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Studies of cimetidine pre-formulated and tablets for TG and DSC coupled to the photovisual system

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Abstract

This work studied the compatibility pre-formulated drug–excipient mixtures and tablets of cimetidine by TG and DSC coupled to a photovisualization system. The excipients PVPK30, explocel, microcel MC101, aerosil, and magnesium stearate were studied. Curves for the phase transitions of pre-formulated, microcel– and explocel–cimetidine were obtained. The results showed that the excipients, microcel and explocel, did not produce changes in the thermal behavior of cimetidine. This fact was confirmed by the DSC coupled photovisualization system. The rate constants for the thermal decomposition reaction were determined by an isothermal thermogravimetric (TG) method using the classical Arrhenius equations. The results showed that cimetidine tablets presented a stability higher than the cimetidine–excipient mixtures.

Keywords: Cimetidine; Tablets; Excipients; Thermal analyses; DSC photovisualization

1. Introduction

The stability over time under given climatic conditions is a very important property of a new pharmaceutical product. Stability studies are routinely conducted by the pharmaceutical industry in order to evaluate any kind of chemical and physical degradation of the product. Individual samples are taken at pre-determined times and analyzed in order to verify the decrease in the active drug content, increase in the degradation product content, and dissolution behavior changes. The specifications for new pharmaceuticals depends on these results. This means that the stability data are very important for the determination of most of the main quality characteristics, such as efficacy, safety and technical feasibility [1–5].

Today, thermal analysis is becoming an important tool in studying and predicting pharmaceutical stability, including the effect of reaction order and temperature, Arrhenius kinetics [6,7] and statistical techniques such as the calculation of linear regression lines and confidence intervals [8,9].

2. Experimental

The excipients microcel MC101, explocel, aerosil, PVPK30, and magnesium stearate, as well as the drug cimetidine and its tablets A, were obtained from the Laboratory of Pharmaceutical Technology of the Federal University of Paraíba (LTF-UFPB). Tablet B was acquired in a local drugstore.

Cimetidine tablet A was prepared with the following composition: cimetidine 74.10%, microcel 17.69%, PVPK30 4.67%, explocel 2.07%, aerosil 0.40% and

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magnesium stearate 1.11%. The binary mixtures for the cimetidine and the other excipients were prepared in the same proportions of the formulation and were sieved using a 100 mesh screen, collected from a porcelain mill which was used to homogenize the powders for 10 min. The phase diagram for cimetidine–microcel® MC101 and cimetidine–explocel® was determined using the proportions 9:1, 8:2, 7:3, 1:1, 3:7, 2:8 and 1:9, respectively.

The DSC curves for the cimetidine drug and tablets A and B, excipients and binary drug–excipient mixtures were obtained using a SHIMADZU calorimeter, model DSC-50 coupled to a photovisual system consisting of a SANYO microscope connected to an OLYMPUS camera, model VCC-D520, using a nitrogen atmosphere at a flow rate of 50 ml min^{-1}, heating rate of 5 °C min^{-1}, up to a temperature of 500 °C. The samples were packed in an aluminum cell with a mass approximately 2.00 mg. The images were captured by DSC coupled to the photovisual system at a similar temperature and time compared to the conventional DSC.

TG isothermal curves for the cimetidine drug and tablets A and B were obtained in a SHIMADZU thermobalance, model TGA-50H, under a flow of air at 10 ml min^{-1}, at 200, 190, 180, 170 and 160 °C over 4 h.

The rate constants were calculated by the Arrhenius equation and its reaction order was similarly determined.

3. Results

3.1. Calorimetric studies

DSC curves for cimetidine drug and tablets A and B (Fig. 1) (pictures D, H and L) show that the drug presented a endothermal peak corresponding to the m.p. at a temperature of 144 °C and having a reaction heat of -36.16 kcal kg^{-1}. Tablet A had a m.p. at 142 °C and a reaction heat of -23.98 kcal kg^{-1}, while tablet B had a m.p. at 142 °C and a reaction heat of -30.87 kcal kg^{-1}.

DSC curves for the binary mixtures of the excipients with cimetidine (Fig. 2) (pictures D, H, L, P and T) showed the following interactions. Cimetidine–PVPK30 showed three phase transitions: the first peak being characteristic of the cimetidine drug at a temperature of 143.5 °C with a reaction heat of -54.35 kcal kg^{-1}; the second exothermal peak presented at a temperature of 207.6 °C with reaction heat of 1.85 kcal kg^{-1}; while the third corresponded to the decomposition temperature of 314.7 °C and a reaction heat of -24.88 kcal kg^{-1}. Cimetidine–explocel® presented three phase transitions: the first peak is the main peak at a the temperature of 143.6 °C and a reaction heat of -40.90 kcal kg^{-1}; the second exothermal peak at a temperature of 204.6 °C with a reaction heat of 1.73 kcal kg^{-1}; while the third corresponds to the decomposition at a temperature of 307.9 °C and reaction heat of -15.11 kcal kg^{-1}. Cimetidine–magnesium stearate presented two phase transitions, the first peak being, characteristic of the cimetidine drug, at a temperature of 145.08 °C and reaction heat of -45.10 kcal kg^{-1}. The second peak presented at the temperature of 319.7 °C and with a reaction heat of -25.10 kcal kg^{-1}. Cimetidine–aerosil® presented two phase transitions: the first is the main peak at a temperature of 144.7 °C and reaction heat of -30.60 kcal kg^{-1}; the second peak occurred at a temperature of 326.5 °C with a reaction heat of -11.72 kcal kg^{-1}. Cimetidine–microcel® MC101 presented a main peak at a temperature of 145.2 °C and a reaction heat of -41.51 kcal kg^{-1} followed by a peak at 322.2 °C with a reaction heat of -31.19 kcal kg^{-1}.

Calorimetric studies with the DSC coupled to the photovisual system (Fig. 1) shows the pictures of the cimetidine drug and tablets A and B in which the physical and chemical changes as a function of the temperature were observed. The pictures A, B and C, correspond to the cimetidine drug and reveals a well defined thermal behavior in its m.p. (picture B). The tablet A, pictures D, E and F presented a m.p. with solid residues (picture E). Tablet B, pictures G, H and I shows thermal behavior different from tablet A.

Binary mixtures of cimetidine–explocel® (Fig. 2) show alterations in the volume and no change in coloration at a temperature of 139 °C, but showed an alteration in its m.p. at the temperature as shown in pictures B followed by darkening at temperatures above 293 °C as shown in picture C. The mixture cimetidine–PVPK30 (pictures E, F, G and H) shows a small volume reduction around 139 °C corresponding

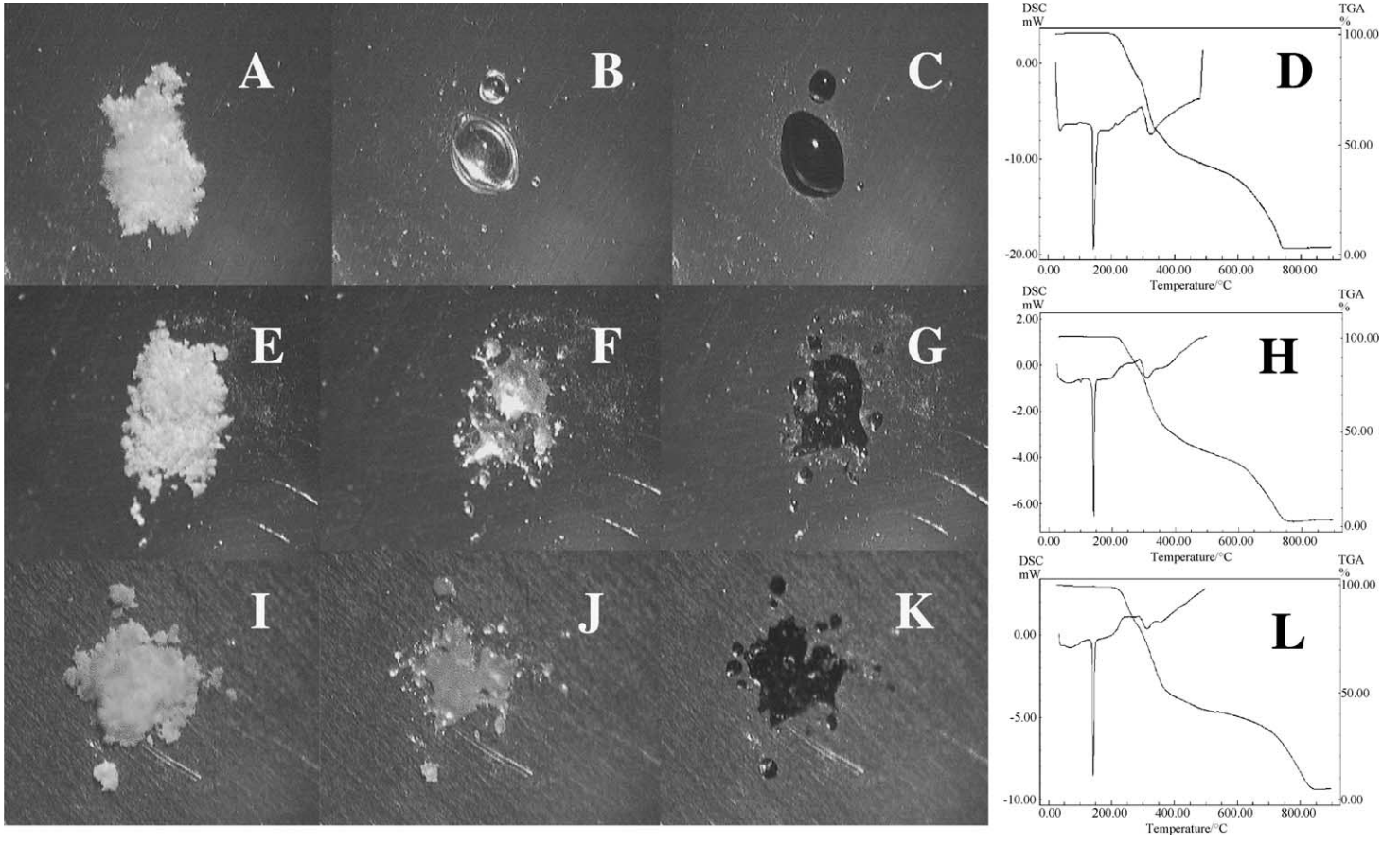

Fig. 1. Pictures of the cimetidine drug and tablets A and B obtained through a camera with image of high resolution of the mark SANYO, model VCC-D520, connected to a microscope of the mark OLYMPUS coupled to calorimeter exploratory differential of SHIMADZU, model DSC-50, in a strip of temperature range of 25–500 °C. The pictures: A (room temperature), B (144 °C), and C (256 °C) cimetidine drug; tablet A pictures: D (room temperature), E (142 °C), and F (256 °C); and tablet B pictures: G (room temperature), H (142 °C), and I (256 °C).

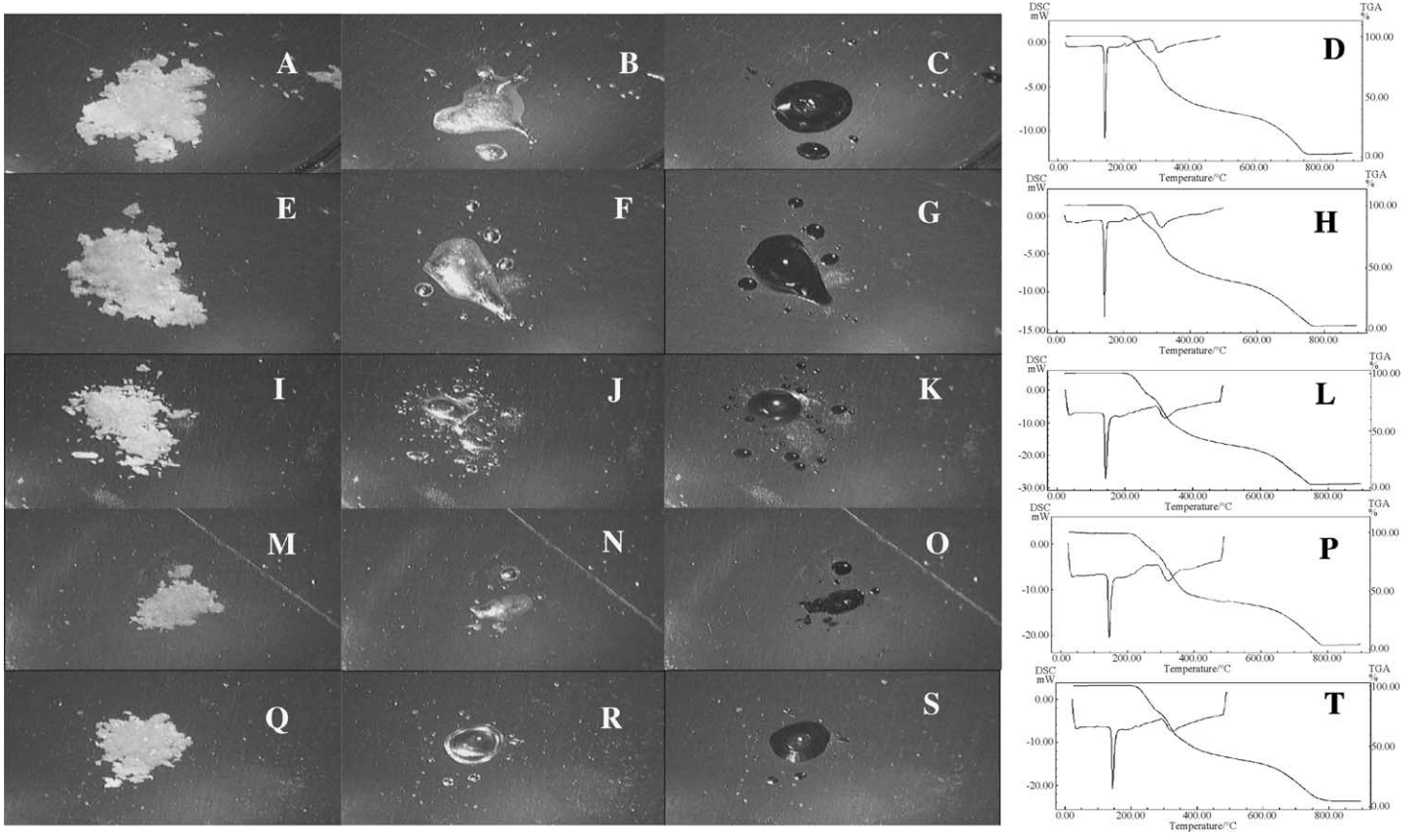

Fig. 2. Pictures of the cimetidine drug and tablets A and B obtained through a camera with image of high resolution of the mark SANYO, model VCC-D520, connected to a microscope of the mark OLYMPUS coupled to calorimeter exploratory differential of SHIMADZU, model DSC-50, in a strip of temperature range of 25–500 °C. The pictures of cimetidine–explocel®: A (room temperature), B (139 °C), C (293 °C), and D (TG and DSC curves); cimetidine–PVPK30 pictures: E (room temperature), F (139 °C), G (293 °C), and H (TG and DSC curves); cimetidine–magnesium stearate pictures: I (room temperature), J (141 °C), K (293 °C), and L (TG and DSC curves); cimetidine–microcel® MC101 pictures: M (room temperature), N (141 °C), O (293 °C), and P (TG and DSC curves); cimetidine–aerosil® pictures: Q (room temperature), R (141 °C), S (293 °C), and T (TG and DSC curves).

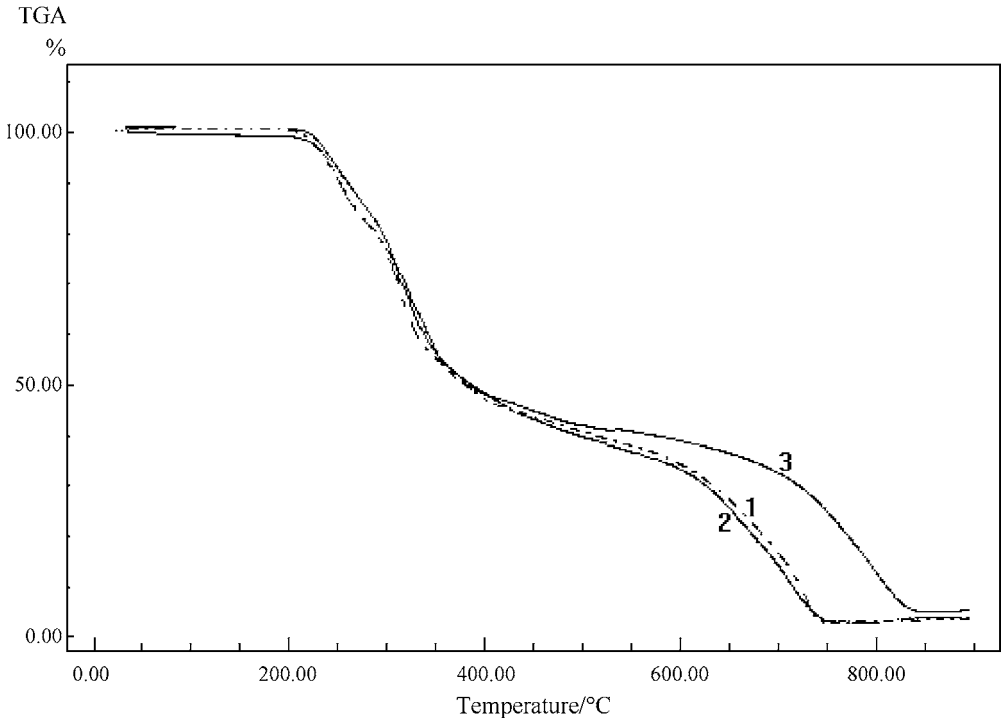

Fig. 3. TG curves of: (1) the cimetidine drug; (2) tablets A; (3) e B.

to the initial m.p. (picture F). It presented a volume reduction around and followed by detachment of gases at a temperature of 293 °C (picture G). The mixtures cimetidine–magnesium stearate (pictures I–K), cimetidine–microcel® MC101 (pictures M–O) and cimetidine–aerosil® (pictures Q–S) showed no alteration in their m.p. in relation to the cimetidine drug, in its decomposition process presented a volume reduction around and followed by detachment of gases at the temperature of 293 °C.

The phase diagrams, constructed using reaction heat and microcel MC101 and explocel difference in percentage, are shown in (Figs. 4–7).

3.2. Thermogravimetric studies

Thermogravimetric (TG) dynamic curves for the cimetidine drug and tablets A and B (Fig. 3), presented three stages of thermal decomposition for all samples, evidencing similar TG profiles with smaller difference in the third stage of tablet B.

TG isothermal data was used to determine the reaction order and rate constants for the thermal decomposition reaction. The results are presented (Table 1), which can verify a major rate of constant value for the cimetidine drug at all temperatures compared to the tablets A and B.

Table 1
Rate constants of thermal decomposition reactions of the cimetidine drug and tablets A and B

Temperature program	Reaction order	Cimetidine (k s^{-1})	Tablet A (k s^{-1})	Tablet B (k s^{-1})
160 °C	0	2.83×10^{-6}	2.37×10^{-6}	1.86×10^{-6}
170 °C	0	1.23×10^{-5}	6.05×10^{-6}	3.76×10^{-6}
180 °C	0	1.69×10^{-5}	1.00×10^{-5}	9.53×10^{-6}
190 °C	0	3.62×10^{-5}	2.34×10^{-5}	2.19×10^{-5}
200 °C	0	9.86×10^{-5}	4.43×10^{-5}	4.33×10^{-5}

4. Discussion

Calorimetric studies for cimetidine in the binary mixtures showed that the excipients used in the formulations did not present significant interactions in relation to the reaction heat and the m.p. temperature. The mixtures cimetidine–explocel® and –PVPK30® would reduce the m.p. temperature in relation to cimetidine drug by about 1 °C (Fig. 2).

The data analysis of DSC coupled to the photovisualization system confirmed incompatibility differences among the mixtures. Such a fact indicates that

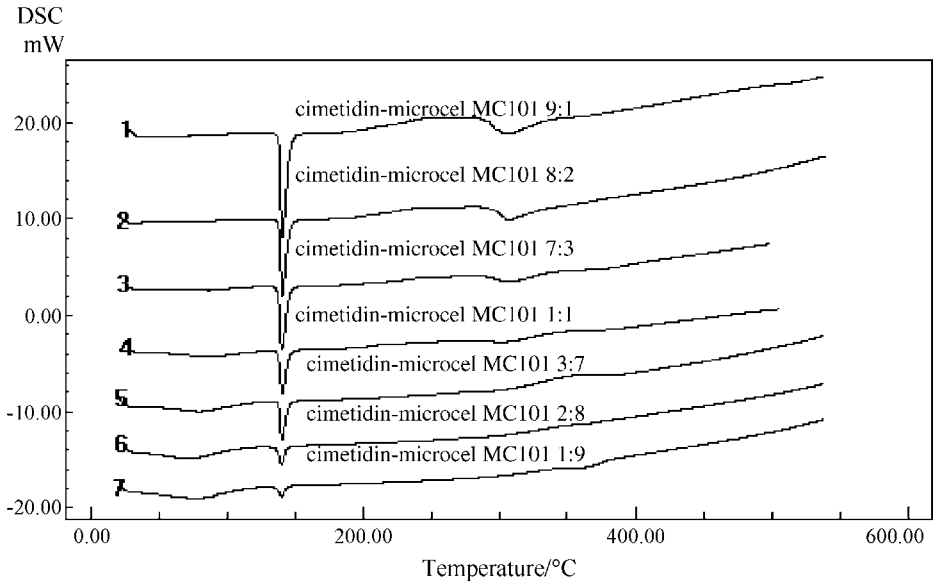

Fig. 4. DSC curves of cimetidine–microcel® MC101.

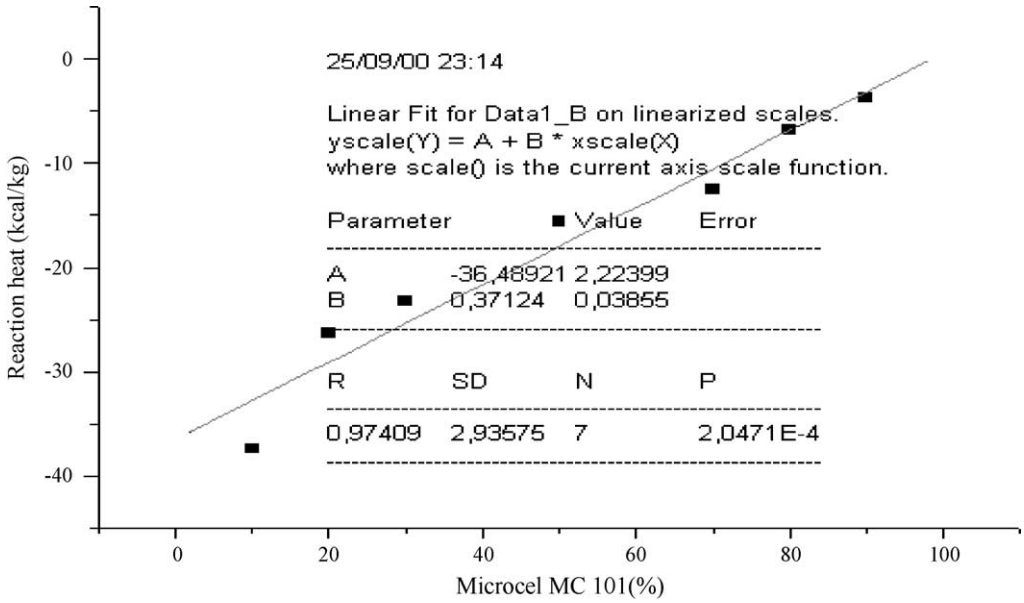

Fig. 5. Phase diagram of cimetidine–microcel® MC101.

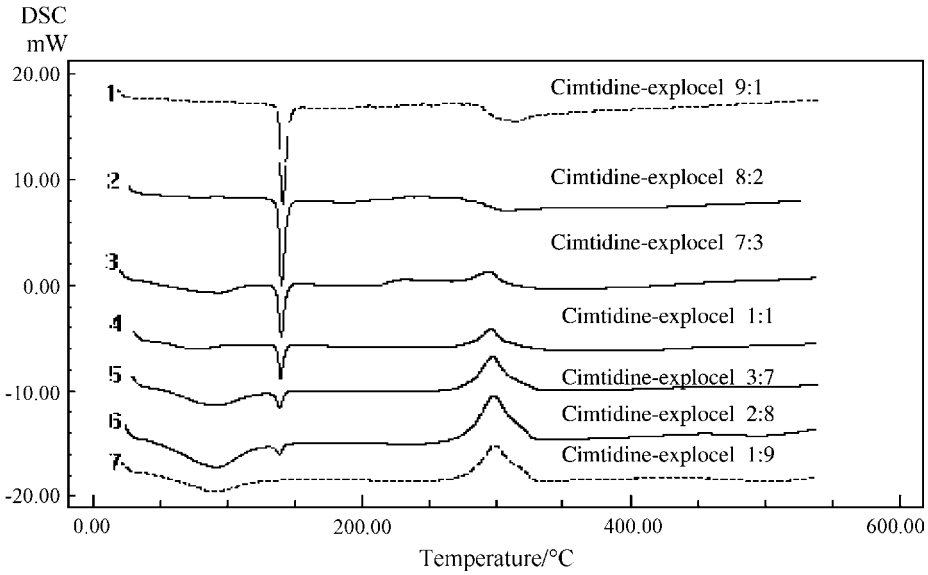

Fig. 6. DSC curves of cimetidine–explocel®.

the comparison of cimetidine drug with different excipients reveals the utility of thermal analysis in the development and quality control of the drug.

Calorimetric data shows a smaller displacement in the m.p. temperature of the cimetidine tablets A and B in relationship to the drug. Such a fact indicates some physical or chemical interaction between the drug and the excipients.

The phase diagrams for cimetidine–microcel® MC101 (Figs. 4 and 5) revealed no evidence of the

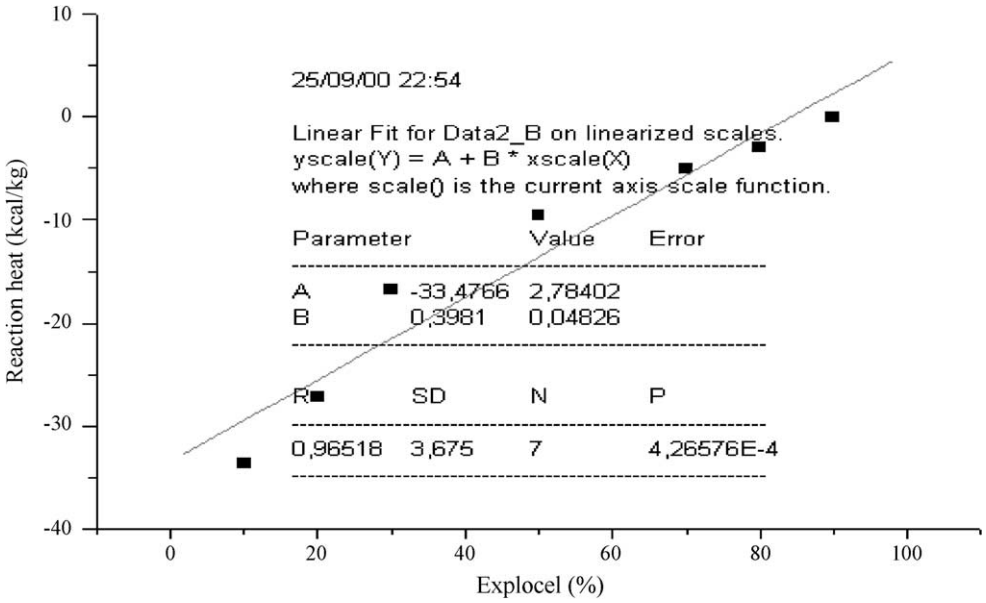

Fig. 7. Phase diagram of cimetidine–explocel®.

presence of an eutetic, since pure drug is a monotectic species. This also did not occur between the other components in the solid state.

The phase diagram data for cimetidine–explocel® (Figs. 6 and 7) showed that no differences were observed in the process of phase transitions, when the ratios were increased. There was no evidence of the presence of an eutetic.

The values for the rate constants for the thermal decomposition reaction showed that formulations A and B demonstrated greater stability in relation to the cimetidine drug. Formulation B is more thermodynamically stable than formulation A. The TG isothermal data showed that it is possible to determine the stability of similar products and also to differentiate among ones.

5. Conclusion

The rate constants for the thermal decomposition reaction and DSC photovisualization data reveals the differences between tablets A and B, thus allowing a formulator to select products with different formulations. These thermal techniques, particularly DSC, are at their earliest stages of pre-formulation development as a useful tool for screening a wide range of candidate excipients, which would allow for a rapid evaluation of possible drug–excipient interactions.

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