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Artículo Original

Design and development of oral controlled release microcapsules containing naproxen

DOMINGOS FERREIRA,[A] BRUNO SARMENTO,[A] HELENA AMARAL,[A *] FRANCISCO VEIGA,[B] AND JOSÉ MANUEL SOUSA LOBO[A]

[(a)] *Faculty of Pharmacy, University of Oporto, Rua Aníbal Cunha, 164, 4050-047 Porto, Portugal*

[(b)] *Faculty of Pharmacy, University of Coimbra, Rua do Norte, 3000 Coimbra, Portugal.*

ABSTRACT

The aim of this work was to prepare microcapsules containing naproxen that could be used in the preparation of oral controlled released forms. The work consisted on the preparation of microcapsules by the solvent evaporation method. Different batches were prepared, in the first step, using different polymers (Eudragit RLPO and Eudragit RSPM) or mixtures of these polymers (Eudragit RLPO/Eudragit RSPM 1/3, 2/2 and 3/1) and, in second step, using Eudragit RLPO and 5% of Cutina (HR, KD 16 and MD). The film-forming properties of polymers and different types of Cutina were examined and the physicochemical factors that influence drug release from the films were studied. The evaluation of the release rate of these preparations was performed in pH 7.4 phosphate buffer solution, during 12 hours. The release studies of naproxen preparations demonstrated differences in the drug release properties depending on the polymer or the content of the polymer in the mixtures and also on the type of Cutina.

Key words: Microcapsules.— Naproxen.— Oral controlled release.

RESUMEN

Diseño y desarrollo de microcapsulas orales de liberación controlada de naproxeno

El objetivo de este trabajo fue preparar micro cápsulas de naproxeno que puedan ser usadas en la preparación de formas orales de libertación controlada.

Las microcápsulas fueron preparadas por el método de la evaporación del solvente. Diferentes lotes fueron preparados, primero usando diferentes polimeros (Eudragit RLPO y Eudragit RSPM) o mezclas de polímeros (Eudragit RLPO/Eudragit RSPM 1/3,2/2 y 3/1) y después usando Eudragit RLPO y 5% de Cutina (HR, KD 16 y MD).

Las propiedades de formación de películas por los polímeros y las diferentes cutinas fueron estudiadas bien como los fatores fisico-quimicos que influencian la libertación del naproxeno por las películas.

El perfil de libertación del naproxeno en las diferentes formulaciones preparadas, fue estudiado en tampón de fosfatos a pH 7.4, durante 12 h.

Los estudios de libertación del naproxeno en las diferentes formulaciones demostraran diferencias en las propiedades de libertación del naproxeno, dependiendo del polimero utilizado, del contenido de las mezclas y del tipo de cutina usados.

Palabras-clave: Micro cápsulas.— Naproxeno.— Libertación oral controlada.

INTRODUCTION

Several drugs, have been microencapsulated to reduce gastric and other gastrointestinal tract irritations including indomethacin (1), aspirin (2) and biphenylylacetic acid (3). In addition, most of the orally administered acidic non-steroidal anti-inflammatory drugs are irritant to the gastric mucosa if taken for a prolonged period of time (4).

Naproxen, a non-steroidal anti-inflammatory agent with anti-inflammatory, analgesic and antipyretic properties, practically insoluble in water and freely soluble in alcohol, was selected since the drug exhibits all the required pharmacokinetic and physicochemical properties, which make it a good candidate to be incorporated in a controlled release dosage form (5).

Polyacrylate-polymethacrylate copolymers (Eudragits) are widely used as tablet adjuvants and coating polymers. These polyacrylate polymers were also used for drug microencapsulation as microcapsule

wall materials. In fact, acrylate polymers and their derivates, collectively known as Eudragit polymers, origin films with excellent strength and good flexibility and aesthetics (6-9).

The two acrylic resins evaluated in this study included Eudragit RLPO and RSPM. The RL and RS acrylic resins are copolymers synthesised from acrylic and methacrylic acid esters with a low content of quaternary ammonium groups as chloride salts. The swelling capacity and the permeability to water and dissolved drugs were defined, which is pH independent. The RL resin is freely permeable whereas the RS resin is slightly permeable to water.

The three different types of Cutina, used as plasticizers, evaluated in this study included Cutina HR (Castor oil, hardened), KD 16 (self-emulsifying mixture of mono- and diglycerides of higher saturated fatty acids and potassium stearate) and MD (mixture of mono- and diglycerides of palmitic and stearic acid).

The aim of this work was to prepare microcapsules containing naproxen that could be used in the preparation of oral controlled release forms. The work consisted on the preparation of microcapsules by the solvent evaporation process. Different batches were prepared using two polymers or mixtures of polymers and adding three types of Cutina. The film-forming properties of polymers were examined and the physico-chemical factors that influence drug release from the films were studied.

EXPERIMENTAL

Materials

Naproxen was kindly supplied by Janssen Cilag and Eudragit RS PM and RL PO by Rohm Pharma GmbH. The different types of Cutina were purchased from Henkel. All other materials and solvents were of analytical reagent grade.

Preparation of naproxen microcapsules

After preliminary studies, the following optimal experimental conditions were chosen for the preparation of naproxen microcapsules on a dissolution apparatus (paddle method). Liquid paraffin (300 ml) was placed on a vessel at 37ºC. A solution containing 0.75 g of naproxen, 2.5 g of polymer or mixtures of polymers, 0.0625 g of Cutina and 0.125 g of magnesium stearate in 60 ml of acetone was added to paraffin through a separating funnel. The mixture was stirred at 200 rpm. The resulting emulsion was agitated at 37ºC for 4 h and during this time acetone was evaporated. The resultant microcapsules were isolated by filtration, washed with cyclohexan and dried at room temperature for 12 h.

The empty microcapsules were prepared using identical experimental conditions but in the absence of naproxen.

The prepared formulations are shown in Table 1.

Table 1. Naproxen microcapsules formulations prepared by the solvent evaporation process.

	Formulations							
Components	A	B	C	D	E	F	G	H
Naproxen	0.750	0.750	0.750	0.750	0.750	0.750	0.750	0.750
Eudragit RS PM	2.500	1.875	1.250	0.625	-	-	-	-
Eudragit RL PO	-	0.625	1.250	1.875	2.500	2.500	2.500	2.500
Cutina (0.0625 g)	-	-	-	-	-	HR	KD 16	MD
Magnesium Stearate	0.125	0.125	0.125	0.125	0.125	0.125	0.125	0.125

Naproxen content

Naproxen microcapsules were weighed, dissolved in chloroform and filtered. Naproxen was assayed by UV analysis using a calibration curve at 331 nm.

Microscopy studies and particle size distribution

Optical microscopy was used to evaluate the drug incorporation and the surface shape of the microcapsules. Particle size was determined by optical microscopy. Samples of microcapsules (200) were dispersed on a slide and its diameter was evaluated. The microcapsules particle size distribution was also evaluated by sieving.

Differential scanning calorimetry

Differential thermal analysis (heating cycles of 25ºC-280ºC) of pure naproxen, empty Eudragit and empty Eudragit/Cutina microcapsules, Eudragit and Eudragit/Cutina microcapsules containing naproxen, mechanical mixtures of naproxen, Eudragit, Cutina and magnesium stearate was carried out with a computer-interfaced Shimadzu differential scanning calorimeter, Model DSC-50. The samples (2.6-2.8 mg), which were stored in a desicator prior to the analysis, were sealed in aluminum pans. The scanning rate throughout the investigation was 10ºC/min. All tests were run in triplicate and the DSC cells were purged with nitrogen at 20.0 ml/min.

Release studies

The dissolution test was carried out using the European Pharmacopoeia apparatus at a basket speed of 100 rpm. The dissolution medium was 500 ml of a pH 7.4 phosphate buffer solution, maintained at 37ºC ± 0.5ºC. At appropriate time intervals (30, 60, 120, 240, 360, 480 and 480 min), 25 ml of each was withdrawn and equal volume of medium was added to maintain a constant volume. Samples were filtered, diluted and analysed by UV spectophotometry at 331 nm on a Hitachi 2000 spectrophotometer.

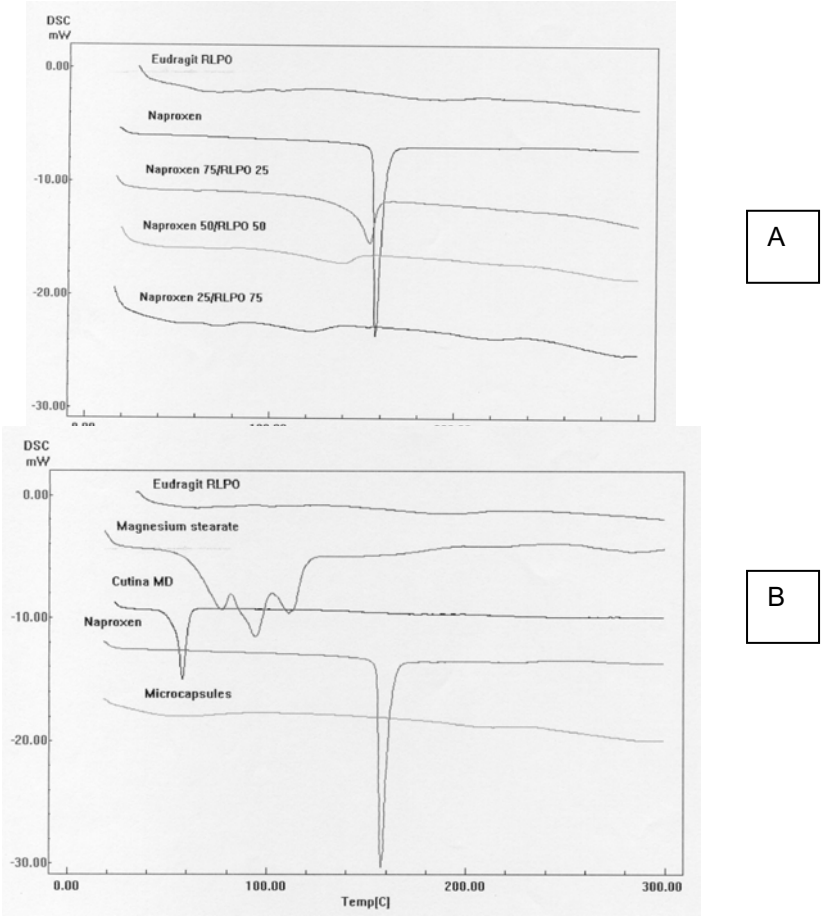
RESULTS AND DISCUSSION

The microcapsules loading of naproxen was theoretically calculated and the intended value was 22.2%. The naproxen content of the microcapsules varied from 14.8% to 15.3 % for microcapsules containing polymer. However, when the microcapsules included plasticizers the naproxen content was between 15.9% and 16.8%, as it can be seen in Table 2.

Table 2. Naproxen loading of the microcapsules.

Formulations	Loading (%)
A	14.8
B	15.2
C	14.8
D	15.3
E	14.9
F	16.8
G	16.1
H	15.9

Figure 1. DSC scans of pure naproxen, Eudragit RL PO microcapsules containing naproxen, Cutina MD and magnesium stearate (A), pure naproxen, mechanicals mixtures of naproxen and Eudragit RL PO (B) at heating rate of 10ºC/min.

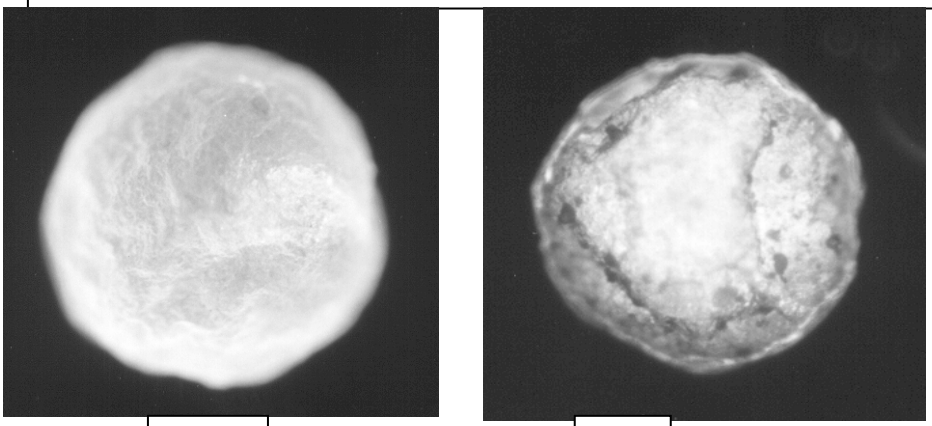


The differential scanning calorimetry (DSC) analysis (Figure 1) showed that there were no thermal events during the examination of

empty microcapsules. However, in the case of the melting phase transition of pure naproxen, a sharp endotherm was observed at approximately 155ºC corresponding exactly to the melting point of naproxen. To shed further light on the nature of Eudragit-naproxen interaction, different mechanical mixtures were prepared and examined by DSC. When the naproxen content in the mixtures was decreased, the peak at 155ºC decreased and became negligible at approximately 50% naproxen. When the microcapsules naproxen content was about 15%, the thermal behaviour of naproxen microcapsules was similar to the observed with pure Eudragit, as the peak at 155ºC became negligible.

The microscopic analysis of microcapsules containing naproxen revealed its spherical shape. As it can be observed in Figure 2, the morphological examination of the microcapsules, performed at the beginning and at different times of the release study by optical microscopy, showed that the products were homogeneous with corrugated surfaces and pores. Higher magnification revealed surface shrinkage. After dissolution test the microcapsules did not change in shape, which suggests that naproxen diffused out through the minor pores and channels.

Figure 2. Scanning optical micrograph of naproxen microcapsules before (A) and after (B) dissolution test.



The results obtained in the sieving evaluation of the microcapsules particle size distribution are shown in Table 3. It is possible to verify that all batches presented a similar and regular size distribution.

Table 3. Microcapsules size distribution (%).

Characteristics	Formulations							
(μm)	A	B	C	D	E	F	G	H
1000-1250	36	31	30	28	22	25	31	41
710-1000	50	49	45	50	53	15	36	16
520-710	14	20	21	18	21	21	27	28
250 - 520	-	-	4	3	2	32	5	12
< 250	-	-	-	1	2	7	1	3

The naproxen release profiles from the eight different microcapsules formulations are shown in Figure 3 and 4. The drug release profiles were plotted against time and some mathematical models (Zero-order, First-order and Higuchi Law) were applied.

Figure 3. Release profiles of A (RS PM), B (RL PO), C (RS PM/RL PO 75/25), D (RS PM/RL PO 50/50) and E (RS PM/RL PO 25/75) formulations.

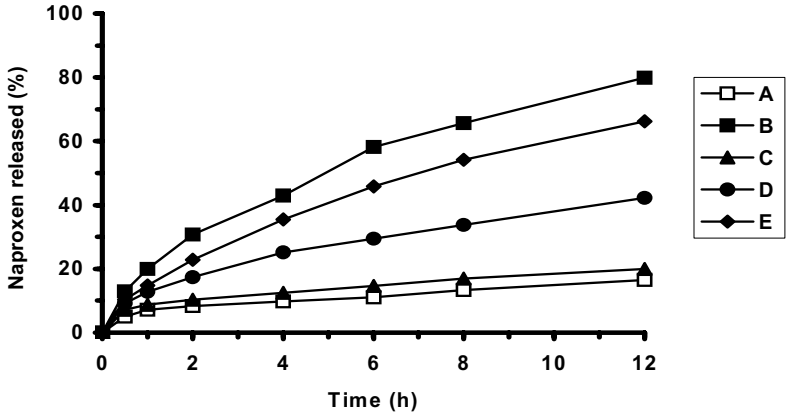
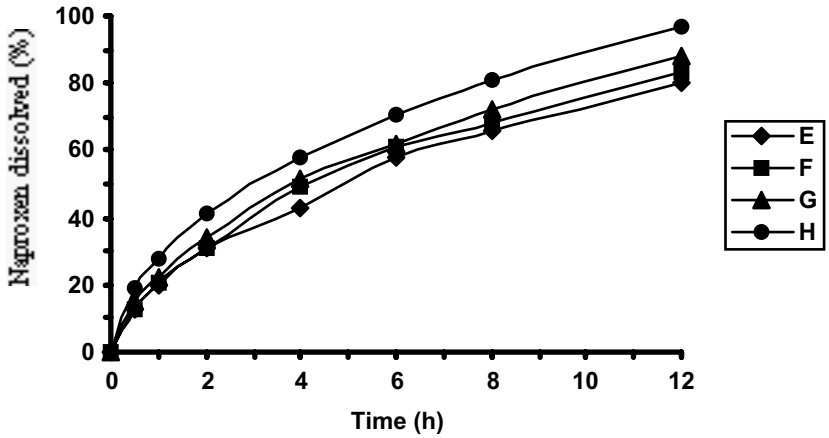


Figure 4. Release profiles of E (RL PO), F (RL PO/Cutina HR), G (RL PO/Cutina KD 16) and D (RL PO/Cutina MD) formulations.



The results obtained in the release studies are shown in Table 4. It is possible to observe that the release kinetics from the microcapsules containing naproxen followed the Higuchi equation up to 79.9% of the cumulative drug release.

As expected, a higher release rate was obtained when the Eudragit RS PM content decreased or when Eudragit RL PO increased. When 0%, 25%, 50%, 75% and 100% of Eudragit RS PM was incorporated into the formulations, the amount of released naproxen decreased to 79.9%, 66.3%, 42.2%, 19.9% and 16.5% after 12 h, respectively.

Table 4. Values of kinetic constant (k), y-intercept (b) and correlation coefficient (R^2) following linear regression of release studies.

		Formulations							
		A	B	C	D	E	D	E	F
Zero-order	k	0.913	5.795	1.076	2.790	4.761	6.085	6.329	6.670
	b	5.830	16.609	7.735	10.930	13.740	17.402	18.966	24.418
	R^2	0.969	0.956	0.979	0.965	0.950	0.947	0.955	0.950
First-order	k	0.089	0.144	0.083	0.121	0.146	0.147	0.142	0.129
	b	1.828	2.930	2.101	2.488	2.722	2.959	3.050	3.278
	R^2	0.883	0.823	0.920	0.855	0.796	0.807	0.818	0.823
Higuchi	k	3.814	24.654	4.519	11.826	20.272	26.018	26.968	28.487
	b	2.644	- 4.484	3.934	0.864	- 3.619	4.999	-4.154	-0.075
	R^2	0.975	0.997	0.994	0.998	0.992	0.997	0.999	0.998

According to the release studies results obtained, Eudragit RSPM microcapsules showed a naproxen release lower than Eudragit RLPO microcapsules. These results suggest that the nature of the polymer has a significant effect on the release rate of naproxen when incorporated into these microcapsules formulations. Therefore, the preliminary results suggest that in the experimental conditions and with the polymers used in the present study, it is possible to prepare microcapsules for an oral controlled release form of naproxen.

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