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THE THERMAL BEHAVIOR OF LOVASTATIN

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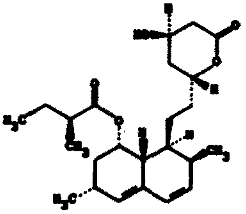
Abstract

The thermal properties of lovastatin were investigated by DSC and TG. Melting point and heat of fusion were determined and the thermo-oxidative stability was studied.

Lovastatin, shown below, is a potent inhibitor of HMG-CoA reductase, the rate-controlling enzyme in cholesterol biosynthesis.



2-methylbutanoic acid 1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester

Following isolation of crude product, it is purified by various crystallization sequences from appropriately chosen solvents, prior to milling to finished product, and subsequent formulation as a drug. In optimizing processing conditions, and scale-up from laboratory via pilot plant to large scale factory production, it is essential that a simple, rapid and reproducible method be available to assess the advantages, disadvantages and limitations of a wide range of purification procedures. In the pharmaceutical field, as in many, such methods very often involve measuring how well a drug withstands physico-chemical stress; a thermal stress method normally being employed. In order to develop a suitable test procedure, it is first necessary to obtain an understanding of the overall thermochemical behavior of the drug. Such an investigation has been made, and in this paper, the salient features will be briefly described.

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Experimental

All heat flow measurements have been made with the Mettler TA 3000 system, using the -160°C to +600°C DSC furnace. In studying the purely thermal behavior, the standard 40 µl aluminum crucibles were firmly packed with Lovastatin, ~12-14 mg. After crimp-sealing, the aluminum lids were depressed, enabling good sample-container contact following fusion, a condition found necessary to ensure repeatable recrystallization. The minute amount of entrapped air does not effect any significant oxidation during fusion, as confirmed by open crucible measurements in a nitrogen atmosphere. For thermo-oxidative studies, ~8-10 mg of sample were loosely placed in the open crucible. All gas flow rates were maintained at 50 ml min^{-1}. The weight-normalized DSC data will be shown as a function of the reference crucible temperature, but quoted significant temperatures are those of the sample. Weight change measurements have been made in open alumina crucibles in the TA 3500 thermogravimetric analyzer, with 100 ml min^{-1} gas flow rates. The TG data is presented as a percentage of initial sample weight as a function of the sample temperature, based on the Mettler Curie Point calibration procedure.

Results

Figure 1A shows the melt endotherms for two specimens of a highly pure reference standard Lovastatin sample, measured in the region 160°C to 180°C at a heating rate of 0.5°C min^{-1}. Eight such measurements on this HPLC standard yielded the following:

$$\Delta H_f = 44.3_1 \pm 0.8_8 \text{ kJ mol}^{-1} \qquad T_f = 173.3_3 \pm 0.0_5 {}^\circ\text{C}$$

The purity of this sample, measured by melting point depression, is $99.9_0 \pm 0.0_4$ mol percent. There is no perceptible degradation of Lovastatin during fusion. Thus, three consecutive melt-recrystallizations on one sample yielded $\Delta H_f = 43.4_4$, 43.6_9 and 43.5_0 kJ mol^{-1}, and T_f = 173.3, 173.1 and 173.1°C. On cooling, irrespective of the rate, the melt solidifies to a vitreous solid, which exhibits a well-defined glass transition in the 20 - 30°C region, followed by a sharp exothermic recrystallization in the 90 - 100°C region. The 8.32 mg sample, whose melt endotherm is shown in Figure 1A, was rapidly cooled to -20°C, and then heated to 150°C at 10°C min^{-1}. The glass transition and recrystallization are shown in Figure 1B, with the glass transition shown in more detail in Figure 1C. It should be pointed out that it is only necessary to cool the melt to below the glass transition region to observe it. It is pertinent to note that the recrystallization enthalpy, 67.12 J g^{-1} (27.12 kJ mol^{-1}), is only 61% of the fusion enthalpy. This is a repeated observation with Lovastatin. Measurements on the fusion and recrystallization of high purity dimethyl terephthalate showed that the fusion and recrystallization enthalpies agree within <1%. Thus, the marked inequality shown by Lovastatin is not an instrumental artifact. Although there is no thermal evidence, during either rapid or slow cooling, of any recrystallization in fused Lovastatin, it is assumed that approximately 30% of the vitreous solid is in an ordered state. However, if indeed correct, it has no effect on the characteristic glass transition temperature region. Arbitrarily, the sample temperature, Tg_2, at the midpoint of the transition (50% ΔCp), has been selected as a measure of the glassiness of the solid melt. Repeated measurements of the purely thermal behavior of Lovastatin have indicated a measurement precision of 0.3°C for Tg_2.

In an air environment, Lovastatin oxidizes exothermically in the 140 - 160°C region, dependent upon the heating rate. Figure 2A shows the exotherms for two specimens of the reference standard heated at 1°C min^{-1}. Prior to the exotherm onset, there is a characteristic weight gain of ~1.0%, as shown in Figure 3A, complete by 135°C, and during the exothermic excursion, a gradual evaporative weight loss commences. By 150°C, the preceding weight gain is lost. In pure oxygen, the characteristic weight gain increases to ~1.6%. This corresponds to

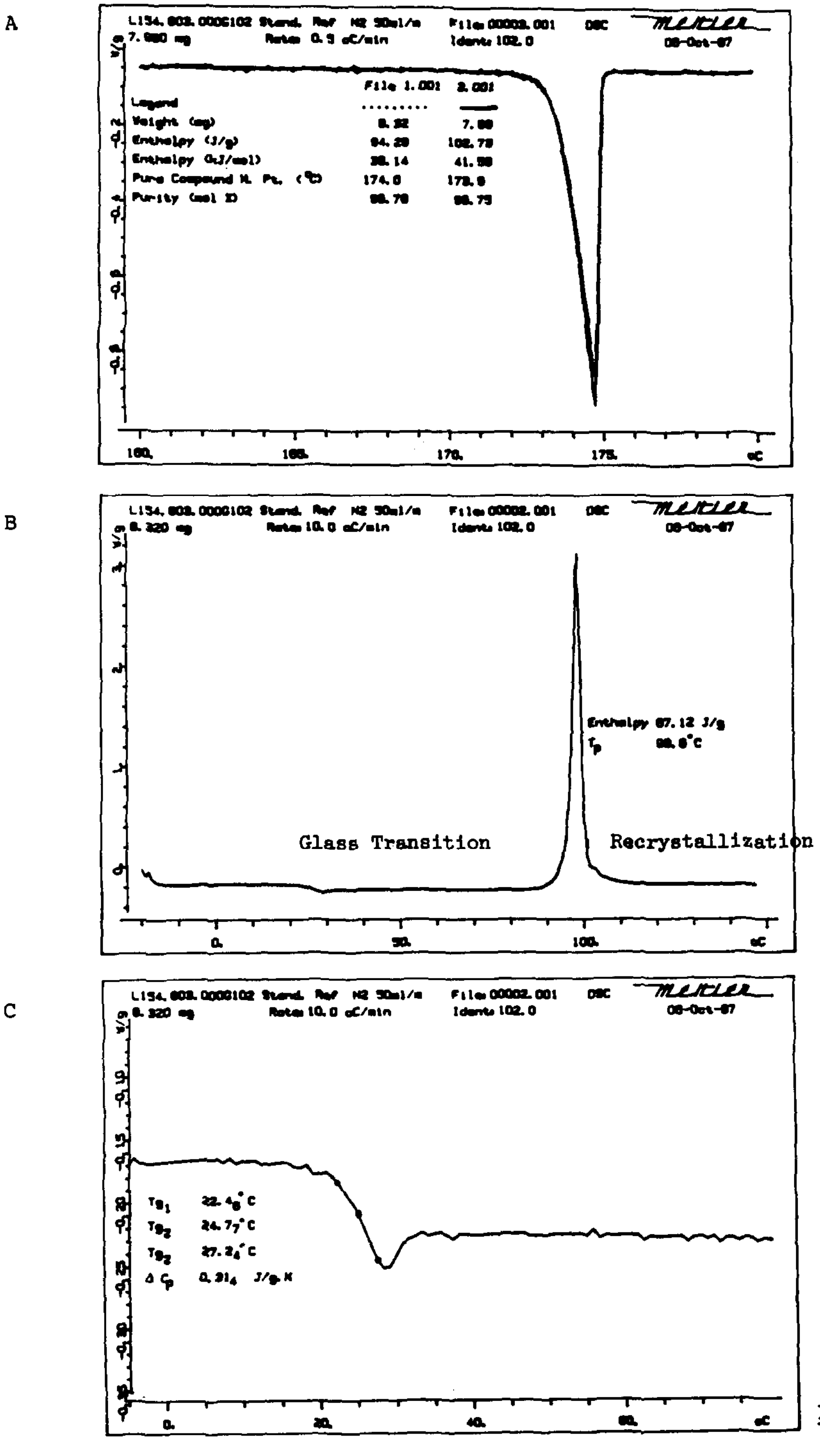
A
L154.808.0006102 Stand. Ref N2 50ml/m
7.980 mg
Rate: 0.5 oC/min
File: 00003.001
Ident: 102.0
DSC
mettler
08-Oct-87
File 1.001 2.001
Legend
Weight (mg) 8.32 7.98
Enthalpy (J/g) 94.29 102.79
Enthalpy (kJ/mol) 38.14 41.58
Pure Compound M. Pt. (°C) 174.0 173.9
Purity (mol %) 98.78 98.73
W/g
-0.2
-0.4
-0.6
-0.8
160.
165.
170.
175.
oC
B
L154.808.0006102 Stand. Ref N2 50ml/m
8.320 mg
Rate: 10.0 oC/min
File: 00002.001
Ident: 102.0
DSC
mettler
08-Oct-87
W/g
3
2
1
0
Enthalpy 87.12 J/g
Tp 98.8°C
Glass Transition
Recrystallization
0.
50.
100.
oC
C
L154.808.0006102 Stand. Ref N2 50ml/m
8.320 mg
Rate: 10.0 oC/min
File: 00002.001
Ident: 102.0
DSC
mettler
08-Oct-87
W/g
-0.10
-0.15
-0.20
-0.25
-0.30
-0.35
Tg1 22.46°C
Tg2 24.77°C
Tg3 27.24°C
Δ Cp 0.214 J/g.K
0.
20.
40.
60.
oC

Fig. 1

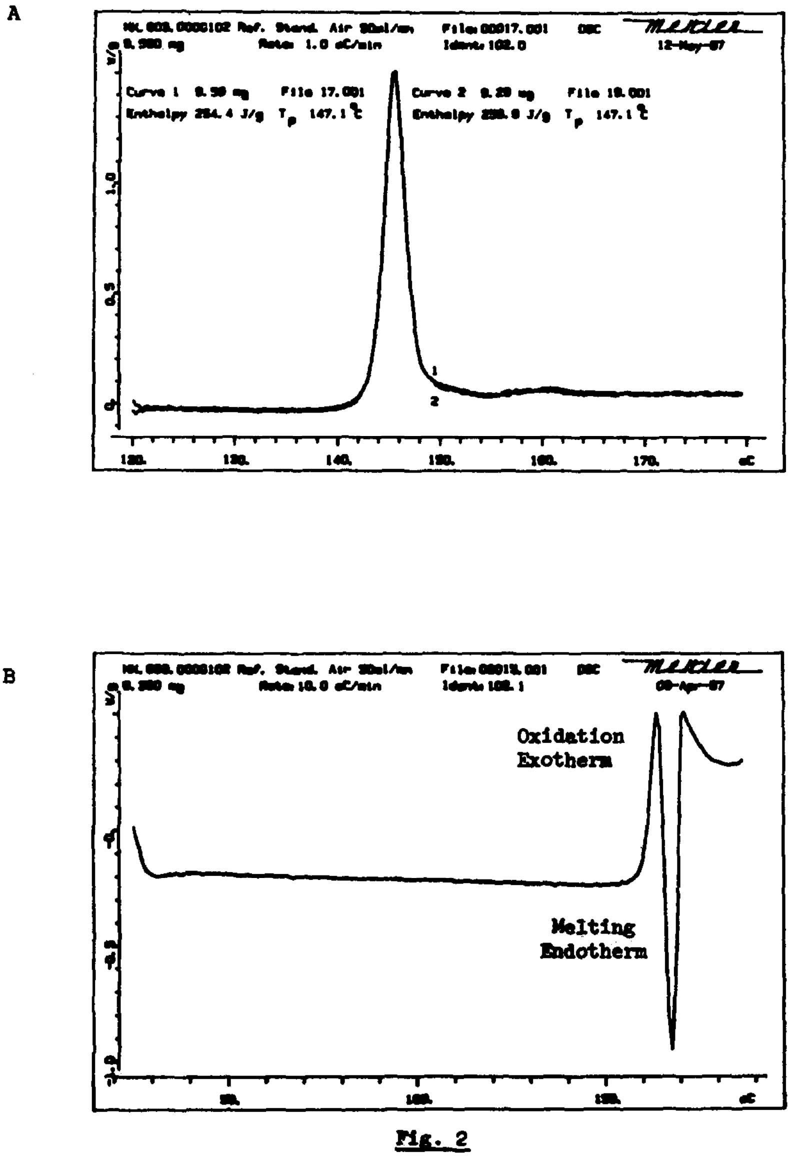
A
File: 00017.001
DSC
Rate: 1.0 oC/min
Ident: 102.0
12-May-87
W/g
Curve 1 9.50 mg File 17.001
Enthalpy 254.4 J/g T_p 147.1 °C
Curve 2 9.20 mg File 18.001
Enthalpy [illegible] J/g T_p 147.1 °C
1.0
0.5
0
1
2
120.
130.
140.
150.
160.
170.
oC
B
DSC
Rate: 10.0 oC/min
W/g
Oxidation
Exotherm
Melting
Endotherm
0
-0.5
-1.0
50.
100.
150.
oC

Fig. 2

an absorption/adsorption of ca. 1 atom oxygen per 2 mols Lovastatin. These events almost completely preclude the observation of any endothermic activity associated with the fusion of residual Lovastatin and its oxidation products above 150°C. As shown in Figure 2A, at the low heating rate, excellent reproducibility in measuring the enthalpy of the oxidation process is obtained. However, at a higher heating rate, 10°C min^{-1}, as shown in Figure 2B, although the early stage of the exotherm is clearly seen, the fusion process commences prior to the commencement of the evaporative weight loss, shown in Figure 3B. Thus, one is severely limited in the range of heating rates that can be used in attempting to study the kinetics of the oxidation process. Furthermore, one cannot use the TG data for a kinetic analysis. The low heating rate oxidation exotherm, Figure 2A, is similar in profile to the recrystallization exotherm, shown in Figure 1B. Both exhibit characteristics of thermal processes controlled by random nucleation (A2, A3) mechanisms.[1]

A limited amount of DSC data characterizing the oxidation of a secondary Lovastatin sample at low heating rates, 0.1 - 0.5°C min^{-1}, was analyzed using the generalized Kissinger equation[1], yielding the following values for the n th order kinetic parameters:

$n = 0.6 - 1.0 \qquad E = 438.9\ kJ\ mol^{-1} \qquad A = 1.25.10^{54}\ min^{-1}$

Although not strong evidence, these results are not inconsistent. As previously shown[1], extremely high values of the kinetic parameters result when data, whose source is an A3 controlling mechanistic reaction, is treated as an n th order reaction.

Oxidatively stressed Lovastatin, when subsequently melted in an inert environment and cooled, also yields a vitreous solid, which also exhibits a characteristic glass transition. Only if the extent of oxidation is minimal will the glassy solid recrystallize following the transition. The temperature range over which the glass transition occurs moves increasingly higher with increase in the extent of the prior oxidation. Extensive measurements have shown that the sample temperature, Tg_2, at the midpoint of the transition, is highly sensitive to the extent of the oxidation of the particular sample. These facts form the basis of a simple procedure for assessing the relative reactivity of Lovastatin samples.

The sample is oxidized isothermally at a suitably chosen temperature for forty five minutes in an air atmosphere in the DSC furnace. The isothermal temperature selected is approximately 10°C below the onset temperature of the oxidation exotherm at a dynamic scan rate of 1°C min^{-1}. Thus, the sample will only be minimally oxidized. Normally, 130°C is used. However, for very unreactive samples, 140°C has been used. Following the low level isothermal stress, the sample is quickly melted in a nitrogen atmosphere isothermally at 180°C for two minutes. It is then rapidly cooled to -20°C before heating at 10°C min^{-1} to 150°C in the same environment to monitor the glass transition. As previously indicated, Tg_2 is employed as a measure of the relative oxidative stability of the sample.

There is a linear relationship between Tg_2 and the lowering of the Lovastatin content in an oxidatively stressed sample as assayed by HPLC. For example, as previously indicated, Tg_2 for an unstressed sample is 25°C, whereas in an overly oxidized sample containing only 66% Lovastatin, the Tg_2 is 30°C. Although the difference of 5°C is small, due to the precision of the measurement of Tg_2, the procedure has proved highly successful in establishing the relative oxidative stability of Lovastatin samples produced by a variety of techniques.

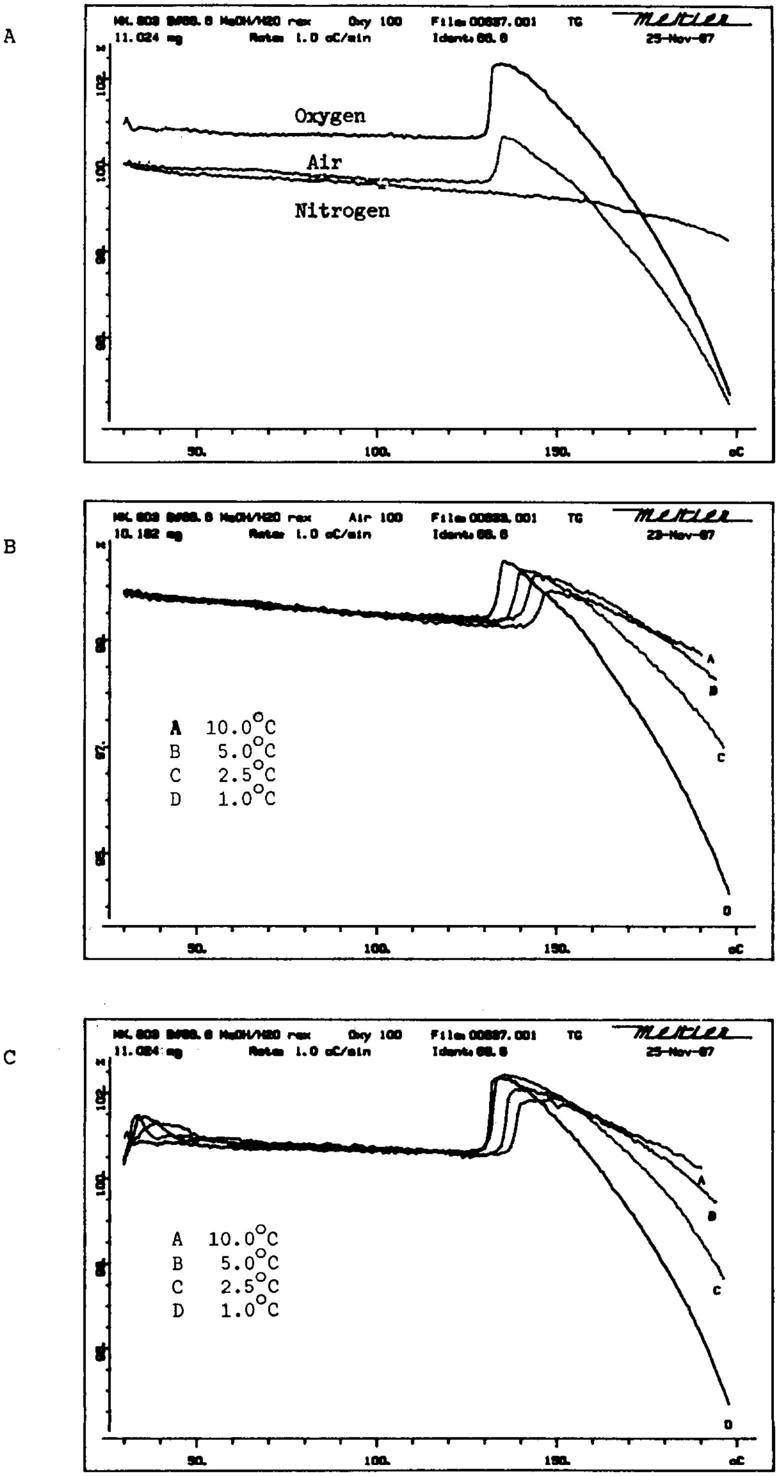
A
HK.809 BW68.6 MeOH/H2O rex
Oxy 100
File:00687.001
TG
Mettler
11.024 mg
Rate: 1.0 oC/min
Ident:68.6
25-Nov-87
%
102
100
98
96
Oxygen
Air
Nitrogen
50.
100.
150.
oC
B
HK.809 BW68.6 MeOH/H2O rex
Air 100
File:00688.001
TG
Mettler
10.182 mg
Rate: 1.0 oC/min
Ident:68.6
29-Nov-87
%
99
97
95
A 10.0°C
B 5.0°C
C 2.5°C
D 1.0°C
A
B
C
D
50.
100.
150.
oC
C
HK.809 BW68.6 MeOH/H2O rex
Oxy 100
File:00687.001
TG
Mettler
11.024 mg
Rate: 1.0 oC/min
Ident:68.6
25-Nov-87
%
102
100
98
96
A 10.0°C
B 5.0°C
C 2.5°C
D 1.0°C
A
B
C
D
50.
100.
150.
oC

Fig. 3

Traditionally, the relative oxidative stability of materials, particularly certain classes of polymers, has been evaluated by measuring the induction time which precedes the onset of exothermic activity. If the isothermal temperature is such that the rate of oxidation is insufficiently large to be observed by DSC, then the method fails. It has been shown for Lovastatin that, under such circumstances, the Tg_2 value is measurably different from the value obtained as a result of a purely thermal stress.

The ease with which a Lovastatin sample can be oxidized will depend upon crystal morphology, mean surface area and particle size distribution. Variations in such factors as a result of changes in sample preparation and pretreatment can be detected by the Glass Transition method.

In conclusion, similar behavior to that found in Lovastatin, has been observed in related compounds. It is highly probable that similar effects could be observed in many other compounds susceptible to oxidation, which form a glass upon solidification of the melt.

References

1. J.P. Elder, J. Thermal Analysis, 30 (1985) 657.