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Enhancement of Dissolution Rate of Valdecoxib Using Solid Dispersions with Polyethylene Glycol 4000

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ABSTRACT The aim of the present study was to enhance the dissolution rate of valdecoxib using its solid dispersions (SDs) with polyethylene glycol (PEG) 4000. The phase solubility behavior of valdecoxib in the presence of various concentrations of PEG 4000 in water was obtained at 37°C. The solubility of valdecoxib increased with increasing amount of PEG 4000 in water. Gibbs free energy (ΔG°_{tr}) values were all negative, indicating the spontaneous nature of valdecoxib solubilization, and they decreased with increase in the PEG 4000 concentration, demonstrating that the reaction conditions became more favorable as the concentration of PEG 4000 increased. The SDs of valdecoxib with PEG 4000 were prepared at 1:1, 1:2, 1:5, and 1:10 (valdecoxib: PEG 4000) ratio by melting method. Evaluation of the properties of the SDs was performed by using dissolution, Fourier-transform infrared (FTIR) spectroscopy, differential scanning calorimetry (DSC), X-ray diffraction (XRD), and scanning electron microscopy (SEM) studies. The SDs of valdecoxib with PEG 4000 exhibited enhanced dissolution rate of valdecoxib, and the rate increased with increasing concentration of PEG 4000 in SDs. Mean dissolution time (MDT) of valdecoxib decreased significantly after preparation of SDs and physical mixture with PEG 4000. The FTIR spectroscopic studies showed the stability of valdecoxib and absence of well-defined valdecoxib-PEG 4000 interaction. The DSC and XRD studies indicated the amorphous state of valdecoxib in SDs of valdecoxib with PEG 4000. The SEM pictures showed the formation of effective SDs of valdecoxib with PEG 4000, since well-defined changes in the surface nature of valdecoxib, SDs, and physical mixture were observed.

KEYWORDS Valdecoxib, Solid dispersion, PEG 4000, Dissolution, Solubility

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INTRODUCTION

Valdecoxib is one of the recently introduced nonsteroidal anti-inflammatory drugs (NSAIDs) used in the management of oesteoarthritis, pain, and dysmenorhea (Ormrod et al., 2002). Traditional NSAIDs are nonselective

cox inhibitors. Cox-2 selective NSAIDs are, therefore, ideal anti-inflammatory drugs with minimum drug-related side effects, since they inhibit cox-1 activity (Bolten, 1998). Valdecoxib has poor solubility in water i.e., 10 μg/mL at 25°C (Barden et al., 2003; Bolten, 1998; Dannhardt & Kiefer, 2001; Ormrod et al., 2002). It is chemically designated as 4-(5-methyl-3-phenyl-4-isoxazolyl) benzenesulfonamide and is a diaryl substituted isoxazole (Fig. 1). For poorly water-soluble, highly permeable (Class II) drugs, the rate of oral absorption is often controlled by the dissolution rate in the gastrointestinal tract (Lobenberg & Amidon, 2000). Therefore, together with permeability, the solubility and/or dissolution rate of a drug are key determinants of its oral bioavailability (Desai et al., 2003; Lobenberg & Amidon, 2000; Rawat & Jain, 2003).

Although numerous methods are available to improve the solubility and/or dissolution rate of poorly soluble drugs, the most promising method for promoting dissolution is the formation of solid dispersions (Ford, 1986; Goldberg et al., 1965, 1966a, 1966b). Dispersion of poorly water-soluble drugs in an inert hydrophilic carrier or matrix at solid state provided by the melting, solvent, or solvent-melting method leads to products referred to as solid dispersions (SDs) (Chiou & Riegelman, 1971; Ford, 1986). These SDs provide the possibility of reducing the particle size of such drugs to nearly a molecular level, to transform the drug from the crystalline to the (partial) amorphous state, and/or to locally increase the saturation solubility (Leuner & Dressman, 2000). In other words, SDs improve the rate of bioavailability of poorly soluble drugs by increasing their saturation solubility in the gastrointestinal fluids (Goldberg et al., 1965, 1966a, 1966b).

Polyethylene glycols (PEGs) with molecular weights of 1500–20,000 are used for the preparation of SDs. Their solubility in water is generally good, but decreases with molecular weight. A particular advantage of PEGs for the formation of SDs is that they also have good solubility in many organic solvents. The melting point of PEGs of interest lies under 65°C in every case (e.g., the m.p. of PEG 1000 is 30–40°C, the m.p. of PEG 4000 is 50–58°C, and the m.p. of PEG 20,000 is 60–63°C (Leuner & Dressman, 2000). These relatively low melting points are advantageous for the manufacture of SDs by the melting method. Additional attractive features of the PEGs include their ability to solubilize some compounds and also to improve compound wettability (Betageri & Makarla, 1995). Even the dissolution rate of a relatively soluble drug like aspirin can be improved by formulating it as a SD in PEG 6000 (Asker & Whitworth, 1975).

Valdecoxib is one of the recently introduced poorly water-soluble NSAIDs and administered orally. It is a white crystalline powder, relatively insoluble in water, and freely soluble in alkaline aqueous solutions (pH 12). The pK_a is around 10. Often such drugs show poor onset of absorption and bioavailability. Therefore, improvement in solubility and/or dissolution rate may lead to enhanced bioavailability. In this paper, the solid dispersions of valdecoxib with PEG 4000 were prepared by the melting method, and the same was characterized by dissolution, Fourier-transform infrared spectroscopy (FTIR), X-ray diffraction (XRD), differential scanning calorimetry (DSC), and scanning electron microscopy (SEM) studies. Based on the preliminary solubility studies, PEG 4000 was chosen as a suitable carrier for preparing valdecoxib SDs, since it exhibited higher solubilizing potential than PEG 6000, PEG 8000, polyvinylpyrrolidone (PVP) K30, urea, and mannitol.

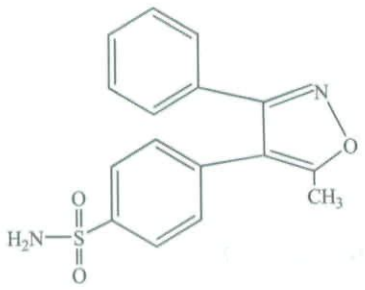

FIGURE 1 Structure of Valdecoxib.

MATERIALS AND METHODS

Materials

A gift sample of valdecoxib was received from Cipla Pharmaceuticals Ltd., (Mumbai, India). PEG 4000 was purchased from Showa Chemicals Inc. (Japan). Sodium lauryl sulfate (SLS) was purchased from Duksan Pure Chemicals, Ltd. (Japan). Ultrapure water (Millipore, USA) was used throughout and all the other chemicals used were of analytical grade.

Solubility Measurements of Valdecoxib

Solubility measurements were performed according to the method of Higuchi and Connors (Higuchi & Connors, 1965). In brief, various (1%, 2%, 5%, and 10% w/v) aqueous solutions of PEG 4000 were prepared, and 10 mL of these solutions were taken into separate screw-cap test tubes. An excess amount of valdecoxib was added to the test tubes. The screw-cap test tubes containing valdecoxib-PEG 4000 mixtures were shaken at 37°C±0.1°C for 48 h in a water bath (Jeio Tech, Japan). (This duration was previously tested to be sufficient to reach equilibrium). After 48 h, samples were filtered through a 0.22 µm membrane filter (Sortorius, Germany). The filtrate was suitably diluted with corresponding PEG 4000 solution (1% or 2% or 5% or 10% w/v) and analyzed spectrophotometrically at the wavelength of 203 nm using a spectrophotometer (Shimadzu 1601PC, Japan). Solubility studies were performed in triplicate (n=3).

Preparation of Solid Dispersions

The SDs of valdecoxib with PEG 4000 were prepared by melting method at 1:1, 1:2, 1:5, and 1:10 (valdecoxib:PEG 4000) ratio. Briefly, a required amount of PEG 4000 was melted in a glass container on a water bath maintained at about 50–60°C. A required amount of valdecoxib was then added to the molten PEG 4000 and mixed thoroughly by a glass rod for 5 min. The molten mixture was cooled rapidly by placing the glass container in an ice bath for about 5 min and solidified. The hardened mixture was then powdered in a mortar, sieved through a 100-mesh screen (Chung Gye Sang Gong Sa, Seoul, South Korea), and stored in a screw-cap vial at room temperature until further use.

Preparation of Physical Mixture

The physical mixture of valdecoxib with PEG 4000 was prepared by mixing the required amount of valdecoxib and PEG 4000 for 5 min in a glass container until a homogeneous mixture was obtained. The resulting mixture was sieved through a 100-mesh screen. The powder was stored in a screw-cap vial at room temperature until use.

Dissolution Studies

Dissolution studies of valdecoxib in powder form, SDs, and physical mixtures were performed by using the U.S. Pharmacopeia (USP) model digital tablet dissolution test apparatus (Wooju Scientific Co., South Korea) at the paddle rotation speed of 100 rpm in 500 mL distilled water containing 0.25% (w/v) of SLS as a dissolution media at 37°C (Damian et al., 2000; Okonogi et al., 1997a). The SDs or physical mixture equivalent to 10 mg of valdecoxib were weighed using a digital adventarer balance (Ohaus Corp.) and added into the dissolution medium. At the specified times (every 10 min for 1 h), 10 mL samples were withdrawn through a sampling tube attached with a 0.22 µm membrane filter (Sortorius, Germany) and then assayed for valdecoxib content by measuring the absorbance at 203 nm using the UV-Visible spectrophotometer (Shimadzu 1601PC, Japan). Fresh medium (10 mL), which was prewarmed at 37°C, was replaced into the dissolution medium after each sampling to maintain its constant volume throughout the test. Dissolution studies were performed in triplicate (n=3), and calculated mean values of cumulative drug release were used while plotting the release curves. Previous tests determined that there was no change in the λ_{max} of valdecoxib due to the presence of PEG 4000 dissolved in the dissolution medium.

Fourier-Transform Infrared Spectroscopy

The FTIR spectra were obtained by using an FTIR spectrometer-430 (Jasco, Japan). The samples (valdecoxib or SDs or physical mixture) were previously ground and mixed thoroughly with potassium bromide, an infrared transparent matrix, at 1:5 (sample: KBr) ratio, respectively. The KBr discs were prepared by compressing the powders at a pressure of 5 tons for 5 min in a hydraulic press. Thirty scans were obtained at a resolution of 2 cm^{-1}, from 4500 to 400 cm^{-1}.

Differential Scanning Calorimetry

The DSC measurements were performed on a DSC-6100 (Seiko Instruments, Japan) differential scanning calorimeter with a thermal analyzer. All accurately weighed samples (about 1 mg of valdecoxib or its

equivalent) were placed in sealed aluminum pans, before heating under nitrogen flow (20 mL/min) at a scanning rate of 10°C min^{-1} from 25°C to 250°C. An empty aluminum pan was used as reference.

X-Ray Diffraction

The X-Ray powder diffraction patterns were obtained at room temperature using a D/max-rB X-ray diffractometer (Rigaku Corporation, Japan), with Co as anode material and graphite monochromator, operated at a voltage of 40 kV. The samples were analyzed in the 2θ angle range of 2°–65° and the process parameters were set as: scan step size of 0.025° (2θ), scan step time of 1.25 s, and time of acquisition of 1 h.

Scanning Electron Microscopy

The surface morphology of valdecoxib, PEG 4000, SDs, and physical mixtures were examined by means of JSM-840 (Jeol Corporation, Japan) scanning electron microscope. The powders were previously fixed on a brass stub using double-sided adhesive tape and then were made electrically conductive by coating, in a vacuum, with a thin layer of platinum (approximately 3–5 nm), for 100 s and at 30 W. The pictures were taken at an excitation voltage of 15 Kv and a magnification of 450 or 30 or 120 or 150 X.

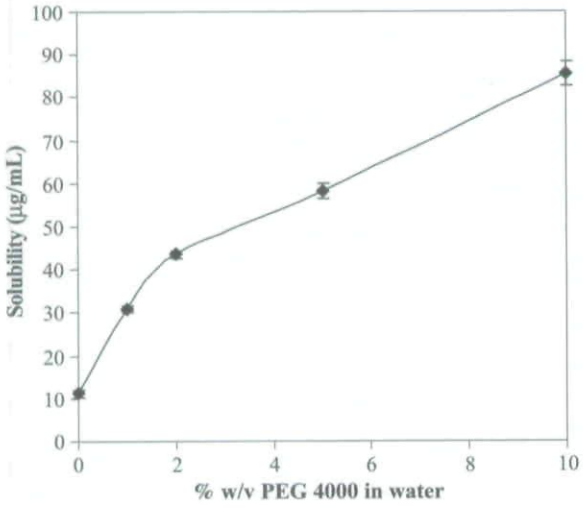

FIGURE 2 Phase Solubility Curve of Valdecoxib in Aqueous Solutions of PEG 4000 at 37°C.

TABLE 1 Thermodynamic Parameters of the Solubility Process of Valdecoxib in PEG 4000-Water Solutions at 37°C

% (w/v) of PEG 4000 in water	ΔG°_{tr} (kJ/mol)[a]
1	−37.66
2	−50.24
5	−61.04
10	−75.26

Note: PEG indicates polyethylene glycol.
[a]Data are obtained by taking mean solubility of valdecoxib from three experiments.

RESULTS AND DISCUSSION

Solubility Studies

The solubility of valdecoxib in water at 25°C is 10 µg/mL; therefore, valdecoxib can be considered to be as a poorly water-soluble drug (Barden et al., 2003; Dannhardt & Kiefer, 2001; Ormrod et al., 2002). The phase solubility curve of valdecoxib in the presence of PEG 4000 is shown in Fig. 2. A systematic increase of solubility of valdecoxib was observed with an increasing concentration of PEG 4000 in water. Increased solubility may be due to improved dissolution of valdecoxib particles in water by PEG 4000. At 10% (w/v) concentration of PEG 4000, the solubility of valdecoxib increased by 7.65-fold. An indication of the process of transfer of valdecoxib from pure water to the aqueous solutions of PEG 4000 was obtained from the values of Gibbs free energy change. The Gibbs free energy of transfer (ΔG°_{tr}) of valdecoxib from pure water to the aqueous solution of PEG 4000 was calculated using Eq. 1.

$$\Delta G^{\circ}_{tr} = -2.303RT\log\frac{S_o}{S_s} \qquad (1)$$

where S_o/S_s = the ratio of molar solubility of valdecoxib in aqueous solutions of PEG 4000 to that of the pure water. The obtained values of Gibbs free energy are presented in Table 1. The data provide the information regarding the increased solubility of valdecoxib in the presence of PEG 4000. In other words, the Gibbs free energy values provide the information whether the reaction condition is favorable or unfavorable for drug solubilization in the aqueous carrier solution. Negative Gibbs free energy values indicate favorable conditions. ΔG°_{tr} values were all negative for PEG 4000 at various concentrations, indicating the spontaneous nature of valdecoxib

TABLE 2 Percent Drug Dissolved Within 30 Minutes ($Q_{10\ min}$, $Q_{20\ min}$, and $Q_{30\ min}$) of Valdecoxib-PEG 4000 Binary Systems

Sample		Valdecoxib dissolved (%)[a]		
		$Q_{10\ min}$	$Q_{20\ min}$	$Q_{30\ min}$
Pure valdecoxib		28.06±1.6	32.46±1.3	37.15±2.1
Valdecoxib: PEG 4000 SDs	1:1	76.00±2.8	87.23±1.9	91.83±1.6
	1:2	77.10±2.4	89.24±2.2	93.87±1.8
	1:5	77.80±1.7	93.91±3.0	96.26±1.3
	1:10	80.90±1.6	97.00±1.1	99.63±1.8
Physical mixture	1:10	56.28±0.9	70.78±1.4	76.30±2.3

Note: PEG indicates polyethylene glycol.
[a]Mean±SD, n=3.

solubilization, and it decreased with an increase in its concentration, demonstrating that the reaction became more favorable as the concentration of PEG 4000 increased.

Dissolution Studies

The dissolution of poorly soluble drugs requires dissolution media that are different from those normally used for water-soluble drugs. One of the techniques that has been found to be useful in dissolution of insoluble drugs is the incorporation of a small amount of surfactant in the dissolution medium (Serajuddin et al., 1990). The use of surfactants in the dissolution systems may be physiologically more meaningful, due to the presence of natural surfactants like bile salts in the gastrointestinal tract. The ability of surfactants to accelerate the in vitro dissolution of poorly water-soluble drugs has been attributed to wetting, micellar solubilization, and/or deflocculation. It is easy to understand that a bio-relevant medium will need similar surface activity as bio-fluids. Studies on SLS solutions indicate that surface tension of sodium lauryl sulfate (SLS) solutions decreased dramatically above the critical micelle concentration (0.023%), and it reached a minimum surface tension at 0.2% with no significant change at higher concentrations (Barzegar-Jalali et al., 2002; Tang et al., 2001). This suggested that a bio-comparable surface activity can be achieved at low surfactant concentrations (0.2%) (Barzegar-Jalali et al., 2002; Tang et al., 2001). Preliminary experiments confirmed that SLS exhibited higher solubilization power for valdecoxib than other surfactants. Therefore, it was chosen as a suitable surfactant in the present dissolution studies. Based on these facts, dissolution of pure valdecoxib and all other prepared systems (SDs and physical mixture) was carried out in aqueous SLS solution (0.25% w/v). When the valdecoxib was immersed on the surface of the aqueous surfactant solution, wetting of the valdecoxib could be observed clearly since it rapidly left the surface and was dispersed in the bulk of the solution, unlike pure water. Since the principal aim of this work was to improve the dissolution rate of valdecoxib, dissolution studies were performed for initially 1 h.

$Q_{10\ min}$, $Q_{20\ min}$, and $Q_{30\ min}$ values (percent drug dissolved within 30 minutes) are reported in Table 2. From Table 2 it is evident that onset of dissolution of pure valdecoxib is very low (37.15% within 30 min). Solid dispersions of valdecoxib with PEG 4000

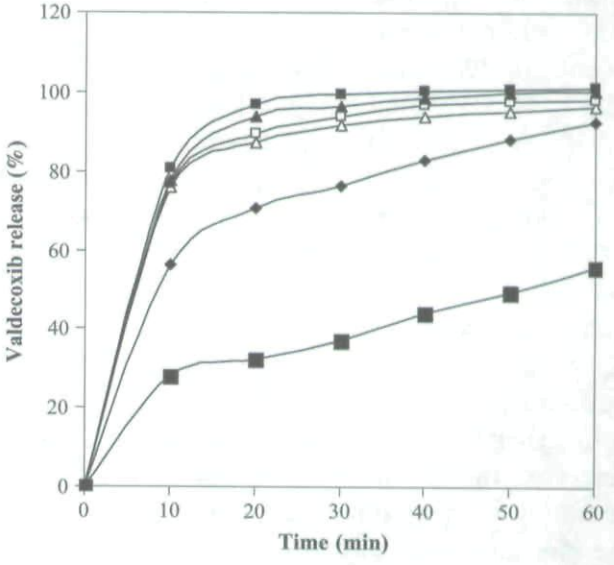

FIGURE 3 In Vitro Dissolution of Pure Valdecoxib (■), Valdecoxib-PEG 4000 SDs at 1:1 (△), 1:2 (□), 1:5 (▲) and 1:10 (●) Ratio Along with Physical Mixture at 1:10 Ratio (◆) (Dissolution Apparatus., USP; rpm 100; Dissolution Medium., 0.25% w/v SLS; Temperature., 37°).

TABLE 3 Mean Dissolution Time (MDT) Values for Pure Valdecoxib, SDs, and Physical Mixture

Valdecoxib:PEG 4000 ratio	MDT (min)[a]
Pure valdecoxib	20.95
1:1	9.04
1:2	8.72
1:5	8.47
1:10	7.66
Physical mixture 1:10 ratio	14.53

[a]Data are obtained by taking mean of cumulative drug release.

considerably enhanced dissolution rates within 30 min compared to the pure valdecoxib and physical mixture. The graphical presentation of the dissolution profile of pure valdecoxib, SDs, and physical mixture samples over a period of 1 hour is shown in Fig. 3 (SD values were less than 3.02%, therefore, SD values are removed from release plot for visual clarity). It is evident that the dissolution rate of pure valdecoxib is very low, about 56% of the drug being dissolved within 1 h. Dispersion of valdecoxib in the PEG 4000 matrix by preparing the SDs enhanced its dissolution rate significantly (96–100%) within 1 h. Possible mechanism of increased dissolution rates of SDs have been proposed by Ford (1986) and include: reduction of crystallite size, a solubilization effect of the carrier, absence of aggregation of drug crystallities, improved wettability, dispersibility of a drug from the dispersion, dissolution of the drug in the hydrophilic carrier, conversion of drug to amorphous state, and finally, the combination of the above-mentioned methods.

The dissolution rate of valdecoxib from valdecoxib-PEG 4000 (1:10 ratio) physical mixture was higher (92.54%) than that of pure valdecoxib (56%) within 1 h (see Fig. 3). Physical mixing of valdecoxib with PEG 4000 brings the drug in close contact with PEG 4000. The increased dissolution rate observed in this case (physical mixture) can be attributed to several factors such as a solubilization effect of PEG 4000, improved wettability of the drug, and inhibition of particle aggregation.

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 O–H present in PEG 4000 and the amine group on the valdecoxib. The strength of bonds between water-PEG 4000 and water-drug molecules may be stronger than or comparable with that between the molecules of the solid dispersions. Upon contact, water molecules solvate the PEG 4000 and valdecoxib molecules and break the hydrogen bonds between the drug-carrier 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 Eq. 2:

$$\frac{dm}{dt} = \frac{DA(C_s - C)}{h} \tag{2}$$

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 (C_s), and concentration of solute in the bulk solution and at time t (C). From the Stokes-Einstein equation Eq. 3:

$$D = \frac{kT}{6r\pi\eta} \tag{3}$$

the diffusion coefficient is inversely proportional to viscosity (η) where T=absolute temperature, k=Boltz-Mann constant, r=radius of the molecule, and $\pi = 3.14$.

In order to understand the extent of valdecoxib dissolution rate enhancement from its SDs and physical mixture, the obtained dissolution data of pure valdecoxib, SDs, and physical mixture were fit into Eq. 4 (Barzegar-Jalali et al., 2002).

$$MDT_{\text{in vitro}} = \frac{\sum_{i=1}^{n} t_{mid}\Delta M}{\sum_{i=1}^{n} \Delta M} \tag{4}$$

Here, i is dissolution sample number, n is number of dissolution sample times, t_{mid} is time at the midpoint between times t_i and t_{i-1}, and ΔM is the amount of valdecoxib dissolved (μg) between times t_i and t_{i-1}. In order to calculate the mean dissolution time (MDT) of pure valdecoxib, SDs, and physical mixture, the mean (n=3) of cumulative drug release (μg) was used. The obtained values of MDT for pure valdecoxib, SDs, and physical mixture are presented in Table 3. The MDT of valdecoxib is 20.95 min, then it

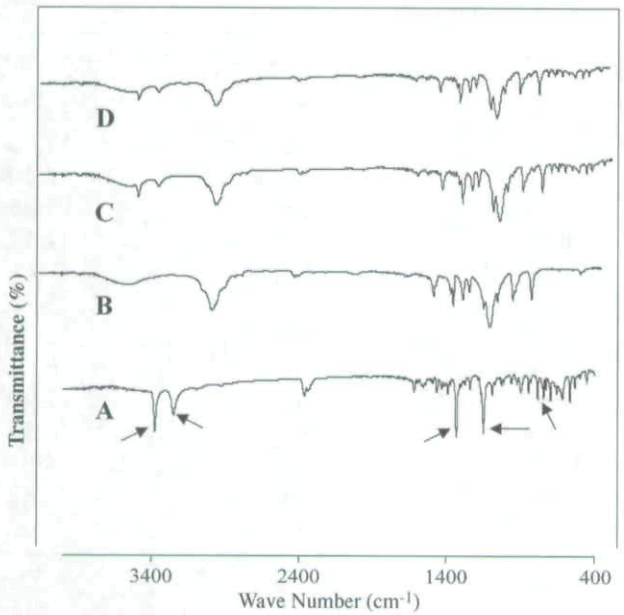

FIGURE 4 FTIR Spectrograms of Pure Valdecoxib (A), Pure PEG 4000 (B), Valdecoxib–PEG 4000 SDs at 1:10 Ratio (C) and Valdecoxib-PEG 4000 Physical Mixture at 1:10 Ratio (D).

decreased to a greater extent 7.66 min after preparing its SDs with PEG 4000 at 1:10 (valdecoxib:PEG 4000) ratio. The MDT of valdecoxib decreases with increasing concentration of PEG 4000 in its SDs.

Fourier-Transform Infrared Spectroscopy

The interaction between the drug and the carrier often leads to identifiable changes in the infrared (IR) profile of SDs (Damian et al., 2000). The IR spectra of SDs and physical mixture were compared with the standard spectrum for valdecoxib (Fig. 4). The presence and absence of characteristic peaks associated with specific structural characteristics of the drug molecule were noted. The spectrum of pure valdecoxib presented characteristic signals at 3376 and 3249 cm^{-1} (N–H stretching vibrations), 1620 cm^{-1} (C=N stretching vibrations), 1334, 1149, and 1093 cm^{-1} (S=O stretching vibrations), respectively. In this case any sign of interaction would be reflected by a change in N–H or C=N or S=O vibrations, depending on the extent of interaction. The spectra of SDs and physical mixture were equivalent to the addition spectrum of PEG 4000 and valdecoxib. These results indicate absence of well-defined interaction between valdecoxib and PEG 4000. Although it could be expected to have hydrogen bonding between the hydrogen atom of the NH_2 of the valdecoxib and one of the ion pairs of the oxygen atom in PEG 4000, this could not be demonstrated.

X-Ray Diffraction

Crystallinity in the sample is reflected by a characteristic fingerprint region in the diffraction pattern. Owing to the specificity of the fingerprint, crystallinity in the drug can be separately identified from crystallinity in the carrier. Therefore, it is possible with X-ray diffraction to differentiate between solid solutions, in which the drug is amorphous, and solid dispersions, in which it is at least partly present in the crystalline form, regardless of whether the carrier is amorphous or crystalline (Leuner & Dressman, 2000). The diffraction spectrum of pure valdecoxib showed that the drug was of crystalline nature as demonstrated by numerous, distinct peaks. Numerous diffraction peaks of valdecoxib were observed at 2θ of 12.08, 15.32, 15.68, 16.56, 16.94, 18.04, 19.26, 19.68, 20.44, 21.86, 22.84, 23.72, 24.4, 25.06, 28.44, and 29.0 (fingerprint region) etc., (see Fig. 5A) indicating the presence of crystalline valdecoxib. The characteristic peaks for valdecoxib and their intensities are presented in Table 4. Pure PEG 4000 showed two peaks with highest intensity at 2θ of 19.3 and 23.36 (Fig. 5B). The SD (1:1, 1:2, 1:5, and 1:10 ratio) samples exhibited the absence of characteristic peaks of valdecoxib, suggesting that valdecoxib is completely soluble in the liquid

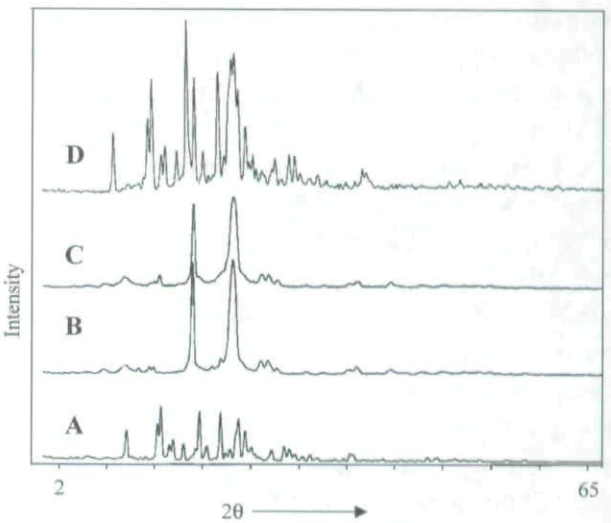

FIGURE 5 X-Ray Diffractograms of Pure Valdecoxib (A), Pure PEG 4000 (B), Valdecoxib-PEG 4000 SDs at 1:10 Ratio (C) and Valdecoxib-PEG 4000 Physical Mixture at 1:10 ratio (D).

TABLE 4 Intensities at Characteristic Diffraction Angles 2θ (°) and *d*-Values (Å) for Valdecoxib

2θ	*d*-value	Intensity	2θ	*d*-value	Intensity
12.08	7.32	23.42	24.40	3.64	22.83
15.32	5.77	27.46	25.06	3.55	11.80
15.68	5.64	39.45	25.42	3.50	7.10
16.56	5.34	13.14	27.16	3.28	9.86
16.94	5.22	16.78	28.46	3.13	12.17
18.02	4.91	13.79	29.00	3.07	10.56
19.26	4.60	10.58	29.54	3.02	6.97
19.68	4.50	36.15	30.60	2.94	5.30
20.44	4.34	12.44	31.14	2.86	6.63
21.86	4.06	35.43	35.36	2.53	7.16
22.40	3.96	7.52	35.68	2.51	6.56
22.84	3.89	10.22	43.44	2.08	4.63
23.46	3.78	20.74	44.40	2.03	4.63
23.72	3.74	31.08			

phase with varying composition of PEG 4000 up to a concentration of 10% w/w. However, only peaks corresponding to pure PEG 4000 (2θ of 19.3 and 23.36) were recorded. The typical X-ray diffractogram of the valdecoxib: PEG 4000 SDs is shown in Fig. 5C. The spectrum of SDs prepared with PEG 4000 was characterized by the complete absence of any diffraction peaks, suggesting that valdecoxib is present in amorphous form. Moreover, no other peaks than those that could be assigned to the pure PEG 4000 were detected in the SDs, indicating absence of chemical interaction in the solid state between the two entities. The positions of PEG 4000 patterns in the SDs were the same and superimposable, which again ruled out the possibility of chemical interaction and compound formation between valdecoxib and PEG 4000. Results of this study imply that valdecoxib is present in an amorphous form in the SDs. Other NSAIDs drugs formulated with PEG 4000 and 6000 have been found to form amorphous systems. For example, solid-state solutions of piroxicam-PEG 4000 and ketoprofen-PEG 6000 were obtained (Fernandez et al., 1992; Margarit et al., 1994). Najib and Suleiman characterized diflunisal-PEG 4000 solid dispersions prepared by melting method and concluded that drug was in amorphous form, and no chemical interaction took place between diflunisal and PEG neither in solution nor in the solid state (Najib & Suleiman, 1989). The present finding i.e., the presence of amorphous valdecoxib in SDs, is in agreement with the reports of several research groups studied for other drugs (Okonogi et al., 1997a, 1997b; Shin & Kim, 2003; Shin et al., 1987). In the case of physical mixture of valdecoxib and PEG 4000, the XRD pattern showed the peaks of both the valdecoxib and PEG 4000 (see Fig. 5D). It was confirmed that the crystallinity of the valdecoxib does not change in the physical mixture with PEG 4000.

Differential Scanning Calorimetry

Differential scanning calorimetry enables the quantitative detection of all processes in which energy is required or produced (i.e., endothermic and exothermic phase transformations). The thermograms for pure valdecoxib, PEG 4000, and SDs at 1:10 (valdecoxib:PEG 4000) ratio and physical mixture at 1:10 (valdecoxib:PEG 4000) ratios are presented in

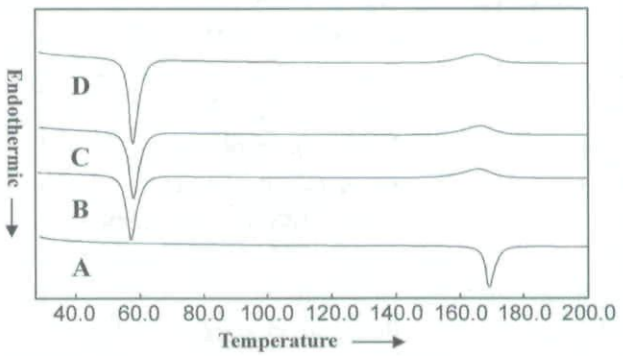

FIGURE 6 DSC Thermograms of Pure Valdecoxib (A), Pure PEG 4000 (B), Valdecoxib-PEG 4000 SDs at 1:10 Ratio (C) and Valdecoxib-PEG 4000 Physical Mixture at 1:10 Ratio (D).

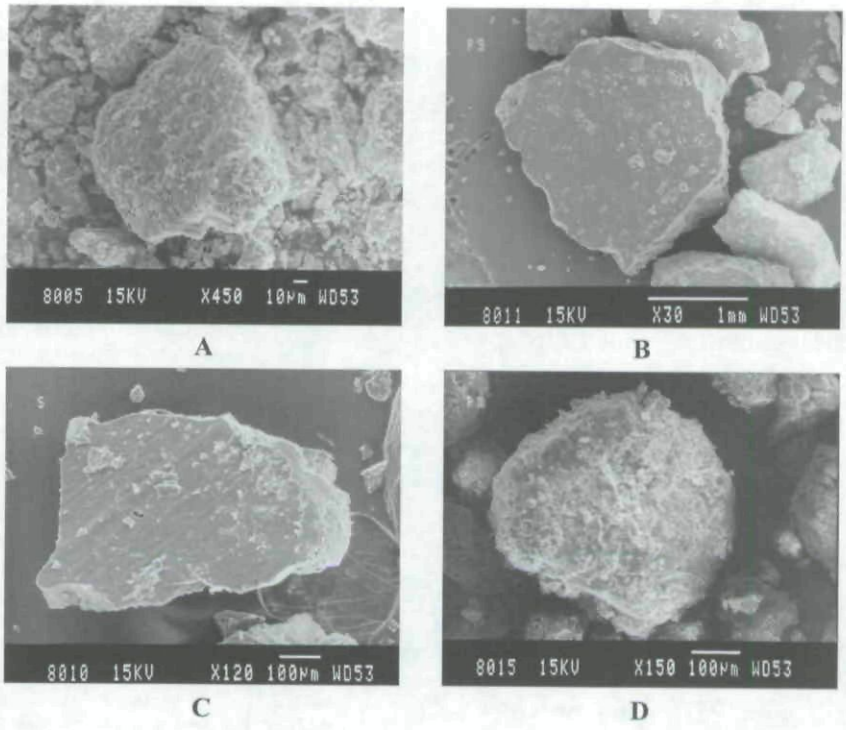

FIGURE 7 **SEM Pictures of Pure Valdecoxib (A), Pure PEG 4000 (B), Valdecoxib-PEG 4000 SDs at 1:10 Ratio (C) and Valdecoxib-PEG 4000 Physical Mixture at 1:10 Ratio (D).**

Fig. 6. The valdecoxib showed a melting endotherm at 169.1°C with enthalpy of fusion (ΔH) 107.16 J/g, whereas pure PEG 4000 showed a melting endotherm at 57.7°C. Thermograms of SDs showed the absence of a valdecoxib peak, suggesting that valdecoxib is completely soluble in the liquid phase with varying amounts of PEG 4000 up to 10% w/w. The typical thermogram of SDs is shown in Fig. 6C. However, the melting peak of PEG 4000 in SDs was observed at slightly lower temperatures (between 56.3–57.0°C) than that of pure PEG 4000 (57.7°C), indicating the miscibility of the drug in PEG 4000. Absence of an endothermic peak of drug in SDs has also been reported by other research groups (Damian et al., 2000; Okonogi et al., 1997a, 1997b; Shin & Kim, 2003; Shin et al., 1987). The physical mixture formulation of valdecoxib and PEG 4000 (1:10 ratio) also showed no endothermic peak of valdecoxib (Fig. 6D), even though the peaks derived from valdecoxib were observed in XRD (Fig. 5D). It is speculated that valdecoxib is dissolved in melted PEG 4000 during the DSC measurement, and only one endothermic peak at around 57°C, which corresponds to the melting of PEG 4000, is observed. This finding is in agreement with the report of Yamashita et al. (2003). In their DSC study, absence of the endothermic peak of tacrolimus in the physical mixture formulation of tacrolimus and PEG 6000 has been reported.

Scanning Electron Microscopy

The scanning electron micrographs of pure valdecoxib, pure PEG 4000, valdecoxib-PEG 4000 SDs at 1:10 ratio and valdecoxib-PEG 4000 physical mixture at 1:10 ratio are shown in Fig. 7. Valdecoxib has appeared as irregular-shaped crystals with rough surface (A) and PEG 4000 has presented as smooth-surfaced particles (B). The solid dispersions of valdecoxib with PEG 4000 appeared as a smooth, uniform, and homogeneously mixed mass (C). Thin-layered wrinkles on the smooth surface of SDs are one of the surface characteristics that would form during the resolidification of melted mass of drug-PEG 4000 mixture. The surface morphology of SDs almost resembled that of pure PEG 4000, indicating that valdecoxib adsorbed into the PEG 4000 and homogeneously dispersed into the PEG 4000 at the molecular level. On the other hand, in the case of physical mixture (D), one can see clearly the adherence of valdecoxib particles on the surface of PEG 4000 due to physical mixing.

CONCLUSION

The solubility and dissolution rate of valdecoxib can be enhanced by the use of SDs of valdecoxib with PEG 4000. The solubilization effect of PEG 4000, reduction of particle aggregation of the drug, absence of crystallinity, and alteration of the surface properties of the drug particles might be responsible for the enhanced solubility and dissolution rate of valdecoxib from its SD and physical mixture. From FTIR spectroscopy, it was concluded that there was no well-defined interaction between valdecoxib and PEG 4000, since no new peaks or shift of peaks could be observed. The absence of an endothermic peak of valdecoxib in the DSC thermograms of SDs with PEG 4000 showed the conversion of valdecoxib from crystalline to amorphous state. In addition, XRD and SEM studies supported the conclusion drawn from the DSC study. It can be concluded that the preparation SDs of valdecoxib with PEG 4000 provides a promising way to enhance its solubility and dissolution rate.

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