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PHYSICOCHEMICAL PROPERTIES OF THE BINARY SYSTEM GLIBENCLAMIDE AND POLYETHYLENE GLYCOL 4000

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Abstract

Solid dispersions of the antidiabetic drug glibenclamide and polyethylene glycol 4000 (macrogol 4000) were prepared by the melting method in order to increase the solubility of this poorly water-soluble compound. The temperature/composition phase diagram of the components was analyzed by hot-stage microscopy and differential scanning calorimetry, showing a monotectic. Polarized light hot stage microscopy and X-ray-powder diffraction confirmed, that glibenclamide is mainly present in a non-crystalline state after melting and solidifying of a 10% (*w*/*w*) mixture, which results in an enhanced solubility compared to physical mixtures. The solubility and dissolution rate of the drug increases clearly with decreasing drug/polymer ratio. Moreover, it was observed for the first time that a drug could crystallize as whiskers at the surface of aged solid dispersion particles. Besides relaxation phenomena, this crystallization mechanism may be responsible for a deterioration of liberation properties and bioavailability of solid dispersion based drug products with increasing storage time.

Keywords: binary phase diagram, dissolution crystal whiskers, glibenclamide, physical mixtures, polyethylene glycol, solid dispersions, solubility, thermal analysis

Introduction

The concept of solid dispersions, *i.e.* the homogeneous distribution of a poorly water-soluble drug in a hydrophilic carrier, is definitely a suitable way to improve the bioavailability of such drugs. As new drug entities become increasingly larger and less water soluble [1] this concept is likely to become more important in the future. However, a fundamental knowledge of the drug-polymer interactions and a comprehensive study of the thermal properties, structural and solubility properties of such binary systems is the prerequisite for the development of useful drug products. The present results on the binary system glibenclamide/macrogol 4000 were required for further studies, applying fluid-bed melt granulation techniques as potential methods for the industrial production of solid dispersion formulations (to be published).

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Glibenclamide is a substituted derivative of the 2nd generation of sulfonylurea antidiabetics. It is one of the most prescribed long-acting, oral pharmaceuticals with anti-hyperglycaemic effects [2]. The first commercial drug product was launched 1969 having the advantage to be 440 times more effective than the predecessor tolbutamide [3]. Glibenclamide (5-chloro-N-[2-[4-[[[(cyclohexylamino)-carbonyl]-amino]-sulfonyl]-phenyl]ethyl]-2-methoxy-benzamide) is also known as glyburide, glybenzcyclamide, HB-419 und U-26452 and official in the European pharmacopoeia (Ph. Eur.) and the United States Pharmacopoeia (USP). Because of its low aqueous solubility (~38 μmol L^{-1} at 37°C) [4] and poor dissolution rate, glibenclamide is classified as class II compound in the Biopharmaceutical Classification System (BCS) [5].

The formulation of solid dispersions is generally accepted as a method to enhance the dissolution behavior of poorly water-soluble drug substances. The dispersion of the drug in the carrier (either small solid particles or as molecular dispersion) as well as the enhanced wettability and microenvironment provided by the carrier, may result in strongly enhanced solubilities and dissolution rates. Moreover, the carrier can stabilize solid drug particles in the amorphous state or a metastable form. In general, it is desirable to preserve such metastable states in a solid dispersion due to their improved dissolution properties in comparison with the crystalline state. However, this high energy states may slowly relax and crystallize or transform to a more stable form, which results in a deterioration of the liberation properties with storage time and affects the bioavailability of the active component [6].

In order to improve the solubility of orally administered glibenclamide, several formulation strategies such as solid dispersions with polyethylene glycols [7, 8] or the formation of cyclodextrin complexes [9], have been reported in the past. Previous results on glibenclamide/polyethylene glycol systems are based on a fairly limited number of experimental methods. Therefore we reinvestigated the physical properties of the binary systems of glibenclamide and polyethylene glycol 4000 applying thermal analysis (hot stage microscopy and differential scanning calorimetry), X-ray powder diffraction, IR- and Raman spectroscopy, microscopic techniques and solubility studies. In order to better understand this binary system, the temperature composition phase diagram should be established and these data should be correlated with the solubility behavior of different drug/carrier ratios. Hence such a thorough investigation of the basic physicochemical properties was desirable for the successful development of potential production methods of solid dispersions on an industrial scale, such as fluid-bed melt granulation and subsequent tableting.

Materials and methods

Two lots of drug substance were available: glibenclamide (#0099004913) for preparation of solid dispersions and glibenclamide micronized (#2002052022) for comparative solubility studies were kindly donated by ratiopharm (Ulm, Germany) respectively. As carrier macrogol 4000 (#2836/0498 Gatt-Koller, A-Absam) was used.

Preparation of physical mixtures and solid dispersions

The preparation of physical mixtures was performed by mixing glibenclamide and polyethylene glycol 4000 with mortar and pestle and then for 10 min in a Turbula-mixer T2A WAB system Schatz (W. A. Bachofen, CH-Basel) at 72 rpm. The ratios are given as mass ratios (*w/w*). After stirring of glibenclamide (4.0 g) and PEG (36 g) for 30 min at 90°C (melting method), the solid dispersions were either quickly (ice-bath) or slowly cooled to room temperature. Due to the relationship between heating rate and drug concentration and their important influence during the pharmaceutical production process a defined heating rate of 30 min and the above mentioned drug/carrier ratio (10:90% *w/w*) were chosen [8]. The samples were stored at controlled temperatures and relative humidity conditions.

Thermal microscopy

For thermomicroscopic investigations a Reichert Thermovar® (Reichert, A-Wien) equipped with a Kofler hot stage (Reichert, A-Wien) was used.

Differential scanning calorimetry

DSC curves were recorded with a DSC-7 (Perkin Elmer, Norwalk, USA) using the Pyris Software Version 2.0 for WinNT, calibrated with benzophenon, caffeine and indium standards. The energy response was calibrated with indium (99.999%). Samples (n =3) of 1 to 5 mg were weighed into Al-pans (25 µL) using an ultramicrobalance UM3 (Mettler Instruments AG, CH-Greifensee). Dry nitrogen was used as purge gas (20 mL min^{-1}).

Powder X-ray diffraction

The powder X-ray diffraction patterns were obtained with a D-5000 Diffrac/AT (Siemens AG, D-Karlsruhe), equipped with θ/θ-goniometer, Goebel mirror (Bruker AXS, D-Karlsruhe), a 0.15° soller slit collimator and a scintillation counter. The diffractograms were recorded with CuK_α radiation (40 kV tube voltage, 35 mA tube current), applying a scan rate of 0.005° (2θ) in the angular range of 2 to 40° (2θ) and a step scan mode of 2 s.

FTIR spectroscopy

IR-spectroscopic investigations were done with an IFS 25 FTIR spectrometer (Bruker Analytische Messtechnik GmbH, D-Karlsruhe). KBr-disks were produced with a hydraulic press using about 1 mg substance and 270 mg KBr. The spectra were recorded in a range of 400 to 4000 cm^{-1} with a resolution of 2 cm^{-1} (64 scans per spectrum).

FT-Raman spectroscopy

Raman spectra were measured with an IFS 100 Raman spectrometer (Bruker Analytische Messtechnik GmbH, D-Karlsruhe) equipped with a Nd:YAG Laser (1064 nm) as excita-

tion source and a liquid-nitrogen-cooled, high sensitivity Ge-detector. The spectra were recorded in small aluminium sample holders at a laser power of 300 mW in a range of 4000 to 100 cm^{-1} and a resolution of 2 cm^{-1} (64 scans per spectrum).

Solubility studies

Solubility studies (n = 5) were performed with desagglomerated samples (ultrasound 10 min) in glass vials using a magnetic stirrer (900 rpm) in a thermostated water bath. The saturation concentration of the drug substance at different temperatures (20, 37, 50 and 60°C) and pH-values was determined by HPLC. Solution sampling was performed as described earlier [10] using membrane filters (0.45 μm, Millipore GmbH, D-Isenburg) and calibrated pipettes.

Dissolution studies

Dissolution experiments (n =6) were carried out according to the European Pharmacopoeia [11] (paddle method) using an Erweka DT6-2 (Erweka Apparatebau GmbH, D-Heusenstamm). The dissolution data were determined after following storage times: 24 h, 48 h, 7 d, 14 d, a half year and one year (20°C and 40% r. H. as room conditions). For all experiments samples equivalent to 3.5 mg drug substance were used. To compare crystalline and glassy glibenclamide as well as physical mixtures and solid dispersions of glibenclamide and PEG, 900 mL of USP-buffer (pH 7.8) with 0.03% Tween 80® were used as dissolution medium. The temperature was kept at 37°C. Samples of 1 mL were withdrawn after 5, 10, 15, 20, 30, 40, 50, 60, 90 and 120 min and the concentration of glibenclamide in the solutions was determined by HPLC.

HPLC

HPLC analysis was performed with a HP-1100 Liquid Chromatograph (Hewlett Packard, USA) equipped with an autosampler and a DAD-detector. The HPLC system consisted of a 150×4.6 mm Nucleosil®100 C18 column (Knauer, D-Berlin) filled with 5 μm material and a LiChrospher®RP-18 (5 μm) pre-column (Merck, D-Darmstadt). Trifluoroacetic acid (TFA) in water (0.1%) and 0.1% TFA in acetonitrile was used as mobile phase. The detection of glibenclamide was performed by UV at 230 nm and an internal standard of 25% tolbutamide stock solution was used for quantification. Glibenclamide was detected at a retention time (t_R) of 2.7 min (typical t_R <5 min [12]).

Scanning electron microscopy

For scanning electron micrographs samples were sputtered with gold/palladium (Polaron E 5100, Great Britain) and recorded with a scanning electron microscope DSM 940 A (Zeiss, D-Oberkochen).

Results and discussion

Microscopical characterization

Figures 1 and 2 show scanning electron micrographs of physical mixtures and solid dispersions. In the physical mixtures the small particles of glibenclamide are homogeneously distributed at the surface of the macrogol particles (Fig. 1). In the solid dispersions lamellar structures (Fig. 2 lower insert) of the polyethylene glycol can be observed.

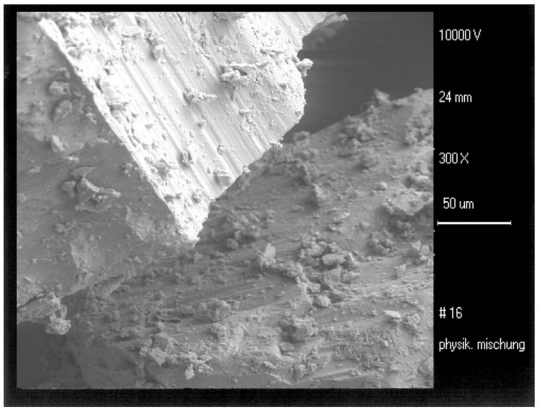

Fig. 1 Physical mixture of glibenclamide (10% *w/w*) and macrogol 4000

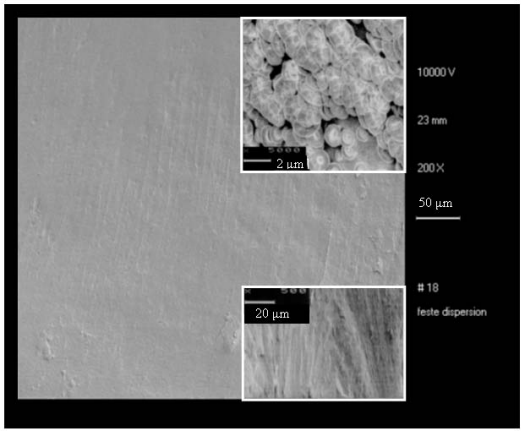

Fig. 2 Solid dispersion of glibenclamide (10% *w/w*) and macrogol 4000

Polarized light hot stage microscopy was applied to evaluate the presence of crystalline glibenclamide in the solid dispersion. At 58°C the polymer melts to an isotropic liquid and thus present anisotropic particles of the drug can be easily observed in the polarized light. The 10% (*w/w*) solid dispersion prepared at 90°C, clearly showed the presence of crystalline particles of glibenclamide when heated at

the hot stage microscope to 60°C. However, the drug particles became smaller compared to the original drug particles and the amount of crystalline drug clearly diminished. This indicates that glibenclamide dissolved partly in the carrier during the preparation but the dissolved drug did not recrystallize on cooling again. Hot stage microscopy of the physical mixtures showed that glibenclamide particles remain unchanged until the macrogol melts at 58°C. Then they start to dissolve in the polymer. The crystals of glibenclamide disappear completely before its melting point is achieved and do not recrystallize on cooling.

Hantke was able to prove with atomic force microscopy (AFM), that the primary crystallization behavior of the polyethylene glycols is hardly affected by glibenclamide inclusion [13]. The polymer just encloses the drug particles, forming fine, lamellar bridges to them (Fig. 2). Neither a disruption of the lamellar growth nor the formation of structures which differ from the helical form (7_2-helix) [14] are observable.

Scanning electron micrographs of aged solid dispersions revealed another phenomenon of this system, namely the crystallization of glibenclamide as whiskers (Fig. 3). Whiskers are defined as thin, needle- or filament like single crystals with large length/diameter-ratios of often more than 1000. Diameters vary between 0.020 and 100 μm. The length axis of the whisker is frequentlmy parallel to the major crystallographic direction. The phenomenon can be explained by the dislocation theory [15]. Whiskers tend to be high in purity and contain very few external or internal defects. As the long lateral crystal faces are of very low energy the vapor pressure of whiskers is generally low explaining their high stability. The formation can occur at increased temperature or humidity or during a long storage time. Up to now this crystal growth has been described mainly for inorganic compounds or metals but also for some drugs such as menthol [16] nifedipine [17], acetylsalicylic acid [18] and theophylline [19]. Whisker growth mostly results in a mechanical consolidation of the tablets or granules produced from solid dispersions and decrease the liberation of the active ingredient.

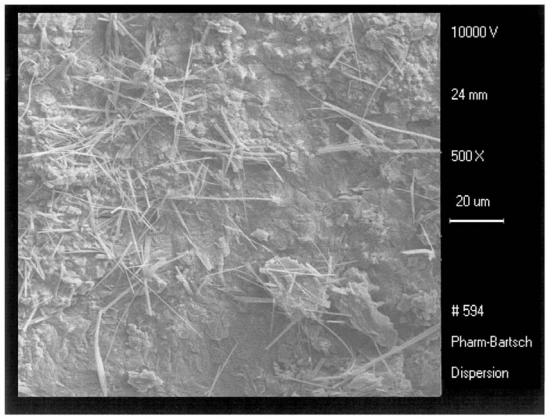

Fig. 3 Aged solid dispersion of glibenclamide (10% *w/w*) and macrogol 4000

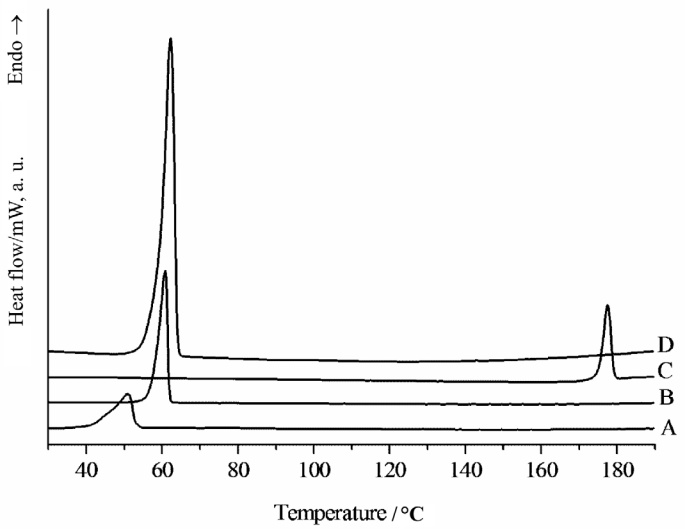

Fig. 4 DSC curves of the 10% (*w/w*) A – solid dispersion, B – physical mixture as well as the pure components, C – glibenclamide and D – macrogol 4000

Differential scanning calorimetry (DSC)

The DSC-curves of the pure components (Figs 4C and D) show a single endothermic melting peak for glibenclamide at 174°C and for polyethylene glycol at 59°C respectively. The DSC curve of the solid dispersion (Fig. 4A) exhibits a melting endotherm of macrogol 4000 only. According to the hot stage microscopy results glibenclamide slowly dissolves in the macrogol melt and therefore no distinct endothermic event can be observed for the active compound in the solid dispersions with DSC. A similar result shows the DSC curve of the mixture (Fig. 4B) where the melting peak of glibenclamide cannot be recorded either, due to the slow dissolution of the glibenclamide in the melt of the carrier on heating and thereafter the stabilization of solid drug particles in a metastable form.

The macrogol peak in the DSC-curve of the solid dispersion is broadened compared to that of pure macrogol, which indicates that the carrier weakly interacts with glibenclamide. Similar observations were reported by Rodriguez *et al.* [20] for diclofenac/macrogol 4000-systems. Also in this system only a broad endotherm can be observed which corresponds to the monotectic melting some degrees below the melting peak of the pure polyethylene glycol.

Powder X-ray diffractometry (XRPD)

In Fig. 5 the X-ray powder patterns of the solid dispersions, physical mixtures and the pure components are illustrated. The physical mixture shows the characteristic peaks of the pure components at identical angles, which proves that no interactions take place during mixing. Otherwise the peaks of glibenclamide are barely noticeable in

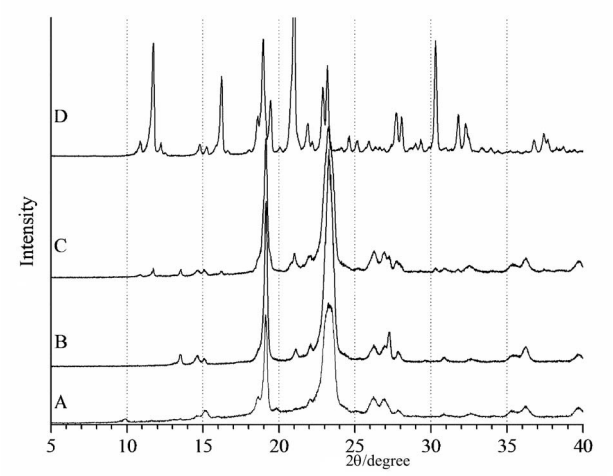

Fig. 5 X-ray powder diffraction patterns of A – the solid dispersion, B – physical mixture, C – the pure components macrogol 4000 and D – glibenclamide

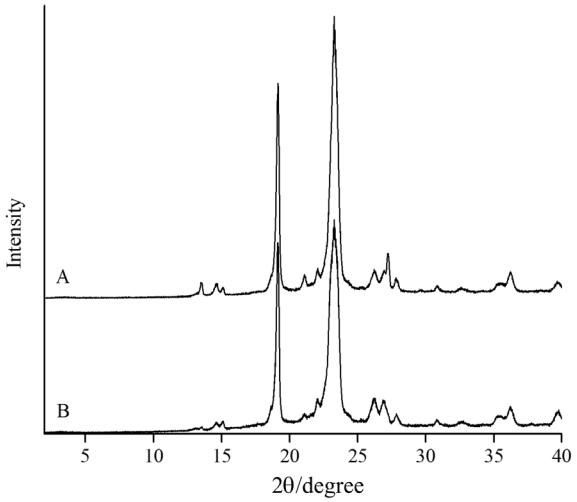

Fig. 6 X-ray powder diffraction patterns of A – untreated and B – quench-cooled melt of macrogol 4000

the pattern of the solid dispersion, which again demonstrates that glibenclamide strongly dissolves in the polymer. However, the pattern of the solid dispersion shows differences to that of the pure carrier, which indicates some structural changes. At about 10°2θ an additional weak peak can be recognized and also one at 20°2θ. As the pure macrogol does not show such reflections after melting and resolidification (Fig. 6) these changes must be attributed to the formation of some structural arrangement between the active component and the carrier.

FTIR- and FT-Raman spectroscopy

From their chemical structures the formation of hydrogen-bonds between the hydroxyl-groups of macrogol and the carbonyl-groups of glibenclamide can be expected. Such interactions would cause a bathochromic shift of the absorption bands. However, the FTIR-spectra (Fig. 7) of the physical mixtures and the solid dispersions are not very distinct from each other. The observable bands of glibenclamide in the spectrum of the solid dispersion are weaker and broader than that of the physical mixture. This circumstance can be explained by the fact that glibenclamide is either molecularly dispersed in the carrier or present as amorphous clusters whereas in the physical mixtures it is present in the crystalline form. As the carbonyl band is slightly shifted to higher wavenumbers (1715 to 1722 cm^{-1}) the hydrogen bond interactions between glibenclamide and macrogol in the solid dispersion must be weaker than in the crystal structure of glibenclamide itself.

The FT-Raman spectra (not shown) of the solid dispersion and the physical mixture are almost identical and also show a lower order of the glibenclamide state in the solid dispersion indicated by a weak but noticeable peak broadening.

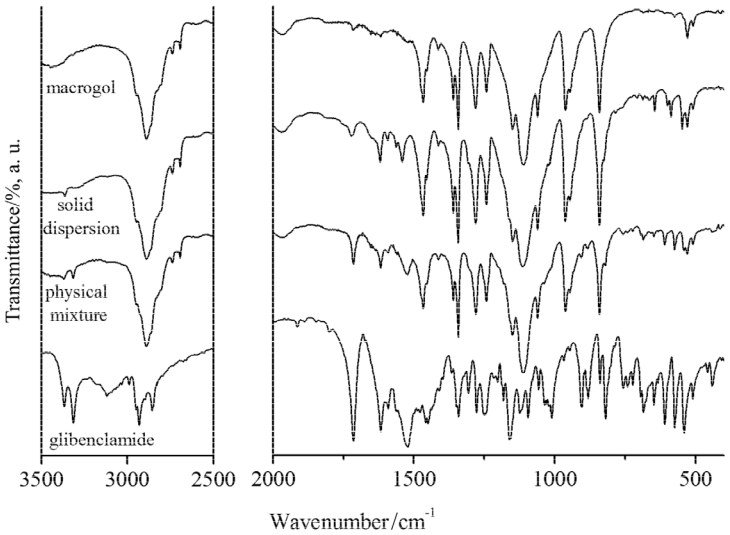

Fig. 7 FTIR-spectra of the pure components, the physical mixture and the solid dispersion of glibenclamide/macrogol 4000

Phase diagram

In Fig. 8 the DSC curves of the pure components and physical mixtures of different ratios are shown. The first peak corresponds to the melting of the polyethylene glycol in the mixtures. Its onset is only weakly affected by the mixing ratio. Even at a mole fraction of 98.6% glibenclamide the melting point depression does not exceed 2.5 K (Table 1). Ex-

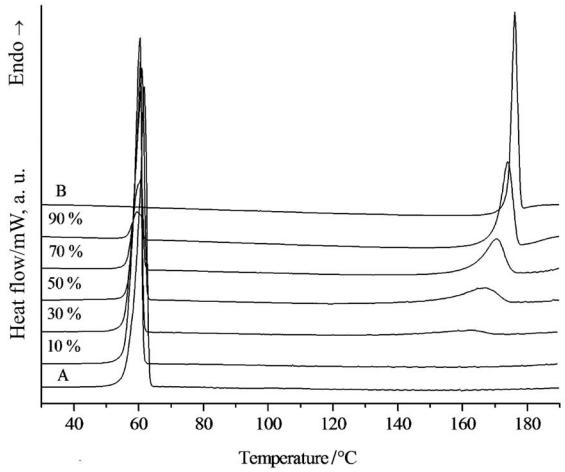

Fig. 8 DSC curves of A – macrogol 4000 and B – glibenclamide as well as their binary mixtures (10 to 90 % drug/carrier ratio)

Table 1 Melting points of the binary mixtures of glibenclamide and macrogol 4000

Composition/%				Melting point/°C	
Glibenclamide		Macrogol 4000		Macrogol 4000[1]	Glibenclamide[2]
mass%	mol%	mass%	mol%		
0	0	100	100	59.0	–
2.5	17.2	97.5	82.8	59.5*	131.6*
5	29.9	95	70.1	59.5*	140.4*
7.5	39.6	92.5	60.4	59.3*	142.9*
10	47.4	90	52.6	59.1*	146.7*
20	67	80	33.0	58.3	156.8
30	77.6	70	22.4	58.2	161.3
40	84.4	60	15.6	57.8	164.3
50	89	50	11.0	57.2	167.1
60	92.4	40	7.6	56.5	168.8
70	95	30	5.0	56.5	170.4
80	97	20	3.0	56.6	172.3
90	98.6	10	1.4	56.5	173.9
100	100	0	0	–	176.1

[1]Onset, [2]$Peak_{max}$,*data from hot-stage microscopy

cept in the 10% mixture, a second endotherm (liquidus peak) can be observed. The peak is becoming narrower and shifted towards the melting temperature of pure glibenclamide with increasing concentration of the drug. This behavior indicates a complete miscibility of glibenclamide and the polymer melt. The phase diagram in Fig. 9 was constructed from the DSC-runs and from hot-stage microscopy observations (data in Table 1) of

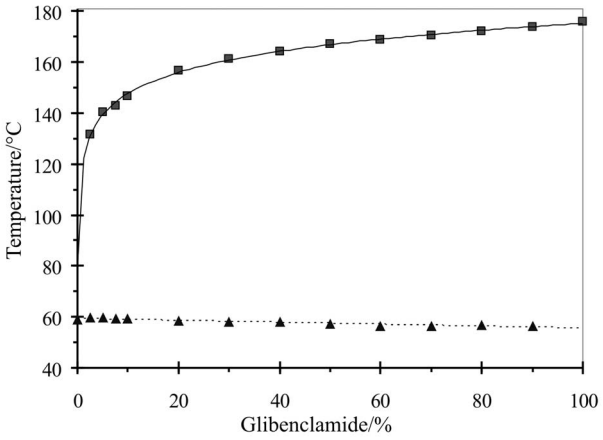

Fig. 9 Composition/temperature phase diagrams of glibenclamide and polyethylene glycol constructed from the DSC and hot stage microscopy data.

physical mixtures of glibenclamide and macrogol 4000 with varying compositions. As the DSC signal did not allow determining the temperature of the liquids curve of mixtures at and below the 10% drug/carrier ratios, these data points were established by thermal microscopy only. The data indicate neither an eutectic system nor the characteristics of a solid solution. The phase diagram can be classified as monotectic system, which is typical for binary mixtures with strongly different melting points and has been also reported for other drug/macrogol systems [21].

Solubility

The data in Table 2 clearly show the increasing solubility of glibenclamide with increasing amount of the macrogol carrier. The dependence is almost linear (R =0.988). Crystalline glibenclamide shows a very low solubility of 51 μmol L^{-1} which is only about 1.5% of the solubility of the amorphous form.

Table 2 Solubility of solid dispersions (glibenclamide/macrogol 4000) as well as crystalline and amorphous glibenclamide (GLI) in phosphate buffer pH 7.8 (USP) at 37°C (standard deviations in brackets)

GLI concentration/% *w/w*	Amount of dissolved GLI/mg mL^{-1}
5	1.204 (±0.011)
10	1.118 (±0.014)
30	0.803 (±0.007)
50	0.481 (±0.003)
70	0.265 (±0.005)
90	0.079 (±0.001)
100 (crystalline)	0.025 (±0.001)
100 (amorphous)	1.622 (± 0.022)

Dissolution

Figure 10 shows the dissolution curves of different physical states of the pure drug substance at 37°C (pH=7.8). As expected, the amorphous drug dissolves much faster than the non-micronized crystalline material. Due to the much larger surface area, the dissolution rate of the micronized drug is initially higher than that of the glassy form, but it slows down quickly and achieves a much lower equilibrium state which in the case of the non-micronized material reaches less than the half of the amorphous form. Particle size analysis of the crystalline samples showed an average size value of 60 μm and a homogeneous distribution (88% of the particles <100 μm).

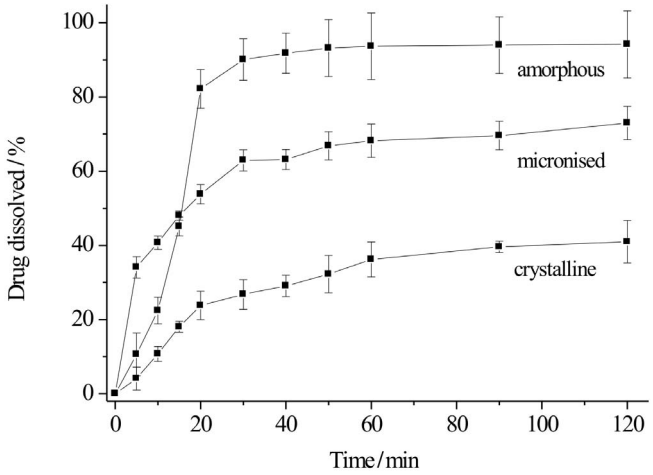

Fig. 10 Dissolution curves of crystalline, micronized and amorphous glibenclamide (buffer solution, pH = 7.8, 37°C) with standard deviations

The solubility and dissolution rate of amorphous glibenclamide decreases with storage time due to the relaxation and slow crystallization of this metastable state. The dissolved amount decreases from 94 to 87% within the first 30 days and then a further linear decrease of 10% was observed within a year (Fig. not shown). Relaxation (compressed areas) and slow crystallization (dilated areas) are characteristic for the dislocation process that occurs during whisker formation. The migration of the partially dissolved glibenclamide into dislocations also results in several physical effects. The most striking effect is the hardening of the solid dispersion caused by the anchoring of the dislocations [22].

Figure 11 displays the dissolution data (equilibria) of solid dispersions and physical mixtures of different compositions. The dissolved amount clearly increases with increasing polymer concentration. This is true for both, the solid dispersion and the physical mixture, which demonstrates the solubilizing effect of the polymer. The effect of the dispersion status in the polymer compared to the crystalline state is ex-

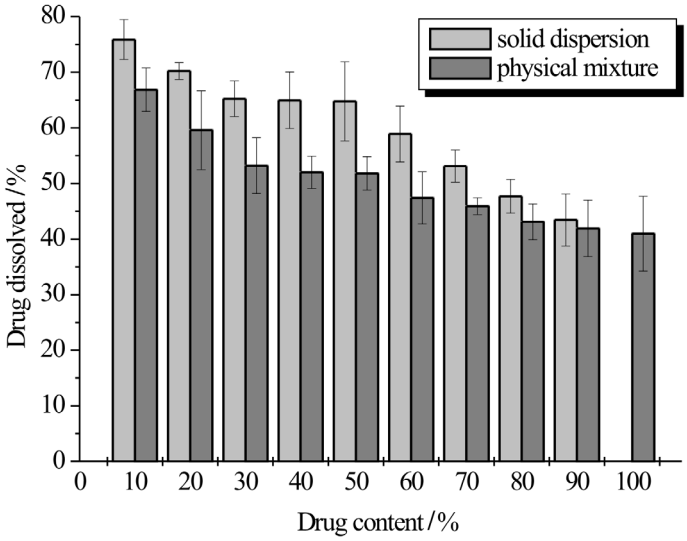

Fig. 11 Amount of dissolved glibenclamide (with standard deviations) of physical mixtures and solid dispersions with macrogol 4000 depending on the drug concentrations

pressed by the difference between the physical mixture and the solid dispersion at the same drug/carrier ratio. At ratios below 60% the solid dispersion achieve about 10±3% higher solubilities than the physical mixture, whereas this difference becomes distinctly smaller at high drug concentrations. As the solubility of glibenclamide in the polymer is limited, the amount of crystalline drug particles in the solid dispersion increases with increasing drug/carrier ratio and thus becomes less distinct to that of a physical mixture. This is the reason why the solubilities of physical mixtures and solid dispersions at 80 and 90% drug concentration and that of the pure crystalline drug are statistically not different. However, the dissolution rate of glibenclamide in solid dispersions is distinctly higher than that of physical mixtures, which is demonstrated by the dissolution curves of the 10% mixtures in Fig. 12. Nearly eighty percent of glibenclamide were released within 20 min from the dispersion, which is about the double value of that of the physical mixture.

Hence, for this system, the improved dissolution behavior of the solid dispersions compared to the physical mixtures can be explained by the change of crystalline glibenclamide to a state of higher energy (*i.e.* amorphous) or by a molecular dispersion in the polymer matrix. As such polymers are not highly ordered and always contain some 'structural voids', it is likely that the amount of the drug that dissolved in the melt is entrapped in such areas after cooling and crystallizing of the carrier. Some evidence of this possible mechanism is given by the X-ray powder diffraction, thermal analysis and spectroscopic results. Nevertheless, the presence of amorphous precipitates of the drug in the solid dispersion is another explanation for the enhanced dissolution properties.

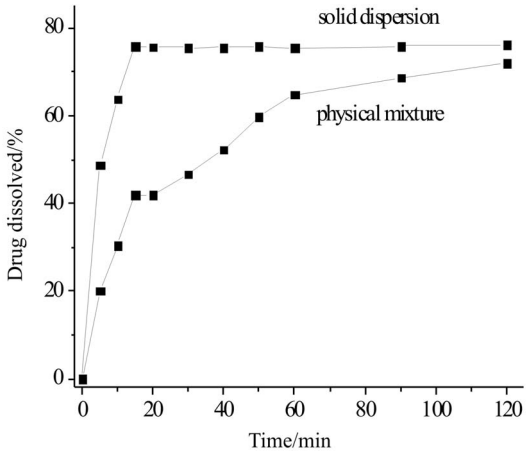

Fig. 12 Dissolution profiles of physical mixtures and solid dispersions (10% *w/w* drug content)

Conclusions

The results obtained in this study demonstrate clearly that the low water solubility and dissolution rate of glibenclamide can be strongly improved by using solid dispersions with polyethylene glycol 4000. Like other drugs, such as naproxen, griseofulvin and ritonavir [21], glibenclamide forms a monotectic with macrogol 4000. The compound shows a limited solubility in the melt of the polymer. It is likely that a part of the drug remains molecularly dispersed in the crystallized polymer carrier, but also the formation of amorphous precipitates of the drug is possible. Anyway, after melting and solidification of a 10% glibenclamide-macrogol mixture the amount and the size of crystalline drug particles in the polymer matrix are strongly diminished.

The formation of glibenclamide whiskers at the surface of the solid dispersion particles on storage could be observed for the first time. This crystallization mechanism may be one reason of decreasing solubilities of solid dispersions with storage time.

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