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THERMAL BEHAVIOUR, COMPATIBILITY STUDY AND DECOMPOSITION KINETICS OF GLIMEPIRIDE UNDER ISOTHERMAL AND NON-ISOTHERMAL CONDITIONS

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In the present work, the thermal decomposition of glimepiride (sulfonylurea hypoglycemic agent) was studied using differential scanning calorimetry (DSC) and thermogravimetry/derivative thermogravimetry (TG/DTG). Isothermal and non-isothermal methods were employed to determine kinetic data of decomposition process. The physical chemical properties and compatibilities of several commonly used pharmaceutical excipients (glycolate starch, microcrystalline cellulose, stearate, lactose and Plasdone®) with glimepiride were evaluated using thermoanalytical methods. The 1:1 physical mixtures of these excipients with glimepiride showed physical interaction of the drug with Mg stearate, lactose and Plasdone®. On the other hand, IR results did not evidence any chemical modifications. From isothermal experiments, activation energy (E_a) can be obtained from slope of ln$t$ *vs.* $1/T$ at a constant conversion level. The average value of this energy was 123 kJ mol^{-1}. For non-isothermal method E_a can be obtained from plot of logarithms of heating rates, as a function of inverse of temperature, resulting a value of 157 and 150 kJ mol^{-1}, respectively, in air and N_2 atmosphere, from the first stage of thermal decomposition.

Keywords: *activation energies, degradation behaviour, glimepiride, kinetic analysis, TG*

Introduction

Thermal analysis is a routine method for analysis of drugs and substances of pharmaceutical interest [1–3]. TG/DTG and DSC curves have related important information about the physical properties of materials (stability, compatibility, polymorphism, kinetic analysis, phase transitions). Kinetic parameters (activation energies, frequency factor and reaction order) can be measured by thermoanalytical methods according to progress of reactions [4–10]. In case of thermogravimetry the quotient from mass loss $\Delta m(t)$ at time t with total mass loss $\Delta m(t=\infty)$ equals proportion which has reacted so far, the degree of conversion. It can be used in the quality control of drugs, with a view to improvement of final product and for determination of drug quality via technological parameters [11].

The compatibility studies using thermal analysis present advantageous to readily available knowledge of any physical and chemical interactions between drugs and excipients which might give rise to changes in chemical nature, stability, solubility, absorption and therapeutic response of drugs. Thermal techniques have been increasingly used for quick evaluation of possible incompatibility between formulation components through comparison of thermal curves of pure substances with curve obtained from a 1:1 mixture [12]. If mixture curve represents thermal events sum observed for the individual components, there is no interaction and therefore no physical-chemical incompatibility between drug and excipient.

In this paper, thermoanalytical techniques were used to study thermal behaviour, compatibility with excipients and kinetic analysis under isothermal and non-isothermal (dynamic) conditions of glimepiride. This substance is an oral antidiabetic drug in sulfonylurea class having a prolonged effect [13, 14]. In order to achieve appropriate control of blood glucose level, treatment of non-insulin dependent Type II diabetes usually starts with diet and exercise.

Experimental

Materials

The glimepiride (1-({*p*-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido)ethyl]phenyl}sulfonyl)-3-(*trans*-4-methylcyclohexyl)urea) was obtained from Aventis Pharma LTDA (lot: A 038.02-SS). Excipients tested were: glycolate sodium starch (Henri-

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farma), microcrystalline cellulose (Blanver), magnesium stearate (Dyne), lactose (Henrifarma) and Plasdone® S-630 (ISP). The mixed samples consisted of equal masses of glimepiride and each excipient was weighed individually into amber glass flasks to originate mass of 20 g of mixture. Physical mixtures were prepared in proportion (*m*/*m*) 1:1 (glimepiride:excipient) by simple mixing.

Methods

DSC curves were obtained in a DSC-50 cell (Shimadzu) using aluminium crucibles with about 2 mg of samples, under dynamic nitrogen atmosphere (50 mL min^{-1}) and heating rate of 10°C min^{-1} in temperature range from 25 to 600°C. 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 thermobalance model TGA 50 (Shimadzu) in temperature range 25–900°C, using platinum crucibles with ~3 mg of samples, under dynamic nitrogen atmosphere (50 mL min^{-1}) and heating rate of 10°C min^{-1}.

Kinetic investigation of glimepiride degradation was obtained from TG data by application of Ozawa's method in which plot slope of log heating rate *vs*. 1/*T* gives activation energy of process. In dynamic experiments were used heating rates 2.5, 5.0, 7.5, 10 and 15°C min^{-1}. For isothermal method temperature was from 170 to 210 with 10°C temperature increment.

IR spectra of drug and drug-excipient blends were obtained at room temperature in the range 4000–400 cm^{-1} in KBr pellets using a Nicolet spectrophotometer, model Magna 550.

Results and discussion

Thermal behaviour and kinetic study of glimepiride

DSC curve of glimepiride (Fig. 1) shows a sharp endothermic peak at 212°C that corresponds to melting followed by thermal decomposition. The decomposition is defined in two endothermic stages. This is confirmed by TG/DTG curves that indicate thermal decomposition in the following temperature range (mass loss): 212–250°C (Δ*m*=27.3%), 250–450°C (Δ*m*=50.4%) and carbonization initiating at about 470°C (Δ*m*=21.9%).

The superposition TG curves obtained to several heating rates for glimepiride is shown in Fig. 2. This figure shows that TG curves are shifted for higher temperatures when heating rates increase. Ozawa's method was applied to data obtained from five TG curves in order to determine the activation energy (E_a) at the beginning of main thermal decomposition step at around 210 to 240°C. The inserted figure presents obtained plots, which demonstrate a fairly good correlation at five heating rates. The E_a calculated was 157 and 150 kJ mol^{-1} in air and nitrogen respectively, for this first stage of thermal decomposition.

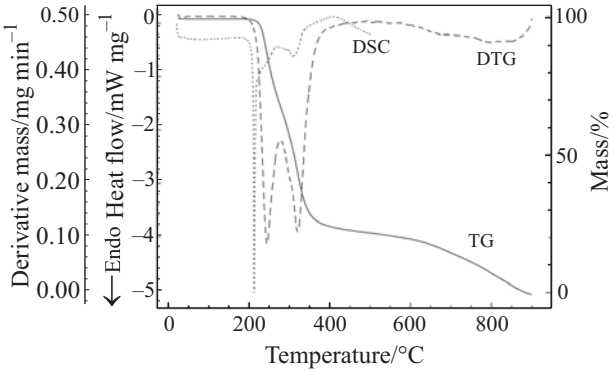

Fig. 1 DSC and TG/DTG curves of glimepiride in dynamic nitrogen atmosphere (50 mL min^{-1}) and heating rate 10°C min^{-1}

The isothermal TG curves superimposed of glimepiride are illustrated in Fig. 3. These curves show mass loss rate dependence in temperature function of isothermal, the larger the temperature smaller will be the necessary time so that occur the same mass loss. These curves were used to obtain the graphic of ln*t* *vs*. the reciprocal of temperature 1/*T* (K^{-1}) for glimepiride. From this linear regression method, the equation for the line is $y=-14752x+27.82$ and R=0.99795 are obtained. The value of the activation energy can be calculated from the product of 14752 with the molar gas constant (R=8.314) this energy is E_a=123 kJ mol^{-1}. This result is in agreement with the values obtained from the dynamic method, and this is an important experimental finding.

Compatibility study with excipients

The DSC curves of the binary mixtures show that, with the exception of microcrystalline cellulose and glycolate sodium starch, the excipient starts the fusion or decomposition at temperatures about 30°C lower than that of pure glimepiride. The thermal be-

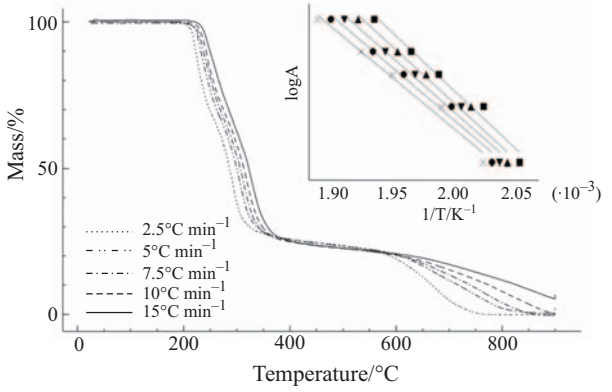

Fig. 2 TG curves of glimepiride obtained at 2.5, 5.0, 7.5, 10 and 15°C min^{-1}. The inserted figure shows Ozawa's plot

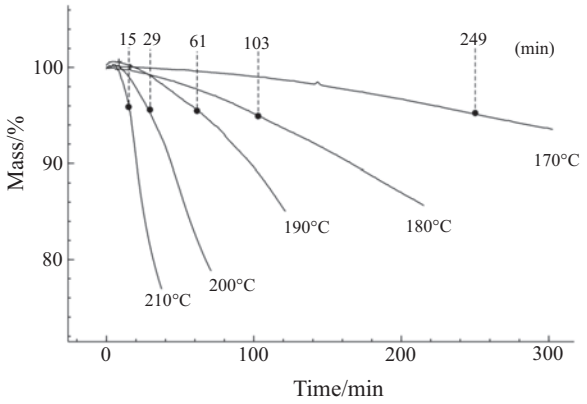

Fig. 3 Isothermal TG curves of glimepiride obtained between 170 and 210°C with a temperature increment 10°C

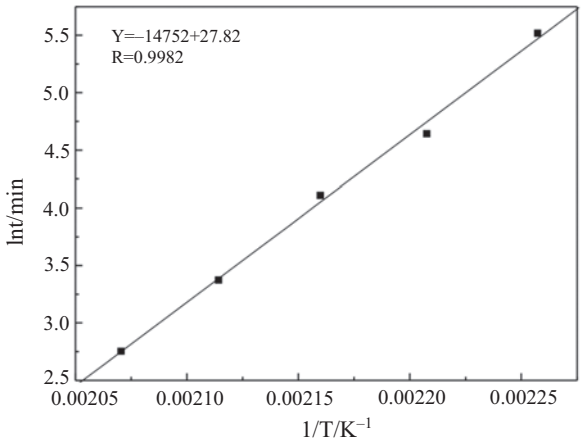

Fig. 4 Plot ln*t vs*. the reciprocal of temperature $1/T$ for glimepiride from the data obtained under the experimental conditions of 2°C min^{-1}, dry N_2 (50 mL min^{-1}), using the Arrhenius equation

haviour of the binary mixture of glimepiride with microcrystalline cellulose and glycolate sodium starch (Figs 5 and 6) show the endotherm and exotherm characteristic of drug, indicating the presumable absence of incompatibility and/or interaction.

Figure 5 shows DSC curve representative of binary mixture of the glimepiride and Plasdone®. Endothermic peak of drug was broadened and shifted to lower temperature. This is indicative of a strong interaction, but not necessarily corresponding to incompatibility. In fact, a similar effect was observed for other drugs in mixtures with polymers, and was attributed to drug dissolution in the melted excipient [12].

The decrease of the melting point of glimepiride also can be observed to the sum of representative curve with magnesium stearate (Fig. 5). The corresponding data of glimepiride-magnesium stearate mixture indicate the occurrence of remarkable interaction, since the endotherm peak of glimepiride shifted from 207 to 183°C. According to their TG/DTG curves the onset temperature of thermal decomposition decreased from 222 to 208°C (Fig. 6).

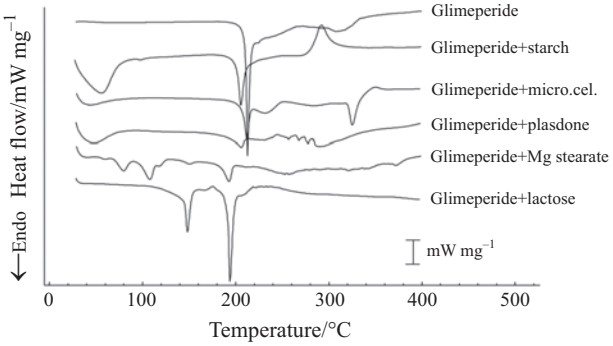

Fig. 5 DSC curves of glimepiride and excipients obtained in dynamic nitrogen atmosphere (50 mL min^{-1}) and heating rate 10°C min^{-1}

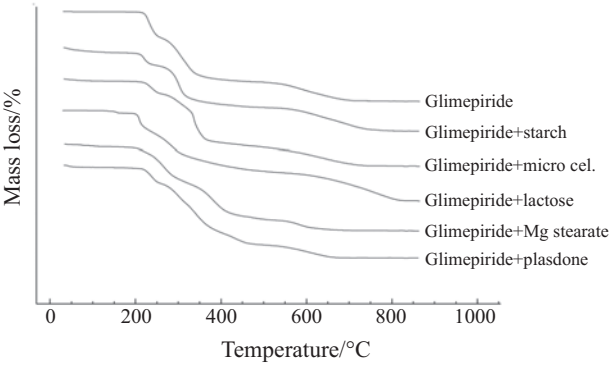

Fig. 6 TG curves of glimepiride and excipients obtained in dynamic nitrogen atmosphere (50 mL min^{-1}) and heating rate 10°C min^{-1}

DSC curve of lactose shows endothermic peak at 149°C (corresponding to dehydration of bound water), exothermic peak at 172°C (crystalline transition), endothermic event at 215°C (melting point), and a small endothermic peak at 221°C (thermal decomposition). DSC curve of the binary mixture revealed interactions between glimepiride and lactose, which might be physical in nature. This fact is justified because the melting of drug and excipient occur in the same temperature range (205–215°C). In this binary mixture the melting point of the drug and excipient was decreased of 207 to 188°C (T_{onset} of physical mixture). This result was confirmed by TG/DTG curves that showed the reduction of the thermal decomposition temperature in about 17°C below that of glimepiride. In fact, a similar effect was observed for other drugs, such as glipizide [15] and glibenclamide [16].

IR spectra of glimepiride, glimepiride-lactose (physical mixture) and glimepiride-lactose (binary mixture melting) showed the presence of characteristic bands corresponding to drug and excipient. There was no appearance of new bands in IR spectra confirming that it did not occur change in drug structure (Fig. 7). Similar results were observed in the mixtures of glimepiride and magnesium stearate (Fig. 8).

Table 1 Peak temperature and enthalpy values of glimepiride and binary mixtures with excipients

Samples	T_{onset} DSC/°C	Enthalpy of fusion/J g^{-1}	T_{onset} TG/°C	T_{peak} DTG/°C	Mass loss/%
Drug					
Glimepiride	207.4	94.6	221.6	229.9	29.7/48.4/21.9
Drug/excipients					
Starch	198.9	39.5	212.5	221.0	6.4/14.4/42.5/31.5
Micro. cellulose	205.8	65.4	221.3	238.1	2.8/14.7/12.7/40.6/26.4
Mg stearate	182.8	28.6	208.4	224.7	1.2/1.2/7.4/33.8/35.3/17.4
Lactose	188.1	*	201.3	209.7	3.2/22/27.8/47.7
Plasdone®	192.8	17.2	220.2	237.1	18.5/21.7/34.3/12.3/13.2

*Melting point of drug and excipient occur in the same temperature range

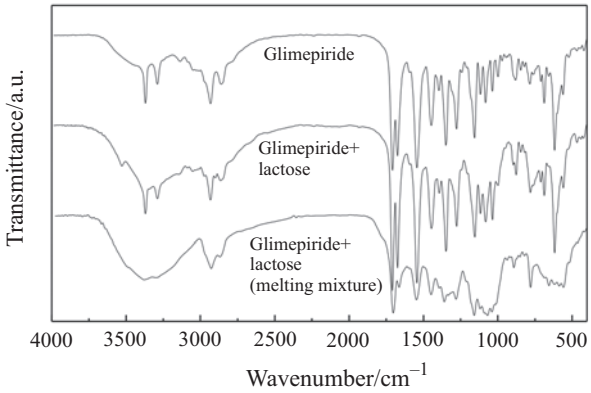

Fig. 7 Infrared spectroscopy (FTIR) spectra of glimepiride, glimepiride-lactose (physical mixture) and glimepiride-lactose (binary mixture melting)

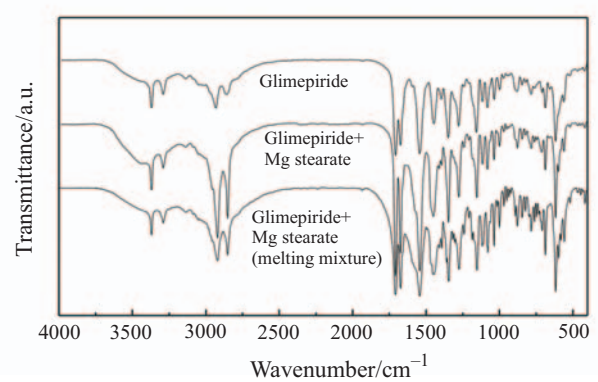

Fig. 8 Infrared spectroscopy (FTIR) spectra of glimepiride, glimepiride-Mg stearate (physical mixture) and glimepiride-Mg stearate (binary mixture melting)

The values of the melting peak temperature, fusion enthalpy, and temperature range of thermal decomposition and mass losses (%) of glimepiride after mixing with excipients are listed in Table 1.

Conclusions

Through isothermal and non-isothermal conditions, the activation energies for the first-step decomposition reaction or glimepiride were determined. The E_a calculated using dynamic method was 157 and 150 kJ mol^{-1} in air and nitrogen, respectively, for this first stage of thermal decomposition. On the other hand, the value of E_a by isothermal method was 123 kJ mol^{-1}. It can be used in the quality control of drug, with a view to improvement of the final product and for the determination of drug quality via the technological parameters. The compatibilities and stabilities of some binary mixtures were studied by using TG/DTG and DSC techniques. The results showed the utility of thermal analysis as a rapid and convenient method of screening candidate excipients during preformulation studies, because it permits the ascertainment of excipients compatibility or demonstration of drug-excipient interaction or incompatibility. In this study was possible to observe the interactions of the glimepiride with Plasdone®, Mg stearate and lactose. The Plasdone® and lactose melts and one part of the glimepiride crystals dissolves in the melt.

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