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Original Article

INCREASING THE SOLUBILITY OF DIPYRIDAMOLE USING POLYETHYLENE GLYCOLS

ALEXANDER V. GERASIMOV, MARAT A. ZIGANSHIN, VALERY V. GORBATCHUK, LIANA S. USMANOVA

Kazan Federal University, 420008, Kremlevskaya 18, Kazan, Russia.
Email: gerasimov@kpfu.ru

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ABSTRACT

Objective: The objective of the present study is a determination of the limiting solubility of dipyridamole in water and optimal ratios of polyethylene glycol:dipyridamole at which formation of solid dispersion is observed.

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

Results: The optimal ratio of polymer:Drug is 1:1, and is 3:1 for PEG-1000 and PEG-1400 respectively. Joint dissolution of dipyridamole with PEG-1400 and PEG-1000 increases the drug content in the water by up to 8.1 times and up to 175 times, compared with the solution containing only dipyridamole.

Conclusion: using systems based on dipyridamole and polyethylene glycol with average molecular weight of 1000, may increase the bioavailability of the drug and consequently reduce the dosages. Wide range of ratios, in which the formation of solid dispersions is possible, enables to adjust the solubility of dipyridamole in neutral aqueous media.

Keywords: Dipyridamole, Polyethylene glycol, Solubility in the water, Solid dispersion, Differential scanning calorimetry, UV spectroscopy.

INTRODUCTION

Dipyridamole is widely used for controlling and treating of angina pectoris, as well as to clinically prevent recurrence of myocardial infarction and thrombosis [1].

Dipyridamole is a drug with pH dependent solubility [2]. Since an increase of pH in gastro-intestinal tract reduces solubility of dipyridamole, the main places of its absorption are stomach and duodenum [3]. As the drug remains in the stomach for a short period of time than in the intestine, the bioavailability of dipyridamole upon oral administration would be low [4].

One of the main solutions to this problem is to create membrane-controlled release pellets, gastric floating prolonged-release beads and none gastric resident sustained-release pellets [5-7]. On the other hand, increase in the aqueous solubility of dipyridamole by solubilizing polymers will improve the bioavailability of the drug in the intestine and would reduce the frequency of drug dose.

Solubilizing agents used in the research work are biocompatible polymers – polyethylene glycols with average molecular weight of 1000 (PEG-1000) and 1400 (PEG-1400). These polymers have proven themselves as a sample in the preparation of solid dispersions of hydrophobic drugs [8-10]. They are biocompatible [11], readily soluble in water [12] and less toxic [13]. It is important to note that highly hydrophilic character of polymer would increase the solubility of hydrophobic drugs associated with it. This improves the physical and chemical stability of formulations by preventing aggregation of drug in living organism and also during storage, due to the formation of so called "conformational cloud" [14].

Formation of dipyridamole solid dispersions based on polyethylene glycol with average molecular weight of 1000-1400 will significantly increase the solubility of the drug and reduce dipyridamole dosage. Wide range of ratios, in which the formation of solid dispersions is possible, will allow to regulate the solubility of poorly water-soluble drug – dipyridamole.

Differential scanning calorimetry has shown the possibility of forming solid dispersions of dipyridamole with studied polyethylene glycols. Optimal ratio of polymer:Dipyridamole is 1:1 and 3:1 for PEG-1000 and PEG-1400 respectively.

UV-spectrophotometry has shown that using of PEG-1000 as a solubilizing agent enables increase in the content of dipyridamole in water by 175 times. Such increase in solubility can be attained both by the solubilizing effect of polyethylene glycol and by decreasing the degree of crystallization of the drug due to the formation of solid dispersions.

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 dipyridamole 98%, Sigma, Lot # BCBK1596V were used without further purification. Deionized water was used as solvent.

Preparation of mechanical mixtures

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

TG/DSC analysis

The method of combined thermogravimetry and differential scanning calorimetry (TG/DSC) using thermal analyzer STA 449 C Jupiter (Netzsch, Germany) determines the thermal stability of dipyridamole, PEG-1000 and PEG-1400 in the temperature range of 30-500 °C. The experiment was carried out in a dynamic atmosphere of argon (75 ml/min), at heating rate of 5 °C/min. Details of experiment are described earlier [15,16].

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

Low-temperature DSC analysis

Enthalpies and transition temperature of dipyridamole, PEG-1000 and PEG-1400, as well as their mechanical mixtures in the

temperature range of -60-200 °C were determined using differential scanning calorimeter DSC 204 F1 Phoenix (Netzsch, Germany), as described earlier [8,17]. Measurements were carried out on samples weighing 4-17 mg, at the heating rate of 5 °C/min (cooling 10 °C/min), in a dynamic atmosphere of argon (150 ml/min).

Study on aqueous solubility of dipyridamole

Effect of polymer content on the limiting solubility of dipyridamole has been determined using the method of UV spectroscopy (UV-spectrophotometer Lambda 35, Perkin-Elmer, USA). Different solutions were prepared with constant drug content of 20 mg/ml using various ratios of polymer:Dipyridamole (1:1, 2:1, 4:1, 6:1, 8:1 and 10:1). After 24 hours, the solutions were separated from the undissolved part using a filter with pore diameter of 0.22 µl, and diluted 5 times for mixtures of PEG-1400:dipyridamole composition of 1-10:1 and PEG-1000:dipyridamole composition at 1:1, 10 times for mixture of PEG-1000:dipyridamole composition at 2:1, 20 times for the mixture of PEG-1000:dipyridamole mixture at 4:1, and 40 times for mixtures of PEG-1000:dipyridamole composition 6-10:1. Solution containing only dipyridamole was not diluted. Increasing the content of the drug in water at 25 °C was determined as the ratio of absorbance values at a wavelength of 288 nm, which was obtained in the presence of various amounts of the polymer and without it.

RESULTS AND DISCUSSION

Results of TG/DSC analysis

Figure 1 shows the results of combined TG/DSC analysis of dipyridamole. It is found that at temperature range of 30-200 °C, there is no significant loss in weight. At temperatures above 230 °C, thermal decomposition of dipyridamole begins and therefore, measurement of composites in low-temperature DSC analysis was carried out up to 200 °C in order to avoid decomposition. DSC curves of dipyridamole in the temperature range of 30-200 °C clearly show the endothermic effects corresponding to the polymorphic transition (peak temperature 130 °C) [18] and melting of the drug. Thermal effects on the DSC curve above 230 °C are associated with thermal degradation of dipyridamole.

Loss of weight in the temperature range of 30-200 °C does not exceed 0.1%. For composites of dipyridamole with polyethylene glycols, weight loss in the temperature range of 30-200 °C does not exceed 1.2% in case of PEG-1000 and 0.3% in the case of PEG-1400, which means a complete absence of volatile impurities in the obtained mixtures.

Data for PEG-1000 and PEG-1400 were obtained earlier [8,9].

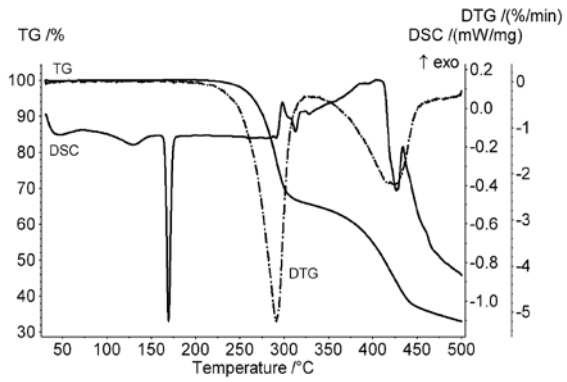

Fig. 1: The results of TG/DSC analysis of dipyridamole in the dynamic atmosphere of argon at 75 ml/min, in the temperature range 30-500 °C. Heating rate is 5 °C/min.

Results of low temperature DSC analysis of individual compounds

For the more precise analysis of the thermal effects of phase transitions, including low-temperature region, method of low temperature differential scanning calorimetry was used. The results of DSC of dipyridamole in the temperature range of -60-200 °C are shown in Figures 2-7. The heating/cooling curves of dipyridamole (Figures 2-4) indicate an endothermic effect of melting which begins from 166.4 °C and 160.8 °C and enthalpy of 66.2 J/g and 54.2 J/g for the initial and second heating respectively. Onset of crystallization and enthalpy of corresponding exothermic peak is 140.9 °C and -51.7 J/g respectively.

DSC curve of initial heating also have endothermic effect with starting temperature of 91.5 °C and enthalpy of -21.6 J/g, which corresponds to the polymorphic transition of dipyridamole. Other effects on DSC curves were not observed in the studied temperature range. Onset temperature of melting/crystallization and corresponding enthalpy for polymers and dipyridamole is shown in Table 1. Data for PEG-1000 and PEG-1400 were taken from [8,9].

Table 1: Onset temperatures and enthalpy of phase transitions in initial samples of dipyridamole, PEG-1000 and PEG-1400. t_1 – onset temperature of endothermic effect at initial heating, t_2 – onset temperature of endothermic effect at second heating, t_3 – onset temperature of exothermic effects while cooling, ΔH_1 – enthalpy of endothermic effect at initial heating, ΔH_2 – enthalpy of endothermic effect at second heating, ΔH_3 – enthalpy at exothermic effects while cooling. Values for endothermic effect associated with polymorphic transition of dipyridamole are provided in brackets.

Substance	t_1, °C	t_2, °C	t_3, °C	ΔH_1, J/g	ΔH_2, J/g	ΔH_3, J/g
Dipyridamole	166.4 (91.5)	160.8	140.9	66.2 (21.6)	54.2	-21.6
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. [9], [b)] Data from ref. [8]

Results of low-temperature DSC analysis of mixtures

Thermo-physical properties of PEG-1000/dipiridamol and PEG-1400/dipiridamol mixtures which are prepared in 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 -60-200 °C. The results of analysis are shown in Figures 2-7.

At initial heating of PEG-1000/dipiridamol mixtures (Figure 2), endothermic effects of polymer melting is fixed, while the endothermic effects of dipyridamole melting are not observed. This fact indicates the formation of solid dispersions of dipyridamole with PEG-1000 while blending. At second heating of the examined mixtures of PEG-1000:Dipyridamole (Figure 4), thermal effect of melting of the drug is also absent. Upon cooling of mixtures of PEG-1000:Dipyridamole (Figure 3), exothermic effect in crystallization of the drug is not fixed, but composite shape of crystallization exothermic effects are observed for polyethylene glycol, which may be due to co-crystallization of dipyridamole with PEG-1000.

In this connection, an optimal ratio of PEG-1000: Dipyridamole has a 1:1, which does not have fixed separate crystalline phase of dipyridamole, and the drug content is maximum.

During initial heating of mixtures PEG-1400/dipiridamol (Figure 5), endothermic effects of polymer melting are fixed. At ratio of polymer:drug 1-2:1 additionally contains less endothermic effects of dipyridamole melting.

Second heating of mixtures PEG-1400/dipiridamol (Figure 7) have a similar pattern, indicating that the formation of solid dispersions at a ratio of PEG-1400:dipyridamole more than 2:1 are observed.

Crystallization exothermic effect of the drug is not fixed upon cooling of mixtures PEG-1400:dipyridamole (Figure 6).

Thus, the optimal polymer:drug ratio is 1:1 and 3:1 for PEG-1000 and PEG-1400 respectively.

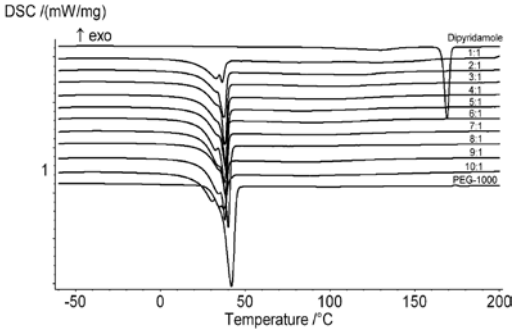

Fig. 2: DSC curves of PEG-1000, dipyridamole initial samples and their mixtures (1-10:1) in dynamic atmosphere of argon at 150 ml/min, in the temperature range -60-200 °C (initial heating). Heating rate is 5 °C/min.

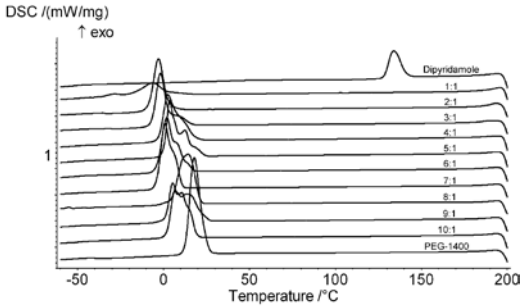

Fig. 3: DSC curves of PEG-1000, dipyridamole initial samples and their mixtures (1-10:1) in dynamic atmosphere of argon at 150 ml/min, in the temperature range -60-200 °C (cooling). Cooling rate is 10 °C/min.

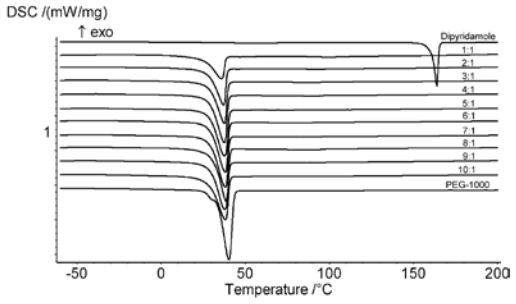

Fig. 4: DSC curves of PEG-1000, dipyridamole initial samples and their mixtures (1-10:1) in dynamic atmosphere of argon at 150 ml/min, in the temperature range -60-200 °C (second heating). Heating rate is 5 °C/min.

Effect of polymer on solubility of dipyridamole in water

Using UV-spectrophotometry technique, it was proved that the presence of polymer increases the concentration of dipyridamole in the water solution. At Figure 8 has plotted values of increase in dipyridamole content in aqueous solution where there is varying amounts of polyethylene glycols.

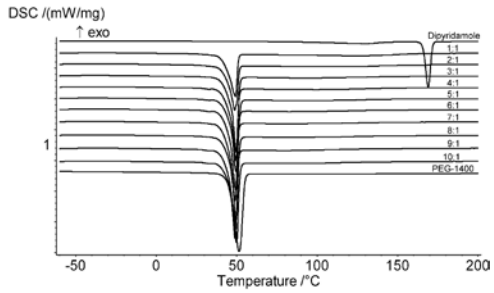

Fig. 5: DSC curves of PEG-1400, dipyridamole initial samples and their mixtures (1-10:1) in dynamic atmosphere of argon at 150 ml/min, in the temperature range -60-200 °C (initial heating). Heating rate is 5 °C/min.

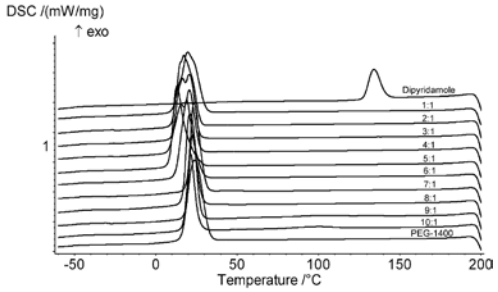

Fig. 6: DSC curves of PEG-1400, dipyridamole initial samples and their mixtures (1-10:1) in dynamic atmosphere of argon at 150 ml/min, in the temperature range -60-200 °C (cooling). Cooling rate is 10 °C/min.

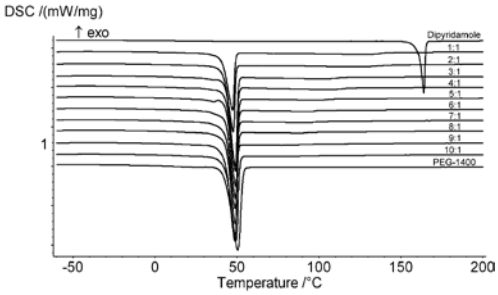

Fig. 7: DSC curves of PEG-1400, dipyridamole initial samples and their mixtures (1-10:1) in dynamic atmosphere of argon at 150 ml/min, in the temperature range -60-200 °C (second heating). Heating rate is 5 °C/min.

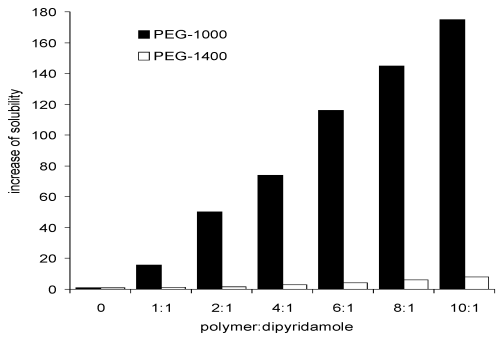

Fig. 8: Increase in dipyridamole content in aqueous solution in the presence of PEG-1000 and PEG-1400 according to UV spectrophotometric analysis. Ratio of polymer:dipyridamole 1:1, 2:1, 4:1, 6:1, 8:1 and 10:1. Optical density is taken at a wavelength of 288 nm.

Figure 8 shows that even at a ratio of PEG-1000:Dipyridamole of 1:1, dipyridamole concentration in the solution is 15 times higher than in the aqueous solution of the drug. When the ratio of PEG-1000: Dipyridamole is equal to 10:1, dipyridamole content in aqueous solution increases in 175 times. Inclusion of polymer in the PEG-1400 solution also increases the solubility of dipyridamole, but to a lesser extent. Thus, when the ratio of PEG-1400:Dipyridamole is equal to 10:1, the increase in solubility is not more than 8.1 times (Figure 8).

Thus, by using polyethylene glycol with an average molecular weight of 1000, solubility of hydrophobic drug – dipyridamole is up to 175 times, which in turn enhance the absorbability of the drug and neutral solutions and as a result, increases its effectiveness.

CONCLUSIONS

At the present work examined the thermal properties of composites based on polyethylene glycol and hydrophobic drug – dipyridamole.

Low temperature differential scanning calorimetry showed that polyethylene glycols with an average molecular weight of 1000 and 1400 are capable of forming solid dispersion with dipyridamole. The optimal ratio of polymer:Drug is 1:1, and is 3:1 for PEG-1000 and PEG-1400 respectively.

UV-spectrophotometry method indicated that joint dissolution of dipyridamole with PEG-1400 and PEG-1000 increases the drug content in the water by up to 8.1 times and up to 175 times, compared with the solution containing only dipyridamole.

Using systems based on dipyridamole and polyethylene glycol with average molecular weight of 1000, may increase the bioavailability of the drug and consequently reduce the dosages. Wide range of ratios, in which the formation of solid dispersions is possible, enables to adjust the solubility of dipyridamole in neutral aqueous media.

CONFLICT OF INTERESTS

Declared None

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