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A THERMAL ANALYSIS STUDY OF ASCORBIC ACID AND ITS PHARMACEUTICAL FORMULATIONS
A consideration of time–temperature plots

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Abstract

In a previous publication, the thermogravimetric (TG) analysis of ascorbic acid was considered. Simultaneously with the production of the TG data, time–temperature plots were also generated on the work station which allowed the process to be classified as exothermic or endothermic and identified the energy change with the reaction sequence. This aspect is investigated in the present study. To maximize the energy change, the model mixtures were assessed at a mass ratio of 1:1. The analytical implications of this approach are explored. To avoid complications in this kind of analysis, the present study is restricted to the behavior of binary systems heat treated in nitrogen.

Keywords: ascorbic acid, time–temperature plot

Introduction

Ascorbic acid ($C_6H_8O_6$), vitamin C, is a pharmaceutical product which is subjected to change in appearance on storage. It is considered that the absence of air and metal, protection from light, and the maintenance of low temperature and acid conditions are essential factors for successful storage of this material. In addition, the presence of excipients is thought to be able to alter the activity of the ascorbic acid. With these points in mind, the present project was started utilizing thermal analysis techniques to study the stability of ascorbic acid.

It was felt to be an advantage to use thermal analysis to study the effect that excipients might play in affecting the stability of the drug in the solid dosage form. Typical excipients include microcrystalline cellulose, stearic acid, magnesium stearate, and colloidal silicon dioxide. Such chemical interaction is only possible in the solid dosage form at points of contact between the solid particles, at least in the initial stages of a solid state reaction process.

In the data collected from a simultaneous TG-DTA unit, the information is presented in the form of a conventional TG signal, a conventional DTA signal and as a plot of temperature *vs.* time. The latter plots enable the heating rate to be confirmed. The plot of temperature *vs.* time shows perturbations in the region of transitions involving energy changes. Where the energy changes are quite small the perturbations are only readily apparent in the first derivative of the time–temperature plot. Such a plot, in addition, demonstrates the accuracy with which the tempera-

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ture control is maintained. This avenue of obtaining information is explored in the present study.

Experimental

Materials

Materials used are: ascorbic acid (Lot # 61 F-0065) supplied by Sigma Chemical Company; microcrystalline cellulose, Avicel® grade PH 101 (Lot # 1401) supplied by FMC Corporation; stearic acid (Lot # 02680) supplied by Sherman Research Laboratories; and colloidal silicon dioxide, Cab–O–Sil® grade M5 (Lot # 1 E252) supplied by Cabot Corporation.

Instrumentation

In the experiments performed in this study, a TA Instrument, SDT 2960, Simultaneous TGA-DTA unit was used with the work station (Thermal Analyst 2000) using a TA Operating System version 1.0B.

Procedure

The thermal analysis data was obtained on the single components and on binary mixtures of the drug and the excipients (1:1 by weight) and on selected binary mixtures of the excipients also in the same ratio. This differs from the ratio used in the commercial vitamin C formulations but provides better indications of any possible interactions. A porcelain mortar was used to mix the binary components. The method adopted was to place the low density material first in the mortar followed by component of higher density. This is in conformity with accepted practice and avoids the settling of the denser solids to the bottom of the mixture.

The thermal analysis experiments were carried out on samples (5–16 mg) at a nominal heating rate of 10°C min^{-1} in an atmosphere of dry nitrogen at a flow rate of 50 mL min^{-1}. An alumina crucible was used for the samples with an empty alumina crucible of the same size for the reference.

Results and discussion

Time–temperature observation

A typical plot of time *vs.* temperature is shown in Fig. 1 for ascorbic acid as an example. If there is no perturbation due to reaction temperature of the sample during the course of an experiment, this plot should give a straight line increasing upward from left to right, and its slope should be equal to the heating rate desired. The plot of the first derivative of temperature with time should then give a constant value of the heating rate at all times. However, the endothermic or exothermic character of the reaction sequence can produce a perturbation in the heating rate, which is more readily apparent in the plot of the first derivative (dT/dt) *vs.* time (t). In

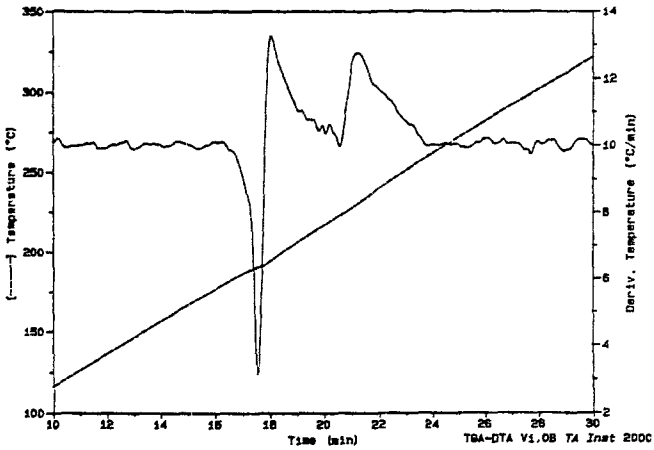

Fig. 1 The time–temperature plot and its first derivative for ascorbic acid

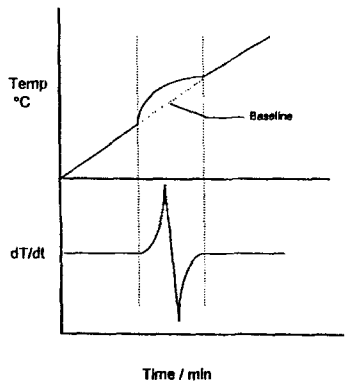

Fig. 2 The schematic diagram showing the exothermic perturbation

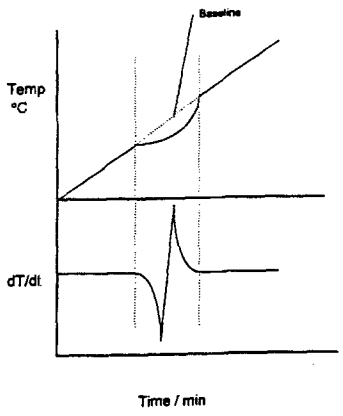

Fig. 3 The schematic diagram showing the endothermic perturbation

schematic form, the exothermic perturbation is illustrated in Fig. 2 while an endothermic event is illustrated in Fig. 3.

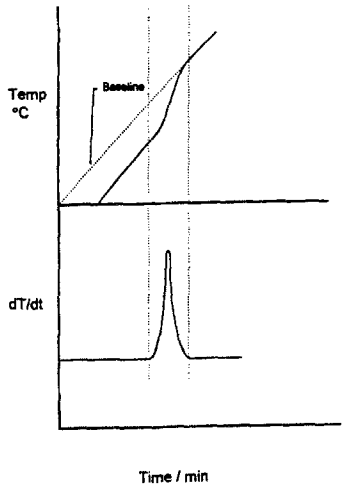

Fig. 4 A displacement of the baseline in the time–temperature plot for an endothermic shift

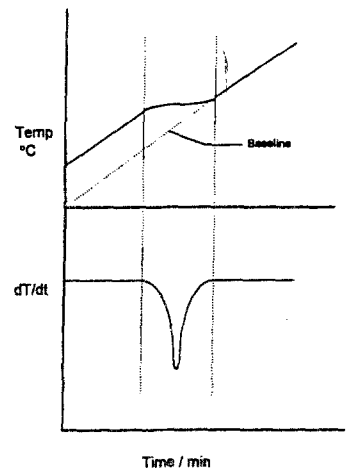

Fig. 5 A displacement of the baseline in the time–temperature plot for an exothermic shift

A displacement of the baseline in the time–temperature plot for an endothermic event is portrayed in Fig. 4. and for exothermic shift in Fig. 5. In many cases, these perturbations may not be noticed on the plot of temperature *vs.* time and only become apparent when the derivative (dT/dt) is plotted *vs.* time. The plot of the first derivative is explicit in allowing a decision to be made as to the endothermic or exothermic character of a chemical reaction process.

Single components

Ascorbic acid

It proved to be difficult to obtain good thermal analysis data for ascorbic acid. A carbonaceous residue was formed during and after melting (starting at 185.1 °C on the DTA plot with a peak maxima at 192.3 °C) and the solid residue of carbon could be confirmed by visual observation. The TG and DTG plot showed an initial mass loss on melting at 185.1 °C, a peak temperature on the DTG at 226.9 °C, with an initial sharp drop in mass followed by a gradual mass loss. The time–temperature plot is shown in Fig. 1 with a noticeable perturbation in the temperature region of 175 °C to 270 °C.

The shape of the perturbation shown in the first derivative plot is seen by examination of the schematic diagrams in Fig. 6 to correspond with an endothermic peak followed by a shoulder before the original temperature baseline is reached. Visual observation and simple tests confirmed that in nitrogen a solid residue of carbon resulted and it occurred from the liquid stage. The viscosity of the carbonaceous liquid mass increased rapidly with increasing temperature to cause comparatively large bubbles to form which finally solidified. On expansion these bubbles often reached the side or the top of the furnace and "stuck" the crucible to the side walls or the ceiling yielding an anomalous signal.

Microcrystalline cellulose

The time–temperature plot for microcrystalline cellulose is shown in Fig. 7. The perturbation on the time–temperature scale is hardly noticeable but is seen from the first derivative plot to be clearly an endothermic event.

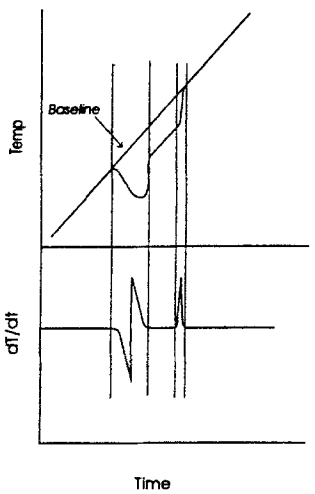

Fig. 6 The schematic diagram showing time–temperature perturbation due to an endothermic character with a shoulder and its corresponding first derivative

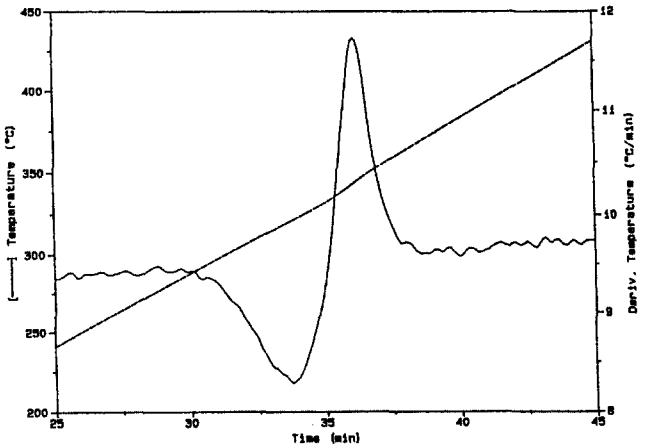

Fig. 7 The time–temperature plot and its first derivative for microcrystalline cellulose

Stearic acid

The TG plot for stearic acid shows a zero order reaction between 150°C and 300°C when the material is dissociated or evaporated. The energy associated with this kind of change is relatively small (87.3 kJ mol^{-1}) and the result is that the perturbation is also small. The derivative time–temperature plot in Fig. 8 shows an endothermic perturbation but it is only just above the normal haphazard modulations caused by the temperature control.

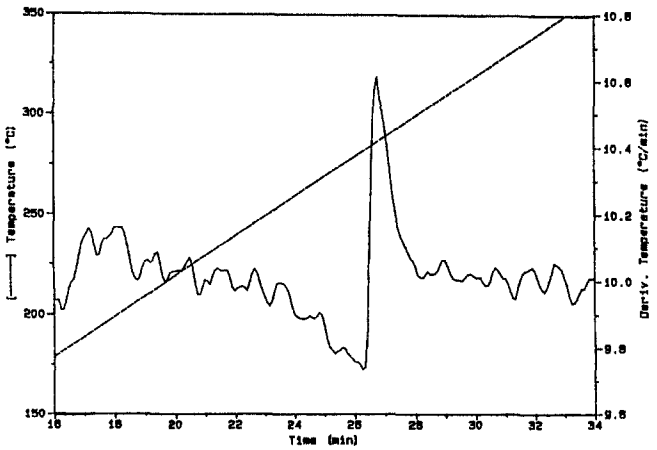

Fig. 8 The time–temperature plot and its first derivative for stearic acid

Magnesium stearate

The data for magnesium stearate collected in the form of a time–temperature plot in Fig. 9 shows a complicated pattern in the temperature range of 281–377°C,

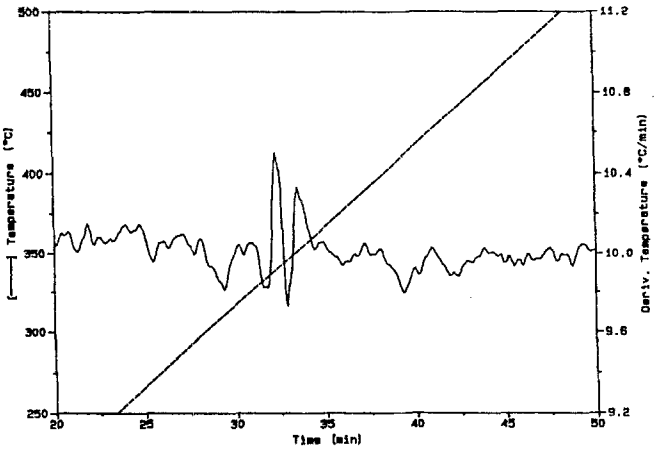

Fig. 9 The time–temperature plot and its first derivative for magnesium stearate

the region in which the main decomposition occurs. This agrees with the DTA plot which is also complicated. The reason is mainly because magnesium stearate sold for pharmaceutical use contains a significant proportion of other carboxylic acid salts of magnesium, particularly magnesium palmitate [1, 2].

Colloidal silicon dioxide

The silicon dioxide showed no perturbation either on the time–temperature plot or in its first derivative.

Binary mixtures

In this study, the binary mixtures are selected to show typical or interesting time–temperature plots from which information can be derived.

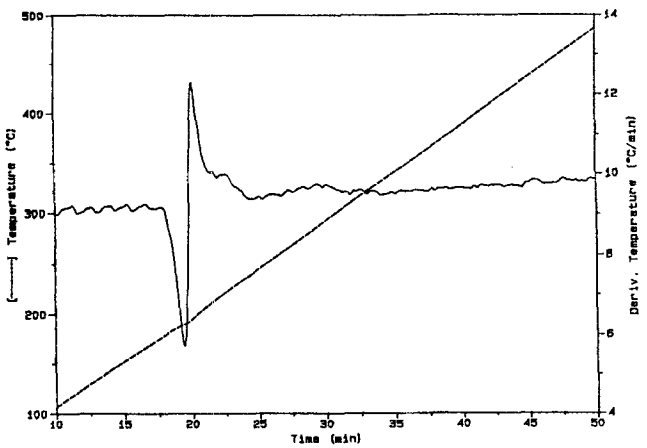

Fig. 10 The time–temperature plot and its first derivative for the binary mixture of ascorbic acid and microcrystalline cellulose

Figure 10 shows a plot of a binary mixture of ascorbic acid with microcrystalline cellulose. The perturbation is seen to show the endothermic ascorbic acid peak, and the microcrystalline cellulose is seen as a very small perturbation. Similar perturbations are seen for the binary mixture of ascorbic acid with stearic acid as well as silicon dioxide.

Table 1 Variation of the time–temperature perturbation as seen in the first derivative plots for ascorbic acid with various excipients

Compound	T_i/°C	T_m/°C	T_f/°C	$T_{DTA\ peak}$/°C
ascorbic acid	180.6	192.8	223.0	192.3
ascorbic acid+microcrystalline cellulose	177.5	193.2	240.4	193.8
ascorbic acid+stearic acid	186.2	194.7	251.7	192.4
ascorbic acid+silicon dioxide	172.6	192.2	222.0	190.7
ascorbic acid+magnesium stearate	complete overlap of signals made interpretation impossible			181.2

T_i initial temperature of perturbation; T_m mean value of peak maxima and minima; T_f final temperature of perturbation

Table 1 shows the variation in the ascorbic acid perturbation caused by the presence of the various excipients. It must be concluded that ascorbic acid can be detected in most mixtures but with magnesium stearate the overlap of the peaks in the plot of dT/dt *vs.* time make analysis impossible. With many of the organic excipients, the product was a carbonaceous residue formed as a coke. In such systems, the viscosity of the residue increased with temperature and the bubbles formed burst as seen in the portion of the binary mixture of ascorbic acid with stearic acid. The signal on the DTG is extremely small but the time–temperature signal shows strong exothermic perturbation as illustrated in Fig. 11.

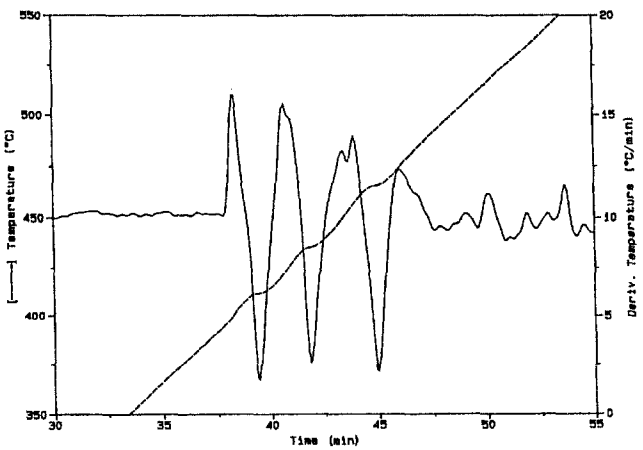

Fig. 11 The time–temperature plot and its first derivative for the binary mixture of ascorbic acid with stearic acid showing a bursting of viscous residue

Table 2 Variation of the time–temperature perturbation as seen in the first derivative plots for microcrystalline cellulose with various excipients

Compound	T_i/°C	T_m/°C	T_f/°C	$T_{DTA\ peak}$/°C
microcrystalline cellulose	286.1	332.9	368.7	335.0
microcrystalline cellulose+ascorbic acid	240.4	288.4	311.3	275.8
microcrystalline cellulose+stearic acid	259.0	334.0	367.1	338.6
microcrystalline cellulose+silicon dioxid	297.9	333.8	368.8	338.9
microcrystalline cellulose+magnesium stearate	complete overlap of signals made interpretation impossible			

T_i, initial temperature of perturbation; T_m mean value of peak maxima and minima; T_f, final temperature of perturbation

With mixtures containing microcrystalline cellulose, the time–temperature perturbation at 332.9°C is particularly susceptible to the presence of ascorbic acid and magnesium stearate but is not effected in the mixture of stearic acid or silicon dioxide. Figure 12 shows a typical plot of time–temperature signal for the binary mixture of microcrystalline cellulose with stearic acid endothermic perturbations. An examination of the microcrystalline cellulose time–temperature variation is given in Table 2.

In practice, a T_m value which is the mean value of the peak maxima and minima of the dT/dt signal is noted in Tables 1 and 2. There is now a good agreement between T_m and the peak temperature in the DTA plot. This would appear to be the case where the perturbation on the first derivative plot is symmetrical.

The final set of observations is a comparison of the size of the "normal or background" fluctuations with the perturbation associated with the physical and chemical transformations seen on the first derivative plots of time–temperature. These observations are summarized in Table 3 for single components and for some binary mixtures. It has to be noted that these fluctuations are reported as °C departure

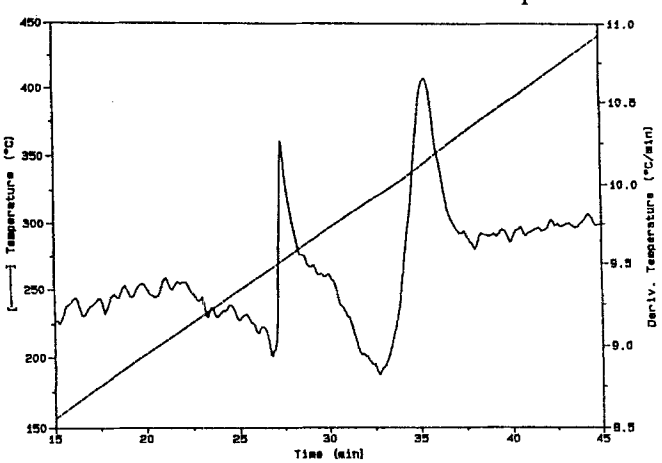

Fig. 12 The time–temperature plot and its first derivative for the binary mixture of microcrystalline cellulose with stearic acid showing 2 endothermic perturbations

Table 3 The background fluctuation of dT/dt compared with the signal associated with the heat transformation for single components and some binary mixture

Compound	Background fluctuation/°C	Fluctuation associated with heat transformation/°C
SINGLE COMPONENTS		
ascorbic acid	−0.73 to +0.47	−6.93 to +3.20
microcrystalline cellulose*	−0.89 to +0.26	−1.74 to +1.74
stearic acid	−0.07 to +0.05	−0.27 to +0.61
magnesium stearate	−0.20 to +0.05	−0.44 to +0.50
silicon dioxide	−0.14 to +0.10	no signal observed
BINARY MIXTURES		
ascorbic acid+microcrystalline cellulose	−0.10 to +0.14	−4.24 to +2.91
ascorbic acid+stearic acid	0.00 to +0.29	−8.38 to +5.90
ascorbic acid+magnesium stearate	−2.50 to +1.79	−6.55 to +13.93
ascorbic acid+silicon dioxide	−0.31 to −0.06	−1.33 to +1.39

Note: A minus sign indicates the departure from 10°C min^{-1} of the dT/dt signal downward and *vice versa* for a plus sign

* system showed an overall linear increase in dT/dt from 9.3 to 10.2°C

from the predetermined heating rate (10°C min^{-1}). It can be observed that the background fluctuation is smaller than the perturbation brought about by the physical and chemical transformations.

Conclusion

The time–temperature plots and the first derivative plot (dT/dt) *vs.* time indicate the endothermic or exothermic character of the thermal analysis data. This is shown here in the study on ascorbic acid and related excipients. It should be possible using such data to obtain this information when a TG unit is used by itself. The use of the simultaneous TG-DTA unit however showed that the T_m in Tables 1 and 2 agreed well with the peak temperature on the DTA signal. The method proved quite sensible in identifying heat changes when a bubble burst (Fig. 11). The background fluctuations were found to be significantly smaller in the plots of the first derivative against time but there was some indication of its dependence upon the material actually under study.

References

1 T. A. Miller and P. York, Int. J. Pharm., 23 (1985) 55.
2 Y. Wada and T. Matsubara, Thermochim. Acta, 196 (1992) 63.