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ORIGINAL PAPER

Ethylcellulose, polycaprolactone, and eudragit matrices for controlled release of piroxicam from tablets and microspheres

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The present paper provides details of the preparation of polymeric tablets and microspheres based on piroxicam as a therapeutic active agent and the drug release study from these formulations. Tablets composed of ethylcellulose, Eudragit® or mixtures of Eudragit® and synthesised poly(oxepan-2-one) were prepared and tested. The effect of the matrix on the drug release at 37 °C was studied. The drug-loaded microparticles were prepared using solvent evaporation microencapsulation. These systems were characterised by SEM and FTIR spectroscopy and the size and size distribution were also determined. The results demonstrated that the drug release could be modified by means of these formulations. Finally, piroxicam dissolution rate constants were calculated from Higuchi's release model.

Keywords: piroxicam, polycaprolactone, ethylcellulose, microspheres, tablet, drug release

Introduction

Micro-encapsulation is a method of fabricating materials with valuable new properties in the pharmaceutical industry (Phutane et al., 2010; Wang et al., 2005) and other fields (Arshady, 1993; Tsuji, 1998; El Bahri & Taverdet, 2007); it is one of the quality preservation techniques of sensitive substances. In current pharmacology, micro-encapsulation is employed as a masking technique and, in particular, to control and modify drug release. However, traditional dosage forms such as tablets still offer important advantages if they are able to decrease the total daily dosage of a medicinal agent (Sastry et al., 2000). These systems are based on a wide range of biopolymers (Prestwich & Luo, 2001; Musial et al., 2010a, 2010b). Hence, the present paper is devoted to the preparation of several formulations (tablets and microparticles) using different techniques in order to modify and control the dissolution of piroxicam which is the active molecule.

This active agent (piroxicam) has anti-inflammatory, analgesic, and antipyretic actions (Rogalsky & Todorov, 2012). It has been formulated using different techniques; for example, Puthli and Vavia (2009) studied the effect of temperature storage on piroxicam release from solid poly(lactic-*co*-glycolic acid) (PLGA) microspheres. Other researchers tested the in vivo release of piroxicam from gelatine microcapsules obtained by a spray-drying technique (Piao et al., 2008). Water-in-oil-in-water double emulsions containing piroxicam were also prepared and tested by Vlaia et al. (2009). Rajesh and Siddaramaiah (2010) reported piroxicam release from pellets of microcrystalline cellulose and hydroxypropyl methylcellulose blends.

Initially, in our research, solid dosage forms (discs) were prepared based on ethylcellulose (EC), Eudragit® RL100 (Eud; a copolymer of ethyl propenoate, methyl 2-methylpropenoate, and a low content of 2-methylpropenoic acid ester with quaternary ammonium groups) and a mixture of Eudragit® and poly(oxepan-2-one) (poly(caprolactone); Pcl) at two different percentages. The "Eudragit" copolymer is largely used for drug formulation in the galenic industry (Khan

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& Reddy, 1997; Fujimori et al., 2002; Wen & Park, 2010; Patel et al., 2010; Jain et al., 2011) and poly(caprolactone) has also recently been employed in the preparation of controlled-release formulations (Sahoo et al., 2010; Mao et al., 2007; Natarajan et al., 2011). Ethyl cellulose has been used as a drug carrier in oral pharmaceutical formulations and food products because it is generally regarded as a non-toxic, non-irritant, very safe and stable material (Wade & Weller, 1994; De Brabander et al., 2003; Kibbe, 2000; Phutane et al., 2010). It has valuable properties: it is water permeable but not water soluble (Moldenhauer & Nairn, 1990). In these experiments, the effect of the matrix on the drug release was studied.

Secondly, the solvent evaporation technique of micro-encapsulation was used for the preparation of solid microspheres based on ethylcellulose as a matrix and the drug release from the microparticles thus obtained was studied. The method is based on an oil-in-water (O/W) emulsion followed by solvent evaporation which leads to monolithic systems known as microspheres (Freiberg & Zhu, 2004). This technique has been the method most commonly used to prepare controlled-release pharmaceuticals (Lai & Tsiang, 2004; Le Corre et al., 1994; Chung et al., 2001; Duarte et al., 2006; Phutane et al., 2010). Ethylcellulose is used for the preparation of these formulations because it is seen to be a polymeric material suitable for micro-encapsulation techniques.

These composite matrices are fabricated in order to modify the release rate of a drug and to improve its protection. The piroxicam release kinetic studies are performed in acidic media at pH 1.2 and in alkaline media at pH 8.0. In neutral pH, piroxicam release was not observed because it is insoluble or only very slightly soluble. Finally, the release data were analysed according to Higuchi's equation (Higuchi, 1963) and the dissolution rate constants were calculated.

Experimental

Chemicals

Piroxicam or feldene was purchased from Sigma–Aldrich (Germany), Eudragit® RL100 ($M_w = 150000$) from Röhm Pharma (Germany). Poly(caprolactone) ($M_w = 7286$) was synthesised from 2-oxepanone and decanedioic acid and characterised by a method published in Belarbi et al. (2009). Ethylcellulose ethoxylate of 48 mass % (viscosity; 0.1 Pa s of 5 mass % in toluene/ethanol solution ($\varphi_r = 4 : 1$) was purchased from Aldrich (USA), poly(vinylalcohol) (PVA; 87–89 % purity, hydrolysed, $M_w = 13000$–23000) from Sigma–Aldrich (USA). Dichloromethane (DCM; > 98 % purity) was purchased from Fluka (Switzerland) and absolute ethanol (99 % purity) from Biochem Chemopharma (Canada). The chemicals were used as received.

For kinetic measurements, the buffer solution with pH 1.2 was prepared by dissolving; 80 mL of 1 M HCl (Cheminova International, Spain) and 2 g of NaCl (Merck, Germany) in 1 L of water; the buffer with pH 8.0 was prepared by dissolving 500 mL of 0.025 M sodium tetraborate decahydrate (Fluka, Switzerland) and 205 mL of 0.1 M HCl made up to 1 L with water.

Disc preparation

The medicinal agent and matrix (EC, Eud or a mixture of Eud/Pcl (1 : 1 mass ratio) or (4 : 1 mass ratio), in powder form (matrix/Piroxicam; 1 : 1 mass ratio)) were well dispersed (using Perkin–Elmer vibrator, Germany), carefully mixed in a mortar and a thick paste was prepared with a small amount of absolute ethanol (2 or 3 pulverisations). Then, the discs with a diameter of 1.3 cm, using a laboratory hydraulic press (Perkin–Elmer, Germany), were prepared from this paste and dried at ambient temperature in desiccators to a constant mass.

Microspheres preparation

Microparticles were prepared in a cylindrical glass reactor (volume of 600 mL, extermal diameter = 80 mm) with six-bladed turbine impeller (blade length = 50 mm, blade width = 10 mm, type IKA RW 20 DZM.n; IKA, USA) plunged in a bath adjusted to 25 °C.

The monolithic systems were obtained by the emulsion solvent diffusion method using de-ionised water as an external phase in which 0.5 % of PVA was dissolved as an emulsifier. The internal phase was composed of piroxicam with EC as the matrix (piroxicam/EC = 30 mass %) and dichloromethane (DCM) as the organic solvent (EC/DCM = 5 mass %).

First, the drug and polymer were co-dissolved in the organic solvent by heating them under slight reflux (30–35 °C) and stirred to allow homogenisation. At the same time, PVA was dissolved in 250 g of deionised water under heating and stirring. After cooling to laboratory temperature, the organic phase was emulsified with the continuous phase under mechanical stirring (500 min^{-1}) for 6 h to complete solvent evaporation. Then, the dispersion was filtered and microspheres were vacuum-dried in a desiccator in the presence of $CaCl_2$.

Microparticles characterisation

The mean diameters and size distribution of microparticles were calculated from the results of optical microscopy (H600LL microscope, Hund Wetzlar, Germany), by counting more than 500 microparticles using appropriate lenses.

The surface morphology of the microparticles was characterised by SEM using Quanta^{TM} 200 (FEI,

France) at 70 Pa under 12.5 kV of accelerated tension. The microspheres were deposited on a double-scotched carbon film fixed on a metal support.

Extractions of the drug from microparticles using an appropriate solvent were performed in triplicate; 50 mg of dried microparticles was soaked in 50 mL of absolute ethanol under stirring in a sealed bottle for 4 h. The resulting solution was analysed by UV-VIS spectroscopy (Shimadzu UV-2401 PC, Shimadzu, Japan) after an appropriate dilution with ethanol. The loading efficiency ($\text{Piroxicam}_{\text{loaded}}$, %) and the encapsulation efficiency (Yield, %) were calculated according to the following equations:

$$\text{Piroxicam}_{\text{loaded}} = \\ = \frac{\text{mass of piroxicam in microparticles}}{\text{mass of microparticles}} \times 100 \quad (1)$$

$$\text{Yield} = \frac{\text{mass of piroxicam in microparticles}}{\text{initial mass of piroxicam}} \times 100 \quad (2)$$

The microspheres were characterised by infrared spectroscopy, and the infrared spectra of pure piroxicam, EC and corresponding microparticles so obtained were compared. The FTIR spectra were recorded from 500 cm^{-1} to 4000 cm^{-1} using an FTIR-8300 Shimadzu spectrophotometer (Shimadzu, Japan). The samples in disc form were prepared with approximately 1 % of solid compound mixed and ground in dried KBr.

The drug-loading in the microspheres and drug release were determined using a UV-VIS spectrophotometer (Shimadzu UV-2401 PC, Shimadzu, Japan). The piroxicam released was analysed in acidic solution (pH 1.2) at a wavelength ($\lambda_{\max}$) of 333 nm at which a molar extinction coefficient (ε) was equal to 25400 L mol^{-1} cm^{-1} and, in alkaline solution (pH 8.0) at $\lambda_{\max}$ = 352 nm where ε = 18300 L mol^{-1} cm^{-1}

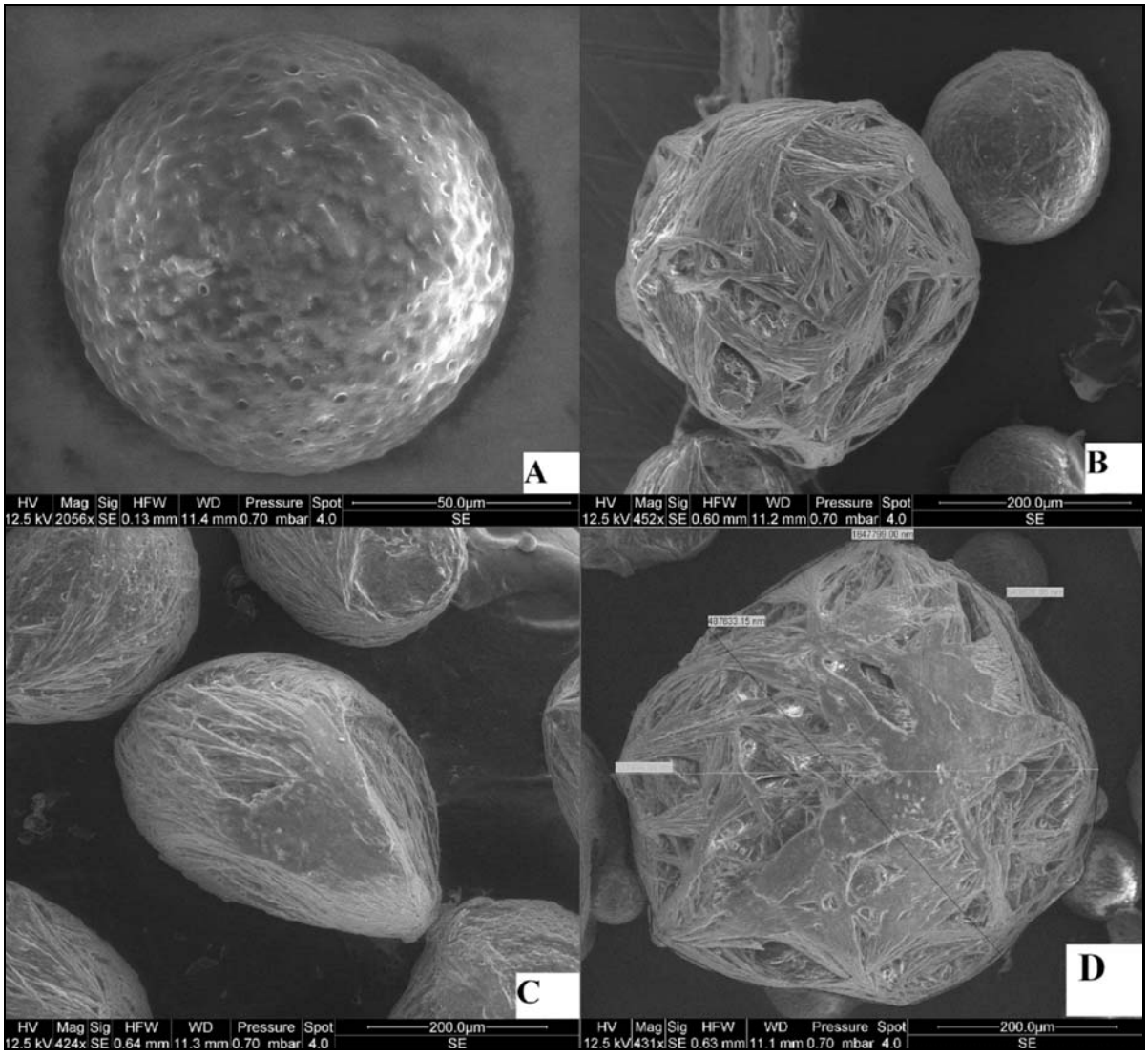

Fig. 1. SEM images of piroxicam-loaded microparticles; spherical form (A), spherical and irregular forms (B–D).

Table 1. Microparticles characteristics and encapsulation results

d_{10}/μm	d_{32}/μm	d_{43}/μm	Dispersion[a]	Piroxicam$_{loaded}$/%	Yield/%
395.7	506.0	550.1	1.39	16.79 ± 1.67	55.96 ± 5.56

a) Calculated as d_{43}/d_{10}; d_{10} – the number mean diameter calculated as $\sum n_i d_i / \sum n_i$, d_{32} – the surface mean diameter calculated as $\sum n_i d_i^3 / \sum n_i d_i^2$, d_{43} – the weight mean diameter calculated as $\sum n_i d_i^4 / \sum n_i d_i^3$.

and in ethanol at λ_{max} = 324 nm where ε = 20800 L mol^{-1} cm^{-1}.

The release kinetic studies of the active agent from formulations (tablets and microparticles) are performed in a cylindrical double-wall glass reactor (100 mL), kept at a temperature of (37 ± 0.5) ℃ (temperature of the human body). The discs, inserted in a permeable fibre glass basket, or 100 mg of microparticles, were soaked in a known volume of simulated liquid at pH 1.2 or pH 8.0 (100 mL for tablets and 50 mL for microspheres). The dissolution medium was stirred magnetically at a rotation speed of 500 min^{-1} to achieve good homogenisation. Samples (1 mL) of the solution were collected for analysis at different time intervals. After an appropriate dilution, the sample was analysed using a UV-VIS spectrophotometer. All the experiments were performed in triplicate.

Results and discussion

Microparticles characterisation

By means of the SEM and optical microscope, the surface and morphology of the microparticles were characterised and the size and size distribution determined. The SEM images in Fig. 1 show the shape and surface morphology of the microparticles. The populations of microparticles have the shape of a woolly ball with spherical and egg forms.

Taking the microparticles' forms into account, the microparticle mean diameter was measured and finally the number mean diameter, the weight mean diameter and the surface mean diameter were calculated by examining more than 500 microparticles. The characteristics of microparticles, including the mean diameter, the percentage of piroxicam-loaded microparticles, and the encapsulation yield obtained by extractions, are given in Table 1.

The IR spectrum of microparticles was compared with the polymer matrix and pure piroxicam spectra (Fig. 2). We noted the presence of some significant IR bands of piroxicam in the microparticles' spectrum at the same wave number: at 750 cm^{-1} for the out-of-plane bending of the ring C_{sp2}—H bonds, at 1560 cm^{-1} of aromatic C=C vibration and at 3360cm^{-1} of free O—H stretch. The microparticles' spectrum appears as the sum of pure piroxicam and EC spectra, so the FTIR analysis confirms the presence of piroxicam in the microparticles.

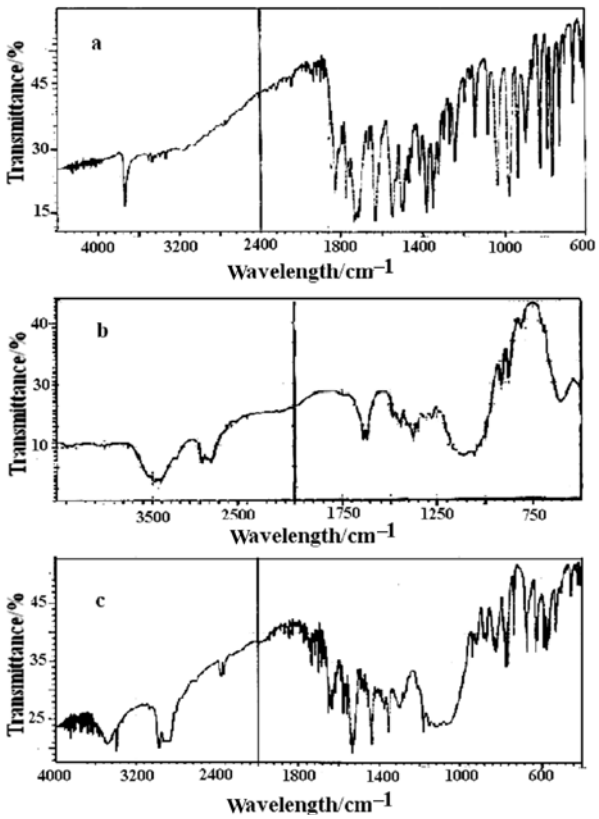

Fig. 2. Infrared spectra of; piroxicam (a), ethylcellulose (b), microparticles (c).

Discs characteristics

The characteristics of the tablets prepared and tested are listed in Table 2.

Study of drug release from tablets

The release studies were carried out in a buffered solution at pH 1.2 and 37 ℃ and the influence of the matrix on the piroxicam release was studied. All formulations were seen to be intact throughout the dissolution studies. The percentage of piroxicam released from discs relative to time is shown in Fig. 3.

In general, the percentage of drug released at infinite time does not exceed 18 % for the reason that the piroxicam is insoluble in water and slightly soluble in a buffered solution at pH 1.2. The effect of the matrix is noticeable; the presence of Pcl in tablets improves the drug release. The piroxicam released is more sig-

Table 2. Piroxicam discs characteristics tested in acidic and alkaline media

Tablet	Composition (mass %)	d cm	h cm	m_0 mg	m_i mg	pH
T1	Eud/Pirox (50/50)	1.25	0.18	262.0	131.00	1.2
T2	Eud/Pcl/Pirox (40/10/50)	1.25	0.18	252.0	126.00	1.2
T3	Eud/Pcl/Pirox (25/25/50)	1.30	0.19	304.8	152.40	1.2
T4	EC/Pirox (50/50)	1.26	0.18	263.0	131.50	1.2
T5	EC/Pirox (50/50)	1.25	0.24	275.7	137.85	8.0

d – Disc diameter, h – disc width, m_0 – disc mass, m_i: initial mass of piroxicam in disc.

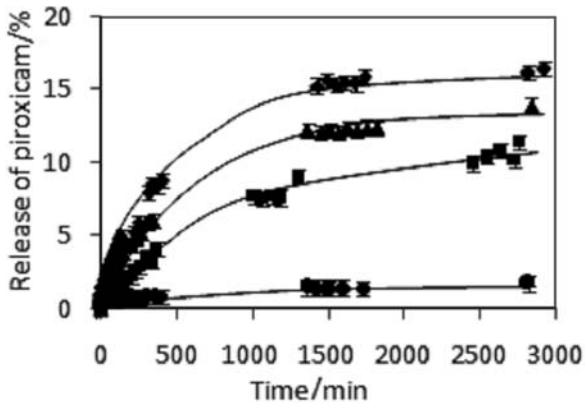

Fig. 3. Release profiles of piroxicam from polymeric tablets; ■ – T1, ▲ – T2, ♦ – T3, and ● – T4.

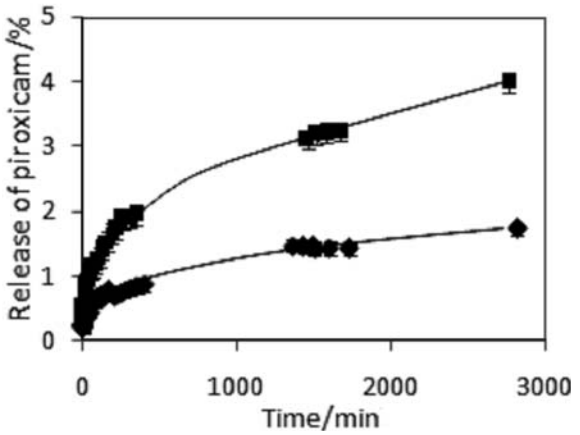

Fig. 4. Release profiles of piroxicam from EC tablets (T4 and T5) at; ♦ – pH 1.2 and ■ – pH 8.0.

nificant when the Pcl percentage in the tablets was increased. For example, after 2 h (the time corresponding to the drug retention in the human stomach), the percentages of the drug released from T1, T2, and T3 are 1.5 %, 3.2 %, and 4.3 %, respectively. The results can be explained by the hydrophilic character of Pcl. The process is not simple; two matter transfers take place when the tablet is in contact with liquid: the liquid enters the matrix-polymer and initiates the drug dissolution. At this stage, the drug can be released from the dosage form. Hence, the tablets containing Pcl absorb a larger volume of liquid which facilitates the drug dissolution and diffusion through the matrix structure. This is confirmed by the experimental results for the water levels absorbed by the dosage form after 30 h, which are respectively: 37.8 %, 54.2 %, and 88.4 % for T1(Eud), T2(Eud/Pcl in mass % 40/10) and T3(Eud/Pcl in mass % 25/25) dosage forms.

As regards the EC matrix, the rate of the drug release is very slow. In effect, after 2 h, the percentage of piroxicam released from T4 does not exceed 0.7 % which is clearly due to the low absorption of water by a tablet (5.4 % after 30 h).

The effect of the pH of the release medium was also studied for tablets composed of EC as the matrix. Fig. 4 presents the release profiles obtained; the piroxicam is released rapidly at pH 8.0.

We noted that, for example, after 5 h the percentage of piroxicam released in an acidic medium was 0.8 %, whereas in an alkaline solution it exceeded 1.8 %. This finding can also be explained by the absorption rate of release medium by the tablet which facilitates dissolution of the active agent and, subsequently, its diffusion. After 30 h of release, the percentage of alkaline liquid (pH 8.0) absorbed by a tablet was 7.6 % while the percentage of absorbed acidic liquid (pH 1.2) was 5.4 %. In addition, the diffusion of piroxicam from these systems may be favoured largely by its solubility in the alkaline medium.

Study of drug release from microparticles

The piroxicam release kinetic studies from microparticles were performed in both a simulated gastric medium (pH 1.2) and intestinal medium (pH 8.0) at 37 ℃. Fig. 5 shows the release profiles obtained. In these formulations, a significant quantity of piroxicam is released (6.8 %) after 2 h when compared with all tablets. In this case, the surface of contact of microparticles with liquid is more pronounced than in tablets; this property favours the drug release.

As regards the effect of the pH of the release medium on the drug release, the release profiles showed a rapid dissolution of the active agent in alkaline medium. After 5 h, the percentage of piroxicam released did not exceed 8 % at pH 1.2; however, 18 % of the drug was released at pH 8.0.

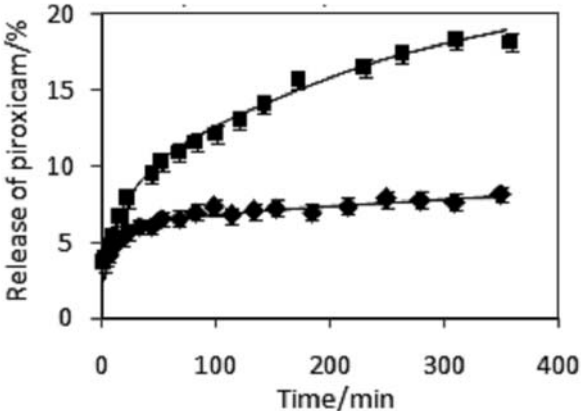

Fig. 5. Release profiles of piroxicam from ethycellulose microparticles at; ♦ – pH 1.2 and ■ – pH 8.0.

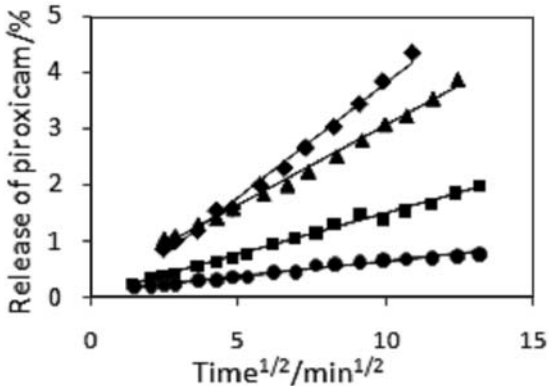

Fig. 6. Fractional release of piroxicam from discs as a function of the square root of time; ■ – T1, ▲ – T2, ♦ – T3, and ● – T4.

Data analysis

Korsmeyer–Peppas (Korsmeyer et al., 1983) derived a simple relationship which described drug release from a polymeric system:

$$M_t/M_\infty = k(t)^n \tag{3}$$

where M_t/M_∞ is the fraction of drug released, t is the release time, k is the kinetic constant (with units of t^{-n}) incorporating the structural and geometric characteristics of the release device and n is the release exponent indicative of the mechanism of release. This equation can be used to analyse the first 60 % of a release curve where the release is linearly related to t^n, irrespective of geometric shape.

Although the constant k in Eq. (3) is one of the constants of the drug release rate, it should not be used for comparison because there is different kinetics with different values of n. Therefore, for calculation of the release rate of the drug, the data in this study were subjected to the Higuchi equation (Higuchi, 1963):

$$W = (2ADC_\mathrm{s}t)^{1/2} \tag{4}$$

where W is the amount of drug released per unit area (cm^2) at time t (min), A ($\mathrm{g\ cm}^{-3}$) is the total concentration of drug in the tablet, while D ($\mathrm{cm}^2\ \mathrm{min}^{-1}$) is the diffusion coefficient of drug in the matrix, and C_s ($\mathrm{g\ cm}^{-3}$) is the solubility of drug in the matrix. This equation may be reduced to a simple equation:

$$Q = at^{1/2} + c \tag{5}$$

Eq. (5), for release data dependent on the square root of time, would give a straight line release profile, where Q is the percentage of drug released at time t (min), a ($\mathrm{min}^{-1/2}$) is the square root time dissolution rate constant, and c is the constant. The lag period, prior to release, is defined as $(-c/a)^2$. In this case, we can compare the dissolution rate constants as reported in various research papers (Vlaia et al., 2009; Casas et al., 2010; Mourão et al., 2010).

Examples of plots of the fractional drug release as a function of the square root of time are given in Fig. 6 and the results of the dissolution data and the coefficients of determination (r^2) for tablets are given in Table 3 and for microparticles in Table 4.

From the results of Higuchi's equation plots, the square root dissolution rate constants varied from 0.055×10^{-2} $\mathrm{min}^{-1/2}$ to 0.987×10^{-2} $\mathrm{min}^{-1/2}$. For the tablets' dissolution at pH 1.2, the piroxicam release rate increases when Pcl matrix is used (Table 3) and it is lower in the EC matrix. The effect of pH media on the dissolution rate is notable both for tablets and microspheres; it increases in alkaline media.

The coefficients of correlation (r^2) are above 0.99 when M_t/M_∞ does not exceed 10 %, except for microspheres' dissolution in acidic media where $r^2 = 0.964$. This may be due to the low concentration of piroxicam in the dissolution liquid. In effect, in the first time of kinetics (the first five hours of the drug release), the liquid concentration does not exceed 0.03 mg mL^{-1}, so it can cause disruptions in the optical density values since the same sampling time schedule is maintained and probably the dissolution equilibrium between samples is not attained for some points.

From the results of the Korsmeyer–Peppas equation, the value of k cannot be compared since n are different. However, the exponent n can be used to characterise the drug release mechanisms as Fick diffusion, when $n = 0.5$ and as a non-Fickian model if n is different from 0.5. From the kinetic results, the exponent n varied from 0.457 to 0.524 which is near 0.5 for Eud and Pcl matrix tablets and from 0.186 to 0.378 so below 0.5 for EC matrix, whatever the type of formulation. We concluded that the drug release behaviour was governed by diffusion, according to a Fickian mechanism in Eudragit® and Pcl matrixes and a non-Fickian mechanism in EC matrix.

Table 3. Coefficients of correlation and dissolution rate constants of piroxicam from tablets

Formulation	Higuchi's equation		Korsmeyer–Peppas's equation		
	$Q \times 10^2 = at^{1/2} + c$	r^2	n	$k/(\min^{-n})$	r^2
T1	$y = 0.146x + 0.019$	0.993	0.484	0.009	0.993
T2	$y = 0.282x + 0.230$	0.994	0.457	0.024	0.989
T3	$y = 0.396x - 0.173$	0.991	0.524	0.022	0.992
T4	$y = 0.055x + 0.089$	0.991	0.378	0.019	0.984
T5	$y = 0.101x + 0.247$	0.992	0.358	0.017	0.996

Table 4. Coefficients of correlation and dissolution rate constants of piroxicam from microparticles

pH	Higuchi's equation		Korsmeyer–Peppas's equation		
	$Q \times 10^2 = at^{1/2} + c$	r^2	n	$k/(\min^{-n})$	r^2
1.2	$y = 0.387x + 3.578$	0.964	0.186	0.161	0.984
8.0	$y = 0.987x + 2.614$	0.991	0.329	0.100	0.994

Conclusions

The study was focused on the preparation of controlled-release formulations based on piroxicam as an active agent. The aim was achieved since we obtained various rates of drug release. The effect of matrix on the drug release was remarkable (Fig. 2). For the tablets tested, the piroxicam release can be improved using the mixtures of Eudragit® and poly(caprolactone) supports and it can be decelerated using ethylcellulose, as a function of the desired properties of dosage form. Also, the use of ethylcellulose microparticles enables the release of a significant percentage of piroxicam. The global effect of the pH of the release medium on the drug release is significant (Figs. 4 and 5).

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