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Original Article

LOW MOLECULAR WEIGHT POLYETHYLENE GLYCOLS AS MATRIX TO OBTAIN SOLID DISPERSIONS OF SULFANILAMIDE

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ABSTRACT

Objective: The objective of the present study is a determination of optimal ratios of polyethylene glycol:sulfanilamide at which formation of solid dispersion is observed. Also study the effect of the polymer on the limiting solubility of sulfanilamide in water.

Methods: Using low-temperature differential scanning calorimetry (DSC), it was made possible to obtain solid dispersions of sulfanilamide with polyethylene glycols having average molecular weight 1000 and 1400. UV-spectroscopy was used to determine the effect of polymer on limiting solubility of sulfanilamide.

Results: An optimal polymer:sulfanilamide ratios are 7:1 and 4:1 for PEG-1000 and PEG-1400, respectively. Polymer in a drug composition allows for the increase the sulfanilamide content in water up to 3.0 times as compared with the solution of individual drug.

Conclusion: These promising materials can be used for manufacture of drugs in various forms: capsular drugs, ointment and suppositories.

Keywords: Solid dispersion, Sulfanilamide, Polyethylene glycol, Differential scanning calorimetry.

INTRODUCTION

Sulfanilamides are effective drugs for treating infections caused by gram-positive and gram-negative bacteria, some primitive and chlamydial ones [1-3]. However, drugs of this group are generally semi-soluble in water and are poorly digested by organism [4-6]. Increasing the solubility of drugs, including through formation of solid dispersion with hydrophylic polymers, allows to increase the bioavailability and, consequently, the effectiveness of sulfanilamide drugs. However, the main problem remains – how to define polymer: drug ratio interval at which the drug phase is not fixed, and the formed composite gets dissolved well in water. Polyethylene glycols are widely used as dispersion medium for formation of solid dispersions. [7]. They are biocompatible [8], get well dissolved in water [9], and have low toxicity [10].

Polyethylene glycols with molecular weight above 4000 g/mole are used most frequently, because they can form solid dispersions with a large number of drugs [9, 11-23]. It is also important that the high hydrophilic nature of a polymer increases the solubility of hydrophobic drugs associated with the polymer. This improves the physical and chemical stability of drugs, preventing their aggregation in a living organism, as well as during their storage through formation of so-called "conformational cloud" [24, 25].

Polyethylene glycols, with melting temperature close to the physiological temperature, can be used to create solid dispersions on their basis with temperature-controlled release of the drug. Low price of polyethylene glycols is also an important factor. Earlier, it was indicated that polyethylene glycols with relatively low molecular weight (900-2000 g/mole) can form solid dispersions with following hydrophobic drugs: phenacetin, furacilin etc. [24, 25]. This paper provides an opportunity to form solid dispersions of sulfanilamide with polyethylene glycols of different molecular weights.

MATERIALS AND METHODS

Materials

Polyethylene glycol with molecular weight 950-1050 (PEG-1000), Aldrich, Lot #MKBH0880V; polyethylene glycol with molecular weight 1305-1595 (PEG-1400), Aldrich, Lot #BCBF0699V and sulfanilamide 98%, Acros Organics, Lot# A0320450 were used without pre-treatment. Deionized water was used as solvent.

Preparation of mechanical mixtures

Mechanical mixtures of polymers with sulfanilamide were prepared by mixing measured quantities of substances in an agate mortar until complete homogenization. Mass ratios of polymer: sulfanilamide were – 1:1, 2:1, 3:1, 4:1, 5:1, 6:1, 7:1, 8:1, 9:1 and 10:1. The mixtures thus obtained were – white paste in case of PEG-1000 and white powder in case of PEG-1400.

TG/DSC analysis

Thermal stability of sulfanilamide, PEG-1000 and PEG-1400 was determined in the temperature range 30-500 °C using combined thermogravimetry and differential scanning calorimetry (TG/DSC) with the help of STA 449 C Jupiter (Netzsch, Germany) thermo analyzer. The experiment was carried out in dynamic atmosphere of argon (gas flow rate 75 ml/min), with heating rate 5 °C/min. Details of the experiment have been described earlier [31, 32].

Presence of volatile impurities in mechanical mixtures polymer: sulfanilamide and their thermal stability were studied in the temperature range 30-200 °C.

Low-temperature DSC analysis

Enthalpies and phase-transition temperatures of sulfanilamide, PEG-1000, and PEG-1400, as well as their mechanical mixtures in the temperature range -60-200 °C were defined using differential scanning calorimeter DSC 204 F1 Phoenix (Netzsch, Germany), as described earlier [27, 32]. Measurements were done for samples weighing 4-17 mg, with heating rate 5 **C**/min (cooling 10 **C**/min), in dynamic atmosphere of argon (150 ml/min).

Solubility of sulfanilamide in water

UV-spectroscopy (UV-spectrophotometer Lambda 35, Perkin-Elmer, USA) was used to determine the effect of polymer on limiting solubility of sulfanilamide. A series of solutions was prepared with fixed content of drug 20 mg/ml at different polymer: sulfanilamide ratios (1:1, 2:1, 4:1, 6:1, 8:1 and 10:1). After 24 hours the solutions were filtered-out from the undissolved part using filter of pore diameter 0.22 μm and diluted by 1000 times. Increase of drug content in water at 25 °C was determined as a ratio of the values of optical density at wavelength 261 nm, obtained in the presence of different quantity of polymer and without it.

RESULTS AND DISCUSSION

Results of TG/DSC analysis

Figure 1 shows the results of combined TG/DSC analysis of sulfanilamide, PEG-1000 and PEG-1400 samples. It can be observed that there is no noticeable loss of weight in the temperature range 30-200 °C. Thermal destruction of polymers begins at temperature above 300 °C. Sulfanilamide starts to lose weight intensively at temperature 250 °C; therefore low-temperature DSC measurements of composites were carried out at temperature below 200 °C so as to avoid decomposition. DSC curves of studied samples show visible endo-effects corresponding to melting of compounds. DSC curve of sulfanilamide also shows a minor endo-effect at temperature 94 °C, which may be associated with polymorphic transformation from α-sulfanilamide to γ-sulfanilamide [34]. No other effects, not related to decomposition, are observed.

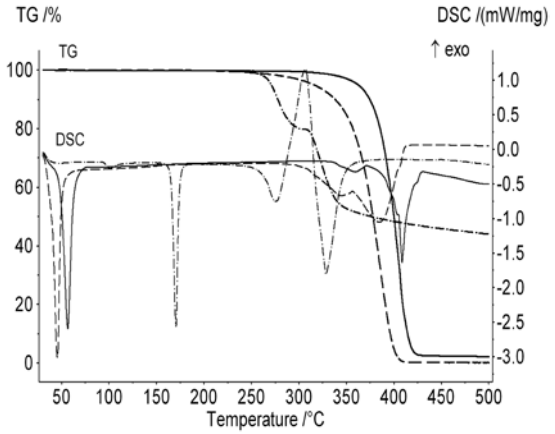

Fig. 1: TG/DSC curves of PEG-1000 (dashed line), PEG-1400 (solid lines) and sulfanilamide (dash and dot line) in dynamic atmosphere of argon 75 ml/min), in the temperature range 30 to 500 °C. Heating rate 5 °C/min.

Weight loss of samples in the temperature range 30 to 200 °C does not exceed 0.2 %, and for composites it does not exceed 1.5% in case of PEG-1000 and 0.1% in case of PEG-1400, which proves that there are practically no volatile impurities in the obtained mixtures.

Results of low-temperature DSC analysis of individual compounds

For a more accurate analysis of phase transitions thermal effects, including in low-temperature region, low-temperature differential scanning calorimetry method was used. Results of the DSC analysis of PEG-1000, PEG-1400 and sulfanilamide in the temperature range -60 to 200 °C have been illustrated in Figures 2-7. Heating/cooling curves of PEG-1000 (Figures 2-4) show melting endo-effect with onset at 35.4 °C and 33.3 °C and with enthalpy 184.9 J/g and 171.4 J/g for the first and second heating, respectively. The starting of crystallization and the enthalpy of respective exo-effect are 23.4 °C, and -167.5 J/g respectively. A similar behavior is observed for heating/cooling curves of PEG-1400 (Figures 5-7). It must be noted that the first and second melting of polymers differ slightly owing to their thermal relaxation [34]. A similar behavior is observed for sulfanilamide. Melting/crystallization onset temperatures and corresponding enthalpies for studied polymers and sulfanilamide are given in Table 1. No other effects are observed on DSC curves in the studied temperature range.

Results of low-temperature DSC analysis of mechanical mixtures

Thermo-physical properties of mechanical mixtures PEG-1000/ sulfanilamide and PEG-1400/sulfanilamide, prepared in ratio 1:1, 2:1, 3:1, 4:1, 5:1, 6:1, 7:1, 8:1, 9:1 and 10:1, were studies using low-temperature DSC in the temperature range -60 to 200 °C. Results of the DSC analysis are given in Figures 2-7 and in Table 2.

During first heating of mixtures PEG-1000/sulfanilamide (Figure 2) polymer's melting endo-effects are observed, and additionally at polymer: drug ratios 1-3:1 sulfanilamide's melting endo-effect is observed. It should be noted that melting enthalpy of polymer varies not proportional to its content in the mixture. So, the enthalpy values, taking into account the content of drug, of first melting of PEG-1000 in studied mixtures are located in the range 61.2-170.0 J/g. For mixture of composition 1:1, the deviation from theoretical values exceeds 200%, and for mixtures of composition 2-6:1 the deviation is lesser and is located in the range 21-32%. Such a difference in theoretical and experimental values can be attributed to low crystallinity fraction of polymer component. For mixtures of composition 7-10:1 the deviation of melting enthalpy experimental values of polymer from theoretical ones does not exceed 12%.

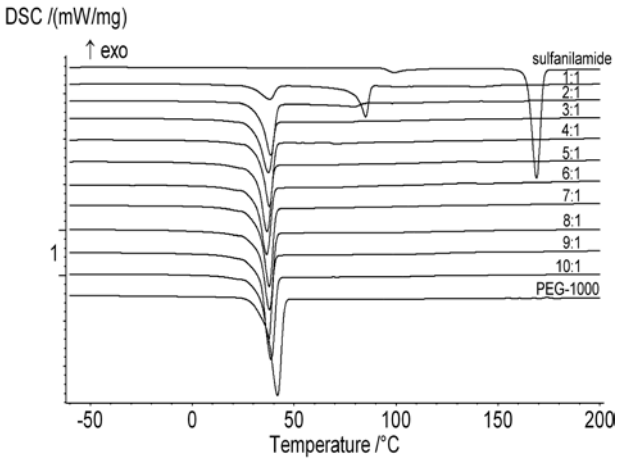

Fig. 2: DSC curves of initial samples of PEG-1000, sulfanilamide and their mixtures of varying composition (1-10:1) in dynamic atmosphere of argon 150 ml/min, in the temperature range of -60 to 200 °C (first heating). Heating rate 5 °C/min.

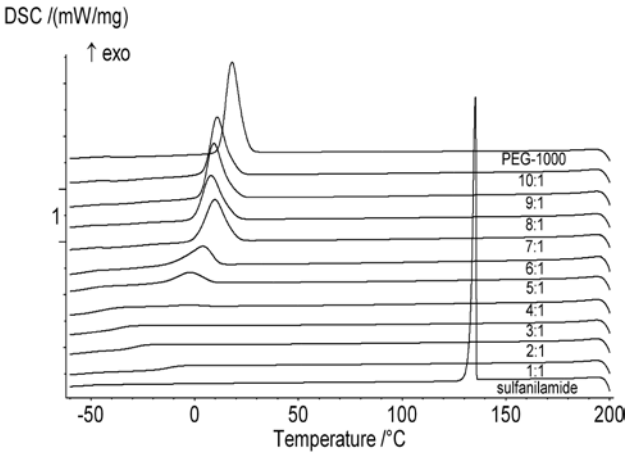

Fig. 3: DSC curves of initial samples of PEG-1000, sulfanilamide and their mixtures of varying composition (1-10:1) in dynamic atmosphere of argon 150 ml/min, in the temperature range of -60 to 200 °C (cooling). Cooling rate 10 °C/min

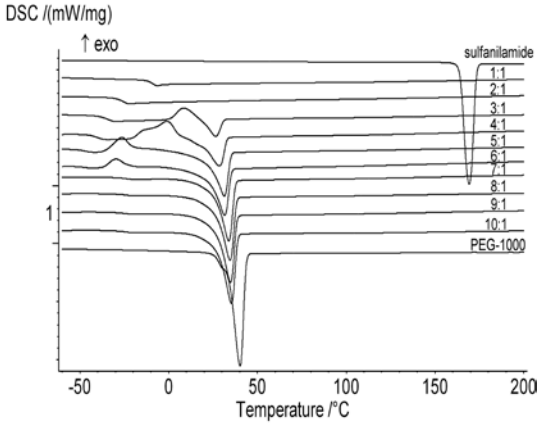

Fig. 4: DSC curves of initial samples of PEG-1000, sulfanilamide and their mixtures of varying composition (1-10:1) in dynamic atmosphere of argon 150 ml/min, in the temperature range of -60 to 200 °C (second heating). Heating rate 5 °C/min.

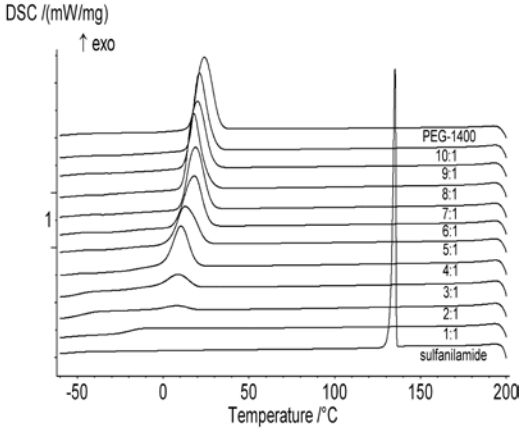

Fig. 6: DSC curves of initial samples of PEG-1400, sulfanilamide and their mixtures of varying composition (1-10:1) in dynamic atmosphere of argon 150 ml/min, in the temperature range of -60 to 200 °C (cooling). Cooling rate 10 °C/min.

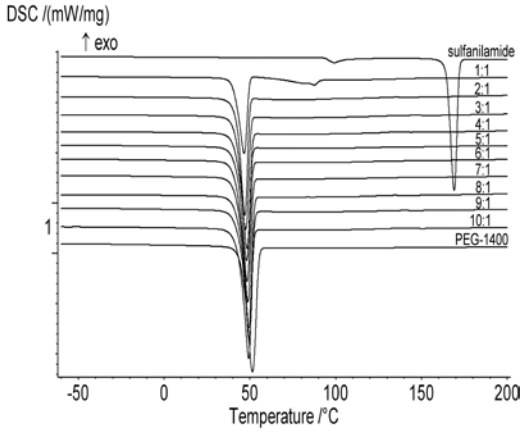

Fig. 5: DSC curves of initial samples of PEG-1400, sulfanilamide and their mixtures of varying composition (1-10:1) in dynamic atmosphere of argon 150 ml/min, in the temperature range of -60 to 200 °C (first heating). Heating rate 5 °C/min

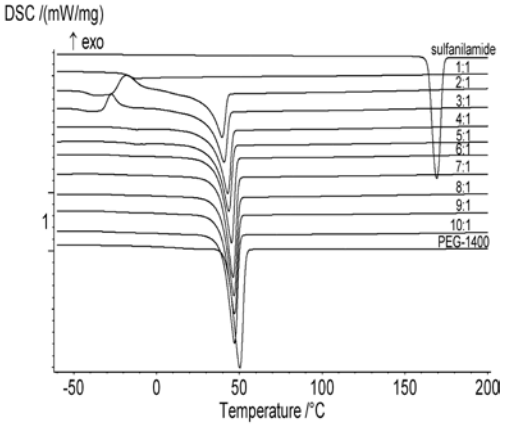

Fig. 7: DSC curves of initial samples of PEG-1400, sulfanilamide and their mixtures of varying composition (1-10:1) in dynamic atmosphere of argon 150 ml/min, in the temperature range of -60 to 200 °C (second heating). Heating rate 5 °C/min.

Table 1: Onset temperatures and phase transition enthalpies in the initial samples of sulfanilamide, PEG-1000 and PEG-1400 t_1 onset temperature of endo-effect at first heating, t_2 onset temperature of endo-effect in second heating, t_3 onset temperature of exo-effect at cooling, ΔH_1 enthalpy of endo-effect at first heating, ΔH_2 enthalpy of endo-effect at second heating, ΔH_3 enthalpy of exo-effect at cooling. Values for endo-effect, associated with polymorphic transformation of sulfanilamide, are given in brackets.

Substance	t_1, °C	t_2, °C	t_3, °C	ΔH_1, J/g	ΔH_2, J/g	ΔH_3, J/g
Sulfanilamide	164.3(93.8)	164.1	135.8	150.2 (12.7)	150.3	-139.0
PEG-1000[a]	35.4	33.3	23.4	184.9	171.4	-167.5
PEG-1400[b]	45.6	42.5	33.1	194.0	174.2	-176.6

[a] Data from ref. [27] [b] Data from ref. [26]

While cooling the mixtures PEG-1000: sulfanilamide (Figure 3), no crystallization exo-effect of drug is observed, and for mixtures of composition 1-4:1 also there is no thermal effect of polymer crystallization, which confirms the formation of super-cooled liquid [35, 36] with sulfanilamide completely dissolved in it. During second heating of studied mixtures PEG-1000: sulfanilamide (Figure 4) no melting thermal effect of the drug is observed. For mixtures of composition 1:1 and 2:1 also, there are no melting endo-effects of the polymer. Deviation of melting enthalpy experimental values for PEG-1000 from theoretically calculated ones are in the range of 27-385% for mixtures of composition 3-6:1 and do not exceed 23% for mixtures of composition 7-10:1. DSC curves of the second heating of 3-6:1 mixtures, in addition to melting effects of polymers, show exo-effect associated with cold crystallization of PEG-1000 specific to crystallizing polymers that can be obtained in amorphized form. Behavior of polymer's cold crystallization is determined by the ratio between the heating rate and the crystallization rate. Spontaneous process begins with exothermic heat effect [37, 38] for polymers with high crystallization ability at a specific temperature.

Table 2: Onset temperatures and phase transition enthalpies in mixtures PEG-1000 and PEG-1400 with sulfanilamide at various ratios.t_1 melting point of polymer at first heating, t_2 melting point of polymer at second heating, t_3 – crystallization point of polymer at cooling, ΔH_1 – melting enthalpy of polymer at first heating, ΔH_2 melting enthalpy of polymer at second heating, ΔH_3 – crystallization enthalpy of polymer at cooling.

Ratio of components	t_1, °C	t_2, °C	t_3, °C	ΔH_1, J/g	ΔH_2, J/g	ΔH_3, J/g
PEG-1000:sulfanilamide						
1:1	28.7 (80.1)[a]	– (-8.7)[b]	–	30.6 (53.5)[a]	–	–
2:1	32.8 (73.4)[a]	– (-25.3)[b]	–	97.1 (12.0)[a]	–	–
3:1	31.1 (62.0)[a]	– (-33.5)[b] (1.3)[c]	–	105.3 (2.8)[a]	26.5 (-27.0)[c]	–
4:1	33.0	– (-39.6)[b] (-20.3)[c]	–	115.1	66.2 (-61.8)[c]	–
5:1	32.0	22.6 (-46.6)[b] (-35.8)[c]	8.8	124.8	112.1 (-27.0)[c]	-40.5
6:1	31.7	22.7 (-47.6)[b] (-36.5)[c]	11.3	130.8	110.1 (-16.3)[c]	-70.2
7:1	32.8	25.4 (-22.7)[b]	18.7	145.8	122.0	-114.0
8:1	33.1	26.1 (-22.8)[b]	17.1	146.9	129.0	-117.9
9:1	33.7	26.3 (-24.3)[b]	16.7	148.3	132.8	-123.9
10:1	34.1	27.1 (-24.2)[b]	16.8	154.5	134.5	-125.2
PEG-1400:sulfanilamide						
1:1	40.6 (70.6)[a]	– (-16.0)[b]	–	107.2 (23.5)[a]	–	–
2:1	42.5	32.4 (-41.3)[b] (-26.0)[c]	17.8	147.9	109.5 (-46.2)[c]	-13.0
3:1	41.9	32.8 (-44.2)[b] (-32.1)[c]	19.1	160.4	119.3 (-25.8)[c]	-55.2
4:1	42.9	35.4 (-14.8)[b]	18.7	167.4	129.5	-126.8
5:1	42.5	35.9 (-15.2)[b]	24.7	165.9	129.6	-132.9
6:1	42.4	37.9 (-15.1)[b]	26.1	179.7	149.5	-161.0
7:1	43.5	38.7 (-13.1)[b]	27.3	181.2	163.5	-171.9
8:1	44.8	38.8 (-15.5)[b]	25.1	186.4	165.5	-176.5
9:1	44.6	38.9 (-14.8)[b]	28.3	185.4	167.3	-175.4
10:1	44.4	39.4 (-16.7)[b]	28.7	186.2	172.6	-176.2

[a] values associated with respective transitions in sulfanilamide. [b] temperature of glass transition. [c] values related to cold crystallization.

Glass transition, whose temperature decreases from -8.7 °C for 1:1 mixture up to -36.5 °C for 6:1 mixture, is observed for all studied mixtures. For mixtures PEG-1000:sulfanilamide of composition 7-10:1, the temperature of glass transition has adjacent values (22.7-24.3 °C).

Thus, mixture 7:1 has the optimum ratio of PEG-1000:sulfanilamide in which no separate crystalline phase of sulfanilamide is observed and there is no exo-effect of polyethylene glycol's cold crystallization, and the content of drug is maximum. During first heating of mixtures PEG-1400/sulfanilamide (Figure 5) polymer's melting endo-effects are observed, and additionally at polymer:drug ratio 1:1 sulfanilamide's melting endo-effect is observed. Deviations of melting enthalpy for PEG-1400 from theoretically calculated values for all studied mixtures do not exceed 13%.

While cooling the mixtures PEG-1400:sulfanilamide (Figure 6), no crystallization exo-effect of drug is observed, and for mixture of composition 1:1 also there is no thermal effect of polymer crystallization, which confirms the formation of super-cooled liquid with sulfanilamide completely dissolved in it.

During second heating of mixtures PEG-1400/sulfanilamide (Figure 7) melting endo-effects of polymer are observed for 2-10:1 mixtures when there is no melting thermal effect of the drug. Deviations of melting enthalpy for PEG-1400 from theoretically calculated values for all studied mixtures do not exceed 12%.

DSC curves of the second heating of 2-3:1 mixtures, in addition to melting effects of polymers, show exo-effects associated with cold crystallization of PEG-1400, which were similarly observed for PEG-1000. Thus, mixture 4:1 has the optimum ratio of PEG-1400: sulfanilamide in which no separate crystalline phase of sulfanilamide is observed and there is no exo-effect of polyethylene glycol's cold crystallization.

Thus, the optimum polymer:drug ratios are 7:1 and 4:1 for PEG-1000 and PEG-1400 respectively.

Effect of polymer on solubility of sulfanilamide in water

Using UV-spectrophotometry technique, it was proved that the presence of polymer increases the concentration of sulfanilamide in the water solution.

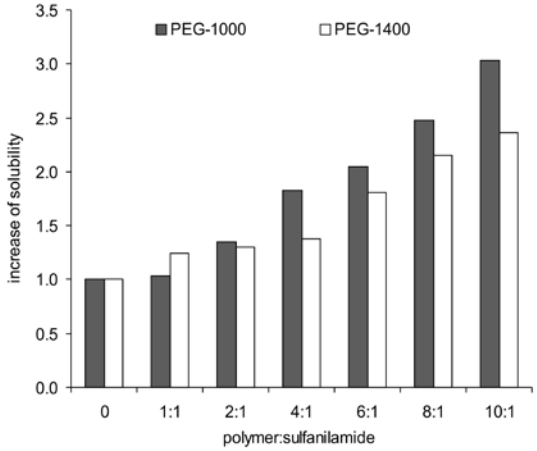

Fig. 8: Results of UV spectrophotometric analysis of water solutions of PEG-1000, PEG-1400 and sulfanilamide at various ratios of components. Optical density is taken at wavelength 261 nm.

Figure 8 shows that when ratio of PEG-1000: sulfanilamide is 1:1, its concentration in the solution is slightly different from the concentration of sulfanilamide in its individual solution. However, when the ratio of PEG-1000:sulfanilamide is 6:1 and 10:1, the concentration of sulfanilamide is 2.5 and 3.0 times more than in its individual solution, respectively. For PEG-1400, adding polymer in the solution leads to increase in the solubility of sulfanilamide by 1.5; 2.0 and 2.5 times for mixtures 1:1, 6:1 and 10:1 respectively (Figure 8). Thus, using polyethylene glycol with average molecular weight 1000 and 1400 the solubility of hydrophobic drug – sulfanilamide can be increased by up to 3.0 times which, in turn, improves the absorbability of drug thereby improving its effectiveness.

CONCLUSIONS

Thermo-physical properties of composites based on polyethylene glycols and hydrophobic drug – sulfanilamide were studied. Using low-temperature differential scanning calorimetry it has been proved that polyethylene glycols with average molecular weight 1000 and 1400 are capable of forming solid dispersions with sulfanilamide. With the optimum polymer:drug ratios are 7:1 and 4:1 for PEG-1000 and PEG-1400 respectively. Using UV-spectrophotometry technique it has been proven that the co-dissolution of sulfanilamide with PEG-1000 and PEG-1400 leads to increase in drug content in the water by up to 3.0 and 2.5 times, respectively, as compared with individual solution of sulfanilamide. It is shown that the melting temperature of the analyzed solid dispersions does not exceed 39.4 °C. These promising materials can be used for manufacture of drugs in various forms: capsular drugs, ointment and suppositories.

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