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ORIGINAL ARTICLE

# Urinary excretion of ciprofloxacin after administration of extended release tablets in healthy volunteers. Swellable drug-polyelectrolyte matrix versus bilayer tablets

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**Abstract** This paper builds on a previous paper in which new ciprofloxacin extended-release tablets were developed based on a ciprofloxacin-based swellable drug polyelectrolyte matrix (SDPM-CIP). The matrix contains a molecular dispersion of ciprofloxacin ionically bonded to the acidic groups of carbomer, forming the polyelectrolyte-drug complex CB-CIP. This formulation showed that the release profile of the ciprofloxacin bilayer tablets currently commercialised can be achieved with a simpler strategy. Thus, since ciprofloxacin urine concentrations are associated with the clinical cure of urinary tract infections, the goal of this work was to compare the urinary excretion of SDPM-CIP tablets with those of the CIPRO XR® bilayer tablets. A batch of SDPM-CIP tablets was manufactured by the wet granulation method and the CB-CIP ionic complex was obtained in situ. Fasted healthy volunteers received a single oral dose of 500 mg ciprofloxacin of either formulation in a randomised crossover study. Urinary concentrations were assessed by HPLC at intervals up to 36 h. Pharmacokinetic parameters (rate of urinary excretion, maximum urine excretion rate, $t_{max}$, area under the curve, amount and percentage of the ciprofloxacin dose excreted in urine) showed no statistical differences between both formulations at any of the time intervals of collection. The processing conditions to obtain SDPM-CIP tablets are easy to scale up since they involve technology currently employed in the pharmaceutical industry and the process is less challenging to implement. In addition, SDPM-CIP tablets met pharmacopoeial quality specifications.

**Keywords** Drug-polyelectrolyte complexes · Urine excretion · Fluoroquinolones · Scaling-up · Wet granulation · Oral absorption

## Introduction

Urinary tract infections (UTI) are frequent among women, affecting as many as one in five at some time during their lives [1, 2]. In addition, 27% of women will suffer at least one episode of UTI in the 6 months following the initial infection [1, 3]. *Escherichia coli* is the most frequently implicated uropathogen reported by virtually all epidemiological studies worldwide [4–6] while infections with multi-resistant pathogens are more likely to occur in complicated UTI [6, 7].

The use of antibiotics with favourable pharmacokinetics/pharmacodynamics profiles and convenient dosing schedules, which effectively increase bacterial eradication and patient compliance, can help to curb the current epidemic of resistance and reduce the rate of clinical failure associated with resistance [8, 9].

It is known that fluoroquinolone resistance has increased in Enterobacteriaceae causing community-acquired or healthcare-associated UTI and intraabdominal infections, exceeding 50% in some parts of the world. In general, the continued increase in fluoroquinolone resistance affects patient management and necessitates changes in some guidelines, for example, treatment of UTI [10].

In 2002, an extended-release formulation of ciprofloxacin was developed by Bayer Healthcare, which introduced two strengths of CIPRO XR® tablet formulations (US-patent

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2004/0024018) for the treatment of UTI. Specifically, they are indicated for the treatment of uncomplicated UTI such as acute cystitis (CIPRO XR® 500 mg), and for complicated UTI and acute uncomplicated pyelonephritis (CIPRO XR® 1000 mg). These formulations showed a reduction in the variability of absorption, thus, improving its therapeutic profile [9, 11].

According to the prescribing information [12], both tablet formulations contain 500 or 1000 mg of ciprofloxacin (as anhydrous base) and are composed of a bilayer matrix containing two types of ciprofloxacin drug substance, ciprofloxacin hydrochloride and ciprofloxacin base. Oral administration of the tablets results in the immediate release of 35% of the total dose, providing a rapid onset of action, and the remaining 65% of the dose is released within 3 h. It is known that the development of bilayer tablets has faced great difficulties and the successful manufacturing of these complex systems poses additional challenges to those required for conventional ones [13–16].

A previous work [17] determined the formulation parameters to obtain 500 mg ciprofloxacin extended release tablets by compaction of complexes of carbomer (CB) partially neutralised with ciprofloxacin as a base (CB-CIP ionic complexes). Such tablets are swellable drug-polyelectrolyte matrices (SDPM) [18]. Unlike other swellable hydrophilic matrices, ciprofloxacin based-SDPM (SDPM-CIP) contains a molecular dispersion of ciprofloxacin in the mass of the matrix, since the drug is ionically bonded to the functional groups of CB as a polyelectrolyte-drug complex [17, 19–21]. SDPM-CIP tablets showed compliance with the limits of the dissolution test described in USP 39 ciprofloxacin extended-release tablets monograph [22].

The major route of elimination of ciprofloxacin in humans is as unchanged drug in urine and urine concentrations are closely associated to the clinical cure of UTI [8]. Thus, urinary excretion of ciprofloxacin is a valid indicator for its anti-infective activity in the urinary tract.

The objectives of the present work were to determine the urinary excretion of ciprofloxacin from SDPM-CIP tablets following administration of a single oral dose of 500 mg in healthy volunteers and compare it with that from the same dose of CIPRO XR® tablets.

## Materials and methods

Ciprofloxacin hydrochloride, enrofloxacin, talc NF, magnesium stearate NF, KCl and NaCl were purchased from Parafarm®, Buenos Aires, Argentina. CB 934-P NF was purchased from Saporitti®, Buenos Aires, Argentina. HCl 37% and 1 M NaOH solution were purchased from Anedra®, Buenos Aires, Argentina. Absolute ethanol was purchased from Cicarelli®, Córdoba, Argentina. All media used to assess the microbiological quality were purchased from Britania, Buenos Aires, Argentina.

Ciprofloxacin (as a base) was obtained according to Bermúdez et al. [17]. Briefly, ciprofloxacin hydrochloride was neutralised with an equimolar amount of 1 M NaOH. The precipitate was washed with cold water, filtered and dried under vacuum at room temperature to constant weight.

Argentine Pharmacopoeia Ciprofloxacin hydrochloride Reference Standard (ciprofloxacin hydrochloride-RS) was provided by the Instituto Nacional de Medicamentos (INAME, Argentina, Control No. 102044) and used as analytical reference.

Phosphoric acid 85% (Ciccarelli ® PA grade), triethylamine (Anhedra ® PA grade), acetonitrile (Sintorgan®, HPLC grade) and methanol (Sintorgan®, HPLC grade) were used for HPLC mobile phase.

Distilled water was used for all assays except for HPLC, in which Milli Q water was used.

CIPRO XR® 500 extended-release tablets (Bayer, lot BXG9TU13) were used for comparison purposes.

### Preparation of SDPM-CIP tablets

A 1:0.5:0.1255 CB:ciprofloxacin:Na ratio was selected, based on our previous studies showing that it can mimic the in vitro release profile of CIPRO XR® [17]. In this composition, 0.5 and 0.1225 represent, respectively, the molar proportion of ciprofloxacin and NaOH that would neutralise the carboxylic groups of CB.

To prepare the CB-CIP ionic complexes, CB (12.0 meq/g, as determined by NaOH titration) was thoroughly mixed with ciprofloxacin in a planetary mixer (all-purpose ERWEKA AR 403, Germany). Then, a sufficient amount of absolute ethanol was carefully added to obtain a semi-solid paste. On this mass, 1 M NaOH was incorporated drop by drop under constant mixing. The resulting semisolid paste was extruded through a 1 mm sieve oscillating granulator (ERWEKA FGS, attached to an all-purpose ERWEKA AR 403, Germany) and the granules were kept for 12 h at room temperature to allow the complete formation of the ionic complex. This time, lapse was defined at the preformulation stage in Bermúdez et al. [17]. The granules were then dried in an oven at 40 °C for 2 h and subsequently sieved to select particle sizes in the range 400–1000 μm. Lastly, magnesium stearate was added as a lubricant and talc as an anti-adherent agent, mixed in a double-cone mixer and compressed on a single-punch tableting machine (Talleres Sanchez, Model CS3-GMP, Argentina) using biconcave oblong punches and a matrix of 22 × 10 mm. A summary of the process to obtain a batch of 500 tablets and the qualitative and quantitative composition are shown in Fig. 1 and Table 1, respectively.

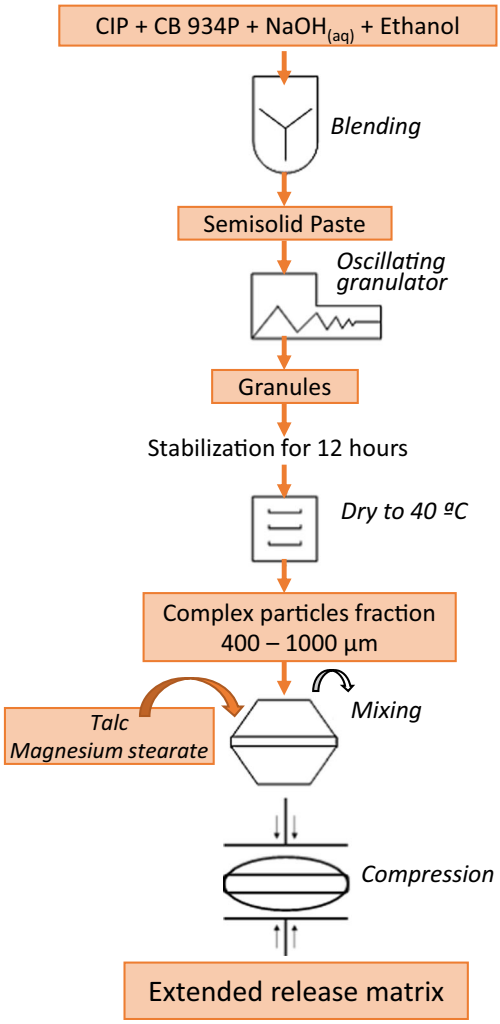


**Fig. 1** Procedure to prepare SDPM-CIP tablets

## CB-CIP granules evaluation

The loss on drying of the granules was assessed by thermogravimetric analysis (Hi-Res-TGA 2950, TA-Instruments, USA) with universal analysis NT-specific software. For this purpose, samples of approximately 5 mg were heated under nitrogen atmosphere in aluminium pans from room temperature to 250 °C at 10 °C/min.

**Table 1** Qualitative and quantitative composition of SDPM-CIP tablets

| Composition | % | Amount per batch (g) |
|---|---|---|
| CB-CIP ionic complex[a] | 98.5[b] | 349.2 |
| Talc NF | 1.0 | 3.5 |
| Magnesium stearate NF | 0.5 | 1.8 |
| Total | 100 | 354.5 |

[a] Prepared from ciprofloxacin (250 g), CB 934-P NF (134.4 g), 1 M NaOH (184.6 mL) and absolute ethanol (250 mL)

[b] Equivalent to 500 ± 10 mg of ciprofloxacin as a base

The complete interaction between ciprofloxacin and CB to form the CB-CIP ionic complex was assessed by hot-stage optical microscopy (HSM, Leitz Wetzlar, Germany). The sample was heated at a rate of 10 °C/min from room temperature to 280 °C.

To assay the ciprofloxacin content uniformity, three samples of granules were randomly taken, homogenised in a mortar and approximately 100 mg of each were accurately weighed and extracted with 0.1 M HCl. An aliquot of 0.25 mL of the supernatant was diluted to 50 mL with 0.1 M HCl and spectrophotometrically assayed at 278 nm (Shimadzu 1240-mini Spectrophotometer, Tokyo, Japan) using a ciprofloxacin hydrochloride-RS solution as a reference. The acceptance value was ≤ 15.0%.

## Characterisation of tablet formulation.

The hardness, friability, thickness and uniformity of content of the SDPM-CIP tablets were determined through process characterisation according to Argentinian Pharmacopoeia [23]. Hardness ($N = 10$) was determined using a Hardness Tester (AVIC, Argentina). Friability ($N = 10$) was evaluated in a friability tester (Scout, Argentina). Dimensions (height, thickness and long) were determined by measuring ten tablets with a Vernier calliper. To assess weight uniformity, 20 tablets from the batch were selected randomly and weighed individually using a highly sensitive electronic balance (Moretti, Argentina).

### *SDPM-CIP tablets assay*

Ten tablets were reduced to fine powder and three samples of approximately 100 mg were accurately weighted. Ciprofloxacin content was assayed following the same methodology described for CB-CIP granules evaluation.

### *Microbiological analysis*

The microbiological quality of tablets was assessed in accordance with the criteria included in USP 39 <1111> acceptance criteria for microbiological quality of nonsterile dosage forms. The load of mesophilic bacteria, moulds and yeasts capable of growing aerobically, and the absence of *Escherichia coli* were verified according to the methods given in the USP chapters on Microbiological Examination of Nonsterile Products: <61> Microbial Enumeration Tests and <62> Tests for Specified Microorganisms [22].

### *Ciprofloxacin dissolution study*

The release rate of ciprofloxacin from the SDPM-CIP tablets was evaluated (in sextuplicate) in a Hanson Research Tablet Dissolution Tester (SR II, USA) using the USP dissolution

method for ciprofloxacin extended release tablets with 900 mL of USP-simulated gastric fluid without pepsin as the dissolution medium (pH = 1.20 ± 0.05, apparatus 2; 75 rpm; 37 ± 0.5 °C).

At predetermined times, 5 mL samples were withdrawn from the dissolution apparatus, filtered, diluted and spectrophotometrically quantified at 278 nm. All the samples were replaced with preheated fresh dissolution medium. The cumulative percentage of ciprofloxacin release was calculated and expressed as a function of time. The same procedure was followed with CIPRO XR® tablets for comparison. Additionally, the release curves obtained from SDPM-CIP and CIPRO XR® tablets were compared using the difference factor $f_1$ and similarity factor $f_2$, calculated by Eqs. 1 and 2, respectively.

$$f_1 = \frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum R_t} \times 100 \quad (1)$$

$$f_2 = 50 \ \log\left\{ \left[ 1 + \frac{1}{n} \sum_{t-1}^{R} (R_t - T_t)^2 \right]^{-0.5} \right\} \times 100 \quad (2)$$

where $R_t$ and $T_t$ are the percentages released at each time point for reference (CIPRO XR®) and test (SDPM-CIP tablets) formulations. An $f_1$ value above 15 and $f_2$ value between 0 and 49 implies difference between the release profiles. The CV was below 15% in all cases. Only one point after 85% of drug release was used for the equation.

## Urinary excretion of ciprofloxacin

### *Study design and subject population*

A randomised, double-blinded, crossover clinical trial was conducted in healthy volunteers. The trial protocol was approved by the ethics committee of the Hospital Nacional de Clínicas, Universidad Nacional de Córdoba, Córdoba, Argentina (69–2008). Twelve volunteers (three men and nine women) were admitted. Mean age was 31 years (range 21–43), mean body weight was 59 ± 9 (range 49–75) and mean height was 169 ± 9 cm (range 156–190). Since this is a preliminary study, the number of subjects participating was the minimal amount required by the National Administration of Medicines, Food and Medical Technology of Argentina (ANMAT) [24] and WHO for pharmacokinetic comparative bioavailability studies in humans [25]. The volunteers were considered healthy on the basis of their medical history, physical examination, urinary analysis (physico-chemical tests: colour, appearance, foam, pH, density, protein, glucose, ketones, bilirubin, urobilin, haemoglobin and nitrites; microscopic examination: flat epithelial cells, isolated white blood cells, red blood cells, streaked mucus, cylinders and crystals). After giving written informed consent, each volunteer received a single oral dose of SDPM-CIP or CIPRO XR® tablets with a washout period of 7 days, according to the randomisation schedule. Both formulations were administered after overnight fasting. After administration of the tablets, subjects remained fasted for 2 h. The volunteers were asked to drink sufficient and comparable amounts of water through both collection periods to ensure sufficient urine production. Standard meals were provided for each volunteer. Alcohol- and xanthine-containing beverages and meals and acidic drinks were not allowed 12 h before and 24 h after drug administration. Urine was collected for 36 h. Adverse events were recorded continuously throughout the trial period.

### *Sample collection*

A urine sample was collected immediately before tablet administration to ascertain that the urine was antibiotic-free and at the following time intervals thereafter: 0–4 h, 4–8 h, 8–12 h, 12–16 h, 16–24 h, 24–28 h, 28–32 h and 32–36 h. All samples were collected in light-protected containers and refrigerated during the collection period. The volume collected at each time interval was measured in a graduated cylinder and its pH was determined. A 15-mL aliquot of each sample was centrifuged (3000 rpm, 15 min) and the supernatant was stored in plastic tubes at − 20 °C until analysis.

### *HPLC method validation for ciprofloxacin determination*

The methodology described by González et al. [26] for the quantification of ciprofloxacin was adapted. Chromatography was performed using a Waters® HPLC system equipped with a 1500 HPLC pump, a 717 auto sampler and a Waters 2475 Fluorescence detector, with data acquisition and processing performed using Empower® system software. The temperature was maintained at 30 °C with a Waters 1500 series column heater. Chromatographic separations were carried out using a Phenomenex® C18 reverse phase column (250 × 4.6 mm, 5 μm particle size) and a Phenomenex® guard column (C18 4 × 3 mm ID). The mobile phase for the separation of ciprofloxacin consisted of 16% of acetonitrile:methanol (13:1) mixture and 84% of an aqueous solution of triethylamine (0.4%) and phosphoric acid (0.3%); pH = 2.5. The flow rate was 1.2 mL/min, the injection volume 100 μL and fluorescence detection was performed at $\lambda_{ex}$ = 294 nm and $\lambda_{em}$ = 500 nm, with peak areas being used for quantitative analysis. The linearity, specificity, recovery, precision, accuracy, limit of quantification, stability and robustness of the method were determined.

The calibration curve was constructed from an aqueous 1 mg/mL ciprofloxacin hydrochloride-RS stock solution and the internal standard stock solution of enrofloxacin (0.2 mg/mL, in methanol). For the curve construction, aliquots of 1 mL of blank urine were thawed at room temperature and different

volumes of aqueous solutions were added, prepared from the ciprofloxacin hydrochloride-RS stock solution in order to obtain ciprofloxacin concentrations between 0.16 and 8 μg/mL. Aqueous dilutions prepared from the enrofloxacin stock solution were also added as the internal standard, to reach a urine concentration of 8 μg/mL.

*Pharmacokinetic parameters*

The following pharmacokinetic parameters were obtained: *dE/dt* vs time, which is the rate of urinary excretion at each time interval, corresponding to the half interval of samples collection; $(dE/dt)_{max}$, which corresponds to the maximum urine excretion rate; $t_{max}$, which is the time in which $(dE/dt)_{max}$ is reached; $E(\infty)$, which is the area under the curve *dE/dt* versus time from 0 to infinite; $E(t)$ and $E\%(t)$, which correspond to the cumulative amount (mg) and percentage of the ciprofloxacin dose, respectively, excreted in urine without change over 36 h. These parameters were estimated using a non-compartmental model (PK solutions® 2.0 software). The normal distribution of the test parameters was confirmed using the Shapiro-Wilks test. All data were compared using ANOVA and statistical calculations were performed using Microsoft Excel® 2010 software.

## Results

### Preparation of CB-CIP ionic complex and tableting

SDPM-CIP tablets were successfully obtained by a wet granulation method using technology currently employed in the pharmaceutical industry. The complete reaction between CB and ciprofloxacin to form CB-CIP ionic complex was achieved under the conditions implemented during the process.

In fact, the HSM showed an absence of fusion or decomposition in the 273–280 °C range, indicating that no free ciprofloxacin was present in the granules. It is important to note that a 1:0.5:0.1255 CB:ciprofloxacin:Na ratio was used to obtain the granules. However, some water coming from the raw materials and the granulation process remains after drying the granules.

The thermogravimetric analysis of the granules showed an 11% weight loss from room temperature to 160 °C, attributed to water evaporation. In addition, the ciprofloxacin content in the CB-CIP granules, as determined by UV spectrophotometry, was (91 ± 1) %. The assay and uniformity content of the SDPM-CIP tablets were within pharmacopoeial limits, with a ciprofloxacin content per tablet of (536 ± 8) mg and a mean weight of SDPM-CIP tablets of (969 ± 12) mg.

The dimensions of the tablets were height, 0.5 cm; thickness, 1 cm and length, 2.2 cm, which are acceptable for administration to adults [27].

The selected particle size of the granules ensured excellent technological properties which required only the addition of talc and magnesium stearate compression adjuvants. The tablet surface was smooth and shiny. SDPM-CIP tablets showed a main hardness of (10 ± 2) kg/cm$^2$ with a friability value of (0.4 ± 0.1)%, suggesting a high mechanical strength. No capping or lamination was observed.

Finally, samples met USP criteria for maximum permitted microbiological limits, and also complied with the requirements for an absence of *Escherichia coli*, indicating an acceptable microbiological quality of the tablets, which consequently can be used for administration to the volunteers of this study.

### In vitro release study

The SDPM-CIP tablets showed a slow and controlled release of ciprofloxacin. Both SDPM-CIP and CIPRO XR® tablets released up to 90% of the dose at 2 h. However, the comparison of the profiles showed an $f_1$ value of 17 and $f_2$ value of 44, indicating that the profiles are different. Such differences are evident in the first time points of the curves and were attributed to the burst effect caused by the immediate release layer of ciprofloxacin hydrochloride in CIPRO XR® (Fig. 2).

### HPLC method validation

Linearity was found over the concentration range of 0.16–8 μg/mL ($y = 0.310\ x + 0.0001$; $R^2 = 0.993$). The specificity of the method was verified and no interference of urine endogenous components was observed. The inter- and intra-day values of precision and accuracy were less than 6%. Stability was verified after a freezing-thawing cycle, with a coefficient of variation < 4% in all cases. The percentages of ciprofloxacin recovery were > 96%, with a CV below 10% in all cases. The quantification limit was 0.16 μg/mL. All the parameters determined were within the internationally accepted criteria [28].

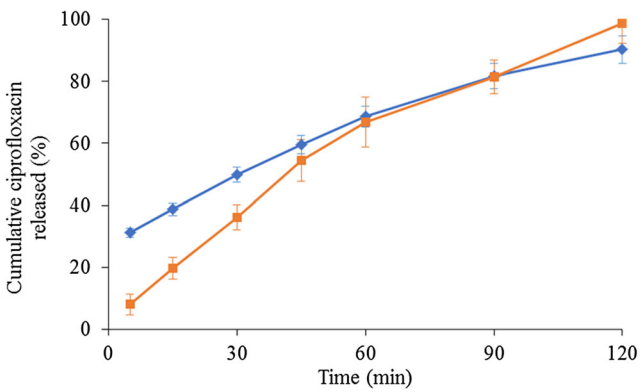


**Fig. 2** In vitro release profiles of SDPM-CIP (-■-) and CIPRO XR® (-♦-) tablets in simulated gastric fluid

### Urinary excretion of ciprofloxacin

Both formulations SDPM-CIP and CIPRO XR® tablets were well tolerated by all volunteers and no adverse events occurred during the study. As shown in Table 2 and Fig. 3, both the volume of urine and the urinary pH values obtained in the collection periods showed no significant differences ($p > 0.05$) between both formulations.

The *dE/dt* vs time profile is shown in Fig. 4. Urinary concentrations and pharmacokinetic parameters obtained are described in Tables 3 and 4, respectively, and no significant differences were observed in the parameters calculated for SDPM-CIP and CIPRO XR® tablets ($p > 0.05$).

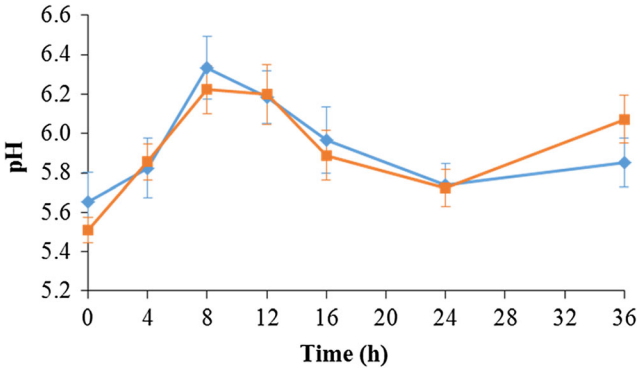


**Fig. 3** Mean pH of urine collected at each time interval following the administration of a single dose of SDPM-CIP (-■-) or CIPRO XR® (-♦-) tablets to healthy subjects

## Discussion

This study compared ciprofloxacin urinary excretion from the new extended-release SDPM-CIP tablets and the reference-marketed CIPRO XR® tablets given at equivalent doses.

Approximately 40 to 50% of an orally administered dose of ciprofloxacin is excreted in urine as unchanged drug, together with four metabolites accounting for 3–8% of the total dose. The urinary excretion of ciprofloxacin and metabolites is virtually complete within 24 h after dosing [12]. It should be noted that the fluorescence detection used in this study provided high sensitivity and specificity and avoided the interference of urine endogenous components as well as metabolites that lack fluorescence, such as oxo-ciprofloxacin, which is the main urinary metabolite [29]. In fact, only the peak corresponding to ciprofloxacin was observed in the HPLC chromatograms.

Antimicrobials which are primarily eliminated via renal excretion can reach high urinary concentrations, sometimes 100 to 1000 times the concomitant serum concentrations. Theoretically, such substances are optimal choices for the treatment of UTI due to the high antibiotic urinary concentrations required, since a significant proportion of the bacteria are freely floating in the urine [30]. In addition, Izawa et al. [8] demonstrated in rats that fluoroquinolones are excreted into urine and then transferred to the surface layer of the bladder transitional epithelium. Therefore, the clinical cure in the treatment of UTIs is more closely associated with urine than with plasma antibiotic concentration.

As mentioned, CIPRO XR® is composed of a bilayer matrix containing one layer of immediate release ciprofloxacin hydrochloride and one of sustained release ciprofloxacin, and its oral administration provides a rapid onset of action as well as higher maximum plasma concentrations with lower inter-patient variability than the conventional, immediate-release, twice-daily formulations.

The maximum urinary excretion rate of ciprofloxacin, $(dE/dt)_{max}$, is obtained from the peak of the plot between the rates of excretion versus the midpoint time of the urine collection period. Since the rate of appearance of ciprofloxacin in urine is

**Table 2** Urine volumes (mL) collected during the trial after the administration of a single dose of SDPM-CIP and CIPRO XR® tablets

| Time interval (h) | Urine volumes (mL) | | *P* value[a] (ANOVA) |
|---|---|---|---|
| | SDPM-CIP tablets (mean ± SD) | CIPRO XR® tablets (mean ± SD) | |
| 0–4 | 484 ± 90 | 464 ± 75 | 0.688 |
| 4–8 | 612 ± 73 | 541 ± 71 | 0.548 |
| 8–12 | 410 ± 46 | 506 ± 68 | 0.361 |
| 12–16 | 340 ± 36 | 355 ± 69 | 0.758 |
| 16–24 | 420 ± 57 | 358 ± 40 | 0.519 |
| 24–36 | 1055 ± 156 | 973 ± 106 | 0.609 |

A total of 12 volunteers were tested

[a] Significantly different ($p < 0.05$) for CIPRO XR® vs. SDPM-CIP

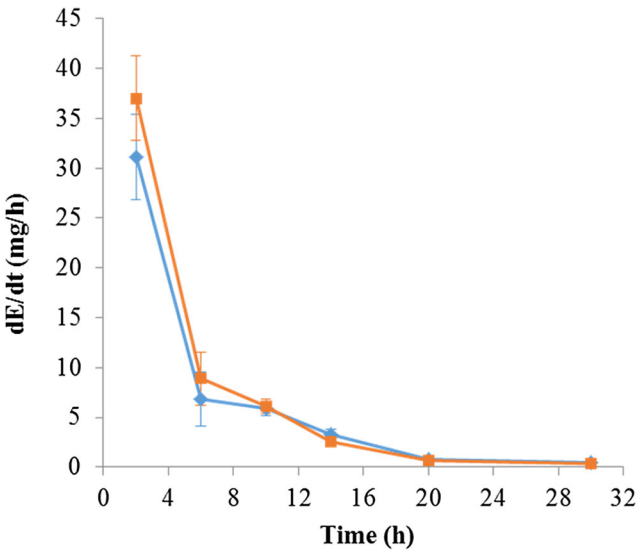


**Fig. 4** Rate of urinary excretion (*dE/dt*) vs time profiles corresponding to the half interval of sample collection following the administration of a single dose of SDPM-CIP (-■-) and CIPRO XR® (-♦-) tablets

**Table 3** Mean urine concentrations of ciprofloxacin (mg/mL) after oral administration of 500 mg single dose of SDPM-CIP and CIPRO XR® tablets

| Time interval (h) | SDPM-CIP tablets (mean ± SD) | CIPRO XR® tablets (mean ± SD) |
|---|---|---|
| 0–4 | 0.3 ± 0.2 | 0.3 ± 0.1 |
| 4–8 | 0.11 ± 0.03 | 0.08 ± 0.01 |
| 8–12 | 0.07 ± 0.02 | 0.05 ± 0.01 |
| 12–16 | 0.037 ± 0.009 | 0.04 ± 0.01 |
| 16–24 | 0.03 ± 0.01 | 0.019 ± 0.003 |
| 24–36 | 0.007 ± 0.002 | 0.0079 ± 0.002 |

A total of 12 volunteers were tested

proportional to its concentration in systemic circulation, $(dE/dt)_{max}$ is analogous to the $C_{max}$ derived from the plasma level studies and its value increases with the rate of absorption. On the other hand, the cumulative urine excretion, $E(t)$, increases with the extent of absorption and is related to the AUC of the plasma level data. In this study, neither $(dE/dt)_{max}$ nor $E(t)$ showed significant differences at any of the time intervals of collection when both formulations were compared.

The in vitro dissolution tests showed that the main differences between SDPM-CIP and CIPRO XR® tablets occurred within the first 45 min of the test. In addition, both systems released in vitro more than 90% of ciprofloxacin after 2 h. However, as the first urine samples were taken within 4 h of administration, this pharmacokinetic study will probably not be able to detect any differences in the bioavailability of ciprofloxacin between the two types of tablets, for which the determination of plasmatic concentrations would be necessary. Since $E(t)$ is directly related to the absorbed dose of ciprofloxacin as a consequence of its bioavailability, the similarity in urine profiles suggests that the differences in in vitro release did not influence the ciprofloxacin absorption rate. This can be explained by the low permeability of the drug, which is class 4 in the Biopharmaceutical Classification System [31].

After administration of a single dose of either extended release formulation, mean urine ciprofloxacin concentration in all the volunteers at the end of the 24-h dosing interval was around 30 mg/L. This is well above MIC for *Enterobacteriaceae*, even for resistant isolates, MIC > 4 mg/L [32].

The physiological conditions, mainly urine pH values, should be considered when performing susceptibility testing of ciprofloxacin activity against *E. coli* in treating UTI. It is well known that urinary pH varies during the day, with higher pHs occurring during the day and lower pHs during the night [33]. In agreement, our study showed that the mean pH for the first collection periods (which were in the morning) were higher than those corresponding to the night. A reduction in the pH can decrease ciprofloxacin bactericidal activity, suggesting that the conditions for bactericidal activity are more favourable during the day. However, as no significant differences were observed in the urinary pH profiles (Fig. 3), no dissimilarities in ciprofloxacin activity would be expected between both formulations.

It is known that the manufacturing of bi- and multi-layer tablets needs to overcome challenges related to formulation design and tablet press monitoring and control. The new SDPM-CIP tablets offer convenience, compared not only with the manufacturing of bilayer tablets but also with other ciprofloxacin modified-release formulations proposed in the literature [34–36]. In this work, the processing conditions for scaling-up SDPM-CIP tablets were established, and these are clearly less challenging to implement than those required to obtain bilayer tablets. One advantage of the process is that the CB-CIP ionic complex can be obtained in situ during the wet granulation process. However, as previously reported by Bermúdez et al. [17], the complex can be obtained at earlier stages and be used as a raw material to obtain the tablets by direct compression. As expected, the CB-CIP granules are uniform in content, and their simple compaction, using equipment currently available in the pharmaceutical industry, led to a formulation whose urinary profile presents concentrations similar to those obtained with the reference formulation CIPRO XR®. Moreover, only one ciprofloxacin drug substance (ciprofloxacin as a base) is used to obtain the SDPM-CIP.

**Table 4** Urinary pharmacokinetic parameters calculated for SDPM-CIP and CIPRO XR® tablets

| Parameter[a] | SDPM-CIP (mean ± SD) | CIPRO XR® (mean ± SD) | *P* value[b] (ANOVA) |
|---|---|---|---|
| $(dE/dt)_{max}$ (mg/h) | 37 ± 4 | 31 ± 4 | 0.3063 |
| $T_{max}$ (h) | 2 ± 0 | 2 ± 0 | N.a. |
| *E*% (%) | 33 ± 2 | 31 ± 3 | 0.4405 |
| $E(t)$ (mg) | (19 ± 2) $10^1$ | (17 ± 2) $10^1$ | 0.6355 |
| $E(\infty)$ (mg) | (19 ± 2) $10^1$ | (18 ± 2) $10^1$ | 0.5062 |

*N.a.* not applicable, $(dE/dt)_{max}$ maximum urine excretion rate, $T_{max}$ time in which $(dE/dt)_{max}$ is reached, *E%* cumulative percentage of the ciprofloxacin dose excreted unchanged in urine, *E(t)* cumulative amount of ciprofloxacin excreted unchanged in urine, *E(∞) (mg)* area under the curve *dE/dt* versus time from 0 to infinite

[a] Estimated using a non-compartmental model (PK solutions® 2.0 software)

[b] Significantly different ($p < 0.05$) for CIPRO XR® vs. SDPM-CIP

SDPM-CIP tablets are thus an interesting option for developing ciprofloxacin extended-release tablets. Standardisation of the process at a larger scale and a stability evaluation of the SDPM-CIP tablets are still required.

## Conclusions

The urinary excretion profiles of ciprofloxacin following oral administration of SDPM-CIP tablets are similar to those of CIPRO XR®. Thus, SDPM-CIP tablets are an accessible and original alternative to develop ciprofloxacin sustained-release formulations and can be produced by a simpler and easy to scale-up process.

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**Compliance with ethical standards**

**Conflict of interest** The authors declare that they have no conflict of interest.

**Informed consent** Informed consent was obtained from all patients for being included in the study.

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