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The definition of ibuprofen melting thermodynamic parameters with differential scanning calorimetry

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ABSTRACT

In the article the ibuprofen enthalpy of fusion and melting temperature data of different researches were analyzed. It was established that there were significant discrepancies between these data. Melting enthalpy and temperature corrections were carried out with Russian high-selective differential scanning calorimeter DSC-500. The experimental method of ibuprofen melting temperature and enthalpy definition was described. The calibration and results processing methods are also described. Melting entropy and cryoscopic constant were also calculated.

KEYWORDS

Ibuprofen;
Melting temperature;
Enthalpy of fusion;
Melting entropy;
Cryoscopic constant;
Differential scanning calorimetry.

It was found that eutectic type interaction can cause dissolution rate rise of hardly soluble substance in the system[1]. And so research eutectic compositions of different dimensionality is of pharmaceutics science interests. The eutectic compositions research can be performed with experimental or calculation methods. Experimental methods are based on the time-consuming carrying out of compositions melting temperature investigation with different possible compositions. But a good advantage of this method is that it allows to define eutectic composition and melting temperature more precisely. Experimental methods labor intensity is caused with a big quantity of experiments and their duplications. Besides, the precision of experimental methods is depended on equipment quality that can be very expensive. Experimental researches carry out for a longer time. Nevertheless the eutectic experimental research is performed now in different countries. Experience is undoubtedly the base source of our knowledge about substances and processes property.

Calculation methods give good results at eutectic composition and temperature determination when eutectic is possible. For medicinal eutectic calculation we used the algorithm[2]. This algorithm allows to calculate eutectic compositions and melting temperatures as in simple cases so in cases with solid solutions, polymorphism and components decomposition having. The simple case is based on Shreder – Le Chatelier equation:

$$\begin{cases} \ln x_1 = \dfrac{\Delta H_{fus,1}(T_e - T_{m,1})}{R \cdot T_e \cdot T_{m,1}}; \\ \ln x_2 = \dfrac{\Delta H_{fus,2}(T_e - T_{m,2})}{R \cdot T_e \cdot T_{m,2}}; \\ x_1 + x_2 = 1. \end{cases}$$

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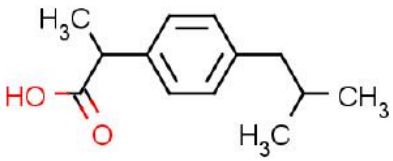
Where: x_1 - molar fraction of 1st component, x_2 - molar fraction of 2nd component, ΔH_{fus1} – 1st component enthalpy of fusion, ΔH_{fus2} - 2nd component enthalpy of fusion, T_e – eutectic temperature, T_{m1} - 1st component temperature of fusion, T_{m2} - 2nd component temperature of fusion, R - universal gas constant, 8,31 J (mol K).

Base difficulty at the theoretic calculation methods using is a lack of precise information for calculation. In our case there are a lack of melting temperature and enthalpy. It is logically to find these characteristics from literature, but unfortunately most of thermodynamic characteristics are absent or have a very contradictory character.

Melting temperatures and enthalpies can be predicted, but unfortunately there has not been universal method that can give precise results for different type of substances. Furthermore medicinal substances are often complex heterocyclic, with condensed nuclear, for which melting characteristics prediction is more complicated. But last time precise Chickos method has appeared and it has been used in this article, but it allows to determine enthalpy of fusion using melting temperature. Therefore there is an impelling need of these characteristics independent determination with available instrument. In our work medicinal substances melting thermodynamic characteristics, that it is necessary for eutectic compositions and temperatures prediction are determined and improved with unique differential scanning calorimeter of heat flow DSC-500.

In this article we study the situation with ibuprofen individual pure substance. Ibuprofen has chemical name as 2-(4-isobutylphenyl)propionic acid. It is widespread in medicinal and pharmacology due to its antipyretic and analgesic therapeutic action. Ibuprofen is a white or almost white crystal powder, isn't soluble in water, but is soluble in organic solvent (ethanol, acetone). Molecular weight of ibuprofen is 206.285.



For eutectic composition theoretical predicting it's necessary to know exact ibuprofen melting temperature and its enthalpy of fusion. Performing literature survey was found up that there are very big differences between these values. For example the melting temperature literature data are ranged from 47[9] to 86^{0}C[19] and is on the average 73-76^{0}C, that we can see from the TABLE 1.

TABLE 1 : Literature data of ibuprofen melting characteristics

Melting temperature, °C	Enthalpy of fusion, J/mol	Reference
47 - 50	…	[3]
69 - 71	…	[4]
75	25000	[5]
75.4	25800	[6]
75.5	24877	[7]
77.7	25715	[8]
78	…	[9]
84 – 86	…	[10]
…	25500	[11]
…	25500	[12]
…	25785	[13]
…	25607	[14]

Such differences in ibuprofen melting temperature are obviously caused by different purity of original ibuprofen, different accuracy and melting temperature finding methods. As for ibuprofen enthalpy of fusion there are some range of data from 24877.4 to 25800 J·mol^{-1}. And so it was necessary to found these ibuprofen melting characteristics in our laboratory with Russian high precise differential scanning calorimeter DSC-500[15].

Differential scanning calorimetry DSC-500 allows to study thermal behavior of substances in temperature interval from – 100 (with using special cryostat) to 500^{0}C: to find thermodynamic phase transition characteristics of substances, to estimate heat capacity and purity, kinetic characteristics (e. g. activation energy). The apparatus allows to study thermal behavior of substances using scanning speed from 0,5 to 64^{0}C/min to select optimal scanning speed for different substances and experimental conditions. DSC-500 is a differential scanning calorimeter, made as a classic calorimeter of heat flow. The disk chromel-constantan thermocouple is the detector of heat flow and sample holder.

The DSC-system is carried out constructively the way all thermo analytical cells be in same thermal (heat) conditions and be identical each other on heat attitude.

That is the condition of heat symmetry is held, that is necessary for straight base line and high temperature resolution. Fundamental difference of proposed scheme from known DSC scheme with compensation is in using the method of dynamic characteristic correction by primary transducer mathematic model and it let increase the speed of scale.

The work principle of calorimeter is based on local temperature difference between two points calorimeter system measurement. The difference appears at heat separation or absorption at reaction space. At differential scanning calorimeter heat block constantan disk is used as base measurement element. The disk is as sample holder, provides necessary thermo conductivity between the calorimeter cover and the sample. The disk is sensor of differential chromel-constantan thermocouple.

Differential scanning calorimeter let investigate different physicochemical processes that is accompanied with heat separation or absorption. It can be used for heat capacity and thermal emission measurement, for purity substances determination, for base thermodynamic and kinetic parameters getting, for polycomponent phase diagram construction. Scanning wished temperature area is carried out with line temperature changing programming within the range from room temperature to 500^{0}C (with using special cryostat up to -100^{0}C)

The heat block is manufactured from corrosion resistant materials and let perform line temperature scanning within the range from 0.1 to 64 Celsius degree per minute. The used sample mass is from 1 to 50 milligram. The detection temperature threshold is 0.0004 Celsius degree, or 10 microwatts capacity.

The apparatus have analog output - for thermo analytical information self-recorder output and digital – for data IBM PC registration and processing. The software for calorimeter is developed by Fedotov S. and let perform:

- thermal processes in real time data reading and imaging
- Experiment results saving in internal format program, standard file format CSV, graphic format BMP.
- Thermo analytical peaks full and fractional squares automatic calculation
- adjusting of curves (noise digital filtration)
- temperature and thermal effect apparatus calibration

Studied ibuprofen sample answers all specifications and was refine additionally with recrystallization from acetone and ethanol. We control the purity testing temperature constancy between two recrystallizations. From our calorimetric data the impurity of ibuprofen test sample was 99,987%.

For purity determination we used Van't Hoff equation, based on impure melting temperature depression:

$$T_s = T_o - \frac{RT_0^2X}{\Delta H_{fus}}\frac{1}{F},$$

where T_s – melting temperature at present time, K, T_o – melting temperature of absolute pure substance, K, R – gas constant, ΔH_{fus} – mole enthalpy of fusion (calculated from the peak area), J/(mol K), X – mole concentration of impurity, F – fraction melted at T_s, ration of peak part before T_s to full content.

From there, dependence T_s from 1/F must be straight and slope must be as

$$tg\alpha = \frac{RT_0^2X}{\Delta H_{fus}},$$

We investigate ibuprofen using two scanning speed 4 and 8^{0}C/min. For investigation on each scanning speed we use 7 samples with 6-17 mg. Samples were weighed on analytical scales «SHIMADZU» AUW 120D and were expanded in aluminum containers on special instrument. Aluminum containers were deoiled in ethanol.

Programmed sample heat was carried out in air atmosphere from 20 to 100^{0}C. For more exact experiment values definition we carried out apparatus temperature and heat careful calibration for used sensibility and scan speed.

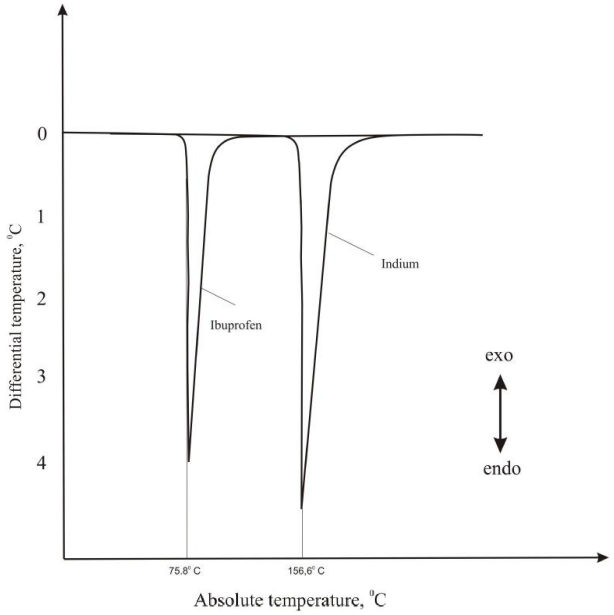
The calibration was carried with using high-purity metals: indium In (t. melt. 156,4^{0}C), stannous Sn (t. melt. 231,9^{0}C) and cadmium Cd (t. melt. 321^{0}C) . For more precise definition the results of calibration benzoic acid, anaestesin were used. It was found out that the class of calibration substances (metals, inorganic salt, organic substances) doesn't affect on melting temperature and enthalpy results.

The ibuprofen melting temperature ranges from 47 to 86^{0}C in different literature sources. It's necessary to take into consideration that there are not mention what

temperatures are used for determination of melting temperature in the most of literary source. The melting temperature can determine as onset temperature T_{on}, peak temperature, and end temperature. It's possible that one of the cause such discrepancies in melting temperature and enthalpy is using peak temperature as melting temperature. But we proved that melting temperature wasn't be determined as peak temperature, because peak temperature is depend highly on sample mass, scanning speed and other factors. With sample mass, scanning speed increasing peak temperature increases too.

And so the melting temperature should be determined as onset temperature T_{on} in thermograph. Onset temperature is graphically determined as the point on the thermograph corresponding crossing base line and tangent line for the onset front of peak.

In consequence of executed experiments we found that ibuprofen melting temperature was 75,8±0,1^{0}C (graphic 1) and these result wasn't depend on scanning speed. Onset temperature doesn't depend on scanning speed and mass. Ibuprofen standard melting enthalpy gives average 25,63 ± 0,1 kJ/mol. And so our results were the same as in[14].



Graphic 1 : Thermogramms of ibuprofen and indium

We also calculate ibuprofen entropy of fusion as 79.18 J/(mol K):

$$\Delta S_{fus} = \Delta H_{fus} / H_m$$

Calculated with Chickos methods[16] ibuprofen entropy of fusion was found as 67.65 J/(mol K) and enthalpy of fusion was 23,552 kJ/mol.

And cryoscopic constant

$$K = \frac{\Delta H_{fus}}{RT_m^2}$$

R –universal gas constant, 8,31 J (mol K)

Cryoscopic constant is 0,027306 K^{-1}. Cryoscopic constant is widely used for purity determination.

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