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RESEARCH PAPER

Physicochemical Characterization of Solid Dispersions of Indomethacin with PEG 6000, Myrj 52, Lactose, Sorbitol, Dextrin, and Eudragit® E100

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ABSTRACT

The purpose of this study was to prepare and characterize solid dispersions of indomethacin with polyethylene glycol (PEG) 6000, Myrj 52, Eudragit® E100, and different carbohydrates such as lactose, mannitol, sorbitol, and dextrin. Indomethacin is a class II substance according to the Biopharmaceutics Classification System. It is a poorly water soluble antirheumatic agent. The goal was to investigate whether the solid dispersion can improve the dissolution properties of indomethacin. The solid dispersions were prepared by three different methods depending on the type of carrier. The evaluation of the properties of the dispersions was performed using solubility measurements, dissolution studies, Fourier-transform infrared spectroscopy, and x-ray powder diffractometery. The results indicate that lactose, mannitol, sorbitol, and especially Myrj 52 are suitable carriers to enhance the in vitro dissolution rate of indomethacin at pH 7.2. Eudragit E100, Myrj 52, and mannitol increase the dissolution properties at pH 1.2. The data from the x-ray diffraction showed that the drug was still detectable in its solid state in all solid dispersions except solid

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dispersions with dextrin and high amounts of mannitol. However, the results from infrared spectroscopy together with those from x-ray diffraction showed well-defined drug–carrier interactions for dextrin coevaporates.

Key Words: Indomethacin; Solid dispersion; Coprecipitate; Coevaporate; X-ray diffraction; FT-IR spectroscopy; Dissolution.

INTRODUCTION

For poorly soluble, highly permeable (Class II) drugs, the rate of oral absorption is often controlled by the dissolution rate in the gastrointestinal tract.[1] Therefore, together with permeability, the solubility and dissolution behavior of a drug are key determinants of its oral bioavailability. There have been numerous efforts to improve drug dissolution rate. These include: 1) reducing particle size to increase surface area, thus increasing dissolution rate of drug; 2) solubilization in surfactant systems; 3) formation of water-soluble complexes; 4) use of prodrug and drug derivatization such as strong electrolyte salt forms that usually have higher dissolution rates; and 5) manipulation of the solid state of the drug substance to improve drug dissolution, i.e., by decreasing crystallinity of the drug substance through formation of solid solutions.[2] The most common method is increasing the surface area of the drug by micronization. But, in practice, the effect of micronization is often disappointing, specially when the drugs are encapsulated or tableted.[3–5] This phenomenon was attributed to the agglomeration tendency of micronized, poorly soluble, hydrophobic drugs, which results in a decreased effective surface area for dissolution. The most promising method for promoting dissolution is the formation of solid dispersion in a proper carrier.[6–8] This approach has the potential to improve the bioavailability of the drug significantly when the absorption is limited by solubility and dissolution rate.[8–10] The antirheumatic agent, indomethacin, exhibits poor solubility.[11] This undesirable physical property may increase the incidence of irritating side effects on the gastrointestinal tract because of prolonged contact time with the mucosa.[11] Numerous attempts[12–14] have been made to improve the dissolution rate of this widely used antirheumatic agent, to obtain more rapid and complete absorption.

In our present study, attempts were made to modify the dissolution behavior and hence absorption of indomethacin by applying the solid dispersion technique using lactose, sorbitol, mannitol, polyethylene glycol (PEG) 6000, Myrj52, and Eudragit® E100 as hydrophilic carriers.

MATERIALS AND METHODS

Materials

For the preparation of solid dispersions the following materials were used: lactose monohydrate (Alpavit, Freiberg, Germany); mannitol, sorbitol, and dextrin (Merck, Darmstadt, Germany); PEG 6000 (BASF, Stuttgart, Germany); indomethacin (Sigma-Aldrich chemie Gmbh, Steinheim, Germany); and Myrj 52 (Polyoxyethylene 40 Stearate, Atlas Chemical Industries, Pasadena, CA). Eudragit E100 was a gift from Röhm Pharma (Darmstadt, Germany). Chemicals used for buffer preparation were reagent grade. All other materials used were of analytical or high-performance liquid chromatography (HPLC) grade.

Preparation of Solid Dispersions and Physical Mixtures

Physical mixtures of indomethacin were prepared by mixing indomethacin with the hydrophilic carriers for 5 min in 100-mL bottles, until a homogenous mixture was obtained. The resulting mixtures were sieved and the 105–250 micron particle size fraction was obtained using 60- and 140-mesh screen. The powders were stored in a screw-cap vial at room temperature until use. Solid dispersions with different concentrations of indomethacin were prepared using the following three methods:

Coevaporates of the Drug with Lactose, Dextrin, Sorbitol, and Mannitol

Coevaporates were prepared in the following indomethacin-carrier ratios: 1:10, 1:20, and 1:40 (w/w). Coevaporates were prepared by dissolving the components separately in a minimum volume of ethanol or distilled water, respectively. The alcoholic solution of indomethacin was then poured into the aqueous solution of the carrier under continuous stirring. The mixture was then heated in a water bath (70° C) under vacuum and vigorous stirring. Initially, a transparent to a translucent viscous mass was observed and finally a pale yellow coevaporate was formed. The moist mass was transferred to a vacuum desiccator with a heating device and kept at 70° C for 120 minutes and finally at 40° C overnight. The solid mass was ground and the particle size fraction of 105–250 micron was obtained by sieving and kept in a screw-capped glass vial until use.

Coevaporates with Eudragit E100

The required amounts of indomethacin and Eudragit E100 to yield drug-carrier proportions of 1:10, 1:20, and 1:40 (w/w) were dissolved in a minimum volume of ethanol [United States Pharmacopoeia (USP) 24] by heating in a water bath. Then the solution was transferred to a vacuum desiccator and was handled as described in section 2.2.1.

Solid Dispersions with Myrj 52 and PEG 6000

Solid dispersions with different concentrations of indomethacin were prepared by adding the drug to PEG 6000 or Myrj 52, which were then melted in a water bath at 70° C. The mixtures were stirred and the resulting homogenous preparations rapidly cooled. Subsequently the dispersions were pulverized and the 105–250 micron particle size fraction was obtained by sieving and kept in a screw-capped glass vial until use.

Solubility Measurement of Indomethacin

Solubility measurements were performed according to the method of Higuchi and Connors:[15] In brief, an excess amount of indomethacin was weighed into test tubes to which 10 mL of dissolution medium (pH 1.2 or pH 7.2 buffered aqueous medium) containing various concentrations of carriers was added. The samples were sonicated (Mettler Electronics, Anaheim, CA model ME5.5) for 2 h at room temperature, thereafter, the capped test tubes were shaken at 37±0.1° C for 48 h in a water bath. (This duration was previously tested to be sufficient to reach equilibrium.) Subsequently, the suspensions were filtered through a 0.22-μm membrane filter. The filtrate was suitably diluted and analyzed spectrophotometrically at the wavelength of 318 nm using a spectrophotometer (Shimadzu–120, Kyoto, Kyoto-fu, Japan). In previous tests, we determined that there is no considerable shift in λ_{max} of indomethacin due to pH change and also there is no drug absorption to the filter. All solubility experiments were done in duplicate. The solubility of indomethacin in the dissolution medium was determined following the same procedure as above.

The Gibbs free energy of transfer (ΔG^0_{tr}) of indomethacin from pure water to the aqueous solution of carrier was calculated as follows:

$$\Delta G^0_{tr} = -2.303RT \log S_0/S_S$$

where S_0/S_s=is the ratio of molar solubility of indomethacin in aqueous solutions of carrier to that of the same medium without carrier.

Dissolution Studies

Hand-filled, hard gelatin capsules of the formulations, containing 30 mg of drug, were used for the dissolution studies. The test was conducted with a USP 24 Apparatus II at 100 rpm. The dissolution medium was 900 mL of simulated gastric fluid without pepsin (pH=1.2) or simulated intestinal fluid without pancreatin (pH=7.2), which was maintained at 37° C (±0.2). The duration of the test was 3 hours. Five-mL aliquots were withdrawn at predetermined time intervals, and the same amount of fresh medium was replaced to keep the volume constant throughout the test. The samples were filtered through a filter paper and the dissolved drug was assayed at a wavelength of 318 nm. Three replicates of each dissolution test were carried out. Previous tests determined that there was no change in the λ_{max} of indomethacin due to the presence of carriers dissolved in the dissolution medium.

Powder X-Ray Diffraction

The powder x-ray diffraction (PXRD) pattern of all ingredients and all binary systems were recorded using an automated Siemens x-ray diffractometer (Siemens D5000, Munich, Germany).

Cross sections of the ingredients and all binary systems were taken and held in place on a quartz plate for exposure to Cu Kα radiation of wavelength 1.5406 Å. The samples were analyzed at room temperature over a range of 5–70° 2θ with sampling intervals of 0.02° 2θ and scanning rate of 6°/min.

Fourier-Transform Infrared Spectroscopy

Fourier transform-infrared spectra (FT-IR) were obtained on a Bomem 2000 FT-IR system (Bomem, Quebec, Canada) using the KBr disk method. Samples were mixed with KBr powder and compressed to

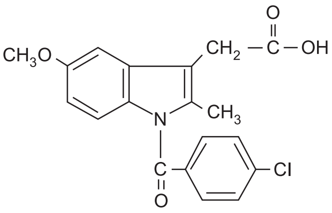

Figure 1. Structural formula of indomethacin.

10-mm discs by hydraulic press at pressure of 10 tons for 30 seconds. The scanning range was 450–4000 cm^{-1} and the resolution was 2 cm^{-1}.

RESULTS AND DISCUSSION

Solubility Studies

The structural formula of indomethacin is shown in Fig. 1. The results of solubility measurements are presented in Table 1. The solubility of indomethacin (pKa=4.5) in pH 1.2 and pH 7.2 buffered aqueous medium at 37° C was found to be 0.01 mmol/L (3.662 µg/mL) and 5.52 mmol/L (1975 µg/mL), respectively. Therefore, according to the USP solubility definition, indomethacin can be considered as a practically insoluble drug at pH 1.2 and slightly soluble at pH 7.2. Aqueous solutions of mannitol did not seem to increase the solubility of indomethacin (Table 1, Fig. 2). Similar observations were obtained for sorbitol and lactose. The phase solubility diagram obtained for indomethacin solutions of Myrj 52 at 37° C and pH=1.2 and 7.2 is shown in Fig. 2. The increase in solubility of indomethacin was linear with respect to the weight fraction of the carrier; at 1% of Myrj 52 the increase in solubility at 37° C was about 57- and 2.2-fold compared to pure indomethacin at pH 1.2 and 7.2, respectively (Table 1). The increase in solubility in the presence of Myrj 52 can be attributed to the micellar solubilization. An indication of the process of transfer of indomethacin from pure water to the aqueous solutions of Myrj 52 may be obtained from the values of Gibbs free energy change. Table 2 presents the values of Gibbs free energy associated with the aqueous solubility of indomethacin in the presence of different carriers. ΔG^0_{tr} values were all negative, indicating the spontaneous nature of drug solubilization. The values decreased by increasing Myrj 52 concentration, demonstrating that the reaction became more favorable as the concentration of Myrj 52 increased.

The results for Eudragit E100 were very interesting. The solubility of indomethacin in an 8% aqueous solution of Eudragit E100 at pH 1.2 was 0.8774 mmol/L (313.9 µg/mL) (Table 1). But when indomethacin was first mixed with Eudragit E100 and then put into pH 1.2 medium, there was a considerable increase in solubility as compared to the aqueous solution of Eudragit E100 containing the same amount of Eudragit E100 [29.82 mmol/L (10669.9 µg/mL)]. In this case, in addition to the solubilizing effect, the increase in solubility in the presence of Eudragit E100 can be explained by an increased pH of the medium by this polymer. Addition

Table 1. Solubility data for indomethacin at pH 1.2 and 7.2 water-carrier systems in 37° C (standard deviations were all less than 10%).

Carrier concentration (% w/w)		0.25	1	4	8	16
pH 1.2	Lactose	1.317	2.880	1.160	2.619	2.150
	Sorbitol	3.610	2.672	4.704	4.391	6.893
	Mannitol	4.860	2.724	4.756	4.235	3.714
	Dextrin[a]	4.496	6.424	–	–	–
	PEG 6000	5.225	6.268	13.981	26.280	60.103
	Myrj 52	54.058	203.663	723.051	1430.05	2167.229
	Eudragit E100[a]	50.879	88.090	195.714	313.913	906.683
pH 7.2	Lactose	1964.24	2500.56	2445.01	2359.54	2434.32
	Sorbitol	1923.64	2011.25	2064.66	1739.88	1365.95
	Mannitol	2148.00	2004.84	1949.28	1731.33	1363.81
	Dextrin[a]	2060.39	2205.69	–	–	–
	PEG 6000	2004.84	2177.91	3199.28	4129.33	5125.06
	Myrj 52	3394.29	4270.36	7101.19	10466.6	15370.44

[a] Measurement of the indomethacin solubility in the presence of Edragit E100 at pH 7.2 and high amounts of dextrin at both pHs was not possible due to carrier solubility problems.

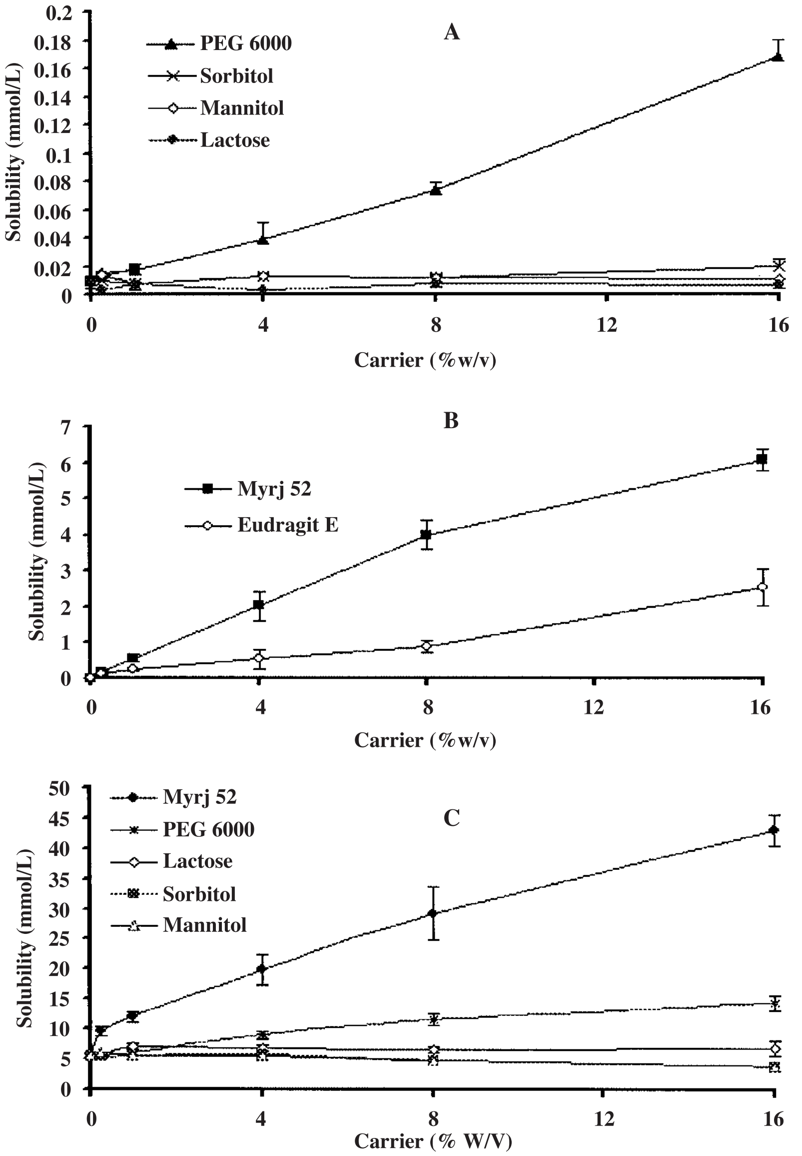

Figure 2. Phase solubility diagram of indomethacin in aqueous solutions of different carriers at 37° C; pH 1.2 A and B and pH 7.2 C.

of Eudragit E100 raises the pH of the medium, which results in a considerable increase in the solubility of indomethacin. In fact, when 0.8 g of Eudragit E100 was added to 10 mL pH 1.2 medium, the pH of the resulting solution was determined to be 6.5. The phase solubility diagram obtained for indomethacin in the presence of Eudragit E100 at 37° C in pH=1.2 is shown in Fig. 2. The increase in solubility was linear with respect to the weight fraction of the carrier. A content of 8% w/v Eudragit E100 at pH 1.2 and 37° C increased the solubility about 86 fold compared to indomethacin by itself (Table 1).

Dissolution Studies

The release of indomethacin from solid dispersions and physical mixtures was analyzed in simulated gastrointestinal fluids. $Q_{5\ \mathrm{min}}$ and $Q_{15\ \mathrm{min}}$ values (percent drug dissolved within 5 and 15 minutes) are reported in Table 3. Since the solubility of indomethacin is considerably pH dependent, dissolution studies of indomethacin from solid dispersions were evaluated in simulated gastric fluid without pepsin (pH 1.2) and simulated intestinal fluid without pancreatin (pH 7.2).

Table 2. The values of Gibbs free energy of transfer for the solubility process of indomethacin at pH 1.2 and 7.2 water-carrier systems in 37° C.

		ΔG°_{tr}	
Carrier	% w/v	pH 1.2	pH 7.2
Lactose	0.25	616.012	3.3672
	1	133.695	−145.4
	4	693.907	−131.5
	8	192.129	−109.6
	16	313.7	−128.8
Sorbitol	0.25	−5.4384	16.236
	1	179.99	−11.2
	4	−168.61	−27.36
	8	−126.22	78.099
	16	−404.02	227.19
Mannitol	0.25	−188.75	−51.74
	1	168.086	−9.238
	4	−175.4	8.0769
	8	−103.89	81.133
	16	−22.978	228.15
Dextrin[a]	0.25	−140.68	−26.08
	1	−360.6	−68.07
	4	–	–
	8	–	–
	16	–	–
PEG 6000	0.25	−233.35	−9.238
	1	−345.41	−60.26
	4	−839.74	−297.2
	8	−1228.6	−454.4
	16	−1738.3	−501.1
Myrj 52	0.25	−1673	−333.7
	1	−2490.3	−389.3
	4	−3270.9	−853.3
	8	−3691.1	−1027
	16	−3947.3	−1135
Eudragit E100[a]	0.25	−1635.7	–
	1	−1973.9	–
	4	−2465.7	–
	8	−2756.8	–
	16	−3410.4	–

[a] Measurement of the indomethacin solubility in the presence of Edragit E100 at pH 7.2 and high amounts of dextrin at both pH 1.2 and 7.2 was not possible due to carrier solubility problems.

From Table 3 it is evident that the dissolution rate of pure indomethacin is very low (less than 0.5% and 20% of the drug being dissolved within 15 min at pH 1.2 and 7.2, respectively). Solid dispersions of indomethacin with hydrophilic carriers except dextrin at both pH 1.2 and 7.2 medium and Eudragit E100 at pH 7.2 medium considerably enhanced dissolution rate compared to the physical mixtures of ingredients. However, the dissolution rate of all physical mixtures was higher compared to pure indomethacin. Possible explanations of the increased dissolution rate of solid dispersions have been proposed by Ford[16] and Craig,[17] and include: reduction of drug crystallite size, a solubilization effect of the carrier, absence of aggregation of drug crystallites, improved wettability and dispersibility of the drug, dissolution of the drug in the hydrophilic carrier, conversion of the drug to the amorphous state, and finally a combination of the above mentioned mechanisms.

Dry mixing of indomethacin with PEG 6000, lactose, dextrin, sorbitol, mannitol, Myrj 52, or Eudragit E100 brings the drug in close contact with the hydrophilic carrier. The increased dissolution rate observed in these cases (physical mixtures) can be contributed to several factors such as a solubilization effect of the carrier, improved wettability of the drug, and inhibition of particle aggregation.

Dissolution profiles of solid dispersions with lactose at pH 1.2 and 7.2 showed an increase in the dissolution rate of indomethacin with respect to the physical mixtures and the drug by itself. Increasing the weight fraction of indomethacin in the solid dispersions did not reduce the dissolution rate for the dispersions prepared with lactose. This is not surprising, as it has been previously shown that an increase in the weight fraction of the drug does not necessarily decrease the dissolution rate.[18] A faster release of indomethacin at pH 7.2 compared to pH 1.2 is due to the higher solubility of the drug at this pH.

Indomethacin alone exhibited the slowest dissolution rate with only about 0.45% and 19% of drug release in 15 min at pH 1.2 and 7.2, respectively. As shown in Table 3, the dissolution rate of indomethacin from all physical mixtures of the drug and mannitol and also the physical mixtures of the drug and dextrin were almost the same, but considerably higher than indomethacin alone. This might be due to the inhibition of drug particle aggregation by the carrier.[19] The dissolution rates for solid dispersions prepared with mannitol were greater than those for physical mixtures or indomethacin alone (Table 3).

In general, dissolution may be described by two processes: the rate of the interfacial or solid-solvent reaction leading to solubilization of the molecule, and the rate associated with the diffusional or transport process of the solvated molecule to the bulk part of the dissolution medium. Since water is strongly polar due to its O–H groups it readily forms hydrogen bonds with polar groups such as the O–H group in dextrin and the electronegative amide group on the indomethacin molecule. The strength of bonds between water–dextrin and water–drug molecules may be stronger

Table 3. Percent drug dissolved within 5 and 15 minutes ($Q_{5\ min}$ and $Q_{15\ min}$) of indomethacin-carrier binary systems at pH 1.2 and 7.2 (standard deviations were all less than 10%).

		pH=1.2				pH=7.2			
		Physical mixture		Solid dispersion		Physical mixture		Solid dispersion	
Sample		$Q_{5\ min}$	$Q_{15\ min}$	$Q_{5\ min}$	$Q_{15\ min}$	$Q_{5\ min}$	$Q_{15\ min}$	$Q_{5\ min}$	$Q_{15\ min}$
Pure indomethacin		0.44	0.45			1	19		
Lactose	1:10	1.6	1.7	4.7	4.8	67	81	84	98.5
	1:20	1.3	2	4.6	5	65	80	84	95
	1:40	2.1	2.3	4.8	5.1	44	65	84.5	95.5
Mannitol	1:10	2.2	2.8	17.4	17.7	54	72	76	87
	1:20	6.8	9.2	22	28.5	62	81	87	95
	1:40	7.6	12	20.6	27	68	84	85	94
Sorbitol	1:10	2.3	2.5	9	11	41	64	67	91
	1:20	3.7	5.2	8.5	13	36	72	68	94
	1:40	4.6	5.9	11.6	15	15.5	59	58	85
Dextrin	1:10	5.2	6	2.1	3	49	71	38	60
	1:20	5.6	7.3	1.5	2.3	60	78	47	73
	1:40	6.2	7.2	1.3	1.9	63	83	42	64
PEG 6000	1:10	4.3	7.8	8	11.6	22	65	40	75.2
	1:20	7	10	7.2	11	19	56	38	97
	1:40	7.4	9.6	5.4	8.2	25	61	27.5	80.3
Myrj 52	1:10	9.6	10.7	43	42	34	78	100	100
	1:20	11.6	13	52	56	39	82	100	100
	1:40	15	19	65	72	43	91	100	100
Eudragit E100	1:10	3.2	3.9	84	75	17.5	38	3	6.7
	1:20	3.2	4	92	84.6	24	56	2.3	4.6
	1:40	5.3	6.6	95	90	29	65	2.8	4.9

than or comparable with that between the molecules of the solid dispersions. Upon contact, water molecules solvate the carrier and the drug molecules, either in the crystalline or amorphous form, and break the hydrogen bonds between the drug-dextrin complex. During this process of solubilization, a stagnant layer, which surrounds the particle, is saturated with dissolved carrier and drug molecules. According to the Noyes and Whitney equation:

$$dm/dt = D\mathrm{A}(Cs - C)/\mathrm{h}$$

The rate of change of mass dissolved (m) with time (t) is governed by diffusion coefficient (D), surface area (A) of the solid, thickness of the diffusion layer (h), solubility of the solid (Cs), and concentration of solute in the bulk solution and at time t (C). From the Stokes–Einstein equation:

$$\mathrm{D} = \mathrm{kT}/6\mathrm{r}\pi\eta$$

The diffusion coefficient is inversely proportional to viscosity (η) where T=absolute temperature, k=Boltzmann constant, r=radius of the molecule, and π=3.14. With respect to the drug alone, an improvement in the dissolution rate was achieved for the formulations containing dextrin. However, the release of indomethacin from physical mixtures was slightly faster than the release from coevaporates. This is due to the different preparation methods of the two systems. In fact, while in the coevaporates the polymer swelling causes a deep and presumably viscous incorporation of the drug into the polymeric network, in the physical mixtures the two components are only mixed in a solid state. The viscosity of 10% w/v solution of dextrin at 20° C is 100 mPa/s, which is about 50 times higher than that of mannitol.[20] With the high viscosity of dextrin, the diffusion coefficient is largely decreased, resulting in a low dissolution rate of the drug from solid dispersions compared to the physical mixtures. The dissolution mechanism of solid dispersion with dextrin might be predominantly diffusion-controlled, and presumably the high viscosity of this carrier is the main factor to control the dissolution rate.

For solid dispersions prepared with mannitol, the diffusional process might not be the major factor to govern the dissolution process. The dissolution rate of the solid dispersion increased until the drug:mannitol ratio of 1:20 was reached. The increase in the dissolution rate was about 50- and 87-fold after 5 min compared to the pure drug at pH 1.2 and 7.2, respectively. However, results of x-ray powder diffractometery showed that indomethacin was in the amorphous state only in solid dispersions with high mannitol content. Further increase in the proportion of mannitol did not affect the drug release. The increase in the amount of mannitol may prevent drug aggregation, decrease crystallinity, decrease drug particle size, or increase wettability, resulting in a higher dissolution rate.[4]

An improved dissolution rate of indomethacin from formulations prepared with sorbitol was obtained, although no complete amorphization of the indomethacin was achieved.

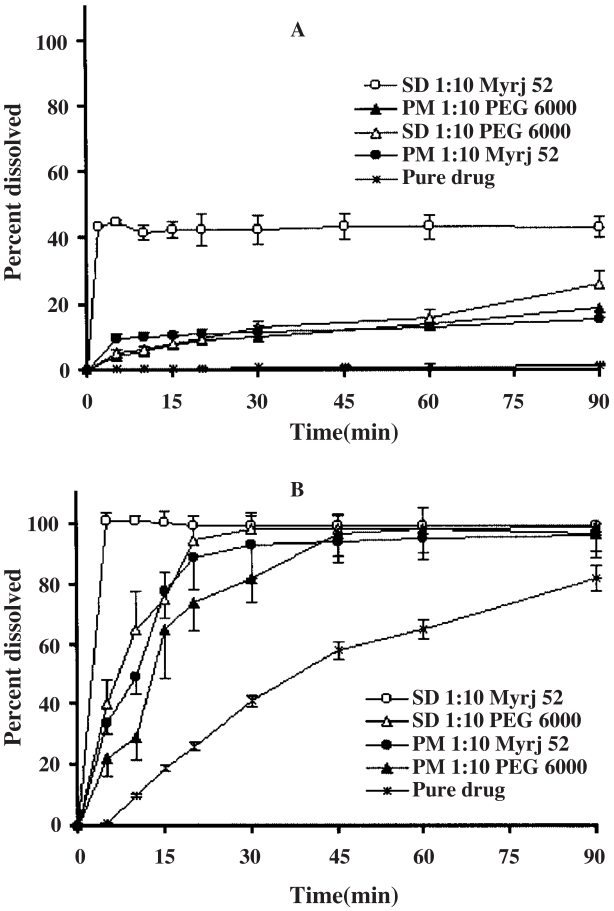

Figure 3. Dissolution profile of indomethacin, from physical mixtures (PM) and solid dispersions (SD) prepared with Myrj 52 and PEG 6000 using a fusion method. pH 1.2 A and pH 7.2 B.

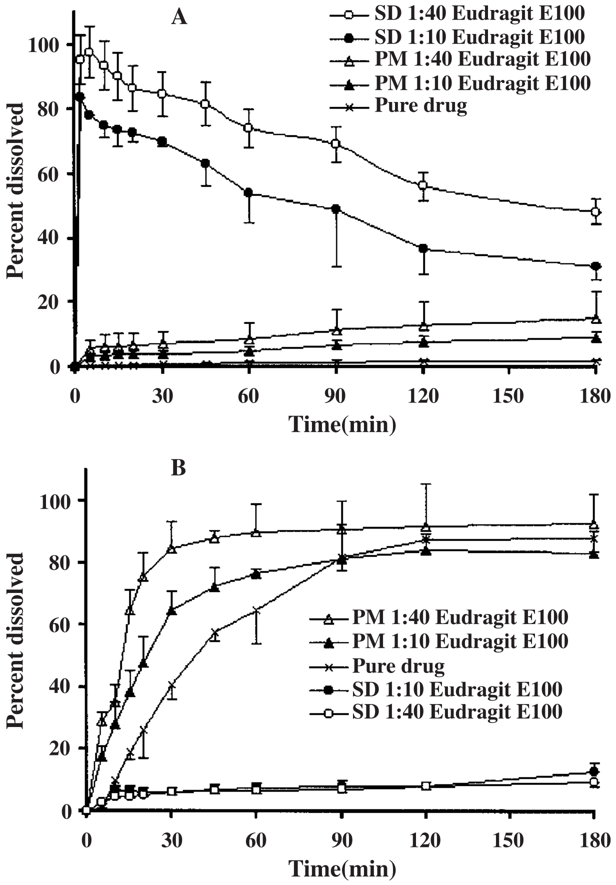

Figure 4. Dissolution profiles of physical mixtures (PM) and solid dispersions (SD) of indomethacin with Eudragit E100, pH 1.2 A; pH 7.2 B.

The enhanced dissolution rates of solid dispersions prepared with lactose, mannitol, and sorbitol may be due to many factors such as the hydrophilic character of these carriers and decreased particle size of the drug[16,21] in solid dispersions. However, the earlier mentioned mechanisms such as the increase in drug wettability and the prevention of aggregation of the drug by its carrier may also apply. Further investigations are in progress in order to elucidate the exact mechanisms.

A fast release of indomethacin from solid dispersions and physical mixtures with PEG 6000 was observed. The release rate inversely correlated to the amount of PEG 6000 in solid dispersions. This can be ascribed to the formation of a viscous hydrophilic layer around the drug particles, as reported by Zingone and Rubessa.[22]

Figure 3 shows the release profiles of the drug from physical mixtures and solid dispersions of indomethacin with PEG 6000 and Myrj 52 (ratio of 1:10). It is evident that the dispersion of the drug in these carriers considerably enhances the dissolution rate of indomethacin. This effect is mainly seen in the case of Myrj 52; the $Q_{5\ \mathrm{min}}$ is 43 and 100 at pH 1.2 and 7.2, respectively (Table 3). This phenomenon can be attributed to the solubilization effect of these carriers, improved wettability, and dispersibility of the drug from the dispersion.

Figure 4 shows the amount of indomethacin dissolved from physical mixtures and coevaporates of indomethacin with Eudragit E100 at ratios of 1:10 and 1:40 at pH 1.2 and 7.2, respectively. The $Q_{5\ \mathrm{min}}$ values of 84% and 95% were observed at pH 1.2 for 1:10 and 1:40 coevaporates, respectively. The rapid drug release can be attributed to the high solubility of the polymer at this pH, as well as a microenvironmental pH increase, around particles, which is favorable to the indomethacin dissolution. However, after a fast release of indomethacin within 5 minutes, parts of the dissolved drug gradually recrystallized from the solution, due to the low solubility of indomethacin at pH 1.2 (Fig. 4A).

Coevaporates with Eudragit E100 delayed and decreased the dissolution of the indomethacin in a simulated intestinal fluid (pH 7.2) (Fig. 4B). After 3 hours only 12.8% of the drug was released from 1:10 coevaporate and 9.2% from 1:40 coevaporate. Compared to the indomethacin alone and physical mixtures, the lower dissolution rate of the drug in the coevaporates can be associated to the insolubility of the polymer at this pH. Furthermore, the higher polymer content led to a decreased drug release. The mechanism of drug release in this case depends on the penetration of the dissolution medium into the coevaporate, the dissolution and subsequent diffusion of the drug through the polymeric matrix, and hence the diffusional process within the drug-polymer system as shown by Abd El-fattah, Salib, and El-Assik.[23]

Table 4. Intensities at characteristic diffraction angles 2θ (°) and d-values (Å) for indomethacin.

2θ	d-value	Intensity
10.5	8.702	102
11.5	7.635	435
12.5	6.960	55
17	6.220	460
18.5	4.776	145
19.5	4.528	725
20.95	4.26	151
21.81	4.074	901
23	3.89	290
24	3.707	362
25.6	3.469	98
26.6	− 3.348	978.5
27	− 3.307	201
27.5	3.244	280
28.5	3.155	186
29.3	3.042	753
30.5	2.910	204
32.5	2.745	100.3
33.7	2.669	278
34.8	2.571	151
35.8	2.919	85
37.3	2.400	310

Powder X-Ray Diffraction (PXRD)

The diffraction spectrum of pure indomethacin showed that the drug was of crystalline nature as demonstrated by numerous distinct peaks. The characteristic peaks for indomethacin and their intensities are listed in Table 4.

PEG 6000 showed two peaks with the highest intensity at 2θ and d-spacings of 19.4 (4.669 Å) and 23.34 (3.835 Å). In the case of pure Myrj 52, the predominant peaks were observed at 19.238 (4.62 Å) and 23.388 (3.805 Å). These two predominant peaks of Myrj 52 had approximately the same parameters as those in PEG 6000, which arises from the fact that Myrj 52 is a polyethoxylated derivative of stearic acid (polyoxyethylene stearate), which has 12–27% of free polyethyleneglycoles. The extent of crystallinity influences the dissolution of the drug. An amorphous or metastable form will dissolve at the fastest rate because of its higher internal energy and greater molecular motion, which enhance thermodynamic properties compared to crystalline materials.[24,25] From our data, it is clear that none of the components (indomethacin, Myrj 52, PEG 6000, sorbitol, and lactose) were converted to the amorphous form. All the principal peaks from Myrj 52, PEG 6000, sorbitol, lactose, and indomethacin were present in their respective physical mixtures and solid dispersions, although with lower intensity, but no new peaks could be observed, suggesting the absence of interaction between the drug and the carrier. However, indomethacin was detected in an amorphous state in solid dispersions with high mannitol content and in solid dispersions prepared with dextrin.

Regarding the peak positions of indomethacin, some changes were observed in samples prepared with PEG 6000 (Fig. 5). The prominent peak from pure indomethacin at 2θ of 21.81° was clearly seen at the same position in the physical mixtures, but in the solid dispersions its intensity was remarkably decreased as the concentration of indomethacin was increased.

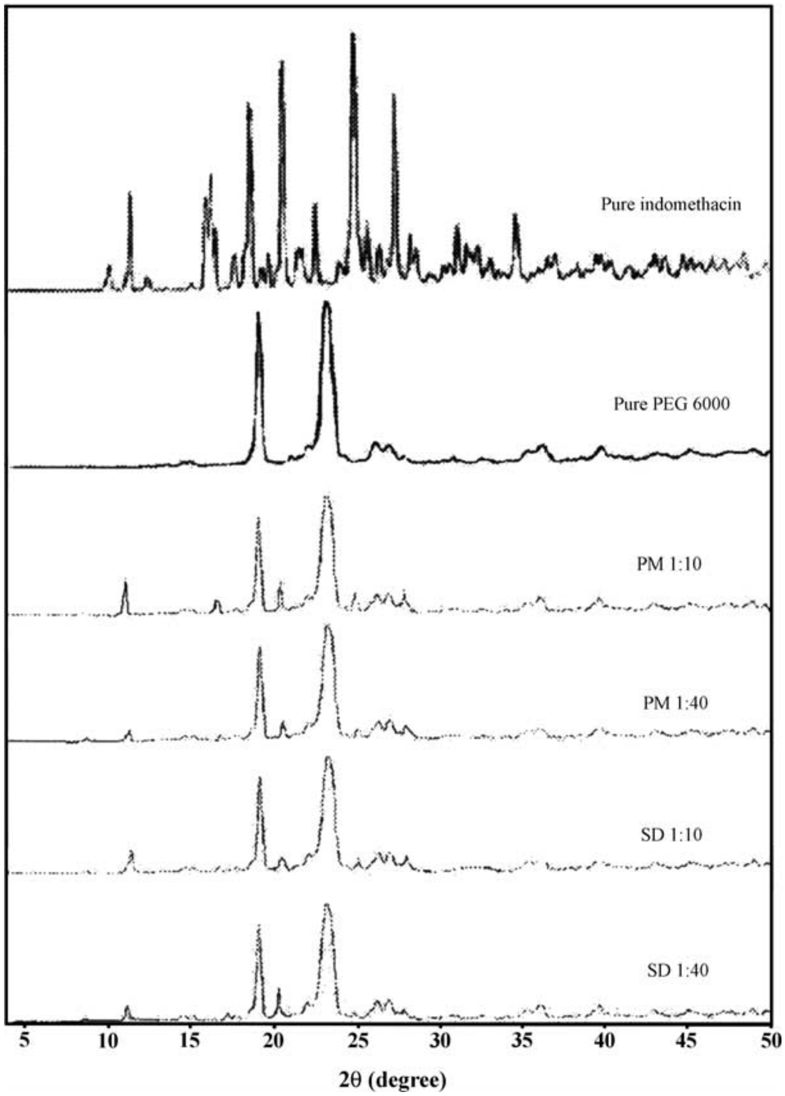

Figure 5. X-ray diffraction patterns of solid dispersions (SD) and physical mixtures (PM) of indomethacin with PEG 6000.

Instead, the peak from indomethacin at 2θ of 10.5° became prominent. The change of the intensity of indomethacin peaks observed in solid dispersions with PEG 6000 as compared to their respective physical mixtures can be explained as a result of the change of the crystal orientation. Likewise, the peak 2θ of 11.5° from indomethacin progressively was increased in intensity as the concentration of indomethacin was increased in both physical mixtures and solid dispersions with PEG 6000. From these observations we can conclude that the crystalline nature of the drug was still maintained, but the relative reduction of diffraction intensity of indomethacin in PEG 6000 preparation at these angles suggests that the quality of the crystals was reduced. The positions of PEG 6000 patterns in the physical mixtures and solid dispersions were the same and superimposable, which again ruled out the possibility of chemical interaction and compound formation between these two components. With regard to Myrj 52, several peaks from indomethacin were also observed in both physical mixtures and solid dispersions, but unlike PEG 6000 preparations, they were all at the same positions.

Mannitol also exhibited a distinct pattern with diffraction peaks at 2θ of 9.50, 18.95, 20, and 22.10°. Solid dispersions with low carrier content and physical mixtures of indomethacin and mannitol showed the same diffraction pattern. In the case of 1:40 solid dispersions, in contrast to the 1:40 physical mixtures, none of the diffraction peaks of the drug could be detected (Fig. 6). Increasing the drug amount (1:20 and 1:10 solid dispersions), the diffraction pattern of

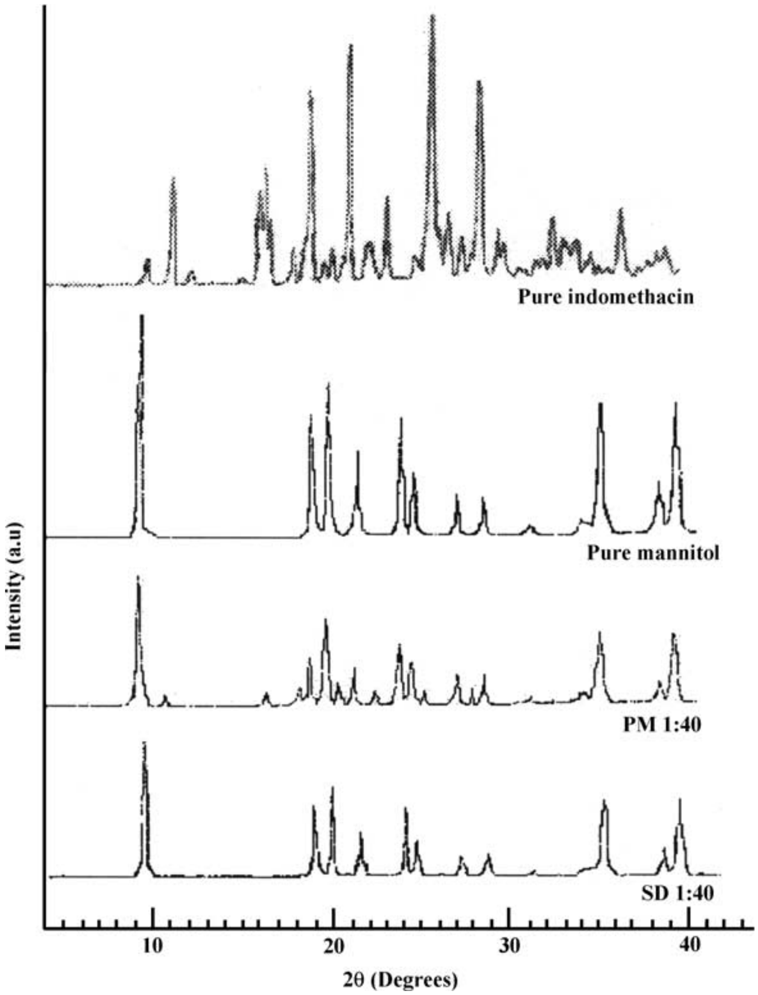

Figure 6. X-ray diffraction patterns of solid dispersions (SD) and physical mixtures (PM) of indomethacin with mannitol for 1:40 ratio.

indomethacin became more distinct. Moreover, no other peaks than those that could be assigned to the pure indomethacin and mannitol were detected in the solid dispersions, indicating no chemical interactions in the solid state between the two entities.

The spectrum of solid dispersions prepared with dextrin was characterized by the complete absence of any diffraction peaks, suggesting a complete amorphization of the drug in the amorphous carrier (Fig. 7). Several diffraction peaks attributable to indomethacin could be detected in physical mixtures with dextrin. However, in the coevaporates, the diffraction peaks of the drug could not be distinguished from the noise, indicating that indomethacin was in the amorphous state (Fig. 7). In the case of solid dispersions prepared with Eudragit E100, indomethacin was still detectable in crystalline form, although the intensity of indomethacin peaks were reduced compared to the physical mixtures with the same composition (Fig. 8). Therefore no complete amorphization occurred.

Fourier-Transform Infrared Spectroscopy

Fourier-transform infrared (FT-IR) spectroscopy was used to further characterize possible interactions between the drug and the carrier in the solid state. From the structures of indomethacin, PEG 6000, Myrj 52, lactose, mannitol, sorbitol, and dextrin it can be assumed that possible interaction could occur between the carboxyl group of indomethacin and the hydroxyl group of these carriers. In this case any sign of interaction would be reflected by a change in O–H vibration, depending on the extent of interaction. In the case of Myrj 52, the site of interaction is expected to be at the C=O and OH group; also in this case the O–H

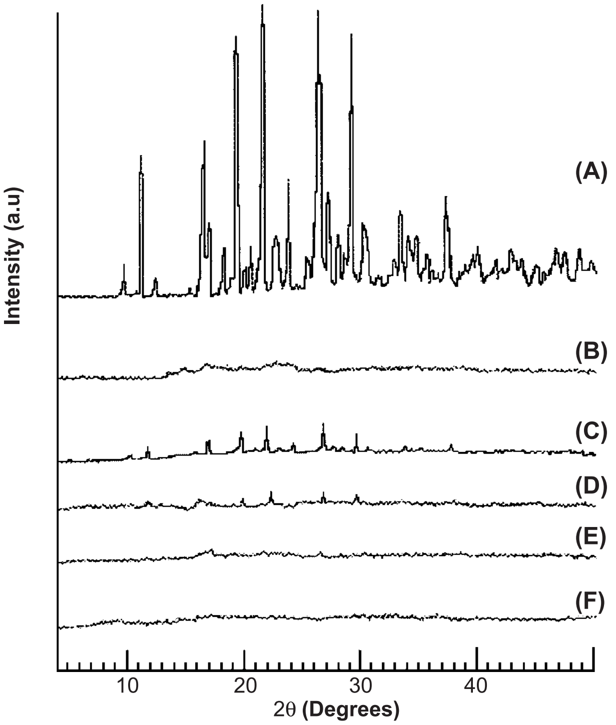

Figure 7. X-ray diffraction patterns of solid dispersions (SD) and physical mixtures (PM) of indomethacin with dextrin. (A) indomethacin alone; (B) dextrin; (C) 1:10 dextrin PM; (D) 1:40 dextrin PM; (E) 1:10 dextrin SD; (F) 1:40 dextrin SD.

vibrations will be affected. From the knowledge of structures of indomethacin and Eudragit E100 the potential interaction could occur between acidic function of the drug and the basic amine group of the polymer. In this case any sign of interaction would be reflected by a change in the position of $C{=}O$ vibration and disappearance of O−H stretching. The results from FT-IR spectroscopy showed that there was no significant change in the FT-IR spectrum of solid dispersions prepared with Eudragit E100, which could be attributed to the acid-base reaction and/or H-bonding. This is in accordance with a previous report by Lovrecich and coworkers,[26] where they could not find any interaction in freshly prepared solid dispersions of indomethacin with Eudragit E. However, they noticed that upon aging, i.e., after 2 years, the interaction took place. The incorporation of indomethacin into PEG 6000, lactose, mannitol, sorbitol, and Myrj 52 did not modify their peaks positions and trends. These results further indicate the absence of well-defined interaction between indomethacin and PEG 6000, Myrj 52, Eudragit E100, lactose, or sorbitol as already confirmed from the x-ray diffraction study. The spectrum of indomethacin showed two characteristic bands of the OH group that were found at 3372 cm^{-1} (free OH), and 2900–3321 cm^{-1} (OH involved in intermolecular association). Two carbonyl stretching peaks appears as a very strong band at 1721 cm^{-1} (acid group) and 1692 cm^{-1} (amide group). The spectrum of dextrin showed, amongst others, important bands at 2953 cm^{-1} (C−H stretching) and 1109 cm^{-1} (C−O stretching). A very broad band was also visible at 3446 cm^{-1}, which was attributed to the presence of water. Important vibrations detected in the spectrum of PEG 6000 are the C−H stretching at 2890 cm^{-1} and the C−O stretching at 1110 cm^{-1} and OH stretching at 3350 cm^{-1}. Comparing the spectra of physical mixtures and solid dispersions of indomethacin with PEG 6000, no difference was shown in the position of the absorption bands. The spectra can be simply regarded as the superposition of those of indomethacin and PEG 6000. Although it could be expected to have hydrogen bonding between the hydrogen atom of the OH of the drug and one of the ion pairs of the oxygen atom in PEG 6000, this could not be demonstrated. When interaction is expected between indomethacin and dextrin in the solid state, it should reasonably involve the OH or $-C{=}O$ function of indomethacin and the OH group of the dextrin in hydrogen bonding. Indeed, the

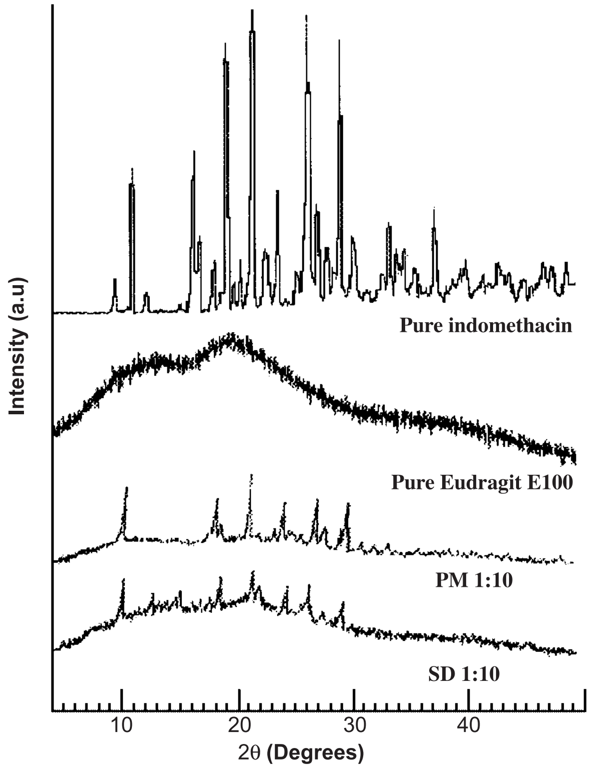

Figure 8. X-ray diffraction patterns of solid dispersions (SD) and physical mixtures (PM) of indomethacin with Eudragit E100 for 1:10 ratio.

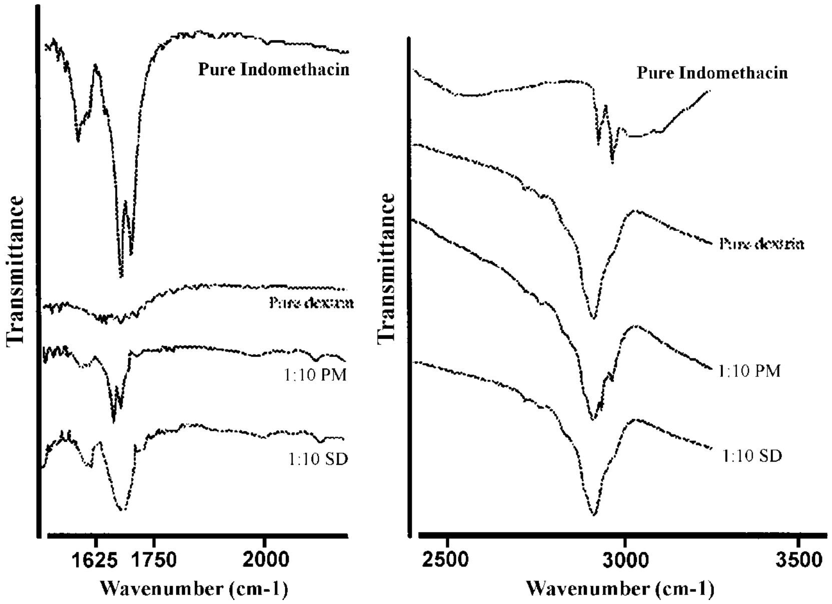

Figure 9. FT-IR spectra of pure indomethacin, dextrin, 1:10 Physical mixture (PM) of indomethacin with dextrin, and 1:10 Solid dispersion (SD) of indomethacin with dextrin.

absorption band, which can be assigned to the free OH, disappeared, and the band due to intermolecular association increased in intensity. The peaks, which were assigned to the amide at 1689 and 1670 cm^{-1}, also disappeared; instead a large band was detected (Fig. 9). The reason for this observation can be interpreted as a consequence of hydrogen bonding between C=O of amide group of indomethacin and the OH of dextrin, since hydrogen bonding is thought to influence the bonding strength between the carbon and the oxygen atom of the carbonyl function of indomethacin, moving the electron density towards the oxygen atom. This will result in a decreased stretching frequency (ν). Further evidence for the involvement of the carbonyl function of the drug in interaction is given by the disappearance of the band assigned to the out-of-plane deformation (γCO at 648 cm^{-1}). Other bands that decreased in intensity, or even disappeared from the spectrum of the solid dispersion are: C–N stretch (1397 cm^{-1}), in-plane deformation of CH3 (1344 cm^{-1}), C–OH stretch (symmetrical: 1028; asymmetrical: 1230 cm^{-1}), CH3 rocking (1153 cm^{-1}), C–N–C stretch (817 cm^{-1}).

CONCLUSION

Solubility studies showed a solubilizing effect of Myrj 52 on indomethacin at pH 1.2 and pH 7.2. The negative values of the Gibbs free energy of transfer from water to an aqueous solution of Myrj 52 indicated the spontaneity of drug solubilization. Increased solubility was also observed in aqueous solutions of PEG 6000 at pH 1.2 and pH 7.2, and for indomethacin mixtures with Eudragit E100 at pH 1.2.

An increased dissolution rate of indomethacin at pH 1.2 and 7.2 was observed when the drug was dispersed in PEG 6000, Myrj 52, lactose, or sorbitol. The solubilization effect of PEG 6000 and Myrj 52 as well as the reduction of particle aggregation and an alteration of the surface properties of the drug particles might be responsible for the enhanced dissolution rate. In the case of mannitol, sorbitol, and lactose, an alteration of surface properties as well as a reduction of the particle size might be responsible for the enhanced dissolution rate.

Solid dispersions of indomethacin with Eudragit E100 markedly improved the dissolution rate and extent at pH 1.2 due to a solubilizing effect and a micro-environmental pH change induced by this polymer.

Results from IR spectroscopy concluded that there was no well-defined interaction between indomethacin and PEG 6000, Myrj 52, lactose, mannitol, sorbitol, or Eudragit E100. The presence of the characteristic peaks of indomethacin in the x-ray diffraction patterns of all binary systems, except for solid dispersions prepared with dextrin and high amounts of mannitol, reveals that there is no significant change in the crystal properties of indomethacin in the formulations. However, x-ray powder diffraction indicated that indomethacin was in the amorphous state when dispersed in dextrin. In this system, a drug-carrier interaction through intermolecular hydrogen bonding was demonstrated using FT-IR.

Since the coevaporates with dextrin, lactose, sorbitol, and mannitol could be prepared by using two different but mutually soluble solvents, the need of a common solvent for the drug and the carrier should not be considered an absolute requirement for preparation of coevaporates. The use of two mutually soluble solvents will broaden the application of the coevaporation technique for a wider range of drugs and carriers.

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