

SOLID DISPERSIONS OF FLUFENAMIC ACID WITH PEG 4000 AND PEG 6000

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Abstract

Non-steroidal anti-inflammatory drugs have an important impact in the actual medicinal therapy, having indications in covering the range from rheumatic inflammations to cardio-vascular, genito-urinary and stomatological diseases. Flufenamic acid is a non-steroidal anti-inflammatory drug, from the class of fenamates. It exhibits poor aqueous solubility, accordingly the aim of this study was to enhance flufenamic acid water solubility, through its amorphization using auxiliary substances with macromolecules.

Since the preliminary analyses with thermomicroscopy and differential scanning calorimetry (DSC) showed that the flufenamic acid dissolves in the molten polyethylene glycol (PEG), we made solid dispersions of flufenamic acid with PEG 4000 and PEG 6000 through the melting method in 1:5 and 1:10 mass ratio. The solid dispersions were analyzed with DSC, X-Ray Diffraction (XRD) and we made dissolution tests in artificial gastric juice and artificial intestinal juice.

Through DSC measurements and thermomicroscopic analysis were verified the amorphization, the dissolution of the flufenamic acid in PEGs. The analysis of the solid dispersions by XRD demonstrates the amorphization of flufenamic acid. The dissolution test shows a 4.4 times better solubility in the artificial gastric juice with the PEG 4000 mixture in 1:10 mass ratio.

Rezumat

Antiinflamatoarele nesteroidiene ocupă un loc important în terapia actuală, cu indicații ce se extind de la afecțiunile inflamatorii reumatismale până la maladiile cardiovasculare, genito-urinare, stomatologice. Acidul flufenamic este un antiinflamator nesteroidian, din grupa fenamaților. Este o substanță greu solubilă în apă, de aceea scopul lucrării a fost creșterea solubilității acidului flufenamic, prin amorfizarea lui, cu ajutorul unor substanțe auxiliare cu molecule mari.

Întrucât analiza termomicroscopică și calorimetria cu scanare diferențială (DSC) preliminară a arătat că acidul flufenamic se dizolvă în polietilen-glicolul (PEG) topit, am preparat dispersii solide cu acid flufenamic și PEG 4000, respectiv PEG 6000 prin metoda topirii în raporturi de masă 1:5 și 1:10. Dispersiile solide au fost analizate prin calorimetrie de scanare diferențială (DSC), difracție de raze X (XRD) și au fost făcute testele de

dizolvare în suc artificial gastric și suc artificial intestinal.

Prin măsurători DSC și analize termomicroscopice a fost pusă în evidență amorfizarea, dizolvarea acidului flufenamic în PEG. Analiza dispersiilor solide prin difracție de raze X demonstrează amorfizarea acidului flufenamic. Pe baza testelor de dizolvare putem constata o creștere de 4,4 ori a solubilității acidului flufenamic în suc gastric artificial în cazul amestecului cu PEG 4000 preparat în raport de masă 1:10.

Keywords: flufenamic acid, macrogols, solid dispersion, XRD, DSC

Introduction

Flufenamic acid (FA), an anthranilic acid derivative related to mefenamic acid, is a non-steroidal anti-inflammatory drug. It is used in musculoskeletal and joint disorders, administered orally and topically [16]. The drug is well absorbed and is extensively bound to plasma proteins. Its most frequent adverse effects are gastrointestinal disturbances (approximately 25% of the users). Diarrhea, steatorrhea and inflammation of the bowel may also occur. [5]

According to the Biopharmaceutical Classification System, FA belongs to class II (drugs with low solubility and high permeability) [15]. The poor solubility of FA is may lead to poor dissolution and hence, variations in bioavailability. Numerous methods have been developed for increasing drug solubility; the solid dispersion is one of the most effective; besides this, the incorporation of drugs in a hydrophilic matrix reduces the gastrointestinal disorders [8]. Because there is an isosteric relation between acetylsalicylic acid and FA [9], presumptive the FA also causes direct gastrointestinal damage by topical irritant effects. Administering the FA in amorphous form or in solid solutions can attenuate this effect because of the faster disappearance of the substance from the mucosa due to the better solubility.

The chemical structure of FA is presented in Figure 1.

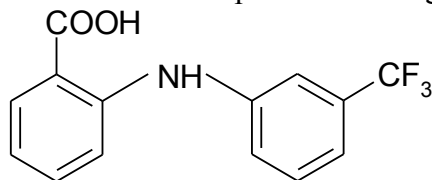


Figure 1

The chemical structure of flufenamic acid [15]

Polyethylene glycols (PEG, Macrogols) are water soluble synthetic polymers based on oxyethylene group, with the general structure $H-[O-CH_2-CH_2-]_n-OH$, where n is the number of repeated units [14]. PEGs can be

used to enhance the aqueous solubility or dissolution characteristics of poorly soluble compounds by making solid dispersions [10]. The term – solid dispersion – refers to the dispersion of one or more active ingredients in an inert carrier or matrix at solid state [7,8]. PEGs with molecular weights between 1500 – 20000 are used as carriers in the solid dispersion (SD) system [8]. The melting point of these PEGs is under 70°C, therefore it is very advantageous to prepare solid dispersions by the melting method [7,8]. In literature there are many reports concerning solid dispersions [1,2,3].

The aim of this study was to investigate the influence of solid dispersions (SD) in polyethylene glycol 4000 (PEG 4000) and polyethylene glycol 6000 (PEG 6000) on the physico-chemical characteristics and the dissolution rate of FA. For this propose SDs of FA with PEG 4000 and PEG 6000 were made and characterized by DCS and X-ray powder diffractometry. Dissolution studies were also carried out [4,11].

Materials and methods

Materials

PEG 6000 and PEG 4000 were purchased from Merck Co. (Germany), flufenamic acid was obtained from Sigma Aldrich (Germany). All solvents and other materials were of analytical grade.

Methods

Thermomicroscopy

Hot stage microscopy was carried out using a Leica thermomicroscopy with scan rate of 1°C/min in the proximity of the most interesting thermal events.

Differential Scanning Calorimetry (DSC)

Measurements were performed using Mettler Toledo STAR 821^e differential scanning calorimeter (Mettler Inc., Schwerzenbach, Switzerland). Samples between 2–5 mg were measured in 40 µL of standard aluminium pans and heated at 10°C/min from 25 to 300°C using argon as a carrier gas (167mL/min). Physical mixtures in 1:1 weight ratio were analyzed.

Preparation of solid dispersion (SD)

Solid dispersions of FA with PEG 4000 and PEG 6000 were obtained by the melting method in 1:5 and 1:10 weight ratios (FA:PEG 4000 1:5; FA:PEG 4000 1:10; FA:PEG 6000 1:5; FA:PEG 4000 1:10). FA was added to the molten PEG 4000 and PEG 6000 respectively (80 °C); the

mixtures were stirred 15 min and rapidly cooled at -20 °C. The samples were passed through a 400 µm sieve.

X-ray powder diffractometry (XRD)

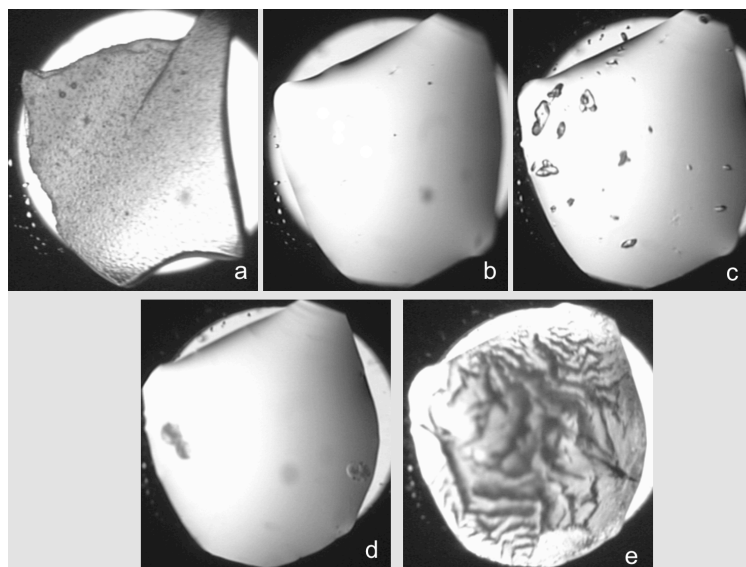
The physical state of FA in solid dispersions was studied using X-ray powder diffraction, using Rigaku MiniFlexTM II X-Ray Diffractometer (Rigaku Co. Tokyo, Japan), where the tube anode was Cu with $K\alpha=1,5405 \text{ \AA}$. The pattern was collected with 30 kV of tube voltage and 15 mA of tube current in step scan mode (4°/min). The instrument was calibrated using silicon.

In vitro dissolution studies

In vitro dissolution studies were performed using paddle apparatus; the volume of dissolution medium was 100 mL. Samples of FA and solid dispersion equivalent to 13.8 mg of the drug were placed in hard gelatin capsules and added to artificial gastric juice (without pepsin) and simulated intestinal fluid at a rotation speed of 100 rpm/min at 37°C. Because of the available gelatin capsules' reduced volume, it was impossible to place in products corresponding to 125 mg FA (each tablet contains 125 mg active substances), therefore the weighed mixtures and dissolution medium was decreased at 1/9 part. 5 mL aliquots were withdrawn at 5, 10, 15, 30, 60, 90, 120 min, filtered and replaced with 5 mL fresh dissolution medium. FA was determined spectrophotometrically at 284 nm (ATI UNICAM UV-VIS Spectrophotometer); there was no interference with PEG 4000 and PEG 6000 at this wavelength. The hard gelatin capsules and PEG's UV absorption values were extracted from the final value. The measurements were performed in triplicate. In artificial gastric juice non-sink condition was applied in order to assess supersaturation.

Thermomicroscopy

The PEG 6000 (Figure 2.a.) was melted at 65 °C (Figure 2.b.). If FA was dispersed on the molten PEG 6000 (Figure 2.c.), the drug was dissolved in the melted PEG 6000 (Figure 2.d.), before reaching its own melting temperature (135°C). When cooled, the recrystallization of the drug didn't take place (Figure 2.e.), therefore it can be hypothesized that it occurs the amorphization of FA; the absence of drug particles may be due to a molecular dispersion of the drug into the polymer. For this reason the solid dispersions of FA with PEG 4000 and PEG 6000 were made by the melting method.

**Figure 2**

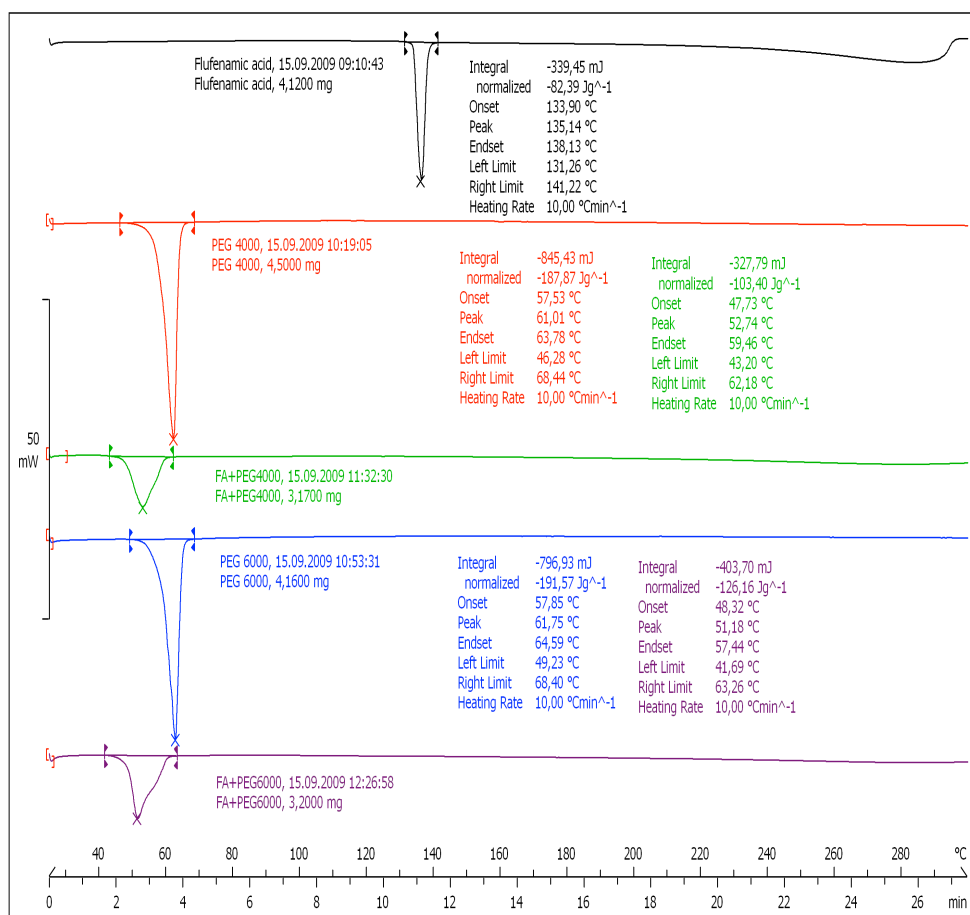
Hot stage images

- a. PEG 6000; b. PEG 6000 melted at 65°C; c. FA dispersed on the molten PEG 6000; d. dissolved FA in melted PEG 6000; e. cooled mixture where recrystallization didn't take place.

Results and discussion

Differential Scanning Calorimetry (DSC)

DSC thermograms of FA, PEG 4000, PEG 6000 and physical mixtures are shown in Figure 3. The PEGs gave a melting endotherms at about 61–62°C. Pure FA exhibits a sharp endothermic peak at 135 °C, due to the melting of the drug. The melting peak of FA in physical mixtures was absent, which – according to thermomicroscopic data – indicates the dissolution of the drug in the melted PEGs, no crystalline FA being present. The physical mixtures's endothermic peaks are with 10 °C lower than those of PEGs, caused by the PEG and FA interaction. The mathematical sum of the enthalpies of FA (82.39 J/g) and PEG 4000 (187.87 J/g) is greater than the observed enthalpy of FA:PEG 4000 physical mixture (103.4 J/g), which indicates that it occurs an endothermic process ($\Delta H > 0$) during FA dissolution in the melted PEG. According to the Gibbs function ($\Delta G = \Delta H - T\Delta S$, ΔG = change in Gibbs free energy, ΔH = change in enthalpy, T = absolute temperature, ΔS = change in entropy), the FA's spontaneous solubilization is associated with entropy gain and increase in enthalpy. Calculating the bond energies, assuming that all amount of FA took part in the reaction, about 20 kJ/mol was obtained, which corresponds to the strength of the hydrogen-bond.

**Figure 3**

The differential scanning calorimetry (DSC) curves of the flufenamic acid and its physical mixtures with PEG 4000 and PEG 6000

X-ray powder diffractometry (XRD)

Figure 4 shows the XRD patterns of FA, PEG 4000 and SDs at 1:5 and 1:10 FA:PEG 4000 weight ratios. PEG 4000 revealed two characteristic peaks, at 19.18°C and 23.34°C. FA can be characterized by 5 prominent diffraction peaks at 17.72°C, 18.88°C, 24.4°C, 27.34°C, 30.78°C. The lack of these distinctive peaks of the drug in the SDs indicates that FA is dissolved in the solid state matrix in an amorphous state and no crystalline FA is present.

Similarly, at the XRD pattern of SDs of FA and PEG 6000 the amorphization of the drug can be observed (Figure 5).

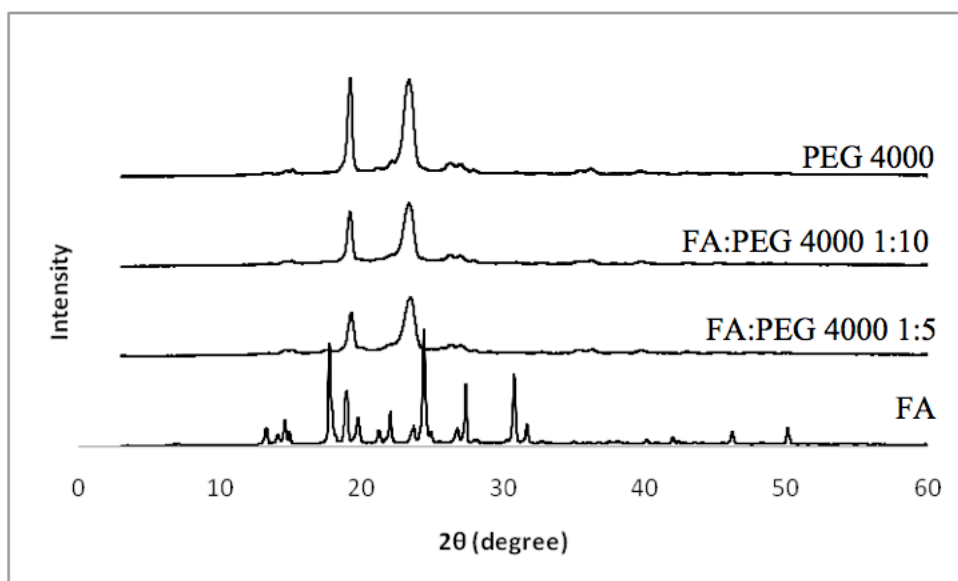


Figure 4
XRD patterns of FA, PEG 4000 and SDs

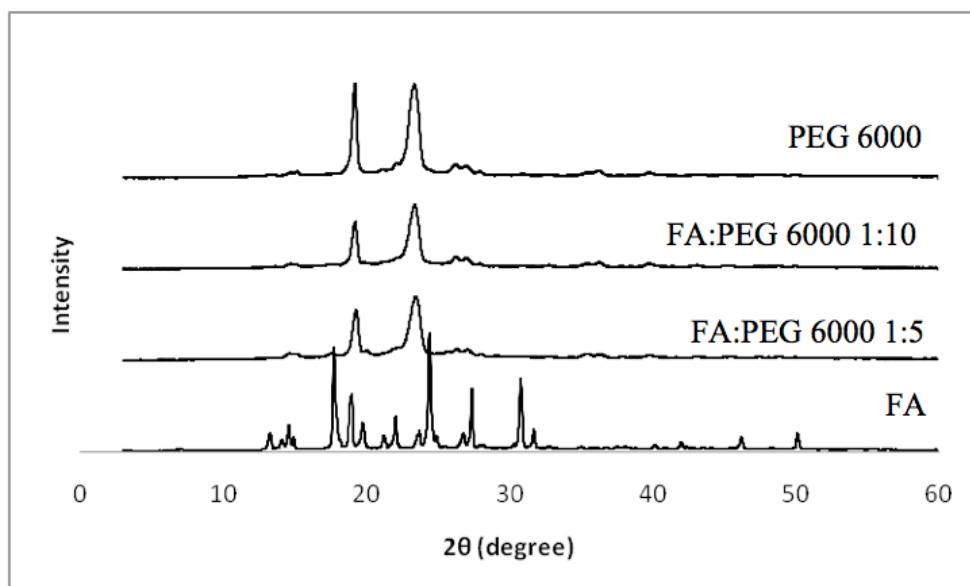


Figure 5
XRD patterns of FA, PEG 6000 and SDs

Dissolution studies

The dissolution profiles of the pure FA and the SDs's are shown in figures 6 and 7. FA is a drug with acidic character; therefore it has better

solubility in artificial intestinal juice (69.1%). SDs with PEG 4000 and PEG 6000 improve the dissolution rate of FA, the best results were obtained by FA:PEG 6000 1:10 weight ratio, when 90.1% was dissolved after 120 minutes.

In artificial gastric juice it occurs a remarkable supersaturation of the FA in the case of SDs with high amounts of PEG (FA:PEG 4000 1:10 and FA:PEG 6000 1:10), therefore an accelerated dissolution can be observed. In artificial gastric juice, only 1.34% of FA dissolves, in the case of FA:PEG 4000 1:10 SD the solubility of FA is 4.4 times greater at the steady-state terminal portion (at 120 min).

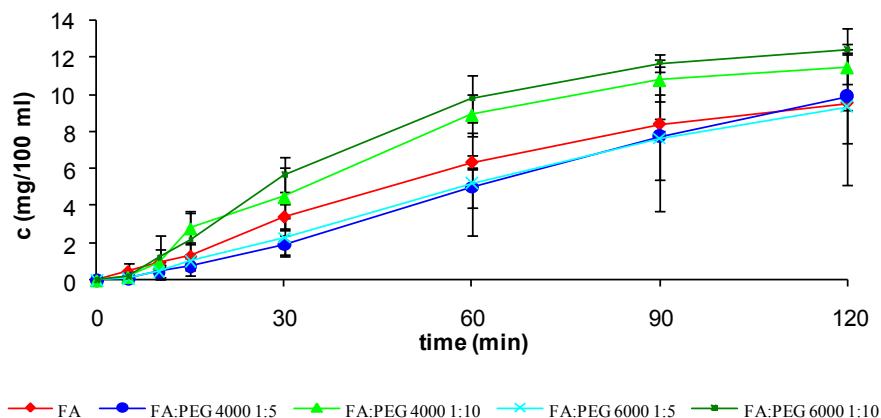


Figure 6

Dissolution profile of the FA and SDs in artificial intestinal juice

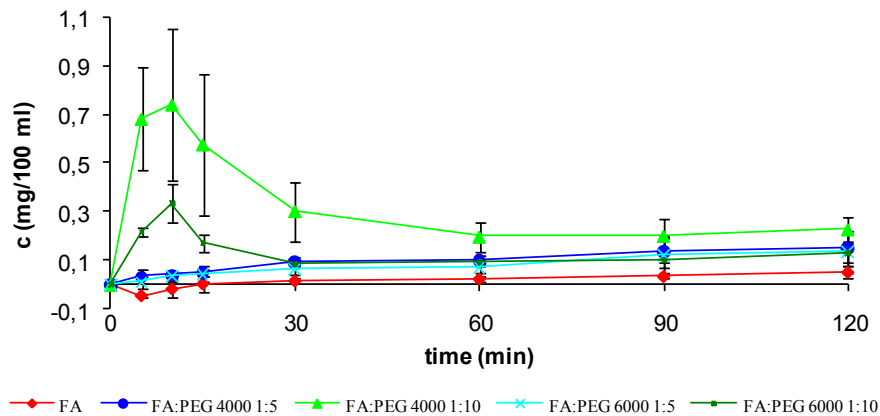


Figure 7

Dissolution profile of the FA and SDs in artificial gastric juice

Conclusions

The thermal analysis (thermomicroscopy, DSC) of FA and its physical mixture prepared with PEG 4000 and PEG 6000 proved that the drug is dissolved in the melted PEG below its melting point, and accordingly SDs were prepared by the melting method. The XRD data proved the amorphization of FA in SDs with PEGs. The dissolution studies show a better solubility of the drug in SDs. In artificial gastric juice FA dissolved rapidly from SDs and showed supersaturation followed by crystallization of the drug. This phenomena frequently occurs when drugs dissolve from a hydrophilic matrix, due to the matrix fast dissolution [6,12,13]. From this supersaturable formulation a higher amount of FA (a drug with high permeability) can be absorbed from the gastrointestinal tract. In addition the PEGs act as polymeric crystallization inhibitor and delay the FA's instantaneous crystallization from this supersaturated solution.

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