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APPLICATION OF THERMAL ANALYSIS OF BINARY MIXTURES WITH METFORMIN

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Thermal analysis is an essential analytical tool in development of new formulations as well as to study the interaction between drugs and excipients. This work aims to investigate the possible interactions between metformin and excipients as microcrystalline cellulose (Microcel MC101®), starch sodium glycolate (Explosol®), sodium croscarmellose (Explosel®), PVP K30, magnesium stearate, starch and lactose, usually employed in pharmaceutical products. TG, DSC and DTA techniques were used for the thermal characterization to track if the thermal properties of the drug substance were modified in the mixture. Disregard of the starch and lactose systems, no changes in thermal behavior of mixtures were found. Thermogravimetric studies (TG) of metformin and its binary mixtures showed different thermal behavior.

Keywords: *compatibility, metformin, thermal analysis*

Introduction

Metformin (MET) is a drug having antihyperglycemic properties and one of most commonly prescribed medicine for Type II diabetes [1]. Its chemical structure is given in Fig. 1.

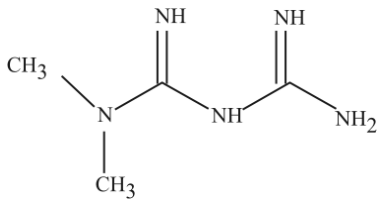

Fig. 1 Chemical structure of MET

Recent works highlighted the application of differential scanning calorimetry (DSC) and differential thermal analysis (DTA) for the rapid evaluation of the drug-excipient compatibility [2].

Thermal analysis is used in the pharmaceutical industry as a reliable technique for quality control and for the development of new pharmaceutical formulations [3, 4]. TG and DSC curves provide important information on the physical properties of substances (stability, compatibility, polymorphism, kinetic analysis, phase transition) [5].

In this work aims the possible interactions between metformin and excipients: microcrystalline cellulose (Microcel MC101®), starch sodium glycolate (Explosol®), sodium croscarmellose (Explosel®), PVP K30, magnesium stearate, starch and lactose – usually employed in pharmaceutical products – was studied. Each above substances were characterized using TG, DSC and DTA techniques.

Experimental

Materials and methods

Metformin (lot: ALC/MTF/040712), lactose (lot: 8090426), PVP K30 (lot: 20040124), magnesium stearate (lot: 200504172), starch (lot: 3012267294) were acquired from the Industrial Pharmaceutical Laboratory of State of Paraiba (LIFESA, João Pessoa, Brazil). Other excipients, as microcrystalline cellulose (Microcel®, lot: 002/05), starch sodium glycolate (Explosol®, lot P: 19032/05) and sodium croscarmellose (Explosel®, lot: 801405) were provided by Blanver Farmacoquímica.

Binary mixtures

Binary mixtures (in 1:1 mass:mass ratio) of metformin and excipients were prepared and analyzed by TG and DTA.

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Phase diagram

The phase diagrams for metformin:starch and metformin:lactose were determined using 2:8, 3:7, 1:1, 7:3 and 8:2 mass:mass proportions, respectively and analyzed by DSC.

Thermogravimetric studies

TG curves of the raw materials as well as of the binary mixtures were recorded using Shimadzu TGA-50H thermobalance in air (flow rate: 20 mL min^{-1}) and nitrogen at a flow rate of 50 mL min^{-1}. The applied heating rate was 10 K min^{-1}, up to 1173 K. The samples were placed to alumina pans and the initial sample masses were 5.5±0.5 mg.

Calorimetric studies

DTA curves to metformin, excipients and binary mixtures were recorded by Shimadzu differential thermal analyzer, model DTA-50, in nitrogen (flow rate: 50 mL min^{-1}). The sample masses were about 8.0 mg, and alumina crucible was used at heating rate of 10 K min^{-1} up to 1173 K. Temperature calibration was done by the melting point and enthalpy of indium and zinc standards under the above written conditions.

DSC curves of metformin and binary mixtures have been recorded using a Shimadzu DSC-50 cell. The operating conditions: nitrogen (flow rate: 50 mL min^{-1}) heating rate: 10 K min^{-1} up to 773 K. Aluminium sample pans and about 2.0 mg initial sample mass was used.

Temperature and calorimetric calibration was done using indium and zinc standards.

The thermoanalytical data were analyzed using TASYS software provided by Shimadzu.

Results and discussion

Differential thermal analysis

DTA curves of metformin and its binary mixtures showed that the drug melts at 505 K, the corresponding heat effect is –320 J g^{-1} is in agreement with the literature data [6]. DTA curves of the binaries show that except of the metformin–lactose and metformin–starch mixtures, the melting peak temperatures did not change remarkably (data in Table 1). Data were confirmed more precisely by phase diagram studies using DSC.

Table 1 Melting peak temperatures and corresponding enthalpies of MET and its 1:1 binary mixtures

Sample	Peak/K	ΔH/J g^{-1}
Metformin	504	–320
Metformin: PVP K30	506	–151
Metformin: Starch	496	–189
Metformin: Glycolate	506	–191
Metformin: MC101®	507	–121
Metformin: Croscarmellose	507	–183
Metformin: Magnesium stearate	504	–133
Metformin: Lactose	462	–233

Differential scanning calorimetry

DSC curve of MET showed that drug substance exhibited an endothermic peak corresponding to the melting 499 K, with a heat effect of –215 J g^{-1}.

Calorimetric studies of MET in its binary mixture with starch and lactose confirmed that the application of these two excipients leads to interaction upon heating changing the melting temperature of MET and the accompanying enthalpy change, too (Fig. 2).

Figure 2a shows the calorimetric curves of MET-Lactose mixture with different drug:excipient compositions. An alteration in the temperature of melting peak of metformin in all proportions was observed. The melting process of metformin is not

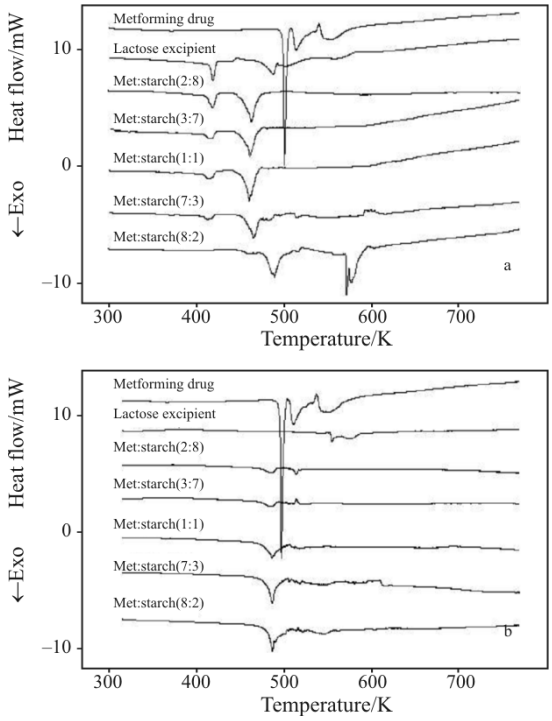

Fig. 2 DSC curves of a– MET:Lactose and b– MET: Starch binary mixtures at different proportions

Table 2 Thermogravimetric data of MET and its binary mixtures

Sample	Number of decomposition steps	Initial decomp. temperature/K	End decomp. temperature/K	Mass loss/%	Residue/%
Metformin	1	524	688	85.4	0.9
	2	688	951	13.7	
Metformin: magnesium stearate	1	308	422	1.7	7.7
	2	485	873	84.4	
	3	873	1168	6.3	
Metformin: MC 101®	1	304	344	0.8	2.5
	2	507	857	64.6	
	3	857	1041	32.0	
Metformin: PVP K30	1	302	374	4.0	2.7
	2	523	777	78.0	
	3	777	1028	14.9	
Metformin: starch	1	300	386	3.6	2.5
	2	501	826	63.6	
	3	826	1043	30.3	
Metformin: glycolate	1	299	458	6.7	4.1
	2	514	852	58.7	
	3	852	1173	30.6	
Metformin: croscarmellose	1	304	437	4.5	4.2
	2	507	926	63.4	
	3	926	1088	25.5	
	4	1088	1171	2.4	
Metformin: lactose	1	432	466	1.0	0.7
	2	466	481	1.7	
	3	481	821	64.8	
	4	821	1037	32.0	

visible in the presence of lactose suggesting the interaction between them.

Figure 2b shows a displacement in the melting temperature of metformin in all proportions of the MET–Starch mixtures confirming the fact of interaction between the two compounds. One possible reason of this interaction can be a Maillard reaction between either of starch or lactose hydroxyls' that can react with the amine group of metformin.

Thermal studies were done using binaries of drug-lactose (glimepiride [5], glipizide [7] and glibenclamide [8]), and evidenced interactions referring to incompatibility of these drugs and the decrease of their stability, which implies in a better evaluation of the pre-formulation studies where the lactose is main excipient.

Starch presents a great variety with regard to its chemical composition (amylose and amylopectin). Besides, this is a natural polymer and can be originated from different regions. Consequently, for its application in the pharmaceutical industry a better quality control is necessary [9].

Thermogravimetric studies

Thermogravimetric studies of MET and its binary mixtures with different excipients showed different thermal behaviour with regard to the number of mass loss stages (data in Table 2).

Kinetic study

Ozawa's model was applied for the kinetic studies to evaluate the thermoanalytical parameters and activation energy (E_a), frequency factor (A) and

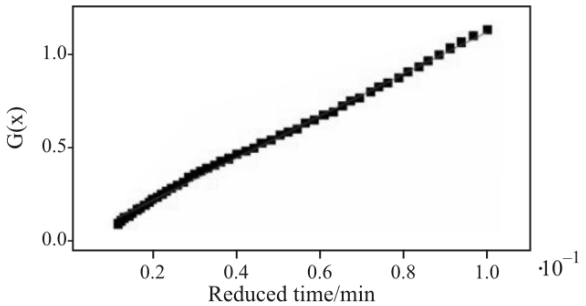

Fig. 3 Thermal decomposition kinetic parameters of MET according to Ozawa's method

reaction order (n). The calculated data evidenced a first order of kinetic behavior for MET with E_a value: 68.0 kJ mol^{-1}; rsd 4.3 kJ mol^{-1}, frequency factor ($1.22 \cdot 10^5$ min^{-1}) (Fig. 4).

Conclusions

DTA and DSC thermal data showed incompatibility between MET and excipients starch and lactose, upon heating changing the melting temperature of MET and the accompanying enthalpy change, too.

In the kinetic study the Metformin showed a thermal behaviour characteristic of first order.

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