Journal of Thermal Analysis and Calorimetry, Vol. 77 (2004) 571–580

BINARY MELTING PHASE DIAGRAMS OF NIFEDIPINE-PEG 4000 AND NIFEDIPINE–MANNITOL SYSTEMS

*Natalija Zajc and Stane Srčič**

Faculty of Pharmacy, University of Ljubljana, Aškerčeva 7, 1000 Ljubljana, Slovenia

Abstract

The phase diagrams of nifedipine-polyethylene glycol (PEG) 4000 and nifedipine–mannitol systems have been determined. Heating experiments on thermodynamically equilibrated co-melts revealed eutectic behaviour for nifedipine-PEG 4000 mixtures, with the composition of the eutectic point between 40 and 45% *w/w* of nifedipine. These observations were supported by optical and hot stage microscopy. Nifedipine and mannitol were negligibly miscible in the solid-state, behaving as a binary system with monotectic characteristics. Application of phase diagrams to the production of solid dispersions is shown to be rational, since they provide valuable information on the state of the binary systems under preparation.

Keywords: differential scanning calorimetry, mannitol, nifedipine, PEG 4000, phase diagram

Introduction

Nifedipine (NIF) is a calcium channel blocking agent of the dihydropyridine type, and is used in treating hypertension and angina pectoris. The combination of low aqueous solubility and rapid absorption from the gastrointestinal tract leads to its classification into class II of the Biopharmaceutical Classification System. Bioavailability of these drugs can generally be improved by formulation techniques such as forming solid dispersions [1]. For this purpose, one or more active ingredients are dispersed in an inert, hydrophilic carrier or matrix in the solid-state, prepared by melting or solvent methods, or a combination of both.

Nowadays, a great number of substances are recognized as meeting the requirements for solid dispersion carriers. Polyethylene glycols (PEG) – hydrophilic polymers with relatively low melting point – have been successfully used for this purpose [2, 3]. The incorporation of nifedipine into a PEG matrix has been reported to result in a much greater dissolution rate than that of the drug alone [4, 5]. In the group of sugars and polyols, mannitol has attracted attention as the most popular substance for a solid dispersion matrix. It has the desired water solubility, low toxicity and appro-

* Author for correspondence: E-mail: srcics@ffa.uni-lj.si

1388–6150/2004/ $ 20.00

Akadémiai Kiadó, Budapest
Kluwer Academic Publishers, Dordrecht

priate compression properties, although its high melting point and the polymorph transition after melting make the melting method of preparation inadvisable [6].

To achieve the optimal degree of drug dispersion, melting phase diagrams can be used for selecting a suitable drug/carrier composition [7]. Differential scanning calorimetry (DSC) is a suitable method for evaluating transition temperatures, which reflect the interactions in the system. On the basis of quantitative measurement with acceptable accuracy [8], the eutectic point may be obtained by studying the composition dependence of the fusion enthalpy in the binary system [7]. Using DSC data, the drug/carrier relationship and solid structure of the system can be characterized, especially in cases where the fusion method is the method of choice for solid dispersion preparation. The aim of the present study therefore is to construct phase diagrams of the nifedipine-PEG 4000 and nifedipine-mannitol binary systems, based on the results of DSC heating experiments. An attempt to clarify the interactions between the components has been made and the type of potential solid dispersion system has been considered.

Experimental

Materials

Nifedipine and *D*-mannitol were supplied by Lek Pharmaceutical d.d., Slovenia, and polyethylene glycol 4000 (PEG 4000) by Merck, Germany. Prior to preparing mixtures, each powder was sieved in order to ensure a particle size ≤ 160 μm. 10.0 g of binary mixtures of 3 to 95% NIF in mannitol or PEG 4000 was prepared by blending the appropriate quantities of components in a mortar for 10 min.

Methods

Differential scanning calorimetry

Differential scanning calorimetry measurements were carried out using a Pyris 1 DSC (PerkinElmer, USA), equipped with an Intracooler 2P cooling accessory. Data were acquired using Pyris software (Version 3.81; PerkinElmer, USA). 4.5–5 mg samples were weighed accurately in standard PerkinElmer aluminium pans and covered with a pierced lid. During experiments, the DSC cell was purged by nitrogen at a flow rate of 20 mL min^{-1}.

Scans were recorded in the temperature range of 20–185°C, using a heating rate of 10 K min^{-1} for NIF-PEG 4000 systems and 145–185°C, with heating rate of 5 K min^{-1}, for NIF–mannitol mixtures. Immediately after the first heating scan, samples were stored for 10 min on an aluminium plate at 20±1°C. They were then returned to the DSC cell, the temperature was adjusted to 20 or 145°C (for PEG 4000 or mannitol systems, respectively) and the second scan triggered. Afterwards, all examined samples were kept in a desiccator (RH 5%) at room temperature and scanned again after storing for 2 months.

Glassy NIF was also heated repeatedly. Glassy samples were obtained by heating NIF in the DSC pan to 180°C and cooling to room temperature under ambient conditions. They were then scanned successively to 130, 155 and 180°C at a heating rate of 10°C min^{-1}. Between the scans, samples were cooled to room temperature.

X-ray diffraction

The X-ray diffraction data were recorded using a Siemens D-5000 X-ray diffractometer (Siemens, Germany) with Ni filtered CuK_α radiation. The angular range from 2 to 35 2θ was scanned with a step size of 0.040 and a time constant of 1.0 s.

Optical microscopy

Samples of physical mixtures (approx. 1 mg) were heated to 180°C on glass slides and then cooled to room conditions. After three weeks the appearance of co-melts at room temperature was observed using an Olympus BX50 microscope with the Highlight 3100 light source (Olympus, Japan), and equipped with a Sony colour video camera DXC-950P.

Hot-stage microscopy

Hot stage microscopy of co-melts was carried out with a hot stage table (Karl Suss GmbH, Germany). Samples were examined on the metal slide three weeks after preparation (melting), over a temperature range from 25 to 180°C. A Mitutoyo microscope (Mitutoyo, Japan) was employed using a HV-C20 Hitachi camera. The heating rate was 2°C min^{-1}.

FTIR spectroscopy

Infrared spectra were recorded using a Nicolet Nexus (Nicolet Instrument Co., USA) equipped with InGaAs detector and ATR Smart DuraSamplIR sampling accessory. Data were acquired using OMNIC software (version 5.2, Nicolet Instrument Co.). MID spectra were measured over the range 4000–400 cm^{-1} with an instrument resolution of 4 cm^{-1}. Each spectrum comprised an average of 32 scans.

Results and discussion

Nifedipine-PEG 4000 system

The DSC scans of pure PEG 4000 and NIF exhibited single melting endotherms, with onset temperatures at 58.1 and 173.4°C, respectively. Heating physical mixtures of PEG and NIF resulted in DSC curves with two endotherms (Fig. 1a). Transitions in the lower temperature region (onset temperature at 55.7±1.0°C) were assigned to melting of PEG 4000 and remained independent of the proportion of drug. The second endotherm reflected NIF melting. Its onset temperature decreased with decreasing percentage of NIF down to approximately 45% *w/w* of NIF, below which there was no appreciable further

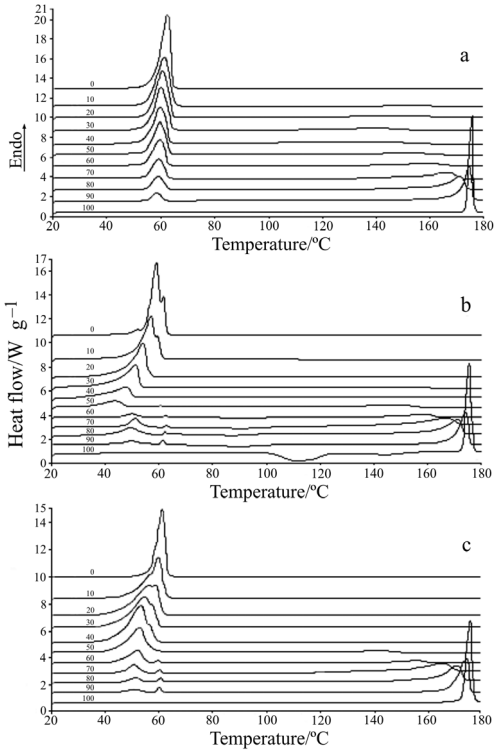

Fig. 1 DSC scans of NIF–PEG 4000 a – physical mixtures, b – co-melts (second heating) after 10 min and c – co-melts after 2 months of storage. Numbers represent the mass fraction of NIF

change. Since both melting endotherms were always detectable, it was concluded that there was no specific interaction between NIF and PEG 4000.

To study phase interactions of more intimately blended systems, melting of ingredients prior to analysis has been suggested [7]. Samples were therefore re-heated after 10 min of storage on an aluminium plate at 20°C. The DSC transitions (Fig. 1b) differed clearly from those for physical mixtures. Pure PEG 4000 displayed a multiple peak endotherm, consisting of a shoulder and two partly overlapping peaks. This was attributed to the presence of different crystal structures of the polymer, namely twice folded, once folded and extended chains, respectively [9, 10]. The shoulder disappeared with increase of NIF above 3% *w/w*, whereas the peak corresponding to the extended form was no longer present above 20% *w/w*. Verheyen and co-workers suggested that the presence of drug influenced the structure of PEG 6000 in the solid dispersion [3]. The drug acts as impurity, promoting formation of metastable, once or twice folded forms at the expense of the stable extended form. Our results support these findings since, on increasing the drug content, the peak of once folded chains gradually dominated. From 20% *w/w* on, only a single peak endotherm was observed for PEG 4000 melting. The absence of the NIF melting peak in PEG-rich samples

(compositions less than 50% *w/w* of NIF) could be explained by the dispersion of NIF subtle crystals into the melted carrier. It could also be the consequence of small glassy NIF compartments, in which crystallization was impossible due to insufficient amounts of the drug. In support of this, samples rich in NIF (> 60% *w/w*) exhibited shallow and broad crystallization exotherms at temperatures between 70 and 100°C [11], showing that at least part of the drug existed in glassy state.

At approximately 60°C, an additional small, but sharp, endotherm appeared (Fig. 1b). The signal increased with drug content from 60% *w/w* upwards, and was therefore attributed to NIF. The occurrence of this endotherm was further studied by successive heating of pure glassy NIF (Fig. 2). The first heating up to 130°C (curve 1) showed the glass transition at approx. 46°C and a crystallization exotherm from 100 to 125°C. Samples were then cooled to room conditions and scanned again to 155°C. This time, a small endotherm appeared with an onset temperature of 59.8°C, followed by an exothermic transition between 130 and 145°C (curve 2). Crystallization of NIF was found to result in a complex transition in which at least three different polymorphs are created in a heating rate dependent process [11, 12]. From this point of view it can be concluded that the endotherm in question is the result of a solid-solid transition from one metastable modification of NIF to another. Finally, the crystallization at 130°C results in a stable modification, which melts at approximately 173°C. The presence of PEG 4000 in the co-melts is seen to have provoked formation of a less stable NIF polymorph, which is subject to a solid-solid transition at around 60°C.

The DSC results of a second heating (Fig. 1b) demonstrated, with respect to the multiple melting peaks of PEG 4000 and the crystallization exotherm of NIF, that the system was not thermodynamically equilibrated within 10 min prior to analysis. Therefore, the samples were scanned once again after 2 months of storage at room temperature and RH 5%. Figure 1c comprises the DSC curves corresponding to pure components and co-melts with different compositions. There are obvious differences detectable in comparison with physical mixtures and thermodynamically non-equilibrated co-melts (Fig. 1a and 1b, respectively). On increasing the amount of NIF in the

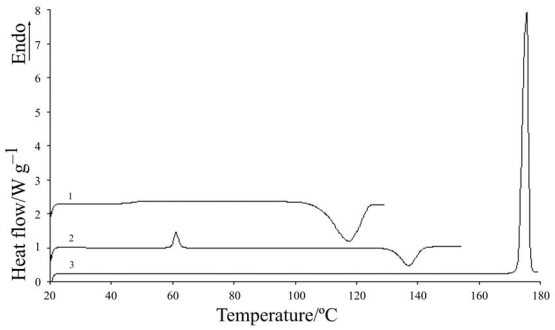

Fig. 2 DSC scans of pure glassy NIF: 1 – heating was stopped at 130°C; 2 – sample (1) was cooled and then re-heated to 155°C; 3 – sample (2) was cooled and re-heated to 180°C

mixtures up to 40% *w/w*, the PEG 4000 melting peak gradually decreased and an additional endothermic peak appeared at approx. 44°C. This temperature is substantially lower than that of the PEG 4000 melting. This peak may be attributed to the melting of a eutectic mixture, since its enthalpy increased with NIF content, reaching a maximum at 40% *w/w* of drug. After that, the area under the peak curve decreased again. In mixtures with 45% *w/w* NIF or more, the DSC curves exhibited an endothermic peak corresponding to the melting of excess NIF. On the same curves, a small endotherm near 60°C was present. As in the case of non-equilibrated co-melts, this peak was found to increase with NIF content suggesting that, after 2 months of storage, the presence of PEG 4000 still favours the NIF metastable phase. PEG 4000 melting peaks were analysed using the maximum peak temperature while, for all other endotherms, the onset peak temperatures were plotted *vs.* NIF mass fraction. A phase diagram was constructed using defined temperatures (Fig. 3).

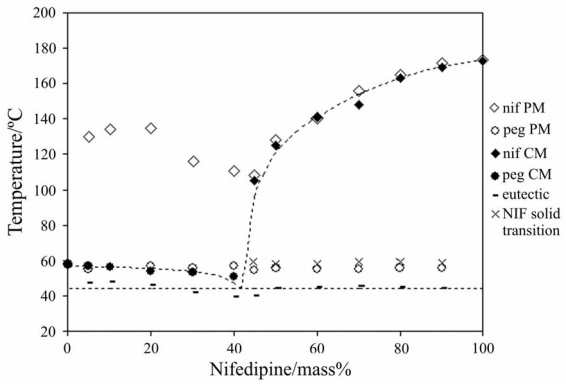

Fig. 3 Binary melting phase diagram of NIF and PEG 4000 systems prepared by physical mixing (PM) or co-melting (CM), the latter preparation being stored for 2 months prior to analysis

In an attempt to clarify the organization and structure of co-melted NIF-PEG 4000 binary systems, they were studied by X-ray diffractometry. In the spectra of thermodynamically non-equilibrated co-melt with 40% *w/w* NIF (Fig. 4b), only PEG 4000 diffraction peaks were present. Deviation of the signal from baseline indicated similarity to the amorphous NIF prepared by melting and subsequent rapid cooling (Fig. 4e). This provides evidence that, in the fresh co-melts, NIF was indeed in the amorphous state, but was unable to crystallize at drug contents of 50% *w/w* and less (Fig. 1b). After storage, the diffraction peaks of each crystalline component became distinguishable (Fig. 4c). Since both components are present in the crystalline form, the eutectic nature of the system had to be established. Optical micrographs of the melted mixture with 40% *w/w* of the drug (Fig. 5) show that, at room temperature, the co-melt area consists of separated NIF (yellow) and PEG 4000 (white) compartments. The PEG spherulite structure is still observable, but formation is disrupted by the presence of subtle NIF crystals. Hot stage microscopy of selected co-melts con-

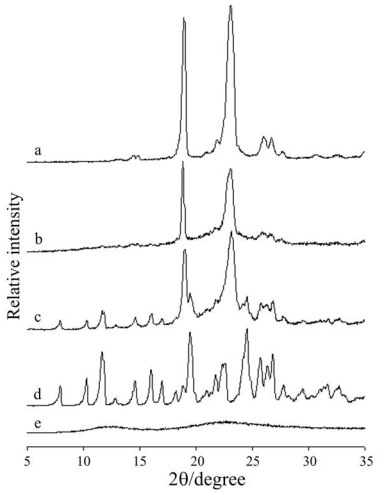

Fig. 4 X-ray diffraction profiles of a – PEG 4000, b – 40% *w/w* (NIF) co-melt after 10 min, c – 40% *w/w* (NIF) co-melt after 2 months, d – crystalline NIF and (e) amorphous NIF

firmed the results of DSC analysis. During heating of the 40% co-melt, the fusion of the material at 55°C resulted in the transparent droplets of uniform colour (Fig. 6a). In the mixtures with NIF content of 45% w/w (Fig. 6b), the isolated crystals of NIF in the PEG-melt were observable at the same temperature. Reduction of the crystals occurred with further heating, until they disappeared at 112°C.

Curves were fitted to the results obtained by DSC of co-melts, leading to makeshift liquidus and solidus lines (dashed lines in Fig. 3). The eutectic characteristics were ascertained for the NIF-PEG 4000 system. As the melting peaks of the eutectic and PEG 4000 partially overlap, it is not possible to calculate the precise eutectic composition using the relationship between drug content and eutectic fusion enthalpy [7]. Although there was no case with only one melting endotherm belonging to the eutectic, we conclude from the present results that the composition of the eutectic point is between 40 and 45% *w/w* of NIF.

Nifedipine-mannitol system

Irrespective of drug content, the DSC scans of NIF–mannitol physical mixtures and co-melts always included two endotherms, attributed to separate melting processes of the two components. The phase diagram of the binary system (Fig. 7) was constructed by plotting the onset temperatures of endotherms as a function of nifedipine mass fraction. In the physical mixtures, the melting temperatures of mannitol and NIF did not change appreciably, being 165.7±0.5°C and 172.3±0.3°C, respectively.

Co-melts, however, exhibited slight deviations from the behaviour of physical mixtures. For the samples rich in mannitol, the NIF peak temperature was lower. On the other hand, the mannitol melting point was independent (at 164.8 ±0.3°C) of NIF

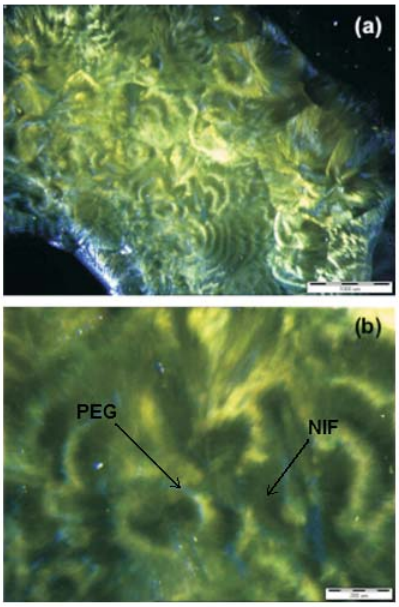

Fig. 5 Optical micrographs of 40% *w/w* NIF-PEG 4000 co-melts; a – magnification 25.6×; b – magnification 100×

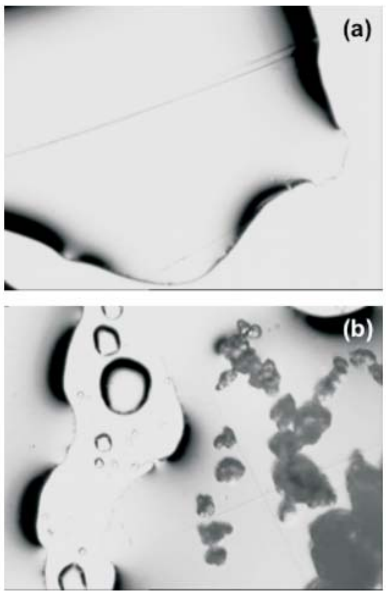

Fig. 6 Hot stage photographs of NIF-PEG 4000 co-melts at 58°C a – with 40% *w/w* and b – with 45% *w/w* of NIF

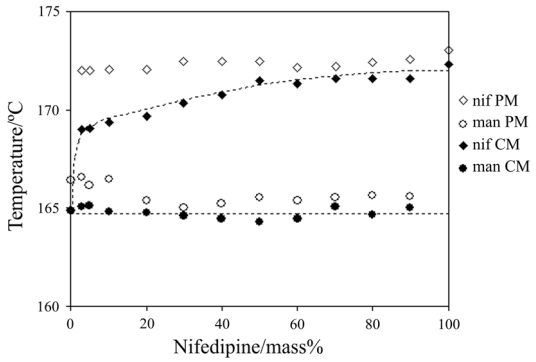

Fig. 7 Binary melting phase diagram of NIF and mannitol (man) systems prepared by physical mixing (PM) or co-melting (CM)

concentration, indicating the monotectic behaviour of the system. A slightly lower melting temperature was observed for mannitol in the second heating, probably due to the presence of a metastable polymorphic modification. FTIR spectra (Fig. 8) exhibit a difference between the physical mixtures and co-melts in the region from 2880 to 3000 cm^{-1}. Peaks were attributed to asymmetric C–H vibrational stretching of mannitol. In the reference to mannitol prior to melting, co-melting caused the formation of thermodynamically less stable modification II, which is monotropically related to modification I [13]. After two months of storage in a desiccator, no major changes of DSC scans or FTIR spectra occurred for this system.

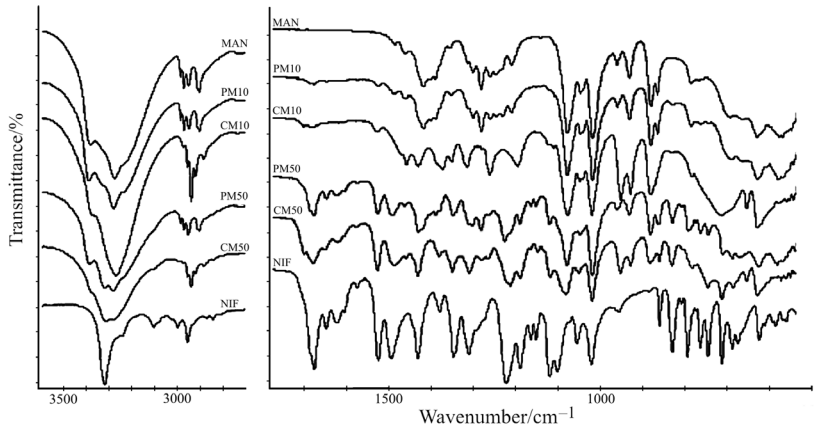

Fig. 8 FTIR spectra of pure NIF, mannitol (MAN), physical mixtures and co-melts (PM and CM, respectively) containing 10 and 50% *w/w* of NIF

The trace of the monotectic has been sketched on the basis of onset temperatures, (dashed lines in the Fig. 7). As in the case of nifedipine-PEG 4000, the system is supported by considerable adhesive interaction in the liquid state, but negligible in

the solid [7]. The melting points determined for NIF and mannitol in the liquid state show that the cohesive interactions in the former are stronger than those in the latter.

Conclusions

NIF–PEG 4000 and NIF–mannitol systems were investigated using DSC. The differences observed between the melting behaviour of physically mixed and previously fused samples were greater in the case of PEG 4000. The melting phase diagram of thermodynamically equilibrated NIF–PEG 4000 co-melts suggest eutectic behaviour with the eutectic composition between 40 and 45% *w/w* of nifedipine. This conclusion was supported by results of optical and hot stage microscopy. NIF–mannitol systems exhibited a monotectic relationship, as deduced from melting phase diagram. Although there are some interactions between NIF and mannitol and between NIF and PEG 4000 in the molten state, their mutual solubility after solidification is close to zero. Therefore, after common melting, only solid suspensions can be expected in the binary systems under investigation, exhibiting the crystalline nature of both active ingredient and auxiliary substance.

* * *

We are very grateful to Dr. Anamarija Zega for providing the FTIR apparatus and Dr. Marjan Bele from National Institute of Chemistry Slovenia for X-ray diffraction measurements.We would also like to express our gratitude to the editors of this special issue, J. M. Rollinger and Cs. Novak, and to the anonymous referees for useful comments.

References

1 W. L. Chiou and S. Riegelman, J. Pharm. Sci., 60 (1971) 1281.
2 J. M. Ginés, M. J. Arias, J. R. Moyano and P. J. Sánchez-Soto, Int. J. Pharm., 143 (1996) 247.
3 S. Verheyen, P. Augustijns, R. Kinget and G. Van den Mooter, Thermochim. Acta, 380 (2001) 153.
4 S. L. Law, W. Y. Lo, F. M. Lin and C. H. Chaing, Int. J. Pharm., 84 (1992) 161.
5 C. W. Lin and T. M. Cham, Int. J. Pharm., 127 (1996) 261.
6 Á. Gombás, P. Szabó-Révész, G. Regdon Jr. and I. Erős, J. Therm. Anal. Cal., 73 (2003) 615.
7 J. L. Ford and P. Timmins, Pharmaceutical Thermal Analysis, Ellis Horwood Limited, Chichester 1989, p. 51.
8 Á. Gombás, P. Szabó-Révész, M. Kata, G. Regdon Jr. and I. Erős, J. Therm. Anal. Cal., 68 (2002) 503.
9 D. Q. M. Craig and J. M. Newton, Int. J. Pharm., 74 (1991) 33.
10 J. M. Ginés, M. J. Arias, A. M. Rabasco, Cs. Novák, A. Ruiz-Conde and P. J. Sánchez-Soto, J. Thermal. Anal., 46 (1996) 291.
11 B. Keymolen, J. L. Ford, M. W. Powell and A. R. Rajabi-Siahboomi, Thermochim. Acta, 397 (2003) 103.
12 A. Burger and K. T. Koller, Sci. Pharm., 64 (1996) 293.
13 A. Burger, J. O. Henck, S. Hetz, J. M. Rollinger, A. A. Weissnicht and E. Stöttner, J. Pharm. Sci., 89 (2000) 457.