

## A Calorimetric Study of the Formation of Phenacetin Solid Dispersions with PEG-1400 and Pluronic F127

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**Abstract:** The formation of solid dispersions is one of the methods of drug hydrophilization. The method of low-temperature differential scanning calorimetry showed the possibility to obtain phenacetin solid dispersions with polyethylene glycol and Pluronic F127. The method of low-temperature differential scanning calorimetry proved that when the polymer/phenacetin ratio is 10:1, the crystalline phase of the drug is not fixed, while when the ratio is 1:1 the pharmacological component exhibits the properties of a separate phase and does not form a solid dispersion. Phenacetin does not exhibit plastifying action and does not change the thermophysical properties of polymer phase that can facilitate an easy release of the drug from the composite.

**Key words:** Phenacetin • Polyethylene glycol • Pluronic F127 • solid dispersion • differential scanning calorimetry

### INTRODUCTION

One of the determining factors in the use of solid drugs is their absorption in the gastrointestinal tract which is to a large degree determined by the solubility of the drug in water [1-3]. Poorly soluble drugs are absorbed slowly in comparison with the substances of high solubility that determines their lower effectiveness [3].

Currently there are several methods of improving the solubility of drugs such as increasing the surface area by reducing the size of the particles [4-7], improved wettability [8, 9], reducing the crystallinity by means of creating a solid dispersion [10-17], the use of inclusion compounds such as cyclodextrin derivatives [18-20], the use of polymorphic forms or solvated compounds [21-23] and also the use of salt forms [1, 10, 24].

Polyethylene glycols and Pluronics are widely used as a water-soluble polymer matrix in the delivery of drugs [25, 26]. These polymers are biocompatible [27-29], have good solubility in water [30, 31] and low toxicity [32-34].

Having in the structure both hydrophobic and hydrophilic fragments, Pluronics facilitate the process of penetration of the drug through the cell membrane and reduce the toxicity of the drug [26, 35-37], in some cases they increase its solubility [13, 38] and provide the prolonged type of action [39, 40].

Polyethylene glycols that have a melting point close to physiological may be used for creating solid dispersions with the thermoregulated release of the drug. An important factor is the relative cheapness of polyethylene glycols and Pluronics.

The main problem of the modern pharmacology is the “hydrophilization” of poorly water-soluble effective drugs. The most convenient method of the “hydrophilization” of drugs is the formation of solid dispersions. In this case the main problem is still the determination of the interval ratio of polymer/drug at which the phase of the drug is not fixed and the formed composite is highly soluble in water.

In this work the method of differential scanning calorimetry determined the optimal polymer/drug ratio using the poorly water-soluble model drug phenacetin as an example. Knowing this ratio one can create solid dispersions of poorly water-soluble drugs with polymers increasing in this way the effectiveness of the drug.

### MATERIALS AND METHODS

**Materials:** The amphiphilic poly(ethylene oxide)-poly(propylene oxide)-poly-(ethylene oxide) (PEO-PPO-PEO) block copolymer, Pluronic F127 (Poloxamer 407), was obtained from Sigma, Lot #BCBH4538V. On the basis of Pluronic F127 12600 molecular weight and 70 wt % PEO

content [41]. Poly(ethylene glycol) molecular weight 1305-1595 (PEG-1400) was obtained from Aldrich, Lot #BCBF0699V. Phenacetin, 98% was obtained from Aldrich, Lot #BCBD7322. All components used as received.

**The Preparation of Mixtures:** Mechanical mixtures of polymers with phenacetin were made by mixing the calculated amounts of the substances in an agate mortar till complete homogenization. Weight ratios of polymer/phenacetin are 1:1, 5:1 and 10:1. The obtained mixture was white powder in the case of Pluronic F127 and white paste in the case of PEG-1400.

**TG/DSC/MS Analysis:** The thermal stability of phenacetin, PEG-1400 and Pluronic F127 within the temperature interval of 30-500°C was determined by the method of combined thermogravimetry and differential scanning calorimetry (TG / DSC) with the help of a thermoanalyzer STA 449 C Jupiter (Netzsch, Germany). To identify the released gaseous products of the thermal analysis of the samples a quadrupole mass spectrometer QMS 403 C Aëolos (Netzsch, Germany) was used that was connected with this thermoanalyzer (MS analysis). All the experiments were conducted in the dynamic argon atmosphere (the gas flow rate is 75 ml / min) with the heating rate of 5 deg/min.

The thermocouple of the device was calibrated according to the standard procedure at the temperature and heat flow with the help of a standard set of samples supplied by Netzsch.

The combined TG/DSC analysis began in 15-20 minutes after placing the sample into the measuring chamber of the device (the time necessary for the thermoscales equilibrium). The accuracy of the estimation of the volatile impurities content in the samples is 2%.

The measurements were conducted for the samples of 7-16 mg in aluminum crucibles of 40 microliter with lids having three openings 0.5 mm in diameter each.

The presence of volatile impurities in mechanical mixtures polymer/drug and their thermal stability were studied within the temperature interval of 30-200 °C.

**Low-Temperature DSC Analysis:** The enthalpies and temperatures of the phase transitions in phenacetin as well as in mechanical mixtures within the temperature range of 60-160 °C were estimated with the help of the differential scanning calorimeter DSC 204 F1 Phoenix (Netzsch, Germany). The measurements were conducted

at the heating rate of 10 deg/min in the dynamic argon atmosphere (150 ml/min). Precooled to -60 °C the samples were heated to 160 °C, then cooled to -60 °C and heated to 160 °C. The thermocouple of the device was calibrated according to the standard procedure at the temperature and heat flow with the help of a standard set of samples supplied by Netzsch.

The samples of pure polymers were studied within the temperature range of -60-200°C according to the above described method.

## RESULTS AND DISCUSSION

### Results of TG/DSC/MS Analysis of Individual

**Substances:** Figure 1 shows the results of the combined TG/DSC/MS analysis of the phenacetin samples, PEG-1400 and Pluronic F127. It is clear that within the temperature interval of 30-160 °C a noticeable mass loss is not observed. At the temperature above 300°C the thermal destruction of polymers starts with the release of water and carbon dioxide that is confirmed by the presence of the ions with  $m/z = 18$  and  $44$  accordingly (not shown in Figure 1) in the mass spectrum. Phenacetin starts to intensively loose mass at the temperature of 165 °C (Figure 1a), that is why low-temperature DSC measurements of the composites were conducted below 160 °C in order to avoid thermal destruction. In the DSC curves of the studied samples endoeffects corresponding to the melting of the compounds are clearly seen. Other effects that are not connected with decomposition are not observed. The mass loss of the samples within the temperature interval of 30-160 °C does not exceed 0.3% that confirms almost complete absence of the volatile impurities in the original samples.

### The Results of Tg / Dsc / Ms Analysis of the Mixture:

In the TG/TDS curves of the composite samples (Figure 2 and 3) within the temperature interval of 30-160 °C the mass loss of the samples does not exceed 0.2% that confirms almost complete absence of the volatile impurities in the obtained mixtures. The mass loss of 0.3-2.6% within the temperature interval of 165-200 °C is connected with phenacetin decomposition that is confirmed by the presence of ions with  $m/z=18$  and  $44$  in mass spectrum corresponding to water and carbon dioxide (not shown in Figure 2 and 3). In the DSC curves the endoeffects connected with the melting of the polymer are observed and in the case of the composites obtained when the ratio of polymer/drug component is 1:1 the endoeffect of phenacetin melting is seen

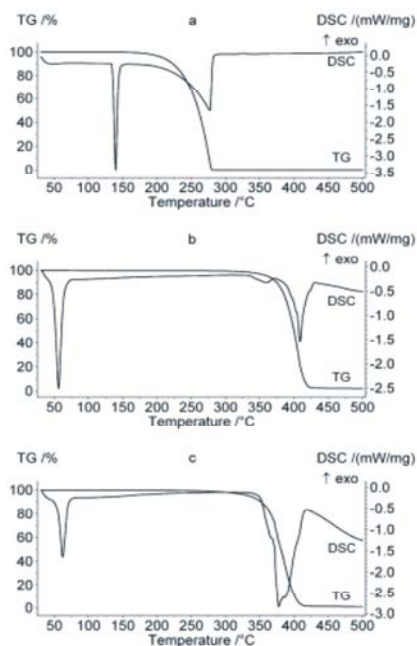


Fig. 1: The curves of the combined TG/DSC analysis of the original samples a) Phenacetin, b) PEG-1400 and c) Pluronic F127 in the dynamic argon atmosphere of 75 ml/min within the temperature interval of 30-500 °C. The heating rate is 5 °C/min.

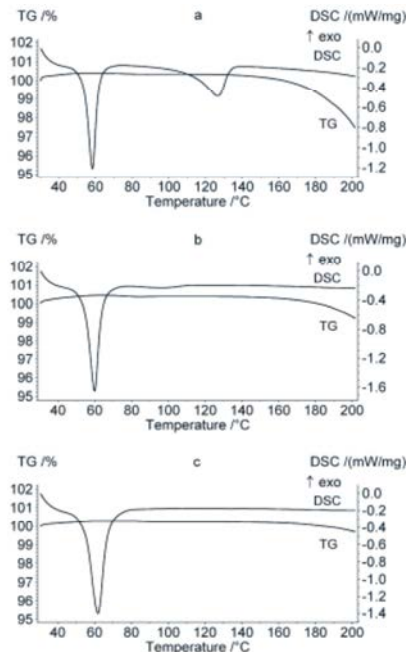


Fig. 3: Curves of the combined TG/DSC analysis of the mixtures of Pluronic F127/phenacetin with the ratio a) 1:1, b) 5:1 and c) 10:1 in the dynamic argon atmosphere of 75ml/min, within the temperature interval of 30-200 °C. The heating rate is 5 °C/min.

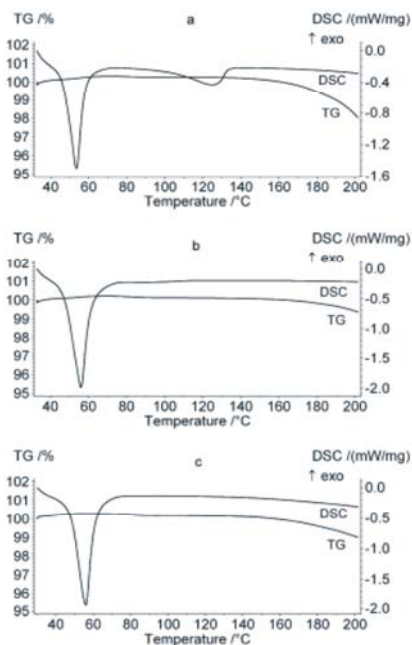


Fig. 2: The curves of the combined TG/DSC analysis of PEG-1400/phenacetin mixtures a) 1:1, b) 5:1 and c) 10:1 in the dynamic argon atmosphere of 75 ml/min, within the temperature interval of 30-200 °C. The heating rate is 5 °C/min.

(Figure 2a and 3a). At the ratio of polymer/drug that equals 1:1 the endoeffect of phenacetin melting is practically not seen (Figure 2b and 3b) and at the ratio of 10:1 is not fixed (Figure 2c and 3c). Other effects that are not connected with the mass loss in the studied temperature interval are not observed.

#### The Results of the Low-Temperature Dsc Analysis of Individual Substances:

For a more precise analysis of the thermal effects of phase transitions the method of a low-temperature differential scanning calorimetry was used. The results of the DSC analysis of the individual polymers within the temperature interval of -60-200°C and phenacetin within the temperature interval of -60-160°C are presented in Fig 4. In the DSC curves of phenacetin heating (Fig. 4a) the endoeffect of melting starting at 134.2°C and 134.1 °C and the enthalpy of 188.8 J/g and 188.3 J/g for the first and the second heating are presented, respectively. The beginning of crystallization and the enthalpy of the corresponding exoeffect are 118.4 °C and -182.3°C J/g, respectively. The difference in the temperatures of melting and crystallization of phenacetin is connected with the rapid cooling rate of 10°C/min and the formation of the supercooled liquid

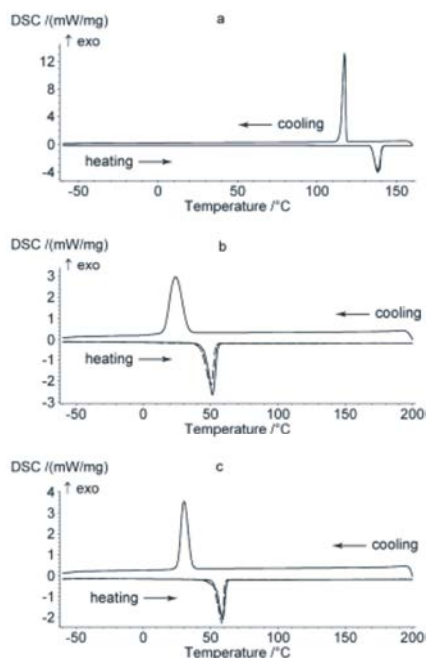


Fig. 4: The DSC curves of the original samples analysis a) Phenacetin, b) PEG-1400 and c) Pluronic F127 in the dynamic argon atmosphere of 150 ml/min, within the temperature interval of -60-160 °C for phenacetin and -60-200 °C for PEG-1400 and Pluronic F127. The heating/cooling rate is 10 °C/min. The solid lines are the first heating and cooling, the dotted lines are the second heating.

[42, 43]. For the curves of the polymer heating/cooling (Fig. 4b and 4c) a similar picture is observed. It should be noted that the enthalpies of the first and the second melting of the polymers differ slightly due to their thermal relaxation [43]. The temperatures of the beginning of melting and corresponding enthalpies are shown in Table 1. Other effects in the DSC curves are not observed.

**The Results of the Low-temperature Dsc Analysis of the Mixture:** The thermal thermophysical properties of the composites of polymer/drug in the ratio of 1:1, 5:1 and 10:1 were studied with the help of the low-temperature DSC within the temperature interval of -60-160 °C. The results of the analysis are presented in Figure 5 and 6.

The temperatures of the beginning of melting/crystallization and also the corresponding enthalpies for all the studied mixtures are presented in Table 2. The decrease of the heat effect of melting/crystallization of the polymer correlates with its ratio in the composite that indicates the absence of any noticeable changes in the thermophysical properties of the polymer matrix.

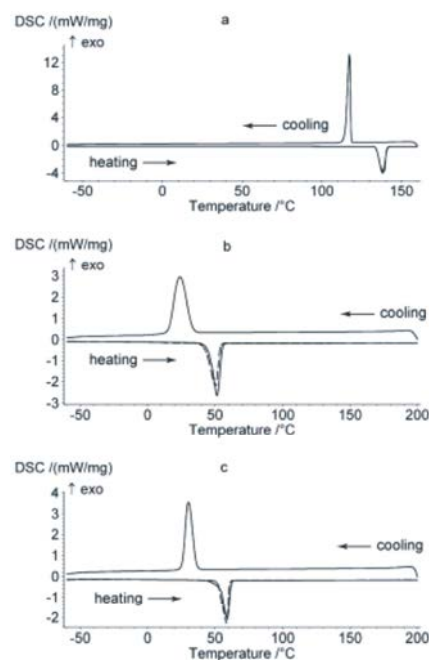


Fig. 5: The curves of the DSC analysis of the mixtures of PEG-1400/phenacetin of the ratio a) 1:1, b) 5:1 and c) 10:1 in the dynamic argon atmosphere of 150 ml/min, within the temperature interval of -60-160 °C. The heating/cooling rate is 10 °C/min. The solid lines are the first heating and cooling, the dotted lines are the second heating.

Thus, calculated, considering the ratio of the drug in the mixture, the value of the enthalpy of the first melting of PEG-1400 is 215.2; 200.9 and 205.5 J/g for the mixtures of PEG-1400/drug with the ratio of 1:1, 5:1 and 10:1, respectively. These values differ not more than 11% from the enthalpy of melting of the pure PEG-1400 that is 194.0 J/g. For the enthalpy of polymer melting during the second heating the difference reaches 14.5% for the mixture with the ratio of 1:1 and do not exceed 5% for other studied mixtures.

The maximum deviation of the enthalpy of melting Pluronic F127 in all the studied mixtures from the enthalpy of melting of the pure polymer is 2.5%. The temperatures of the beginning of the processes of melting/crystallization of phenacetin and also thermal effects of these processes depend on the ratio of the drug in the composite.

Thus, when the phenacetin ratio in the mixture with PEG-1400 is 1:1, the initial melting temperature is 95.0 °C (the first heating) and 102.1 °C (the second heating) while for the pure phenacetin this value is 134.2 and 134.1 °C,

Table 1: The temperatures of the beginning and the enthalpy of the phase transitions in the original samples of phenacetin, PEG-1400 and Pluronic F127.  $t_1$  – the temperature of the beginning of the endoeffect during the first heating,  $t_2$  – the temperature of the beginning of the endoeffect during the second heating,  $t_3$  – the temperature of the beginning of the exoeffect during cooling,  $[\Delta H]_1$  – the enthalpy of the endoeffect during the first heating,  $[\Delta H]_2$  – the enthalpy of the endoeffect during the second heating,  $[\Delta H]_3$  – the enthalpy of the exoeffect during cooling.

Substance	$t_1$ , °C	$t_2$ , °C	$t_3$ , °C	$[\Delta H]_1$ , J/g	$[\Delta H]_2$ , J/g	$[\Delta H]_3$ , J/g
phenacetin	134.2	134.1	118.4	188.8	188.3	-182.3
PEG-1400	45.6	42.5	33.1	194.0	174.2	-176.6
Pluronic F127	53.7	52.0	36.0	136.4	127.4	-124.5

Table 2: The temperatures of the beginning and the enthalpy of the phase transitions in the mixtures of polymers and phenacetin at different ratios.  $t_1$  – the temperature of the initial melting point of the polymer during the first heating,  $t_2$  – the temperature of the initial melting point during the second heating,  $t_3$  – the initial crystallization temperature of the polymer during cooling,  $[\Delta H]_1$  – the enthalpy of the polymer melting during the first heating,  $[\Delta H]_2$  – the enthalpy of the polymer melting during the second heating,  $[\Delta H]_3$  – the enthalpy of the polymer crystallization during cooling. The values relating to the corresponding transitions in phenacetin are given in brackets.

The ratio of the components	$t_1$ , °C	$t_2$ , °C	$t_3$ , °C	$[\Delta H]_1$ , J/g	$[\Delta H]_2$ , J/g	$[\Delta H]_3$ , J/g
PEG-1400/phenacetin						
1:1	44.1 (95.0)	41.4 (102.1)	27.2 (96.8)	107.6 (53.3)	99.6 (53.3)	-97.63 (-52.28)
5:1	45.2	41.6	23.6	167.4	145.8	-160.0
10:1	43.5	41.6	27.8	186.8	166.1	-173.9
Pluronic F127/phenacetin						
1:1	50.6 (111.8)	50.1 (113.7)	34.1 (108.7)	68.7 (71.2)	64.6 (70.3)	-62.2 (-69.3)
5:1	50.8 (77.1)	49.5 (80.7)	32.5	114.2 (8.5)	106.7 (9.5)	-118.0
10:1	51.8	49.3	30.7	127.1	118.4	-122.4

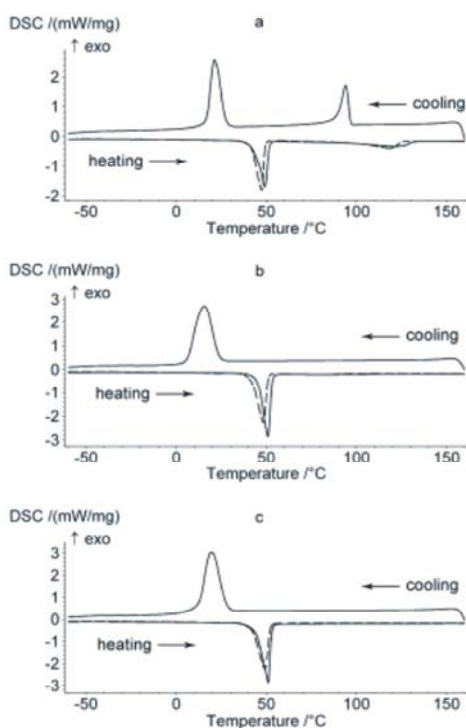


Fig. 6: The DSC analysis curves of the mixtures of Pluronic F127/phenacetin with the ratio a) 1:1, b) 5:1 and c) 10:1 in the dynamic argon atmosphere of 150 ml/min, within the temperature interval of -60-160 °C. The heating/cooling rate is 10 °C/min. The solid lines are the first heating and cooling, the dotted lines are the second heating.

respectively. The enthalpies of phenacetin melting in the mixture and in pure form differ by 43.6 and 43.4%, respectively. When the polymer/drug ratio is 5:1 and 10:1 the endoeffect of phenacetin melting is not fixed, that confirms complete dissolution of the hydrophobic drug in the polymer phase.

For the mixture of phenacetin with Pluronic F127 the deviation percent of the enthalpy of phenacetin melting is 24.6 and 25.3% for the first and the second melting, respectively, at the polymer/drug ratio of 5:1 these changes become even more significant and reach 73.0% and at the ratio of 10:1 the endoeffect of phenacetin melting is not fixed that confirms the complete dissolution of the hydrophobic drug in the polymer phase.

The formation of phenacetin solid dispersion with PEG-1400 is observed at the component ratio of 1:5, in the case of Pluronic F127 this ratio increases and is 1:10 that is in contradiction with the hydrophobicity of the polymers which is the basis for the assumption that the hydrophobic phenacetin will dissolve in Pluronic F127 better. The observed effect may be connected with a significantly lower molecular mass of polyethylene glycol.

Lesser difference of the polymer melting enthalpies in the mixture and in pure form confirms lesser influence of phenacetin on Pluronic F127.

The observed absence of a significant temperature change and polymer melting enthalpies is important both in pure form and in mixtures that shows the absence of the phenacetin plastifying effect on the studied polymers.

This effect shows the realization of relatively weak interactions in the mixtures and the release of phenacetin in an aqueous solution will not be a serious problem.

## CONCLUSIONS

The method of the low-temperature differential scanning calorimetry helped to ascertain that the mechanical mixture of the studied polymers PEG-1400 and Pluronic F127 with the hydrophobic phenacetin drug may be used for getting solid dispersions. The optimum ratio of polymer/drug was discovered that equaled 5:1 in the case of PEG-1400 and 10:1 in the case of Pluronic F127, at the same time phenacetin does not exhibit a noticeable plastifying effect that may contribute to its release in hydrophilic environments.

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## REFERENCES

1. Patel, R.P., D.J. Patel, D.B. Bhimani and J.K. Patel, 2008. Physicochemical characterization and dissolution study of solid dispersions of furosemide with polyethylene glycol 6000 and polyvinyl pyrrolidone K30. *Dissolution Technologies*, 15(3): 17-25.
2. Kang, B.K., J.S. Lee, S.K. Chon, S.Y. Jeong, S.H. Yuk, G. Khang, H.B. Lee and S.H. Cho, 2004. Development of self-microemulsifying drug delivery systems (SMEDDS) for oral bioavailability enhancement of simvastatin in beagle dogs. *International Journal of Pharmaceutics*, 274(1-2): 65-73.
3. Grove, M., G.P., Pedersen, J.L., Nielsen and A. Müllertz, 2005. Bioavailability of seocalcitol I: Relating solubility in biorelevant media with oral bioavailability in rats - Effect of medium and long chain triglycerides. *Journal of Pharmaceutical Sciences*, 94(8): 1830-1838.
4. Chen, W., X. Hu, Y. Hong, Y. Su, H. Wang and J. Li, 2013. Ibuprofen nanoparticles prepared by a PGSS<sup>TM</sup>-based method. *Powder Technology*, 245: 241-250.
5. Nagarwal, R.C., R. Kumar, M. Dhanawat, N. Das and J.K. Pandit, 2011. Nanocrystal technology in the delivery of poorly soluble drugs: An overview. *Current Drug Delivery*, 8(4): 398-406.
6. Keck, C.M. and R.H. Müller, 2006. Drug nanocrystals of poorly soluble drugs produced by high pressure homogenization. *European Journal of Pharmaceutics and Biopharmaceutics*, 62(1): 3-16.
7. Habib, F.S. and M.A. Attia, 1985. Effect of particle size on the dissolution rate of monophenylbutazone solid dispersion in presence of certain additives. *Drug Dev. Ind. Pharm*, 11: 2009-2019.
8. Chow, A.H.L., C.K. Hsia, J.D. Gordon, J.W.M. Young and E.I. Vargha-Butler, 1995. Assessment of wettability and its relationship to the intrinsic dissolution rate of doped phenytoin crystals. *International Journal of Pharmaceutics*, 126(1-2): 21-28.
9. Blagden, N., M. de Matas, P.T. Gavan and P. York, 2007. Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates. *Advanced Drug Delivery Reviews*, 59(7): 617-630.
10. Patel, R. and M. Patel, 2008. Preparation, characterization, and dissolution behavior of a solid dispersion of simvastatin with polyethylene glycol 4000 and polyvinylpyrrolidone K30. *Journal of Dispersion Science and Technology*, 29(2): 193-204.
11. Sonpal, R.N., A.N. Lalwani, V.C. Darji and K.R. Patel, 2011. Solid dispersion: An efficient tool for increasing bioavailability of poorly soluble drugs. *International Journal of Pharmaceutical Sciences Review and Research*, 8(1): 37-52.
12. Chiou, W.L. and S. Riegelman, 1971. Pharmaceutical applications of solid dispersion systems. *Journal of Pharmaceutical Sciences*, 60(9): 1281-1302.
13. Iqbal, B., A. Ali, J. Ali, S. Baboota, S. Gupta, S. Dang, S. Muhammad and J.K. Sahni, 2011. Recent advances and patents in solid dispersion technology. *Recent Patents on Drug Delivery and Formulation*, 5(3): 244-264.
14. Onoue, S., Y. Kojo, Y. Aoki, Y. Kawabata, Y. Yamauchi and S. Yamada, 2012. Physicochemical and Pharmacokinetic characterization of amorphous solid dispersion of tranilast with enhanced solubility in gastric fluid and improved oral bioavailability. *Drug Metabolism and Pharmacokinetics*, 27(4): 379-387.
15. Kawakami, K., 2012. Modification of physicochemical characteristics of active pharmaceutical ingredients and application of supersaturatable dosage forms for improving bioavailability of poorly absorbed drugs. *Advanced Drug Delivery Reviews*, 64(6): 480-495.

16. Newman, A., G. Knipp and G. Zografí, 2012. Assessing the performance of amorphous solid dispersions. *Journal of Pharmaceutical Sciences*, 101(4): 1355-1377.
17. Singh, A., Z.A. Worku and G. Van Den Mooter, 2011. Oral formulation strategies to improve solubility of poorly water-soluble drugs. *Expert Opinion on Drug Delivery*, 8(10): 1361-1378.
18. Stella, V. and H. Qanren, 2008. Cyclodextrins. *Toxicol. Pathol.*, 36: 30-42.
19. Davis, M.E. and M.E. Brewster, 2004. Cyclodextrin-based pharmaceuticals: past, present and future. *Nat. Rev. Drug Dis.*, 3: 1023-1035.
20. Pitha, J. and J. Pitha, 1985. Amorphous water-soluble derivatives of cyclodextrins: Nontoxic dissolution enhancing excipients. *Journal of Pharmaceutical Sciences*, 74(9): 987-990.
21. Sekiguchi, K., M. Kanke, Y. Tsuda, K. Ishida and T. Tsuda, 1973. Dissolution behavior of solid drugs. III. Determination of the transition temperature between the hydrate and anhydrous forms of phenobarbital by measuring their dissolution rates. *Chem. Pharm. Bull.*, 21: 1592-1600.
22. Merisko-Liversidge, E. and G.G. Liversidge, 2011. Nanosizing for oral and parenteral drug delivery: A perspective on formulating poorly-water soluble compounds using wet media milling technology. *Advanced Drug Delivery Reviews*, 63(6): 427-440.
23. Otsuka, Y., M. Yamamoto, H. Abe and M. Otsuka, 2013. Effects of polymorphic transformation on pharmaceutical properties of direct compressed tablets containing theophylline anhydrate bulk powder under high humidity. *Colloids and Surfaces B: Biointerfaces*, 102: 931-936.
24. Kaminski, K., E. Kaminska, K. Adrjanowicz, K. Grzybowska, P. Włodarczyk, M. Paluch, A. Burian, J. Ziolo, P. Lepek, J. Mazgalski and W. Sawicki, 2010. Dielectric relaxation study on tramadol monohydrate and its hydrochloride salt. *Journal of Pharmaceutical Sciences*, 99(1): 94-106.
25. Torchilin, V.P., 2006. *Nanoparticulates As Drug Carriers*. Imperial College Press, pp: 756.
26. Hussein, G.A. and W.G. Pitt, 2008. Micelles and nanoparticles for ultrasonic drug and gene delivery. *Advanced Drug Delivery Reviews*, 60(10): 1137-1152.
27. Park, H.D., J.W. Bae, K.D. Park, T. Ooya, N. Yui, J.H. Jang, D.K. Han and J.W. Shin, 2006. Surface modification of polyurethane using sulfonated PEG grafted polyrotaxane for improved biocompatibility. *Macromolecular Research*, 14(1): 73-80.
28. Cellesi, F., N. Tirelli and J.A. Hubbell, 2002. Materials for cell encapsulation via a new tandem approach combining reverse thermal gelation and covalent crosslinking. *Macromolecular Chemistry and Physics*, 203(10-11): 1466-1472.
29. Lavasanifar, A., J. Samuel and G.S. Kwon, 2002. Poly(ethylene oxide)-block-poly(L-amino acid) micelles for drug delivery. *Advanced Drug Delivery Reviews*, 54(2): 169-190.
30. Moore, T., S. Croy, S. Mallapragada and N. Pandit, 2000. Experimental investigation and mathematical modeling of Pluronic® F127 gel dissolution: Drug release in stirred systems. *Journal of Controlled Release*, 67(2-3): 191-202.
31. Craig, D.Q.M., 2002. The mechanisms of drug release from solid dispersions in water-soluble polymers. *International Journal of Pharmaceutics*, 231(2): 131-144.
32. Desai, S.D. and J. Blanchard, 1998. In vitro evaluation of pluronic F127-based controlled-release ocular delivery systems for pilocarpine. *Journal of Pharmaceutical Sciences*, 87(2): 226-230.
33. Pisal, S.S., A.R. Paradkar, K.R. Mahadik and S.S. Kadam, 2004. Pluronic gels for nasal delivery of Vitamin B12. Part I: Preformulation study. *International Journal of Pharmaceutics*, 270(1-2): 37-45.
34. Wang, J., L.S. del Rosario, B. Demirdirek, A. Bae and K.E. Uhrich, 2009. Comparison of PEG chain length and density on amphiphilic macromolecular nanocarriers: Self-assembled and unimolecular micelles. *Acta Biomaterialia*, 5(3): 883-892.
35. Nagant, C., P.B. Savage and J.P. Dehaye, 2012. Effect of pluronic acid F-127 on the toxicity towards eukaryotic cells of CSA-13, a cationic steroid analogue of antimicrobial peptides. *Journal of Applied Microbiology*, 112(6): 1173-1183.
36. Lin, C.H., W.C. Lin and M.C. Yang, 2009. Fabrication and characterization of ophthalmically compatible hydrogels composed of poly(dimethyl siloxane-urethane)/Pluronic F127. *Colloids and Surfaces B: Biointerfaces*, 71(1): 36-44.
37. Zhang, W., J. Rong, Q. Wang and X. He, 2009. The encapsulation and intracellular delivery of trehalose using a thermally responsive nanocapsule. *Nanotechnology*, 20(27): 275101.
38. Kwon, G.S., 2003. Polymeric Micelles for Delivery of Poorly Water-Soluble Compounds. *Critical Reviews in Therapeutic Drug Carrier Systems*, 20(5): 357-403.

39. Pepiæ, I., N. Jalšenjak and I. Jalšenjak, 2004. Micellar solutions of triblock copolymer surfactants with pilocarpine. *International Journal of Pharmaceutics*, 272(1-2): 57-64.
40. Desai, S.D. and J. Blanchard, 1998. Evaluation of Pluronic F127-based sustained-release ocular delivery systems for pilocarpine using the albino rabbit eye model. *Journal of Pharmaceutical Sciences*, 87(10): 1190-1195.
41. Schmolka, I.R., 1977. A review of block polymer surfactants. *Journal of the American Oil Chemists' Society*, 54(3): 110-116.
42. Elleithy, R.H., I. Ali, M.A. Ali and S.M. Al-Zahrani, 2010. High density polyethylene/micro calcium carbonate composites: A study of the morphological, thermal, and viscoelastic properties. *Journal of Applied Polymer Science*, 117(4): 2413-2421.
43. Privalko, V.P., R.V. Dinzhos and E.G. Privalko, 2005. Enthalpy relaxation in the cooling/heating cycles of polypropylene/ organosilica nanocomposites II. Melting behavior. *Thermochimica Acta*, 428(1-2): 31-39.