THE STUDY OF PIROXICAM DISSOLUTION FROM EUDRAGIT RS-COATED PELLETS

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Abstract

The objective of this work was to study the dissolution process from piroxicam pellets, coated with Eudragit® RS 30 D by fluidized bed, in order to achieve an enteric release of the drug. The coating product contains a methacrylic copolymer which is insoluble, but permeable. The drug-loaded pellets were prepared by extrusion-spheronization using microcrystalline cellulose (Avicel PH 101) as a spheronization agent, lactose as a filler and polyvinylpyrrolidone K30 as a binder. A dissolution study was performed using two dissolution media with different pH values, corresponding to the pH values of the stomach and intestinal environment (hydrochloric acid 0.1N, pH=1.2 for the first two hours of the test and phosphate buffer 50 mM, pH 6.8 for the next 4 hours interval of the dissolution test). The *in vitro* dissolution profile obtained for the piroxicam pellets coated with Eudragit RS 30 D was compared with the one corresponding to the piroxicam pellets coated with Eudragit RS 30 D associated with Methocel E5. The influence of the association of the pore-forming agent in the coating formula on the percentages of piroxicam dissolved was established.

Rezumat

Obiectivul acestei lucrări a fost studierea profilului de dizolvare a piroxicamului din pelete acoperite în pat fluidizat cu o dispersie de Eudragit® RS 30 D. Sistemul de acoperire conține un copolimer metacrilic insolubil în apă şi cu permeabilitate redusă. Peletele cu piroxicam au fost obținute prin metoda extrudării-sferonizării, urmată de acoperirea cu Eudragit® RS 30 D. Profilul de dizolvare al peletelor obținute a fost comparat cu cel al peletelor încărcate cu piroxicam, acoperite cu un film în care Eudragit RS 30 D a fost asociat cu Methocel E5 Premium LV ca formator de pori. Testul de dizolvare s-a efectuat în două medii de dizolvare cu pH diferit, corespunzând valorilor de pH ale mediului stomacal şi intestinal (acid clorhidric 0,1 N, pH 1,2 pentru primele două ore ale testării, respectiv tampon fosfat 50 mM, pH 6,8 pentru intervalul 2 – 4 ore ale testului de dizolvare). S-a comparat profilul de dizolvare *in vitro* obținut pentru peletele cu piroxicam acoperite cu Eudragit RS 30 D cu cel corespunzând peletelor cu piroxicam acoperite cu Eudragit RS 30 D asociat cu Methocel E5, evindențiindu-se influența prezenței formatorului de pori în formula filmului de acoperire asupra procentului de piroxicam dizolvat.

Keywords: pellets, piroxicam, extrusion-spheronization, film coating, Eudragit RS 30 D, dissolution test.

Introduction

The use of pellets allows a rationalisation of the drug release, thus improving bioavailability, reducing plasmatic peak fluctuations, increasing clinical safety and efficacity and minimizing adverse effects of drugs [1–4]. Furthermore, pellets are less susceptible to produce a dose-dumping effect because the drug is released in small amounts from the pellets as individual entities of the dosage form.

Piroxicam is a non-steroidal anti-inflammatory drug (NSAID) used in the treatment of rheumatoid arthritis. Its non-selective inhibition of the COX (cyclo oxygenase) enzymes, which gives its antiinflamatory effects, is also responsible for the digestive adverse effects (gastric irritation, nausea, gastro-intestinal ulcer, gastric bleeding, perforation) associated with long-term administration of oral immediate-release dosage forms (tablets, capsules) [5]. Still, it has been reported that the gastric irritation is caused not only by the inhibition of the prostaglandin synthesis, but also by the direct contact of the low-soluble drug with the stomach mucosa [6] and by its enterohepatic recirculation [7,8].

Therefore, taking advantage of the intrinsic properties of the pellets, the objective of this work was to formulate piroxicam in a multiparticulate drug delivery system, such as coated pellets.

The coating of the drug pellets was performed using Eudragit RS 30 D, a methacrylic copolymer, insoluble, but permeable, which minimizes the contact between the low soluble drug and the gastric mucosa, thus reducing its adverse effects. Given the low permeability of the Eudragit RS film, the association of Methocel E5 Premium LV as a pore forming agent in the coating formula was considered adequate as a means of increasing the percentage of dissolved drug.

The piroxicam pellets were prepared using the extrusion-spheronization technique and then coated with the Eudragit RS 30 D dispersion, respectively the Eudragit RS 30 D associated with Methocel E5.

The dissolution profiles of piroxicam from the pellets coated with the two types of film have shown differences, showcasing the positive influence of the incorporation of the pore-forming agent in the film formula on the dissolution of piroxicam [9].

Materials and Methods

Materials

Piroxicam (LaborMed Pharma, România), microcrystalline cellulose – Avicel PH 101 (FMC, Cork, Irlanda), monohydrate lactose 200 mesh

(Meggle GmbH, Germania), polivynilpirrolidone Kollidon K 29/32 (BASF AG, Germania), Eudragit® RS 30-D (Evonik Industries), Methocel™ E5 Premium LV (Dow Chemical Industries), PEG 400 (BASF Chem Trade GmbH, Germania), hard gelatin capsules (Gelcaps, Romania).

All the materials used for the formulation and manufacture of the pellets comply with compendial or manufacturer's requirements.

Equipments

Extruder Model 25 (Caleva Process Solutions Ltd., UK), Spheronizer Model 120 (Caleva Process Solutions Ltd., UK), CISA Sieve Shaker (CISA Cedaceria Industrial, Spain), UE/BE 200 – 800 oven (Memmert GmbH + Co. KG, Germany), Caleva Minicoater/Drier 2 (Caleva Process Solutions Ltd., UK), Hanson SR8 Dissolution Test System, Apparatus 2 USP, Spectrophotometer Jasco UV-Vis V-530 (Spectra Manager for Windows 95/NT vers. 1.54.03.), Poroplast-Fiterkerze filters (PharmaTest GmbH), pH-meter Combo HI 98130 (Hanna Instruments), SG Ultra Clear UV plus TM water purification system.

Methods

The preparation of piroxicam pellets by extrusion-spheronization

The optimal formula and processing conditions were established in previous experiments. Piroxicam (2.5 g) was uniformly dispersed in a mycrocrystalline cellulose:lactose blend (50:80).

The dry mixture was sprayed with 70 grams of a 2.5% polyvinylpyrrolidone K30 (PVP K30) aqueous solution, until a wet mass, adequate for extrusion, was obtained. The wet mass was extruded into short, cylindrical extrudates, using the extuder with screen openings of 1 mm.

The resulting extrudates were fed into the spheronizer, equipped with a cross-hatch pattern friction plate of 12 cm in diameter. The spheronization process was performed at a speed of 1000 rpm for 5 minutes. Because the pellets had a significant content of residual moisture at this stage, they were oven-dried at 40ºC for 1 hour before further processing. The pellets were then sieved and the fractions larger than 1.18 mm and smaller than 0.8 mm were discarded. The pellets with a size withing the range of 0.8-1.18 mm were subsequently coated with the two polymeric films.

Coating the piroxicam pellets by fluid bed technology

Eudragit® RS 30 D is a coating system which forms water-insoluble films with a low permeability. It is a copolymer of ethyl acrylate, methyl methacrylate and a low content of methacrylic acid ester with quaternary ammonium groups. The ammonium groups are present as salts and make the polymers permeable [10, 11].

Preparing the coating dispersion

A 10% Eudragit® RS 30 D aqueous dispersion was prepared according to the coating polymer manufacturer's guidelines. Polyethylene glycol 400 was included in the formula as a plasticizing agent, in a concentration of 1% (10% of the polymer content of the aqueous coating dispersion).

For the second film formula, a content of 5% Methocel E5 Premium LV was added.

Coating the pellets with the enteric coating dispersion

30 grams of pellets were transferred into the top-spray fluid bed minicoater and coated with the dispersion which was continuously stirred during spraying. The pellets were coated to a 5% weight gain (based on the initial weight of the pellets). The operating conditions during the coating process were as follows:

Table I

Operating conditions in the coating stage of the pellets

Operating conditions	***Values***
Inlet air temperature (°C)	42°C
Pellet bed temperature (°C)	42°C
Inlet air flow rate (m/sec)	11
Liquid flow rate (mL/hour)	20
Atomization pressure (psi)	12
Size range of pellets (mm)	0.8 – 1.18

Dissolution test of the piroxicam pellets coated with Eudragit RS 30 D and Eudragit RS 30 D associated with Methocel E5 Premium LV

The dissolution test was performed on hard gelatin capsules containing piroxicam pellets coated with the polymeric films, according to USP 30 National Formulary 25 requirements.

The dissolution media selected for the test was represented by hydrochloric acid 0.1N, pH 1.2 (750 mL) for the first two hours of the test, and phosphate buffer 50 mM, pH 6.8 (1000 mL) for the next four hours of the test, generated by adding after two hours from the beggining of the test of 250 mL trisodic phosphate solution 0.2 M. The pH of the media was verified using a pH-meter Combo HI 98130 (Hanna Instruments).

The Hanson SR8 Dissolution Test Station was used, respectively apparatus 2 (paddle method), set at 75rpm and a media temperature of 37°C.

In all experiments, the dissolution test was performed on six capsules, inserted in hellicoidal sinkers of an adequate capacity.

Samples of 5 mL were withdrawn at preset time intervals (30, 60, 120, 180, 240, 300 and 360 minutes). The sample volume was replaced with an equal volume of corresponding dissolution media at 37°C. The samples were filtered through regenerated cellulose filters Poroplast-Fiterkerze (PharmaTest GmbH), and then diluted with the dissolution media. The absorbance of the diluted samples was spectrophotometrically determined against the dissolution media, at 332 nm wavelength for the samples taken in the first two hours of the test and 352.2 nm for the samples taken in the 2 to 4 hours time interval of the test.

Results and Discussion

The results of the dissolution test are shown in the following tables and figures.

Table II

Total amount of piroxicam (corrected) (µg) released from the piroxicam pellets coated with Eudragit RS 30 D in the hydrochloric acid 0.1N, pH=1.2 (0-2 hours) and phosphate buffer 50 mM, pH=6.8 (2-6 hours) dissolution media

Time (hours)	*Vessel 1*	*Vessel 2*	*Vessel 3*	*Vessel 4*	*Vessel 5*	*Vessel 6*
0	0	0	0	0	0	0
0.5	58.87	43.52	110.92	88.74	94.71	73.38
1	269.16	294.66	435.89	448.54	351.31	368.24
2	2162.94	1997.03	2231.72	2371.01	2029.07	2187.18
3	3139.76	3241.02	3294.07	3290.76	3099.98	3334.83
4	4817.17	4131.89	4644.48	4672.46	4470.31	4236.59
5	5916.26	5175.35	5245.81	6257.23	5924.65	5257.61
6	6100.04	6194.71	6315.59	7515.78	7206.61	6790.93

Table III

Total amount of piroxicam (corrected) (%) released from the piroxicam pellets coated with Eudragit RS 30 D in the hydrochloric acid 0.1N, pH=1.2 (0-2 hours) and phosphate buffer 50 mM, pH=6.8 (2-6 hours) dissolution media. Descriptive statistics

Time (hours)	*Vessel 1*	*Vessel 2*	*Vessel 3*	*Vessel 4*	*Vessel 5*	*Vessel 6*	*Average*	*Standard deviation*	*Variation coefficient (%)*
0	0	0	0	0	0	0	0	0	-
0.5	0.29	0.22	0.55	0.44	0.47	0.37	0.39	0.12	31.54
1	1.35	1.47	2.18	2.24	1.76	1.84	1.81	0.36	20.06
2	10.81	9.99	11.16	11.86	10.15	10.94	10.82	0.69	6.34
3	15.70	16.21	16.47	16.45	15.50	16.67	16.17	0.47	2.90
4	24.09	20.66	23.22	23.36	22.35	21.18	22.48	1.34	5.94
5	29.58	25.88	26.23	31.29	29.62	26.29	28.15	2.30	8.16
6	30.50	30.97	31.58	37.58	36.03	33.95	33.44	2.91	8.70

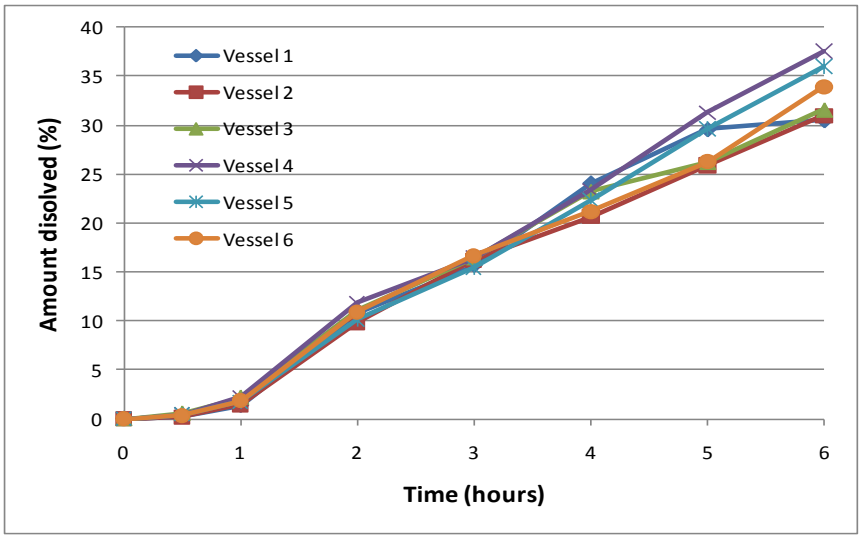

Figure 1

The individual dissolution profiles for the six units of capsules with Eudragit RS 30 D-coated piroxicam pellets (20 mg piroxicam/capsule), dissolution media: 0-2 hours: hydrochloric acid, 0.1N, 750 mL; 2-6 hours: phosphate buffer pH=6.8, 50 mM, 1000 mL.

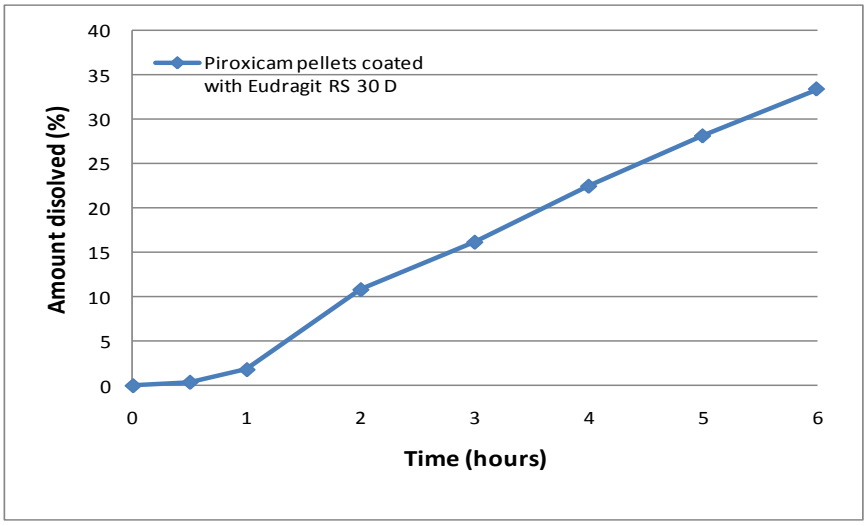

Figure 2

The average dissolution profile for the Eudragit RS 30 D-coated piroxicam pellets (20 mg piroxicam/capsule), dissolution media: 0-2 hours: hydrochloric acid, 0.1N, 750 mL; 2-6 hours: phosphate buffer pH=6.8, 50 mM, 1000 mL.

The data obtained showed that after six hours of dissolution testing, the maximum percentage of drug dissolved from the pellets was of approximately 33%. After 2 hours at pH 1.2, the average amount dissolved was of 10.82%. Except the first two sample points, the values of the variation coefficients for all the other points were under 10%, within the official limits of acceptance criteria.

Table IV

Total amount of piroxicam (corrected) (μg) released from the piroxicam pellets coated with Eudragit RS 30 D associated with Methocel E5 Premium LV in the hydrochloric acid 0.1N, pH=1.2 (0-2 hours) and phosphate buffer 50 mM, pH=6.8 (2-6 hours) dissolution media

Time (hours)	*Vessel 1*	*Vessel 2*	*Vessel 3*	*Vessel 4*	*Vessel 5*	*Vessel 6*
0	0	1	2	3	4	5
0.5	180.89	194.54	88.74	67.41	56.31	204.78
1	637.72	604.54	355.54	263.25	258.91	565.36
2	3102.53	2699.99	2027.49	1805.96	1702.52	2731.12
3	6656.58	7388.63	6256.54	6784.58	6364.17	6799.92
4	10000.79	9477.65	10392.12	9273.55	8512.83	9004.99
5	12392.88	11378.60	12627.56	11603.60	11423.64	11308.60
6	13974.13	14249.15	13698.55	13061.98	13465.71	13120.38

Table V

Total amount of piroxicam (corrected) (%) released from the piroxicam pellets coated with Eudragit RS 30 D associated with Methocel E5 Premium LV in the hydrochloric acid 0.1N, pH=1.2 (0-2 hours) and phosphate buffer 50 mM, pH=6.8 (2-6 hours) dissolution media. Descriptive statistics

Time (hours)	*Vessel 1*	*Vessel 2*	*Vessel 3*	*Vessel 4*	*Vessel 5*	*Vessel 6*	*Average*	*Standard deviation*	*Variation coefficient (%)*
0	0	0	0	0	0	0	0	0	-
0.5	0.90	0.97	0.44	0.34	0.28	1.02	0.66	0.34	51.75
1	3.19	3.02	1.78	1.32	1.29	2.83	2.24	0.87	39.05
2	15.51	13.50	10.14	9.03	8.51	13.66	11.72	2.87	24.52
3	33.28	36.94	31.28	33.92	31.82	34.00	33.54	2.00	5.97
4	50.00	47.39	51.96	46.37	42.56	45.02	47.22	3.39	7.18
5	61.96	56.89	63.14	58.02	57.12	56.54	58.95	2.86	4.85
6	69.87	71.25	68.49	65.31	67.33	65.60	67.97	2.35	3.46

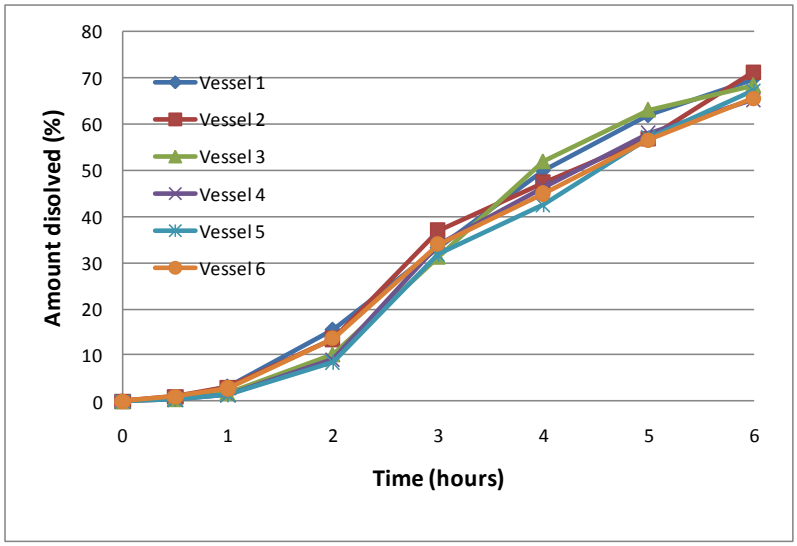

Figure 3

The individual dissolution profiles for the six units of capsules with piroxicam pellets coated with Eudragit RS 30 D associated with Methocel E5 Premium LV (20 mg piroxicam/capsule). dissolution media: 0-2 hours: hydrochloric acid, 0.1N, 750 ml; 2-6 hours: phosphate buffer pH=6.8, 50 mM, 1000 mL.

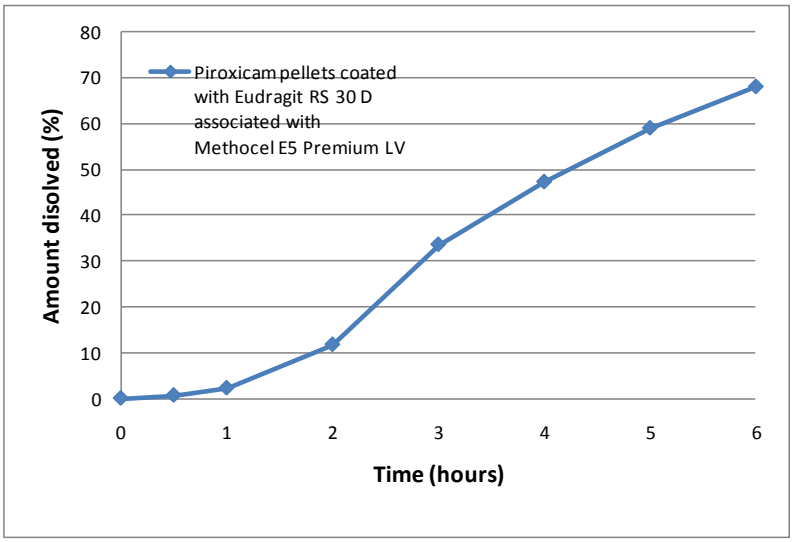

Figure 4

The average dissolution profile for the piroxicam pellets coated with Eudragit RS 30 D associated with Methocel E5 Premium LV (20 mg piroxicam/capsule), dissolution media: 0-2 hours: hydrochloric acid, 0.1N, 750 mL; 2-6 hours: phosphate buffer pH=6.8, 50 mM, 1000 mL.

The data obtained after the dissolution test shows that in the case of the piroxicam pellets coated with the film in which Eudragit RS 30 D was associated with Methocel E5 Premium LV, the maximum percentage of dissolved drug after six hours of testing was of 67.97%, the double value obtained for the pellets coated only with Eudragit RS 30 D. The percentage of drug dissolved after 2 hours at a pH value of 1.2 was of 11.72%. Also, in this case, for all sampling points, except the first three, the recorded values of the variation coefficients were under 10%, within the limits of the official acceptance criteria for dissolution testing.

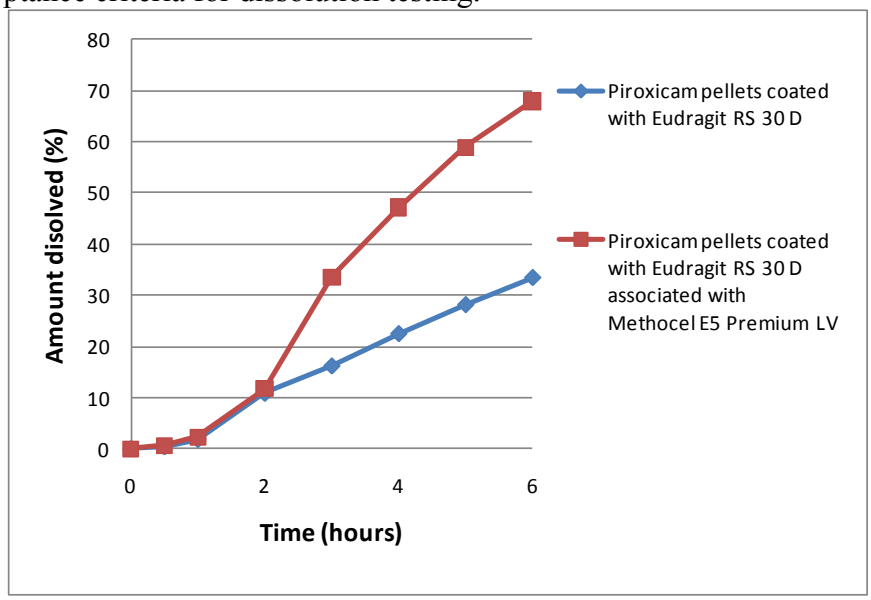

Figure 5

The average dissolution profiles for the piroxicam pellets coated with Eudragit RS 30 D and with Eudragit RS 30 D associated with Methocel E5 Premium LV (20 mg piroxicam/capsule), dissolution media: 0-2 hours: hydrochloric acid, 0.1N, 750 mL; 2-6 hours: phosphate buffer pH=6.8, 50 mM, 1000 mL

It can be seen that when Eudragit RS 30 D was used as a single film forming agent, the dissolution of piroxicam from the pellet capsules was slow, almost constant, independent to the pH of the dissolution media, but dependent on the physicochemical characteristics of the drug (sollubility, pKa). The dissolution profile shows two distinct segments, almost linear, corresponding to the simultaneous variation of the pH value and of the media volume.

The Eudragit RS 30 D coating is controlling the global dissolution profile, acting as an insoluble, semipermeable barrier for the dissolved drug.

By comparing the two average dissolution profiles obtained, it can be seen that the influence of the presence of a pore-forming agent in the film has led to a much higher percentage of drug released from the pellets. This can be attributed to the fact that the pores formed have allowed an easier acces of the dissolution media with a pH value favourable to the dissolution of piroxicam inside the pellets, thus promoting the dissolution process of the drug.

Conclusions

This study describes the preparation and *in vitro* dissolution study of piroxicam pellets coated with two types of polymeric films, based on Eudragit® RS 30 D in a fluid-bed minicoater.

The association of 5% Methocel in the coating dispersion based on Eudragit RS 30 D has had a favourable influence on the dissolution of piroxicam from the pellets.

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