Macrogol. With temperature rising to 68°C, their size decreased and at a temperature of 68°C (before reaching the melting point of ketoprofen), the crystals melted. The same process, i.e. the dissolution of crystals in droplets of melted Macrogol, was observed, when Macrogol 6000 was used as a carrier. The difference in the thermal behaviour of solid dispersion in Macrogol 9000 was connected with the presence of the crystals of ketoprofen not only in the droplets of Macrogol, but also outside them as well. Eventually they all melted at 88°C.

Due to the better results of the dissolution test obtained from solid dispersion ketoprofen–Macrogol 6000 by using the melting method with fast cooling, this method was chosen for the formulation of ternary solid dispersion. The adding of KLH_T to ketoprofen–Macrogol resulted in the best dissolution of the drug (Fig. 2). After 10 min the amount of the drug dissolved was 10 times greater than from the drug alone, and 2.8 times greater than from physical mixture. The same amount of the dissolved drug, approx. 93%, was obtained in a shorter time, from ternary solid dispersion (5 min) whereas it took 30 min to obtain the dissolved drug from binary solid dispersion. The formulation of solid dispersion results enhances the dissolution rate of ketoprofen when compared with both binary and ternary physical mixture and binary solid dispersion. The thermal observation of ternary solid dispersion showed that at a temperature of 55°C, before reaching the melting temperature of Macrogol, the whole sample was melted. DSC results confirmed this observation. The solid dispersion is characterized by the endothermic peak of Macrogol 6000 and KLH_T in the 48–58°C range (Fig. 5). Ketoprofen and Macrogol 6000 alone gave 2 different endotherms at 96 and 60°C, respectively. In the sample of solid dispersion the endotherm characteristic of ketoprofen does not exist because, due to the low concentration of ketoprofen, the crystalization does not occur.

Fig. 6 shows the X-ray diffractogram for ketoprofen, Macrogol and ternary solid dispersion. The characteristic peaks attributed to ketoprofen crystals are absent, only the peak characteristic of Macrogol 6000 is visible.

It can be concluded that the ternary solid dispersion with Macrogol 6000 and KLH_T prepared using the melting method with fast cooling is recommended to enhance the dissolution rate of ketoprofen.

The parameters of pellets prepared with ketoprofen as solid dispersion were satisfactory. The possibility of making extrudates and pellets was preliminarily studied using microcrystalline cellulose and lactose at different ratios, and with various water content. It was especially important due to the fact that solid dispersion contains a great amount of Macrogol 6000. The proportion of 30% microcrystalline cellulose and 70% lactose was the best one for optimum extrusion and a spheronization process that achieved round pellets with binary and ternary solid dispersions. Different amounts of the mixture of microcrystalline cellulose and lactose (3 + 7) were added depending on the amount of Macrogol in solid dispersions. In the production of pellets with a higher content of Macrogol in solid dispersion, a greater amount of the mixture of microcrystalline cellulose and lactose had to be used. The analysis of the properties of pellets shows that the breaking strength and friability of the pellets were similar with both kinds of solid dispersions and physical mixture (Table 1). The pellets with ketoprofen were characterized by better mechanical strength.

As shown in Fig. 4 the release of ketoprofen from solid dispersion pellets was greater than from pellets of the drug alone. After 2 h of dissolution, 74.71% of ketoprofen was dissolved from pellets containing ternary solid dispersion, whereas only 20.32% was dissolved from ketoprofen pellets. The release of ketoprofen from pellets proceeded more gradually when compared with solid dispersion in a powdered form (Figs. 2 and 4). After 10 min of dissolution approximately 25.5% of ketoprofen was dissolved from pellets, while after the same time, almost all the drug was dissolved from the powdered form of solid dispersion.

Due to the fact that in ternary solid dispersions the amount of carriers was 9 times greater than the drug, additional studies were carried out with binary solid dispersion (1 + 1) pellets. Here the difference in dissolution profiles between pellets and the powdered form was not as evident as in the ternary system. The release from both samples proceeded gradually, however, the process from the powdered form was faster. After 2 h of dissolution the amount of the dissolved drug received from solid dispersion was 66.76%, while from pellets it was 54.93%.

The studies of ketoprofen released from pellets containing ternary solid dispersion confirmed the results obtained for the powdered samples. The dissolution rate of the drug from solid dispersion pellets is greater than from pellets containing

physical mixture (Fig. 5). The results obtained in the stability test showed that ternary solid dispersion incorporated in pellets was stable. The release of ketoprofen from solid dispersion pellets stored at a temperature 25°C and a humidity of 60% was unchanged during 6 months of storage (Table 3).

4. Conclusion

The present work has demonstrated that the preparation of ternary solid dispersion of ketoprofen considerably improves the dissolution rate of ketoprofen from powdered forms and pellets. The release of ketoprofen from pellets is prolonged in comparison with powdered forms. The stability of ketoprofen in pellets containing solid dispersion is satisfactory.

Acknowledgements

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