Journal of Thermal Analysis and Calorimetry, Vol. 93 (2008) 3, 881–886

STABILITY AND COMPATIBILITY STUDY ON ENALAPRIL MALEATE USING THERMOANALYTICAL TECHNIQUES

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This paper demonstrates the application of thermal analysis in compatibility and stability studies between an ACE inhibitor (enalapril maleate) and excipients. The results have helped to elucidate the reason of a stability problem observed during the storage of enalapril maleate tablets. Incompatibility between enalapril maleate and colloidal silicon dioxide was detected. Besides, it was confirmed that the reaction between enalapril maleate and $NaHCO_3$ increases the thermal stability of the drug. This study supports the importance of using thermoanalytical methods in the development of pharmaceuticals.

Keywords: *compatibility, DSC, enalapril maleate, stability, TG, thermal stabilization*

Introduction

Thermoanalytical methods are among the frequently used techniques for problems solving in pharmaceutical technology areas. Amongst others, one of their frequent applications is the compatibility study between drugs and excipients, mainly in preformulation studies. Drug-excipient compatibility studies are essential steps of the development of different drug formulations, helping in the selection of the proper excipients which increase the probability to obtain a stable solid dosage form.

The use of thermoanalytical methods in drug-excipient compatibility studies offers many advantages over the classical methods of incompatibility detection between the active compound and the excipients. In the conventional methods, drug is added to the excipients and they are subjected to high temperatures and high percentages of relative humidity for a considerable time. Then, they are analyzed using different techniques, e.g. high-performance liquid chromatography (HPLC), thin-layer chromatography (TLC), etc. This procedure often takes several weeks or even months to generate sufficient data supporting or denying the compatibility. On the contrary, one of the major advantages of the thermoanalytical techniques is the rapid analysis, and besides, the possibility of detecting physical interactions such as the formation of eutectic mixture or adsorption between drug and excipients [1, 2].

Among the various existing thermoanalytical methods, differential scanning calorimetry (DSC) is the most important one employed in drug-excipient compatibility studies, but the data provided by DSC can be more easily interpreted when they are supported by thermogravimetry (TG). The application of both DSC and TG in the same study is very common [3–8].

Incompatibilities between drug and excipient(s) can change the stability and bioavailability of drug products and can also affect their stability as well as the efficiency during their administration. Loss of biological activity, formation of complexes or eutectics and acid-base interactions may occur due to these incompatibilities [1].

Enalapril maleate (EM) is an angiotensin-converting enzyme (ACE) inhibitor and it is used in the treatment of cardiovascular diseases, which are known to be the principal cause of mortality in modern societies. Cardiovascular diseases for which EM is prescribed include hypertension, left ventricular systolic dysfunction and myocardial infarct, and it is also known to significantly retard renal function loss associated with diabetic nephropathy, which is caused by a combination of diabetes mellitus and hypertension [9].

EM alone is temperature stable either under dry or different humidity conditions. However, it becomes unstable when it is mixed with the matrix, during tablet making and exposed to the same conditions [10]. Since EM is incompatible with most of the commonly used excipients, it is very difficult to formulate a stable solid oral dosage form for it [11]. Ungboriboonpisal *et al.* [12] expressed the necessity of the analysis of EM formulations and the importance of searching for suitable storage conditions. In their study, from a total of 54 samples with a declared expiration date of 3 years, 48.1% were found to contain degradation products exceeding the adopted

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1388–6150/$20.00

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5.0% limit. In order to better interpret the results, the 54 samples were divided in three sub-groups according to their date of manufacturing. Those manufactured until a year before the study comprised 26 samples, those manufactured between one to two years before the study comprised 17 samples and those manufactured between two to three years before the study comprised 8 samples. It was found that 26.9, 70.6 and 87.5% of the samples from each sub-group, respectively, were substandard medicines as defined by the World Health Organization [13]. Moreover, most of the approved samples were less than 7 months old.

In addition, EM exhibits two polymorphic forms, which – according to their melting behavior – are very similar [14]. Nevertheless, Eyjolfsson [15] found evidence suggesting that Form II is much less stable than Form I when it is in a tablet formulation matrix containing sodium hydrogen carbonate ($NaHCO_3$) as stabilizer.

In the present work, the compatibility of EM with excipients of a specific tablet formulation was investigated by DSC and TG. The selected formulation seemed to show a stability problem, characterized by the apparent formation of gas or the release of some volatile substance during the storage of the drug product. The problem was observed even under normal storage conditions but became even more evident when the product was stored under controlled, drastic conditions (accelerated stability studies). The packaging material became distended because of gas release by the product, allowing the tablets to move around inside the packaging (Fig. 1). At the time, this behavior was attributed to an incompatibility between some of the components used in the formulation.

In fact, the aim of this study was to explain the reason of the above problem and to find a solution for it. Besides, two methods of thermal stabilization of EM already reported in the literature were also evaluated by TG. One of these consists in reacting EM with sodium hydrogen carbonate ($NaHCO_3$) [16] and the other one consists in reacting EM with magnesium oxide (MgO) [17]. The thermal degradation kinetics for the pure EM and for its mixture with colloidal silicon dioxide (SiO_2) was also investigated in order to determine the activation energy (E_a) in the degradation reaction in each case.

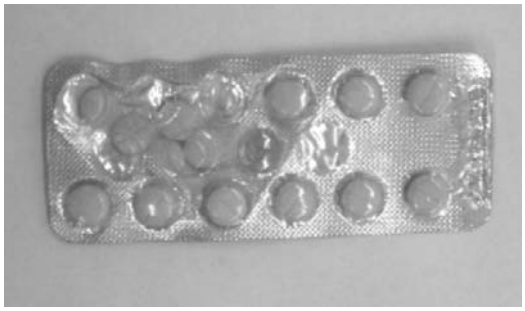

Fig. 1 Distension of the packaging material and release of tablets from PVC blisters

Experimental

Materials

EM and excipients were of pharmaceutical grade, except for the colorants, which were of food grade. They were all kindly donated by a Brazilian company. The excipients were spray-dried lactose (Super-Tab®), microcrystalline cellulose (Microcel®), magnesium stearate, colloidal silicon dioxide (Cab-O-Sil® M5-P), $NaHCO_3$ and the colorants Red n° 40 and Yellow n° 6, both aluminum lake pigments. Compatibility studies were carried out using 1:1 mass/mass binary mixtures of drug and excipient. Each excipient was mixed with the drug by grinding them together in a mortar with a pestle.

Pharmaceutical grade $NaHCO_3$ and analytical grade MgO were used to evaluate the thermal stabilization methods. The two products were reacted separately with EM after solubilizing all the reactants in water. Stoichiometrically, one mole of EM reacts with 3 moles of $NaHCO_3$ and with 1.5 mole of MgO. Once the reactions were completed, the resulted products were dried overnight in an Edwards do Brasil® model L4KR lyophilizer.

The thermal degradation kinetics were studied by the standard isothermal isoconversional method, where the E_a can be calculated from the slope of the ln$t$ *vs.* $1/T$ plot (for a given conversion fraction and without assuming any decomposition model).

Methods

DSC curves were obtained using a Shimadzu® DSC-50 cell. About 1 mg of pure drug and about 2 mg of drug-excipient mixture was weighted to aluminum pans in order to keep the amount of drug approximately constant. Dynamic purging (nitrogen, flow rate: 100 mL min^{-1}) and a heating rate of 10°C min^{-1} from room temperature up to 300°C was applied. Indium (*m.p.*=156.6°C; ΔH_{fus}=28.54 J g^{-1}) and zinc (*m.p.*=419.5°C) standards were used to calibrate the DSC cell previously.

TG/DTG curves were obtained with a Shimadzu® TGA-50 thermobalance using platinum crucibles containing about 5 mg of samples, under dynamic nitrogen atmosphere (50 mL min^{-1}) and at a heating rate of 10°C min^{-1} from room temperature up to 300°C for the drug-excipient compatibility studies, and from room temperature up to 600°C for the evaluation of the thermal stabilization methods.

For the kinetic studies the same experimental conditions were applied. Five different kinetic curves were obtained in each study, with temperatures ranging from 125 to 145°C (for EM alone) and from 105 to 125°C (for 1:1 mass/mass binary mixture of EM and SiO_2), with 5°C increments for each curve. Calculations were performed from the curves at the same degree of conversion, which was made equal to 5% of mass loss under isothermal conditions.

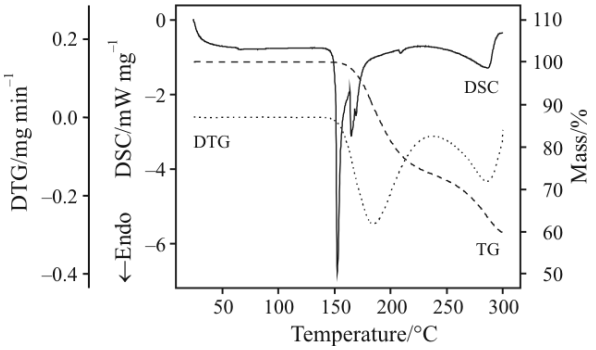

Fig. 2 TG/DTG and DSC curves of enalapril maleate

Results and discussion

The thermoanalytical curves of enalapril maleate are presented in Fig. 2.

The TG/DTG curves show that EM is thermally stable up to 140°C and presents a noteworthy mass loss step between 140–235°C (Δm_l=26.2% and T_{peak}DTG=182.9°C). The endothermic DSC peak is related to the melting of the substance ($T_{on\text{-}set}$=150.2°C) followed by another partially overlapped endothermic event due to thermal decomposition. The apparent heat of fusion was 59.1 kJ mol^{-1}. These results are in reasonable agreement with the ones reported in [2, 14, 18–21]. The thermal decomposition of EM starts with the loss of one molecule of maleic acid together with one molecule of water, which is eliminated in an intramolecular cyclization reaction of the enalapril molecule that leads to the formation of enalapril diketopiperazine [18–21]. The degradation pathway of EM was found to be pH dependent. While enalapril diketopiperazine is the main degradation product formed when EM is not mixed with any excipient or when EM is in an acidic matrix, enalaprilate is the major degradant formed when EM is in a basic matrix [10].

Consequently, the first result of the present study was the observation that the manufacturer was making incorrect use of $NaHCO_3$ in the formulation. The manufacturer added $NaHCO_3$ to the formulation in order to maintain a basic pH for the drug product matrix, based on the work of Al-Omari *et al.* [10]. In this work, the authors investigated the influence of parameters such as heat, moisture and light on two different EM tablet formulations: one with an acidic matrix and the other with a basic matrix containing $NaHCO_3$. It was demonstrated that the latter was almost resistant to photolysis. This was considered an important observation by the manufacturer because its EM tablets were packed in PVC-aluminum blisters, while presumably all the other manufacturers use aluminum–aluminum blisters to pack their EM tablets. Although the cost of packing the tablets in PVC–aluminum blisters is lower, this kind of blister does not provide complete protection against light as the aluminum–aluminum blister does (since that PVC does not act as a barrier to light transmission). This was the reason which led the manufacturer to use $NaHCO_3$ in the formulation in order to ensure a basic matrix and, therefore, to minimize the susceptibility of the drug to photolysis.

In fact, $NaHCO_3$ reacts with EM according to the following equation:

$$C_{20}H_{28}N_2O_5{\cdot}C_4H_4O_4 + 3NaHCO_3 \rightarrow C_{20}H_{27}N_2NaO_5 + C_4H_2Na_2O_4 + 3CO_2 + 3H_2O$$

The TG curve of the 1:1 mass/mass binary mixture between EM and $NaHCO_3$, shown in Fig. 3, when compared to the TG curve of the pure EM and to the TG curve of the pure $NaHCO_3$ (both also shown in Fig. 3), confirms the reaction between the drug and the excipient, evidenced by the premature mass loss. The same TG curve (magnified in its initial part) also demonstrates that this reaction may occur even at temperatures below 30°C. This finding suggests that, if the chemical reaction does not complete before the packaging process, it may certainly continue further, since it does not require temperatures higher than room temperature to take place. The reaction can be easily predicted since EM contains three carboxyl groups, which lends acidic character to the molecule (structural formula in Fig. 4), while $NaHCO_3$ is a basic salt. Nevertheless, one cannot consider this an incompatibility attributed to an acid-base interaction.

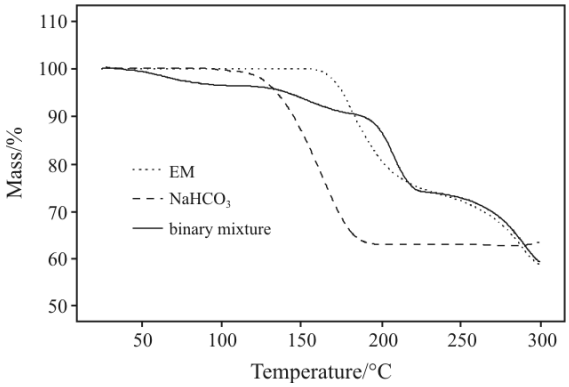

Fig. 3 TG curves of enalapril maleate, of $NaHCO_3$ and of their 1:1 physical mixture

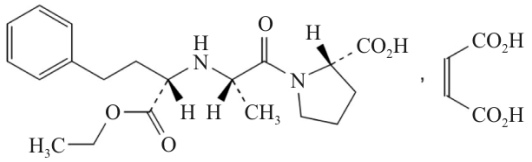

Fig. 4 Structural formula of EM showing its 3 carboxyl groups

The reaction is, in fact, a thermal stabilization method for EM already described in the literature [16]. Besides, there is a release of CO_2 during the reaction, which was indeed the responsible for the packaging swelling. A single tablet containing 20 mg of EM is able to release approximately 2.7 cm^3 of CO_2 (STP) assuming a complete reaction between the $NaHCO_3$ and the total amount of EM in the tablet.

In spite of the fact that the reaction takes place by the simple physical contact among the species in the solid state and at room temperature, for solid oral dosage forms of EM where $NaHCO_3$ is present, the correct manufacturing process must ensure that the reaction between the two components has finished before the packaging step. It can be done by the addition of $NaHCO_3$ previously dissolved in water, followed by an oven drying at 50°C, according to [16]. The previous dissolution of $NaHCO_3$ facilitates its contact with the drug, while heating during drying accelerates the reaction. The end-point of the reaction must be monitored by weighing with the aid of stoichiometric calculations (here one has to consider the mass of CO_2 lost to the atmosphere and the total amount of water lost during the drying stage which includes the added water and the water formed during the reaction).

Although the interaction between EM and $NaHCO_3$ is rather an expected reaction than an incompatibility, at least one of the other excipients studied here interacts with the drug, probably decreasing the stability of the formulation. The TG/DTG and DSC curves of the binary mixtures of EM and SiO_2 (Figs 5 and 6, respectively) indicate that SiO_2 results in a decrease of more than 20°C in the onset temperature of degradation for the drug.

The superimposed isothermal TG curves obtained for the EM degradation kinetic study are collected in Fig. 7 (the ones related to the degradation kinetic study of the 1:1 mass/mass binary mixture of EM and SiO_2 were obtained as described above, but will not be shown herein). These curves indicate the dependence of the mass loss rate on the isothermal temperature, i.e., the higher the temperature the less time is needed to reach the same mass loss. These curves were used to plot the graph of ln*t vs.* the reciprocal of temperature, $1/T$ (K^{-1}) (Fig. 8). The data shown in Table 1 were obtained from this graph using a linear regression. The value of E_a was calculated by multiplying the slope of the appropriate linear equation by the molar gas constant (R=8.314 J K^{-1} mol^{-1}). A 40% decrease in the E_a value can be observed for the thermal degradation reaction of EM when it is mixed with SiO_2 keeping 1:1 mass/mass ratio. Therefore, the use of SiO_2 as excipient should be avoided in formulations containing EM, since it may act as a catalyst in the thermal decomposition of this drug even though SiO_2 is usually employed at low concentra-

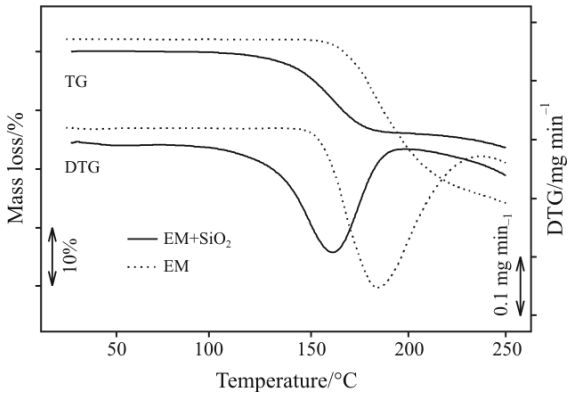

Fig. 5 TG and DTG curves of enalapril maleate and its 1:1 physical mixture with SiO_2

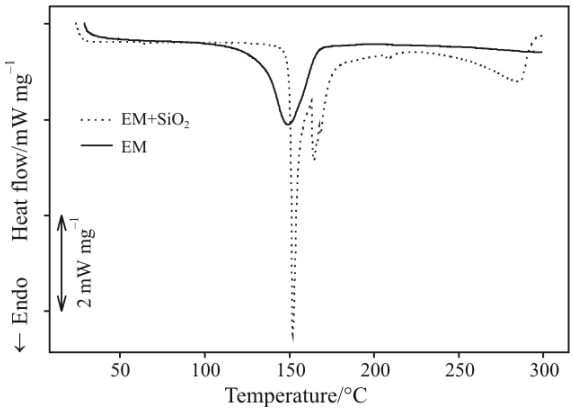

Fig. 6 DSC curves of enalapril maleate and its 1:1 physical mixture with SiO_2

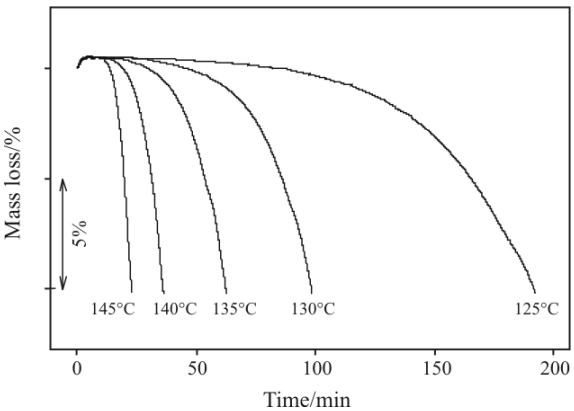

Fig. 7 Isothermal TG curves of EM obtained between 125–145°C, with increments of 5°C

Table 1 Representative kinetic parameters calculated from data presented in Fig. 8

	Linear regression equation	Regression coefficient, (r^2)	Activation energy/kJ mol^{-1}
EM	ln$t$=24226 1/T–55.78	0.992	201
EM:SiO_2 binary mixture	ln$t$=14615 1/T–33.95	0.995	122

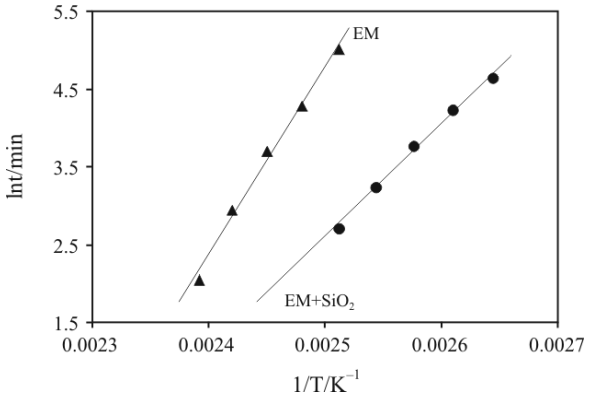

Fig. 8 ln$t$ *vs.* 1/T plot for EM and its 1:1 mass/mass mixture with SiO_2

tions (as it is the case for the studied formulation, in which SiO_2 is employed at 1% mass/mass).

In 1987, Cotton *et al.* [2] reported an interaction in which the degradation rate of EM was accelerated by several orders of magnitude in the presence of microcrystalline cellulose (MC). It was noticed that this excipient seemed to reduce the apparent heat of fusion of the drug. As mentioned earlier, at a heating rate of 10°C min^{-1}, the DSC curve of EM shows two partially superimposed endothermic events. The first is due to melting and the second one is due to thermal decomposition. This indicates that decomposition takes place during the melting in some extent. Moreover, in the DSC curve of the EM:MC binary mixture there is an increase in the degree of overlapping of the two events. For this reason, the accurate determination of the heat of fusion is unrealistic. Consequently, the decrease of the heat of fusion in the presence of MC could not be confirmed. No attempts were made in order to separate the thermal events by decreasing the heating rate. More recently, Devi and Babu [22] also demonstrated the increase in the degradation rate of EM in presence of MC by performing DTA studies and accelerated stability test. The interaction between EM and dibasic calcium phosphate was also reported. Therefore, we believe there is sufficient evidence in the literature to avoid the use of MC in EM formulations.

The magnesium stearate (MgE), in its turn, is a mixture of magnesium salts of different fatty acids, consisting mainly of stearic acid and palmitic acid and, in minor proportions, other fatty acids. Commercial MgE samples melt in the range of 117–150°C, while high purity MgE melts at 128±2°C [23]. Since EM melts only at 150.2°C (T_{onset}) the earlier melting of MgE can lead to partial or complete solubilization of EM in the melted excipient, what makes the research on incompatibilities impossible, as far as solid-state interactions are concerned. However, based on data from classical accelerated stability studies [11], it was found that MgE as well as MC, calcium phosphates and also many of the common disintegrants (starch, sodium starch glycolate, crospovidone and croscarmellose sodium) contribute to the EM decomposition. No interactions were observed between EM and the other excipients studied in the present work.

There are two described thermal stabilization methods for EM in which the drug is made to react with a basic compound to form a new enalapril salt. One method consists in reacting EM with an alkaline sodium compound, such as NaOH, Na_2CO_3 or $NaHCO_3$ to yield enalapril sodium and disodium maleate [16]. The other consists of reacting EM with MgO, which, in its turn, yields the magnesium salts of enalapril and maleic acid [17]. The latter is claimed to be a method of thermal stabilization for various ACE inhibitors, including EM, but is preferably applied to quinapril. To evaluate and compare these two methods, TG/DTG curves were recorded for the products of the reaction between EM and MgO (P1) and between EM and $NaHCO_3$ (P2). These TG/DTG curves are depicted in Fig. 9.

Only the first step of the whole thermal degradation process of a substance gives information with regard to its stability, since the subsequent steps are no longer directly related to the original molecule. The TG/DTG curves show that while the first mass loss step for EM reaches its maximum rate at 182.9°C (T_{peak}DTG), for P2 it shifts to 297.9°C. On the other hand, for P1 the first stage of thermal degradation appears in the same temperature range as that observed for EM. However, this could be attributed to an incom-

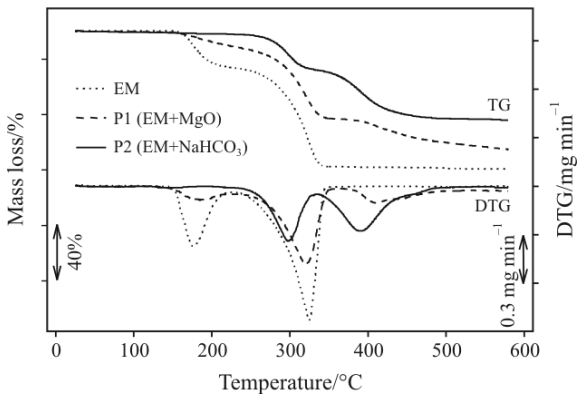

Fig. 9 TG/DTG curves of enalapril maleate and of the reaction products, P1 and P2

plete reaction between EM and MgO. If the reaction between EM and MgO has not reached the theoretical yield (100%) for the expected products, the TG/DTG curves of P1 could have been affected by the remaining EM (the nonreacted fraction). This fraction would be present as contaminant, mixed with the reaction product. Moreover, if this hypothesis is true, then it would indicate that, according to the yield of the stabilization reactions, the stabilization of EM by the reaction with $NaHCO_3$ is more easily achieved than by the reaction with MgO. On the other hand, the second mass loss step for P1 starts almost at the same temperature where the thermal degradation of P2 begins. Once again, if the first mass loss step for P1 could be attributed to non-reacted EM, this would indicate that the second mass loss step is indeed the product of the reaction between EM and MgO. Consequently, both products (P1 and P2) would have similar thermal stabilities.

Conclusions

Although thermoanalytical methods are not able to completely replace the classical methods for incompatibility detection, they are valuable tools in the analysis of formulation problems. TG/DTG and DSC experiments made it possible to recognize the reason of the blisters' distension, which was attributed to the inappropriate use of $NaHCO_3$ in the formulation. Moreover, incompatibility was found between EM and SiO_2, since the excipient noticeably decreased the thermal stability of the drug. However, since SiO_2 is used at low concentrations in tablet making, the impact of this interaction must be carefully evaluated. Also, the reaction product between $NaHCO_3$ and EM was found to be unambiguously more stable than EM itself. However, further studies are necessary to reach a conclusion regarding the stabilization of EM using MgO.

Acknowledgements

The authors acknowledge the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and the Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) for their financial support.

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Received: August 29, 2007
Accepted: January 11, 2008

DOI: 10.1007/s10973-007-8187-4