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Research Article

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A Ciprofloxacin Extended Release Tablet Based on Swellable Drug Polyelectrolyte Matrices

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Abstract. The aim of this work was the development of extended release tablets of 500 mg of ciprofloxacin based on swellable drug polyelectrolyte matrices (SDPM). A set of complexes of carbomer, ciprofloxacin and sodium, $(CB–Cip)_{50}Na_x$, having a molar ratio Cip/CB acid groups of 0.5 and variable proportions of Na^+ was used to prepare SDPM. Characterization of complexes by FT-IR, powder X-ray diffraction and thermal analysis revealed that Cip, in its protonated form, is ionically bonded to the functional groups of CB. Rates of fluid uptake of $(CB–Cip)_{50}Na_x$ matrices as well as Cip release in simulated gastric fluid were modulated by changes in the proportion of Na^+ incorporated in the complexes. A direct correlation between fluid uptake and delivery rate was observed along the series of matrices. Release rates were modulated from 1.4 mg/min to 25 mg/min in going from $(CB–Cip)_{50}Na_{10}$ to $(CB–Cip)_{50}Na_{14}$. The analysis of kinetic data suggest that rates of swelling, ionic pair dissociation and drug diffusion play a role in the kinetic control of delivery. Complexes were satisfactorily prepared and processed together with small amounts of antiadherent and lubricant excipients to obtain a series of extended release SDPM tablets through the current tableting technology processes. Cip release from matrices was widely modulated by the composition of the complexes yielding a flexible system that allows selecting a composition that releases in 120 min 90% of the dose in simulated gastric fluid.

KEY WORDS: ciprofloxacin; extended release; swellable drug–polyelectrolyte matrices.

INTRODUCTION

Many controlled drug delivery systems have been introduced in pharmacotherapy along time exhibiting a number of advantages over conventional dosage forms. A great proportion of research on this subject deals with oral drug delivery systems. In this area, swellable hydrophilic matrices have attracted the attention of many authors in recent years (1–3). These matrices are monolithic systems having one or more powdered drugs homogeneously dispersed in a hydrophilic polymeric matrix (4).

In this field, the delivery properties of novel swellable drug polyelectrolyte matrices (SDPM) obtained by compaction of powdered complexes of a polyelectrolyte (PE) fully or partially neutralized with an ionizable drug (D) (5–7) have been evaluated. Unlike other swellable hydrophilic matrices, SDPM's contain a molecular dispersion of D in the mass of the matrix since D is ionically bonded to the functional groups of PE as a PE-D complex.

In the same way as it has been described for conventional hydrophilic matrices, (4) the external surface of a SDPM in contact with an aqueous medium is quickly wetted and swollen, developing a hydrogel layer that acts as a barrier between the external medium and the unwetted portion of the matrix.

In the early works concerning with SDPM, carbomer (5) (CB) and alginic acid (6) (AA) were used as acid PEs that were loaded with model D possessing an appropriate basic group such as atenolol, metoclopramide and lidocaine. In CB based SDPM, the main mechanism of delivery is the diffusion of the free D arising from the dissociation of ionic pairs CB-D in the hydrogel layer (5). In contrast, in AA based SDPM the erosion of the hydrogel layer is the main delivery route (6). In such works, the delivery properties of SDPM were characterized using PE-D complexes as the unique component of the matrices. In this work, matrices were processed by the current tablet technology; therefore, appropriate excipients were added to optimize the tableting process. In this way, the aim of this article is the development of an extended release tablet containing 500 mg ciprofloxacin (Cip) (Fig. 1), based on CB–Cip complexes. This antimicrobial fluoroquinolone was selected because the properties of hydrogels of CB–Cip were previously evaluated (8). In such hydrogels, a high degree of counterionic condensation is generated by the acid base reaction between the carboxylic groups of CB and the aliphatic piperazine nitrogen of Cip. Besides, two extended release tablets of Cip have been recently introduced in therapeutic, (9–11) which is indicative about the interest on this kind of systems.

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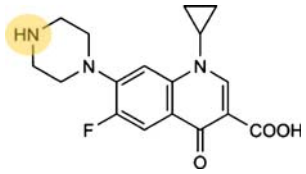


Fig. 1. Structural formula of ciprofloxacin

MATERIALS AND METHODS

MATERIALS

The following materials were used: carbomer 934-P (Carbopol® 934-P NF, kindly supplied by BFGoodrich, Cleveland, OH). Cip (mp: 269.9) obtained by neutralization of a Cip hydrochloride (Parafarm®, USP grade, Bs.As., Arg.) solution with NaOH 1 N. The precipitate was washed, filtered and dried to constant weight. Talc NF (Parafarm®, Bs.As., Arg.) and magnesium stearate NF (Parafarm®, Bs.As., Arg.). CIPRO XR® 500 extended release tablets commercialized in Argentina (Bach: 7100D, Bayer AG, Bs.As., Arg.). KH_2PO_4 p.a. (Anedra®, Bs.As., Arg.), NaCl p.a. (Parafarm®, Bs.As., Arg.), NaOH (Anedra®, Bs.As., Arg.), HCl conc. soln. (Anedra®, Bs.As., Arg.), ethanol (Porta®, Córdoba, Arg.).

Preparation of Complexes and Physical Mixtures

Complexes in solid state were prepared by mixing in a mortar 10 g of CB (12.0 meq/g as determined by NaOH titration) with 6.65 g of Cip and the appropriate volume of ethanol to get a semisolid paste of $(CB–Cip)_{50}$. The subscript means that 50% of carboxylic groups of CB were neutralized with Cip. Additionally, appropriate amounts of NaOH 1.0 N were added during the mixing process to obtain a series of $(CB–Cip)_{50}Na_x$ complexes, in which x refers to the mole percent of Na^+ incorporated (x=5.0, 10.0, 12.0, 12.25, 12.50, 13.0, 14.0, 20.0 and 30.0). The mixture was kept for about 12 h at room temperature and then processed according to Scheme 1 using two ways to obtain either granules or dry particles. In both cases the products were dried at 70 °C to constant weight. Loss of weight of dry complexes, determined by thermogravimetric analysis, was in the range of 6.0–7.0% (water content). Complexes obtained either as powder or granules were sieved to select particle sizes in the range 212–425 μm to be further compacted.

Physical mixtures were prepared by mixing in a mortar Cip and CB in the same proportion used to obtain the complex.

Spectroscopic and Thermal Characterization

Complexes were characterized using:

FT-infrared spectroscopy (Avatar 360, ESP-Nicolette) of complex samples dispersed at 1.5% in KBr discs.

Powder X-ray diffraction (Rigaku Miniflex Diffractmeter) equipped with specific software (Standard monitoring 3.2) operated in scan mode over 3 to 70° $2\theta/\theta$ and scan speed of 0.066° 2θ/s.

Differential scanning calorimetry (Modulated-DSC 2920, TA-Instruments, USA) and Thermogravimetric analysis (Hi-Res-TGA 2950, TA-Instruments, USA) equipped with Universal analysis NT specific software. Samples of approximately 2 mg were heated under nitrogen atmosphere in non-hermetic aluminum pans from room temperature to 300 °C at 10 °C/min as well as Cip and CB alone and physical mixtures.

Preformulation

Preparation of Complex Matrices

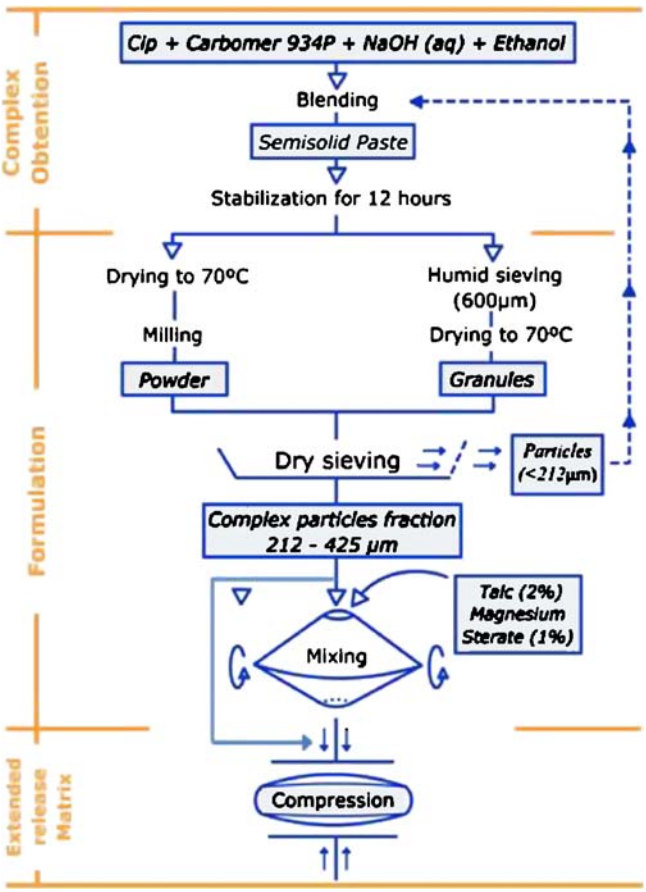
A series of matrices were prepared by compacting 200 mg of each $(CB–Cip)_{50}Na_x$ complex at 1.5 tons by 10 s using a hydraulic press equipped with flat punch and matrix of 12.8 mm in diameter. These matrices, constituted by complexes as unique components, were used to obtain both fluid uptake and delivery profiles.

Fluid Uptake

Sorption kinetics of USP-simulated gastric fluid from SDPM's were determined using the Enslin's apparatus described by Nogami *et al.* (12) which was adapted as described by Llabot *et al.* (13)

Flow Properties

The angle of repose (α) was determined as $tg(\alpha)=h/r$ where h and r are respectively height and base radius of the



Scheme 1. Procedure to prepare extended release tablets of $(CB–Cip)_x–Na_x$ complexes

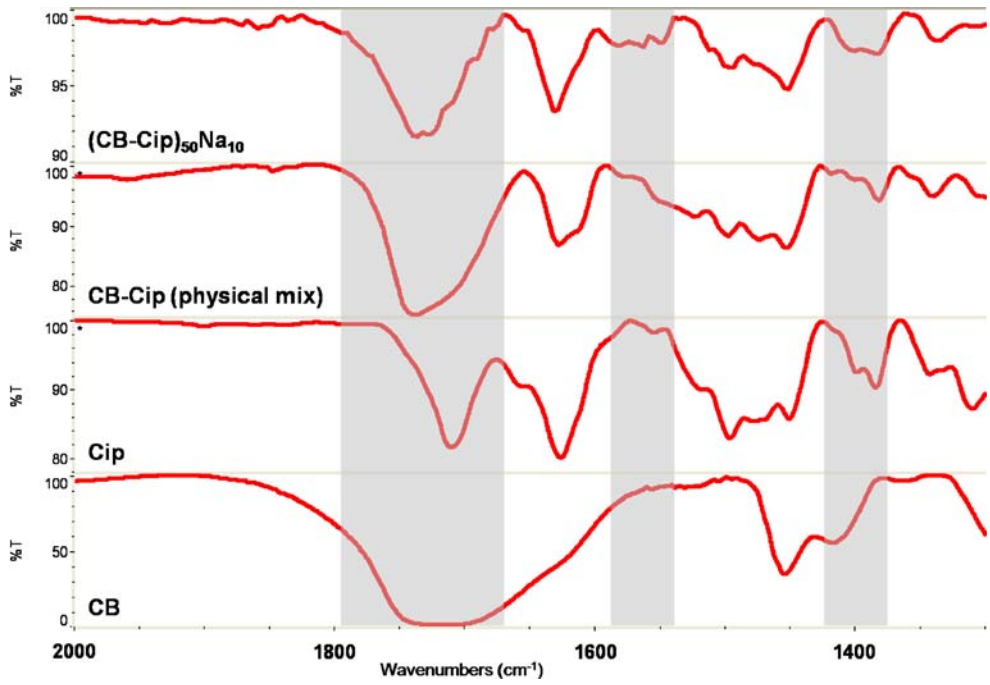


Fig. 2. FT-IR spectra of solid samples

cone formed by the particles (14). Compressibility index ($CI\%$) was determined as $CI\% = (D_{tb})/D_t.100$ in which D_b and D_t are respectively bulk and tapped densities (Section 2.9.15 of Eur. Ph).

Drug Release

Release profiles of Cip from the matrices were performed in a USP-dissolution apparatus 2 (Hanson Res., USA) at 50, 75 and 100 rpm, 37.0±0.5 °C, using 900 mL of USP simulated gastric fluid without pepsine as dissolution medium (pH=1.20±0.05). Samples of 5.0 ml were taken at predetermined time intervals and the amount of Cip released was measured spectrophotometrically at maximum absorbance wavelength, 276 nm (Shimatsu, 1240-mini Spectrophotometer, Tokio, Japan). The experimental data are the average of three experiments and are expressed as a percentage of Cip released. Drug release profiles were analyzed by means of equations 1 (linear model) (15–17) and 2 (Korsmeyer–Peppas model) (18,19) fitting release data in the range 5 to 60%:

$$M_t/M_\infty = k_0 t \tag{1}$$

$$M_t/M_\infty = k_K t^n \tag{2}$$

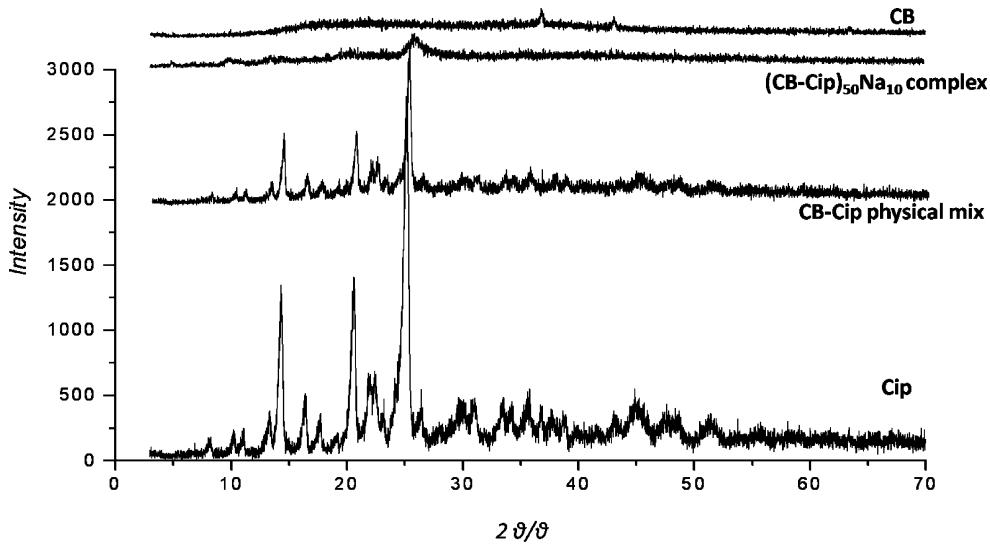


Fig. 3. Powder X-ray spectra

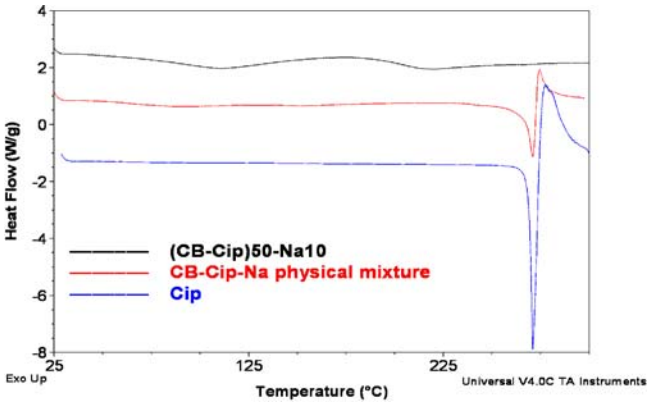


Fig. 4. DSC profiles of samples in non-hermetic aluminum pans heated under N_2 atmosphere at 10 °C/min from room temperature to 300 °C

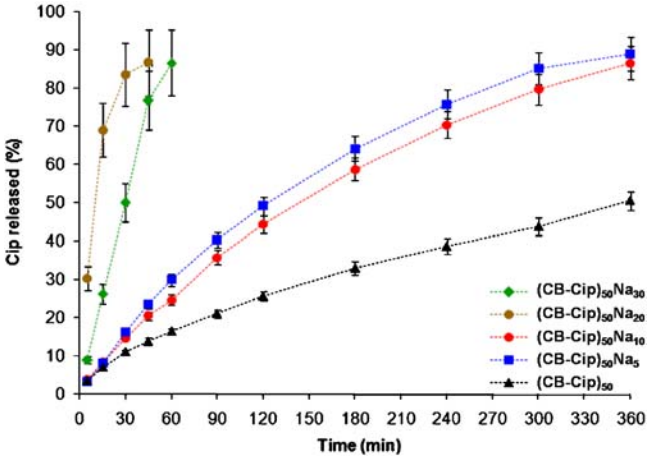


Fig. 6. Cip release profiles from SDPM matrices in simulated gastric fluid at 37 °C

where $M_{t\infty}$ is the fraction of drug released at time t, k_0 and k_K are the release constants, and n is the diffusional exponent.

Preparation of Tablets

Extended release SDPM tablets of Cip 500 mg were prepared by direct compaction of a mixture constituted by 810±8 mg of $(CB–Cip)_{50}Na_x$ complex, 16 mg of talc and 8 mg of magnesium stearate using an alternating tableting machine (Talleres Sanchez, Bs.As., Arg.) equipped with flat punches and matrix of 13.0 mm in diameter. Tablet hardness (n=10; Hardness tester DU4, AVIC, Bs.As., Arg.) and friability (<1,216>test, USP XXIX) were measured. Release rates were measured as described previously.

RESULTS AND DISCUSSION

Properties of Complexes

To develop a tablet with the desired release properties, the basic proportion of 50 moles of Cip respect to 100 moles of carboxylic groups of CB was selected as the starting material. However, matrices of this complex exhibit poor swelling and release properties (see Figs. 5 and 6). It has been previously reported (8) that the introduction of Na cation as third component of CB–Cip complexes increases their water affinity. Therefore, in order to improve the swelling properties of the complexes, increasing proportions of Na^+ were introduced as a third component. Then, a series of $(CB–Cip)_{50}Na_x$ complexes was generated according to Scheme 1.

Complexes were characterized through FT-infrared spectroscopy, powder X-ray diffraction and thermal analysis.

In the FT-IR analysis, the indicative bands of the acid-base interaction were analyzed to further characterize the interaction between CB and Cip. As a general trend, the FT-IR spectra of the $(CB–Cip)_{50}$ and $(CB–Cip)_{50}Na_x$ complexes showed differences as compared to that of the physical mixtures of CB–Cip and the pure materials. The complexes show a narrowing in the strong band at 1710–1736 cm^{-1} ascribed to the carbonyl of undissociated carboxylic groups of Cip and CB. Such changes in the complexes are paralleled by the appearance of bands at 1581–1562 cm^{-1} and 1401 cm^{-1} which were assigned to the asymmetric and symmetric absorption bands of the carboxilate groups that form the

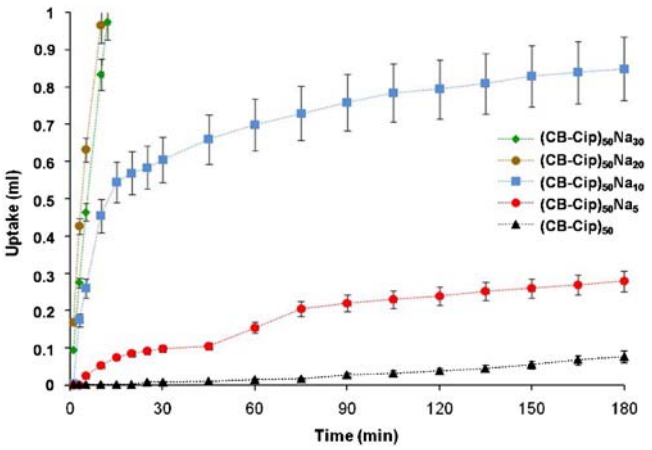


Fig. 5. Simulated gastric fluid uptake of complex matrices prepared by compacting

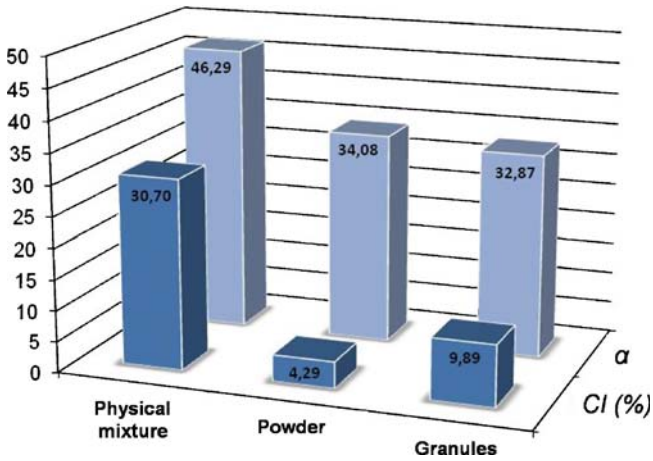


Fig. 7. Angles of repose (α) and compressibility index (CI) of $(CB–Cip)_{50}–Na_{10}$, 212–425 μm fraction obtained as granules or powder, and the physical mixture of Cip and CB

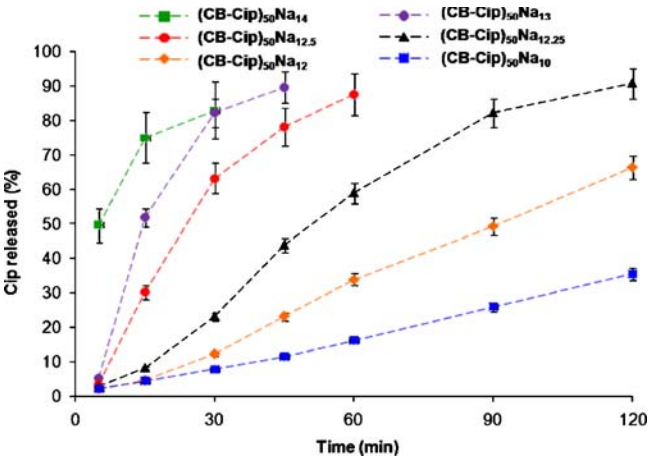


Fig. 8. *In vitro* release profiles in simulated fluid gastric of Cip from $(CB–Cip)_{50}–Na_x$ SDPM tablets with different proportion of Na^+, all containing the equivalent at 500 mg of Cip

ionic bonds with Na^+ atoms and NH groups of piperazine (Fig. 2).

In addition, in the powder X-ray diffraction analysis (Fig. 3) can be observed that the physical mixture showed a profile similar to the sum of that of CB and Cip. Besides, no reflections characteristic of crystalline Cip were present in the complexes, which showed a profile characteristic of amorphous compounds, similar to that of CB. In line with that, DSC profiles show that the melting endotherm (269.8 °C) as well as the decomposition exotherm (273–277 °C), corresponding to free Cip, is not present in the complexes runs. This behavior was also observed by TGA where the weight loss observed during Cip decomposition in Cip and physical mixture is not observed in the complexes until 300 °C (data not shown), suggesting that all Cip is bonded to CB. A typical DSC profile of a complex together with those of Cip and a physical mixture is shown in Fig. 4.

All these evidence taken together confirm that $(CB–Cip)_{50}$ and $(CB–Cip)_{50}Na_x$ complexes are amorphous stable solid products, and a ionic interaction seems to be the primary binding force for the complex formation between CB and Cip. These results are consistent with those previously reported on other CB-D,[5] AA-D complexes (6) and Eudragit®-D complexes (7).

Preformulation

Swelling and release properties of compacted matrices of the series of complexes were measured in simulated gastric fluid. This medium was selected since it has been well established that the oral bioavailability of Cip is related to the proportion of drug molecules that reach upper small intestine in solution state, as it is absorbed by passive paracellular transport (10,20,21).

Figure 5 shows the uptake of simulated gastric fluid along time for the series of matrices. As can be seen there the complex $(CB–Cip)_{50}$ exhibits a very slow rate of fluid sorption. However, the introduction of Na^+ into the composition of the complexes produces a dramatic increase of fluid uptake as the proportion of Na^+ is raised to 5, 10 and 20 mol%. This behavior would be related to the increasing ability of the complex to neutralize the HCl that is introduced in the incipient hydrogel layer during the swelling, and therefore keeping ionized a significant proportion of carboxylic groups of CB.

This view is also consistent with the fact that those complexes with lower proportions of Na^+ (5 and 10 mole%) exhibit biphasic profiles, in which their second portions are almost parallels to that of the complex without Na^+.

Release rates of Cip from the matrices were measured in a USP-dissolution apparatus. Figure 6 shows that the complex $(CB–Cip)_{50}$ exhibits the slowest release rate. Complexes with 5 and 10 mol% of Na^+ both exhibit higher and similar rates while that with 20 mol% of Na^+ exhibits the highest rate and can not be considered as a modified release material. A higher proportion of Na^+ does not produce significant changes in delivery rate.

Therefore, on one hand there is a correlation between gastric fluid uptakes and delivery rates while, on other hand, both properties are strongly dependent on the proportion of Na^+ in the composition of the complexes in the range from 0 to 20 mol%.

Formulation of Extended Release Tablets

A series of complexes $(CB–Cip)_{50}Na_x$ having a proportion of Na^+ in the range from 10% to 14% were prepared by both procedures described in Scheme 1.

Both, angle of repose (α) and compressibility index (*CI* %), were assayed on $(CB–Cip)_{50}–Na_{10}$. Figure 7 shows that both, granules or particles (fraction 212–425 μm), exhibited α

Table I. Kinetic Data of Cip Release Profiles from SDPM Matrices at 75 rpm and 37 °C

		Linear kinetic		Korsmeyer–Peppas kinetic		
Na^+ proportion (%)	Release rate[a] (mg/min)	k_0	r^2	k_K	n	r^2
10.0	1.4	0.301	0.998	0.248	1.03 (± 0.02)	0.999
12.0	2.8	0.594	0.996	0.335	1.11 (± 0.06)	0.997
12.25	4.7	1.153	0.996	0.275	1.32 (± 0.09)	0.997
12.5	10.7	n/d	–	n/d	–	–
13.0	17.7	n/d	–	n/d	–	–
14.0	25.0	n/d	–	n/d	–	–

[a] Data calculated from t_{50} of Cip release profiles

Table II. Cip Release Rate Variation from $(CB–Cip)_{50}–Na_{10}$ Matrices at Different Rotation Speed of the USP-Dissolution Paddles

	Speed		
Rotation speed (rpm)	50	75	100
Release rate (mg/min)	1.2	1.4	1.6

[a] Data calculated from t_{50} of Cip release profiles

and *CI%* that indicate an acceptable flowbility and compressibility to intend a direct compression process of tableting. All complexes showed similar properties and after mixing with 2% of talc and 1% of magnesium stearate, as antiadherent and lubricant agents respectively, were satisfactorily compressed in the tableting machine. The weight of the series of SDPM tablets was 834.0±8.3 mg having 500 mg of Cip. The hardness was 8.01±0.80 kg cm^{-1} (n=10) and friability was <1% in all cases (0.4±0.3%).

The release profiles of Cip SDPM tablets shown in Fig. 8 exhibited a high sensitivity of release rate towards the proportion of Na^+ incorporated in the complexes. In fact, the release rate was raised from 1.4 to 25 mg/min in going from $(CB=Cip)_{50}Na_{10}$ to $(CB–Cip)_{50}Na_{14}$ (Table I).

To gain further knowledge about the main route of release of Cip SDPM tablets, delivery rates were measured at three different stirring rates (100, 75, and 50 rpm) showing a very small decrease of release as the stirring rate was slowered (Table II). It is well know that if erosion is the main route of delivery, the releasing rate is quite sensitive to the stirring rate (6). Therefore, in this case such mechanism appears to be of low significance and the main route of release would be ascribed to swelling, dissociation of ionic pairs, and further diffusion of the free API through the hydrogel layer, as previously described for other CB based SDPM's (5,6).

In line with this view, the analysis of the release profiles using the diffusional exponential equation 2, proposed by Korsmeyer and Peppas for conventional swellable-hydrophylic matrices (Table I), yielding n values close to one, also suggests that other factors than drug diffusion are also involved in the kinetic control. Therefore, according with this model, rates of swelling and ionic pairs dissociation would also contribute to the kinetic control of release.

The CB based Cip SDPM appears to be a versatile delivery system that provides a wide range of release rates. For example tablets of $(CB–Cip)_{50}Na_{12.25}$ deliver 90% of the dose in simulated gastric fluid in about 120 min. as it is delivered by CIPRO XR®, 2002b (Fig. 9). Additionally, the swollen Cip SDPM maintains their integrity during the release experiments. Such behavior would allow the intragastric release of Cip, which can reach the first portion of the intestine as a solution and might contribute to improve its bioavailability (22,23).

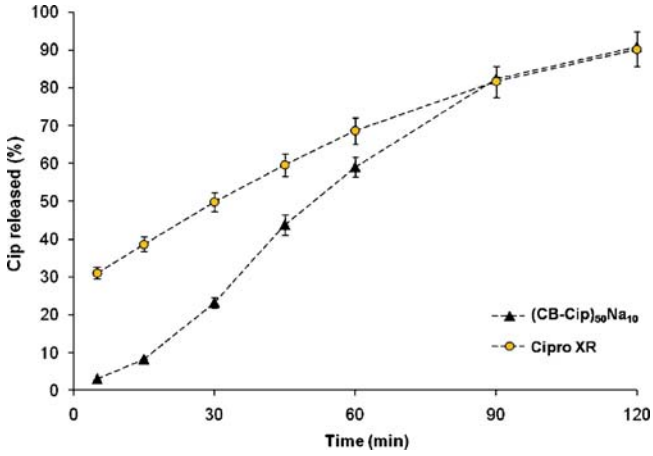


Fig. 9. *In vitro* Cip release profiles from two extended release tablets in simulated fluid gastric

CONCLUSIONS

It has been shown that:

Extended release SDPM tablets of CB–Cip–Na complexes can be satisfactorily prepared through the current processes of tableting technology. Ciprofloxacin release in simulated gastric fluid from such matrices can be widely modulated by changes in CB–Cip–Na complex composition. On these bases an extended release SDPM tablet that releases 90% of the dose in simulated gastric fluid in about 120 min has been developed.

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