Journal of Pharmaceutical and Biomedical Analysis 53 (2010) 821–825

Contents lists available at ScienceDirect

Journal of Pharmaceutical and Biomedical Analysis

journal homepage: www.elsevier.com/locate/jpba

Calorimetric determination of dissolution enthalpy with a novel flow-through method

Vesa-Pekka Lehto[a,*], Mikko Tenho[b], Olli-Pekka Hämäläinen[b], Jarno Salonen[b]

[a] Department of Physics and Mathematics, University of Eastern Finland, POB 1627, FI-70211 Kuopio, Finland
[b] Department of Physics and Astronomy, University of Turku, FI-20014 Turku, Finland

ARTICLE INFO

Article history:
Received 19 April 2010
Received in revised form 23 June 2010
Accepted 24 June 2010
Available online 3 July 2010

Keywords:
Dissolution
Enthalpy
Heat conduction microcalorimeter
Solution calorimetry
Theophylline

ABSTRACT

A new calorimetric flow-through system for determining the enthalpies of dissolution with small amount of solids (<1 mg) was developed. The system was designed to be used as an add-on cell with a 4 ml twin heat conduction calorimeter 2277 TAM but the principle is adoptable also for other heat conduction calorimeters. The system was tested with two salts (NaCl, KCl), sucrose and different polymorphic forms of theophylline at 25 °C and 40 °C by using water as the solvent. The system gave more accurate and precise results at 25 °C. The precision was not affected by the extent of the dissolution enthalpy. The accuracy was dependent on the calibration utilized but even the normal electrical calibration gave acceptable values. The results obtained at 40 °C were also acceptable but not as good as at 25 °C due to heat leaks. The effect of heat leaks can be minimized by heating the inflowing solvent outside the calorimeter prior to entering the flow-through cell.

1. Introduction

Enthalpy change for dissolution of solids ($\Delta_{sol}H$) is an important characteristic of solute–solvent interaction [1]. It can be utilized for example for determining the degree of crystallinity [2], polymorph composition [3], or when comparing the stabilities of different polymorphic forms [4]. Traditionally, macro-scale calorimeters have been used to measure dissolution enthalpies, which provide the use of large samples. These methods involve typically crushing of a glass ampoule containing the sample in a solvent chamber and measuring the released heat while stirring the solution [5]. In some cases, especially at the early phase of the drug formulation development, the amount of material available is limited and thus methods for microgram-sized samples have been developed [6–9]. These methods are either batch of flow techniques which are based on heat conduction, semi-adiabatic or isoperibolic principle. Each of the methods has drawbacks and for example the practical use of the flow method developed by Nillson and Wadsö [6] seems to be problematic and risky for failures as the methods utilizes saturated solutions. Regarding the batch techniques, the opening or crushing of the sample container and variables during the assembly of the system (e.g., creasing of the seals) tends to have major impact on the reproducibility of the blank effect. The precision of the results is typically between 1% and 3% for dissolution of pharmaceutical solids in water [6–8,10] and a bit larger with other solvents [11]. In any cases, the measurements are very time consuming (e.g., it takes at least 1 h to equilibrate after entering the sample in the isothermal microcalorimeter) and laborious.

The measurement set-up presented here is based on the previous microcalorimetric accessory developments for photoreactivity [12] and sorption processes [13] realized by the research group of the correspondence author. In the present study the constructed device is depicted and tested with various salts and temperatures. Sucrose [10] and various polymorphic forms of theophylline [14] were also applied as model compounds.

2. Materials and methods

2.1. Materials

The water used as the solvent was filtered with activated carbon, purified with reverse osmosis and further deionized. Potassium chloride and sodium chloride were Baker analysed grade (99% and 99.5%, respectively). These salts were treated at 30 °C overnight and stored in silica desiccators prior to measurements. The anhydrous theophylline form II was purchased from Sigma. The theophylline form I was obtained with the treatment of form II at 268 °C for 1 h [15]. The monohydrate form of theophylline was produced by storing the form II in a desiccator with a relative humidity of 97% at a room temperature for several days. The polymorphic forms were verified with X-ray powder diffraction (Philips X'Pert Pro)

* Corresponding author. Tel.: +358 40 3552470.
E-mail address: vesa-pekka.lehto@uef.fi (V.-P. Lehto).

0731-7085/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.jpba.2010.06.029

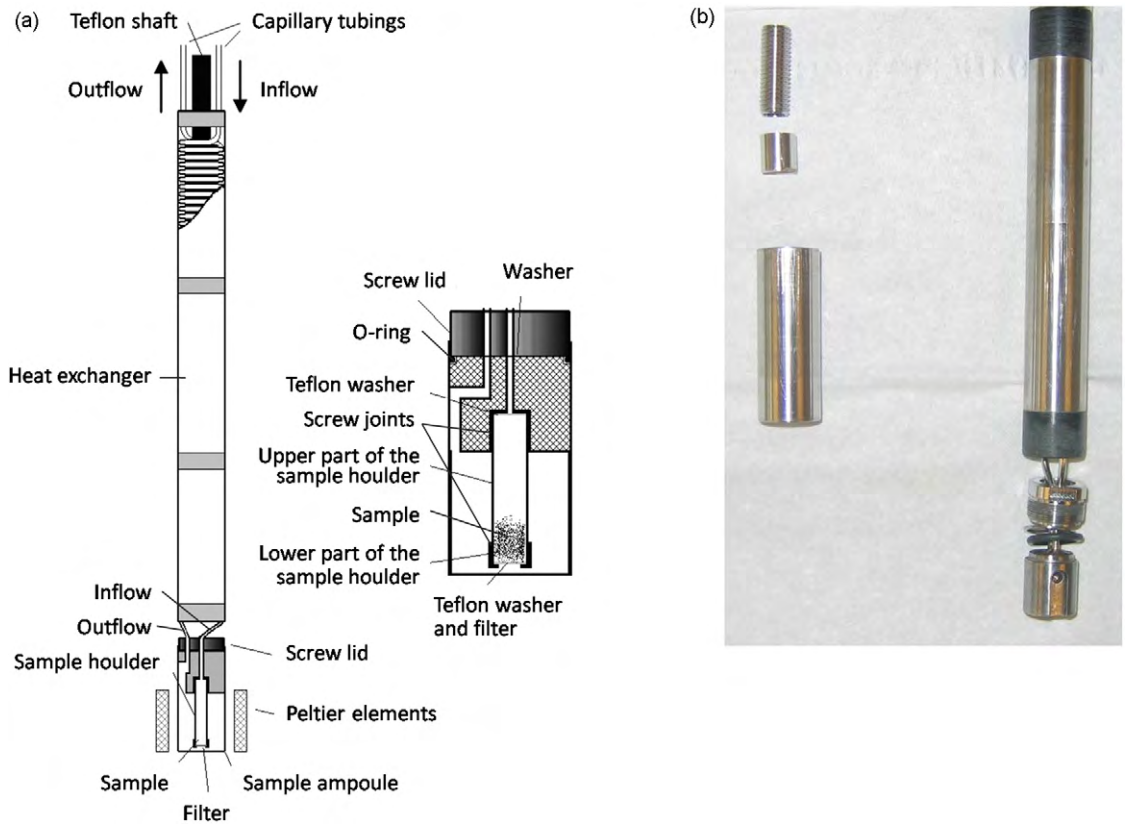

Fig. 1. (a) A schematic drawing of the flow-through cell. All the metal parts of the cell are made from stainless steel, washers are from Teflon and O-rings from. On the right side is a close-up of the sample ampoule. (b) A photograph of the cell. On the left side are the upper and lower parts of the sample holder together with the sample ampoule. The Teflon filter is located on the bottom of the lower part of sample holder and it is tightened in its place with the upper part.

and differential scanning calorimetry (PerkinElmer Pyris Diamond). Calorimetric measurements were made with the particles of the size <53 μm obtained after sieving. No further size analysis was performed. However, particles size was not found to be a critical parameter in these measurements.

2.2. Experimental set-up

The calorimetric flow-through cell constructed is depicted in Fig. 1. The cell was planned to be used with a 4 ml twin heat conduction calorimeter 2277 TAM made by Thermometric Ab, Sweden (presently TA Instruments). The solvent is pumped (NE501, Pump System Inc.) outside the calorimeter through capillary tubing into the sample ampoule. In the capillary tubing (1 mm in inner diameter, ca. 2 m in length) the solvent is equilibrated at the measurement temperature. The flow must be slow enough so that the equilibrium can be achieved. In the sample ampoule solvent enters the sample holder (Fig. 1) where the sample is placed on a membrane filter (Nylaflo 0.2 μm). The maximum rate that could be used without any significant heat flow signal due to the friction was 3.5 ml/h in the present set-up. With this flow rate it took 20–27 min for the solvent to flow through the capillary tubing into the sample ampoule depending on the length of the tubing between the pump and the flow-through cell. It was assumed that even though particles <0.2 μm can go through the filter the small particles will dissolve entirely before leaving the sample ampoule. Calibration of the calorimeter was performed electrically according to the Users' manual (Thermometric AB) to 1000 μW. An empty stainless steel sample was used as a reference. The samples were weighed (Mettler MT5 microbalance, ±1 μg) directly on the filter assembled with the lower and upper part of the sample holder (Fig. 1).

2.3. Data analysis

Data analysing was performed with Origin software and consisted of the setting the start of the pumping (opening of the flow switch) as $t = 0$ s, baseline correction and integration to calculate the heat associated to the dissolution process. Due to the minor heat leaks the baseline differed from the 0-level, and this was corrected by subtraction a linear baseline based on the heat flow level measured before and after the pumping of the solvent. Due to the blank effect (pumping the solvent through the pure and dry cell also caused heat flow signal as such) the measurements were made with various sample sizes. When the measured heat flow signal after the baseline correction was integrated the corresponding heat value was obtained. When these heat values were plotted against the sample masses, the heat of dissolution was obtained from the slope of the linear fit and the heat effect of the blank measurements was obtained from the intercept. The errors indicated in the present report are the standard errors.

3. Results

3.1. Measurements at 25 °C

Fig. 2 represents three baseline corrected blank measurements made with water at 25 °C. The baseline differed ca. −0.5 μW from the 0-level. The heat flow curves consist of different phases which are due to the flow of the solvent into and through the sample ampoule. During the first ca. 27 min after switching the pump on the interaction is mainly between the surfaces of the ampoule and the solvent vapor yielding a broad endothermic signal due to adsorption. When the solvent (liquid) enters the sample holder a

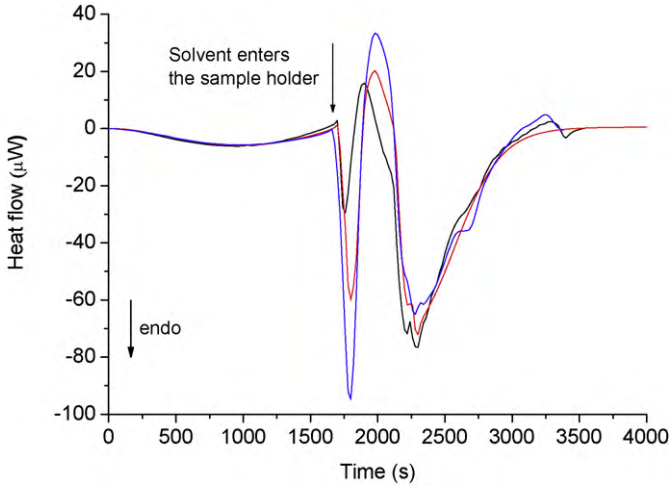

Fig. 2. Heat flow curves of blank measurements with water at 25 °C.

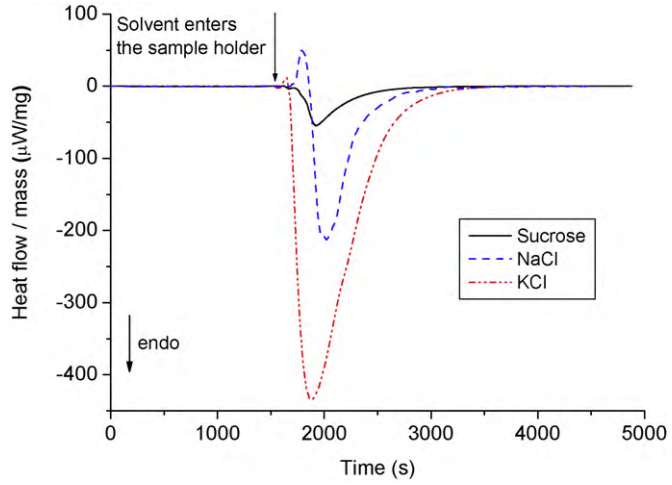

Fig. 3. Typical heat flow curves for dissolution of sucrose (solid line), sodium chloride (dashed line) and potassium chloride (dotted line) at 25 °C.

sharp endothermic peak is seen. The subsequent larger endothermic peak is due to filling the sample ampoule which after the 'reactive position' is totally filled by the solvent and the heat flow signal stabilizes on the baseline level. The baseline stability during the solvent flow was ±0.3 μW. The reproducibility (heat effect) of the blank effect was 42.2 ± 0.7 mJ. This values corresponds the intercept of the linear correlation fitted to the heat values obtained from samples with various masses.

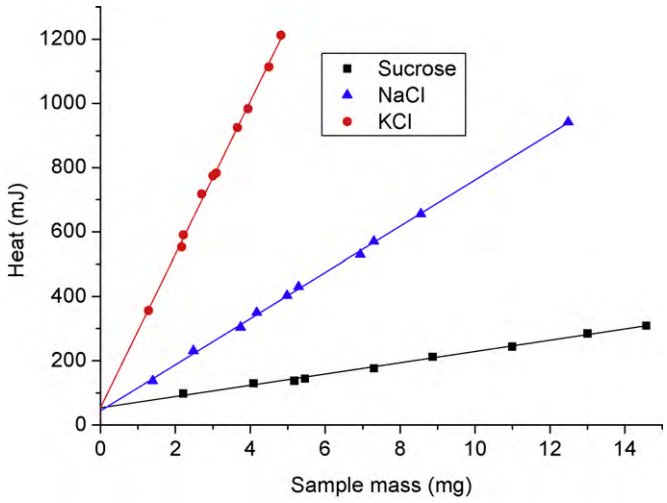

Fig. 4. Determination of the dissolution enthalpies (slopes of the lines) of sucrose (squares), sodium chloride (triangles) and potassium chloride (circles) at 25 °C. The intercepts refer to the blank effects.

Typical heat flow curves for the dissolution of sucrose, NaCl and KCl at 25 °C are seen in Fig. 3. The exothermic peaks visible in the heat flow curves for NaCl and KCl are due to the blank effect (cf. Fig. 2). As the heat flow values are corrected for the sample masses the relative order of the dissolution enthalpy can instantly be seen. All the enthalpies are endothermic and the values are determined from the slopes of the fitted lines (Fig. 4) the results being presented in Table 1. Comparing these values with the values reported in the literature [10,16,17] the calibration coefficient of 1.006 ± 0.015 is obtained (see Table 1 for details).

3.2. Measurements at 40 °C

Measurements were performed also at 40 °C. Here the baseline deviated ca. −10 μW from the 0-level indicating a heat leak due to the capillary tubing. However, as the difference was reproducible and it could be corrected via appropriate baseline subtraction no modification was made in the system. Adding a heater outside the calorimeter on the top of the flow-through cell would have minimized the effect like in the commercial perfusion cells. The blank effect was determined using water as the solvent (Fig. 5) giving the value of 102 ± 3 mJ. The value equaled with the intercepts of the linear correlations obtained with theophylline samples even though the value was two times higher than the one obtained at 25 °C. The functionality of the flow-through cell at 40 °C was verified with NaCl same way like at 25 °C. The dissolution enthalpy obtained was 45.9 ± 2.0 J/g. When comparing this value with the one from the literature, 45.2 ± 1.5 J/g

Table 1
Results of the calorimetric dissolution experiments made under various temperatures and with various solutes. Water was used as a solvent in all measurements. The volume of the sample ampoule available for dissolution was 1.5 ml and the masses of the samples are indicated in Figs. 4 and 7. These values can be used to estimate the maximum concentrations of the solutions utilized in the study, which, e.g., in case of KCl are 0.7–3.3 mg/ml.

Temperature	Solute	$\Delta_{sol}H_{meas}$ (J/g)[a,b]	$\Delta_{sol}H_{literat}$ (J/g)[c]	Refs.
25 °C	NaCl	71.73 ± 0.77 (1.1%)	72.1 ± 0.2	[16]
25 °C	KCl	238.1 ± 3.7 (1.6%)	235.9 ± 0.3	[17]
25 °C	Sucrose	17.53 ± 0.42 (2.4%)	17.9 ± 0.3	[10]
40 °C	NaCl	45.9 ± 2.0 (4.4%)	45.2 ± 1.5	[18]
40 °C	Theophylline form I	109 ± 6 (5.7%)	103 ± 2[d]	[14]
40 °C	Theophylline form II	119 ± 8 (6.9%)	108 ± 2[d]	[14]
40 °C	Theophylline monohydrate	163 ± 8 (4.7%)	144 ± 8[d]	[19]

[a] Uncertainties reported are standard errors of the fitting.
[b] Precision (%) in parenthesis.
[c] Uncertainties reported are standard deviations of the means.
[d] Values are obtained at 25 °C.

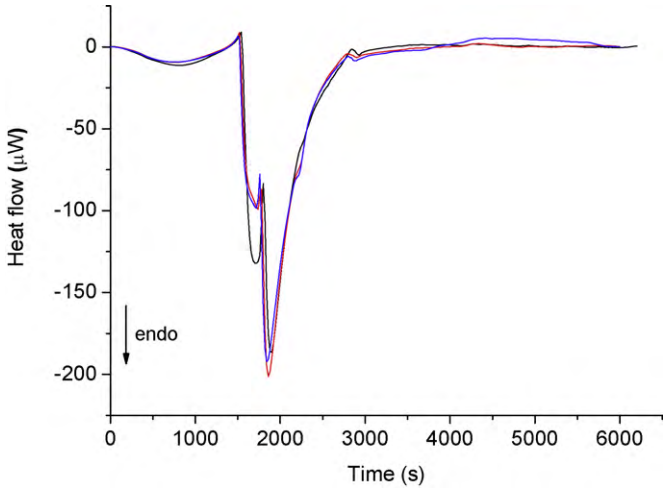

Fig. 5. Heat flow curves of blank measurements with water at 40 °C.

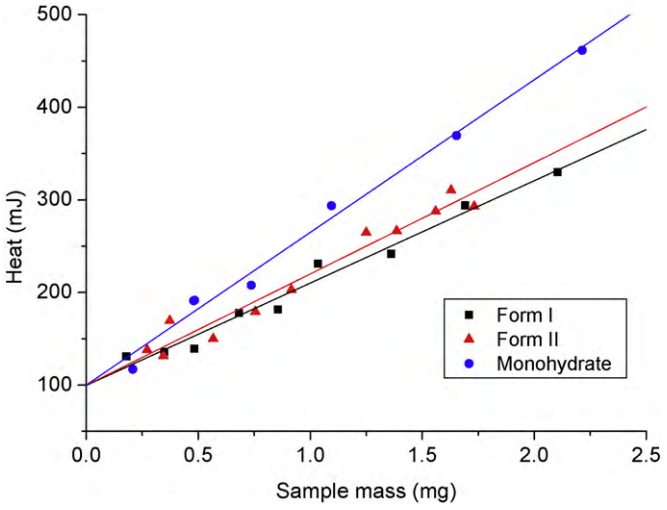

Fig. 7. The heats accompanied to the dissolution of various theophylline forms at 40 °C; form I (squares), form II (triangles) and monohydrate (circles).

[18] the calibration coefficient of 0.984 (45.15 J/g/45.87 J/g) is obtained.

Different forms of theophylline were dissolved to compare the values of dissolution enthalpy for different polymorphic forms which are typically of great interest in the field of pharmaceutical sciences. Typical heat flow curves for the dissolution of different polymorphic forms of theophylline are shown in Fig. 6. The order of the magnitude of dissolution enthalpies is clearly present but no clear differences in the dissolution kinetics can be observed; it might be expected that as the sample masses in the measurements were about the same the form I would dissolve fastest. The data of the heat flow signal was not dynamically corrected which might be the reason for this illogical finding. It is worth mentioning that phase transitions taking place during the dissolution process should be visible in the heat flow curves thus revealing the possible phase transition taking place prior to the actual dissolution. However, in the present study that kind of phase transition was not detected. The various phases present in the heat flow curves are now due to the blank effect. The dissolution enthalpies obtained from the linear correlations (Fig. 7) are presented in Table 1.

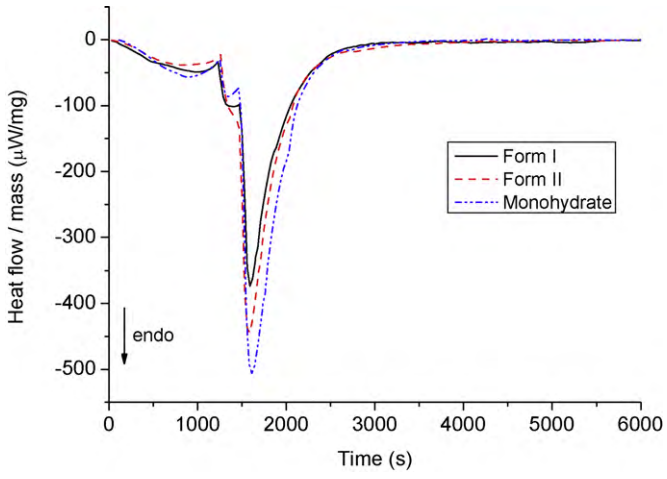

Fig. 6. Typical heat flow curves for dissolution of various theophylline forms at 40 °C; form I (solid line), form II (dashed line) and monohydrate (dotted line).

4. Discussion

The results obtained with the salts and sucrose are in good agreement with the literature. The accuracy and precision for the measurements at 25 °C are fairly good and exhibit the typical variability reported previously in corresponding studies. Variations in the results at 40 °C are a bit larger but they do correlate with the literature values even though only the values at 25 °C are available for theophylline. The errors tend to increase as a function of temperature which stems from the increased blank effect and from the increased deviation of the baseline from the 0-level due to the heat leaks from the calorimetric unit. Heat leak can also be verified by comparing the values for the dissolution enthalpies determined on the basis of electrical calibration: the calibration coefficient was close to 1 but above it at 25 °C (1.006) but at 40 °C the coefficient was below 1 (0.984). When comparing these values it should be noticed that the dissolution enthalpies are endothermic. Heat leak can be reduced by heating the inflow line prior to entering the calorimeter. The times needed for the measurements are typical for this type of measurements. Increasing of the flow rate of the solvent would decrease the measurement time and accelerate the dissolution process thus making also sparingly dissolving materials applicable for the methods. However, increasing flow rate would also increase friction yielding more pronounced exothermic effect. The material and the pore size of the filter play important roles in this sense. It is worth mentioning that due to the flow principle the solvent can be changed in the course of the measurement. Also, ad/absorption of ad/absorbate from the liquid stream to the ad/absorbent located on the filter can be studied with the device.

Acknowledgements

Mika Aarnio, B.Sc. and Aleksi Helle, M.Sc. are thanked for the technical assistance in construction of the device.

References

[1] H. Piekarski, Calorimetry—an important tool in solution chemistry, Thermochim. Acta 420 (2004) 13–18.
[2] V.-P. Lehto, M. Tenho, K. Vähä-Heikkilä, P. Harjunen, M. Päällysaho, J. Välisaari, P. Niemelä, K. Järvinen, The comparison of seven different methods to quantify the amorphous content of spray dried lactose, Powder Technol. 167 (2006) 85–93.
[3] D. Giron, Contribution of thermal methods and related techniques to the rational development of pharmaceuticals—Part 1, Pharm. Sci. Technol. Today 1 (1998) 191–199.

[4] R. Willson, T. Sokoloski, Ranking of polymorph stability for a pharmaceutical drug using the Noyes–Whitney titration template method, Thermochim. Acta 417 (2004) 239–243.
[5] B. Yff, P. Royall, M. Brown, G. Martin, An investigation of calibration methods for solution calorimetry, Int. J. Pharm. 269 (2004) 361–372.
[6] S.-O. Nillson, I. Wadsö, A flow-microcalorimetric vessel for solution of slightly soluble solids, J. Chem. Thermodyn. 18 (1986) 1125–1133.
[7] M. Bastos, G. Baia, E. Qvarnström, I. Wadsö, A new dissolution microcalorimeter: calibration and test, Thermochim. Acta 405 (2003) 21–30.
[8] D. Russell, D. Thomas, L. Hansen, Batch calorimetry with solids, liquids and gases in less than 1 mL total volume, Thermochim. Acta 446 (2006) 161–167.
[9] J. Moreno-Piraján, L. Giraldo-Gutierréz, New mixing system in dissolution isoperibol microcalorimeter, Rev. Sci. Instrum. 78 (2007) 046105.
[10] R. Ramos, S. Gaisford, G. Buckton, P. Royall, B. Yff, M. O'Neill, A comparison of chemical reference materials for solution calorimeters, Int. J. Pharm. 299 (2005) 73–83.
[11] N. Alves, G. Bai, M. Bastos, Enthalpies of solution of paracetamol and sodium diclofenac in phosphate buffer and in DMSO at 298.15 K, Thermochim. Acta 441 (2006) 16–19.
[12] V.-P. Lehto, J. Salonen, E. Laine, Real time detection of photoreactivity in pharmaceutical solids isothermal microcalorimetry, Pharm. Res. 16 (1999) 368–373.
[13] V.-P. Lehto, E. Laine, Simultaneous determination of the heat and the quantity of vapor sorption using a novel microcalorimetric method, Pharm. Res. 17 (2000) 701–706.
[14] P. Szterter, Thermodynamic properties of polymorphic forms of theophylline. Part II. The enthalpies of solution in water at 298. 15 K, J. Therm. Anal. Calorim. 98 (2009) 337–341.
[15] E. Suzuki, K. Shimomura, K. Sekiguchi, Thermochemical study of theophylline and its hydrate, Chem. Pharm. Bull. 37 (1989) 493–497.
[16] D. Archer, D. Kirklin, NIST and standards for calorimetry, Thermochim. Acta 347 (2000) 21–30.
[17] I. Wadsö, R. Goldberg, Standards in isothermal microcalorimetry, Pure Appl. Chem. 73 (2001) 1625–1639.
[18] S. Sanahuja, E. Cesari, Enthalpy of solution of aqueous sodium chloride at 303.15, 308. 15, and 313. 15 K, J. Chem. Thermodyn. 17 (1985) 823–827.
[19] E. Suihko, J. Ketolainen, A. Poso, M. Ahlgren, J. Gynther, P. Paronen, Dehydration of theophylline monohydrate—a two step process, Int. J. Pharm. 158 (1997) 47–55.