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An approximative method for the evaluation of the partial heats of fusion of the once folded and extended modification of poly(ethylene oxide) 6000

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Abstract

PEG 6000 can exist in an once folded and in an extended modification. The small difference in the melting temperatures of the two forms results in a significant overlap of the corresponding melting peaks. After completion of the phase transition the shape of a melting peak (second branch) registered by DSC is determined by the relaxation of the measuring system only. Therefore it is possible to separate overlapping melting peaks by means of the standardised relaxation function of the DSC system. This approach was used to separate the overlapping melting peaks of the two PEG modifications. The partial heats of fusion as well as the peak maxima characterising the individual melting processes were determined from the separated peaks. Furthermore, this technique enables an observation of changes in the modifications of PEG and could possibly be a useful tool for investigations of other polymers which show similar characteristics. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Poly(ethylene oxide); Once folded modification; Extended modification; Thermal analysis; Deconvolution; Solid dispersions

1. Introduction

In the manufacture of solid dispersions PEG 6000, a water soluble polymer, is often used as a carrier for dispersed active ingredients [1]. Many polymers are sensitive to thermal treatment. The thermal history induced by the manufacturing process of solid dispersions is of great importance for the conformation of the PEG chains and in consequence for the amount of stored energy [2]. For PEG 6000 Buckley and Kovacs [3] described an extended (n_0), once (n_1) and twice folded (n_2) modification. The twice folded chains are thermodynamically unstable and extend spontaneously during thermal treatment. The forms with n_0 and n_1 were found to be metastable. If both modifications (n_0 and n_1) exist simultaneously in a crystal, they will remain in their original state until complete melting [3]. The extension of the once folded chains is a very slow process for PEG 6000. Therefore with a heating rate of 2 K min^{-1}, as used in our investigations, such extensions could be excluded [3,4]. On the other hand a very detailed characterisation of the melting process was possible under those conditions. The formation of the modifications n_0 and

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n_1 is also dependent on the molecular weight distribution and in consequence on the polydispersity index (PI) of PEG [4]. An overlapping of the melting ranges of these modifications could be observed due to a broader molecular weight distribution of the polymer [4]. This overlapping makes it difficult to determine the heat of fusion for each of both modifications. The present paper suggests a method for solving this problem.

2. Experimental

2.1. Materials

PEG 6000 (Riedel-de-Haën, D-Seelze) has been of pharmaceutical quality as described in Ph. Eur. [5]. Molecular weight determination (with MALDI-TOF-MS) revealed for $M_w = 5570$ g mol^{-1}, $M_n = 4580$ g mol^{-1} and PI $= 1.22$ [4]. Indium (purity: 99.999%) and nitrogen gas (purity: 99.999%) were supplied by Fluka Chemie AG (CH-Buchs) and Messer (D-Griesheim), respectively.

2.2. Apparatus and procedures

For all measurements a TG-DSC 92-12 (Setaram®, F-Lyon) including the "Bitasking software" of Setaram® was used. Samples of 20 mg were investigated in platinum crucibles at a constant heating rate of 2 K min^{-1} in a nitrogen atmosphere (40 mm constant flow) in order to avoid oxidation. The detection limit of the TG-balance is 1 μg. The DSC was calibrated with indium as described by Hoehne et al. [6] and Cammenga et al. [7].

To standardise the thermal history of PEG all samples were prepared according to the following procedure. Irregular polymer flakes were put into weighing bottles of glass, each equipped with a small magnetic stirring bar. These tightly closed glass bottles were placed in a preheated (67°C) heating chamber (Memmert, D-Schwabach) for a total of 60 min. After 30 and 45 min the heating proces was interrupted for 5 min in order to allow for an intensive stirring of the molten material on preheated (70°C) magnetic stirrers. To standardise the crystallisation the glass bottles containing the molten polymer were placed in a bath with silicon oil at a constant temperature of 10°C for 60 min. Thereafter the closed weighing bottle was stored in an desiccator ca. at room temperature overnight. The solidified PEG was carefully ground with a pistil and mortar and fractionated by vibrator sieving (stainless steel microsieves DIN/ISO 3310/1; Retsch GmbH, D-Haan). For all subsequent measurements samples of the particle size fraction 125–250 μm were used.

3. Results and discussion

Fig. 1 shows the heatflow associated with the melting of PEG 6000 which was prepared as described above. As can be seen it consists of two overlapping peaks. According to Buckley and Kovacs [3] the once folded form melted at a lower temperature than the extended one, but the two processes are too close together for a simple separation.For this reason a deconvolution of the original melting curve was carried out.

The deconvolution of a time-dependent signal has been described by Hemminger et al. [8]:

$$U_{\text{in}}(t) = U_{\text{out}}(t) + \tau_1 \times \frac{\mathrm{d}U_{\text{out}}(t)}{\mathrm{d}t}, \tag{1}$$

where $U_{\text{in}}(t)$ is the input signal, $U_{\text{out}}(t)$ the output signal, τ_1 the time constant of the instrument/s. τ_1 was determined by linear regression of the standardised relaxation functions of several indium melting peaks as suggested by Hemminger et al. [8]:

$$\tau_1 = 25.2\ (\pm 0.25)s \quad (\mathrm{SD}_{\text{rel}} = \pm 0.9\%\ n = 3).$$

However, with the DSC the heatflow is determined in dependency on the temperature. Therefore the heating rate has to be considered in Eq. (1):

$$\frac{\mathrm{d}Q_{\text{corr.}}}{\mathrm{d}t} = \frac{\mathrm{d}Q_0}{\mathrm{d}t} + \beta \times \tau_1 \frac{\mathrm{d}\left(\frac{\mathrm{d}Q_0}{\mathrm{d}t}\right)}{\mathrm{d}T}, \tag{2}$$

where $\mathrm{d}Q_{\text{corr}}/\mathrm{d}t$ is the corrected heatflow (mW), $\mathrm{d}Q_0/\mathrm{d}t$ the original heatflow (mW), β heating rate (K/s), T temperature (K). Eq. (2) was used for the deconvolution, which is shown in Fig. 2. The deconvolution led to an intensification of the shoulder due to the additive term of the derivative (1. derivative, Fig. 2). Nevertheless, an exact splitting was impossible because of the still unknown peak maximum of the once folded modification. Therefore a method for finding this

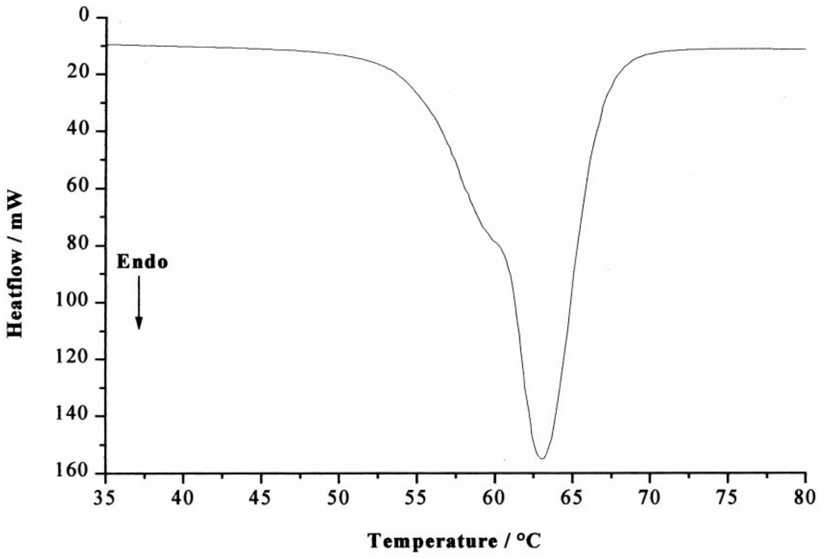

Fig. 1. Original melting peak of PEG 6000 (overlapping of the melting ranges of the once folded and extended modification).

hidden peak maximum ($T_{\mathrm{HiddenMax1}}$) has been developed and in consequence used for evaluating the heats of fusion of each modification.

For melting processes of pure metals and many low molecular weight components, the second branch of the melting peak (after peak maximum) contains mainly information about the relaxation of the DSC instrument. Although for polymers this is not completely valid, the shape of the second branch can be approximated by an exponential function. Starting from the relaxation function ($(\mathrm{d}Q_{\mathrm{Relax}}/\mathrm{d}t)(T)$), which has been used for the evaluation of τ, it should be

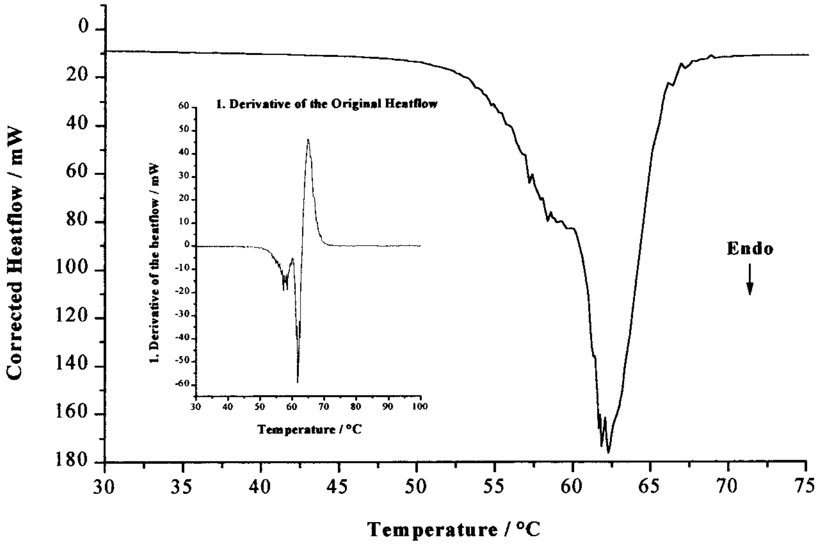

Fig. 2. Deconvolution of the original melting peak of PEG 6000 (in addition: 1. derivative).

Table 1
Regression data of temperatures and corresponding logarithmic heatflows of $(\mathrm{d}Q_{\mathrm{Relaxl}}/\mathrm{d}t)(T)$ taken from different melting experiments with indium (Eq. (3)) (SD in brackets)

Indium samples (mg)	A	B	Correlation *r*
19.763	185.54 (±2.31)	−1.14478 (±0.01450)	0.99824
27.563	193.19 (±1.42)	−1.18927 (±0.00890)	0.99939
33.354	176.05 (±1.84)	−1.07788 (±0.01149)	0.99870

possible to use this function to find $T_{\mathrm{HiddenMax1}}$ in the melting diagram of PEG 6000. If $(\mathrm{d}Q_{\mathrm{Relax}}/\mathrm{d}t)(T)$ is an exponential function, it will be described by the following equation:

$$\ln\left(\frac{\mathrm{d}Q}{\mathrm{d}t}\right) = \ln A + B \times T. \tag{3}$$

The regression data in Table 1 show that $(\mathrm{d}Q_{\mathrm{Relax}}/\mathrm{d}t)(T)$ is really based on an exponential function given in Eq. (3). Therefore $(\mathrm{d}Q_{\mathrm{Relax}}/\mathrm{d}t)(T)$ could be described generally by:

$$\frac{\mathrm{d}Q_{\mathrm{Relax}}}{\mathrm{d}t} = A \times \mathrm{e}^{B \times T}. \tag{4}$$

Considering the small SD given in Table 1 the average value of $\overline{B} = -1.13731$ has been used in the following steps.

The peak of the once folded form can be described by the following Equation. For orientation and a comprehensive overview see also Fig. 3:

$$\frac{\mathrm{d}Q_1}{\mathrm{d}t}(T) = \frac{\mathrm{d}Q_{1a}}{\mathrm{d}t}(T) + \frac{\mathrm{d}Q_{1b}}{\mathrm{d}t}(T), \tag{5}$$

where$(\mathrm{d}Q_1/\mathrm{d}t)(T)$ is the heatflow as function of the temperature of the once folded modification, $(\mathrm{d}Q_{1a}/\mathrm{d}t)(T)$ the function starting from the baseline until $T_{\mathrm{HiddenMax1}}$ is reached, $(\mathrm{d}Q_{1b}/\mathrm{d}t)(T)$ the function starting from $T_{\mathrm{HiddenMax1}}$ until the baseline value is recovered (=relaxation of the instrument, $(\mathrm{d}Q_{\mathrm{Relax}}/\mathrm{d}t)(T)$, in which $(\mathrm{d}Q_{1a}/\mathrm{d}t)(T)$ is identical with the original measured curve $(\mathrm{d}Q_{\mathrm{Original}}/\mathrm{d}t)(T)$ until reaching $T_{\mathrm{HiddenMax1}}$.

For the determination of $T_{\mathrm{HiddenMax1}}$ it is necessary to transform $(\mathrm{d}Q_{\mathrm{Relax}}/\mathrm{d}t)(T)$ into the original melting

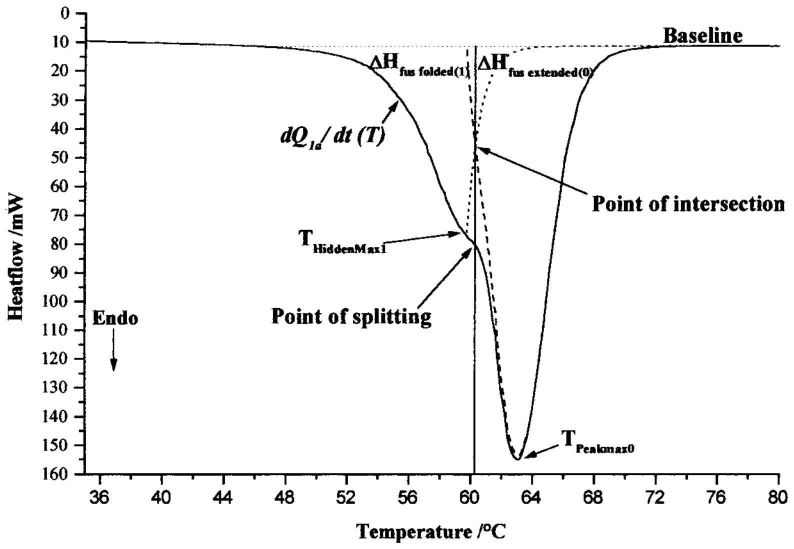

Fig. 3. Splitting of the melting peak of PEG 6000 for evaluating the heats of fusion for each modification ($\Delta H_{\mathrm{fusfolded(1)}}$: heat of fusion of the once folded form, $\Delta H_{\mathrm{fusextended(0)}}$: heat of fusion of the extended form: (—) $(\mathrm{d}Q_{\mathrm{Original}}/\mathrm{d}t)(T)$, (—) $(\mathrm{d}Q_0/\mathrm{d}t)(T)$, (···) $(\mathrm{d}Q_{1\mathrm{b}}/\mathrm{d}t)(T)$).

diagram of PEG. In this case the temperature differences between the starting point (at $T_{\mathrm{HiddenMax1}}$) of $(\mathrm{d}Q_{\mathrm{Relax}}/\mathrm{d}t)(T)$ and the respective temperature values (T_i) of the original melting curve of PEG have to be considered:

$$\frac{\mathrm{d}Q_{\mathrm{Relax}}}{\mathrm{d}t}(T) = A \times \mathrm{e}^{-1.13731T_i - T_{\mathrm{HiddenMax1}}}. \qquad (6)$$

Based on the thesis, that the relaxation function starts from $T_{\mathrm{HiddenMax1}}$ the second branch of the curve $(\mathrm{d}Q_{1b}/\mathrm{d}t)(T)$ will be delivered under consideration of Eq. (6) by:

$$\frac{\mathrm{d}Q_{1b}}{\mathrm{d}t}(T) = \frac{\mathrm{d}Q_{\mathrm{HiddenMax1}}}{\mathrm{d}t} \times \mathrm{e}^{-1.13731T_i - T_{\mathrm{HiddenMax1}}} + \frac{\mathrm{d}Q_{\mathrm{Baseline}}}{\mathrm{d}t}, \qquad (7)$$

where $(\mathrm{d}Q_{\mathrm{HiddenMax1}}/\mathrm{d}t)$ is the heatflow value of the hidden peak maximum of the once folded modification, $(\mathrm{d}Q_{\mathrm{Baseline}}/\mathrm{d}t)$ the heatflow value of the baseline of the original curve $(\mathrm{d}Q_{\mathrm{Original}}/\mathrm{d}t)(T)$. But there is one exception for $T_{\mathrm{HiddenMax1}}$ itself: For a correct starting point of $(\mathrm{d}Q_{1b}/\mathrm{d}t)(T)$ it is necessary that $(\mathrm{d}Q_{\mathrm{Baseline}}/\mathrm{d}t)$ is subtracted from the calculated heatflow value $(\mathrm{d}Q_{\mathrm{HiddenMax1}}/\mathrm{d}t)$. This exception is only valid for the point $T_{\mathrm{HiddenMax1}}$, because this point is also a part of $(\mathrm{d}Q_{\mathrm{Original}}/\mathrm{d}t)(T)$.

The peak of the extended form $(\mathrm{d}Q_0/\mathrm{d}t)(T)$ results from the difference:

$$\frac{\mathrm{d}Q_0}{\mathrm{d}t}(T) = \frac{\mathrm{d}Q_{\mathrm{Original}}}{\mathrm{d}t}(T) - \frac{\mathrm{d}Q_1}{\mathrm{d}t}(T) + \frac{\mathrm{d}Q_{\mathrm{Baseline}}}{\mathrm{d}t}. \qquad (8)$$

The peak maximum of $(\mathrm{d}Q_0/\mathrm{d}t)(T)$ — T_{peakmax0} — corresponds to the peak maximum of the original curve $(\mathrm{d}Q_{\mathrm{Original}}/\mathrm{d}t)(T)$. Fig. 3 shows how the peak of the once folded form can be extracted by means of Eq. (7) from the overall melting peak given in Fig. 1: $T_{\mathrm{HiddenMax1}}$ was determined empirically by searching the optimal point in the original curve $(\mathrm{d}Q_{\mathrm{Original}}/\mathrm{d}t)(T)$. Criterion for its fixing has been the optimal adaptation of the both resultant (calculated) curves to the original one (Fig. 3). Additionally, Fig. 4 gives two examples for fixings of $T_{\mathrm{HiddenMax1}}$ leading not to an optimal adaptation $(\mathrm{d}Q_{1b}/\mathrm{d}t)(T)$ intersects with $(\mathrm{d}Q_0/\mathrm{d}t)(T)$ at one point (Point of intersection). A normal line drawn through that point of intersection leads to the point of splitting in $(\mathrm{d}Q_{\mathrm{Original}}/\mathrm{d}t)(T)$. The sums of both corresponding areas formed by the normal line and each calculated curve are equal, so that the whole

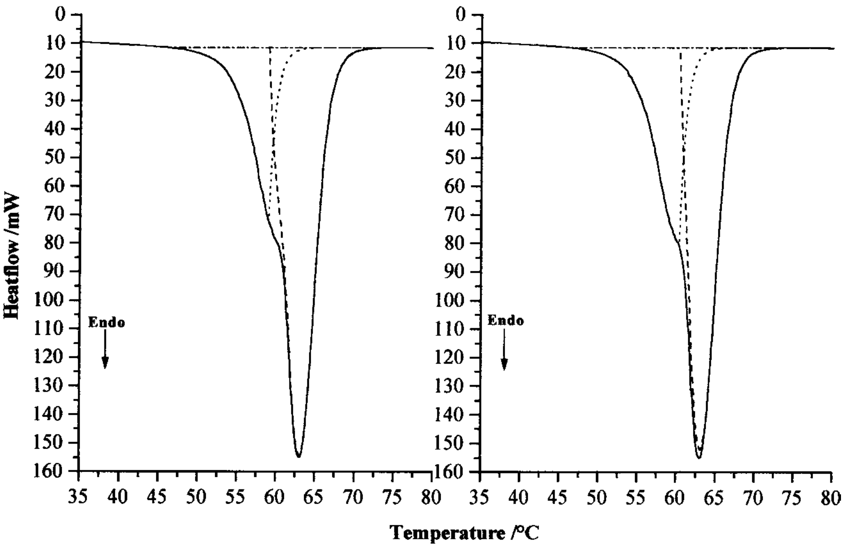

Fig. 4. Splitting of the melting peak of PEG 6000: Two examples for a fixing of the $T_{\mathrm{HiddenMax1}}$ leading not to an optimal (Fig. 3) adaptation (—— $(\mathrm{d}Q_{\mathrm{Original}}/\mathrm{d}t)(T)$, ——— $(\mathrm{d}Q_0/\mathrm{d}t)(T)$, ······· $(\mathrm{d}Q_{1\mathrm{b}}/\mathrm{d}t)(T)$).

Table 2
Thermoanalytical characteristics of the melting endotherm of PEG 6000 (partial heats of fusion of the once folded (1) and the extended (0) modification) (SD in brackets, $n = 3$)

$\Delta H_{\mathrm{fus(total)}}$ (kJ mol^{-1})	$\Delta H_{\mathrm{fusfolded(1)}}$ (kJ mol^{-1})	$\Delta H_{\mathrm{fusextended(0)}}$ (kJ mol^{-1})	T_{onset} (°C)	$T_{\mathrm{HiddenMax1}}$ (°C)	T_{Peakmax0} (°C)
1009 (±15)	351 (±7)	658 (±13)	54.4 (±0.2)	59.7 (±0.6)	63.1 (±0.2)

area under the curve remains constant. This is important because the area under the original curve represents the whole enthalpy independent of the temporal progress of single processes.

After splitting of the original peak, the two resulting areas represent the heats of fusion of each modification. Integration of each area delivers the heat of fusion value of the once folded and the extended form, respectively. Table 2 gives a comprehensive overview: As can be seen from Table 2, with this technique it is possible to achieve a relatively exact evaluation of the partial heats of fusion ($\mathrm{SD_{rel}} = \pm 2\%$).

4. Conclusions

A method is suggested to overcome the difficulty of the overlapping melting peaks due to a broader molecular weight distribution of PEG 6000. With this method it is possible to separate the melting peaks and to evaluate the partial heats of fusion belonging to the once folded and extended modification of PEG 6000. Furthermore, this technique enables an observation of changes (enthalpy) in each modification of the polymer. For example, the method has been used for splitting the melting peaks (PEG) of solid dispersions. Subsequently it was possible to monitor the incorporation of an active ingredient into the different modifications of PEG due to changes in the partial heats of fusion [4]. Therefore the suggested method could possibly be a useful tool for investigations of other polymers, which show similar characteristics.

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