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THERMOANALYTICAL STUDY OF GLIBENCLAMIDE AND EXCIPIENTS

G. G. G. Oliveira[1*], *H. G. Ferraz*[1] *and J. S. R. Matos*[2]

[1]Department of Pharmacy, College of Pharmaceutical Sciences, Universidade de São Paulo, SP, Brazil
[2]Department of Elementar Chemistry, Chemistry Institute, Universidade de São Paulo, SP, Brazil

Sulfonylureas are widely used for the treatment of non-insulin dependent diabetes mellitus. Glibenclamide belongs to the group of substituted arylsulfonylureas. Many representative of this group shows polymorphism. The purpose of this work was to investigate the thermal behaviour and compatibility between glibenclamide and some excipients using thermoanalytical techniques (TG-DTG/DSC). The thermal and isothermal kinetics data showed incompatibility between glibenclamide and magnesium stearate.

Keywords: *compatibility, DSC, glibenclamide, glyburide, isothermal kinetics, magnesium stearate, pharmaceuticals, TG*

Introduction

By the end of 40's, the sulfonylureas were widely applied drugs for typhoids fever treatment. However, some curious syntoms related to hypoglicemic effects on animals indicated an alternative effect. Then several other molecules have been synthesized and their application to treat non-insulin dependent diabetes mellitus therapeutics increased widely. Glibenclamide (1-{4-[2-(5-chloro-2-methoxybenzamide)ethyl]benzenosulfonyl}-3-cyclohexylurea) belongs to substituted arylsulphonylurea groups. They differ by their substitutions at the *para* position of the benzene ring [1, 2].

Many of the first and second generation representatives of this group have polymorph forms [3–7]. Tolbutamide has four polymorphic forms, one of them is more soluble and less stable compared to the others [8]. Chlorpropamide, similarly presents many forms, but there is no clear evidence of its biopharmaceutical properties [9]. Suleiman and Najib [10] observed that after crystallization of glibenclamide under fast cooling and using different solvents crystals with irregular and asymmetrical structure were formed. The isolated crystals were characterized by thermal techniques, X-ray powder diffraction and equilibrium solubility methods. Crystallization of glibenclamide from pentanol resulted needle shape crystals with a melting point of 166°C and led to higher solubility (50 times higher compared to the same drug crystallized at ambient conditions). Hassan *et al.* [11] observed that fast cooling soon after melting results an amorphous compound. This new form presents glass transition at 71.3ºC and its solubility is 10 times higher. Panagopoulou-Kaplani and Malamataris [12] identified that upon slow cooling followed the melting of glibenclamide results on a new crystalline arrangement with melting at 42ºC (T_{onset}), which is lower than the commercial drug has, and besides the solubility of this newer form was 20 times higher.

Thermal analysis is one of the most frequently used instrumental technique on pharmaceutical researches to solve technological problems [13–16]. Thermoanalytical techniques can be applied successfully to investigate different materials from solids to semi-solids, which have pharmaceutical relevance [17–20]. Thermoanalytical techniques are widely applied alone or as combined with microscopy, spectroscopy (UV, IR), X-ray powder diffractometry and mass spectrometry [21–23]. During preformulation (tablet making, capsules, powders, etc.) and for characterization of drugs.

Thermoanalytical techniques are also used for incompatibility studies between drug(s) and excipient(s) upon preformulation. Incompatibility can lead to the loss of biological activity of drugs, complex formation, acid-base interactions and formation of eutectic mixtures [24–26].

The aim of this work was to evaluate possible interactions between some pharmaceutical excipients and glibeclamide using thermoanalytical techniques (TG/DSC).

Experimental

Materials

The excipients and drug used on this work were of pharmaceutical grade, kindly provided by Brazilian industries. The drug chosen for this work was glibenclamide, a second generation sulfonylurea. The excipients were:

* Author for correspondence: ggualter@usp.br

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Akadémiai Kiadó, Budapest, Hungary
Springer, Dordrecht, The Netherlands

starch, cellulose microcrystalline, dibasic anhydrous calcium phosphate, croscarmellose sodium, magnesium stearate, sodium lauril sulphate and lactose. The compatibility studies were carried out using 1:1 mass/mass binary mixtures of drug and excipient.

Measurements

DSC curves were obtained with a Shimadzu DSC-50 cell using aluminium crucibles with about 2 mg of samples, under dynamic nitrogen atmosphere (100 mL min^{-1}) and at a heating rate of 10 K min^{-1} in the temperature range of 25–500°C. The DSC cell was calibrated with indium (*m.p.*=156.6°C; ΔH_{fus}= 28.54 J g^{-1}) and zinc (*m.p.*=419.6°C).

TG/DTG curves were obtained with a Shimadzu TGA-50 thermobalance between 25–650°C, using platinium crucibles with 4.0±0.1 mg of samples, under dynamic nitrogen atmosphere (50 mL min^{-1}) and a heating rate of 10 K min^{-1}.

Isothermal thermogravimetric studies were carried out using the same conditions of the dynamic TG, however, the samples were heated to 10°C lower than T_i (where T_i is the isothermal temperature) at a heating rate of 20 K min^{-1} and that at 2 K min^{-1} to reach T_i. The samples were kept at different T_i temperatures (150, 155, 160, 165, 170 and 175°C, respectively, to reach 10% of mass loss) and the Arrhenius plot was established on the base of the experimental data.

Results and discussion

The thermoanalytical curves of glibenclamide are presented in Fig. 1.

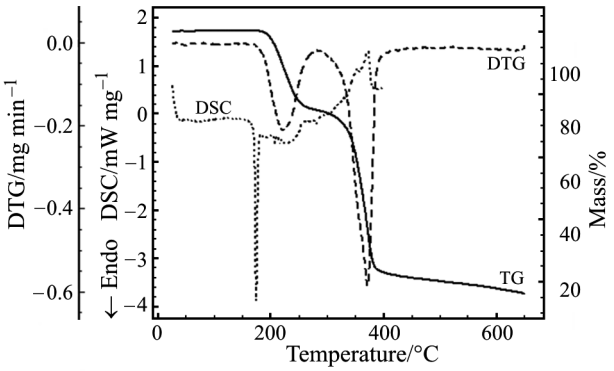

Fig. 1 TG/DTG and DSC curves of glibenclamide

The TG/DTG curve shows that glibenclamide is thermally stable upto 180°C and presents two significant mass loss steps between 180 and 400°C (Δm_1= 26.7% and T_{peak}DTG=222°C; Δm_2=67.8% and T_{peak}DTG=372.2°C). The endotherm DSC peak is related to the melting of the substance (T_{onset}=171.5°C) followed by other endo- and exotherm events due to evaporation and decomposition.

Over 400°C, the TG/DTG curves indicate a slow and continuous mass loss caused by elementary carbon formation from the previous steps, as consequence of the rupture of the aromatic ring.

TG and DSC curves of the pure glibenclamide and the 1:1 drug:excipient physical mixtures are shown in Figs 2 and 3.

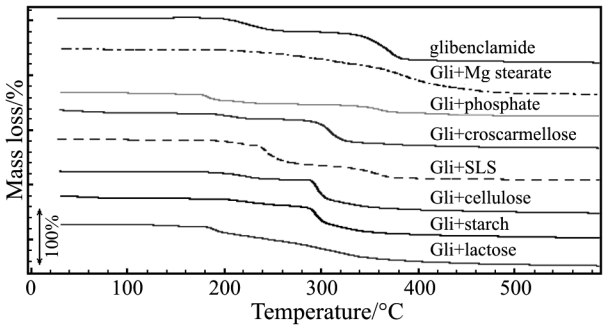

Fig. 2 TG curves of glibenclamide and 1:1 physical mixtures (glibenclamide/excipient)

Most of the thermal profiles of the mixtures can be considered as a superposition of the TG and DSC curves of the pure glibenclamide and the excipients. Differences were observed in case of glibenclamide/lactose and glibenclamide/magnesium stearate binaries. According to the authors' experiences the mass loss is frequently related to structural change and indicate interaction incompatibilities between the compounds.

The DSC method is more sensitive to indicate the compatibility/incompatibility of the binary mixtures (Fig. 3).

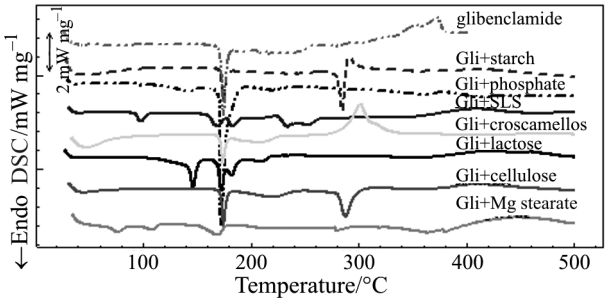

Fig. 3 DSC curves of glibenclamide and glibenclamide/excipient 1:1 physical mixtures

By the comparison of the DSC curves of pure glibenclamide and Mg stearate with their 1:1 physical mixture, the differences are well visible, which can be attributed to any incompatibility (interaction) between the two components.

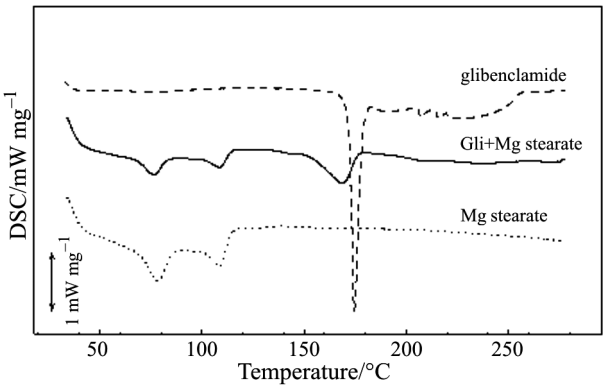

Fig. 4 DSC curves of glibenclamide, magnesium stearate and their 1:1 physical mixture

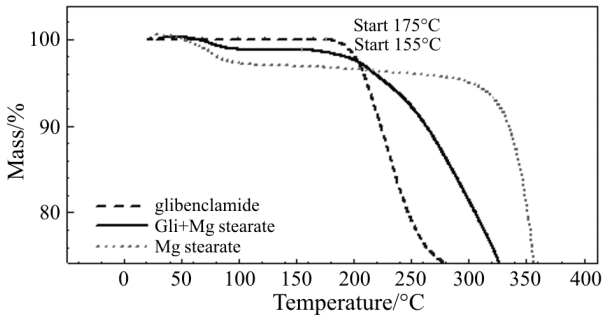

Fig. 5 TG curves of glibenclamide, magnesium stearate and their 1:1 physical mixture

The melting peak of the drug (T_{onset} at 170°C) disappears and a new appears at 20°C below, as it can be seen in Fig. 4.

The results taken from the TG and DSC curves of the binary mixtures are collected in Table 1.

It is important to know that the large ΔH value associated to the endotherm peak on the DSC curve of phosphate/drug mixture are the sum of different thermal events, which involve the melting of glibenclamide, but irrelevant with the T_{onset} displacement. Besides, the corresponding data of the glibenclamide–magnesium stearate mixture indicate the occurence of remarkable interaction, since the endotherm peak of glibenclamide shifted from 174.7 to 168.7°C and the DTG peak temperature decreased from 222 to 211°C and from 361 to 328°C. Pyramides *et al*. [27] observed differences in the DSC curves of the melting point of atenolol (154.8ºC) in the drug:magnesium stearate mixtures. The temperature of the endotherm peak shifted down from 153 to 137ºC while the amount of magnesium stearate increased from 30 to 50 mass/mass%. It means that magnesium stearate promotes an interaction in reducing the melting temperature of the drug which depends on the amount of excipient.

Started from these results, kinetic experiments have been carried out on glibenclamide/magnesium stearate mixture. According to its TG curve the decomposition of drug starts at 175ºC (Fig. 5). Consequently the following temperatures were selected for isothermal treatments: 175°C (only for drug), 170, 165, 160, 155 and 150ºC (for drug excipient mixtures). The samples were kept on these temperatures while 3 and 5% of mass losses were obtained. From these data the Arrhenius plots (ln*t vs*. 1/*T*) were constructed (Fig. 6). In order to provide kinetic parameters which can be used to obtain extrapolated data at ambient temperature [28] or to use for accelerated thermal stability studies.

According to the results obtained from TG curves, the mass losses took place through a different mechanism when the magnesium stearate was mixed with the drug (Fig. 6). Furthermore a decrease in the activation energy values and a shorter time to reach 5 and 3% of mass losses, related to the first event (melting followed by partial decomposition) is promoted by the presence of magnesium stearate, which is a clear evidence of an incompatibility (Table 2).

Table 1 Thermoanalytical data of glibenclamide and drug:exipient physical mixtures

	T_{fus}/°C	ΔH_{fus}/J g^{-1}	T_{onset}/°C	Δm/%	DTG_{peak}=°C
Drug					
Glibenclamide	174.7	92.1	171.6	25.7/57.6	222/361
Drug/excipient					
Starch	174.6	38.4	172.3	5.1/12.4/57.8	224/355
Lactose	173.0	26.2	168.9	2.0/72.8	189/321
Phosphate	172.3	276.3	170.3	20.9/20.5	221/372
Cellulose	174.9	45.1	171.8	13.4/59.6	221/345
Mg stearate	168.7	41.3	155.0	31.1/52.9	211/328
Sodium lauril s.	168.5	25.7	161.8	36.4/26.9	223/358
Croscarmellose	174.2	35.8	171.2	11.0/52.0	208/309

Table 2 Mass loss and activation energy values of glibenclamide–Mg stearate mixtures

Assay	Δm/%	E_a/kJ mol^{-1}
Glibenclamide	5	175
Glibenclamide+Mg stearate	5	115
Glibenclamide	3	165
Glibenclamide+Mg stearate	3	106

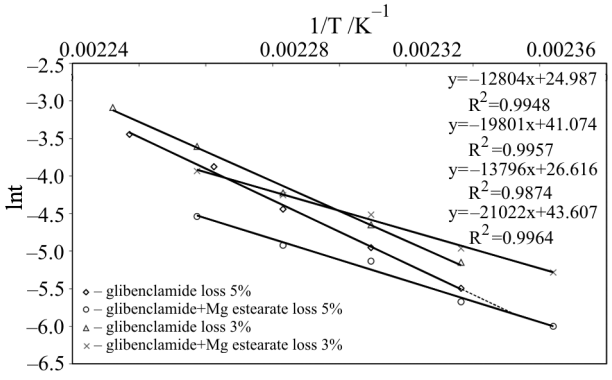

Fig 6 ln$t$–1/T plots drawn from isothermal studies

Conclusions

According to the thermoanalytical studies, among all studied mixtures incompatibility was found between glibenclamide and magnesium stearate.

However, this excipient is used at low concentration (0.5–1.0%) in the pharmaceutical dosage forms so far, another set of stability tests should be carried out to confirm the real impact of this interaction together with other common pharmaceutical excipients.

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