

Preparation, characterization, and dissolution studies of naproxen solid dispersions using polyethylene glycol 6000 and labrafil M2130

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Abstract

Naproxen is a poor water soluble, non-steroidal analgesic and anti-inflammatory drug. The enhancement of oral bioavailability of poor water soluble drugs remains one of the most challenging aspects of drug development. Although salt formation, solubilization and particle size reduction have commonly been used to increase dissolution rate and thereby oral absorption and bioavailability of low water soluble drugs, there are practical limitation of these techniques. However, the most attractive option for increasing the release rate is improvement of solubility through formulation approaches. In this study, solid dispersions (SD) of naproxen were prepared by hot melt method using various ratios of drug to polymers (PEG6000) separately and characterized for physical appearance, FTIR, DSC, X-Ray crystallography, and in-vitro dissolution studies. The influence of several amounts of Labrafil M2130 was also studied. FTIR study revealed that drug was stable in SDs, and great state of amorphous formed particles was proofed by DSC analysis. The in vitro dissolution studies were carried using USP type II (paddle) dissolution apparatus at medium (pH 1.5). Solubility of naproxen from SDs was increased in dissolution media. The prepared dispersion showed increase in the dissolution rate of naproxen comparing to that of physical mixtures of drug and polymers and pure drug. Percent of drug released in 60 minutes was 23.92% for pure naproxen which is increased in SDs and reached to 100% for best formulations of PEG6000 and labrafil based SDs respectively, considering ratio of drug to polymers.

It is concluded that dissolution of the naproxen could be improved by the solid dispersion. Although physical mixtures have increased the rate of dissolution, dissolution shows faster release from SDs which would therefore be due to formation of amorphous particles through the hot melt process which was also revealed by DSC analysis and XRD.

Keywords: Naproxen, release rate, hot melt method, solid dispersion

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Introduction

The enhancement of oral bioavailability of poorly soluble drugs remains one of the most challenging aspects of drug product formulation especially in view of the fact that of all the newly discovered drug entities; more than 40% are lipophilic in

nature and fail to reach the market due to their poor solubility (1).

Dissolution is the rate limiting step for the poorly water soluble drugs. Poor solubility results in low bioavailability, increase in the dose, large inter and intra subject variation and large variations in blood drug

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concentrations depending on fed and fasted conditions. Enhancement of solubility and dissolution rate is an important step in drug development (2).

To improve the dissolution and bioavailability of poorly water-soluble drugs, researchers have employed various techniques such as micronization, solubilization, salt formation, use of surfactant, use of cosolvent, complexation with polymers, use of prodrug and drug derivatization, pH alteration and others (3-5). The mechanisms involved in solubility and dissolution rate enhancement include transformation of unstable modifications into more stable ones or even into the amorphous state, reduction of particle size possibly to the molecular level as well as enhancement of wettability and solubility of the drug by the carrier material (6, 7). Preparation of solid dispersion includes fusion or melting method, solvent evaporation method, freeze drying, lyophilisation, hot melt extrusion, etc. (8). Naproxen is a non-steroidal anti-inflammatory drug which, as a consequence of its scarce wettability and very poor water-solubility (0.025 mg/ml at 25 ± 8 °C), can exhibit and/or variable bioavailability after oral administration. This undesirable physical property may increase the incidence of its irritating side effect on the gastrointestinal tract because of prolonged contact time with the mucosa (9). The purpose of this study was to prepare solid dispersion by hot melt method, to improve the dissolution rate of naproxen.

Materials and methods

Materials

Naproxen (Alborz Co., Iran), PEG 6000 (Merck, Germany), Labrafil M2130 (Gattefosse, France). Other materials and solvents were of analytical grade and used without further purification.

Preparation of solid dispersions

To prepare solid dispersions, appropriate quantities of Naproxen and polymer (PEG 6000) at ratios of 1:1, 1:2 and 2:1, respectively, were accurately weighed and mixed well in a glass mortar for 5 min. In four formulations, different amounts of surfactant (Labrafil M2130) were added. The mixture was heated on a hot plate at 75 °C for 3 min and the melted mixture was mixed for 10 min. The mixture was immediately cooled in a freezer for 60 min. The precipitates were scrapped, milled and then passed through a #30 and 50 sieve and stored in well closed containers. For comparison purposes, physical mixture with 1:1 ratio of Naproxen and polymer were prepared by gently mixing Naproxen and the polymer in a glass mortar, and the mixtures were then passed through a #30 and 50 sieve. The composition of these formulations and their corresponding codes were outlined in Table 1.

In-vitro dissolution studies

All *in-vitro* dissolution studies were carried out using 900 ml of 0.1 M hydrochloric acid at 37 ± 1 °C as the dissolution medium in a USP II Dissolution Apparatus (Erweka, Germany) at a stirring speed of 100 rpm. Accurately weighed solid dispersions and physical mixtures containing 40 mg of spironolactone were used for dissolution studies. Sink conditions were not maintained, as the focus of this investigation was to evaluate solubility of naproxen.

Five-milliliter samples of dissolution medium were withdrawn at predetermined intervals and immediately replaced with an equal volume of the dissolution medium (maintained at 37 ± 1 °C) in order to maintain constant volume of dissolution medium. The withdrawn samples were filtered and analyzed for naproxen content at 329 nm and cumulative

Table 1 Composition and codes of physical mixtures and solid dispersions.

Formulation code	Drug	Carrier (PEG 6000)	Labrafil 2130 (%w/w)
F1	1	-	-
F2	1	1	-
F3	1	2	-
F4	2	1	-
F5	1	1	0.25%
F6	1	1	0.5%
F7	1	1	1%
F8	1	1	2%
F9 ^a	1	1	-

a: Physical mixture

percentage of naproxen dissolved was calculated. The amount of naproxen removed in each sample was compensated in the calculations. All experiments were performed in triplicate.

Fourier transform infra-red spectroscopy

The FT-IR measurements of naproxen and its dispersion were taken in Perkin Elmer, spectrum one (USA), and the samples were dispersed in KBr powder and discs were made. The spectra of solid dispersion were compared with the fingerprint region of drug and polymer.

Differential scanning calorimetry

DSC was performed using DSC Perkin Elmer, Pyris6 instrument (USA). Samples were accurately weighed (4-5 mg) in aluminum pans, and sealed and thermograms were obtained at the heating rate of 10 °C per min and in range of 30-300 °C. Ultrahigh purity nitrogen was used as the purge gas at a flow rate of 50 mL/min.

Powder X-ray diffraction (PXRD)

X-ray diffractometer (D8, Advanced Bruker, Germany) was used for the evaluation of type of the solid dispersion. The samples were exposed to CuK α radiation under 20 mA current and 40 kV voltage. The scanning angle ranged from

4° to 40° of 2θ and at a scan rate of 0.5 degree/min.

Statistical analysis

Statistical analysis among formulations was performed by one way ANOVA followed by Tuckey's multiple comparison test using SPSS Statistics 17 software and $P < 0.05$ was used as the criterion to assess statistical significance.

Results

The effects of varying drug/ PEG6000 (w/w) ratio, Labrafil 2130 content and preparation method of the drug- polymer mixture on naproxen dissolution rate are shown in Figs. 1 and 2. As expected, the dissolution rate of pure Naproxen was extremely poor with only about 23.92 % of drug released within 60 min of the dissolution run (Figs. 1 and 2). The most rapid dissolution was observed with the F6 solid dispersion in comparison with the other dispersions. However, independent of the polymer type, all drug dissolution parameters progressively improved with increasing the polymer proportion in the mixture and reached the highest values at the 1: 2 (w/w) drug/polymer ratio. The thermal curves of naproxen, and of the different examined binary combinations are collected in Fig. 3. The DSC curve of naproxen was typical of a crystalline

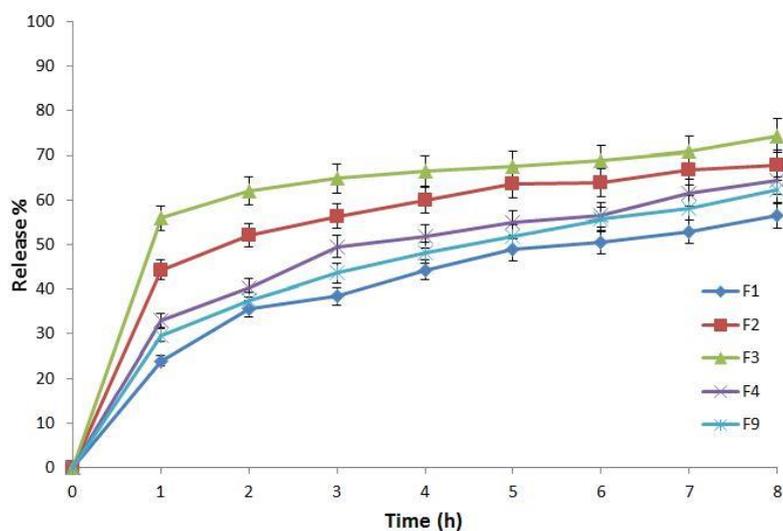


Figure 1 Dissolution profiles of naproxen from physical mixtures and solid dispersions containing (F1) pure drug; (F2) naproxen and PEG 6000 solid dispersion [1:1]; (F3) naproxen and PEG 6000 solid dispersion[1:2], (F4) naproxen and PEG 6000 solid dispersion(2:1) and (F9) physical mixture of naproxen and PEG 6000 [1:1] in 0.1 M hydrochloric acid (data shown as mean \pm standard deviation, $n = 3$).

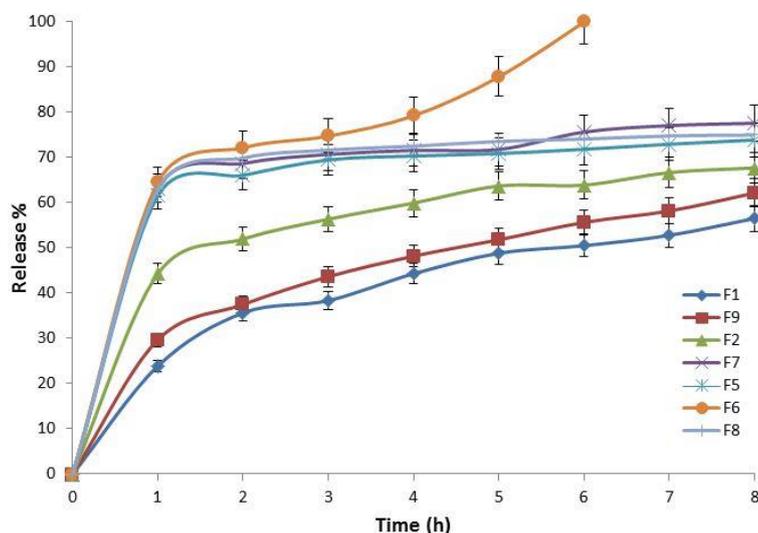


Figure 2 Dissolution profiles of naproxen from physical mixtures and solid dispersions containing (F1) pure drug; (F2) naproxen and PEG 6000 solid dispersion[1:1]; (F5) Naproxen and PEG 6000 solid dispersion[1:1] with 0.25% Labrafil, (F6) Naproxen and PEG 6000 solid dispersion[1:1] with 0.5% Labrafil; (F7) naproxen and PEG 6000 solid dispersion[1:1] with 1% Labrafil; (F8) naproxen and PEG 6000 solid dispersion[1:1] with 2% Labrafil and (F9) physical mixture of naproxen and PEG 6000 [1:1] in 0.1 M hydrochloric acid (data shown as mean \pm standard deviation, $n = 3$).

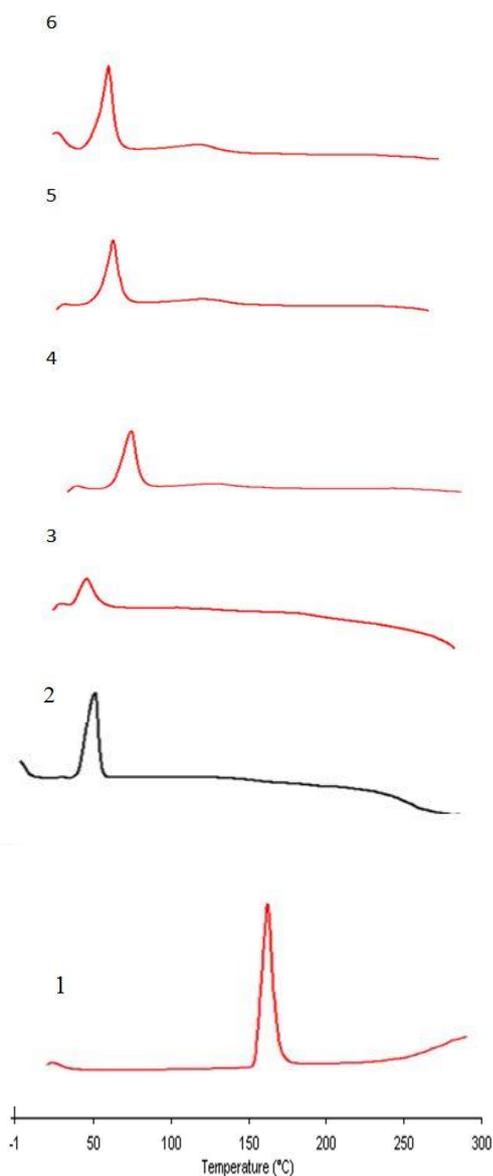


Figure 3 DSC thermograms, 1: Pure Naproxen, 2: PEG 6000, 3: Labrafil 2130, 4: naproxen and PEG 6000 physical mixture (1:1), 5: naproxen and PEG 6000 solid dispersion (1:1) with 1% Labrafil, 6: naproxen and PEG 6000 solid dispersion (1:1).

anhydrous substance, showing a sharp endothermic peak ($T_{\text{onset}} = 153\text{ }^{\circ}\text{C}$, $T_{\text{peak}} = 156\text{ }^{\circ}\text{C}$), corresponding to the drug melting. The different treatments (kneading, evaporation or grinding) did not produce significant modifications of the drug

thermal behavior in comparison with that of the intact naproxen.

Fourier transform infrared (FT-IR) spectra of naproxen, polymers, physical mixture and solid dispersions of naproxen are shown in Fig. 4. The IR spectrum of naproxen was characterized by bands at 1727 cm^{-1} corresponding to the carboxylic, (C=O) group, 1686 cm^{-1} (C=O), stretching hydrogen bond, 1090 cm^{-1} (C-O) stretching, 1264 cm^{-1} (aryl-O) symmetric stretching, 1028 cm^{-1} (aryl-O) symmetric stretching, 1604 cm^{-1} , 1481 cm^{-1} (C=C) aromatic stretching and another band at 3188 cm^{-1} corresponding to the (O-H) stretching.

The spectra of the physical mixtures as well as those of the different examined binary systems did not differ from that of the drug alone in the area of the main naproxen absorption bands, and, in particular, the frequencies of its characteristic quartet of bands in the carbonyl stretching region appeared almost unchanged, indicating the absence of any hydrogen bonding interaction between drug and polymer.

XRD diffractograms (Fig. 5) revealed that pure naproxen showed distinctive peaks in 6.5° , 12.4° , 16.6° , 19° , 20° , 22.5° , 24° and 28.5° which indicate the crystalline nature of pure naproxen. However, in treated naproxen powder, the height and number of peaks were decreased, indicating the reduced crystallinity of the treated naproxen powder.

Discussion

In-vitro dissolution

As expected in Figs. 1 and 2, the dissolution rate of pure naproxen was extremely poor. As stated, this observations might be attributed to poor wettability and particle agglomeration during the run. When incorporated into solid dispersions, the dissolution rate of naproxen from all

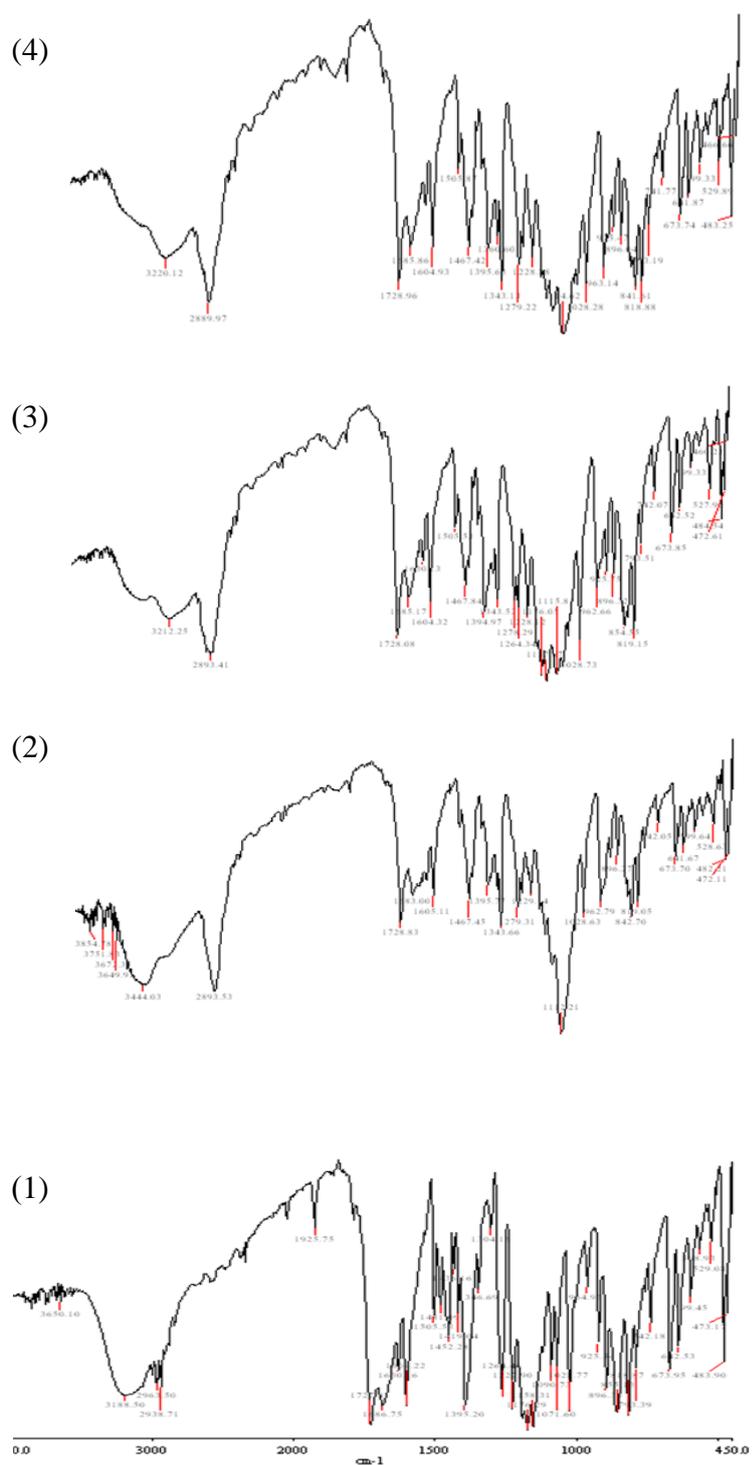


Figure 4 FT-IR Spectrums, 1: Pure naproxen, 2: Naproxen and PEG 6000 physical mixture (1:1), 3: Naproxen and PEG 6000 solid dispersion (1:1), 4: Naproxen and PEG 6000 solid dispersion (1:1) with 1% Labrafil

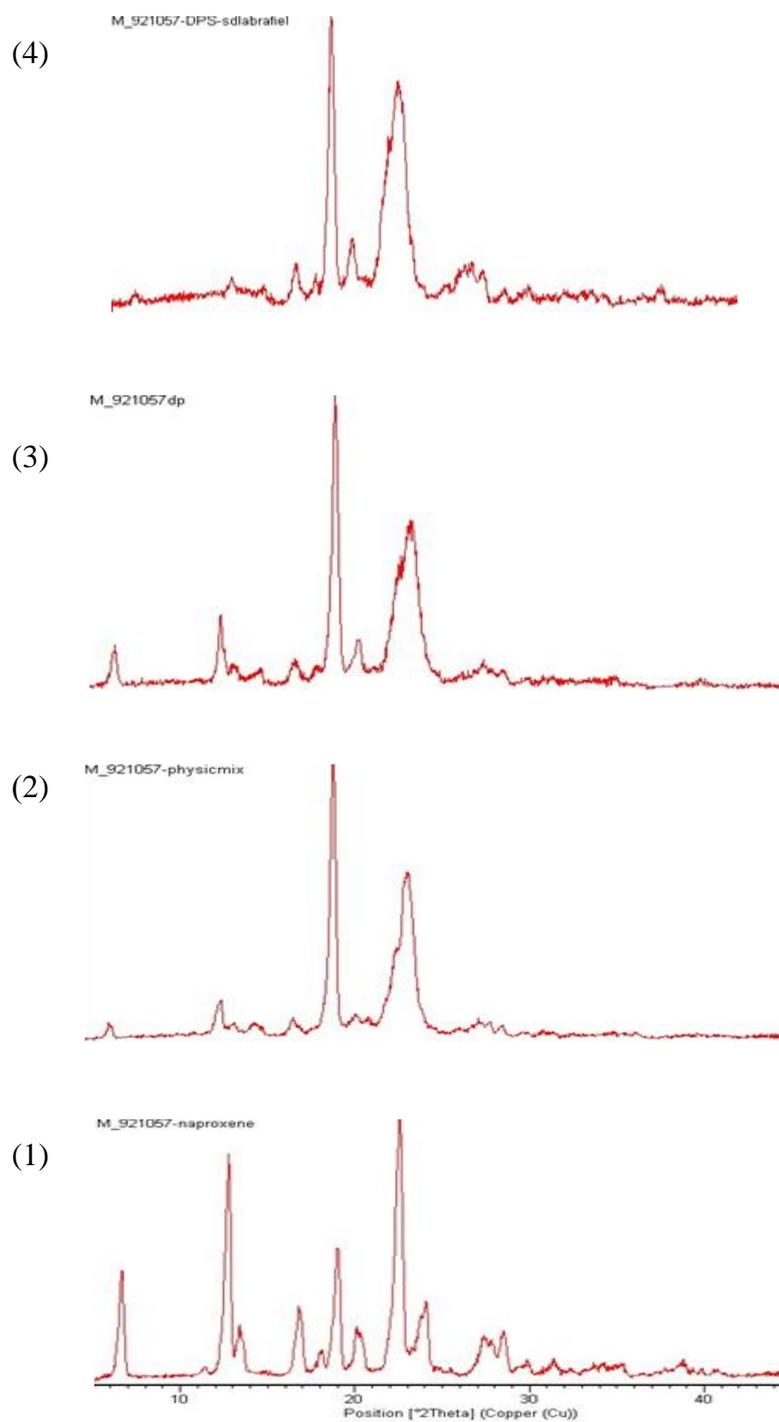


Figure 5 XRD spectrums, 1: Pure naproxen, 2: Naproxen and PEG 6000 physical mixture (1:1), 3: Naproxen and PEG 6000 solid dispersion (1:1), 4: Naproxen and PEG 6000 solid dispersion (1:1) with 1% Labrafil

dispersions was significantly higher than that of pure naproxen (Figs. 1 and 2). The most rapid dissolution was observed with the F6 solid dispersion in comparison with the other dispersions. However, independent of the polymer type, all drug dissolution parameters progressively improved with increasing the polymer proportion in the mixture and reached the highest values at the 1:2 (w/w) drug/polymer ratio. The slight positive effect on drug dissolution rate shown by simple physical mixtures could be due to a reduction of the interfacial tension between the hydrophobic drug particles and the dissolution medium, owing to the presence of the hydrophilic polymer, as well as to a local solubilizing effect acting during the early stages of the dissolution process in the microenvironment surrounding the drug particles (10). The fastest dissolution from F6 dispersion might be attributed to the solubilizing effects of F6 on the active drug. Overall, the increase in dissolution rates of drugs with different carriers and their combinations may be due to lower contact angle, improved wettability and increased surface area. Several mechanisms have been proposed to account for the increase in the dissolution rates of drugs from polyethylene glycol solid dispersions. These mechanisms include the carrier controlled dissolution (11-13), the continuous drug layer formation (12) and that involving the release of intact particles with dissolution occurring over a large surface area (14). The latter mechanism has been suggested to be important at low drug levels. It is also clear that a modification of the surface properties and hence a reduction of the value of the contact angle which improves the wettability of the powder should lead to an increase of dissolution kinetics. An improvement of wettability of the powder could result from the formation of a film of polyethylene glycol around the

drug substance particles which modifies the hydrophobicity of their surfaces (15). Which mechanism is involved in the increase in the dissolution kinetics of Naproxen from PEG 6000 or PEG 4000 dispersions could not be at present established. The utility of the surfactant systems in solubilization is very important. Adsorption of surfactant (Labrafil M2130) on solid surface can modify their hydrophobicity, surface charge, and other key properties that govern interfacial processes such as flocculation/dispersion, floatation, wetting, solubilization, detergency, and enhanced oil recovery and corrosion inhibition. Surfactants have also been reported to cause solvation/plasticization, manifesting in reduction of melting the active pharmaceutical ingredients, glass transition temperature and the combined glass transition temperature of solid dispersions. Because of these unique properties, surfactants have attracted the attention of investigators for preparation of solid dispersions (16).

Differential scanning calorimetry

The characteristic thermal profile of the drug was present in physical mixtures with both polymers at all the examined drug-polymer (w/w) ratios, even though a progressive size reduction of its endothermic peak, with a concomitant lowering of the onset temperature, was observed with increasing the carrier content in the mixture. This effect became more marked in coevaporated systems, due to the finest and more homogeneous dispersion of the drug into the polymeric matrix obtained through the solid dispersion preparation. An even more intense reduction of drug fusion enthalpy, which can be considered directly related to the loss of naproxen crystallinity, was observed in kneaded and particularly in

coground systems, as a consequence of the sample mechanical treatment.

Fourier transform infrared spectroscopy

In order to find out the possible intermolecular interactions between the naproxen and carriers, FT-IR studies were conducted. The spectra of the physical mixtures as well as those of the different examined binary systems did not differ from that of the drug alone in the area of the main naproxen absorption bands, and, in particular, the frequencies of its characteristic quartet of bands in the carbonyl stretching region appeared almost unchanged, indicating the absence of any hydrogen bonding interaction between drug and polymer.

X-Ray diffraction studies

Comparing height of the peaks in the physical mixtures of both carriers demonstrated the reduction in magnitude of peaks due to the dilution effect of the carriers. Reduction in the height of the peaks and absence of some major peaks were seen in XRD patterns of the solid dispersions represented a decrease in naproxen crystallinity in these preparations.

The results confirmed the transformation of crystalline polymorph of naproxen into its amorphous polymorph in the form of solid dispersion. These results were in agreement with DSC findings and allowed exclusion of a possible effect of drug amorphization due to the thermal energy supplied during the DSC scan.

Conclusion

It is concluded that dissolution of the naproxen could be improved by the solid dispersion. Although physical mixtures have increased the rate of dissolution, dissolution shows faster release from SDs which would therefore be due to formation of amorphous particles through the hot melt process which was also revealed by DSC analysis and XRD.

Conflict of interest

The authors declared no potential conflict of interest with respect to the authorship, and/or publication of this study.

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