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RESEARCH ARTICLE

The use of spray-drying to enhance celecoxib solubility

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Abstract

The present research investigates the enhancement of the dissolution rate of celecoxib by using spray-drying to prepare a solid dispersion with various polymers, namely Kollicoat IR® (Kollicoat), polyvinyl alcohol (PVA) 22000, or polyethylene glycol 6000 (PEG). The investigated drug-to-polymer mass ratios were 1:1, 1:2, and 1:4 by weight. Hydroalcoholic or methylene chloride solvent systems were used. The obtained yields ranged from 65% to 78%, whereas the entrapment efficiencies were between 68% and 82%. The results revealed an increase in the dissolution rate of the prepared particles up to 200% within 20 min. The prepared particles were investigated using differential scanning calorimetry, scanning electron microscopy, X-ray diffraction, and Fourier transform infrared spectroscopy. The increased dissolution rate was attributed to hydrogen bond formation between celecoxib and each polymer together with the reduced size of the formed particles offering a greater overall surface area. It was concluded that spray-drying may be considered a successful one-step technique to improve the dissolution rate of celecoxib when using Kollicoat, PVA, or PEG as the carrier polymer.

Keywords: Spray-drying, celecoxib, Kollicoat IR®, polyvinyl alcohol, polyethylene glycol, dissolution rate

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Introduction

Oral drug administration is perhaps the most appealing route for drug delivery[1]. The poor solubility of drugs is a common concern since, to achieve good oral bioavailability, drugs must first dissolve to allow their absorption. Celecoxib, 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide, is a selective cyclooxygenase (COX-2) inhibitor that is widely prescribed for pain and inflammation[2]. It inhibits the conversion of arachidonic acid to the prostaglandins that mediate pain and inflammation while having no effect on the formation of the prostaglandins that mediate normal homeostasis in the gastrointestinal (GI) tract[3]. It is also used in the treatment of arthropathies and adenomatous polyps[4] and in dentistry[5]. It has a comparable efficacy and superior gastric tolerability[6] and is safer when compared with conventional nonsteroidal anti-inflammatory drugs[7]. Celecoxib has a pK_a of 11.1[8], with a low aqueous solubility of 3–7 μg/mL[9]. With a pK_a of 11.1, celecoxib is unionized at physiological pH. It is not surprising that celecoxib is well-absorbed from the GI tract considering its log*P* of 2.82 between buffer and octanol at pH 7.4 and room temperature[8,10].

After oral solution dosing in dogs, celecoxib was rapidly absorbed and reached maximum concentrations by 1 h; absorption was delayed 1 to 2 h when administered as a solid. The absolute bioavailability of celecoxib was higher when given as a solution (64–88%) compared with a capsule dosage form (22–40%)[9]. According to the biopharmaceutical classification system, celecoxib can be categorized as class II that includes poorly water-soluble drugs with high GI permeability[11].

In addition, celecoxib has handling problems due to its needle-shaped crystals[12] that have high surface

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energy. Modification of the crystal habit or solid structure of celecoxib would be advantageous. Celecoxib can form a metastable polymorph, but the difference in melting point from that of the stable polymorph is negligible and it is capable of reverting to the stable form[12].

Several formulation approaches have been attempted to improve the dissolution properties of celecoxib for faster onset of action and improved bioavailability. Examples include formulation of self-microemulsifying drug delivery systems (SMEDDS)[13], solid dispersions (SD)[14], complexation with β-cyclodextrins[15], and manipulation of the solid state of the drug[16,17]. However, some of these formulations employ or contain a high concentration of surfactants (20–60%), which may eventually compromise their uses in chronic treatment[18].

Kollicoat IR®, a polyvinyl alcohol (PVA)–polyethylene glycol (PEG) graft copolymer, is a pharmaceutical excipient that was developed as a coating polymer for immediate release tablets[19]. PVA has good film-forming properties and the PEG portion acts as an internal plasticizer. The molecule is hydrophilic and readily soluble in water. As its structure is non-ionic, its solubility does not change when pH is altered along the GI tract.

The major drawback of celecoxib is its poor aqueous solubility and consequently its slow dissolution in gastric fluid. Hence, we sought to enhance these properties by using spray-drying to prepare binary mixtures with Kollicoat IR® (Kollicoat), PVA 22000, and PEG 6000.

Materials and methods

Materials

Celecoxib was kindly donated by Searle (Augusta, GA). Kollicoat IR® (Molecular weight = 45,000 Da) was obtained from BASF (Ludwigshafen, Germany). PVA with a molecular weight of 22,000 and PEG 6000 were purchased from BDH Chemicals Ltd. (Poole, England). Silicon dioxide was obtained from Serva Fine Biochemical GmbH Co. (Heidelberg, Germany). Sodium lauryl sulfate was obtained from E-Merck (Darmstadt, Germany). All other chemicals were of reagent grade.

Preparation of binary mixtures

Physical mixtures (PMs) were prepared by mixing celecoxib and each of the carriers in a mortar. The ratio of celecoxib to the carrier used was 1:1 or 1:4 by weight.

Spray-dried binary systems using Kollicoat IR® or PVA

Appropriate mass ratios (1:1, 1:2, and 1:4) of celecoxib and either Kollicoat IR® or PVA were prepared in a 2:1 v/v hydroalcoholic solution where celecoxib was completely dissolved in ethanol and Kollicoat or PVA was dissolved in distilled water. The aqueous solution was added gradually to the ethanolic drug solution with subsequent vigorous stirring for 1 h to assure equilibrium. The resultant suspension was spray-dried in a Mini Spray-Dryer B-290 (Büchi Labortechnik AG, Flawil, Switzerland) with the following conditions: inlet temperature 130°C, outlet temperature 60–65°C, suspension flow rate 5 mL/min, air flow rate 40–50 m^3/h, and atomizing air pressure 1.0–1.1 bar. The batch size of the prepared ratios was 10 g each.

Spray-dried binary systems using PEG

Celecoxib in combination with PEG 6000 in different mass ratios (1:1, 1:2, and 1:4) was dissolved in 100 mL of dichloromethane. To these clear solutions, silicon dioxide (2% w/v) was slowly added to obtain uniform suspensions. The suspension was spray-dried in the Büchi mini spray-dryer with the following conditions: inlet temperature 50°C, outlet temperature 30°C, solution flow rate 5 mL/min, air flow rate 40–50 m^3/h, and atomizing air pressure 1.0–1.1 bar. The batch size was again 10 g.

Microparticle characterization

Drug loading

The efficiency with which celecoxib was entrapped in the particle powder after spray-drying was determined as the mass ratio of the entrapped drug to the theoretical amount of celecoxib used in the preparation. Spray-dried particles equivalent to 5 mg of drug were accurately weighed and dissolved in a suitable quantity of ethanol. The drug content was determined spectrophotometrically at 252 nm[18].

Morphological analysis

The morphological characteristics of spray-dried particles were observed by scanning electron microscopy. The samples were sputter-coated with a thin gold palladium layer under an argon atmosphere using a sputter module in a high-vacuum evaporator. The coated samples were then scanned and photomicrographs were taken with a JSM-1600 scanning electron microscope (Jeol, Tokyo, Japan).

Differential scanning calorimetry

Calorimetric studies of the drug and the prepared microparticles were performed using a DSC-60 (Shimadzu, Kyoto, Japan). The 3–5 mg samples were placed in hermetically sealed aluminum pans. A 10°C/min scanning rate was used over the 25–200°C temperature range. Indium was used as the temperature and enthalpy standard.

Powder X-ray diffractometry

Powder X-ray diffraction patterns of the drug, polymers, and the prepared spray-dried microparticles were generated using a wide-angle Rigaku Ultima IV X-ray diffractometer (Rigaku Corporation, Tokyo, Japan). The instrument was operated on the 2θ scale. The angular range was 10° to 50° (2θ) and counts were accumulated for 1 sec at each step.

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Fourier transform infrared spectroscopy

Infrared spectra were recorded on a PerkinElmer spectrum BX FTIR (PerkinElmer, Waltham, MA). Samples were prepared as KBr pellets and scanned against a blank KBr pellet at wave numbers ranging from 4000 to 650 cm^{-1} with resolution of 1.0 cm^{-1}.

Dissolution study for microparticles

The drug dissolution studies were performed using a Caleva Model 85T (Philips, Maidstone, UK) USP dissolution apparatus II at 50 rpm. A continuous automated monitoring system, consisting of an IBM PK 8620 computer and PU 8605/60 dissolution test software, was used with a Philips Model PU 8620 Vis/UV/NIR single beam eight cell spectrophotometer and a Watson-Marlow peristaltic pump. Each vessel, containing 900 mL of 1.0% sodium lauryl sulfate[20] in demineralized water, was maintained at 37.0 ± 0.5°C. Microparticles containing 100 mg of drug were sieved through a 200-μm sieve and then dispersed in the dissolution medium. Dissolved drug was determined spectrophotometrically at 252 nm. The dissolution experiments were conducted in triplicate and the means of the percent of drug dissolved were calculated.

Results and discussion

Carriers for the production of SDs via spray-drying should be chemically and physically stable with a low melting point and solubility in the solvent systems whether aqueous or nonaqueous. Further requisites are chemical compatibility with the drug, miscibility with the drug in the liquid state, and the ability to increase the solubility of the drug in an aqueous medium. These properties can be achieved with water-soluble excipients that exhibit rapid dissolution themselves. Excipients with a high number of functional groups are typically able to engage in intermolecular hydrogen bonds, van der Waals forces, and ionic interactions.

Differential scanning calorimetry

Differential scanning calorimetry (DSC) thermograms for crystalline celecoxib, the 1:4 PM, and SD at mass ratios of 1:1, 1:2, and 1:4 celecoxib:polymer are shown in Figures 1–3. A loss of drug crystallinity increases its dissolution rate. The pure drug melted at 159.49°C (Figure 1), which agrees well with the literature value of 160.8°C[21] and the PM with PVA had essentially the same onset temperature. The endothermic peak for spray-dried particles shifted to 157.8°C, 157.8°C, and 155.3°C for the mass ratios 1:1, 1:2, and 1:4, respectively, indicating drug–polymer interactions. The enthalpy likewise decreased compared with that of pure celecoxib, yielding 6.77, 7.64, 4.95, and 3.4 J/g for the PM and spray-dried particles at mass ratios of 1:1, 1:2, and 1:4, respectively. These are dramatic reductions in comparison with the 82.8 J/g enthalpy of fusion of celecoxib[18,21,22]. With PEG 6000, the endothermic peak for celecoxib disappeared in the thermogram for each combination, whether the drug was in a PM or spray-dried particles (Figure 2). The specific PEG endothermic peak decreased in intensity with the spray-dried particles. The thermograms for celecoxib and Kollicoat mixtures showed celecoxib endothermic peaks at

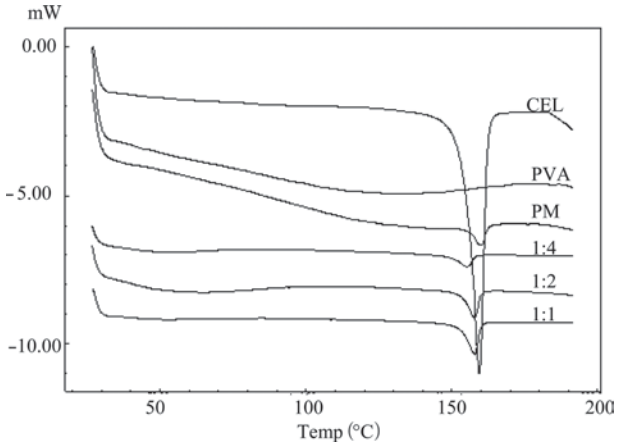

Figure 1. Differential scanning calorimetric (DSC) thermograms of celecoxib, polyvinyl alcohol (PVA) 22000, their physical mixture, and various spray-dried particles.

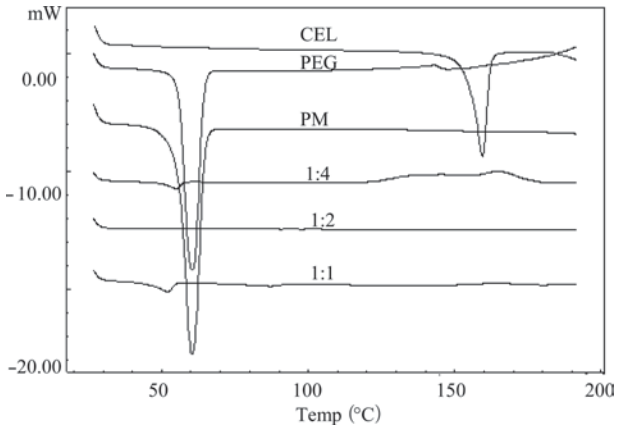

Figure 2. Differential scanning calorimetric (DSC) thermograms of celecoxib, polyethylene glycol (PEG) 6000, their physical mixture, and various spray-dried particles.

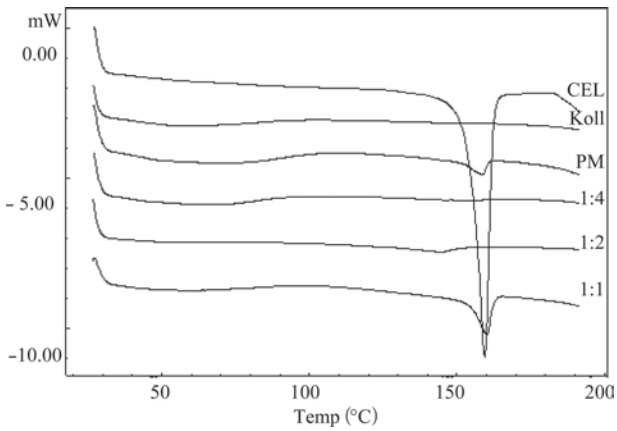

Figure 3. Differential scanning calorimetric (DSC) thermograms of celecoxib, Kollicoat, their physical mixture, and various spray-dried particles.

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158.6°C, 160.1°C, 144.6°C, and 156.1°C for the PM, and spray-dried particles at mass ratios of 1:1, 1:2, and 1:4, respectively (Figure 3). The peaks showed decreasing enthalpy of 17.11, 12.5, 8.62, and 0.23 J/g for the PM, and spray-dried particles at mass ratios of 1:1, 1:2, and 1:4, respectively.

Each of the polymers either softens when heated above its glass transition temperature or melts at a temperature below that of celecoxib and this may lead to dissolution of the drug in the polymer. Accordingly, this will lead to disappearance of the drug melting endotherm in the DSC thermogram of the PM.

Using calorimetric data, the solubility factor for celecoxib in the different polymers was calculated (Table 1) by dividing the enthalpy obtained from the endothermic peak for celecoxib in prepared particles by that for pure celecoxib. As the solubility factor decreases, the solubility of celecoxib in the polymer increases. If it reaches one, celecoxib did not dissolve in the polymer. The data show that the drug is soluble in PEG at each of the tested mass ratios. Particles containing PVA and Kollicoat showed increases in drug solubility as the polymer level

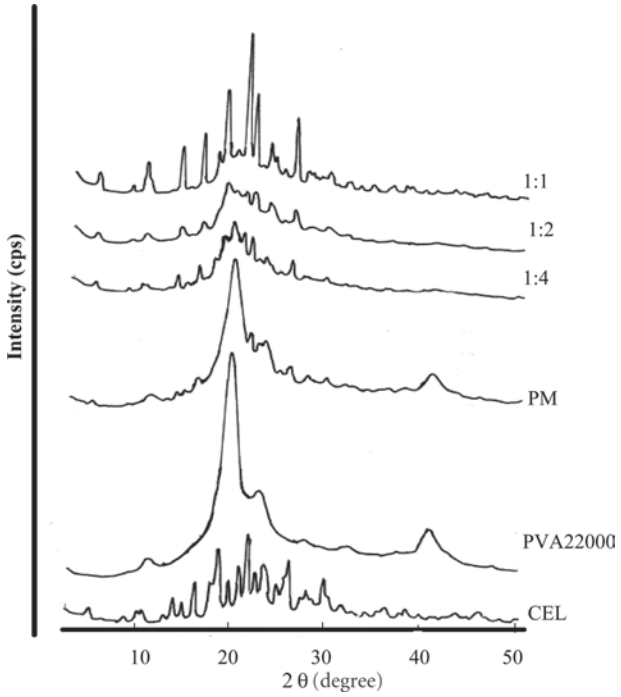

Figure 4. X-ray diffractograms of the spray-dried dispersions of 1:1, 1:2, and 1:4 mass ratios with polyvinyl alcohol (PVA), their physical mixture, PVA 22000 alone, and celecoxib alone.

Table 1. Solubility factor of celecoxib in different polymers.

	Polymers		
Combination	Polyvinyl alcohol (PVA) 22000	Polyethylene glycol (PEG) 6000	Kollicoat IR®
Physical mixture	0.29	0	1.00
SD 1:1	0.39	0	0.42
SD 1:2	0.18	0	0.20
SD 1:4	0.12	0	0.01

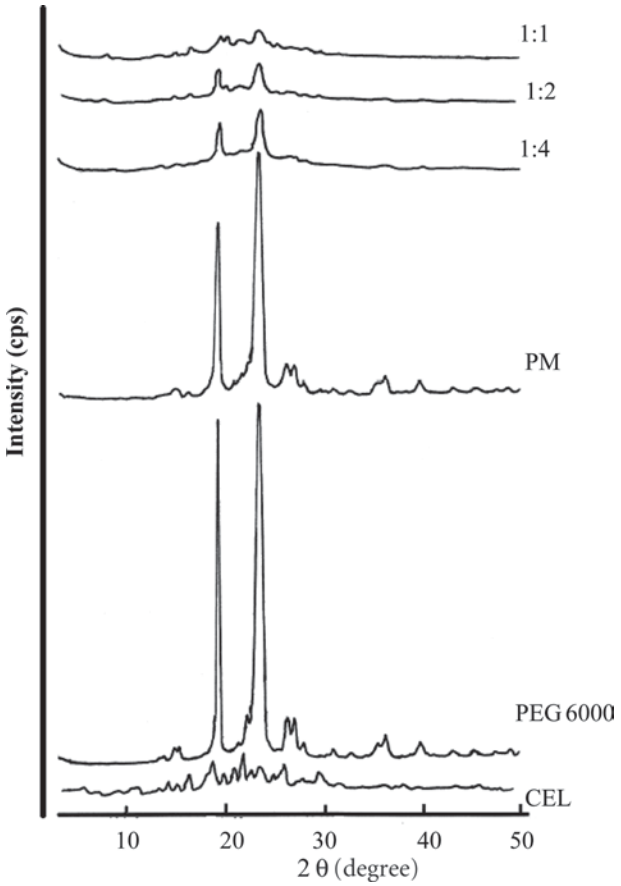

Figure 5. X-ray diffractograms of the spray-dried dispersions of 1:1, 1:2, and 1:4 mass ratios with polyethylene glycol (PEG), their physical mixture, PEG 6000 alone, and celecoxib alone.

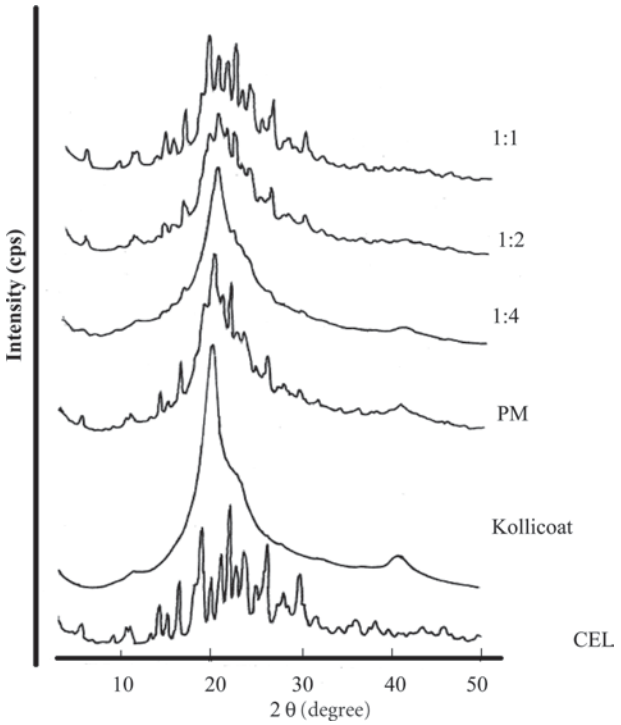

Figure 6. X-ray diffractograms of the spray-dried dispersions of 1:1, 1:2, and 1:4 mass ratios with Kollicoat, their physical mixture, Kollicoat alone, and celecoxib alone.

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in the particle increased. Celecoxib dissolved to a limited extent in the PM with PVA, dissolved completely with PEG, and proved to be insoluble with Kollicoat in the PM. The spray-drying process resulted in an increase in the solubility factor in going from the PM to the SD of celecoxib with PVA or Kollicoat. This may be attributed to a polymer effect on the celecoxib crystal form or an interaction of the drug with the polymer. As the drug level increases in the mass ratio, the solubility factor decreases because surplus crystalline drug is present.

Powder X-ray diffraction

Powder X-ray diffractograms of crystalline celecoxib, the 1:4 PM, and the SD at 1:1, 1:2, 1:4 mass ratios are presented in Figures 4–6. Characteristic peaks of celecoxib appear at 5.6°, 10.6°, and 16.4° 2θ corresponding to reported crystal lattice parameters for celecoxib at 5.0°, 10.1°, and 16.8° 2θ[23]. For PVA, diffraction peaks appear at 19.7° and 40.7° 2θ (Figure 4) corresponding to reported peaks at 19.4° and 40.4° 2θ[24]. The diffraction pattern for PEG exhibited the two strong characteristic peaks at 19.3° and 23.5° 2θ (Figure 5) that have been reported[25]. For Kollicoat, the diffraction pattern showed a strong broad peak at 19.6 with a shoulder at 23.5° 2θ representing the overlapping peaks for PVA and PEG chains present in Kollicoat, and a small one at 40.7° 2θ corresponding to the peak for the PVA portion (Figure 6).

With the exception of PEG, the PM diffraction patterns still reveal peaks characteristic of crystalline celecoxib,

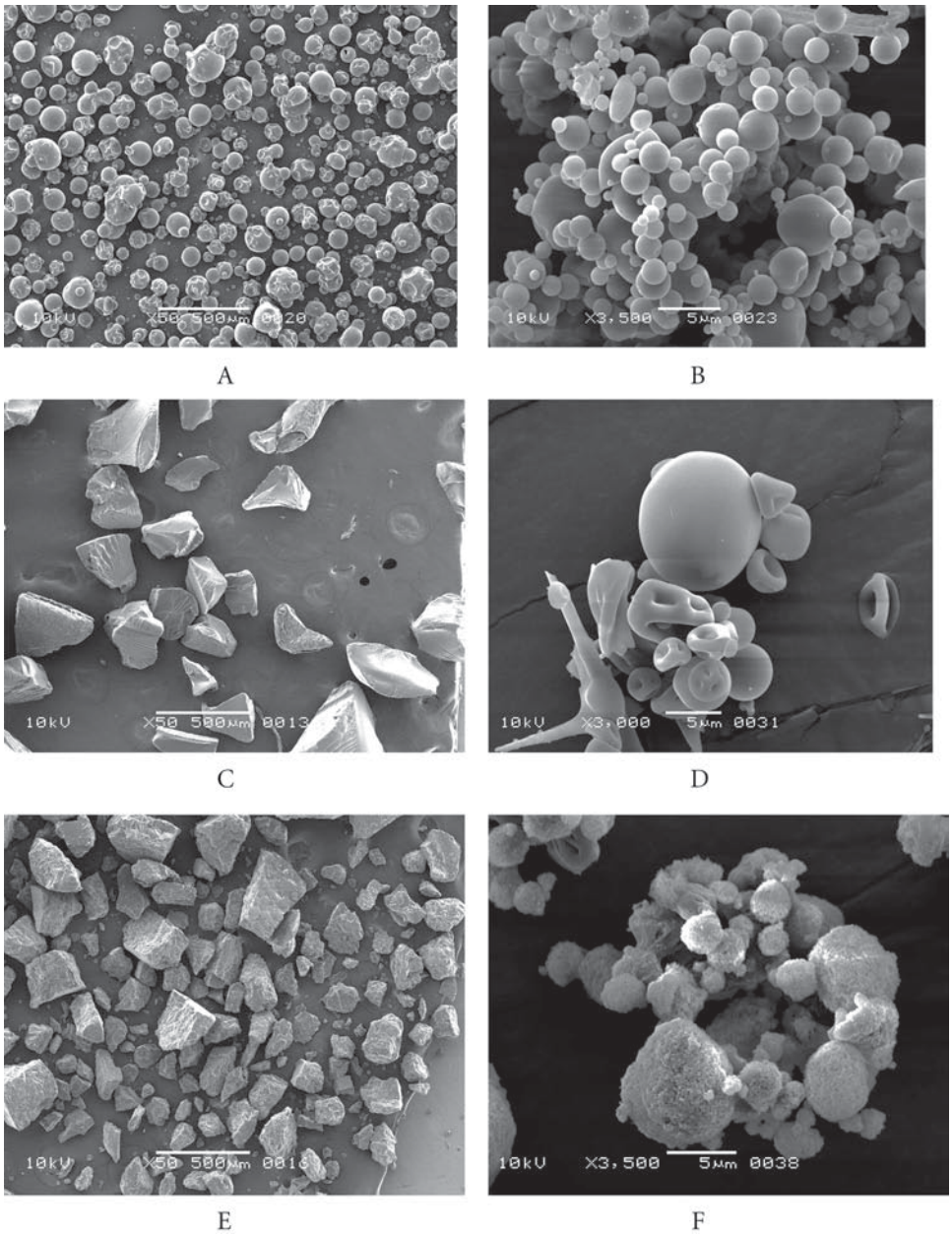

Figure 7. SEM photomicrographs of Kollicoat IR (A), polyvinyl alcohol (PVA) 22000 (C), polyethylene glycol (PEG) 6000 (E), and spray-dried particles in 1:4 ratio (B, D, F), respectively.

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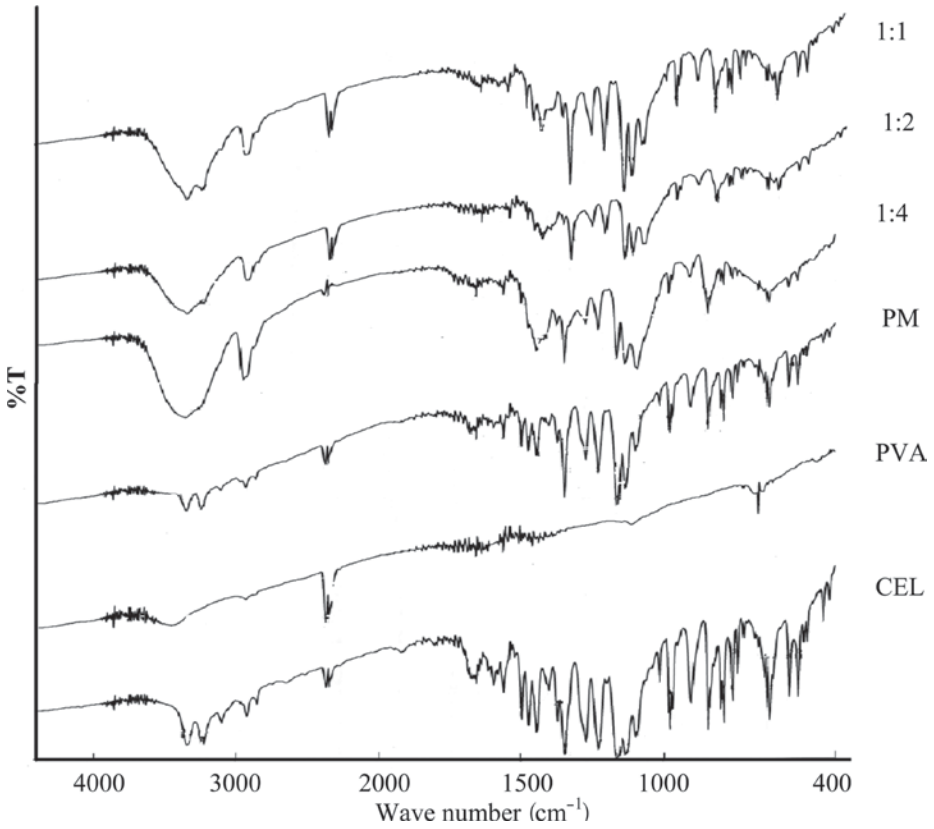

Figure 8. FTIR spectra of the various spray-dried dispersions with mass ratios of 1:1, 1:2, and 1:4 with polyvinyl alcohol (PVA), the physical mixture, PVA 22000 alone, and celecoxib alone.

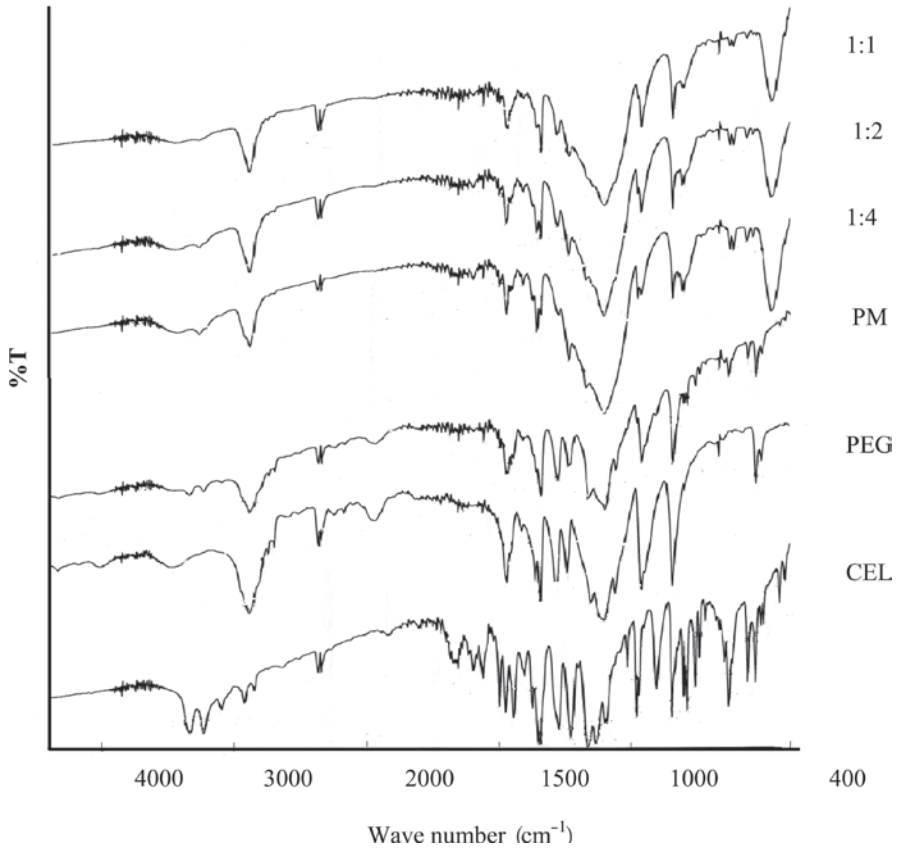

Figure 9. FTIR spectra of the various spray-dried dispersions with mass ratios of 1:1, 1:2, and 1:4 with polyethylene glycol (PEG), the physical mixture, PEG 6000 alone, and celecoxib alone.

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although the intensity of the peaks is reduced. The PEG peaks in the 1:4 mass ratio PM or the 1:4 mass ratio SD are intense and the drug peaks are likely of negligible intensity in comparison with those of PEG or are undetectable, respectively (Figure 5). For each SD with a 1:1 mass ratio, the polymer and celecoxib peaks both exist and diminish in intensity, revealing that at least part of the celecoxib present is crystalline in the SD at this mass ratio. Drug peaks in the diffractograms continue to diminish as the polymer level in the mass ratio is increased.

Scanning electron microscopy

The scanning electron micrographs for PM and SD particles with PVA, PEG, and Kollicoat are presented in Figure 7. Spray-drying solutions of celecoxib with PVA formed rings and spherical particles both with a smooth surface (Figure 7d), whereas with Kollicoat smaller spherical particles with a smooth surface were produced (Figure 7b). For SDs with PEG, the particles appear larger with a nearly spherical shape and a rough surface likely due to the presence of silicon dioxide (Figure 7f).

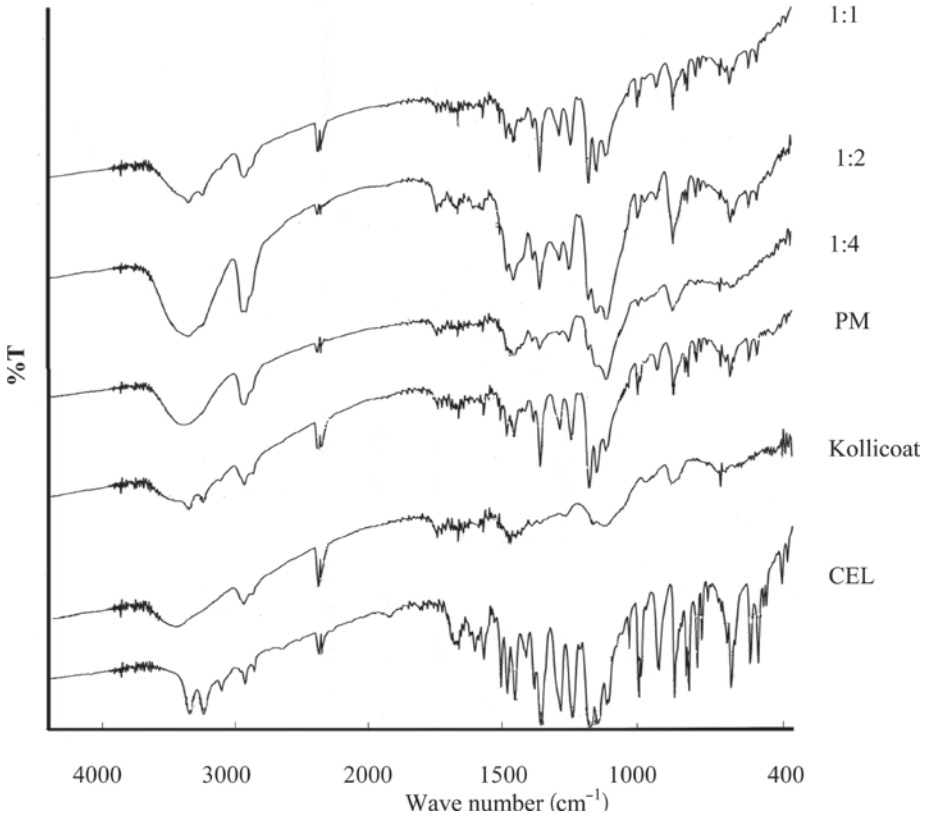

Figure 10. FTIR spectra of the various spray-dried dispersions with mass ratios of 1:1, 1:2, and 1:4 with Kollicoat, the physical mixture, Kollicoat alone, and celecoxib alone.

Table 2. Major infrared peaks (cm^{-1}) of pure celecoxib, physical mixture, and different spray-dried ratios.

Group	Celecoxib	Physical mixture	SD 1:1	SD 1:2	SD 1:4
Polyvinyl alcohol (PVA) 22000					
NH_2 str	3340.5	3340.7	3342	3346	3345.9
NH_2 str	3234.5	3234.1	—	—	—
S=O sym str	1348.7	1348.3	1348.2	1348.9	1348.2
S=O asym str	1165.5	1165.2	1164.9	1165.7	1165.4
Polyethylene glycol (PEG) 6000					
NH_2 str	3340.5	3341.5		—	—
NH_2 str	3234.5	—	3266.1	—	—
S=O sym str	1348.7	1348.3	1343.2	1343.3	1343.2
S=O asym str	1165.5	1165.5	—	—	—
Kollicoat IR®					
NH_2 str	3340.5	3342.0	3342.7	3341.6	3379.8
NH_2 str	3234.5	—	—	—	—
S=O sym str	1348.7	1343.3	1348.1	1348.1	1348.3
S=O asym str	1165.5	1164.9	1165.6	1165.4	1165.2

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FTIR spectroscopy

Celecoxib has certain characteristic peaks that are evident in Figures 8–10. These include bands at 3340.5 and 3234.5 cm^{-1} that correspond to N–H stretching in the SO_2NH_2 group, and 1348.7 and 1165.5 cm^{-1} for the S=O asymmetric and symmetric stretching[21]. The manner in which these bands change when drug is physically mixed with the polymers or existing in the different solid dispersions with the polymers is presented in Table 2. The PEG bands corresponding to the CH_2 was at 1370 cm^{-1} and the C–O–C asymmetric stretching at about 1100 cm^{-1} overshadow or obscure the 1348.7 and 1165.5 cm^{-1} band for celecoxib and make interpretation difficult. However, in the 1:1 mass ratio SD where the influence of drug on PEG can be greatest, it is apparent that the PEG O–H stretching vibration at about 3400 cm^{-1} diminishes in intensity and the two celecoxib bands at 3340.5 and 3234.5 also diminish and broaden, suggesting that N–H from the drug engages in an interaction with the O–H of PEG, likely by hydrogen bonding with the acidic hydrogen of the N–H as the hydrogen donor. The spatial arrangement of molecules in the crystalline drug do not allow hydrogen bonding between the N–H and S=O to take place and thus the N–H bands are sharper and of higher intensity[21].

Dissolution studies

A high amount of hydrophilic polymer may increase the availability of moisture, which may aid in devitrification[26,27]. The low-melting-point excipients such as PEGs and polyglycolized glycerides have been used widely as excipients in SD[28,29]. These excipients have increased drug dissolution rates by improving the wettability of the drug particles, by significant reducing the drug particle size during the formation of the SD, or by the inherently higher dissolution rate of the soluble component of the SD introducing the less-soluble component as finely divided particles into the dissolution medium[30–32].

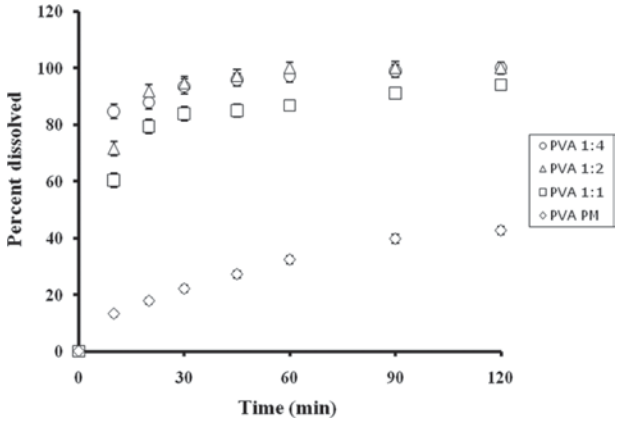

Figure 11. Dissolution profiles of the spray-dried particles of celecoxib with polyvinyl alcohol (PVA) 22000 and the physical mixture.

The dissolution profiles of the spray-dried particles and the PMs are presented in Figures 11–13. For SD containing PEG, complete dissolution in 900 mL occurred within 10 min for the 1:4 ratio and within 20 min for the 1:2 ratio (Figure 12). However, the SD with the 1:1 mass ratio required 45 min for complete dissolution. Only 59.94% of the celecoxib present in the PM was dissolved in 30 min. Table 3 presents the relative dissolution rate (RDR) of the different particles to that of pure celecoxib.

Since sufficient medium was present to allow sink conditions, dissolved drug did not reach saturation. The maximum amount of drug attained in the dissolution medium was 15.3 mg by the end of 2 h. Complete dissolution of the celecoxib in the different PMs was never achieved in the dissolution study time. The lowest dissolution rate for celecoxib from a PM was observed in the case of PVA (Figure 11). Comparing this result with the dissolution rates of the spray-dried particles with 1:2 and 1:4 mass ratios with PVA, one can see the outstanding improvement in the dissolution rate of celecoxib following spray-drying.

Table 4 presents the efficiency with which the spray-drying process entraps celecoxib in the particles as well

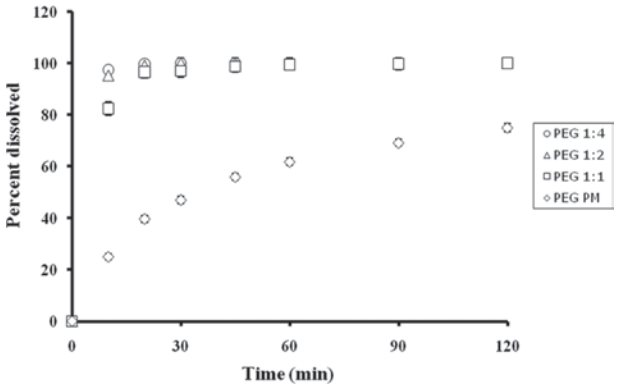

Figure 12. Dissolution profiles of the spray-dried particles of celecoxib with polyethylene glycol (PEG) 6000 and the physical mixture.

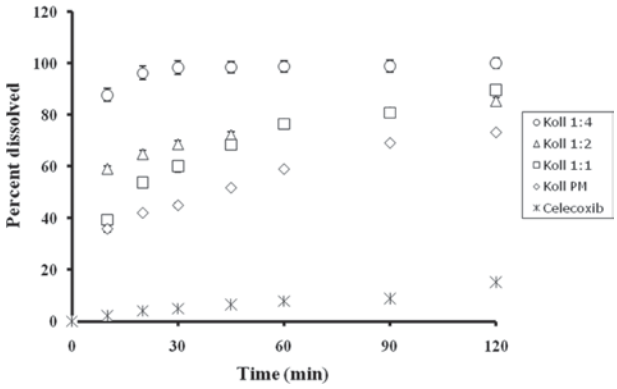

Figure 13. Dissolution profiles of the spray-dried particles of celecoxib with Kollicoat IR®, the physical mixture, and pure celecoxib.

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Table 3. Relative dissolution rate (RDR) of celecoxib–polymer particles to that of pure celecoxib.

Polyvinyl alcohol (PVA) 22000				
Time (min)	SD 1:1	SD 1:2	SD 1:4	Physical mixture
10	27.3	40.7	34.0	6.0
20	19.6	23.0	23.8	4.4
30	17.0	20.1	20.1	4.5
Polyethylene glycol (PEG) 6000				
10	37.7	44.4	45.4	11.3
20	24.1	25.2	—	9.8
30	19.9	—	—	9.5
Kollicoat IR®				
10	17.9	26.8	42.9	15.9
20	13.3	16.0	25.7	10.4
30	12.2	13.9	—	9.0

All particles were passed through 200 μm sieve before dissolution.

Table 4. Spray-dried particulate properties.

Spray-dried particles	Production yield (%)	The actual drug load (%)
Polyvinyl alcohol (PVA) 22000		
SD 1:1	75.0	77.0
SD 1:2	75.0	71.6
SD 1:4	70.0	81.9
Polyethylene glycol (PEG) 6000		
SD 1:1	66.5	68.7
SD 1:2	75.0	79.3
SD 1:4	75.0	68.6
Kollicoat IR®		
SD 1:1	65.0	75.0
SD 1:2	78.0	76.0
SD 1:4	70.0	81.0

as the yield of the process. On the average, a 73% yield with an average of 76% entrapped drug can be noted. The lost amounts are attributed to the polymer allowing adherence to the wall of the spray-dryer and to the formation of very small particles that escaped with nitrogen gas and were lost to the filter. The 70% yield with 81% entrapment for celecoxib in a 1:4 mass ratio with either PVA or Kollicoat is a promising result.

An increased dissolution rate for celecoxib and a change from its crystalline form to the amorphous form can result from interactions with these polymers[33,34]. The spray-dried particles showed a spherical shape with both Kollicoat and PVA and a nearly spherical shape with a porous, spongy surface in the case of PEG, likely due to the presence of silicon dioxide. The small particle size provides a much greater overall surface area for dissolution and the highly hydrophilic polymers provide ready dissolution of the excipient[35].

Conclusion

Spray-drying is a good technique to utilize a hydrophilic polymer as a carrier in the formation of a SD. The promising results recommend the improvement of the dissolution rate of poorly water-soluble drugs using Kollicoat IR® or its constituents PVA or PEG. With the enhanced dissolution rate of celecoxib, categorized as class II in the Biopharmaceutical Classification System, its oral bioavailability is expected to increase. The potential for spray-dried particles with a spherical shape as well as the presence of an interaction between celecoxib and the polymer involved are important factors in the improvement of celecoxib dissolution rate.

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Declaration of interest

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