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Application of thermal analysis and pyrolysis coupled to GC/MS in the qualification of simvastatin pharmaceutical raw material

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Abstract The simvastatin (SV) is nowadays produced semi-synthetically from lovastatin. It's one of the statins most commonly used to treat several forms of hypercholesterolemia. This study aimed to apply the thermal characterization of the SV raw material using thermoanalytical techniques and its degradation products by Pyrolysis coupled to Gas chromatography/Mass spectrometry (Pyr-GC/MS). It was studied three samples of SV (SVA, SVB, and SVC). The results showed thermal behavior differences of the samples during the melting process transition and the activation energies (E_a) of the thermal decomposition, which were correlated to the thermal stability of them. The first decomposition step of Pyr-GC/MS showed two new compounds of *m/z* 284 and 207, in proportions dependents according to the pyrolysis temperature.

Keywords Simvastatin · Thermal analysis · Pyrolysis · Thermal kinetics

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Introduction

The Fig. 1 shows the chemical structure of SV that is nowadays produced semi-synthetically from lovastatin.

It's one of the statins most commonly used to treat several forms of hypercholesterolemia [1, 2].

The thermal analysis is applied to any technique which involves a measurement of a material's specific property while the temperature is controlled (either changed or maintained) and monitored [3].

Thermal analytical methods prove to be as rapid and reproducible methods that can be used, alone or combined with other techniques, with different purposes in the pharmaceutical industry, for example: study of the characterization and thermal decomposition of drugs [4–7], in the development of solid pharmaceutical forms [8, 9].

This study aimed to apply the thermal analysis (Termogravimetry (TG), Differential scanning calorimetry (DSC) and Differential scanning calorimetry coupled to Photovisual system (DSC-Photovisual)) and Pyrolysis coupled to Gas chromatography/Mass spectrometry (Pyr-GC/MS) to characterize the pharmaceutical raw material simvastatin.

Experimental

Samples

It was used three different SV samples (SVA, SVB, and SVC). All gases utilized were chromatographic grade.

Thermal analysis studies

The calorimetry curves were recorded with a differential scanning calorimeter (Shimadzu, model DSC-50) using a

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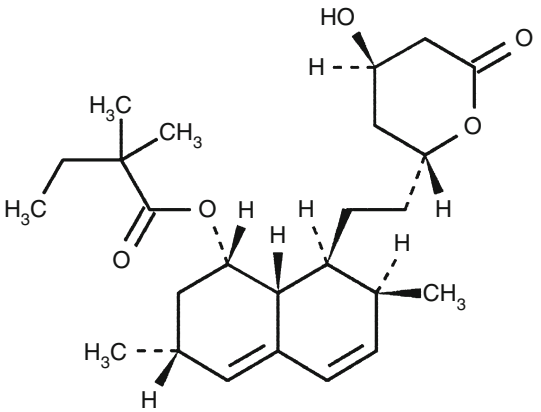

Fig. 1 Chemical structure of simvastatin

closed aluminum crucible. The apparatus was calibrated using indium (156.6 ± 0.3 °C) as standard. The heat flow signal was calibrated by melting heat of indium (28.59 ± 0.3 J g^{-1}). Rising temperature experiments were conducted in the temperature range 25–250 °C at heating rates of 2, 5, 10, 20, and 40 °C min^{-1} in dry nitrogen flow 50 mL min^{-1} with a sample mass in the 2.0 ± 0.1 mg. The DSC data were analyzed using the Tasys software from Shimadzu.

DSC-Photovisual data were recorded with a differential scanning calorimeter (Shimadzu, model DSC-50) coupled to a photovisual system, equipped with a microscope (Olympus, model SZ-CTV60) and a camera (Sony, model VCC-520). The samples were placed into an opened aluminum crucible and heated in the temperature range 25–300 °C at heating rate of 10 °C min^{-1} under the same conditions of nitrogen flow from conventional DSC. The pictures were taken by Asymetrix DVP 4.0 program at real time to observe the phase transitions in the samples.

The dynamic thermogravimetric curves were recorded with a thermobalance (Shimadzu, model TGA-50) using alumina crucible. The apparatus was calibrated with calcium oxalate monohydrate. Rising temperature experiments were conducted in the temperature range 25–900 °C at heating rates of 10, 20, and 40 °C min^{-1} in synthetic air and nitrogen flow 20 and 50 mL min^{-1}, respectively, with a sample mass in the 5.2 ± 0.1 mg. The isothermal curves were obtained in the same equipment under the same conditions of air and mass from dynamic thermogravimetric curves. The temperatures used for isothermal studies were: 165, 175, 185, 195, and 205 °C. The isothermal TG data were analyzed using the Tasys software from Shimadzu. The reaction order (n) and activation energy (Ea) were determined using the Ozawa's model for the TG dynamic data in the synthetic air and nitrogen atmosphere [10]. The kinetic parameters of decomposition were calculated using the Arrhenius's equation on the basis of TG isothermal data [11].

The reaction order was made by graphic method using the following relations: order zero $\Delta m/\Delta t$, first order $\Delta \ln n_m/\Delta t$ and second order $\Delta(1/m)/\Delta t$.

The reaction rate constant of order zero was obtained using the classical Arrhenius's equation $k = (m_0 - m_t)t^{-1}$, where, m_0 (initial mass) and m_t (mass at time t).

The curves k versus T were adjusted to an exponential equation, from which it was possible to extrapolate back to room temperature and hence determine the rate constant at temperature 30 °C.

The time required for decomposition of 2% of the initial mass in isothermal decomposition was determinate using the equation $m_{100} - m_{98} = k_{30}t$

The correlation of the activation energy determined by the Ozawa's model and the extrapolated constant (30 °C) obtained by the Arrhenius's equation was determinate by plotting k_{30} versus E_a.

Pyrolysis coupled to Gas chromatography/Mass spectrometry (Pyr-GC/MS)

Pyrolysis studies were conducted at pyrolyzer coupled to a gas chromatograph system (Shimadzu, GCMS-QP5050A), directly interfaced with a mass spectrometer with electron ionization source. The fragmentation was performed by electronic impact with ionization energy of 70 eV. The spectrometer was operated in SCAN mode, scanning a range mass of m/z 50–550. The temperature of the ion source was 290 °C. It was used a capillary column with stationary phase phenyl:dimethylpolysiloxane (5:95), with 30 m length, 0.25 mm internal diameter, and 0.25 μm particle size. The temperature program consisted of two segments: first, the column was rising temperature segment with a heating rate of 15 °C min^{-1} up to the final temperature of 290 °C, and second, an isothermal segment with the probe held at the final temperature for 10 min. Helium was used as carrier gas at a flow rate of 1 mL min^{-1} with split ratio of 1:5. The samples corresponds to a little simvastatin crystal put in platinum crucible and introduced to the pyrolyzer at the temperatures of 200, 250, 300, 400, and 550 °C, separately for each experiment.

Results and discussion

Thermal analysis studies

The analysis of DSC curves of the samples SVA, SVB, and SVC in the heating rates of 2, 5, 10, 20, and 40 °C min^{-1}

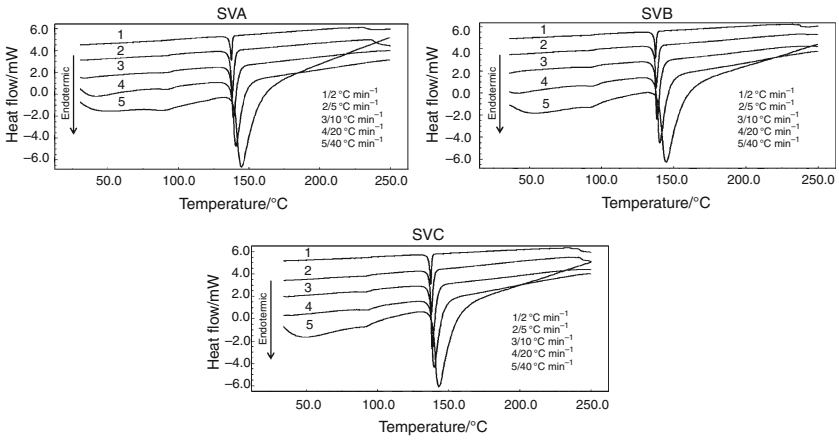

Fig. 2 DSC curves of SVA, SVB, and SVC samples in the heating rates of 2, 5, 10, 20, and 40 °C min^{-1}

shown in Fig. 2 revealed the existence of two endothermic transitions in the range 25–250 °C. The first phase transition in the temperature range 90–100 °C corresponds to the water volatilization. The second in the range 130–160 °C at heating rates of 2–20 °C min^{-1} is due to the melting process. In the heating rate of 40 °C min^{-1} it is observed an enlargement in the endothermal peak correspondingly to the simvastatin fusion. Such fact can be explained by occurrence of the thermal processes of fusion and decomposition simultaneously, where in the temperature onset begin the melting process and before temperature endset start thermal decomposition process with mass loss.

Figure 3 shows the pictures obtained in the DSC-Photovisual where is possible to visualize different behavior between simvastatin raw materials. The SVA presented a process of fusion more slow than SVB and SVC in the temperature about 137 °C. The total volatilization process of sample SVA in temperature below 250 °C was faster than SVB and SVC. The different thermal behavior suggests that the simvastatin pharmaceutical raw material from different manufacturers presents different physical qualities. The SVA is different than SVB and SVC.

Figure 4 shows the dynamic thermogravimetric curves of the samples SVA, SVB, and SVC in the heating rates 10, 20, and 40 °C min^{-1} and DSC curve at a heating rate of 10° °C min^{-1}. The DSC curve shows the melting point of simvastatin occurring about 137 °C, while the TG curves show different behavior between heating rates for each sample of simvastatin. In the heating rate of 10 °C min^{-1} can be verified three consecutive steps of mass loss in all samples studied. With increasing of heating rate it is observed a displacement in the temperatures of thermal decomposition associated with the tendency to form a unique step.

TG data was used to calculate kinetics parameters of activation energy (*E*a) and reaction order (*n*) using Ozawa's model. The results obtained for different samples showed a kinetic process with zero order reaction for all samples in first and main step of decomposition. The activation energy values were different among the samples, where SVA presented *E*a about 73.10 kJ mol^{-1}, while SVB and SVC showed values about 98.67 and 99.67 kJ mol^{-1}, respectively.

Isothermal TG data was used to determine kinetic parameters using Arrhenius's equation. The reaction order was obtained by graphic method and its linear correlation presented similar values for zero, first and second order. The decision about reaction order of simvastatin thermal decomposition was resulting of the comparison between TG dynamic and TG isothermal data after to compare the results of Arrhenius and Ozawa models. The reaction order chosen was zero order. The rate constants were calculated from TG isothermal data using Arrenhius's equation for reaction of zero order.

The correlation of the activation energy determined by the Ozawa's model and the extrapolated constant (30 °C) obtained by the Arrhenius's equation showed inversely linear correlation, Fig. 5a, where the SVC sample with the higher activation energy of dynamical thermal decomposition (99.67 kJ mol^{-1}) showed the lesser reaction constant of isothermal decomposition with value of k_{30} (1.88×10^{-8} s^{-1}), whereas the SVA sample had lesser activation energy of dynamical thermal decomposition (73.10 kJ mol^{-1}) and showed the higher reaction constant of isothermal decomposition k_{30} (2.14×10^{-8} s^{-1}).

Using the Arrhenius equation for zero order reaction was obtained the time required for decomposition of 2% of the initial mass in isothermal decomposition and correlated with activation energies in dynamical thermal decomposition for those samples, Fig. 5b. The SVC sample with the higher activation energy of decomposition would require 3.38 years while the SVA would need only 2.96 years. These results validate the model for analysis and differentiation among samples of SV, where the kinetic process for

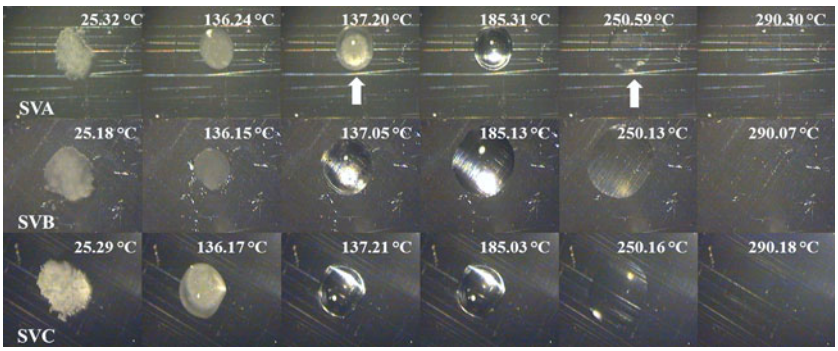

Fig. 3 DSC-Photovisual of SVA, SVB, and SVC samples in the heating rate of 10 °C min^{-1}

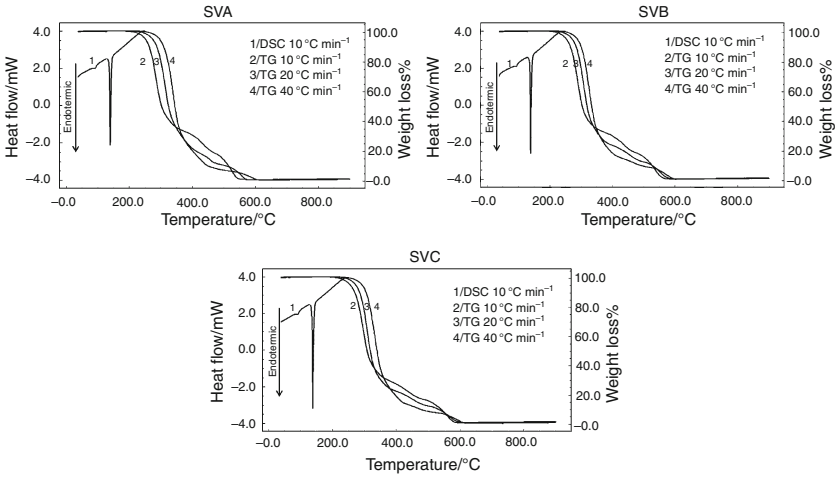

Fig. 4 Dynamic thermogravimetric curves of SVA, SVB, and SVC samples on different heating rates 10, 20, and 40 °C min^{-1} and DSC heating rate of 10 °C min^{-1}

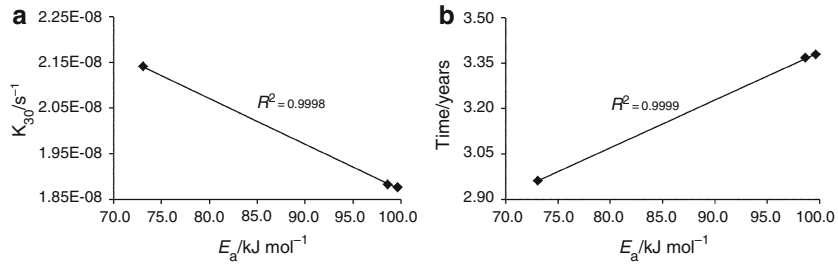

Fig. 5 Correlation between the average kinetic energy of degradation for each sample, and their extrapolated constant at 30 °C in (**a**) and the time required for mass loss of 2% in (**b**)

reaction of zero order presented good correlation between Ozawa and Arrhenius models.

Pyrolysis coupled to Gas chromatography/Mass spectrometry (Pyr-GC/MS)

Figure 6 shows pyrograms obtained at temperatures of 200, 250, 300, 400, and 550 °C where was possible to identify the fragmentation of SV in the thermal decomposition. Any peak of SV molecular ion at *m/z* 418 was founded in the spectra. This fact means that SV was decomposed in all temperatures used in this study.

The temperatures of 200 and 250 °C corresponding to the first stage of dynamical thermal decomposition showed the formation of two compounds in different proportions if 200 or 250 °C was applied into pyrolyzer. At the temperature of 200 °C, Fig. 6, the peak 1 in pyrogram corresponding to the fragment of a *m/z* 284 which presented 95.67% of relative area. The second peak in pyrogram was identified as a fragment of a *m/z* 207 corresponding to the 4.33% of relative area. At the temperature of 250 °C the peaks 1 and 2 attributed to the same fragments at the temperature of 200 °C changed in the proportion of them, the peaks 1 and 2 presented 87.52 and 12.48% of relative areas.

The mass loss in the pyrolyzer corresponding to the two fragments calculated in relation to the molecular weight of the SV (*m/z* 418.57) using the equation 1:

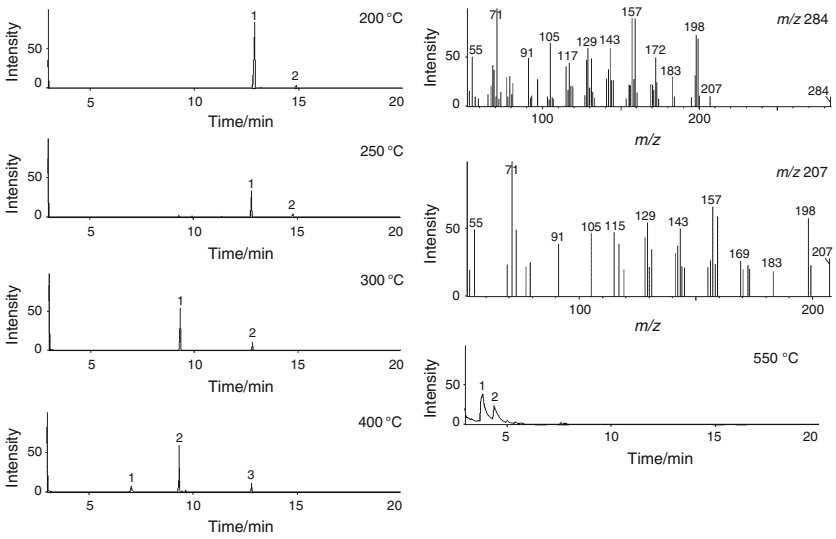

Fig. 6 Pyrograms obtained for SV, at a temperatures of 200, 250, 300, 400 e 550 °C, showing the degradation products of the drug thermal decomposition process; 200 and 250 °C (*1*) *m/z* 284, (*2*) *m/z* 207; 300 °C (*1*) *m/z* 240, (*2*) *m/z* 207; 400 °C (*1*) *m/z* 238, (*2*) *m/z* 240, (*3*) *m/z* 207; 550 °C (*1*) *m/z* 142, (*2*) *m/z* 156

$$\text{Mass loss } (\%) = \left\{ \left[\left(\frac{284}{418.57} \right) (\%\text{peak1}) \right] + \left[\left(\frac{207}{418.57} \right) (\%\text{peak2}) \right] \right\} \quad (1)$$

It presented 67.14% at a temperature of 200 °C and 65.64% at a temperature of 250 °C. These values were compared with that obtained in the first stage of dynamical thermal decomposition in termogravimetric curves for three batches of SV which presented a mass loss average of 64.16% at a heating rate of 10 °C min^{-1}.

At the temperatures higher of 300 °C, corresponding to the other steps of thermal decomposition in TG curves, the fragment *m/z* 284 was not detected showing a difference on pyrolytic fragments. At 300 °C the peaks 1 and 2 were identified as *m/z* 240 and 207 with 75.94 and 24.06% of relative areas. At the 400 °C three peaks were observed in pyrogram where peak 1 was identified as a new compound with *m/z* 238 responsible for 19.66% of relative area. The peaks 2 and 3 were similar that founded at 300 °C, respectively *m/z* 240 and 207 with relative areas of 60.03 and 20.31%. At 550 °C, the pyrogram in Fig. 6 shows peaks 1 and 2 which were identified, respectively, as a new compounds with *m/z* 142 and 156 presenting relative areas of 65.28 and 34.72%.

The values obtained showed a good correlation between the reaction mechanisms of thermal decomposition products obtained in the thermogravimetry and pyrolyzer.

The comparison between thermal decomposition into pyrolyzer with formation of two new compounds at 200 °C can be compared with kinetic behavior of simvastatin analyzed with dynamic thermogravimetric data. It was difficult to decide the reaction order, because in the first step of decomposition, it wasn't observed the direct dependency degradation of simvastatin, but the simultaneous formation of two compounds.

Conclusions

The results DSC and DSC-Photovisual showed differences in the thermal behavior of the samples in the phase transitions of melting and volatilization processes.

The kinetics parameters obtained by dynamical and isothermal termogravimetric data showed that simvastatin mass loss obey a kinetic process for a reaction of zero order. The activation energies were directly correlated with thermal decomposition constants with all samples.

Pyr-GC/MS data showed a good correlation between the mass losses of pyrolyzer process with dynamical thermal decomposition in the thermogravimetry.

The identification of new compounds in the pyrograms with *m/z* 284 and 207 in first step of the thermal decomposition allowed to confirm the complexity in the interpretation about reaction order in isothermal decomposition of simvastatin.

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