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# THERMAL AND KINETIC STUDY OF STATINS
## Simvastatin and lovastatin

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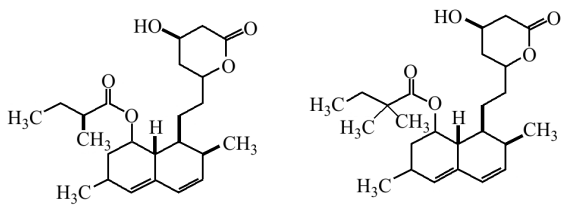
Statins are a group of lipoproteins that are used in medicine to treat the high cholesterol level. The effectiveness of statins in reducing the cholesterol level is significant and in long time scale the reduction of the cholesterol level helps to avoid the incidence of degenerative diseases. Simvastatin and lovastatin are belonging to the 'statins' family, one of the pharmacologic groups used in the control of dislipidemy. The objective of this work is the thermal stability and kinetic study of the active forms of simvastatin and lovastatin.

Thermal data indicated that lovastatin and simvastatin are stable up to 190 and 170°C in air and up to 205 and 203°C in nitrogen, respectively. For melting temperatures DSC curves showed good correlation with the literature data. Comparing the activation energies of the statins at heating rate of 10°C min$^{-1}$, lovastatin is more stable than simvastatin under the applied experimental conditions.

***Keywords:*** *kinetic, statins, thermogravimetry*

## Introduction

Hyperlipidaemia, presence of excess lipids in the blood is the manifestation of a disorder in the synthesis and degradation of lipoproteins in the plasma. The main lipids that are responsible by hyperlipidaemia are cholesterol and triglycerides. High cholesterol blood levels are known to cause coronary atherosclerosis, which is one of the main causes of deaths among men and women all over the world. According to the statistics, about 38–42% of all cases of death in the western countries and other developed countries are related to coronary atherosclerosis. Statins, drugs used to decrease the cholesterol level are highly efficient pharmacos against hypercholesterolemia especially in reducing the LDL and VLDL cholesterol furthermore they reduce meaningfully mortality associated to coronary heart disease (CHD). Two main types and frequently used statins are simvastatin and lovastatin. According to Fig. 1 they have similar chemical structures (the only difference is in one methyl group attached to simvastatin, Fig. 1) [1–4].




Lovastatin Simvastatin

**Fig. 1** Chemical structure of lovastatin and simvastatin

Thermal analysis is frequently applied technique in studying the stability of pharmaceuticals. The obtained information is useful in determining the bioavailability of pharmaceuticals [5–7].

The aim of this work is to study the thermal and kinetic behavior of the active forms of simvastatin and lovastatin by using thermogravimetry (TG) and differential scanning calorimetry (DSC).

## Experimental

### *Thermal study*

TG curves were recorded using a TA SDT 2960 TG-DTA unit (TA Instruments, USA) in synthetic air and nitrogen with a flow rate of 110 mL min$^{-1}$ and at heating rates of 10, 15 and 20°C min$^{-1}$ using 10.00±0.5 mg initial sample masses. The curves were recorded from room temperature up to 800°C.

The DSC curves were recorded using TA 2920 Modulated DSC (TA Instruments, USA). The initial sample mass was 3.00±0.5 mg, flow rate of purging gas was 50 mL min$^{-1}$ (nitrogen) and the heating rate was 10°C min$^{-1}$.

### *Kinetic study*

Kinetic study has been done in order to determine the reaction mechanism and the kinetic parameters as apparent activation energy ($E$) and pre-exponential factor ($A$). The applied heating rates were 10, 15

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and 20°C min$^{-1}$ and only the decomposed fraction ($\alpha$) from 0.10 to 0.90 was taken into account.

The determination of the best describing kinetic mechanism was done by means of the $g(\alpha)$ function applying the Coats–Redfern method, in agreement with Eq. (1) [8–14]. The kinetic analysis program was developed in the Thermochemistry, Materials and Fuels Laboratory of UFPB.

$$\ln\left[\frac{g(\alpha)}{T^2}\right] = \ln\left(\frac{AR}{\phi E}\right) - \frac{E}{RT} \quad (1)$$

## Results and discussion

*Thermal study*

TG curves of simvastatin in synthetic air (Fig. 2b) present three mass loss steps, attributed to the thermal decomposition process without any residue. The representative thermogravimetric data obtained at 10°C min$^{-1}$ heating rate are sumarized in Table 1. The TG curves at heating rates of 15 and 20°C min$^{-1}$ presented the same profile, just the initial temperatures shifted towards slightly higher values. In nitrogen (Fig. 2a), simvastatin presented two mass loss steps, attributed to the thermal decomposition. The sample was more stable in nitrogen than in air.

TG curves of lovastatin in synthetic air atmosphere (Fig. 3b) exhibited three mass loss steps attributed to the decomposition process with a complete mass loss in the investigated temperature range (representative data at heating rate of 10°C min$^{-1}$ are collected in Table 1). The TG curves applying 15 and 20°C min$^{-1}$ heating rates presented the same profile with a small shift in the values of the initial decomposition temperatures.

In nitrogen (Fig. 3a) lovastatin showed two mass loss steps, attributed to the decomposition process. This compound has also higher thermal stability in nitrogen than in air. Besides, in nitrogen less number of TG steps were representative for the mass loss process than in oxidizing atmosphere, which favors the decomposition. Comparing the two statins, lovastatin showed a higher thermal stability than the other compound in both atmospheres.

DSC curves of simvastatin and lovastatin present two endothermic transitions (Fig. 4). In the DSC curve of simvastatin the representative peak temperature for the first transition (fusion) is 142°C with an enthalpy of 75.9 J g$^{-1}$. The fusion temperature is (onset temperature) shows a good agreement with the literature data, $T_0$=138°C [15]. The second transition with a peak temperature of 302°C and enthalpy of 59.9 J g$^{-1}$ is representative for the thermal decomposition (Fig. 4a).

In the DSC curve of lovastatin the peak at 172°C represents the fusion of the substance which correlates well with the literature data, 174.5°C [15]. The corresponding melting enthalpy is 106.6 J g$^{-1}$. The second broad endotherm peak at 285°C is representative to the thermal decomposition of lovastatin. The corresponding melting enthalpy is 47.2 J g$^{-1}$, (Fig. 4b).

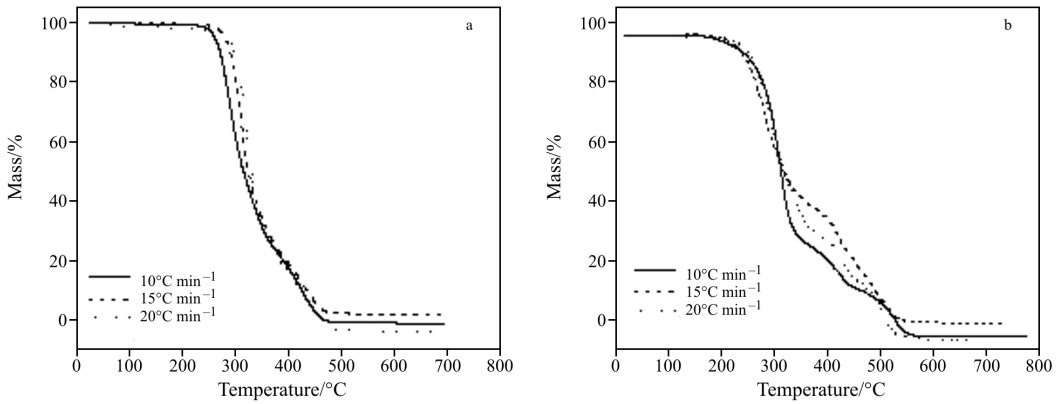


**Fig. 2** TG curves of simvastatin in a – $N_2$ and b – air

**Table 1** Thermogravimetric data obtained at the heating rate of 10°C min$^{-1}$

| Simvastatin | | | | Lovastatin | | | |
|---|---|---|---|---|---|---|---|
| synthetic air | | $N_2$ | | synthetic air | | $N_2$ | |
| step/°C | mass loss/% | step/°C | mass loss/% | step/°C | mass loss/% | step/°C | mass loss/% |
| 170–368 | 72.8 | 203–376 | 76.1 | 190–378 | 65.0 | 205–380 | 73.4 |
| 368–461 | 15.1 | 376–493 | 23.5 | 378–473 | 24.0 | 380–504 | 25.5 |
| 461–569 | 12.1 | | | 473–573 | 11.0 | | |

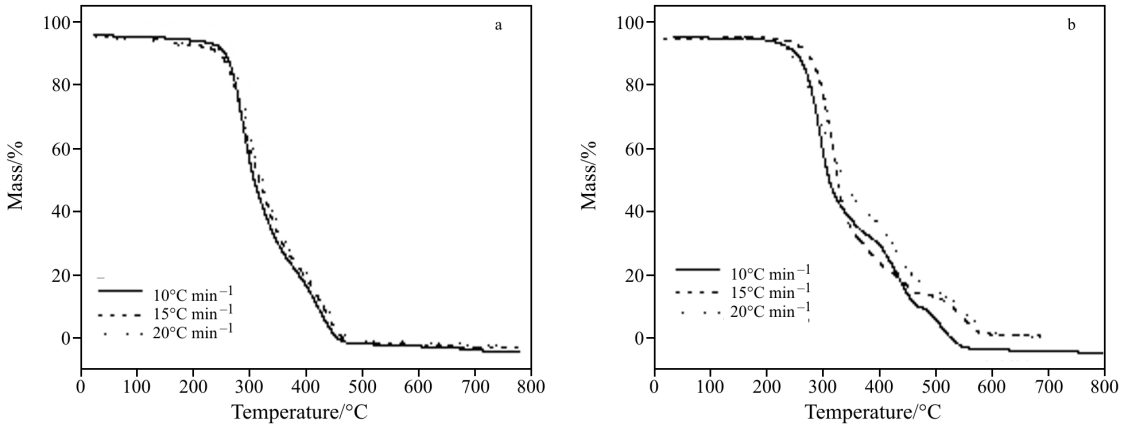


**Fig. 3** TG curves of lovastatin in a – $N_2$ and b – air

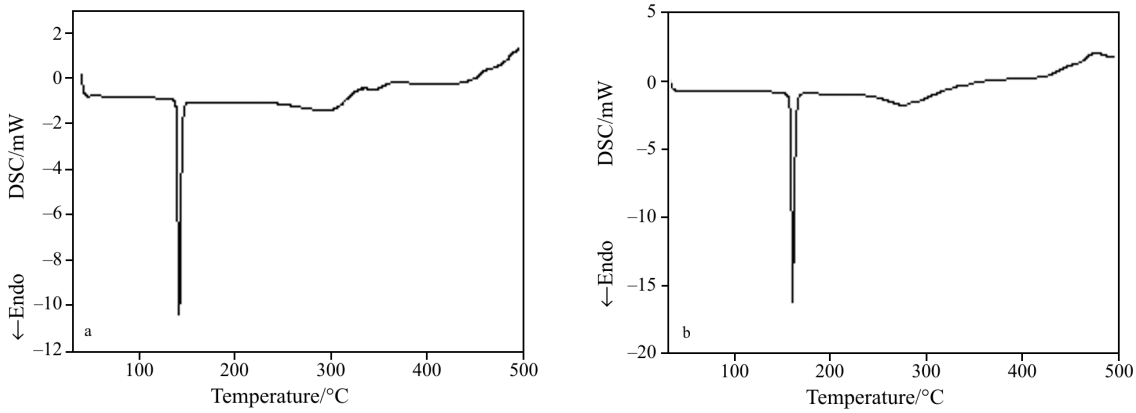


**Fig. 4** DSC curves of a – simvastatin and b – lovastatin

*Kinetic study*

The decomposition mechanism was determined according to the first step of the thermal decomposition process using the decomposed fraction ($\alpha$) from 0.10 to 0.90. The results are shown in Table 2.

The best kinetic model was selected where the linear correlation coefficient ($r$) was closest to one and where the lowest standard deviation ($sd$) was obtained.

F1 was the best fit model for simvastatin at three different heating rates in synthetic air, while in nitrogen the best fit model was for F3. Lovastatin has F1 mechanisms in both atmospheres. F1 and F3 refer to first and third order mechanisms, random nucleation followed by nuclear growth at a constant rate, without overlapping of nuclei.

By the comparison of the activation energies of the statins at heating rate of 10°C $min^{-1}$, lovastatin is more stable than simvastatin in both atmospheres.

The effect of the kinetic compensation was calculated for all the samples. This effect states that any variation in the activation energy originated from the change of the experimental conditions corresponds to a variation in the pre-exponential factor and it can be expressed as:

$$\ln A = a + bE \quad (2)$$

where $a$ and $b$ are characteristic constants of the system.

This linear relation can be associated to the Arrhenius equation by:

$$\ln A = \ln k_{iso} + E/RT_{iso} \quad (3)$$

where $k_{iso}$ is the isokinetic rate constant and $T_{iso}$ is the isokinetic temperature.

In order to validate the calculated kinetic data, the kinetic compensation effect was determined. This is based on the mean of the obtained results with three different heating rates (Table 3). Besides, the isokinetic rate constant ($k_{iso}$) and isokinetic temperature ($T_{iso}$) were calculated.

A good linearity of experimental results was observed. Both the natural logarithm of the pre-exponential factor ($\ln A$) and the apparent activation energy ($E$) indicating a good precision in the analyses (Figs 5 and 6).

**Table 2** Mechanism and parameters of the statins decomposition, using different heating rates

| Compound | Atmosphere | Mechanism | Kinetic parameters | Heating rates/°C min$^{-1}$ | | |
|---|---|---|---|---|---|---|
| | | | | 10 | 15 | 20 |
| Simvastatin | synthetic air | F1 | $E$/kJ mol$^{-1}$ | 69.65 | 98.32 | 114.67 |
| | | | $A$/s$^{-1}$ | $4.28\cdot10^{3}$ | $1.36\cdot10^{7}$ | $4.09\cdot10^{8}$ |
| | | | $r$ | 0.998 | 0.996 | 0.999 |
| | | | $sd$ | 0.020 | 0.035 | 0.017 |
| | $N_2$ | F3 | $E$/kJ mol$^{-1}$ | 166.52 | 248.04 | 288.98 |
| | | | $A$/s$^{-1}$ | $1.90\cdot10^{13}$ | $3.84\cdot10^{20}$ | $1.14\cdot10^{24}$ |
| | | | $r$ | 0.998 | 0.999 | 0.999 |
| | | | $sd$ | 0.039 | 0.011 | 0.028 |
| Lovastatin | synthetic air | F1 | $E$/kJ mol$^{-1}$ | 165.91 | 133.84 | 76.19 |
| | | | $A$/s$^{-1}$ | $2.45\cdot10^{13}$ | $7.41\cdot10^{9}$ | $7.31\cdot10^{4}$ |
| | | | $r$ | 0.998 | 0.999 | 0.999 |
| | | | $sd$ | 0.036 | 0.013 | 0.014 |
| | $N_2$ | F1 | $E$/kJ mol$^{-1}$ | 168.94 | 121.25 | 121.11 |
| | | | $A$/s$^{-1}$ | $2.92\cdot10^{13}$ | $9.03\cdot10^{8}$ | $8.21\cdot10^{8}$ |
| | | | $r$ | 0.998 | 0.998 | 0.998 |
| | | | $sd$ | 0.033 | 0.037 | 0.033 |

**Table 3** Kinetic parameters obtained under different atmospheres

| Kinetic parameters | Simvastatin | | Lovastatin | |
|---|---|---|---|---|
| | synthetic air | $N_2$ | synthetic air | $N_2$ |
| $E$/kJ mol$^{-1}$ | 94.21 | 234.51 | 125.31 | 137.10 |
| $A$/s$^{-1}$ | $1.40\cdot10^{8}$ | $3.80\cdot10^{23}$ | $7.0\cdot10^{13}$ | $2.92\cdot10^{13}$ |
| $k_{iso}$/s$^{-1}$ | $82.05\cdot10^{-6}$ | $40.87\cdot10^{-3}$ | $3.169\cdot10^{-3}$ | $2.75\cdot10^{-3}$ |
| $T_{iso}$/°C | 311.37 | 318.77 | 277.57 | 277.57 |

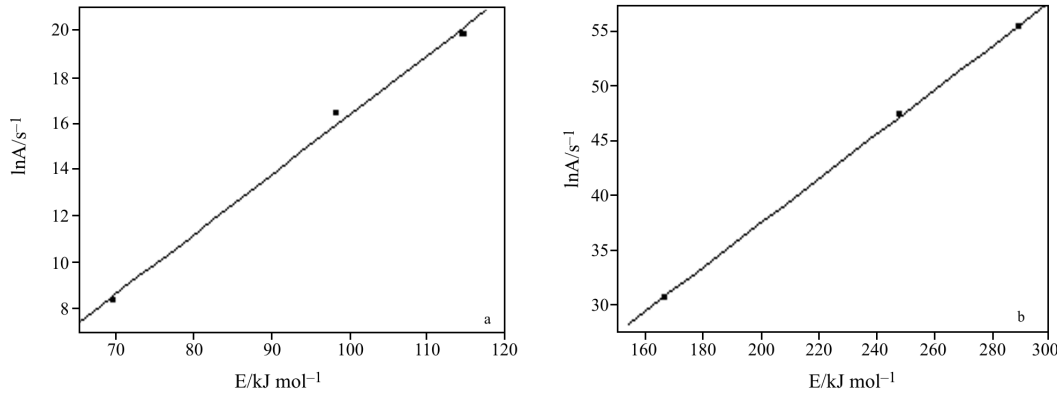


**Fig. 5** Effect of kinetic compensation for simvastatin in a – synthetic air and b – $N_2$

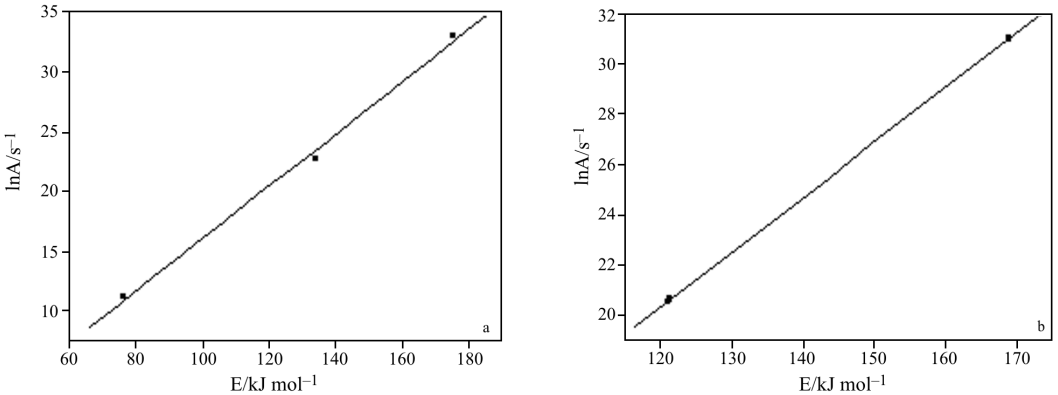


**Fig. 6** Effect of kinetic compensation for lovastatin in a – synthetic air and b – $N_2$

## Conclusions

Between the two statins, both in air and nitrogen lovastatin presented a higher thermal stability than simvastatin. In nitrogen less number of mass loss steps occurs since oxidizing atmosphere favors the thermal decomposition. DSC curves indicated the fusion, which agreed well with literature data which was followed by their thermal decomposition.

The model that best fitted the experimental data for simvastatin for the three heating rates in air was F1 (first order) model. In nitrogen, the best describing model was F3 (third order), while in both atmospheres F1 (first order) model was the best representative for the decomposition of lovastatine.

Comparing the activation energies of the statins in both atmospheres at 10°C $min^{-1}$ heating rate, lovastatin is more stable than simvastatin.

In all the samples a good linearity of the experimental results was observed both for the natural logarithm of the pre-exponential factor ($\ln A$) and the apparent activation energy ($E$), thus validating the kinetic data determination.

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