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Research paper

Development and in vitro evaluation of an enteric-coated multiparticulate drug delivery system for the administration of piroxicam to dogs

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Abstract

The aim of the study was to develop enteric-coated pellets for the administration of piroxicam (a poorly water-soluble drug) to small animals in order to avoid local gastrointestinal irritation, one of the major side effects of nonsteroidal anti-inflammatory drugs after oral ingestion. Pellets were made by an extrusion–spheronization process. The influence of several excipients on the in vitro drug release was evaluated. Piroxicam release from the uncoated pellets was measured in phosphate buffer (pH 6.8) using the paddle dissolution method (USP XXIII). The enteric-coated pellets were tested in 0.1 N HCl and phosphate buffer, pH 6.8. The addition of sodium croscarmellose (Ac-Di-Sol) did not influence the piroxicam release from microcrystalline cellulose pellets. Sodium carboxymethyl starch (Explotab) increased the release from 30 to 65% at 45 min. The incorporation of sodium carboxymethyl cellulose on its own or as a co-processed blend with microcrystalline cellulose (Avicel RC 581 and CL 611) enhanced the release of piroxicam at 45 min from 30% (pure Avicel PH 101) to 95% (combination of Avicel PH 101 and CL 611 in a ratio of 1:3). Additional use of cyclodextrins had only a minor influence on the dissolution rate. An Eudragit L 30 D-55 and FS 30 D (6/4) film was applied to the core pellets (containing 2.5% (w/w) piroxicam and a combination of Avicel PH 101 and CL 611 in a ratio of 1:3) in order to obtain gastroresistant properties. The coated pellets retained their dissolution characteristics after compression into fast disintegrating tablets because waxy cushioning beads were added to minimize film damage.

Keywords: Pellets; Extrusion-spheronization; In vitro drug release; Coating; Compression

1. Introduction

Piroxicam is a potent nonsteroidal anti-inflammatory drug (NSAID) used for its analgesic, antipyretic and anti-inflammatory properties in humans [1] and small animals [2,3]. Irritation of the gastrointestinal tract is, as with most NSAIDs, one of the major side effects reported after oral administration of piroxicam [1,4]. Since its gastrointestinal intolerance is not only related to the inhibition of the prostaglandin synthesis, but also to acute local contact of the drug with the gastric mucosa [5], the development of an enteric-coated multiparticulate drug delivery system might reduce or even avoid the mucosal irritation. This objective could be achieved by formulating piroxicam-loaded pellets (800–1250 μm) which are not only easy to coat, but offer several additional advantages including good flow properties and a less variable gastric emptying time compared with larger monolithic dosage forms [6]. According to the Biopharmaceutical Classification System (BCS) piroxicam is regarded as a class II compound characterized by a low water solubility and since drug release from the dosage form is strongly influenced by the drug solubility, the development of immediate release piroxicam pellets will be mainly based upon incorporation of fillers capable of accelerating the dissolution rate [7]. The dissolution properties of piroxicam can be improved by reducing the drug particle size [8], by increasing its wettability (through the addition of hydrophilic fillers and surfactants) [8], by formulating solid dispersions (e.g. based on polyvinylpyrrolidone (PVP)) [9] and cyclodextrin (CD) inclusion complexes [8,10–12]. Cyclodextrin complexes offer the additional advantages of increasing the in vivo absorption rate [13] as well as reducing the acute gastric damage [14].

The aim of this study was to develop an enteric-coated pellet formulation for the administration of piroxicam to small animals. In addition to the optimization of the in vitro drug release profile by evaluating the influence of a series of excipients, the objective of this study was also to

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Table 1
Composition of pellets loaded with 2.5% (w/w) piroxicam

Formulation	Composition		
A	97.5% Avi PH 101[a]		
B	86.5% Avi PH 101	11% Explotab[d]	
C	86.5% Avi PH 101	11% Ac-Di-Sol[e]	
D	86.5% Avi PH 101	11% Blanose[f]	
E	48.75% Avi PH 101	48.75% Avi RC 581[b]	
F	24.4% Avi PH 101	73.1% Avi RC 581	
G		97.5% Avi RC 581	
H	48.75% Avi PH 101	48.75% Avi CL 611[c]	
I	24.4% Avi PH 101	73.1% Avi CL 611	
J		97.5% Avi CL 611	
K	77.5% Avi PH 101	20% HP-β-CD[g]	
L	19.4% Avi PH 101	20% HP-β-CD	58.1% Avi CL 611
M	19.4% Avi PH 101	20% β-CD[h]	58.1% Avi CL 611

[a] Avicel PH 101 (microcrystalline cellulose).
[d] Sodium carboxymethyl starch.
[e] Sodium croscarmellose.
[f] Blanose 7MF (sodium carboxymethyl cellulose 300–600 mPa s).
[b] Avicel RC 581 (co-processed microcrystalline cellulose and 8.3–13.8% sodium carboxymethyl cellulose).
[c] Avicel CL 611 (co-processed microcrystalline cellulose and 13.5–16.4% sodium carboxymethyl cellulose).
[g] Hydroxypropyl-β-cyclodextrin.
[h] β-Cyclodextrin.

compress the enteric-coated pellets into a rapid disintegrating tablet.

2. Materials and methods

2.1. Materials

Piroxicam (Px) was purchased from Sagran (Milan, Italy). The microcrystalline cellulose grades (Avicel) were obtained from FMC (Cork, Ireland), while sodium carboxymethyl cellulose (Blanose 7MF) was provided by Hercules (Dusseldorf, Germany). Hydroxypropyl-β-cyclodextrin (HP-β-CD) was obtained from Janssen Pharmaceutica (Beerse, Belgium), β-cyclodextrin (β-CD) from Cerestar (Vilvoorde, Belgium), sodium croscarmellose (Ac-Di-Sol) from FMC (Brussels, Belgium) and sodium carboxymethyl starch (Explotab) from Penwest Patterson (New York, NY, USA). Demineralized water was used as granulation fluid. The Eudragit polymers were kindly donated by Röhm (Darmstadt, Germany). Drum dried cornstarch (DDCS) was purchased from Cerestar Pharma (Vilvoorde, Belgium) and Paracera P from Paramelt (Heerhugowaard, The Netherlands). Kollidon CL was obtained from BASF (Ludwigshafen, Germany).

2.2. Pellet production and evaluation

2.2.1. Extrusion–spheronization

The batch size was 200 g of dry material and the drug load in all formulations was 2.5% (w/w). The different components were dry mixed for 10 min at 60 rpm using a planetary mixer (Kenwood Chef, Hampshire, UK) with a K-shaped mixing arm. Subsequently the powder mixture was wetted with demineralized water and granulated for 5 min at 60 rpm. The amount of granulation fluid used depended on the composition of the formulation. Next the wet mass was extruded at an extrusion rate of 45 rpm by means of a single screw extruder (Dome extruder lab model DG-L1, Fuji Paudal, Tokyo, Japan) equipped with a screen having 1-mm cylindrical perforations. The extrudates were spheronized in a spheronizer (Caleva Model 15, Sturminster Newton, UK) using a friction plate with crosshatched geometry. The spheronization time and speed depended on the composition of the formulation. The pellets were tray dried in a hot air oven at 40 °C until constant weight and the 800–1250 μm fraction was separated using a sieve shaker (Retsch, Haan, Germany) at an amplitude of 2 mm.

To optimize the dissolution rate of piroxicam from the pellets, the influence of disintegrants (Ac-Di-Sol, Explotab), cyclodextrins (HP-β-CD, β-CD) and sodium carboxymethyl cellulose (NaCMC) (Blanose 7MF, 450 mPa s, degree of substitution: 0.65) either on its own or as a co-processed blend with microcrystalline cellulose (Avicel RC 581 and CL 611 grades) was investigated. The Avicel RC and CL grades are manufactured using a type of NaCMC having a viscosity ranging from 300 to 600 mPa.s (2% dispersion) and a degree of substitution of 0.75 ± 0.15 [15]. Table 1 shows the composition of the pellet formulations. A pellet formulation was selected for enteric coating if at least 75% of the total drug amount was released within 45 min in phosphate buffer, pH 6.8.

2.2.2. Coating of the pellets

As the final goal of the project was to compress the enteric-coated pellets into a fast disintegrating tablet with-

Table 2
Coating conditions

Coating process parameters	Set values
Product load (g)	750 g
Nozzle diameter (mm)	1.2
Spraying rate (g/min)	3.5–4.5
Atomizing air pressure (bar)	1.5
Inlet air temperature (°C)	35–45
Outlet (bed) temperature (°C)	26–28

out damaging the film coat during compression, the pellets were coated with a flexible polymer film consisting of Eudragit L 30 D-55 and FS 30 D (ratio 6:4) using the bottom-spray technique with the Wurster setup (Uniglatt, Glatt, Binzen, Germany). The coating conditions are shown in Table 2. The pellets were preheated for 5 min at an outlet temperature of 26–28 °C. Both aqueous Eudragit dispersions were mixed by means of a magnetic stirrer. The excipient dispersion was prepared separately: water, triethyl citrate (plasticizer) and polysorbate 80 (used to disperse glyceryl monostearate) were homogenized with a rotor-stator mixer (Silverson, Bucks, UK) for 10 min, after which glyceryl monostearate (anti-adhesive) was added. The excipient dispersion was added to the Eudragit mixture and stirred gently for 30 min with a magnetic stirrer. Upon complete coating, the pellets were dried for 10 min at 26–28 °C. Afterwards the pellets were cured on trays for 48 h at room temperature. At least 10% dry polymer substance was applied to obtain a gastroresistant effect.

2.2.3. Pellet evaluation

The USP general drug release standard for delayed release dosage forms specifies that enteric-coated formulations should withstand 0.1 N HCl for 2 h after which no more than 10% of the total drug amount should be released. After transferring the formulation to a pH 6.8 phosphate buffer the drug should be released according to the specifications in the monographs. Usually at least 75% drug release after 45 min is required. Dissolution tests, according to the USP (XXIV) paddle method, were carried out on uncoated (in pH 6.8 phosphate buffer (PB)) and on enteric-coated pellets (in 0.1 N HCl and pH 6.8 PB) using a paddle speed of 100 rpm (Van Kel, Edison, NJ, USA). Five-millilitre samples were taken from the dissolution medium over a period of 2.5 h. At each sampling point an amount of blank dissolution medium equal to the sample volume was added to the dissolution vessel. The concentration of piroxicam at each sampling point was measured spectrophotometrically at 333 and 353 nm for the 0.1 N HCl and PB pH 6.8 samples, respectively. As sink conditions are required during dissolution testing, the drug concentration should not exceed 10% of its saturation solubility [16]. The maximum solubility of piroxicam in both dissolution media was determined from saturated piroxicam solutions prepared by stirring a drug suspension for 48 h on a magnetic stirrer. After filtration the piroxicam concentration in the supernatant was determined spectrophotometrically (Lambda 12, Perkin Elmer, Norwalk, CT, USA) at 333 and 353 nm for 0.1 N HCl and PB pH 6.8 samples, respectively.

The pellets were stored for 7 months under controlled conditions (25 °C/60% relative humidity (RH) and at 40 °C/75% RH) to evaluate their stability. Immediately after production and after 1, 3, 5 and 7 months of storage the water content (Karl Fischer titrator, DL 35, Mettler-Toledo, Beersel, Belgium) and dissolution profiles were determined.

2.3. Tablet formulation and evaluation

To protect the enteric coating during compaction soft placebo wax beads, consisting of Paracera P/DDCS/Kollidon CL (50:33.3:16.7; w/w/w) and ranging from 800 to 1250 μm, were used as cushioning agents and were prepared as described by Vergote et al. [17]. To enhance the tablet disintegration sodium croscarmellose (Ac-Di-Sol), sodium carboxymethyl starch (Explotab) and cross-linked PVP (Kollidon CL) were added in concentrations up to 10% (w/w) of the tablet mass. Disintegrant pellets consisting of Kollidon CL (25 and 50%) and MCC were prepared by extrusion–spheronization and used as disintegrant in the tablets. The coated pellets and cushioning beads (40:60) were mixed for 10 min with a Turbula mixer (W.A. Bachofen Maschinenfabrik, Basel, Switzerland). The disintegrant powder or pellets were added and the mixture was mixed for another 5 min. For each tablet 600 mg of the pellet blend was weighed and manually filled into the die of a compaction simulator (Puuman, Kuopio, Finland). Flat punches with 12 mm diameter were used and the compression force ranged from 10 to 30 kN. The punches were powdered with magnesium stearate (Alpha Pharma, Eke, Belgium) to avoid adhesion of the tablets. The resulting tablet thickness was 4.40 ± 0.10 mm. Tablet disintegration and drug release from the tablets was evaluated in 0.1 N HCl and in PB pH 6.8 by means of a disintegration apparatus (Pharma Test, Hainburg, Germany) and the USP dissolution testing apparatus 2, respectively. The release profiles of the tablets were compared with the drug release from the enteric-coated pellets to detect film damage during compression. Other tablet properties determined included friability (friabilator type PTF E, Pharma test, Hainburg, Germany) and diametrical crushing strength (hardness tester PTB 311, Pharma test, Hainburg, Germany).

3. Results and discussion

From the solubility tests, maximum solubility values of 43.8 and 112.5 μg/ml in 0.1 N HCl and PB pH 6.8, respectively, were calculated. To maintain sink conditions during dissolution testing, the sample size for dissolution testing was set at 72 mg of pellets in each vessel, equivalent to 1.8 mg piroxicam.

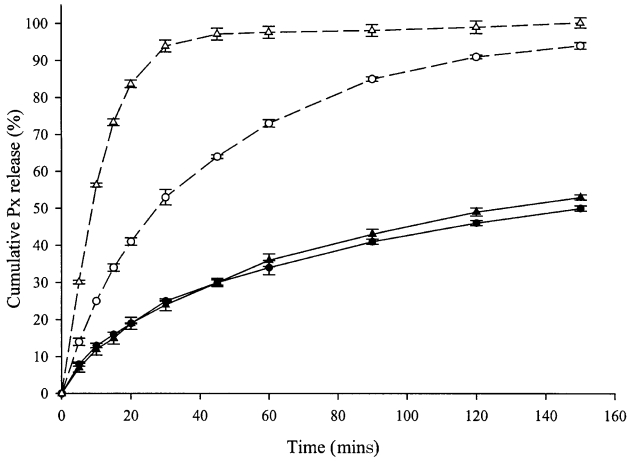

Fig. 1. Influence of disintegrants on the release profiles in phosphate buffer (pH 6.8) of piroxicam pellet formulations A (●), B (○), C (▲) and D (△).

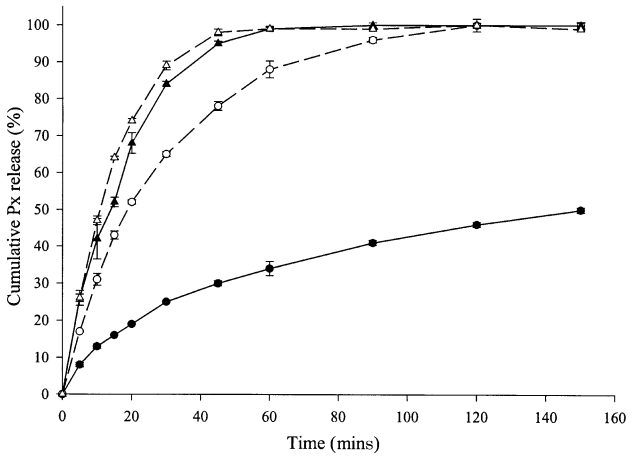

Fig. 3. Influence of Avicel® CL 611 grade on the release profiles in phosphate buffer (pH 6.8) of piroxicam pellet formulations A (●), H (○), I (▲) and J (△).

As the development of enteric-coated pellets for the administration of piroxicam to small animals was considered as a tool to reduce gastrointestinal discomfort caused by direct contact of the drug with the mucosa and as microcrystalline cellulose (MCC) is well established as an excellent excipient for extrusion–spheronization, the initial pellet formulation consisted only of drug (2.5%, w/w) and microcrystalline cellulose (Avicel PH 101). However, the release of piroxicam from these pellets was too slow, within 45 min only 30 and 20% of the drug was released in PB pH 6.8 and 0.1 N HCl, respectively. Because neither swelling nor erosion of the microcrystalline cellulose pellet matrix was observed in either of the dissolution media, the authors concluded that piroxicam release was mainly a diffusion-controlled process. Therefore a disintegrant was included in the formulation to improve water penetration in the matrix and to increase the extent and the rate of swelling of the pellets. Fig. 1 shows that the incorporation of highly hydrophilic but insoluble super disintegrants [18] such as sodium croscarmellose (Ac-Di-Sol) did not influence the dissolution rate, while sodium carboxymethyl starch (Explotab) doubled the amount of piroxicam released within 45 min from 30 to 65%. However, none of the formulations disintegrated or released at least 75% piroxicam within 45 min in PB pH 6.8. Although sodium carboxymethyl cellulose (NaCMC) is water soluble and probably exhibits less pronounced disintegration properties than the cross-linked NaCMC, a formulation with 11% (w/w) NaCMC was found to release nearly its entire piroxicam content within 45 min. This was attributed to the fact that these pellets disintegrated within 15 min in PB pH 6.8. Instead of preparing a physical mixture of MCC and NaCMC, co-processed MCC/NaCMC blends (Avicel RC 581 and CL 611) were used for pelletization. The influence of the Avicel PH 101/RC 581 and CL 611 ratio, and thus of varying amounts of NaCMC, on the dissolution behavior of piroxicam was investigated. The results (Figs. 2 and 3) show that a combination of Avicel PH 101 and Avicel RC 581 or CL 611, increased the dissolution rate of piroxicam in PB from 30% release within 45 min to 60 and 80%, respectively, for the 1:1 blend ratios, and to 70 and 95%, respectively, for the 1:3 blend ratios. Although it has been reported by some authors that MCC–NaCMC blends decreased the drug release rate from pellets due to the swelling of the pellets [19], the Avicel CL 611 formulations were observed to be superior to the ones based on Avicel RC 581. The higher NaCMC concentration in the Avicel CL 611 pellets increased the swelling capacity of and the water uptake into the pellet matrix and in this way enhancing the dissolution rate of piroxicam. Piroxicam pellets containing only Avicel RC 581 or CL 611 were observed to enhance the drug release even more (Figs. 2 and 3), but the extrusion process was hindered due to material sticking to the screw and to clogging of the die perforations. Therefore the use of this formulation was limited by manufacturing difficulties. Pellets containing Avicel PH 101 and CL 611 in a ratio of 1:3 (equivalent to a NaCMC

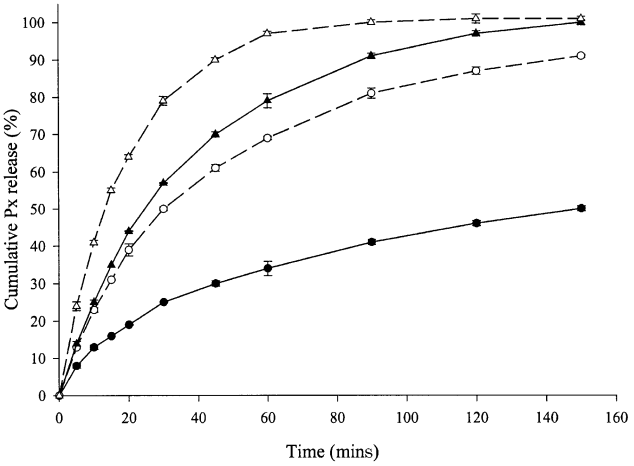

Fig. 2. Influence of Avicel RC 581 grade on the release profiles in phosphate buffer (pH 6.8) of piroxicam pellet formulations A (●), E (○), F (▲) and G (△).

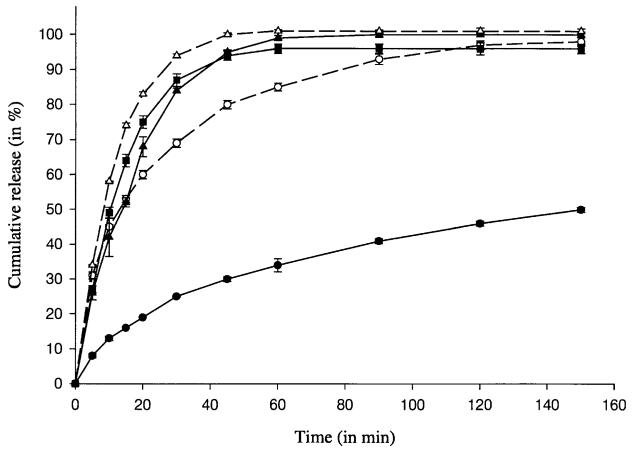

Fig. 4. Influence of cyclodextrins on the release profiles in phosphate buffer (pH 6.8) of piroxicam pellet formulations A (●), K (○), I (▲), L (△) and M (■).

concentration of 11% (w/w)) had a piroxicam release similar to the Blanose formulation, however they did not disintegrate. This is probably due to the manufacturing process of the co-processed material during which hydrogen bonds are formed between the unsubstituted hydroxyl groups of NaCMC and the individual cellulose microcrystals which prevent the disintegration of the pellets after water uptake [15].

To enhance the solubility and thus the dissolution rate of poorly water-soluble drugs, non-covalent molecular inclusion complexes between the drug, e.g. piroxicam and cyclodextrins (CD) can be formed, resulting in solubilization of the drug [12]. However, relatively large amounts of cyclodextrins are required to complex small amounts of piroxicam (typically a 1:2.5 molar ratio of piroxicam to β-CD). As complexation efficiency might be increased by the addition of compounds such as water-soluble polymers [10], pellets containing cyclodextrin derivatives were combined with Avicel CL 611 (Fig. 4).

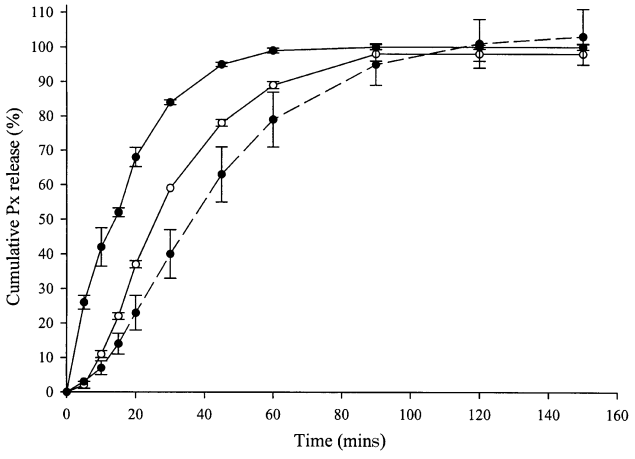

Fig. 5. Influence of coating and compaction on the release profiles in phosphate buffer (pH 6.8) of piroxicam pellets I with Avicel PH 101/CL 611 (ratio 1:3, w/w) uncoated (—●—), coated (—○—), compressed (- -●- -).

It can be concluded from Fig. 4 that the addition of 20% (w/w) hydroxypropyl-β-cyclodextrin (HP-β-CD) (1:2.5 molar concentration) to the pellets based on Avicel PH 101 increased the release from 30 to 80% after 45 min; however, the release from this formulation was similar to that from the formulation based on a mixture of Avicel PH 101 and CL 611 (ratio 1:3) and therefore offered no advantages. Combining HP-β-CD (20%, w/w) with a mixture of Avicel PH 101 and CL 611 (ratio 1:3) did not improve the release rate dramatically (from 95 to 100% after 45 min), hence the use of HP-β-CD did not offer any additional advantage to improve the dissolution profile. The influence of β-CD on the dissolution rate of piroxicam was less pronounced compared with HP-β-CD and can be explained by the lower water solubility of β-CD.

Based on the formulation study and the in vitro release profiles, pellets combining Avicel PH 101 and CL 611 in a ratio of 1:3 were selected for enteric coating with Eudragit L 30 D-55/FS 30 D (60/40). No release of piroxicam from the coated pellets was detected after 2 h dissolution testing in 0.1 N HCl, indicating that the coating applied to the pellets was gastroresistant. When the pellets were tested in PB the release from the coated pellets fulfilled the requirement of at least 75% piroxicam released within 45 min (Fig. 5).

After storage of the enteric-coated pellets for 7 months at 40 °C and 75% RH agglomeration of the individual pellets was observed, yielding a pellet cake. As the water content increased from 2 to 4% during the stability test, this agglomeration process is probably due to the plasticizing effect of water [20,21] in the polymer film, decreasing the minimum film-forming temperature and increasing the tackiness of the film [22,23]. Similar agglomeration phenomena of pellets coated with acrylic and cellulosic polymer films have been described [20,22,24] following their storage at elevated temperature and high relative humidity. Storage for 7 months at 25 °C and 60% RH did not significantly affect the piroxicam release in PB pH 6.8.

In the final part of the study it was attempted to formulate the enteric-coated pellets into fast disintegrating tablets [25]. In addition to the flexible coat that was applied to the pellets, placebo cushioning beads (ratio piroxicam pellets/cushioning beads 60:40) were added to the tablet formulation with the aim of minimizing damage to the film coat due to compaction. However, such tablets were still intact after 1 h in the disintegration apparatus and they did not disintegrate during the entire dissolution test (Table 3). Therefore disintegrants such as sodium croscarmellose and sodium carboxymethyl starch were added to the tablet, however, they did not affect the disintegration properties of the tablets in 0.1 N HCl, due to the limited swelling properties of these anionic components in acid media. Using 10% (w/w) cross-linked PVP (Kollidon CL) reduced the disintegration time of the tablets markedly and resulted in tablets with a low friability and a hardness of approximately 30 N.

Table 3
Influence of Kollidon CL powder and pellets on the disintegration properties of the tablets

	Disintegrant	Hardness (N)	Disintegration time (min)
	None	24.3 ± 3.6	> 60
Powder	Kollidon CL 2%	20.9 ± 2.6	> 60
	Kollidon CL 5%	24.0 ± 3.1	16
	Kollidon CL 7.5%	25.3 ± 3.5	12
	Kollidon CL 10%	25.2 ± 6.3	3
Pellets	Kollidon CL 25%	18.8 ± 4.0	30
	Kollidon CL 50%	19.1 ± 2.1	30

When tested in 0.1 N HCl these tablets disintegrated within 15 min and since less than 1% of the drug was released from the tablets within 120 min, it was concluded that the film coat was not damaged during compression. A similar piroxicam release was obtained in PB pH 6.8 from the tablets compared with the coated pellets in PB pH 6.8. To avoid segregation problems the disintegrant Kollidon CL added in powder form was replaced by disintegrant pellets (Kollidon CL/MCC; 25:75 and 50:50) but the resulting tablets showed longer disintegration times (Table 3). From our study it could be concluded that compaction of enteric-coated pellets, waxy cushioning beads and external disintegrant (Kollidon CL powder, 10%; w/w) resulted in tablets rapidly disintegrating in 0.1 N HCl while retaining the gastroresistant properties of the coated pellets.

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