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ORIGINAL PAPER

Piroxicam/β-cyclodextrin complex included in cellulose derivatives-based matrix microspheres as new solid dispersion-controlled release formulations

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New formulations capable to enhance piroxicam (PRX) water solubility and at the same time to control and adjust its release have been developed. For this purpose, two methods have been used and combined to achieve this goal, namely complexation and microencapsulation by O/W emulsion solvent evaporation. In order to modify the drug release, first, microparticles composed of pure PRX and ethylcellulose (EC) or mixtures of EC and hydroxypropylmethylcellulose (HPMC) were prepared, and then, other micropaticles containing the β-cyclodextrin/piroxicam (β-CD/PRX) complex obtained by the solvent evaporation technique and EC or a mixture of EC and HPMC were produced and tested. These formulations were characterized by FT-IR, XRD, optical microscopy, and SEM methods. Drug dissolution tests were carried out in acidic media at pH = 1.2 and 37 °C. Depending on the microparticles composition, their size (d_{10}) ranged between 49 μm and 121 μm and PRX_{loaded} varied from 10.8 % to 27.7 %. The effect of complexation and HPMC polymer on the drug release was investigated; the results demonstrated that the Higuchi's release constant significantly increased when using the EC/HPMC mixture as a matrix with pure PRX or only EC as a matrix with the β-CD/PRX complex. The results are remarkably promising since the combination of these processes provided new SD-CR formulations of piroxicam which enabled simultaneous enhancement and control of its release from the carriers.

Keywords: piroxicam, complex inclusion, microencapsulation, ethylcellulose, β-cyclodextrin, SD-CR formulation

Introduction

Microencapsulation becomes the most method of producing controlled release (CR) formulations of pharmaceutical drugs with valuable properties (Jyothi et al., 2010); but, the oral route of drug administration requires a drug soluble in the gastrointestinal fluid which is then transferred to the bloodstream (Wen & Park, 2010). Subsequently, the drug solubility in aqueous media is the most important factor affecting the dissolution and oral drug absorption. Thus, for poorly water-soluble drugs, the development of controlled-release drug delivery systems is of special interest. Several methods have been developed in order to modify the drug solubility such as the chemical modification or crystalline forms modification of drugs, the use of buffers or co-solvents, addition of surfactants, or complexation methods. These are the most common pharmaceutical techniques used to enhance drug solubility (Loh et al., 2015; Chaudhary et al., 2012; Savjani et al., 2012).

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Concerning piroxicam (PRX), which is a non-steroidal anti-inflammatory drug with analgesia activity (Brunton et al., 2011; Moffat et al., 2004) and is widely used in the treatment of rheumatic diseases, it is a poorly water-soluble polymorphic drug and several formulations have been developed to enhance its solubility (Lai et al., 2011; Dukić-Ott et al., 2007; Paaver et al., 2012).

Among these methods, the inclusion complexes of piroxicam with cyclodextrins are well known and largely studied and discussed, and their efficiency has also been proved (Canto et al., 1999; Lee & Balfour, 1994); the complexation occurs via several routes such as dissolution-solvent evaporation, co-precipitation, kneeding method, and others (Patil et al., 2010).

Besides the simple techniques of microencapsulation which are used to modify and/or increase the drug release, like solvent evaporation (Joseph et al., 2002; Diaf et al., 2012), spray-drying method (Wagenaar & Müller, 1994; Cilurzo et al., 2005; Piao et al., 2008), acoustically modified spraying methods (Berkland et al., 2003), encapsulation of the drug in liposomes (Canto et al., 1999), and other microencapsulation techniques (Xua et al., 2013; Aquino et al., 2012), novel dissolution-modifying approaches and strategies have been developed for poorly water soluble drugs in general and especially for piroxicam.

In fact, Tran et al. (2011) reported the efficiency of solid dispersion (SD) combined with CR formulations, which provide both functions of SD and CR for poorly water-soluble drugs. Also, Bouchal et al. (2015) prepared binary and ternary solid dispersions of drug/PEG or drug/cyclodextrin/PEG by evaporation and melting methods. In other studies, electrospinning has been proved to be an effective and continuous method for the production of polymeric nanofibers (Agarwal et al., 2008; Lu et al., 2009; Paaver et al., 2014; Pelipenko et al., 2013; Taepaiboon et al., 2006); recently, supersaturating CR-SD nanofibers of PRX and HPMC have been produced and used to stabilize the amorphous state of PRX by Paaver et al. (2015).

The use of complex β-CD/PRX in controlled release dosage form concerned only tablets (Jug & Bećirević-Laćan, 2004; Nagabhushanam, 2010) and solid dispersions obtained by freeze-drying or spray-drying (Bouchal et al., 2015). Thus, in our research, complexation and microencapsulation by solvent evaporation methods were combined to produce microparticles as new PRX-SD-CR formulations; the strategy simultaneously exploits the complexation technique to enhance the PRX solubility and microencapsulation in hydrophobic matrix (EC) for the drug release adjustment at a predetermined time.

In the first stage, piroxicam/β-cyclodextrin complex inclusion (β-CD/PRX) was prepared using the classical method of solution/solvent evaporation and in the second stage, microspheres loaded with the obtained complex (β-CD/PRX) were prepared using ethylcellulose (EC) and ethylcellulose–hydroxypropylmethylcellulose (EC-HPMC) mixtures as matrices. For their non-toxic and non-irritant properties, EC and HPMC were selected as drug carriers in these oral pharmaceutical formulations (Wade & Weller, 1994; Kibbe, 2000; Ghosal et al., 2011).

The emulsion-solvent evaporation technique, a simple technique of microencapsulation, was used to prepare these formulations and other microspheres for drug dissolution comparison. Based on oil-in-water (O/W) emulsion, followed by solvent evaporation, monolithic systems known as microspheres (Freiberg & Zhu, 2004) were prepared. EC was used as the basic matrix in this process because it is water permeable but not water soluble (Moldenhauer & Nairn, 1990) and thus it is a suitable polymer material forthis microencapsulation process (Phutane et al., 2010; Mostafa Kamal et al., 2008). Also, EC has been largely used and tested for controlled release formulations and especially for floating microspheres preparation for various drugs such as ranitine hydrochloride (Saravanan & Anupama, 2011), clarithromycin (Aejaz & Sadath, 2013), metoprolol succinate (Raut et al., 2013), and cimetidine (Srivastava et al., 2005).

Experimental

Piroxicam (PRX) or feldene was purchased from Sigma–Aldrich (Germany), ethylcellulose (EC) (10 mPa s) and hydroxypropylmethylcellulose (HPMC) were purchased from Fluka analytical (USA) and Sigma–Aldrich (USA), respectively. Hydrolyzed polyvinylalcohol (PVA) 87–89 % (M_W = 13000–23000) was purchased from Aldrich Fine Chemicals (USA) and β-cyclodextrin (β-CD) from Sigma–Aldrich (USA). Dichloromethane (DCM) ($\geq$ 99 of purity) and absolute ethanol (99 % of purity) were purchased from Riedel–de Haën (USA).

Solid inclusion complex of piroxicam and β-CD was prepared in the 1 : 1 molar ratio by the solution/solvent evaporation method. In one hand, 1.7 g of β-CD was dissolved in 100 mL of distilled water at 25 ℃ under stirring (600 min^{-1}). In the other hand, 0.49 g of PRX was dissolved in 100 mL of absolute ethanol at (50 $\pm$ 2) ℃ under stirring (600 min^{-1}). The two solutions were then merged and stirred for 2 h at 50 ℃. Solvents were then evaporated under vacuum (5.6–5.1 kPa) using rotavapor AGCH-9230 Flawil type: 1000147175 (Buchi Labortechnik, Switzerland). The obtained β-CD/PRX complex was dried at 40 ℃.

The drug content in the complex was determined by extraction; a sample of the complex was dissolved in an excess volume of ethanol under stirring for 4 h in a sealed bottle. PRX concentration was determined by the UV-VIS analysis. Extractions were carried out in triplicate and the drug content in the complex was

calculated from the following equation:

$$\mathrm{PRX}_{\text{content in complex}}/\% = \\ = \frac{\text{mass of PRX extracted}}{\text{mass of complex}} 100 \quad (1)$$

A cylindrical glass reactor (volume of 600 mL, external diameter = 80 mm) equipped with a six-bladed turbine impeller (blade length = 50 mm, blade width = 10 mm, type VELP stirrer DLS, 0–2000 min^{-1}) was used to prepare microparticles. Microspheres were obtained by the emulsion solvent diffusion method at room temperature. The external phase was composed from 250 mL of a 0.74 mass % PVA aqueous solution. In the organic phase, matrix (EC or mixture of EC/HPMC with the mass ratio of 80/20 or 50/50) was dissolved in 32 g of dichloromethane (DCM) (%Pol./solvent = 5 mass %) and drug (pure PRX or β-CD/PRX complex, or β-CD–PRX physical mixture with the molar ratio of 1 : 1) was added to the organic solvent by heating under reflux (30–35 ℃) and stirred to allow homogenization; in all experiments, the percentage of pure PRX against matrix was 30 % (%PRX/Pol. = 30 mass %). After cooling to laboratory temperature, the organic phase was emulsified with the continuous phase under mechanical stirring (600 min^{-1} or 1000 min^{-1}) for 6 h to complete solvent evaporation. Then, microspheres were filtered, washed twice with distilled water, and vacuum-dried in a desiccator in the presence of $\mathrm{CaCl_2}$.

The β-CD/PRX complex was characterized by FT-IR spectroscopy (ATR ALPHA FT-IR spectrometer) (Bruker, Germany), the sample in its powder form was scanned for absorbance in the 4000–375 cm^{-1} region. The X-ray powder diffraction patterns were collected at room temperature (25 ℃) using copper radiation on a Bruker D8 DISCOVER diffractometer (Germany) in the range of 1° to 40° at the scanning rate of 0.020° min^{-1} of 2θ. The infrared spectra and X-ray diffractograms of pure PRX and β-CD were compared to those of the β-CD/PRX complex.

The mean diameters (d_{10}, d_{32}, d_{43}) and size distribution (δ) of microparticles were calculated from the results of optical microscopy (Optikam B1, Optika, Italy) by applying the following equations and using the Excel worksheet. More than 500 microspheres were placed on a glass slide and the particle size was measured using appropriate lenses:

$$d_{10} = \sum_i n_i d_i \Big/ \sum_i n_i \quad (2)$$

$$d_{32} = \sum_i n_i d_i^3 \Big/ \sum_i n_i d_i^2 \quad (3)$$

$$d_{43} = \sum_i n_i d_i^4 \Big/ \sum_i n_i d_i^3 \quad (4)$$

$$\delta = d_{43}/d_{10} \quad (5)$$

where d_{10}, d_{32}, and d_{43} are the number, surface (or Sauter), and volume mean diameters, respectively.

The shape and surface morphology of the microparticles were characterized by scanning electron microscopy using SEM – JSM 7100F (Jeol, Japan), microparticles were deposited on a carbon film and examined without metalizing at ×200 of magnitude under vacuum and at the acceleration tension of 10 kV.

The loading efficiency ($\mathrm{PRX_{loaded}}/\%$) and the encapsulation efficiency (Yield/%) were determined after the extraction in an appropriate solvent according to the following equations:

$$\mathrm{PRX_{loaded}}/\% = \frac{\text{mass of PRX extracted}}{\text{mass of microparticles}} 100 \quad (6)$$

$$\text{Yield}/\% = \frac{\text{mass of PRX extracted}}{\text{initial mass of PRX}} 100 \quad (7)$$

Extraction of the drug from microparticles was performed in triplicate; 50 mg of dried microparticles were soaked in 50 mL of absolute ethanol under stirring in a sealed bottle for 4 h. The resulting solution was analyzed by UV-VIS spectroscopy, (Shimadzu UV-2401 PC, Shimadzu, Japan) after its appropriate dilution with ethanol, at the wavelength ($\lambda_{\max}$) of 324 nm where the molar extinction coefficient (ε) was equal to 20240 L mol^{-1} cm^{-1}.

To confirm the effective PRX encapsulation, microspheres were characterized by infrared spectroscopy, and infrared spectra of pure piroxicam and the obtained formulations in powder form were compared. The FT-IR spectra were recorded from 400 cm^{-1} to 4000 cm^{-1} using a Bruker-ATR spectrometer.

The PRX release kinetics from the obtained formulations was followed in an appropriate dissolution reactor plunged in a bath regulated at (37 ± 1) ℃. The reactor (Erlenmeyer flask) was equipped with a filter tube to enable solution withdrawal without microparticles.

At the beginning, 100 mg of microparticles were soaked in the reactor containing 900 mL of buffered solution at pH = 1.2 ± 0.1 obtained by a classical preparation method (80 mL of 1 M HCl and 2 g of NaCl to 1000 mL of aqueous solution) at the stirring rate of 250 min^{-1}.

At the desired time, 3 mL of the solution were withdrawn, analyzed by UV spectroscopy (Shimadzu UV-2401 PC, Shimadzu, Japan) without dilution, and returned back to the Erlenmeyer flask.

The piroxicam released was analyzed in an acidic solution (pH = 1.2) at the wavelength ($\lambda_{\max}$) of 333 nm, where ε = 26500 L mol^{-1} cm^{-1}. The kinetic experiments were carried out in duplicate.

Results and discussion

Inclusion complex formation and characterization

The complexation yield which corresponds to the ratio between the experimental and theoretical complex mass was 91.8 % and the drug content in the complex was (15.54 ± 1.35) % (mean ± SD, $n = 3$). As it is known, cyclodextrins are chemically stable, water-soluble compounds that form complexes with water insoluble or lipophilic molecules increasing thus the aqueous solubility of poorly soluble drugs; therefore, they are recognized as an important group of pharmaceutical excipients enhancing drug dissolution and bioavailability of poorly soluble drugs (Del Valle, 2004). Several authors have described the inclusion complexes of β-CD with piroxicam and several stoichiometries (mole ratio) of guest : host such as 1 : 1, 1 : 2, and 1 : 2.5; complex forms have been suggested and proved by analytical techniques (Escandar, 1999; Kim et al., 1994; Bertoluzza et al., 1999; Rozou et al., 2004). As mentioned by Scarpignato (2013) and based on the chemical form of the inclusion complex of β-CD/PRX, it contains the equivalent of 20 mg of piroxicam in 191.2 mg of the complex molecule which corresponds to 10.46 % and the 1 : 2.5 guest : host molar ratio. However, our results show 15.5 % of PRX in the inclusion complex which corresponds to 31 mg of PRX in 200 mg of the complex and the 1 : 1.6 PRX : β-CD molar ratio.

Also, solubility of the obtained β-CD/PRX in water was 130 mg L^{-1}; however, Scarpignato (2013) determined the solubility of this complex to be 150 mg L^{-1}.

Possible complexation of β-CD with PRX was verified by FT-IR and XRD characterization methods and the infrared spectra and X-ray diffractograms of β-CD, PRX, and the obtained complex shown in Figs. 1 and 2, respectively, were compared.

Concerning pure crystalline form of piroxicam, the FT-IR spectrum (Fig. 1a) exhibited characteristic peaks for the N—H amide group at 3336 cm^{-1}, stretching of amide carbonyl (C═O) at 1627 cm^{-1} and stretching of the second amide band (C—N) at 1524 cm^{-1}. Other characteristic bands were attributed to the stretching of the asymmetric methyl group at 1433 cm^{-1}, stretching of the symmetric methyl group at 1348 cm^{-1}, stretching of the –SO_2—N– group at 1147 cm^{-1} and (C—H) stretching of *ortho*-disubstituted phenyl at 770 cm^{-1}. In the FT-IR spectrum of the obtained complex, PRX bands are almost completely obscured by very intense and broad β-CD bands and hardly influenced by complex formation. The stretching of the second amide band at 1524 cm^{-1} shifted to 1519 cm^{-1}, that of the symmetric methyl group appeared at 1346 cm^{-1} and that of the –SO_2—N– group shifted to 1151 cm^{-1}. Also, absorption bands of PRX at 1427 cm^{-1} in the complex spectrum showed a remarkable broadening. Moreover, typical bands of PRX at 1593 cm^{-1} and 3336 cm^{-1} were in the complex spectrum shifted and appeared at 1598 cm^{-1} and 3292 cm^{-1}, respectively. Moreover, the stretching of the *ortho*-disubstituted phenyl band at 770 cm^{-1} disappeared completely in the β-CD/PRX complex spectrum. All these changes are probably re-

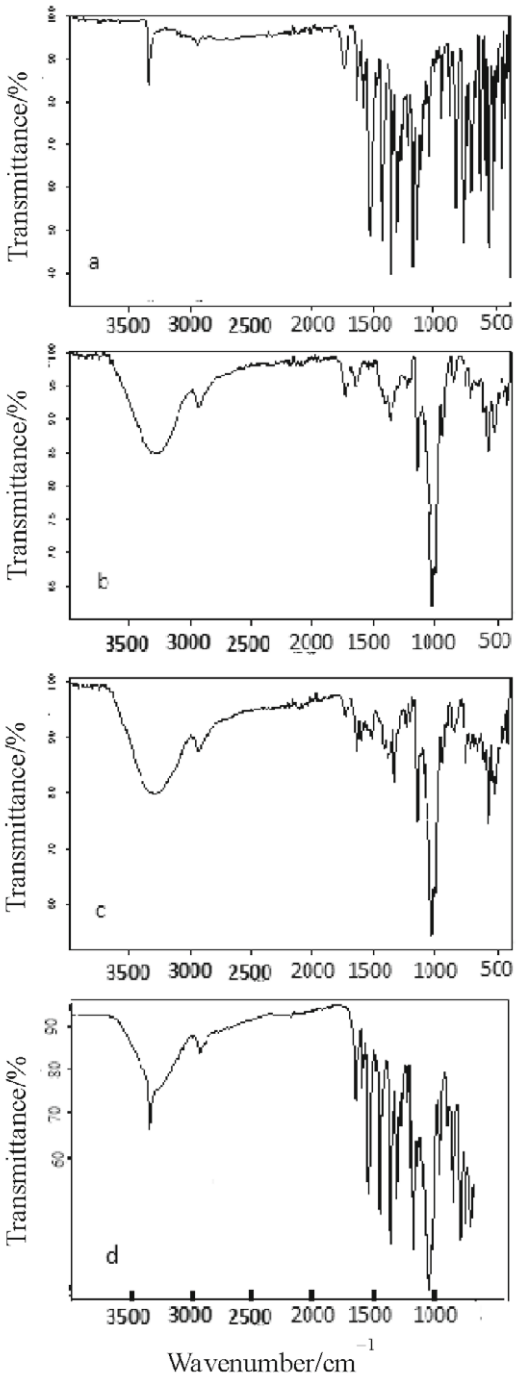

Fig. 1. FT-IR spectra of pure PRX (a), β-CD (b), β-CD/PRX inclusion complex (c), and β-CD–PRX physical mixture (d).

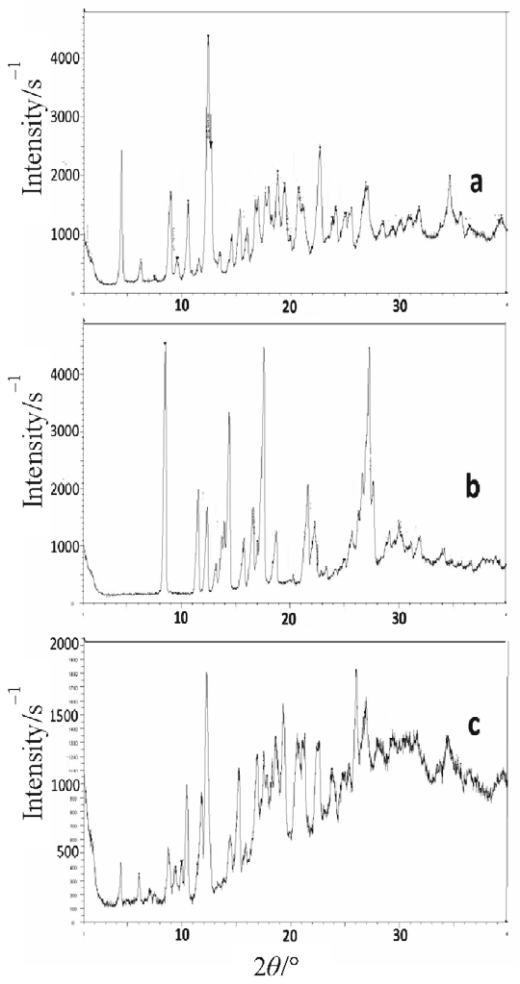

Fig. 2. X-Ray diffractograms of β-CD (a), PRX (b), and β-CD/PRX inclusion complex (c).

lated to the interaction between the guest and host molecules provided either by C—H· · ·O interactions between the aromatic ring of the benzo-thiazinone scaffold in the guest molecule and three glycosidic oxygen atoms at the inner surface of β-CD or by hydrogen bonds involving the hydrophilic moiety of the guest molecule as well as the primary and secondary ends of the adjacent β-CD molecules (Scarpignato, 2013; Redenti et al., 1996).

In addition, the pattern of the physical mixture of β-CD and PRX as shown in Fig. 1d is entirely different from that of the β-CD/PRX complex, showing approximate superposition of the patterns of cyclodextrin and the drug. For example, the vibration of the N—H amide group appeared clearly at the same wavenumber of 3336 cm^{-1}.

From the X-ray diffraction analysis (Fig. 2), the presence of many diffraction peaks in the PRX diffractogram indicates that the drug was in its crystalline form and the very intense peaks at 8.5°, 14.3°, 17.7°, and 27° have been selected as characteristic peaks for PRX. In the XRD pattern of the β-CD/PRX complex, some diffraction peaks disappeared and other appeared. In fact, the peaks at 8.5°, 11°, 14°, and 21.6° disappeared completely and a new peak at 26° appeared. Some interesting but very low intensity PRX peaks, i.e. at 2θ equal to 17.7° and 27°, appeared in the spectra. These changes are indicative of simultaneous interaction between PRX and β-CD in the inclusion complex and the diminution of its crystalline form and thus the formation of a new solid phase (Mura, 2015; Jug et al., 2005).

Microparticles characterization

Microparticles were characterized in terms of shape and surface morphology, drug entrapment and size (mean diameter). As reported in Table 1, ten batches of microparticles were prepared by emulsion-solvent evaporation at different experimental conditions. The results of drug loading (PRX_{loaded}/%) and encapsulation efficiency (Yield/%) are also provided in Table 1. As reported, the PRX_{loaded}/% varied from 10.8 % to 27.7 % and the yield varied from 27.2 % to 52.9 %.

Loading efficiency (PRX_{loaded}/%) was close to 30 % in some cases, however, the yield did not ex-

Table 1. Microencapsulation results; %PRX/Pol. = 30 mass %, %PVA/water = 0.5 mass %, %Pol./DCM = 5 mass %

Lot no.	Composition (matrix–drug[a])	Stirring speed/min^{-1}	PRX_{loaded}/%[b]	Yield/%[b]
1	EC–PRX	600	10.80 ± 1.23	27.22 ± 3.11
2	EC–PRX	1000	13.80 ± 2.74	33.64 ± 6.68
3	EC/HPMC(80/20)–PRX	600	27.56 ± 5.44	52.24 ± 10.31
4	EC/HPMC(80/20)–PRX	1000	26.59 ± 0.70	47.40 ± 1.26
5	EC/HPMC(50/50)–PRX	600	27.71 ± 3.46	46.76 ± 5.85
6	EC/HPMC(50/50)–PRX	1000	19.72 ± 0.52	37.79 ± 0.99
7	EC–(β-CD/PRX)	600	20.90 ± 0.81	48.78 ± 1.89
8	EC/HPMC(80/20)–(β-CD/PRX)	600	15.29 ± 0.91	35.69 ± 2.13
9	EC/HPMC(80/20)–(β-CD/PRX)–PRX	600	11.15 ± 0.23	20.68 ± 0.42
10	EC–(β-CD–PRX)	600	17.42 ± 1.35	54.58 ± 4.25

a) PRX for pure piroxicam, β-CD/PRX for complexed β-CD with PRX, and β-CD–PRX represents physical mixture of β-CD and PRX; *b*) $n = 3$, mean value ± SD.

ceed 55 %; it was not excellent because an oil-in-water (O/W) emulsion was used to prepare the microparticles and the low yield can be caused due to the water solubility of both HPMC and β-CD and their possible transfer to the external phase (water). However, this technique was applied to minimize the employment of organic and toxic solvents in the microparticles preparation.

The loading efficiency and yield were found to be dependent on the nature of the polymer used in the

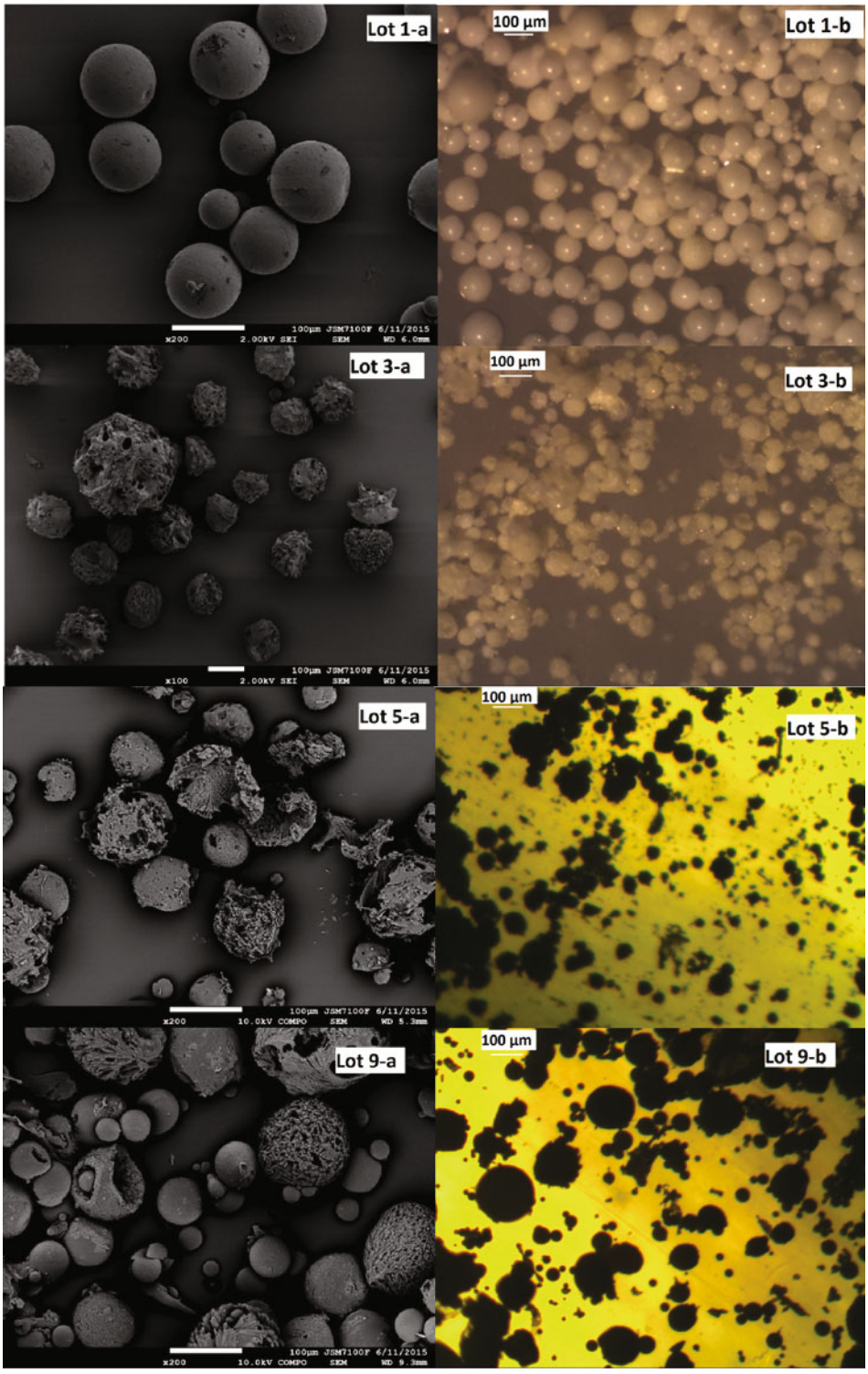

Fig. 3. Microparticles' shape and surface morphology characterization by scanning electron microscopy (a) and optical microscopy (b).

Table 2. Size and size distribution of microparticles

Lot no.	d_{10}/μm	d_{32}/μm	d_{43}/μm	Dispersion, δ
1	92.2	115.7	126.2	1.37
2	57.8	73.1	77.9	1.35
3	92.2	122.8	132.0	1.43
4	92.8	98.6	170.2	1.83
5	56.2	62.9	85.0	1.51
6	47.2	61.1	66.8	1.42
7	41.4	66.3	78.4	1.89
8	121.2	156.8	168.6	1.39
9	49.4	107.4	138.1	2.80
10	92.3	113.3	119.5	1.29

formulation. In general, for microparticles containing only pure drug, the PRX_{loaded} and Yield values increased whenthe two polymers EC/HPMC were combined;while the loading efficiency and yield decreased in the presence of HPMC for microparticles based on the β-CD/PRX complex. Also, for microspheres composed only of EC as the matrix, the use of the β-CD complex or its physical mixture (lot no. 7 and 10) improved the drug entrapment.

Table 2 resumes the size distribution and the mean diameters (d_{10}, d_{32}, and d_{43}) of microparticles calculated considering more than 500 microparticles. Depending on the microparticles composition, the number mean diameter (d_{10}) of microparticle batches ranged between 41 μm to 121 μm.

Results of the microparticle size showed that the mean diameter decreased when the impeller speed increased; the results are in agreement with the theory, except for the percentage of HPMC of 50 mass %, where, the effect of the stirring speed was not notable probably due to the high irregularity of the microparcticles shape.

The number mean diameter (d_{10}) of EC–(β-CD/PRX) microspheres (lot no. 7) was lower than that of simple EC-PRX microspheres (lot no. 1) which was in the same range of microspheres composed from a physical mixture of β-CD–PRX (lot no. 10). This result confirms that the β-CD/PRX complex form differs from that of the physical mixture decreasing the viscosity of the organic phase which leads to the formation of small microparticles.

Moreover, the combination of EC and HPMC increased the size of microparticles; the same result was reported by Raut et al. (2013) and Phalguna et al. (2010).

The results of both the optical and the scanning electron microscopy analyses identified the morphology and surface of microparticles (Fig. 3). In fact, the SEM and optical microscopy analysis provided photographs of microparticles composed only of ethylcellulose, which were spherical in shape with smooth surface and small pores (Fig. 3, lot no. 1a and 1b). In contrast, microparticles containing HPMC or composed of the β-CD/PRX complex were irregular in shape with rough and very porous surface, and large particle size as observed in Fig. 3 (lot no. 3, 5, and 9).

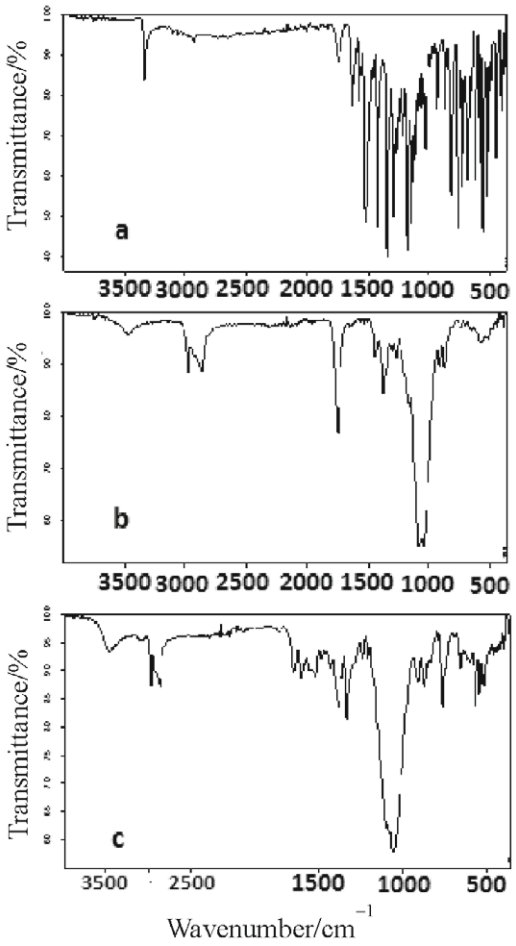

Fig. 4. FT-IR spectra of pure PRX (a), EC matrix (b), and EC–PRX microparticles (lot no. 2) (c).

Moreover, the FT-IR spectrophotometric analysis of pure drug, β-CD/PRX complex, polymers (EC and HPMC) and microparticles were recorded and depicted in Figs. 4 and 5 for comparison.

The bands at 3478 cm^{-1}, 2971 cm^{-1}, and 2869 cm^{-1} were attributed to the presence of the –OH and C—H stretch groups of pure ethyl cellulose (EC), respectively. Similar band peaks were observed in the HPMC spectrum (Fig. 5a) at 3446 cm^{-1} (–OH stretch) and 2902 cm^{-1} (C—H stretch).

FT-IR spectrum of microspheres (Fig. 4c) consisting of PRX and a polymer (EC) showed the characteristic peaks at 3448 cm^{-1}, 2973 cm^{-1}, and 2871 cm^{-1} corresponding to the –OH and C—H stretching vibrations, respectively. The major characteristic bands of PRX are overlapped by very broad polymer bands. Nevertheless, some characteristic bands of PRX such as the C—N stretching band at 1520 cm^{-1} and the stretching band of the SO_2—N group at 1149 cm^{-1} are shown clearly in microparticle spectrum (Fig. 4c).

In the FT-IR spectra of EC–(β-CD/PRX) mi-

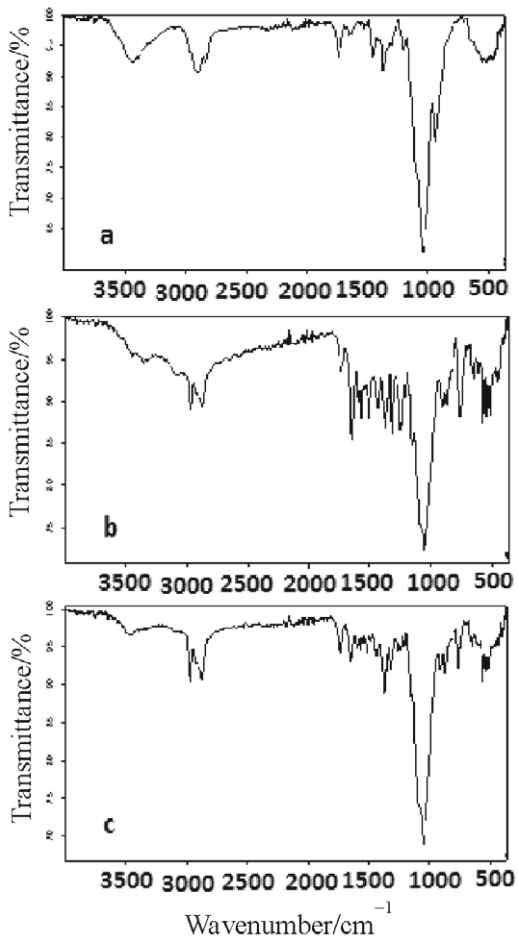

Fig. 5. FT-IR spectra of HPMC matrix (a), EC–(β-CD/PRX) microparticles (lot no. 7) (b), and EC/HPMC(80/20)–(β-CD/PRX) microparticles (lot no. 8) (c).

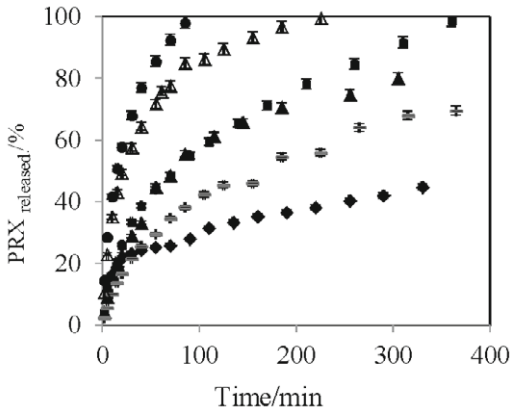

Fig. 6. PRX release profiles from microparticles batches lot no. 1 (◆), 2 (■), 3 (▲), 4 (—), 5 (△), 6 (●) based on pure PRX.

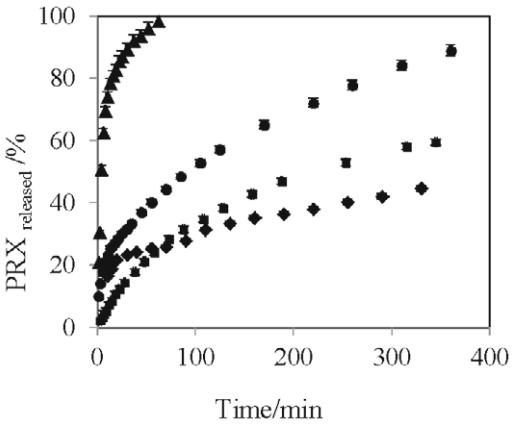

Fig. 7. PRX release profiles from microparticles batches lot no. 1 (◆), 7 (■), 8 (▲), 9 (●) based on β-CD/PRX inclusion complex.

croparticles (lot no. 7) and EC/HPMC–(β-CD/PRX) microparticles (lot no. 8), shown in Figs. 5b and 5c, bands corresponding to the –OH and C—H stretching vibrations of matrix appeared at 3446 cm^{-1}, 2971 cm^{-1}, 2870 cm^{-1}, while characteristic bands of PRX in the complex were shifted, such as the C—N stretching band at 1518 cm^{-1} for EC/HPMC–(β-CD/PRX) microparticles shifted to 1510 cm^{-1} for EC–(β-CD/PRX) microparticles, also, the stretching of the –SO_2—N– group appeared at 1159 cm^{-1} and 1158 cm^{-1} for EC–(β-CD/PRX) and EC/HPMC–(β-CD/PRX) microparticles, respectively.

Hence, the FT-IR analysis confirmed the presence of PRX in microparticles with no chemical reaction between the drug and the polymers since no new bands occurred.

Drug dissolution

Dissolution behavior of PRX in the microparticle samples was investigated in simulated gastric liquid at 37 ℃. All drug release profiles are presented in Figs. 6–8. Also, release kinetics of PRX from these formulations was evaluated according to the following models in the earlier stage; until 65 % of the drug was released:

Higuchi model:

$$\frac{M_t}{M_\mathrm{i}} = K_\mathrm{H} t^{1/2} + a \tag{8}$$

Korsmeyer–Peppas model:

$$\frac{M_t}{M_\mathrm{i}} = K_\mathrm{K} t^n \tag{9}$$

where M_t/M_i is the fractional drug release; K_H and K_K are the Higuchi's and the Korsmeyer's release constants, respectively; a and n are a constant and an exponent characterizing the drug release mechanism, respectively (Higuchi, 1963; Korsmeyer & Peppas, 1983); results of data analysis are provided in Table 3.

Table 3. Results of data analysis of drug release kinetics

Lot no.	Higuchi's model (Eq. (8))			Korsmeyer–Peppas's model (Eq. (9))			$PRX_{released}/\%^a$
	$K_H \cdot 100/min^{-1/2}$	$a \cdot 100$	r^2	n	K_K/min^{-n}	r^2	
1	1.75	12.47	0.990	0.26	0.0907	0.980	31.9 ± 1.2
2	6.11	–2.40	0.991	0.63	0.0351	0.968	59.5 ± 0.5
3	6.37	–5.12	0.994	0.65	0.0308	0.991	62.8 ± 1.6
4	4.12	–1.88	0.991	0.65	0.0204	0.975	44.4 ± 0.8
5	12.65	–6.08	0.995	0.66	0.0728	0.987	91.2 ± 1.8
6	13.10	–1.52	0.991	0.56	0.1075	0.986	total
7	3.62	–4.33	0.994	0.70	0.0120	0.984	39.5 ± 1.2
8	27.45	–25.60	0.974	0.85	0.0863	0.983	total
9	4.39	7.98	0.996	0.35	0.0983	0.996	58.7 ± 1.5
10	2.70	–6.96	0.995	0.84	0.0037	0.988	21.4 ± 0.3

a) Release after 2 h, mean value ± SD ($n = 2$).

Several parameters were varied in microparticles preparation and their effect on the drug release is discussed below. As stated previously, the release rate was largely affected by the microparticles' characteristics; namely the particle size, nature of the matrix, and the drug formulation.

Firstly, the effect of the impeller speed was significant especially for EC microspheres, the PRX release was improved when the microparticles were prepared at high impeller speed, comparison of lot no. 1 (600 min^{-1}) with lot no. 2 (1000 min^{-1}). In this case, the microparticles size decreased when the impeller speed increased; consequently, the surface contact of microparticles with the released medium increased and the drug release was favored. However, the effect of this parameter was not clear for the EC/HPMC microspheres; the dissolution efficiency increased with the increasing impeller speed for the microspheres composed of EC/HPMC in the ratio of 50/50 (lot no. 5 and 6) but an inverse effect was observed for microspheres of the ratio of 80/20 of EC/HPMC (lot no. 3 and 4). These results can be explained by the competition of the effects of size and porosity of microparticles on the PRX dissolution rate.

Secondly, concerning the nature of the matrix and microparticles prepared at the impeller speed of 600 min^{-1}, PRX was released at a higher rate when the ethylcellulose matrix was combined with the HPMC polymer. The release rate increased also with the increase of the HPMC concentration; comparing lot no. 1 (EC), lot no. 3 (EC/HPMC(80/20)), and lot no. 5 (EC/HPMC(50/50)). In fact, HPMC is a hydrophilic matrix which, when combined with EC as a hydrophobic matrix, increases the release of dispersed PRX within the matrix microspheres and provides its control. Nevertheless, for very small microparticles prepared at the impeller speed of 1000 min^{-1}, the PRX release increased only at high HPMC concentration (50 mass %). It was also observed that EC microspheres exhibited a lower drug release rate which was accompanied with a burst effect; this phenomenon can be caused by the probable presence of high concentrations of PRX near the surface of microparticles.

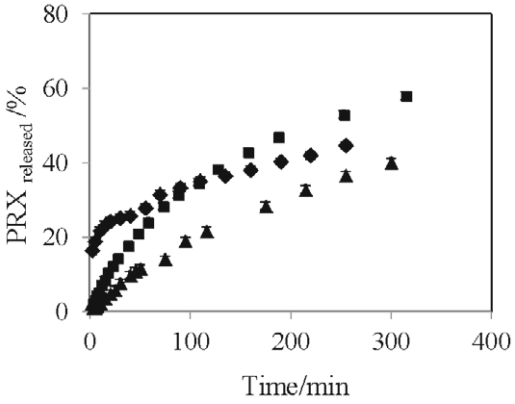

Fig. 8. PRX release profiles from EC microparticles batches lot no. 1 (◆), 7 (■), 10 (▲), based on pure PRX, β-CD/PRX inclusion complex, and β-CD–PRX physical mixture.

Thirdly, results of dispersion of the β-cyclodextrin complex with PRX in EC and EC/HPMC matrices by microencapsulation, are remarkably promising; the drug dissolution was improved and the drug release was controlled. In fact, when comparing lot no.1 (EC-PRX microspheres) and lot no. 7 (EC–(β-CD/PRX) microparticles), Fig. 7 and Table 3, the PRX release increased from 31.9 % to 39.5 % after two hours and the release profile was similar to that of controlled release formulations.

Really, complexation of cyclodextrin molecules occurred via a dynamic process. Non-covalent and hydrophobic interactions between the drug molecule (guest) and the cyclodextrin (host) cavity resulted in possible drug solubility modification (Turro et al., 1982). Therefore, the guest molecule continuously associates and dissociates from the host, and the drug included within the cyclodextrin cavity can be dissociated upon dilution (Bibby et al., 2000). So in an aqueous solution, dissolution of the PRX–cyclodextrin complex is favored and consequently the dissolution rate and release of the pure drug increase.

Also, it has been proved that CDs enhance the drug dissolution even when no complexation occurs (Challa et al., 2005). Although, the incorporation of cyclodextrin into polymeric drug delivery systems like microspheres influences the drug release mechanisms. It was shown that cyclodextrin modifies the drug solubility or diffusivity, improves hydration of the polymer matrix or enables its erosion and it can act as a channeling or wicking agent (Filipović-Grčić et al., 1996). These properties have been confirmed by our own results as shown in Fig. 8 and Table 3, the release rate of PRX from lot no. 10 (physical mixture of β-CD–PRX) was higher than that of lot no. 1 (pure PRX) but lower than that from microspheres based on the β-CD complex with PRX (lot no. 7). Thus, the release kinetics results also proved the complexation of PRX and its solubility improvement enabling easier drug diffusion from the polymeric matrix.

In addition, both the drug solubility and the polymer characteristics play a combined role in the drug release from microspheres. It is well known that a more permeable and swellable polymer facilitates drug dissolution and release from its dosage form. Thus, the mixture of hydrophobic and hydrophilic matrices (EC/HPMC) allowed high-speed release of PRX which was complete in one hour (see lot no. 8, Fig. 7); this batch of microparticles showed the speedy drug release due to the hydrophilic nature of both HPMC and β-cyclodextrin. However, when using a mixture of the (β-CD/PRX) complex and pure PRX in the preparation of EC/HPMC microparticles (lot no. 9), another release profile was obtained, with lower release rate and a 58.7 % drug release after 2 h. Thus, a new release rate was obtained.

Therefore, the aim of the combination of these processes was achieved since each formulation provided a release rate and a profile different from the other one and enable control, modification, and improvement of the PRX release rate.

Release data analysis

As mentioned previously, two mathematical models were tested in order to identify the mechanism of drug dissolution from the studied formulations. From the results presented in Table 3 and on basis of the values of the coefficient of determination (r^2), the Higuchi's model seems to be the most suitable model for the description of the PRX dissolution process, exceeding the value of 0.99 for all formulations except for lot no. 8 ($r^2 = 0.974$) which is composed of EC/HPMC(80/20) as matrices and the (β-CD/PRX) inclusion complex. The results demonstrated that the release mechanism of PRX is governed by the diffusion phenomenon.

The drug release is a result of the combined diffusion of the free drug and the dissolved β-CD complex. However, diffusivity of the drug/β-CD complex is lower due to its higher molecular mass, thus, the diffusion rates of the free drug and the drug/β-CD complex are additive.

By applying the Korsmeyer–Peppas model, the diffusion type can be discussed. In fact, exponent n of the Korsmeyer–Peppas model can be used to characterize the drug release mechanisms as a Fick's diffusion when $n = 0.5$ and as a non-Fickian model when $n > 0.5$.

From the kinetic results, exponent n varied from 0.26 to 0.85 (Table 3); thus, we concluded that the drug release is governed by diffusion, according to the non-Fickian mechanism since $n > 0.5$. In this case, the diffusion is anomalous and it can include both diffusion and erosion phenomena due to the dissolution of HPMC. For lot no. 1 and 9, $n < 0.5$ and the diffusion mechanism can be related to the quasi-Fickian model.

Moreover, the value of the Higuchi's dissolution constant confirmed the results obtained for the PRX release rate from the studied formulations. K_H really increased when using the mixture of EC/HPMC as a matrix with pure PRX or when using only EC as a matrix with the β-CD/PRX inclusion complex.

Conclusions

In this paper, development of new SD-CR formulations based on piroxicam was attempted combining complexation and microencapsulation methods. Different lots of microparticles composed of pure PRX or modified PRX (β-CD/PRX inclusion complex or a physical mixture) were prepared using EC or mixtures of EC/HPMC as matrices. The results proved that the drug release is mainly affected by the nature of the matrix, the drug formulation using β-cyclodextrin and the microparticle size (Figs. 6–8). Drug release significantly increased for microparticles composed of the β-CD/PRX inclusion complex; so, the effect of complexation on the drug release is notable. In addition, the use of EC as a primary matrix provided sustained release formulation and, consequently, these new formulations enhanced the drug solubility while controlling its release; this is the first attempt to incorporate solid dispersions of the β-CD/PRX inclusion complex in ethylcellulose microspheres.

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