



Scholars Research Library

Der Pharma Chemica, 2013, 5(6):149-155
(<http://derpharmachemica.com/archive.html>)



ISSN 0975-413X
CODEN (USA): PCHHAX

Formation of solid dispersion of PEG-1000 with phenacetin according to differential scanning calorimetry

Alexander V. Gerasimov*, Marat A. Ziganshin, Valery V. Gorbachuk and Liana S. Usmanova

Kazan (Volga Region) Federal University, Kazan, Russia

ABSTRACT

The formation of solid dispersions is one of the methods for drug hydrophilization. The data obtained by low temperature differential scanning calorimetry (DSC) has shown an opportunity to formation of solid dispersions of a hydrophobic drug – phenacetin with a biocompatible polymer – polyethylene glycol. It was established that in case of polymer:phenacetin 5-10:1 ratios the crystalline phase of the drug is not formed, while in case of 1-4:1 ratios the pharmacological component shows features of a separate phase and does not form a solid dispersion. The observed exo-effects on DSC curves of the mixtures of polymer:phenacetin with ratios of 1-2:1 and 7-10:1 are related to low-temperature crystallization of polymer. Optimal polymer:drug ratio is 5-6:1. At these ratios phenacetin completely dissolved in the polyethylene glycol phase and the quasi-stationary state caused amorphous part in solid dispersion is not observed. This together with absence of polymer plasticization by phenacetin may facilitate the release of the drug from the composite in hydrophilic media. The melting temperature of solid dispersions does not exceed 35.2 °C allowing their use as capsular drugs, ointments and suppositories.

Keywords: phenacetin, polyethylene glycol, solid dispersion, differential scanning calorimetry.

INTRODUCTION

The majority of modern drugs are poorly soluble in water and this fact leads to poor absorption in the gastrointestinal tract [1-3]. Formation of solid dispersions is one of the promising methods for the increasing the hydrophobic drug biocompatibility [4-11]. Homogeneous distribution of a drug in hydrophilic polymer phase increases solubility and, therefore, bioavailability of the drug. The rate of dissolution increases in case of amorphous drugs based on solid dispersion [6, 12].

Polyethylene glycols are widely used as a water-soluble polymer matrix to deliver drugs [13]. These polymers are biocompatible [14, 15], have good water solubility [16] and low toxicity [17].

Polyethylene glycols with molar mass of 4000 and more are most often used as polymer matrix. For these polymers a possibility of solid dispersion formation with a large amount of drug is shown [18-22]. However such solid dispersions have a relatively high melting temperature.

Previously [23] it had been shown that for polyethylene glycol with a molar mass of 1305-1595 g/mol the formation of the solid dispersions with hydrophobic drug (phenacetin) is observed when the polymer:phenacetin ratio is more than 5:1. Phenacetin in this case does not have any noticeable plasticizing influence on the polymer matrix and the softening temperature of the formed composite does not exceed 45.2 °C. This value is a few degrees higher than the standard human body temperature. So such solid dispersions may be used only in tableted drug manufacture. Polyethylene glycols with melting temperature close to the physiological one may be used to form solid dispersions with temperature regulated drug release. It is also important that the polyethylene glycols are relatively cheap.

The main problem in solid dispersion design is the determination of the interval of polymer:drug ratio at which the crystalline phase of the drug does not formed and the obtained composite is highly soluble in water.

In the present study the optimum ratio between polyethylene glycol which has the melting point close to the physiological temperature and poorly soluble model drug – phenacetin was determined using the differential scanning calorimetry. This information can help to prepare the solid dispersions of poor water-soluble drugs with polymers for increase the effectiveness of the drug and a variety of potential drug forms.

MATERIALS AND METHODS

2.1. Materials.

Polyethylene glycol molecular weight 950-1050 (PEG-1000) was obtained from Aldrich, Lot #MKBH0880V. Phenacetin, 98% was obtained from Aldrich, Lot #BCBD7322. All components were used as received.

2.2. Preparation of mixtures.

Mechanical mixtures of polymer and phenacetin were prepared by mixing of calculated amounts of these materials in an agate mortar until complete homogenization. Mass polymer:phenacetin ratios are 1:1, 2:1, 3:1, 4:1, 5:1, 6:1, 7:1, 8:1, 9:1 and 10:1. The mixtures received represent white paste.

2.3. TG/DSC/MS analysis.

Using combined thermogravimetry and differential scanning calorimetry method (TG/DSC) with the help of STA 449 C Jupiter thermoanalyzer (Netzsch, Germany) the thermal stability of PEG-1000 was determined in the 30-500 °C temperature range. For the identification of the evolved gases QMS 403 C Aëolos quadrupole mass-spectrometer (Netzsch, Germany) coupled with the thermoanalyzer (MS-analysis) was used. The experiment was carried out for samples 7-27 mg in the argon dynamic atmosphere (gas flow rate of 75 ml/min) with the heating speed 5 °C/min. Experiment details are described in [23-25].

The presence of volatile impurities in polymer:drug mechanical mixtures and their thermal stability were studied in temperature range 30-200 °C.

2.4. Low-temperature DSC analysis.

The enthalpies and temperatures of phase transition of PEG-1000 as well as its mechanical mixtures with phenacetin from -60 °C to 160 °C were determined using differential scanning calorimeter DSC 204 F1 Phoenix (Netzsch, Germany), as described in [23]. Measurements were carried out for 8-17 mg samples in the argon dynamic atmosphere (150 ml/min) with the heating/cooling speed 10 °C/min.

RESULTS AND DISCUSSION

3.1. Results of TG/DSC/MS analysis of PEG-1000 and its mechanical mixtures with phenacetin.

Results of the simultaneous TG/DSC/MS analysis for PEG-1000 are shown in Figure 1. It was shown that there is no significant loss of sample weight up to 160 °C. Above 300 °C the thermal destruction of the polymer takes place. This process is accompanied with evolution of water and carbon dioxide as evidenced by the presence of ions with $m/z=18$ and 44 in the mass spectrum, accordingly. On the DSC curve is clearly visible endothermic effect corresponding to the melting of the polymer. The endo-effects above 300 °C are associated with the decomposition of PEG-1000.

For the mechanical mixtures of phenacetin-PEG-1000 the insignificant mass loss (from 0.12% for 1:1 mixture to 1.91% for 10:1 mixture) associated with loss of adsorbed water was observed up to 160 °C (Figure 2). Subsequent sample mass loss in the temperature range 165-200 °C is associated with decomposition of phenacetin (in the mass spectrum there are ions with $m/z=18$ and 44) [23].

On DSC curves the endo-effects of polymer melting are observed. In case of composites of polymer:drug with ratio of 1:1-5:1 also the endo-effect of phenacetin melting are present. For mixtures with polymer:drug ratios above 5:1 the endo-effect of phenacetin melting is not found. No other effects associated with mass loss within the analyzed temperature range were revealed.

Thermal stability of phenacetin was determined earlier [23].

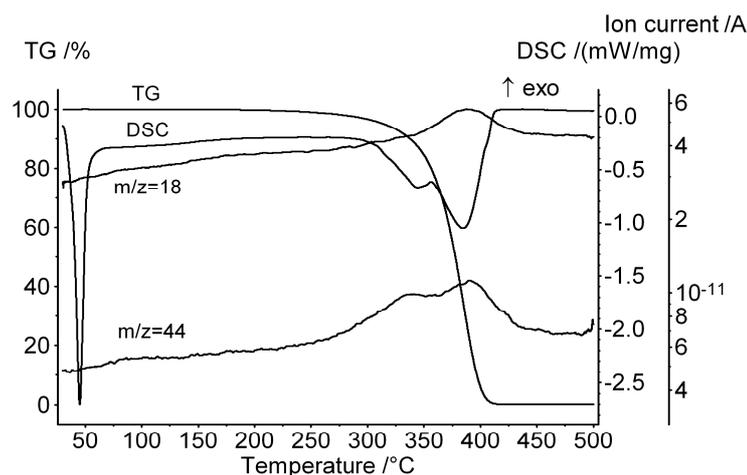


Figure 1: The curves of simultaneous TG/DSC/MS for initial sample of PEG-1000. Argon flow is 75 ml/min, heating rate is 5 °C/min

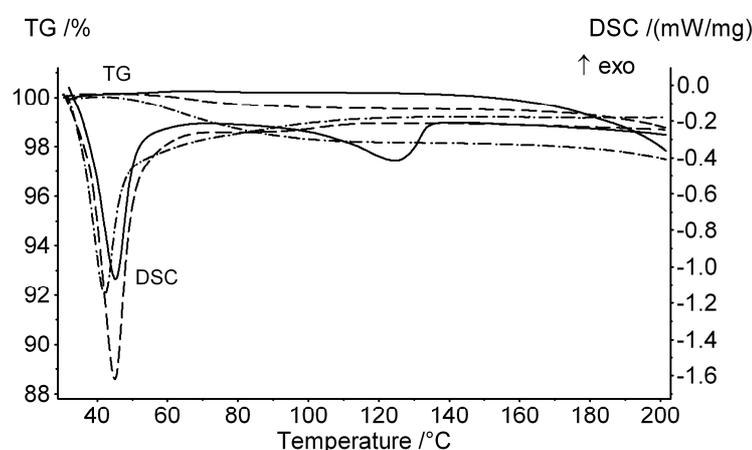


Figure 2: The curves of simultaneous TG/DSC for PEG-1000:phenacetin mechanical mixture with ratio of 1:1 (solid lines), 5:1 (dashed line) and 10:1 (dash-and-dot-line). Argon flow is 75 ml/min, heating rate is 5 °C/min

3.2. Results of low-temperature DSC analysis of PEG-1000 and phenacetin.

In order to obtain precise results of the phase transitions thermal effects a low-temperature differential scanning calorimetry was used. Results of DSC analysis of PEG-1000 and phenacetin in the range -60-160 °C are shown in Figures 3-5. The onset temperatures and enthalpies of melting/crystallization of phenacetin were taken from [23]. Accordantly to heating/cooling curves (Figures 3-5) the melting of PEG-1000 begins at 35.5 °C (enthalpy 184.9 J/g) and 33.3 °C (enthalpy 171.4 J/g) for the first and second heating, accordingly. The onset temperature and enthalpy of the crystallization are equal to 23.4 °C and -167.5 J/g, accordingly. Difference between temperatures of PEG-1000 melting and crystallization is related to fast cooling speed (10 °C/min) leading to formation of supercooled liquid [26-30]. The difference in melting enthalpies at the first and second heating is related to thermal relaxation of polymer [27, 31-33]. The onset temperatures and enthalpies of melting/crystallization for PEG-1000 and phenacetin are represented in Table 1.

Table 1: The data of thermal analysis for initial samples of PEG-1000 and phenacetin

Material	$t_1, ^\circ\text{C}^b$	$t_2, ^\circ\text{C}^c$	$t_3, ^\circ\text{C}^d$	$\Delta H_1, \text{J/g}^e$	$\Delta H_2, \text{J/g}^f$	$\Delta H_3, \text{J/g}^g$
Phenacetin ^a	134.2	134.1	118.4	188.8	188.3	-182.3
PEG-1000	35.4	33.3	23.4	184.9	171.4	-167.5

^a Data from ref. [23].

^b t_1 – onset temperature of endo-effect (first heating).

^c t_2 – onset temperature of endo-effect (second heating).

^d t_3 – onset temperature of exo-effect (cooling).

^e ΔH_1 – enthalpy of the endo-effect (first heating).

^f ΔH_2 – enthalpy of the endo-effect (second heating).

^g ΔH_3 – enthalpy of the exo-effect (cooling).

3.3. Results of low-temperature DSC analysis of PEG-1000:phenacetin mixtures.

Thermophysical properties of PEG-1000:phenacetin mechanical mixtures prepared with ratios w/w of 1:1, 2:1, 3:1, 4:1, 5:1, 6:1, 7:1, 8:1, 9:1 and 10:1 were investigated using the low-temperature DSC in temperature range -60-160 °C. The results of the analysis are presented in Figures 3-5.

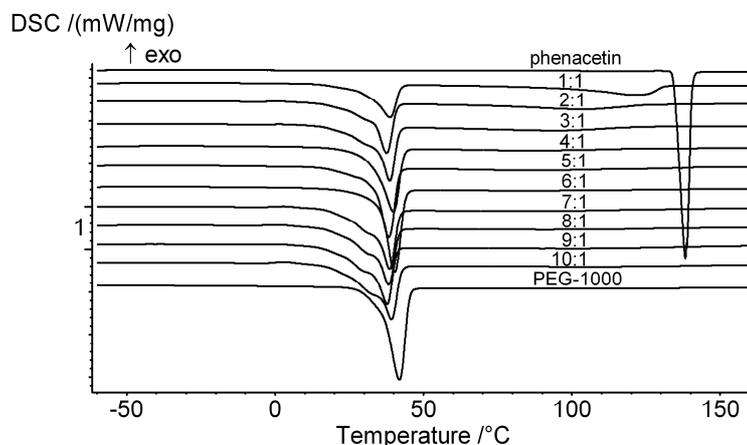


Figure 3: The curves of DSC analysis (first heating) of initial samples of PEG-1000 and phenacetin, and their mixtures. Argon flow is 150 ml/min, heating rate is 10 °C/min

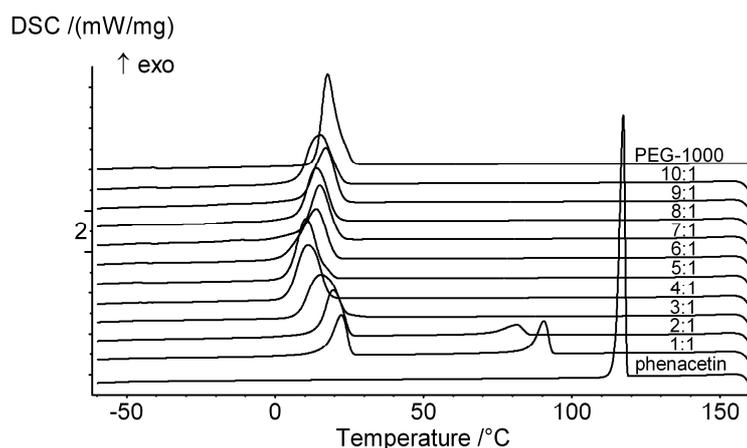


Figure 4: The curves of DSC analysis (cooling) of initial samples of PEG-1000 and phenacetin, and their mixtures. Argon flow is 150 ml/min, heating rate is 10 °C/min.

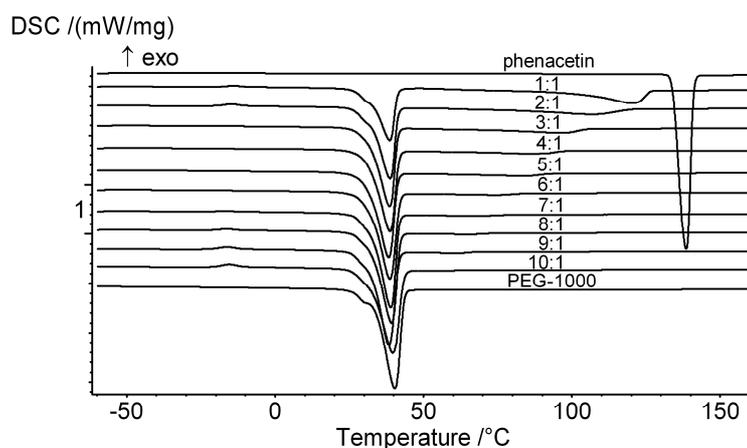


Figure 5: The curves of DSC analysis (second heating) of initial samples of PEG-1000 and phenacetin, and their mixtures. Argon flow is 150 ml/min, heating rate is 10 °C/min

The onset temperatures and enthalpies of melting/crystallization for all analyzed mixtures are shown in Table 2. Alteration of PEG-1000 melting/crystallization thermal effect correlates with polymer amount in the composite that evidences the absence of any significant changes in thermophysical properties of the polymer matrix.

The enthalpies of the first melting of PEG-1000 in the analyzed mixtures calculated with regard to content of the drug are between 179.5-197.7 J/g. These values differ from the melting enthalpy of pure PEG-1000 (Table 1) no more than 6.5%. The deviations of enthalpies of polymer melting for the second heating are less and do not exceed 5.3%. The deviations between the melting onset temperatures of PEG-1000 for mixtures and for individual form do not exceed 2-3 °C in the most cases.

Difference between the enthalpy of crystallization for pure PEG-1000 and for 3:1 mixture is 11.8%, while temperature difference is 6.5 °C.

The onset temperatures of phenacetin melting/crystallization as well as thermal effects ΔH of these processes significantly depend on the content of drug in the composite.

Table 2: The data of thermal analysis for mixtures of PEG-1000 with phenacetin
Values in parenthesis are related to phase transitions of phenacetin

Component ratio (w/w)	t_1 , °C ^a	t_2 , °C ^b	t_3 , °C ^c	t_4 , °C ^d	ΔH_1 , J/g ^e	ΔH_2 , J/g ^f	ΔH_3 , J/g ^g	ΔH_4 , J/g ^h
1:1	30.3 (104.0)	31.5 (103.5)	25.7 (93.1)	-18.8	91.6 (62.6)	90.5 (74.9)	-82.9 (-51.4)	-2.1
2:1	32.5 (80.3)	31.7 (87.3)	25.4 (85.3)	-19.3	123.2 (36.3)	119.1 (41.3)	-107.6 (-25.9)	-3.1
3:1	33.5 (65.1)	31.1 (78.7)	23.8	–	138.4 (25.6)	128.9 (20.9)	-142.4	–
4:1	32.0 (61.9)	31.1 (71.1)	18.1	–	150.3 (15.8)	137.6 (12.2)	-146.6	–
5:1	33.1	31.1	16.9	–	149.6	140.3	-147.0	–
6:1	35.2	31.4	20.1	–	161.3	149.7	-149.4	–
7:1	32.9	31.9	21.7	-22.1	169.8	152.7	-138.3	-1.3
8:1	32.5	31.7	20.6	-21.6	169.8	154.6	-136.1	-2.0
9:1	31.5	31.5	22.7	-21.3	168.9	158.7	-140.4	-3.8
10:1	33.1	31.5	22.7	-20.6	179.7	163.2	-146.1	-4.5

^a t_1 – onset temperature of polymer melting (first heating).

^b t_2 – onset temperature of polymer melting (second heating).

^c t_3 – onset temperature of polymer crystallization (cooling).

^d t_4 – onset temperature of polymer cold crystallization (second heating).

^e ΔH_1 – polymer melting enthalpy (first heating).

^f ΔH_2 – polymer melting enthalpy (second heating).

^g ΔH_3 – polymer crystallization enthalpy (cooling).

^h ΔH_4 – polymer cold crystallization enthalpy (second heating).

For the 1:1 mixture the onset temperature of phenacetin melting is 104.0 °C (first heating) and 103.5 °C (second heating) while values for pure phenacetin are 134.2 °C and 134.1 °C, accordingly. Phenacetin melting enthalpies for the 1:1 mixture and pure form differ on 50.7% (first heating) and 25.7% (second heating). For mixtures with ratio above 5:1 the endo-effect of phenacetin melting is not observed. This fact confirms the complete dissolution of the hydrophobic drug in the polymer phase.

Melting temperature of the polymer in the analyzed solid dispersions does not exceed 35.2 °C, which is close to the standard human body temperature. So, compositions based on PEG-1000 can be used for production of solid drug forms, ointments and suppositories.

As seen from the DSC curves of the second heating for mixtures with ratio 1-2:1 and 7-10:1 additional exo-effects are observed at -18.8 ÷ -22.1 °C. Their values do not exceed -4.5 J/g (Table 2). This phase transition is associated with cold crystallization of PEG-1000 that is specific for crystallizing polymers which can be obtained in the amorphized form. Possibility of cold crystallization of polymer is determined by the ratio between the heating and the crystallization speeds. For highly crystallizable polymers the spontaneous process of cold crystallization with exo-effect is observed at specific temperature [34, 35]. Hence PEG-1000:phenacetin ratios of 5:1 and 6:1 are preferred, because the separate phenacetin crystal phase and the exo-effect of cold crystallization are not observed.

It is necessary note, that for studied mixtures there are no significantly change of the onset temperature and enthalpies of PEG-1000 melting. So, there is no plasticizing effect of the drug on the analyzed polyethylene glycol. Thereof one can expected the easy release of phenacetin in the water solution from the polymer matrix.

CONCLUSION

It was found that mechanical mixing of the PEG-1000 with hydrophobic drug – phenacetin can be used for formation of solid dispersions.

For polymer:drug mixtures with ratio 1-2:1 the crystal phase of phenacetin and exo-effect associated with cold crystallization are observed. The same exo-effect also was found for 7-10:1 mixtures of PEG-1000 with phenacetin. Presence of a quasi-stationary phase in the composite can lead to crystallization of the drug in a supercooled polymer. The resulting crystallites will be marginally soluble and bioavailability of drug will decrease.

The optimum ratio of polymer:drug mixtures is 5-6:1. This ratio prevents any significant plasticizing effect and may facilitate to release of hydrophobic drug in hydrophilic media.

Since PEG-1000 melting temperature does not exceed 35.2 °C, this polymer can be used for formation of capsular drugs for internal use, ointments for external use as well as suppositories.

Acknowledgements

The reported study was supported by RFBR, research project No. 12-03-31788 mol-a.

REFERENCES

- [1] R.P. Patel, D.J. Patel, D.B. Bhimani, J.K. Patel, *Dissolution Technol.*, **2008**, 15, 17-25.
- [2] B.K. Kang, J.S. Lee, S.K. Chon, S.Y. Jeong, S.H. Yuk, G. Khang, H.B. Lee, S.H. Cho, *Int. J. Pharm.*, **2004**, 274, 65-73.
- [3] M. Grove, G.P., Pedersen, J.L., Nielsen, A. Müllertz, *J. Pharm. Sci.*, **2005**, 94, 1830-1838.
- [4] R. Patel, M. Patel, *J. Dispersion Sci. Technol.*, **2008**, 29, 193-204.
- [5] R.N. Sonpal, A.N. Lalwani, V.C. Darji, K.R. Patel, *Int. J. Pharm. Sci. Rev. Res.*, **2011**, 8, 37-52.
- [6] W.L. Chiou, S. Riegelman, *J. Pharm. Sci.*, **1971**, 60, 1281-1302.
- [7] B. Iqbal, A. Ali, J. Ali, S. Baboota, S. Gupta, S. Dang, S. Muhammad, J.K. Sahni, *Recent Pat. Drug Deliv. Formul.*, **2011**, 5, 244-264.
- [8] S. Onoue, Y. Kojo, Y. Aoki, Y. Kawabata, Y. Yamauchi, S. Yamada, *Drug Metab. Pharmacokinet.*, **2012**, 27, 379-387.
- [9] K. Kawakami, *Adv. Drug Delivery Rev.*, **2012**, 64, 480-495.
- [10] A. Newman, G. Knipp, G. Zografis, *J. Pharm. Sci.*, **2012**, 101, 1355-1377.
- [11] A. Singh, Z.A. Worku, G. Van Den Mooter, *Expert Opin. Drug Deliv.*, **2011**, 8, 1361-1378.
- [12] D. Law, E.A. Schmitt, K.C. Marsh, E.A. Everitt, W. Wang, J.J. Fort, S.L. Krill, Y. Qiu, *J. Pharm. Sci.*, **2004**, 93, 563-570.
- [13] V.P. Torchilin, *Nanoparticulates As Drug Carriers*, Imperial College Press, London, **2006**, 756.
- [14] H.D. Park, J.W. Bae, K.D. Park, T. Ooya, N. Yui, J.-H. Jang, D.K. Han, J.-W. Shin, *Macromol. Res.*, **2006**, 14, 73-80.
- [15] F. Cellesi, N. Tirelli, J.A. Hubbell, *Macromol. Chem. Phys.*, **2002**, 203, 1466-1472.
- [16] D.Q.M. Craig, *Int. J. Pharm.*, **2002**, 231, 131-144.
- [17] J. Wang, L.S. del Rosario, B. Demirdirek, A. Bae, K.E. Uhrich, *Acta Biomater.*, **2009**, 5, 883-892.
- [18] M.P. Patil, N.J. Gaikwad, *Acta Pharm.*, **2009**, 59, 57-65.
- [19] A. Bashiri-Shahroodi, P.R. Nassab, P. Szabó-Révész, R. Rajkó, *Drug Dev. Ind. Pharm.*, **2008**, 34, 781-788.
- [20] D.Q.M. Craig, *Drug Dev. Ind. Pharm.*, **1990**, 16, 2501-2526.
- [21] F. Fawaz, F. Bonini, M. Guyot, J. Bildet, M. Maury, A.M. Lagueny, *Int. J. Pharm.*, **1996**, 132, 271-275.
- [22] J.M. Ginés, P.J. Sánchez-soto, A. Justo, M.T. Vela, A.M. Rabasco, *Drug Dev. Ind. Pharm.*, **1990**, 16, 2283-2301.
- [23] A.V. Gerasimov, M.A. Ziganshin, V.V. Gorbachuk, *World Appl. Sci. J.*, **2013**, 24, 920-927.
- [24] L.S. Yakimova, M.A. Ziganshin, V.A. Sidorov, V.V. Kovalev, E.A. Shokova, V.A. Tafeenko, V.V. Gorbachuk, *J. Phys. Chem. B*, **2008**, 112, 15569-15575.
- [25] A.V. Gerasimov, M.A. Ziganshin, A.E. Vandyukov, V.I. Kovalenko, V.V. Gorbachuk, A.-M. Caminade, J.-P. Majoral, *J. Colloid Interface Sci.*, **2011**, 360, 204-210.
- [26] R.H. Elleithy, I. Ali, M.A. Ali, S.M. Al-Zahrani, *J. Appl. Polym. Sci.*, **2010**, 117, 2413-2421.
- [27] V.P. Privalko, R.V. Dinzhos, E.G. Privalko, *Thermochim. Acta*, **2005**, 428, 31-39.
- [28] P.G. Debenedetti, F.H. Stillinger, *Nature*, **2001**, 410, 259-267.
- [29] J.W. Mullin, *Crystallization*. Butterworth-Heinemann, Oxford, **2001**, 4, 600.
- [30] F. Qian, J. Tao, S. Desikan, M. Hussain, R.L. Smith, *Pharm. Res.*, **2007**, 24, 1551-1560.
- [31] C. Bhugra, M.J. Pikal, *J. Pharm. Sci.*, **2007**, 97, 1329-1349.

- [32] R. Surana, A. Pyne, R. Suryanarayanan, *Pharm. Res.*, **2004**, 21, 1167-1176.
[33] R. Surana, A. Pyne, R. Suryanarayanan, *Pharm. Res.*, **2004**, 21, 867-874.
[34] T. Hatakeyama, H. Kasugab, M. Tanakac, H. Hatakeyama, *Thermochim. Acta*, **2007**, 465, 59-66.
[35] B.C. Hancock, G. Zografi, *J. Pharm. Sci.*, **1997**, 86, 1-12.