European Journal of Pharmaceutics and Biopharmaceutics 80 (2012) 203–208

Contents lists available at SciVerse ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research paper

Thermal degradation of amorphous glibenclamide

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ARTICLE INFO

Article history:
Received 11 April 2011
Accepted in revised form 21 July 2011
Available online 2 September 2011

Keywords:
Glibenclamide
Polymorphism
Thermal degradation
1,3-Dicyclohexylurea
Amorphous

ABSTRACT

A glibenclamide polymorph published by Panagopoulou-Kaplani and Malamataris (2000) [1], obtained by sublimation of amorphous glibenclamide, was analysed. A new interpretation of the data is presented and experimentally confirmed by X-ray powder diffractometry, Fourier transformation infrared spectroscopy, differential scanning calorimetry, and mass spectrometry. The crystals formed during sublimation of amorphous glibenclamide do not represent a glibenclamide polymorph, but a thermal degradation product, namely 1,3-dicyclohexylurea. The reaction mechanism is suggested to be an elimination of cyclohexylisocyanate from glibenclamide. Cyclohexylisocyanate may decompose to carbon monoxide and cyclohexylamine, which may react in an addition reaction with another cyclohexylisocyanate molecule forming 1,3-dicyclohexylurea.

1. Introduction

Glibenclamide (5-chloro-*N*-(4-[*N*-(cyclohexylcarbamoyl)sulphamoyl]phenethyl)-2-methoxy-benzamide) (Scheme 1) is an orally administered sulphonylurea antidiabetic drug. As a result of its good biomembrane permeability and its very poor water solubility, it is rated as a class II drug of the Biopharmaceutics Classification System [2]. Since bioavailability is a major concern with class II drugs, Blume et al. investigated the in vitro dissolution and the bioavailability of marketed glibenclamide tablets. Significant differences between tablets manufactured by different companies were observed, the reasons of which remained unclear [3].

Glibenclamide is a drug with sulphonylurea structure containing two moieties, which are susceptible to degradation at least under harsh conditions: on the one hand the benzamide group and on the other hand the sulphonylurea moiety, which can be split at the urea amide bonds. Bansal et al. investigated the degradation of glibenclamide in acidic and basic media as well as under influence of UV light and at elevated temperatures (50 °C). While glibenclamide degradation occurred in hot acidic and basic media, UV light-induced decomposition and thermal degradation at 50 °C was not observed [4]. Wojnarowska et al. observed thermal degradation during analysis of glibenclamide by thermal Fourier transformation infrared spectroscopy (FTIR) only at temperatures above approximately 190 °C [5].

Sulphonylureas decompose during dry heating by elimination of isocyanates [6,7], for example, pyrolysis of the sulphonylurea tolbutamide leads to n-butyl isocyanate [8].

Glibenclamide shows polymorphism. Polymorphism is defined as the ability of a substance to crystallize in more than one crystalline form [9,10]. Depending on the literature source consulted, between approximately 30% [11] and 50% [10] of recently developed drugs exist in at least two different crystalline forms.

There are several reasons why polymorphism plays an important role in preformulation such as regulatory issues and processing properties. Polymorphs may differ in many of their physicochemical properties such as melting point, mechanical behaviour, storage stability, solubility, and bioavailability resulting from different thermodynamic energies [9,10].

In the literature, the amorphous form and four polymorphs of glibenclamide are described. In 1991, Hassan et al. investigated the properties of amorphous glibenclamide, which was obtained by melting the crystalline drug using an oil bath at 185 °C and quickly cooling the melt in liquid nitrogen [12]. According to Patterson et al., 16% of glibenclamide decomposed during this so-called quench-cooling process, whereas only 0.3% of the drug degraded during amorphization by ball milling [13]. The amorphous glibenclamide obtained by ball milling showed a glass transition temperature (T_g) of 73 °C, while that of the quench-cooled glibenclamide was 58.5 °C. This decrease in the T_g was explained by thermal degradation products acting as plasticizers [13]. In contrast, Wojnarowska et al. observed complete amorphization without any degradation during melting of glibenclamide at 174 °C with subsequent quench-cooling and by cryo-milling of glibenclamide [5].

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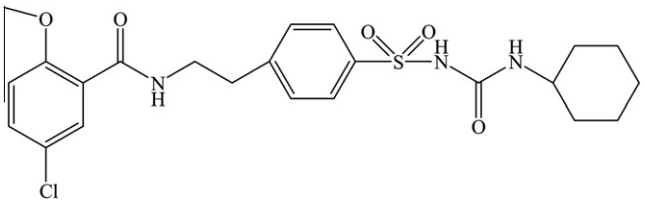
0939-6411/$ - see front matter © 2011 Published by Elsevier B.V.
doi:10.1016/j.ejpb.2011.07.009



Scheme 1.

The amorphous form of glibenclamide recrystallized within two months dependent on temperature [12] and humidity [13].

In 1989, Suleiman and Najib prepared a new polymorph (form II, recrystallization from acetonitrile) and two solvates (pentanol solvate and toluene solvate) of glibenclamide by recrystallization [14]. The solvates showed higher water solubility than the polymorphs I and II. A third polymorph (form III, recrystallization from a mixture of chloroform and ether) and another solvate (recrystallization from a mixture of carbon tetrachloride and chloroform) were obtained by Hassan et al. [15]. Form III showed a higher solubility than form I and II and a lower melting point (T_m) than form I. The authors concluded that form II and form III are metastable and that form I as the marketed form of the drug is the stable form.

In 2000, Panagopoulou-Kaplani and Malamataris described a new glibenclamide polymorph (form IV), which was obtained by sublimation of the amorphous form [1]. This new polymorph showed a higher T_m than form I and was even less water soluble than the marketed polymorph. The authors concluded that the new polymorph is more stable than the other three known polymorphs [1]. In the present study, a new interpretation of the data by Panagopoulou-Kaplani and Malamataris [1] is presented and experimentally confirmed.

2. Materials and methods

2.1. Materials

Crystalline glibenclamide (pharmaceutical grade) was kindly supplied by Berlin Chemie (Berlin, Germany). 1,3-Dicyclohexylurea as reference substance (DCU) was purchased from TCI Europe (Eschborn, Germany).

2.2. Methods

2.2.1. Preparation of the sublimate

Glibenclamide was melted at 185 °C using a paraffin bath. The melt was poured into liquid nitrogen. The resulting amorphous glibenclamide was heated in a Petri dish covered by a watch glass on a conventional hot plate at 130–160 °C, as described by Panagopoulou-Kaplani and Malamataris [1]. As expected, crystals resublimated on the watch glass.

2.2.2. Stereomicroscopy

Stereomicroscopic pictures were taken with a Stereo Discovery V8 Microscope (Zeiss, Jena, Germany), equipped with a Zeiss Axio Cam ICc1. The objective used was a Zeiss Achromat S 1.0× FWD 63 mm.

2.2.3. Scanning electron microscopy (SEM)

SEM pictures were taken on a Leo 1525 scanning electron microscope (Zeiss, Jena, Germany) with a working voltage of 5.00 kV.

2.2.4. X-ray powder diffractometry (XRPD)

Differences in crystal lattice configuration were examined using an X'PERT X-ray diffractometer (Philips, Almelo, The Netherlands, Cu Kα radiation 1.54 Å) in continuous scanning mode, and step size was 0.02°2θ. Powder samples were analysed in aluminium sample holders and scanned at 40 kV and 30 mA from 5 to 35°2θ.

2.2.5. Fourier transform infrared spectroscopy (FTIR)

FTIR spectra were recorded on a Tensor 37 spectrometer (Bruker, Bremen, Germany), equipped with an Attenuated Total Reflectance module (Pike MIRacle). Spectra were detected by an RT-DLaTGS detector over a 4000–600 cm^{-1} range with a resolution of 4 cm^{-1}, and 16 scans were obtained. Spectral analysis was done using the OPUS® 6.5 software.

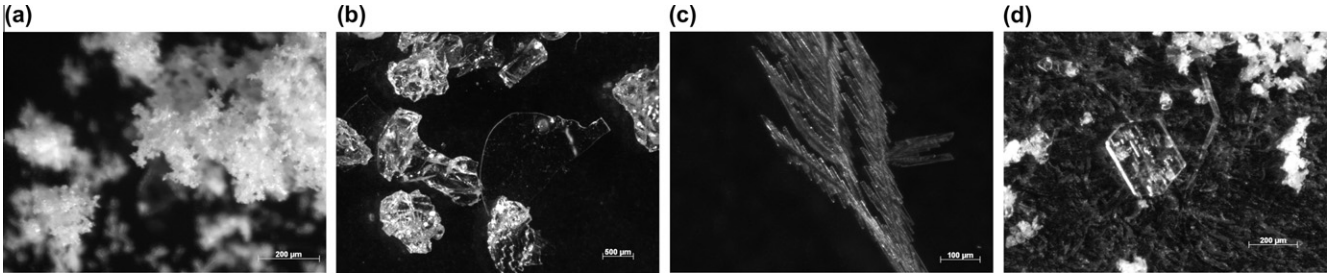


Fig. 1. Stereomicroscopic photographs of (a) crystalline glibenclamide, (b) amorphous glibenclamide, (c) sublimate, and (d) 1,3-dicyclohexylurea reference substance (DCU).

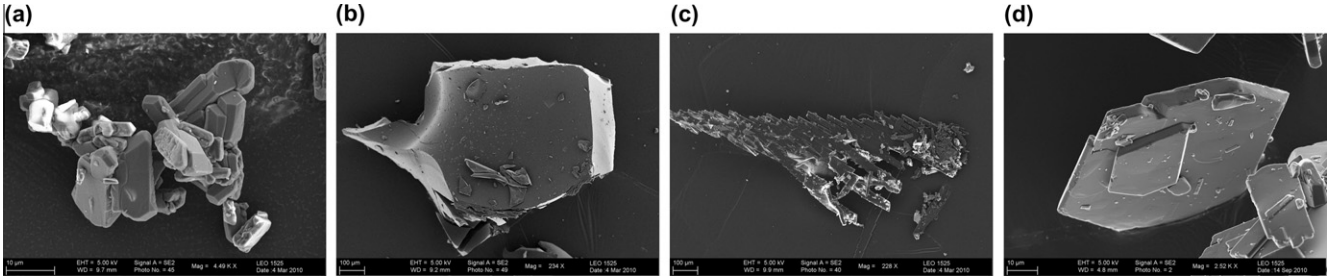


Fig. 2. SEM photographs of (a) crystalline glibenclamide, (b) amorphous glibenclamide, (c) sublimate, and (d) 1,3-dicyclohexylurea reference substance (DCU).

2.2.6. Mass spectrometry (MS)

MS was performed with a VG 70-S (VG Analytical, Altrincham, England) coupled with a SEV detector, employing electron impact (70 eV) and a source temperature of 200 °C. The mass range examined in this study was m/z 35–800. The obtained mass spectra were interpreted using the MassLib software (MSP Kofel, Zollikofen, Switzerland, MassLib V9.3–106, MPI für Kohleforschung).

2.2.7. Differential scanning calorimetry (DSC)

DSC scans were recorded in triplicate using a DSC 7 (Perkin Elmer, Rodgau, Germany) between 0 °C and 250 °C at a heating rate of 10 K/min. For temperature calibration, a two-level calibration was performed using indium and water. Enthalpy calibration was done with indium.

3. Results and discussion

In Figs. 1 and 2, the stereomicroscopic and SEM photographs of crystalline glibenclamide, amorphous glibenclamide, the sublimate, and DCU are shown. It is obvious that glibenclamide in its untreated form is an aggregate of very small flaky crystals with a primary particle size of about 10 µm. The quench-cooled amorphous glibenclamide exhibits large glassy particles including a conchate fraction. The sublimate crystals are of feathery-needle shape with a primary particle size of several hundred micrometres and look similar to the crystals found by Panagopoulou-Kaplani and Malamataris in 2000 [1]. DCU crystals exhibit a hexagonal shape.

In Fig. 3, the XRPD patterns of crystalline glibenclamide, the amorphous form, the sublimate, and DCU are displayed. The diffractogram of crystalline glibenclamide is consistent with the published pattern with sharp characteristic peaks at 11.6°2θ, 18.9°2θ, and 20.9°2θ [13,14]. The halo shape of the diffractogram shown in Fig. 3b proves the amorphous structure of the quench-cooled glibenclamide.

The diffractogram of the sublimate is comparable to the diffractogram reported by Panagopoulou-Kaplani and Malamataris [1]. It differs completely from the pattern of crystalline glibenclamide in both intensity and position of the reflexes. Distinct peaks can be identified at 7.6°2θ, 17.3°2θ, and 22.0°2θ. The 7.6°2θ peak has a high intensity of about 45,000 counts, while the other peaks show intensities between 2000 and 9000 counts.

Comparison of the pattern of the sublimate with an XRPD pattern database (Powder Diffraction File, 2003, The International Centre for Diffraction Data, Newtown Square, USA) led to the conclusion that the sublimate represents DCU. In Fig. 3d, the pattern of the DCU reference substance is shown. It is congruent with the pattern of the sublimate.

Isomorphism, i.e. an identical crystal lattice configuration of two different substances (here a polymorphic form of glibenclamide and DCU), is rarely observed, especially if dealing with organic compounds. Moreover, it is difficult to distinguish different isomorphic forms solely by XRPD.

To exclude isomorphism and to verify the interpretation of the XRPD results, FTIR spectroscopy (Fig. 4), MS (Fig. 5), and DSC (Fig. 6) are performed. The FTIR spectrum of the crystalline glibenclamide is shown in Fig. 4a. It is similar to the FTIR spectra of crystalline glibenclamide published previously [1,12,13]. The urea NH stretch vibrations can be identified at 3360 cm^{-1}, and the amide NH stretch vibrations are found at 3300 cm^{-1}. The peak slightly above 3000 cm^{-1} results from aromatic CH vibrations, and the peak slightly below 3000 cm^{-1} is caused by aliphatic CH vibrations. The amide carbonyl moiety is responsible for the peak at 1714 cm^{-1}, and the urea carbonyl for the peak at 1615 cm^{-1}. The sulphonyl stretch vibrations are found at wave numbers 1340 cm^{-1} and 1157 cm^{-1}, respectively [16].

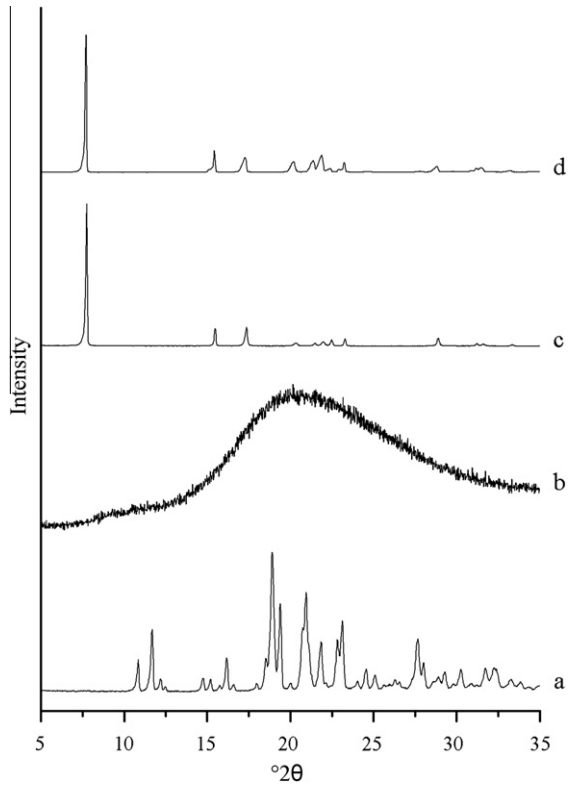


Fig. 3. XRPD patterns of (a) crystalline glibenclamide, (b) amorphous glibenclamide, (c) sublimate, and (d) 1,3-dicyclohexylurea reference substance (DCU).

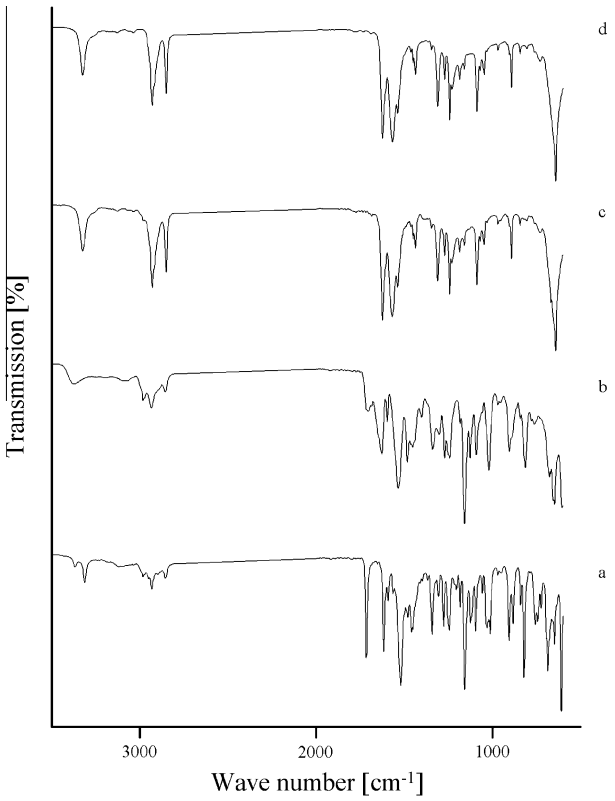


Fig. 4. FTIR spectra of (a) crystalline glibenclamide, (b) amorphous glibenclamide, (c) sublimate, and (d) 1,3-dicyclohexylurea reference substance (DCU).

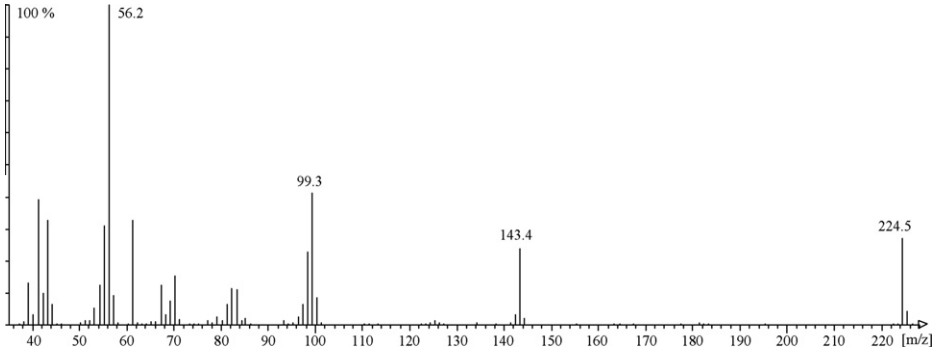


Fig. 5. Mass spectrum of the sublimate.

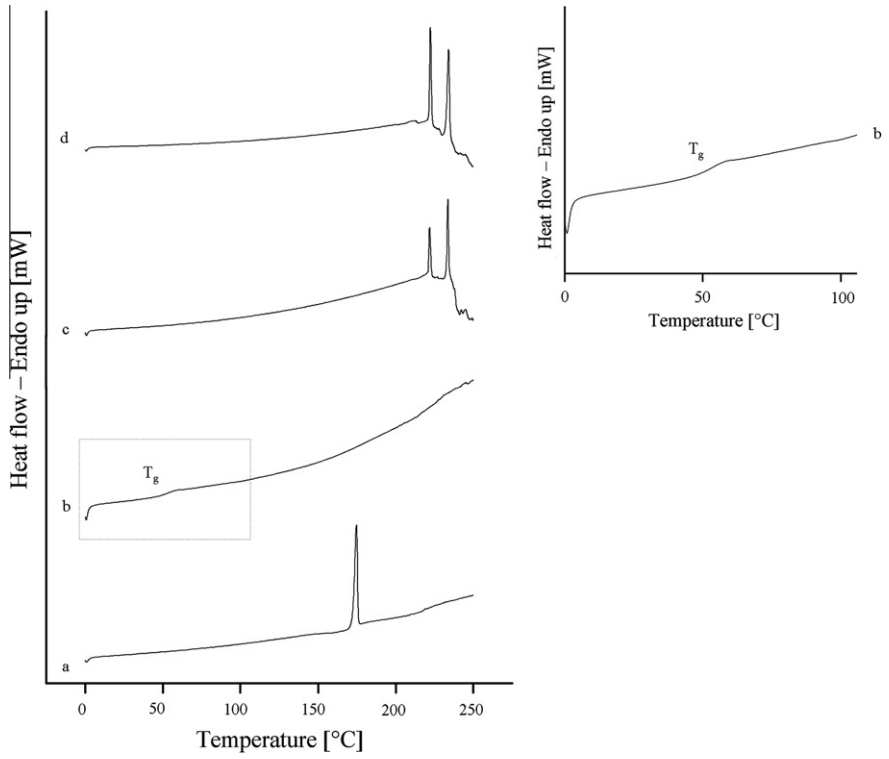


Fig. 6. DSC thermograms of (a) crystalline glibenclamide, (b) amorphous glibenclamide, (c) sublimate, and (d) 1,3-dicyclohexylurea reference substance (DCU). Inset: glass transition temperature of amorphous glibenclamide.

The FTIR spectrum of amorphous glibenclamide shown in Fig. 4b shows significant differences from the crystalline glibenclamide spectrum: While CH and sulphonyl stretch vibrations of the crystalline and amorphous substance remain unchanged, the urea NH stretch vibrations manifest themselves in a rather broad peak and the amide NH band disappeared. The intensity of the amide carbonyl stretch vibrations decreases. Moreover, a peak shoulder at 1654 cm^{-1} appears. This shoulder has been interpreted as C=N stretch vibrations of imidic acid [5,12,13]. Glibenclamide has two moieties, which could show this tautomerism of amide and imidic acid: the amide group and the urea group. To determine the moiety being responsible for the tautomerism, the DCU spectrum is recorded. Since there is no amide moiety in DCU, the carbonyl band at 1622 cm^{-1} results from the urea carbonyl. This means that the 1714 cm^{-1} band of the glibenclamide spectrum is likely to be caused by the amide carbonyl stretch vibrations. As the 1714 cm^{-1} band decreases in favour of the appearance of the 1654 cm^{-1} shoulder, it may be concluded that in fact the amide is converted into the imidic acid form, which was confirmed by Wojnarowska et al. [5]. These observations lead to the assumption that the conversion of crystalline glibenclamide into its amorphous form changes the drug's predominantly amide conformation to a predominantly imidic acid conformation. The amide form is thermodynamically more stable and seems to be stabilized by NH···O intermolecular hydrogen bonding. The thermodynamically less stable imidic acid structure appears to be stabilized by intramolecular hydrogen bonding between the imidic acid and the aryl ether oxygen [5,12,13].

The spectrum of the sublimate is identical to the spectrum published by Panagopoulou-Kaplani and Malamataris in 2000 [1] (Fig. 4c). It shows several characteristic differences compared to the spectrum of crystalline glibenclamide: While the urea NH stretch vibration at 3320 cm^{-1}, the aliphatic CH stretch vibrations at wave numbers directly below 3000 cm^{-1}, and the urea carbonyl peak at 1622 cm^{-1} can still be identified, the aromatic CH stretch vibrations at 3000 cm^{-1}, the amide carbonyl peak at 1714 cm^{-1},

and the sulphonyl peaks at 1340 cm^{-1} and 1157 cm^{-1} disappeared. As this spectrum does not show any aromatic and sulphonyl bands and because it is congruent to that of DCU, the XRPD results are confirmed: The sublimate represents 1,3-dicyclohexylurea.

The mass spectrum of the resublimated crystals is presented in Fig. 5.

Again, comparison of the spectrum with a database (NIST/EPA/NIH Mass Spectral Database, Standard Reference Database 1, 1992, National Institute of Standards and Technology, Gaithersburg, USA) reveals that the sublimate is 1,3-dicyclohexylurea. The m/z 224.5 peak is identified as the DCU peak.

DSC thermograms of the investigated compounds are presented in Fig. 6. The thermograms are evaluated with regard to the position of the thermal events and the melting/sublimation enthalpies (ΔH). The crystalline glibenclamide shows a melting incidence at a mean onset temperature of 169.7 ± 0.3 °C and a mean ΔH of 114.9 ± 3.1 J/g (Fig. 6a). This corresponds to the onset melting behaviour of the stable anhydrous form of crystalline glibenclamide as found in the literature [1,12,13,17].

The thermogram of amorphous glibenclamide is displayed in Fig. 6b. It shows a glass transition temperature (T_g) of approximately 42 °C, which is in good agreement with the T_g of 40–56 °C determined for the quench-cooled substance [1]. Interestingly, the T_g of amorphous glibenclamide determined in this study is approximately 30 °C lower than the T_g of ball milled glibenclamide and about 10 °C lower than the T_g of amorphous glibenclamide obtained by quench-cooling [13]. These observed T_g shifts might be explained by differences in the duration of the melting process at 185 °C before quench-cooling. As it was shown in this study as well as by Wojnarowska et al. [5] that glibenclamide decomposes around 190 °C, thermal degradation during melting in the quench-cooling process is expected. Small molecules resulting from degradation, which are miscible with the sample, could act as plasticizers and lower the T_g. Another reason for the T_g depression might be condensed water vapour from the quench-cooling process on the surface of the amorphous glibenclamide also acting as a plasticizer [18].

The thermograms of the sublimate and of DCU show two endothermic events at about 222 °C and 234 °C, respectively (Fig. 6c and d). Since there is no exothermic event observable, polymorphic transition can be excluded. Hot stage microscopy revealed that the first endothermic event results from a partial sublimation of DCU and the second event represents the melting point of the remaining substance. Panagopoulou-Kaplani and Malamataris [1] detected the first peak at 218 °C, and the second peak was not found. In the present study, the sublimation peak has an onset temperature of 222.4 ± 0.3 °C and a ΔH of 68.61 ± 1.15 J/g, whereas the sublimation peak of DCU shows an onset temperature of 223.4 ± 0.7 °C and a ΔH of 73.73 ± 0.94 J/g. The temperature and enthalpy differences between the sublimation events of the sublimate and of DCU are about 1.0 °C and approximately 5 J/g, respectively. The melting peak of the sublimate shows an onset temperature of 233.1 ± 0.6 °C and a ΔH of 86.11 ± 3.15 J/g, while the melting peak of DCU exhibits an onset temperature of 235.3 ± 0.5 °C and a ΔH value of 96.28 ± 2.02 J/g. The temperature and enthalpy differences between the melting events are about 2.0 °C and approximately 10 J/g, respectively. The melting point is in good agreement with the literature value of DCU of 236 °C (Safety Data Sheet of 1,3-dicyclohexylurea, 2007, TCI Europe NV, Zwijndrecht, The Netherlands).

DCU is obviously formed by thermal degradation of amorphous glibenclamide during dry heating. The baseline shift of amorphous glibenclamide in Fig. 6b at temperatures above 190 °C is an indication for thermal degradation. This observation is in good agreement with the results by Wojnarowska et al. [5], who observed thermal degradation of amorphous glibenclamide at temperatures above approximately 190 °C confirmed by thermal FTIR. Thermal degradation is also observed with crystalline glibenclamide (Fig. 6a) at temperatures of above 200 °C.

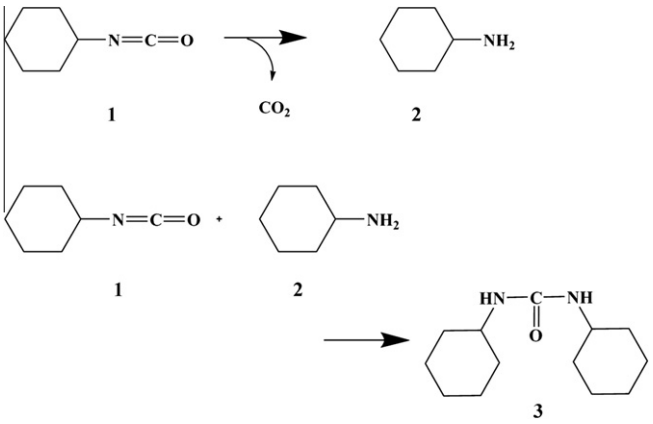


Fig. 7. Decomposition of cyclohexylisocyanate into cyclohexylamine and carbon monoxide, which is oxidized to carbon dioxide. Subsequent additive reaction of cyclohexylisocyanate and cyclohexylamine forming 1,3-dicyclohexylurea.

Surprisingly, in this study, as well as in the study by Panagopoulou-Kaplani and Malamataris [1], thermal degradation is observed on a hot plate set to temperatures of only 130–160 °C. To explain this inconsistency regarding the degradation temperature, the actual hot plate temperature in our laboratory was determined over two hours with an external IR thermometer. It could be shown that setting the temperature to 145 °C leads to a plate and sample temperature of over 300 °C, possibly because of energy loss resulting from the small size of the Petri dish as well as the sample compared to the hot plate diameter. As a result of thermal degradation and formation of DCU, sublimation could already be observed after approximately 15 min of heating. If the hot plate temperature was set to only 65 °C, the measured hot plate and sample temperature was of about 145 °C. In this case, no degradation and thus no sublimation occurred within six hours.

The XRPD, FTIR, MS, and DSC results prove that the sublimate obtained in the described sublimation process is not a polymorphic form of glibenclamide, but its thermal degradation product 1,3-dicyclohexylurea (DCU) **3**.

Dry heating of sulphonylureas leads to the formation of an isocyanate and a primary sulphonamide [6,8]. Thus, cyclohexylisocyanate **1** is eliminated from glibenclamide. The suggested reaction mechanism is displayed in Fig. 7; **1** is unstable and decomposes to cyclohexylamine **2** and carbon monoxide, which is oxidized to carbon dioxide [4], and **2** can react with another cyclohexylisocyanate **1** in an addition reaction to **3**.

4. Conclusion

The results of this study are in contrast to the observations of Panagopoulou-Kaplani and Malamataris [1]. The substance obtained by sublimation of amorphous glibenclamide is not a further polymorphic form of glibenclamide, but the thermal degradation product 1,3-dicyclohexylurea **3**.

If there was a more stable glibenclamide form than the commercially available form I, polymorphic transformation into the more stable crystalline form during processing or shelf life should occur. Consequently, this should lead to a decrease in water solubility and, thus, a potentially reduced bioavailability. From the results of this study, it may be concluded that the differences in in vitro dissolution and bioavailability between various marketed glibenclamide tablets reported by Blume et al. [3] are not caused

by polymorphic transformation into a thermodynamically more stable polymorph, as stated by Panagopoulou-Kaplani and Malamataris [1].

Acknowledgements

The authors would like to thank Berlin Chemie for kindly supplying glibenclamide. Special thanks go to the following co-workers from the University of Hamburg: Joachim Ludwig from the 'Mineralogisches and Petrochemisches Institut' for XRPD analysis, Renate Walter from the 'Biocentrum Grindel + Zoological Museum' for taking the SEM pictures, and Manfred Preuße from the Department of Chemistry for MS analysis. Furthermore, the authors would like to thank the students Isabelle Faas from the Ludwig Maximilians-University of Munich and Catharina Clauß from the Julius Maximilians-University of Würzburg for their support.

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