Thermodynamics of dissolution and infrared-spectroscopy of solid dispersions of phenacetin

Abstract

In this work enthalpies of dissolution in water of polyethylene glycols (PEGs) having an average molecular weight of 1000 and 1400, Pluronic-F127, phenacetin as well as the composites prepared from them were measured using solution calorimetry at 298.15 K. Intermolecular interaction energies of polymer-phenacetin were calculated on the basis of an additive scheme. It was shown that for mixtures with high content of polymer (>90 wt%) Pluronic-F127 has the highest solubilizing effect, while for mixtures with (4–6):1 polymer:phenacetin ratio the best solubilizing agent is PEG-1400. Infrared-spectra showed a decrease of the number of self-associated molecules of phenacetin with increasing of polymer content in the composites. The obtained results enabled us to identify the features of intermolecular interactions of polymers with a model hydrophobic drug and may be used for optimizing the conditions for preparing solid dispersions based on hydrophilic polymers.

Key words: Enthalpy of solution, molecular interaction, phenacetin, Pluronic-F127, polyethylene glycol, solution calorimetry

INTRODUCTION

One of the important factors which define the bioavailability of drugs for oral administration is their ability to dissolve in water.\footnote{1} It is a well-known fact, that hydrophobic drugs are only partially soluble in aqueous media, resulting in a significant reduction in their effectiveness. Usage of solid dispersions of such drugs as dosage forms for pharmaceutical applications can significantly improve their solubility.\footnote{2-5}

In the last few years, neutral polymeric materials capable of forming solid dispersions with various drugs attracted the attention of chemists, biologists, and pharmacists.\footnote{6-7} Most effective among such polymers are Pluronics,\footnote{6,8-11} as well as polyethylene glycol (PEG) with different molecular mass.\footnote{6,12-15}

The possibility of formation of solid dispersions of the hydrophobic drug that is, phenacetin with Pluronic-F127 and PEG’s was shown previously.\footnote{16,17} It was established that the complete dissolution of the drug in polymer phase occurs when the ratio of polymer: The drug is more than 5:1. Such systems can be used to improve the solubility of hydrophobic drugs by reducing the degree of crystallinity.

The formation of stable intermolecular contacts of a polymeric matrix with the drug can enhance its solubility.\footnote{18,19} So, information about the interaction energies of hydrophobic drugs with polymers helps us to optimally

Address for correspondence:
Dr. Alexander V. Gerasimov,
Department of Physical Chemistry, Butlerov Institute of Chemistry, Kazan Federal University, Kremlevskaya 18, Kazan 420008, Russia.
E-mail: Alexander.Gerasimov@kpfu.ru

How to cite this article: Gerasimov AV, Varfolomeev MA, Ziganshin MA, Gorbatchuk VV, Rakipov IT, Klimovitski AE, et al. Thermodynamics of dissolution and infrared-spectroscopy of solid dispersions of phenacetin. J Adv Pharm Technol Res 2016;7:6-12.
choose a polymer matrix to obtain highly effective drugs based on solid dispersions.

In this paper, we determined thermochemical parameters of dissolution of pure polymers and model hydrophobic drug that is, phenacetin as well as their solid dispersions in water by the method of solution calorimetry. Based on the solubility data the intermolecular interaction energies of PEG and Pluronic-F127 with the phenacetin were calculated. The monotonic increase in the number of free molecules of phenacetin by reducing its content in the studied composites has been ascertained.

**MATERIALS AND METHODS**

**Materials**

Poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) (PEO-PPO-PEO) block copolymer, Pluronic-F127 (Sigma, Lot #BCBH4538V) has 12600 molecular weight and 70 wt% PEO content.\(^{[20]}\) Poly(ethylene glycol) with molecular weight 1305–1595 (PEG-1400) and 950–1050 (PEG-1000) was obtained from Aldrich, Lot #BCBF0699V and Lot #MKBH0880V. Phenacetin with purity >98% was obtained from Aldrich, Lot #BCBD7322. All components used as received. De-ionized water was used as a solvent.

**Methods**

**Preparation of polymer/drug composites**

Composites of phenacetin/polymers were prepared by melting of mechanical mixtures with the required content of components in the ratios 1:1, 6:1 and 10:1 by weight. Melting was carried out under an inert atmosphere at 140°C and then cooled down to room temperature.

**Fourier transform infrared analysis of solid samples**

Fourier transform infrared (FTIR) spectra were collected using Bruker Vertex 70 FTIR spectrometer with a single reflection, germanium crystal ATR accessory (MI Racle, PIKE Technologies) with a resolution of 2 cm\(^{-1}\) in dry air. Recorded complex-shaped contours were fitted with linear combinations of mixed Gaussian-Lorentzian components using OPUS software. Fitting procedures were performed in 1580–1685 cm\(^{-1}\) spectral range to account the influence of neighbor bands.

**Solution calorimetry**

Enthalpies of solution were measured at 298.15 K using handmade semi-adiabatic calorimeter as described earlier.\(^{[21,22]}\) The weight of the solute samples was 0.04–0.06 g. Obtained values of solution enthalpies correspond to the limiting dilution conditions which were confirmed by the absence of concentration dependence of solution enthalpies within the boundaries of their uncertainties. Each experiment was reproduced at least 4 times.

**Solubility of phenacetin in water**

Ultraviolet (UV)-spectrophotometer (Lambda 35, Perkin-Elmer, USA) was used to determine the effect of polymer on limiting solubility of phenacetin. A series of solutions was prepared with fixed content of drug 20 mg/ml at different polymer: phenacetin ratios (1:1, 2:1, 4:1, 6:1, 8:1, and 10:1). After 24 h solutions were filtered-out using a filter (0.22 µm) and diluted by 100 times. The drug content in water at 25°C was determined at 245 nm.

Gibbs free energy \(\Delta_G\) of phenacetin dissolution in an aqueous solution of polymer were calculated according to Eq. (1):

\[
\Delta_G = -2.303 \, R \, T \, \lg(K).
\]  

Where \(K\) is the ratio of phenacetin concentrations in polymer and water, calculated according to Eq. (2):

\[
K = (D_{\text{pol},W} - D_{W})/D_W.
\]  

Where \(D_{\text{pol},W}\) and \(D_W\) are the optical densities of an aqueous solution of phenacetin in the presence and absence of polymer.

Table 1 shows enthalpies of dissolution in water of PEG-1000, PEG-1400, Pluronic-F127 and phenacetin composites with these polymers in the ratios 1:1, 1:6, and 1:10 measured at 298.15 K. Such composition of mixtures was chosen because the crystal phase of the drug is in mixture with 1:1 ratio of polymer: phenacetin, while at the ratios 6:1 and 10:1 the crystal phase absent.\(^{[16,17]}\) The enthalpy of dissolution of phenacetin in water is 29.3 ± 1.1 J/g. For solid dispersions of phenacetin the enthalpies of dissolution increase with increasing the mass fraction of the drug. Only for the

| Polymer              | Polymer: phenacetin ratio |
|----------------------|---------------------------|
| Pluronic-F127        | 10:1                      |
|                      | 6:1                       |
| −34.0±0.2            | 29.5±1.8                  |
| PEG-1000             | 10:1                      |
|                      | 6:1                       |
| −16.6±0.8            | 11.5±0.3                  |
| PEG-1400             | 10:1                      |
|                      | 6:1                       |
| −27.7±0.1            | 0.8±0.4                   |

PEG: Polyethylene glycol
dispersion 1:1 of PEG-1000 with model drug heat effect stays exothermic.

Figure 1 shows that experimentally measured enthalpies of dissolution of the composite \( \Delta_{soln} H^{mix/W} \) in most cases, differ from the values calculated theoretically \( \Delta_{soln} H^{mix/W(calc)} \) Eq. (3). Consequently, the difference between the sum of enthalpies of dissolution of individual compounds, taking into account the mass of components \( \Delta_{soln} H^{mix/W} \) and \( \Delta_{soln} H^{mix/W(calc)} \), can be assumed as a measure (enthalpy) of intermolecular interactions polymer-phenacetin \( \Delta_{int} H^{pol/phenacetin} \) Eq. (4). For some mixtures polymer-phenacetin, \( \Delta_{soln} H^{mix/W} \) are less then calculated \( \Delta_{soln} H^{mix/W(calc)} \). This may be due to the reduced crystallinity of the drug in the solid dispersion.

\[
X \Delta_{soln} H^{pol/W} + Y \Delta_{soln} H^{phenacetin/W} = \Delta_{soln} H^{mix/W(calc)}. \tag{3}
\]

where \( X \) and \( Y \) – mass fractions of polymer and phenacetin in the mixture and \( \Delta_{soln} H^{pol/W} \) and \( \Delta_{soln} H^{phenacetin/W} \) – the molar enthalpies of dissolution of polymer and phenacetin in water, respectively.

\[
\Delta_{soln} H^{mix/W} - \Delta_{soln} H^{mix/W(calc)} = \Delta_{int} H^{pol/phenacetin}. \tag{4}
\]

The calculated \( \Delta_{int} H^{pol/phenacetin} \) values are presented in Table 2 and Figure 2.

A simple thermodynamic diagram was proposed to have a better understanding of dissolution process of studied systems in water [Figure 3].

In this diagram \( \Delta H_i \) corresponds to the energy required to break the intermolecular bonds phenacetin-phenacetin (polymer-phenacetin or polymer-polymer), \( \Delta H_2 \) – solvation energy of free molecules formed during the first stage. \( \Delta H_3 \) (\( \Delta_{soln} H \)) represents the enthalpy of dissolution of phenacetin (a polymer composite with phenacetin or polymer), and \( \Delta H_4 \) is the sum of \( \Delta H_i \) and \( \Delta H_2 \). Thus, the enthalpy of dissolution depends on the energy of intermolecular interactions in a solid substance and the enthalpy of solvation. A positive value of the enthalpy of dissolution indicates the greater energy of intermolecular interactions in the solute compared to a gain in energy due to solvation.

It was found that the enthalpy of interaction of phenacetin with Pluronic-F127 [Table 2] becomes negative upon increasing the fraction of polymer in the mixture, which is associated with less energy consumption for the destruction of crystal lattice of phenacetin and a huge gain in energy due to the formation of intermolecular contacts of polymer-drug. Moreover, the enthalpy of

| Table 2: The enthalpy of polymer-phenacetin intermolecular interactions, J/g |
|------------------------------------------|
| Polymer | Polymer: phenacetin ratio | 10:1 | 6:1 | 1:1 |
|----------|--------------------------|------|-----|-----|
| Pluronic-F127 | 25.5 | 13.1 | 31.8 |
| PEG-1000 | -19.2 | -11.6 | -17.9 |
| PEG-1400 | -10.5 | 6.6 | 0.0 |

PEG: Polyethylene glycol
intermolecular interactions of PEG-1000 and PEG-1400 with phenacetin in the mixtures of different compositions varies in the same way. However, its values in the case of PEG-1000 are negative. Therefore, this system has weaker polymer-drug interactions, and they are less stable than the intermolecular interactions in the crystal lattice of phenacetin. This enhancement of intermolecular interactions of the hydrophobic drug that is, phenacetin with PEG upon increasing their molecular weight can be attributed to an increased hydrophobicity of polymer molecules with its increasing size.[23,24]

**Effect of polymer on solubility of phenacetin in water**

The increase of phenacetin content in the solution with increasing of the PEG’s fraction in the mixture has been observed [Figure 4] using the method of UV-spectrophotometry.

In the case of Pluronic-F127, the maximum phenacetin concentration in solution is achieved at the ratio of polymer:phenacetin 8:1. For ratio 10:1 a reduction of phenacetin content in solution, associated with the formation of a hydrogel, was observed.

The maximum increase of phenacetin content in solution due to the addition of polymer is 2.7, 2.8, 3.7 times for PEG-1000, PEG-1400 and Pluronic-F127, correspondingly. For the mixtures of Pluronic-F127 with phenacetin, a sharp increase in the solubility of the drug [Figure 4] at the ratios above 6:1 was observed. This increasing correlates with a change in the interaction energy of Pluronic-F127 with phenacetin [Figure 2]. For the studied mixtures based on PEG’s, the change in the solubility parameters of phenacetin and the intermolecular interaction energy PEG-phenacetin is not significant.

The results obtained for Gibbs free energy [Table 3] demonstrate the spontaneity of the solubilization process for the polymer-drug ratios (8–10):1 for PEG-1000, (4–10):1 for PEG-1400 and (6–10):1 for Pluronic-F127. The more negative value of $\Delta G$ determines the better solubilizing effect of the polymer.[12] In accordance with the results described above, the most negative value of $\Delta G$ was found for Pluronic-F127 at 8:1 polymer: phenacetin ratio.

The results obtained show that at high concentration of polymer in the mixture, the Pluronic-F127 exerts the biggest solubilizing effect, while for composites with the polymer: phenacetin ratios (4-6):1, the best solubilizing agent is PEG-1400.

**Data of Fourier transform infrared-spectroscopy**

To evaluate the proportion of free and H-bonded molecules of phenacetin in the studied mixtures, the method of infrared (IR)-spectroscopy was used. IR-spectra of the solid samples of PEG-1000, PEG-1400, Pluronic-F127, phenacetin and their solid mixtures are presented in Figures 5-6.

The ratio of integrated intensities of stretching vibration bands of carbonyl groups of phenacetin was used as a measure of the relation between free and H-bonded molecules of phenacetin.

The IR-spectra of the crystal phase of phenacetin in the C=O groups stretching vibrations region contain two contours with peaks maximum at 646 and 1659 cm$^{-1}$,[25] which correspond to the stretching vibrations of the free and H-bonded C=O groups, respectively. The position of maxima of these bands in the polymer: phenacetin composite does not vary.

Complex absorption contours in the IR-spectra were divided into separate components, as the resulting shape of the band, we selected the derivative of Gaussian and Lorenz functions, and the relative contribution of both the functions varied. The results of the analysis of the IR-spectroscopic data are presented in Table 4.

**Table 3: Values of Gibbs free energy of dissolution ($\Delta G^\circ$) of phenacetin in water at different ratios of polymer: phenacetin**

| Polymer: phenacetin ratio | $\Delta G^\circ$, J/mol |
|---------------------------|-------------------------|
|                           | PEG-1000 | PEG-1400 | Pluronic-F127 |
| 1:1                       | 3464.9   | 2759.2   | 5099.1        |
| 2:1                       | 2497.1   | 485.8    | 3353.2        |
| 4:1                       | 1254.0   | −302.4   | 1028.9        |
| 6:1                       | 464.7    | −841.0   | −537.1        |
| 8:1                       | −144.6   | −1173.1  | −2459.4       |
| 10:1                      | −1313.0  | −1520.1  | 719.3         |

PEG: Polyethylene glycol

---

Figure 4: Results of ultraviolet spectrophotometric analysis of aqueous solutions of mixtures polyethylene glycol-1000, polyethylene glycol-1400, Pluronic-F127, and phenacetin at different ratios of components. The optical density is taken at a wavelength of 245 nm.
An analysis of the given data shows an increase in the number of free C=O groups with respect to H-bonded ones, upon decreasing the phenacetin content in all polymers.
The dissolution enthalpies of PEGs having an average molecular weight of 1000 and 1400, Pluronic-F127, phenacetin as well as their solid dispersions were determined. The increase in the concentration of polymer in the mixture with drug leads to a more exothermic dissolution of the solid dispersion, because of a decrease in the drug crystallinity.

The Gibbs energies of dissolution of phenacetin in water show that at ratios of polymer: phenacetin (4–6):1, the best solubilizing agent is PEG with a molecular weight of 1305–1595.

The monotonic increase in the number of non-H-bonded C=O groups of phenacetin due to decreasing of crystallinity of the drug was observed.

Obtained results help us to identify the features of intermolecular interactions of polymers with the model hydrophobic drug and to optimize the conditions for preparing solid dispersions based on hydrophilic polymers.

**Acknowledgment**

This work has been performed according to the Russian Government Program of Competitive Growth of Kazan Federal University.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES**

1. Leuner C, Dressman J. Improving drug solubility for oral delivery using solid dispersions. Eur J Pharm Biopharm 2000;50:47-60.
2. Gerasimov AV, Ziganshin MA, Gorbachuk VV, Usmanova LS. Low molecular weight polyethylene glycols as a matrix to obtain solid dispersions of sulfanilamide. Int J Pharm Pharm Sci 2014;6:372-7.
3. el-Gazayerly ON. Characterization and evaluation of tenoxicam coprecipitates. Drug Dev Ind Pharm 2000;26:925-30.
4. Mura P, Manderioli A, Bramanti G, Ceccherelli L. Properties of solid dispersions of naproxen in various polyethylene glycols. Drug Dev Ind Pharm 1996;22:909-16.
5. Chiou WL, Riegelman S. Pharmaceutical applications of solid dispersion systems. J Pharm Sci 1971;60:1281-302.
6. Vasconcelos T, Sarmento B, Costa P. Solid dispersions as a strategy to improve oral bioavailability of poor water soluble drugs. Drug Discov Today 2007;12:1068-75.
7. Jenkins M. Biomedical Polymers. Cambridge, England: Woodhead Publishing; 2007.
8. Vippagunta SR, Maul KA, Tallavajhala S, Grant DJ. Solid-state characterization of nifedipine solid dispersions. Int J Pharm 2002;236:111-23.
9. Chen Y, Zhang GG, Neilly J, Marsh K, Mawhinney D, Sanzgiri YD. Enhancing the bioavailability of ABT-963 using solid dispersion containing pluronic F-68. Int J Pharm 2004;286:69-80.
10. Bley H, Fussnegger B, Bodmeier R. Characterization and stability of solid dispersions based on PEG/polymer blends. Int J Pharm 2010;390:165-73.
11. Qian F, Tao J, Desikan S, Hussain M, Smith RL. Mechanistic investigation of nifedipine solid dispersions. Int J Pharm 2007;45:1551-60.
12. Patel RF, Patel DJ, Bhimani DB, Patel JK. Physicochemical characterization and dissolution study of solid dispersions of furosemide with polyethylene glycol 6000 and polyvinylpyrrolidone K30. J Dispers Sci Technol 2008;29:17-25.
13. Patel R, Patel M. Preparation, characterization, and dissolution behavior of a solid dispersion of simvastatin with polyethylene glycol 4000 and polyvinylpyrrolidone K30. J Dispers Sci Technol 2008;29:193-204.
14. Law D, Schmitt EA, Marsh KC, Everitt EA, Wang W, Fort JJ, et al. Ritonavir-PEG 8000 amorphous solid dispersions: In vitro and in vivo evaluations. J Pharm Sci 2004;93:563-70.
16. Gerasimov AV, Ziganshin MA, Gorbachtuk VV. A calorimetric study of the formation of phenacetin solid dispersions with PEG-1400 and pluronic F127. World Appl Sci J 2013;24:920-7.

17. Gerasimov AV, Ziganshin MA, Gorbachtuk VV, Usmanova LS. Formation of a solid dispersion of PEG-1000 with phenacetin according to differential scanning calorimetry. Pharma Chem 2013;5:149-55.

18. Zheng X, Yang R, Tang X, Zheng L. Part I: Characterization of solid dispersions of nimodipine prepared by hot-melt extrusion. Drug Dev Ind Pharm 2007;33:791-802.

19. Li Y, Pang H, Guo Z, Lin L, Dong Y, Li G, et al. Interactions between drugs and polymers influencing hot melt extrusion. J Pharm Pharmacol 2014;66:148-66.

20. Schmolka IR. A review of block polymer surfactants. J Am Oil Chem Soc 1977;54:110-6.

21. Zaitseva KV, Varfolomeev MA, Solomonov BN. Thermodynamics of hydrogen bonding of weak bases in alcohol solutions: Calorimetry of the solution, IR-spectroscopy and vapor pressure analysis. J Mol Struct 2012;1018:1-20.

22. Zaitseva KV, Varfolomeev MA, Solomonov BN. Thermodynamic functions of hydrogen bonding of amines in methanol derived from solution calorimetry data and headspace analysis. Thermochim Acta 2012;535:8-16.

23. Oelmeier SA, Dismer F, Hubbuch J. Molecular dynamics simulations on aqueous two-phase systems – Single PEG-molecules in solution. BMC Biophys 2012;5:14.

24. Dismer F, Oelmeier SA, Hubbuch J. Molecular dynamics simulations of aqueous two-phase systems: Understanding phase formation and protein partitioning. Chem Eng Sci 2013;96:142-51.

25. Burgina EB, Baltakhinov VP, Boldyrev VP, Shakhtschneider TP. IR spectra of paracetamol and phenacetin. 1. Theoretical and experimental studies. J Struct Chem 2004;45:64-73.