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Pharmaceuticals

A THERMAL ANALYSIS STUDY OF IBUPROFEN

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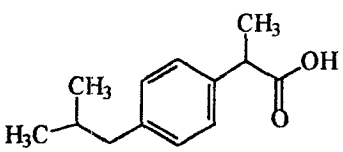
Abstract

Ibuprofen has been subjected to a TG/DTA study over the temperature range of 30 to 350°C in a flowing atmosphere of nitrogen. The heating rate and the flow rate were varied. The DTA shows a melting at around 80°C and boiling point range from 212 to 251°C depending upon the heating rate. The mass loss in the TG data confirms the evaporation of Ibuprofen between the *m.p.* and the normal *b.p.* Evaporation is limited to the surface area, which is a constant in the crucible holding the sample. The DTG plot shows clearly a zero order process which is consistent with the process of evaporation. The enthalpy of vaporization (ΔH_{vap}) calculated by Trouton's rule is found to be in the range of 42.7–46.1 kJ mol^{-1}. The E_{act} for the zero order reaction is in the range of 81.8–87.0 kJ mol^{-1} and is calculated by use of the derivative method. The value of E_{act} is about twice that for ΔH_{vap} in Ibuprofen and differs from other compounds, where $E_{act} \approx \Delta H_{vap}$. It is suggested that the Ibuprofen molecule is existing as a dimer in the liquid state and dissociates to a monomer in the vapor state.

Keywords: enthalpy of vaporization, Ibuprofen, zero order reaction

Introduction

Ibuprofen is a non-steroidal anti-inflammatory drug. Its systematic name is α-methyl-4-(2-methylpropyl)benzeneacetic acid, with the formula



with an empirical formula $C_{13}H_{18}O_2$ and a molecular mass of 206.27. The melting point of this colorless, crystalline material is commonly quoted as 75–77°C [1].

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Studies using differential scanning calorimetry (DSC) show that the degree of crystallinity and the nature of the solvents used for crystallization have an effect on the melting point [2]. It has also been demonstrated using a conventional melting point apparatus that the Ibuprofen crystallized from various solutions or dispersions involving propylene glycol, diethylene glycol, polyethylene glycol (PEG) 3000, PEG 4000, glycerin, etc. showed variations in the melting point which could be related to crystal habit [3]. Romero *et al.* [4–5] suggested that the stereochemical aspects of Ibuprofen affect the properties of the samples and the crystal habit. They showed in particular that the (+)-isomer had a lower melting point than the racemate. In one of their publications Romero and Rhodes [5] were able to produce a phase diagram showing the formation of a true racemic compound which has been substantiated in somewhat more detail by Dwivedi [6]. Commercial samples of the (+)-form and the racemic form are available; Dwivedi constructed the entire condensed phase diagram of the (+) and (–) form and the racemic. The (+) and the (–) isomers have a low *m.p.* around 47–54 °C and the racemic compound a *m.p.* around 76–78 °C. In our study, the melting point was in the range of 75–85 °C, and was described as racemic. The project reported here concerns the marked evaporation which occurs between the *m.p.* and the reported boiling range.

Experimental

Materials

The material was supplied by Pharmacia & Upjohn Inc. The material was described as racemic and in view of literature reported can be regarded as a racemic compound.

Epuipment and procedure

The equipment used to study evaporation was a Simultaneous TGA-DTA unit (SDT 2960 Simultaneous TGA-DTA, TA Instruments). The thermal analysis data was collected between ambient and 350 °C, and the thermogravimetry plot (TG), derivative thermogravimetry data (DTG), and differential thermal analysis (DTA) were determined. Three sets of experiments can be found in this study. Firstly, six isothermal experiments with a nitrogen flow rate of 50 mL min^{-1} were carried out at the temperature of 130 to 180 °C with 10 °C increment. Secondly, six linear ramping experiments varying in heating rates from 2 to 12 °C min^{-1} with 2 °C increment were performed at a constant nitrogen flow rate of 50 mL min^{-1}. Finally, six linear ramping experiments varying in nitrogen flow rates from 50 to 150 mL min^{-1} with 20 mL increment were determined at a constant heating rate of 6 °C min^{-1}. The sample mass were in a range of 10.26 to 14.03 mg. The platinum crucible with a capacity of 110 μL was used to contain the Ibuprofen sample and the reference crucible was left empty.

Results and discussion

Isothermal experiments

Figure 1 represents an isothermal run for Ibuprofen at a flow rate of 50 mL min^{-1} in dry nitrogen at temperature of 130°C. Similar experiments were reported at temperatures of 140, 150, 160, 170, 180°C. These results showed a zero order reaction. As the Ibuprofen was evaporating, the % weight represents the % reactant remaining. Evaporation from a platinum crucible shows a constant area of surface

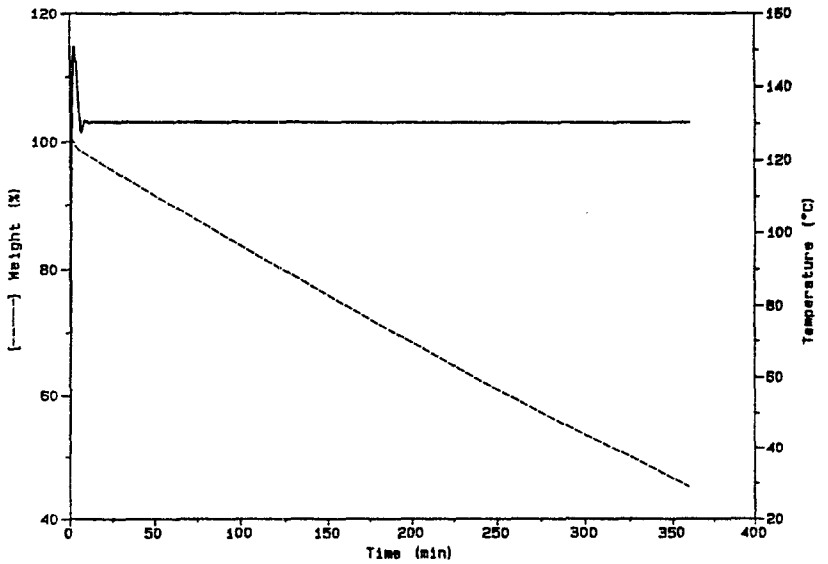

Fig. 1 The isothermal plot of mass *vs.*time for racemic Ibuprofen at a temperature of 130°C together with a plot of temperature *vs.* time

Table 1 The results of evaporation of racemic Ibuprofen at isothermal temperature

T/K	1/*T*/ K^{-1}	@Coef. of evap. dw/dt = slope	ln(dw/dt)	+Coef. of evap. per unit area/ K_A
403	2.48×10^{-3}	1.91×10^{-2}	-3.96	1.08×10^{-3}
413	2.42×10^{-3}	3.43×10^{-2}	-3.37	1.95×10^{-3}
423	2.36×10^{-3}	7.08×10^{-2}	-2.65	4.02×10^{-3}
433	2.31×10^{-3}	10.62×10^{-2}	-2.24	6.02×10^{-3}
443	2.26×10^{-3}	18.15×10^{-2}	-1.71	1.03×10^{-2}
453	2.21×10^{-3}	27.99×10^{-2}	-1.27	1.59×10^{-2}

@Coefficient of evaporation has a unit of mg min^{-1},
+$K_A = (dw/dt)\cdot(1/\text{surface area of the crucible})$; K_A has a unit of mg cm^{-2} s^{-1}

between the liquid and the air. A zero order reaction for evaporation is to be expected because of the surface control of the evaporation process. The plot of temperature *vs.* time allows the nominal temperature to be converted to a real temperature reading. The isothermal temperature and the coefficient of evaporation in each case are summarized in Table 1.

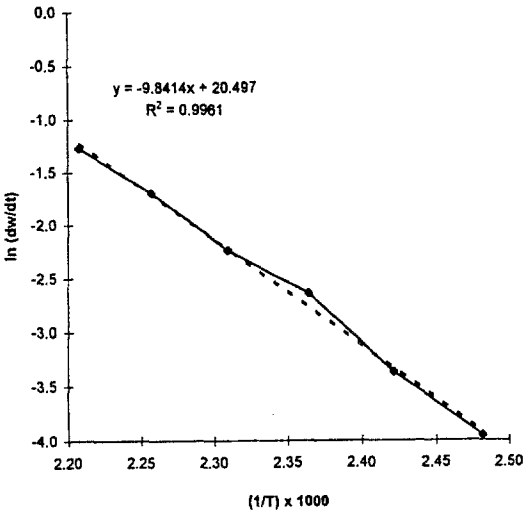

Fig. 2 A plot of ln(dw/dt) *vs.* $1/T$ for isothermal experiment using the data shown in Table 1 for racemic Ibuprofen

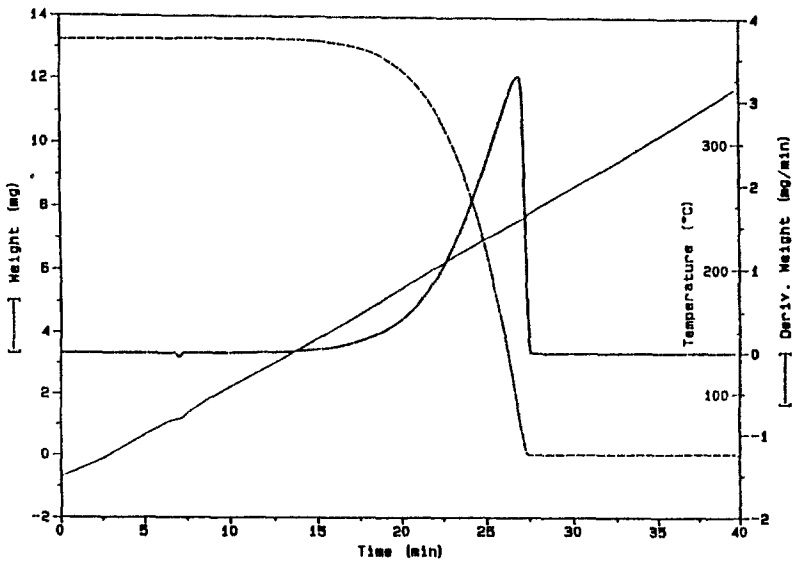

Fig. 3 The linear ramping plot of mass *vs.* time for racemic Ibuprofen at a heating rate of 8 °C min^{-1} in nitrogen with its first derivative and a plot of temperature *vs.* time superimposed

The coefficient of evaporation would be more meaningful if expressed as milligrams per square centimeter per second (mg cm^{-2} sec^{-1}). Thus a separate column is given in Table 1 by reference to the surface from which evaporation is occurring, namely the cross-sectional area of the crucible used in the isothermal experiment. Accordingly, the measurements are made from plots of mass (w in mg) *vs.* time (t in min). A plot of $\ln(dw/dt)$ *vs.* $1/T$ where T is temperature in Kelvin can be constructed. The energy of activation for evaporation was measured from the slope. The Arrhenius type equation is of the form:

$$\ln\frac{dw}{dt} = \ln A - \frac{E}{RT} \tag{1}$$

where A - pre-exponential parameter, E - activation energy of evaporation
A plot of $\ln(dw/dt)$ *vs.* $1/T$ for this calculation is shown in Fig. 2. From these plots, the activation energy and the pre-exponential parameter are 81.8 kJ mol^{-1} and 7.98×10^8 respectively.

The melting point and the boiling point of Ibuprofen has already been noted. It will be observed that the evaporation is occurring from the liquid surface. The literature value for the enthalpy of fusion [4] is around 25–26 kJ mol^{-1} and the enthalpy of sublimation measured by Knudsen effusion technique [7] is 121 kJ mol^{-1}. The enthalpy of vaporization (ΔH_{vap}) for Ibuprofen is 42.7–46.1 kJ mol^{-1} calculated by the use of Trouton's rule [8]. Trouton's rule as stated in all Physical Chemistry text books is simply that $\Delta H_{vap}/T_b$ is approximately 88 J K^{-1} mol^{-1} for almost all liquid (T_b is the normal boiling point in Kelvin).

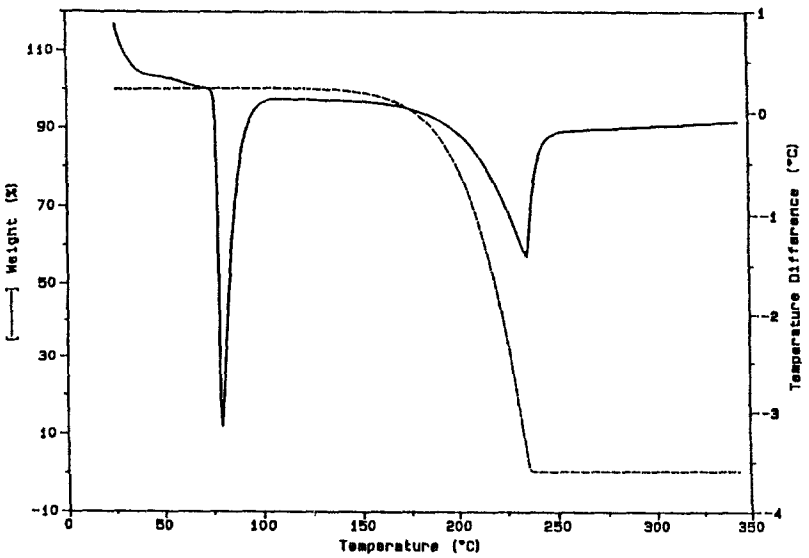

Fig. 4 The TG and DTA plot of racemic Ibuprofen at a heating rate of 6°C min^{-1} in nitrogen

Ramping experiments

In Fig. 3, there are three plots: weight (w in mg) *vs.* time (t in min.), dw/dt plot *vs.* time and temperature *vs.* time. The DTG plots of different kinetic exressions assume characteristic shapes that enables the expression to be identified [9–10]. The dw/dt plot is characteristic of a zero order reaction and the results are interpreted on this basis. A DTA plot superimposed on the TG plot (see as an example Fig. 4) shows that the evaporation occurs between the melting point and the boiling point. The collected data for the melting point and boiling point is recorded in Table 2. It should be noted that the melting points recorded in this study are the DTA peak temperature. A close inspection of this data we see that the boiling point obviously varies with the heating rate in a systematic fashion. Another observation is that, at

Table 2 Physical data from Ibuprofen ramping experiments with varying heating rate (β)

β/°C min^{-1}	*m. p.*/°C	*b. p.*/°C
2	78.28	212.05
4	79.14	224.69
6	80.07	235.72
8	80.23	240.93
10	80.77	245.19
12	81.40	251.35

Table 3 Arrhenius parameters of Eq.(1) for Ibuprofen ramping experiments with varying heating rate (β)

β/°C min^{-1}	A	E/kJ mol^{-1}
2	1.55×10^9	84.04
4	1.02×10^9	82.56
6	1.29×10^9	83.37
8	1.73×10^9	84.48
10	3.13×10^9	86.95
12	1.17×10^9	83.00

Table 4 Physical data from Ibuprofen ramping experiments with varying N_2 flow rate

Flow rate/ mL min^{-1}	*m. p.*/°C	*b. p.*/°C
50	80.07	235.72
70	79.33	233.65
90	79.09	232.21
110	79.33	232.21
130	79.33	231.49
150	79.33	230.77

Table 5 Arrhenius parameters of Eq.(1) for Ibuprofen ramping experiments with varying N_2 flow rate

Flow rate/mL min^{-1}	A	E/kJ mol^{-1}
50	1.29×10^9	83.37
70	9.17×10^9	82.11
90	1.35×10^9	83.64
110	1.28×10^9	83.44
130	1.46×10^9	83.84
150	1.52×10^9	84.06

the melting point there is a small perturbation clearly seen in plots of dw/dt *vs.* t. A speculation on this point is that it represents occluded moisture being lost at the melting point. The coefficient of evaporation at any temperature can be obtained directly from the plot of dw/dt *vs.* time.

The Arrhenius parameters for various values of heating rate are recorded in Table 3. There is no correlation between heating rate, which range from 2 to 12°C, and the activation energy.

From the ramping experiments in different N_2 flow rate, the DTA peaks for melting points and boiling points were recorded in Table 4. Plots of ln(dw/dt) *vs.* $1/T$ as mentioned earlier were constructed yielding the Arrhenius parameters as seen in Table 5. Again, there is no significant correlation between N_2 flow rates, which range from 50 to 150 mL min^{-1}, and the activation energy.

Conclusion

The coefficient of evaporation depends on the method used. In terms of dw/dt, the coefficient of evaporation (mg min^{-1}) varies from 1.91×10^{-2} to 27.99×10^{-2} corresponding to the temperature of 403 K to 453 K, respectively. The energy of activation (E_{act}) and the pre-exponential factor (A) in the isothermal experiments for evaporation are 81.8 kJ mol^{-1} and 7.98×10^8, respectively. It was found that the ramping experiments show the E_{act} in the range of 82.6–87.0 kJ mol^{-1} and A in the range of 1.02×10^9 to 3.13×10^{-9} depending on the heating rate. The evaporation measurements started at the melting point and continued until the mass loss was complete from a constant area of interface. The data between the ramping experiments and the isothermal experiments show agreement. The E_{act} calculated in ramping experiments with various values of the N_2 flow rates are also in the same range of other calculated values.

The energy of vaporization is seen to be in the region of 82 to 87 kJ mol^{-1}. The process of evaporation is endothermic and it can be seen that in the case of Ibuprofen, the value of E_{act} is about twice that for ΔH_{vap}. In instances of calculating E_{act} for other components [11–12],E_{act} is equal to ΔH_{vap}. This suggests that Ibuprofen exists as a dimer in the liquid state and dissociated to a monomer in the vapor state.

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