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RESEARCH PAPER

Thermal Behavior and Dissolution Properties of Naproxen from Binary and Ternary Solid Dispersions

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ABSTRACT

Solid dispersions of 10% w/w naproxen (NAP) in poly(ethylene glycol) (PEG) (4000, 6000, or 20,000) as a carrier with or without incorporation of anionic (sodium dodecyl sulfate; SDS) or nonionic (Tween 80; Tw80) surfactant were prepared by the melting method. Physicochemical characteristics were determined by differential scanning calorimetry (DSC) and X-ray diffraction analysis. The results of dissolution studies showed that drug dissolution properties were better from ternary systems than from binary systems since in the former the wetting and solubilizing effects of surfactant and polymer were additive. No influence of the PEG molecular weight was found. The best performance given by anionic surfactant has been attributed to several factors, such as higher hydrophilicity, better solubilizing power, and most facile interaction with both drug and PEG. No important changes in solid-state characteristics or in drug dissolution properties were found after 30 months storage for dispersions with or without surfactant. Only a slight decrease in initial drug dissolution rate was observed at the highest concentration (10% w/w) of SDS.

INTRODUCTION

Dissolution in biological fluids is the limiting step in the absorption of many sparingly water-soluble drugs. The use of solid dispersions of drugs in highly water-soluble carriers to increase their solubility and dissolution rate, and therefore bioavailability, has been widely studied and reviewed (1,2). In previous papers, the formation of solid dispersions with hydrosoluble polymers such as poly(vinyl pyrrolidone) (PVP) or poly(ethylene glycol)

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(PEG) has successfully been used to improve the dissolution properties of naproxen (NAP) (3,4), a nonsteroidal anti-inflammatory drug that is very poorly water soluble (about 27 mg L^{-1} at 25°C). A number of factors have been put forward to explain the increased dissolution rates of solid-dispersed drugs, including decreased particle size, reduction in the aggregation and/or agglomeration phenomena, solubilization effects associated with the carrier, and wettability improvement (1). On the other hand, it is known that the presence of a surfactant can enhance the solubility and dissolution of drugs (5,6). Therefore, several authors experimented with the use of surfactants to increase further the dissolution rate of drugs included in solid dispersion (7–11). Possible mechanisms proposed are the solubilization of the drug in the hydrophobic portion of the surfactant micelles (12), the reduction of interfacial tension between the solid and the dissolution medium (and hence improvement of the wettability of the drug particles) (7,8), or the formation of solid solutions (9,13). The effect on drug dissolution rate was found to depend on the type and concentration of surfactant added to the solid dispersion (7,14).

The aim of the present work was to investigate the effect of incorporating a non-ionic (Tween 80; Tw80) or anionic (sodium dodecyl sulfate; SDS) surfactant on the dissolution rate of NAP from its solid dispersions with PEGs of various molecular weights. The effect of aging on binary and ternary solid dispersions was also studied in order to evaluate the eventual influence of presence of surfactant on long-term system stability.

MATERIALS

Naproxen (NAP) (Sigma Chemical Co., St. Louis, MO) and polyethylene glycol (PEG) 4000, 6000, and 20,000 (Merck, Darmstadt, Germany) were used as obtained from the suppliers. Tween 80 (Tw80) (Merck, Darmstadt, Germany) was selected as the nonionic surfactant [hydrophilic-lipophilic balance (HLB) = 15 (15); critical micelle concentration 0.0014% w/v (16)] and SDS (Aldrich Chemical Co.) as anionic surfactant [HLB = 40 (15); critical micelle concentration 0.2% w/v (17)]. All other materials and solvents were of analytical reagent grade.

METHODS

Preparation of Solid Dispersions

Solid dispersions of 10% w/w NAP in PEG were prepared according to the melting method (1) by adding, under constant stirring, the drug to the melted carrier (at about 70°C) and mixing until a homogeneous system was obtained. In dispersions incorporating surfactant (5% or 10% w/w), the surfactant was dissolved in the melted carrier prior to the addition of NAP. The melts were quickly cooled and solidified on an ice bath to entrap the drug particles in as fine a state as possible. The dispersions were stored 48 hr in a desiccator under vacuum at room temperature before being pulverized and sieved (75–150 μm). The NAP-PEG 10/90 w/w physical mixtures were prepared for comparison purposes by simple mixing in an agate mortar with a spatula of proper amounts of the two components previously sieved (75–150 μm).

Differential Scanning Calorimetry

The differential scanning calorimetry (DSC) analysis was performed with a Mettler TA4000 apparatus equipped with a DSC 25 cell on 5–10 mg (Mettler M3 microbalance) samples scanned at 10 K min^{-1} between 30°C and 180°C in pierced aluminum pans under static air.

X-Ray Diffractometry

X-ray powder diffraction patterns were obtained with a Philips PW 1130 diffractometer (CoKα radiation) at a scan rate of 2° min^{-1} over the 5–50° 2θ range.

Solubility Studies

Solubility measurements of NAP were carried out by adding an excess of drug (15 mg) to 15 ml of water or aqueous solution containing different concentrations of SDS, Tw80 (from 0.25% to 1.5% w/v), or PEG (from 2% to 10% w/v) in sealed glass containers that were electromagnetically stirred at constant temperature (37°C ± 0.3°C) until equilibrium was achieved (2 days). An aliquot was withdrawn and filtered (pore size 0.45 μm), and the NAP concentration was determined by a second derivative ultraviolet absorption method at 274 nm (3). The presence of PEG, SDS, or Tw80 did not interfere with the NAP assay. The results presented are mean values of at least three determinations.

Dissolution Studies

Dissolution rates of NAP, alone or from the various binary and ternary systems, were determined in water at 37°C ± 0.3°C according to the dispersed amount method. In a 400-ml beaker, 15 mg of NAP or NAP equivalent

were added to 250 ml of bidistilled water. Stirring was provided by a three-blade (19-mm diameter) glass stirrer rotating at 100 rpm and immersed in the beaker 2.5 cm from the bottom. At suitable time intervals, 3.0-ml samples were withdrawn, filtered (pore size 0.45 μm), and spectrophotometrically assayed for NAP content as in the solubility studies. The same volume of fresh medium was added, and the correction for the cumulative dilution was calculated. Each test was repeated four times (coefficient of variation [CV] $< 1.5\%$).

Effect of Aging

Samples of all prepared dispersions were stored in amber glass jars with lids at room temperature (20°C–23°C) for 30 months. Dissolution rate studies and DSC analysis were then performed as described above.

RESULTS AND DISCUSSIONS

Phase-Solubility Studies

The solubility of NAP linearly increased as the concentration of both surfactants increased above their critical micelle concentration (Fig. 1). Such a relationship between equilibrium solubility of drug and concentration of surfactant has already been observed (18,19). Drug solubility linearly increased also in the presence of increasing polymer concentrations, indicating formation of soluble complexes (20). The slopes of straight-line relationships, assumed to be indicative of the relative solubilizing efficiency (21), showed that the solubilizing power of surfactants was one order of magnitude higher than those of polymers. The SDS showed the best performances between surfactants, whereas, in the case of PEGs, the solubilizing power slightly decreased with increasing PEG molecular weight.

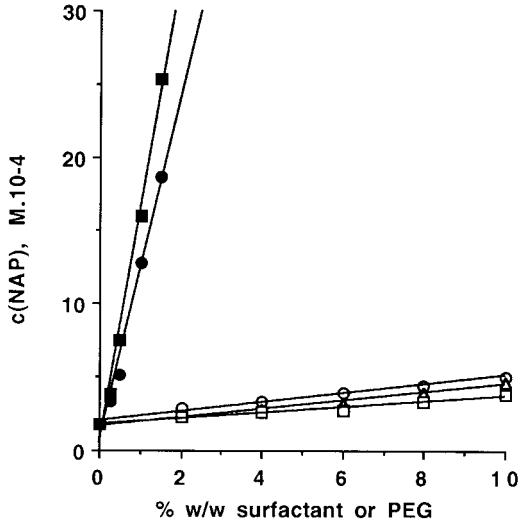

Figure 1. Solubility of naproxen as a function of surfactant or PEG concentration in water at 37°C. ■ sodium dodecyl sulfate; ● Tween 80; ○ PEG 4000; △ PEG 6000; □ PEG 20,000.

Solid-State Studies

Figure 2 shows the DSC scans of solid dispersions of NAP in binary and ternary systems with PEG 4000, 6000, and 20,000. The scans of pure drug and excipients and their physical mixtures are also given for comparison purpose. The DSC curves of pure NAP exhibited a sharp endothermic peak at 156.1 ± 3°C, which corresponds to

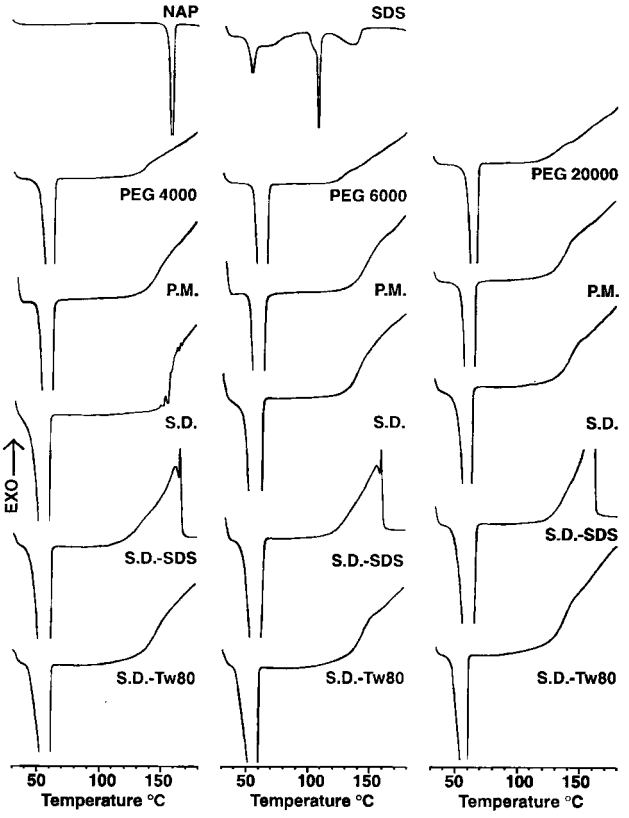

Figure 2. DSC curves of naproxen, sodium dodecyl sulfate, and poly(ethylene glycol) 4000, 6000, and 20,000 and corresponding physical mixtures and solid dispersions with or without surfactant (SDS or Tw80).

its melting. Analogously, the thermal curves of the polymers, typical of crystalline anhydrous products, showed a single endothermic effect, with a peak at 60.4 ± 6°C for PEG 4000, 61.0 ± 6°C for PEG 6000, and 62.6 ± 6°C for PEG 20,000, corresponding to the melting of the polymer. The SDS thermal curve, analogous to that reported by Sjökvist, Nyström, and Aldén (9), showed three endothermal effects: one short broad peak at around 55°C, a sharper peak at around 110°C, and another broad peak with a maximum at about 140°C. The Tw80 was liquid at room temperature, and therefore it was not possible to record a DSC trace under the experimental conditions used.

No differences were apparent between DSC scans of physical mixtures and solid dispersions with or without surfactant. In fact, independent of both the PEG molecular weight and the presence, concentration (5% or 10% w/w), or type of surfactant (Tw80 or SDS), all the systems always displayed only one endothermal peak, corresponding to the polymer fusion, whereas drug and surfactant endothermal effects were not detected. The only observed difference was a slight temperature downshift of the exothermal effect due to PEG decomposition in solid dispersions containing SDS. The disappearance of the drug melting peak was due to its dissolution in the melted carrier: NAP-PEG systems were found to be completely miscible in the liquid phase and completely immiscible in the solid state (4). The decrease in peak melting temperature of PEG due to the presence of drug or both drug and surfactant was always less than 2°C. The heat of fusion values for the raw materials and binary and ternary systems are presented in Table 1. As may be observed, the values for all solid dispersions were about 10% lower than those for the corresponding physical mixture, indicating a slight reduction in PEG crystallinity (2,9).

X-ray diffraction analysis (Fig. 3) showed that both the pure NAP and the pure PEG phases could be identified not only in physical mixtures, but also in all dispersed systems. The relative amounts of each phase can be calculated as the quotient of the intensity of a characteristic line of the NAP phase and the intensity line of the PEG phase (9). The intensity quotient was about 0.1 in physical mixture and remained practically unchanged in cofused systems, with or without surfactant, indicating the absence of solid solution formation. The presence of surface-active agent did not appear to affect the solid state characteristics of NAP significantly, and, as the only difference, a slightly more pronounced amorphous character of the whole system was observed in ternary dispersions, indicated by the appearance of a typical hump in the baseline profile.

Dissolution Studies

Figure 4 shows the mean dissolution profiles of NAP alone and from the various binary and ternary systems. The results in terms of dissolution efficiency (2) and percentage of active ingredient dissolved are collected in Table 2. Physical mixtures gave a slight enhancement of

Table 1

Heat of fusion (J g^{-1}) of Pure Components and 10% w/w Naproxen (NAP) Physical Mixtures (PM) or Solid Dispersions (SD) in Poly(Ethylene Glycol) (PEG) With or Without Sodium Dodecyl Sulfate (SDS) or Tween 80 (Tw80) (Standard Uncertainties in Parentheses)

	PEG 4000		PEG 6000		PEG 20,000	
Sample	Fresh	Aged	Fresh	Aged	Fresh	Aged
NAP	134 (5)	—	134 (5)	—	134 (5)	—
PEG	175 (7)	—	182 (9)	—	168 (8)	—
SDS[a]	90 (9)	—	90 (9)	—	90 (9)	—
Tw80[b]	—	—	—	—	—	—
PM NAP-PEG	180 (6)	—	178 (5)	—	174 (5)	—
SD NAP-PEG	167 (5)	170 (4)	166 (4)	169 (5)	160 (4)	165 (5)
SD NAP-PEG-Tw80 (5%)	170 (5)	172 (5)	168 (6)	172 (4)	163 (4)	167 (4)
SD NAP-PEG-Tw80 (10%)	169 (6)	174 (4)	168 (6)	174 (5)	164 (5)	167 (5)
SD NAP-PEG-SDS (5%)	170 (4)	175 (4)	170 (5)	177 (6)	162 (5)	168 (4)
SD NAP-PEG-SDS (10%)	169 (4)	178 (5)	168 (4)	177 (5)	161 (6)	170 (4)

[a]The value of heat of fusion is derived from the integration in the temperature range 40°C–150°C.

[b]Tw80 is liquid at room temperature, and a heat of fusion value cannot be obtained in the studied temperature range.

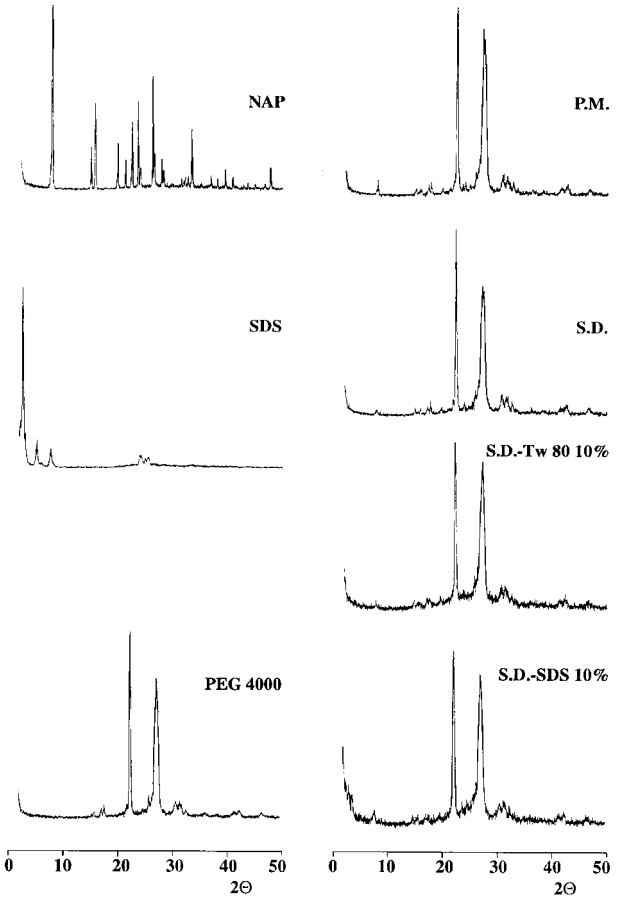

Figure 3. X-ray diffraction patterns of naproxen, sodium dodecyl sulfate, PEG 4000, and corresponding physical mixtures and solid dispersions with or without surfactant (SDS or Tw80).

drug dissolution because only a superficial interaction exists between drug and carrier particles. This effect is probably attributable to reduction of the electrostatic charges, which tend to keep drug particles united together, owing to the presence of the hydrophilic polymer. A considerable improvement of dissolution rate in comparison with the physical mixtures is obtained when the drug is formulated as a solid dispersion. In this case, true dissolution of the drug in the melted excipient happened during the preparation of the system (as is confirmed by DSC analysis), and fast cooling yielded a very fine dispersion of NAP crystals into the hydrophilic polymeric matrix, even though solid solution formation was not found (4).

With both the surface-active agents tested, the release obtained was higher than that obtained from binary solid dispersions. With increasing content of surfactant, the

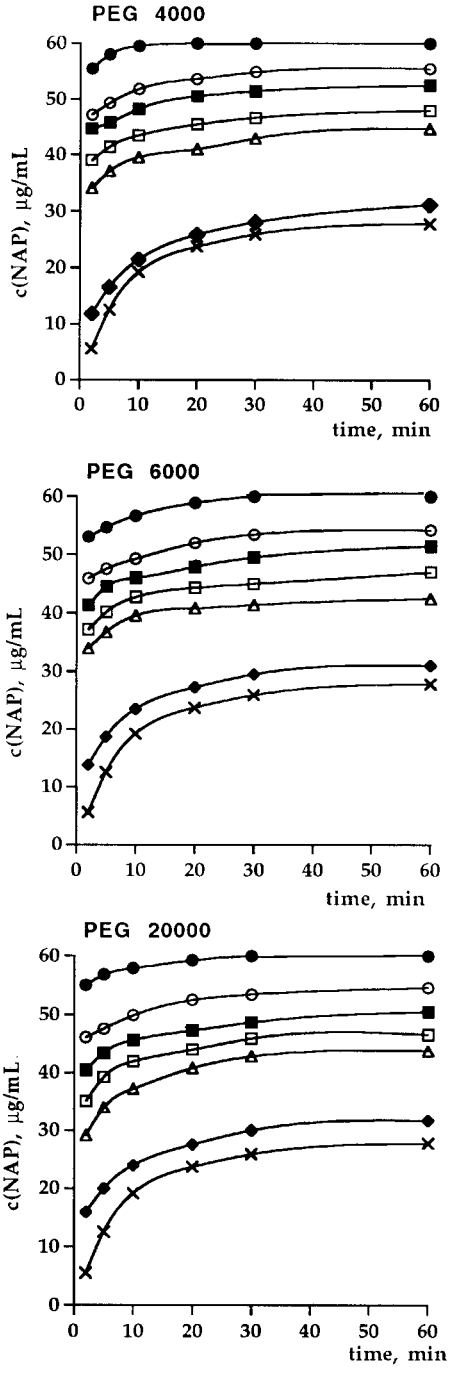

Figure 4. Dissolution curves of naproxen alone and from its physical mixtures (PM) and solid dispersions (SD) in PEG 4000, 6000, and 20,000 with or without sodium dodecyl sulfate or Tween 80. ×, NAP; ◆ PM; △ SD; □ SD 5% Tw80; ■ SD 10% Tw80; ○ SD 5% SDS; ● SD 10% SDS.

Table 2

Dissolution Parameters of Naproxen (NAP) Alone and from Its Physical Mixtures (PMs) and Solid Dispersions (SDs) in PEG With or Without Sodium Dodecyl Sulfate (SDS) or Tween 80 (Tw80)

Sample		$t_{60\%}$[a] (min)	DP_{30}[b]	DE_{60}[c]
NAP	—	>60	43.2	38.3
	PM	>60	46.7	42.8
NAP-PEG 4000	SD	<5	71.7	68.7
	SD 5% Tw80	<2	77.8	75.0
	SD 10% Tw80	<2	85.8	82.8
	SD 5% SDS	<2	91.4	88.1
	SD 10% SDS	<2	100	97.7
	PM	>60	49.2	44.8
NAP-PEG 6000	SD	<5	69.0	66.8
	SD 5% Tw80	<2	75.0	72.8
	SD 10% Tw80	<2	82.5	79.6
	SD 5% SDS	<2	89.0	85.4
	SD 10% SDS	<2	100	96.2
	PM	>60	50.0	45.8
NAP-PEG 20,000	SD	<10	71.3	66.9
	SD 5% Tw80	<5	76.5	72.7
	SD 10% Tw80	<2	81.1	78.4
	SD 5% SDS	<2	89.0	85.9
	SD 10% SDS	<2	100	97.7

[a]Time necessary to dissolve 60% of drugs.
[b]Percentage of drug dissolved after 30 min.
[c]Dissolution efficiency calculated from area under the dissolution curve at $t = 60$ min expressed as % of the area of the rectangle described by 100% dissolution in the same time (average of four determinations, coefficient of variation CV < 1.5%).

dissolution rate further increased. Probably, the surfactant mainly acts as a wetting agent by decreasing the interfacial tension between drug particles and dissolution medium, thus giving the observed increment in dissolution profiles of solid dispersions. It should be considered that the final concentration of surfactant in the dissolution medium after complete dissolution was not high enough to affect the drug solubility to any large extent. In fact, at the highest content of surfactant in the solid dispersion (10% w/w), its final concentration in the dissolution medium was 6×10^{-3}% w/v (see Fig. 1).

Nevertheless, it is true as well that, during the dissolution process, the concentration of surfactant is high around the dispersion, affecting the diffusion layer that surrounds the drug particles and thus improving its microenvironmental solubility. In fact, the increase in dissolution rate was greater at first, as the surfactant dissolves, and then gradually decreased, as may be observed by comparing the relative dissolution rates at 2 and 30 min of the various solid dispersions, calculated by dividing the amount of drug dissolved at the given time by that obtained with the pure drug after the same time (Fig. 5). However, it is evident that the anionic surface-active agent was more effective than the nonionic Tw80 in improving the drug dissolution rate and was the only one to allow achievement of 100% dissolved drug (see Table 2). The greater efficacy of SDS could be attributed to both its higher hydrophilic character, as indicated from the HLB values (15), and its higher solubilizing ability, as found in solubility studies. Also, the alkaline nature of SDS could have a role in enhancing the dissolution of a weakly acidic drug such as NAP (8). Moreover, interaction between polymer and surfactant seems to be most facile with the anionic surfactant and least with the nonionic one (23). In any case, both in binary and ternary systems, the drug release rate was almost independent of the PEG molecular weight.

Effect of Aging

The thermal behavior of systems aged for 30 months was practically unchanged. The only difference observed

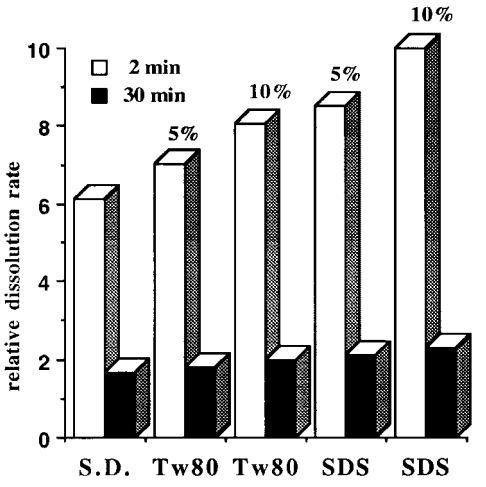

Figure 5. Relative dissolution rate of NAP at 2 and 30 min from solid dispersions in PEG 4000 with or without sodium dodecyl sulfate or Tween 80.

was a slight increase of the heat of fusion of all dispersed systems, particularly of those containing the highest percentage of SDS (see Table 1). This effect could be explained by an increase in crystallinity of the systems (24).

The results of dissolution experiments performed on samples after 30 months of storage at room temperature are summarized in Table 3. The drug dissolution rate was practically unchanged for the dispersions without surfactant and for those containing Tw80 irrespective of the concentration incorporated. On the contrary, some decrease of the drug dissolution properties, particularly evident during the initial phase of the dissolution process, was found for the dispersions containing the higher concentration of SDS, even though they still gave the best performances. A possible explanation for this effect could be that, on storage, the dissolution of PEG itself is decreased by the incorporation of SDS (14).

CONCLUSIONS

Despite the vast amount of research conducted in the field of solid dispersions, the major problem that limits their applications in the market is still their long-term stability. This study has demonstrated that it is possible to prepare solid dispersions of NAP in PEG with improved drug dissolution properties that remained unchanged for a long time. Moreover, inclusion of surface-active agents (particularly SDS) in these solid dispersions resulted in further enhancement of the drug dissolution rate. Also, ternary systems were stable on storage for 30 months, showing practically unchanged physicochemical characteristics, as well as dissolution properties, with the exception of solid dispersions containing the highest content of SDS (10% w/w), for which a reduction of initial dissolution rate was observed.

ACKNOWLEDGMENT

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Table 3

Dissolution Parameters of Naproxen (NAP) from Aged 30 Months Solid Dispersions (SDs) in Poly(Ethylene Glycol) (PEG) With or Without Sodium Dodecyl Sulfate (SDS) or Tween 80 (Tw80)

Sample		$t_{60\%}$[a] (min)	DP_{30}[b]	DE_{60}[c]
	SD	<5	71.0	68.5
NAP-PEG 4000	SD 10% Tw80	<2	84.2	81.2
	SD 10% SDS	<2	93.3	89.9
	SD	≈5	68.3	66.0
NAP-PEG 6000	SD 10% Tw80	<2	80.0	77.4
	SD 10% SDS	<2	92.8	89.5
	SD	≈10	69.5	65.3
NAP-PEG 20,000	SD 10% Tw80	<2	78.8	76.2
	SD 10% SDS	<2	93.8	90.2

[a]Time necessary to dissolve 60% of drugs.
[b]Percentage of drug dissolved after 30 min.
[c]Dissolution efficiency calculated from area under the dissolution curve at $t = 60$ min expressed as % of the area of the rectangle described by 100% dissolution in the same time (average of four determinations, coefficient of variation CV < 1.5%).

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