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Thermal behavior of verapamil hydrochloride and its association with excipients

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Abstract The thermal properties of verapamil hydrochloride (VRP) and its physical association as binary mixtures with some common excipients were evaluated. Thermogravimetry (TG) was used to determine the thermal mass loss, as well as to study the kinetics of VRP thermal decomposition, using the Flynn-Wall-Ozawa model. Based on their frequent use in pharmacy, five different excipients (microcrystalline cellulose, magnesium stearate, hydroxypropyl methylcellulose, polyvinylpyrrolidone and talc) were blended with VRP. Samples were prepared by mixing the analyte and excipients in a proportion of 1:1 (m/m). DSC curves for pure VRP presented an endothermic event at 143 ± 2 °C ($\Delta H_{melt} = 132 \pm 4$ J g^{-1}), which corresponds to the melting (literature $T_m = 143.7$ °C, $\Delta H_{melt} = 130.6$ J g^{-1}). Comparisons among the observed results for each compound and their binary physical mixtures presented no relevant changes. This suggests no interaction between the drug and excipient.

Keywords Excipient interaction · Thermal analysis · Verapamil hydrochloride

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Introduction

Thermal analysis has been applied in the pharmaceutical industry for basic research but also to improve the solutions of practical problems (e.g. quality control, characterization of components, etc.) [1].

The study of drug–excipient interactions is an important element in preformulation activities. The classic procedure usually employed, involves preparing a powder sample containing the drug and the excipient, this sample is stored at elevated temperatures for several months and then, systematically analyzed using a suitable stability-indicating method. This process is time-consuming and, in general, detects only chemical instability. The results are not necessarily indicative of possible problems with extraction, disintegration or dissolution [2].

In some reviews have highlighted the application of DSC and a related technique, differential thermal analysis (DTA), for the rapid evaluation of the compatibility of drugs with excipients [3, 4]. In general, evaluations and conclusions are made on the basis of the modifications observed in DSC scans of the active pharmaceutical ingredient (API) in the absence and in the presence of the tested excipient.

Although some authors acknowledge that the presence of a physical or chemical interaction does not necessarily indicate incompatibility, they all agree that a change observed in DSC curves is unambiguous proof of interaction between drug and excipient [5, 6]; these interactions can be, on the other hand, exploited in order to reach specially planned matrixes for controlled-release formulations. When it is not possible to obtain, the controlled-release formulation must be done by coat technology [7].

Verapamil, a phenylalkylamine calcium-channel blocker, has been widely used as an anti-arrhythmic agent to control

supraventricular tachyarrhythmias. It is also useful for the treatment of hypertension, ischemic heart disease, and hypertrophic cardiomyopathy based on its potent vasodilating and negative inotropic properties. After oral administration of VRP to humans, the drug is rapidly absorbed and widely distributed. It undergoes an extensive hepatic and intestinal first-pass metabolism, resulting in a low extent of absolute oral bioavailability in humans [8, 9].

In this study the thermal properties of VRP and its physical association (binary mixtures) with some common excipients were evaluated. Thermogravimetry (TG) was used to determine the thermal mass loss properties as well as to study the kinetics of VRP thermal decomposition by applying the Flynn-Wall-Ozawa model [10–13].

Experimental

Verapamil hydrochloride, pharmaceutical grade min. 99.0% (Natural Pharma, Brazil) was used without further purification. Microcrystalline cellulose (MC), magnesium stearate, hydroxypropyl methylcellulose (HMPC), polyvinylpyrrolidone (PVP) and talc were obtained from Sigma Aldrich. Samples were prepared by mixing the analyte and excipients in a proportion of 1:1 (m/m).

Simultaneous TG/DTG and DTA analysis were carried out with an initial sample mass of 5.0 mg, in alumina pans (90 μL). A simultaneous SDT-Q600 equipment (TA Instruments) was applied in these studies. Experimental parameters for TG curves were mass of ca. 5 mg, heating rate of 10 °C min^{-1} under N_2 flow (50 mL min^{-1}) and final temperature of 600 °C.

The analyte and its mixtures were assessed by using different experimental conditions such as atmosphere (dynamic nitrogen and synthetic air, flowing at 50 mL min^{-1}) and heating rates (2.5, 5.0, 7.5, 10, 15 and 20 °C min^{-1}). For the kinetic study, the experiments were performed at least in duplicates, using the previously described conditions. The apparatus was calibrated for temperature with a zinc standard. Standard calibration masses were used for mass calibration, as recommended by TA Instruments in Thermal Advantage for Q-Series software.

DSC curves were obtained using masses of 2 mg, heating rate of 10 °C min^{-1} under N_2 flow rate (25 mL min^{-1}), in a temperature interval of −65 to 300 °C, in a covered aluminum pan with a central pinhole in the lid, 10 °C min^{-1} heating rate under a 25 mL min^{-1} nitrogen flow. A TA DSC-Q10 unit controlled by the Thermal Advantage for Q-Series software (both from TA Instruments) was used in this case. Calibrations of the equipment for temperature and enthalpy measurements were performed using the indium metal (99.99% purity) as a standard.

Results and discussion

Thermal decomposition of VRP in a nitrogen atmosphere occurs in one event and starts at 190 °C, as presented in Fig. 1a. The thermal decomposition in air starts at 170 °C and about 78% mass loss occurs in the first step (up to 340 °C) resulting in a carbonaceous residue (Fig. 1b). Between 340 and 695 °C, the remaining 22% of initial mass is lost in a second decomposition step, as the carbonaceous residue combusts.

The DTA curve in nitrogen atmosphere exhibits two peaks. The first one is attributed to melting of the API (onset temperature: 142.1 °C) and the second related to the decomposition. The DTA curve in air atmosphere shows an endothermic peak related to the melting (T_{onset} = 144.1 °C). The decomposition is accomplished by an exothermic peak at 287.9 °C, followed by the exothermic combustion of the carbonaceous material that also presented exothermic peaks at 371.6 and 423.1 °C and an endothermic one at 518.5 °C.

TG/DTG curves of VRP and their mixtures with the excipients chosen for the present work are presented in Fig. 2. Each curve shows a specific behavior depending on the characteristics of each excipient.

Verapamil HCl decomposes in a single step between 185 and 376 °C, apparently in two successive steps as presented in the DTA curve (271 and 312 °C). The binary mixture with MC presents a loss relative to humidity (7.4%, 25–155 °C) followed by decomposition in a single step (67.9%, 155–400 °C). With HPMC the mixture lost

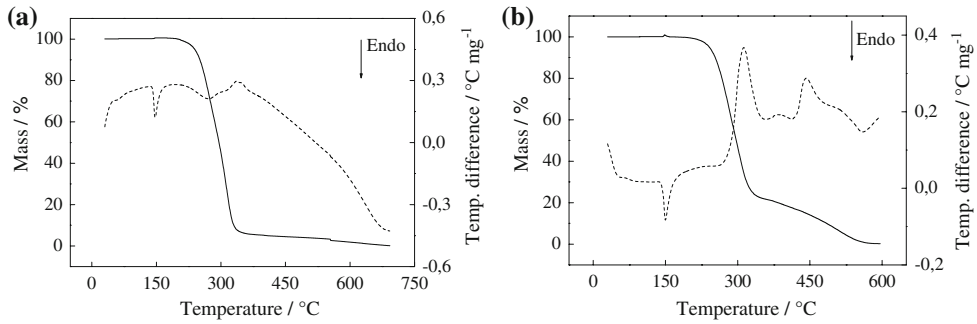

Fig. 1 TG (*solid*) and DTA (*dash*) curves of verapamil HCl in (**a**) nitrogen and (**b**) air

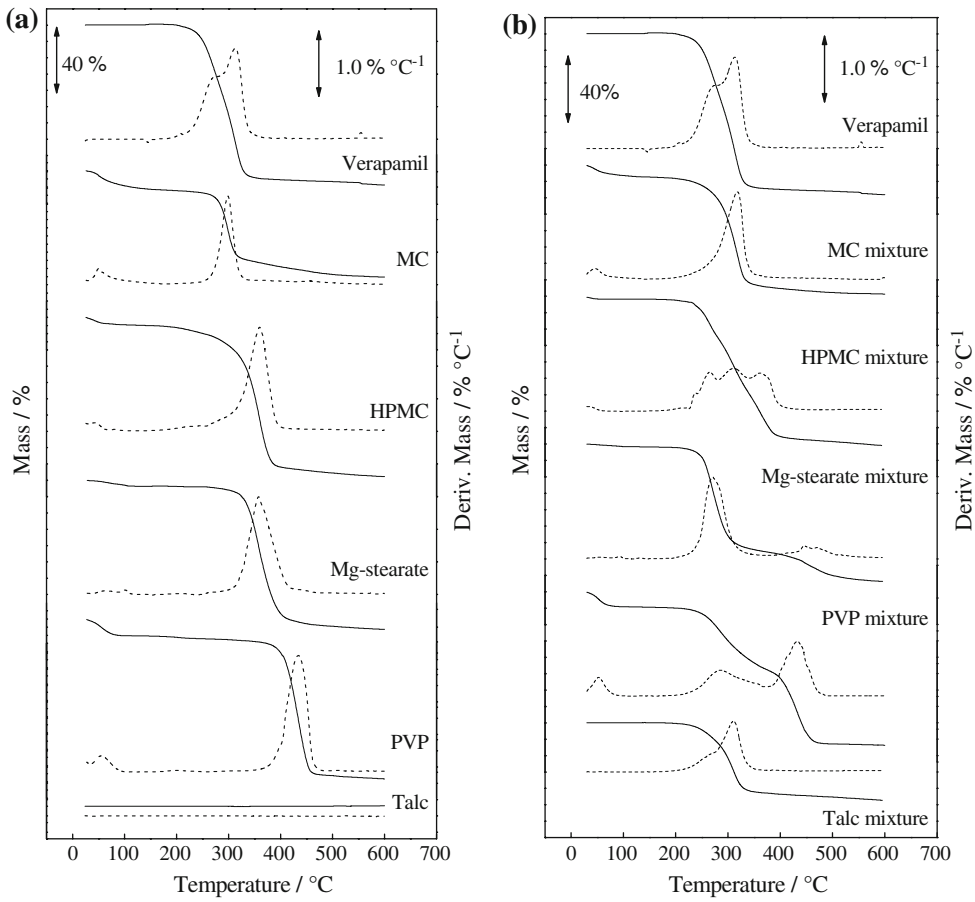

Fig. 2 TG (*solid*) and DTG (*dash*) curves of (**a**) verapamil HCl, and each studied excipients and (**b**) verapamil HCl and its binary mixtures, obtained in N_2 dynamic atmosphere, flow rate of 50 mL min^{-1}, heating rate 10 °C min^{-1} and sample mass of 5 mg in an open γ-alumina pan

approximately 2% between room temperature until 180 °C, and the decomposition appeared as a single step in TG, but in multiple events as represented by DTG (84.2%, 224–455 °C), showing that both components in the binary mixture decomposed individually.

The stearate presented a 3.4% mass loss that starts at the beginning of the TG run and extends up to 112 °C, attributed to the dehydration. A second event is related to the decomposition of the sample between 233 and 485 °C in which 85.2% of the initial mass is lost. In the DTA curve this process is represented by a broad peak with a maximum in 358 °C. Its mixture with VRP presented an interesting feature in which the decomposition of the stearate appeared in a lower temperature than that of the individual drug, as presented in DT curves. The TG curve presented a 1.5% initial mass loss attributed to the dehydration of stearate up to 100 °C. The decomposition takes place in a single mass loss of 64% between 185 and 370 °C. The DTG curve reveled only one decomposition step, which presented a peak at 270 °C, which is coincident with the first DTG peak observed for the VRP alone. This peak appeared ~85 °C before the peak observed in the case of the Mg-stearate alone.

The TG/DTG curves for the PVP presented dehydration with loss of 10.2% between room temperature and 100 °C, followed by the decomposition from 223 to 522 °C with loss of 85%. In its mixture with VRP these events are observed in as well as the antihypertensive decomposition exactly as observed for the individual compounds.

The TG/DTG curve of talc present any significative events under the conditions used in the present work. The mixture presented a TG/DTG very similar to that observed for the VRP.

In the DSC curve of VRP (Fig. 3) it can be observed one endothermic peak at 143.3 °C, corresponding to the melting of compound. The area of this peak revealed a melting heat of 132.3 J g^{-1}.

The DSC curves for MC and PVP presented only the dehydration endothermic broad peak in concordance with the TG. Talc curve did not present any significant thermal event. During the loss of humidity a sharp endothermic peak could be observed in both pure and mixture of HPMC without any additional mass loss suggesting that this is a physical nature thermal event. Heating the sample in a test tube up to 150 °C the condensation of water was noted at cold part of the tube while the solid

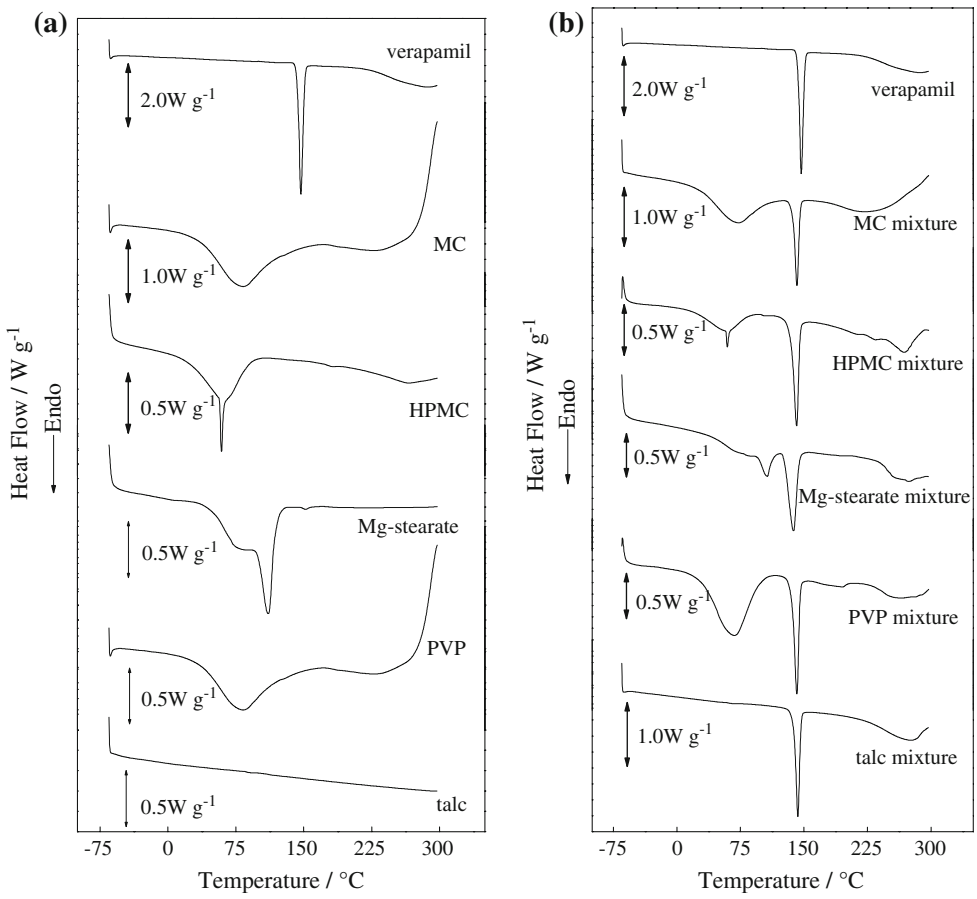

Fig. 3 DSC curves for pure substances (**a**) and (**b**) their mixtures with verapamil HCl, obtained in N_2 dynamic atmosphere (flow rate of 25 mL min^{-1}), heating rate 10 °C min^{-1} and sample mass of 2 mg

phase did not present any visible change showing that this is probably a solid transition. Near of 150 °C the melting of VRP was observed in the mixture. Magnesium stearate and its mixture DSC curves present the profile of the constituents.

Finally we can say that the DSC curves for the binary mixtures demonstrated that there are any significant interaction between the excipients used here and the antihypertensive drug VRP.

The enthalpy values for the melting processes ($\Delta H \pm$ standard deviations, $n = 5$) were assessed not only for the analyte but also for each binary mixture, being 132 ± 4 J g^{-1} for VRP and 51 ± 2; 58 ± 2; 50 ± 2; 52 ± 2 and 61 ± 2 J g^{-1} for each of its binary mixture with MC, Mg stearate, HPMC, PVP and talc, respectively. Their onset temperature values were 143 ± 2; 137 ± 2; 127 ± 1; 134 ± 1; 136 ± 2 and 138 ± 2 °C, respectively. Literature values are $\Delta H_{melt} = 130.6$ J g^{-1} and $T_m = 143.7$ °C [14].

Crystalline Mg stearate showed an endothermic peak related to melting at 107.0 °C (Fig. 2d). The onset temperature of the melting process was measured as 95.8 °C (literature describes $T_{onset} = 96.5$ °C and $T_m = 105.3$ °C) [15].

A modified ASTM procedure, E2009-07-C, was used to determine the VRP oxidation onset temperature (OOT) as 287.3 °C (TG/DTA) [16]. The thermal stability (N_2 atmosphere) is about 225 °C and is almost the same for all binary blends. The OOT being at a higher temperature than the endothermic decomposition implies that the primary decomposition step is not dependent on air (oxygen), but is a thermal process.

The shape of the DSC curves and enthalpy values determined for the binary mixtures suggest that there are any significant interactions between VRP and the excipients used in the present work.

Kinetic studies were carried out by a non-isothermal procedure based on TG experiments, performed at six different heating rates 2.5, 5.0, 7.5, 10, 15, 20 °C min^{-1} in nitrogen atmosphere (50 mL min^{-1}).

Guinesi et al. [17] presented a detailed description on the equations involved and its application. The TG curves at different heating rates are shown in Fig. 4.

Figure 5 presents the dependence of the activation energy (E_a) with the decomposed fraction α for verapamil HCl. In the $51 < \alpha < 66\%$ mean values of activation energy $E_a = 230.1 \pm 0.1$ kJ mol^{-1} and a pre-exponential factor of $\log A = 11.0 \pm 0.3$ s^{-1} were found in this range of decomposition, in which the plateau suggests that a single decomposition process takes place.

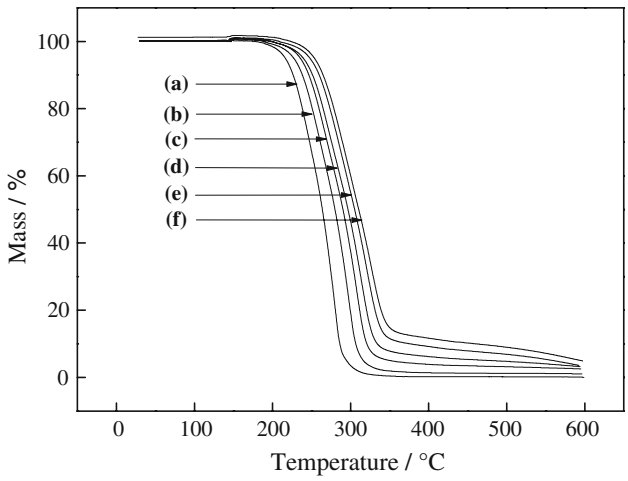

Fig. 4 TG curves of verapamil HCl at different heating rates under dry nitrogen atmosphere. (*a*) 2.5, (*b*) 5.0, (*c*) 7.5, (*d*) 10.0, (*e*) 15.0 and (*f*) 20.0 °C min^{-1}

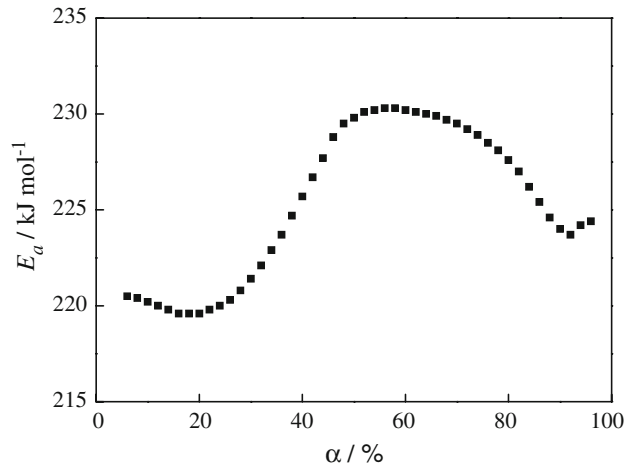

Fig. 5 E_a versus α plots for verapamil HCl decomposition

Conclusions

Verapamil HCl melting properties were in good agreement with the literature. The TG/DTA and DSC results suggested that the decomposition of VRP occurred after melting in a single endothermic step in a nitrogen atmosphere.

The results also suggest that excipients used in formulating the commercial drug (microcrystalline cellulose, hydroxypropylmethylcellulose, poly(vinyl)pyrrolidone, magnesium stearate and talc) did not presented important interactions with VRP. When necessary the use of a special coating is appropriate in cases of controlled-release tablet manufacturing.

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