Journal of Pharmaceutical and Biomedical Analysis 52 (2010) 37–42

Contents lists available at ScienceDirect

Journal of Pharmaceutical and Biomedical Analysis

journal homepage: www.elsevier.com/locate/jpba

In vitro food–drug interaction study: Which milk component has a decreasing effect on the bioavailability of ciprofloxacin?

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ARTICLE INFO

Article history:
Received 22 October 2009
Received in revised form
30 November 2009
Accepted 1 December 2009
Available online 6 December 2009

Keywords:
Milk–drug interaction study
In vitro dissolution
Ciprofloxacin
Milky medium
Casein

ABSTRACT

The purpose of the present work was developing an *in vitro* dissolution test to highlight the possible molecular background causing ciprofloxacin (CPFX)–milk interaction. The *in vitro* dissolution of CPFX from film-coated tablets (Ciprinol® 500 mg) was examined at different pH values, simulating certain parts of the gastrointestinal tract, in the presence of water, low-fat milk, casein- or calcium enriched water. In order to determine the amount of dissolved CPFX, solid phase extraction sample preparation followed by high performance liquid chromatography coupled with mass spectrometry was applied. Comparing the dissolution efficiency values in various media, it can be concluded, that casein has a more pronounced effect on the absorbable amount of the antibiotic at each pH value studied, than calcium. In the case of concomitant intake of CPFX film-coated tablet and milk or other dairy products not only the complexation with calcium, but also the adsorption of CPFX on the surface of proteins decreases the absorbable amount of CPFX.

1. Introduction

Fluoroquinolones (FQs) are a relatively new class of antibiotics widely used in human and veterinary medicine, with broad-spectrum activity against infections of the urinary tract, skin, soft tissues and respiratory tract, as well as against sexually transmitted diseases [1]. FQs (*e.g.* ciprofloxacin, ofloxacin, enrofloxacin, norfloxacin) act by inhibiting DNA gyrase, thus inhibiting bacterial DNA replication and transcription, culminating in rapid cell death [2,3]. Patients often take antibiotics with meals or dairy products to help swallowing them easier and to lessen their gastrointestinal side effects [4]. The current meal required by the US Food and Drug Administration (FDA) used to quantify drug–food interaction consists of two eggs fried in butter, two strips of bacon, two slices of toast with butter, four ounces of hash brown potatoes, and eight ounces of whole milk [5].

It is known, that food–drug interactions may occur by many mechanisms, and they can result in changes both in the rate and the extent of absorption [6–9].

Studies of the interaction between calcium and FQs have produced conflicting results. A 'standard breakfast' did not appear to impair the absorption of quinolones [10–12] and had only a minimal effect on their bioavailability – as it was observed with concomitant food administration of fleroxacin [13]. A further FQ–food interaction study did not result in any significant effect on CPFX's bioavailability [14], being consistent with another study where calcium carbonate capsules did not affect the absorption of CPFX [15]. Non-significant effect was observed, if CPFX was administered with a high-calcium-breakfast [16]. According to an FDA monograph, the bioavailability of CPFX did not alter significantly, if it was administered with orange juice, but it did alter, if orange juice was calcium-fortified, highlighting the potential role of calcium in the FQ–food interaction [17]. On the other hand, there are a number of studies, stating that the bioavailability of FQs is significantly influenced by selected alimentary components. According to *in vivo* data the gastrointestinal absorption of norfloxacin and CPFX was markedly decreased by the concomitant ingestion of milk or yoghurt [18,19]. Studying levofloxacin co-administered with mineral-fortified breakfast consisting of juice, cereal with or without milk, it could be concluded, that none of the studied fed phases (breakfast with or without milk) were bioequivalent to the fasting arm [20]. Similarly, concomitant administration of calcium carbonate tablets reduced the mean bioavailability of CPFX by 43% [21]. In an *in vitro* experiment on the release of CPFX over a cellulose membrane it was observed, that in the presence of calcium, aluminum or iron cations the CPFX release was slower than in the absence of the metal ions [22]. It can be stated that the circumstances of the above-mentioned studies (pH, food content, like fat, protein, calcium amount, etc.) were not the same, thus the results cannot be compared directly.

As all the examined alimentary components/meals contain large amounts of calcium an interaction with FQs seems to be likely.

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doi:10.1016/j.jpba.2009.12.003

Because of their high-calcium content, milk and other dairy products may impair the gastrointestinal absorption of FQs, which form sparingly soluble chelates with di- and trivalent metal ions [23–29]. The pH of the gastric milieu may also be an important determinant of the magnitude of the interaction, since ionization of the carboxylic group of the quinolone molecule allows for more effective chelating with the cation [30].

The contradictory interaction results published in the literature indicate the limitations in the field of food–drug interaction [31], at the same time emphasizing the need of *in vitro* studies observing FQ-milk interaction. In the present work we aimed to develop an *in vitro* dissolution test to highlight the possible molecular background causing CPFX–milk interaction. The *in vitro* dissolution of CPFX from film-coated tablets (Ciprinol® 500 mg) was analyzed at three different pH values (pH 1.2, 4.5 and 6.8) simulating certain parts of the gastrointestinal tract in the presence of water, low-fat milk, casein- or calcium enriched water. The effect of these alimentary components was compared to the results obtained for the CPFX-dissolution in the appropriate aqueous medium. In order to determine the amount of dissoluted CPFX originating from various matrices of the dissolution test, a previously validated method – using solid phase extraction (SPE) sample preparation followed by high performance liquid chromatography coupled with mass spectrometry (HPLC–MS) – was used in our study [32].

2. Materials and methods

2.1. Reagents and chemicals

Acetonitrile, methanol and water originated from Sigma–Aldrich Ltd. (Steinheim, Germany) were gradient grade. Ammonium-acetate, calcium chloride hexahydrate, casein (technical grade), CPFX hydrochloride salt (98.0% by HPLC), formic acid, sodium hydroxide and trifluoroacetic acid (TFA) (99%) were purchased from Sigma–Aldrich Ltd. (Budapest, Hungary). Milk Quick® Instant low-fat milk powder was delivered by Instantpack Ltd. (Berettyóújfalu, Hungary). Calibration standards of milk analyses were kindly offered by the Hungarian Dairy Research Institute (Mosonmagyaróvár, Hungary). To clean and to set the zero point of Milko-Scan 130-Series milk analyzer system 0.1% Triton X-100 (Sigma–Aldrich Ltd., Germany) solution was used. Aripiprazole (ARI) – as internal standard – was obtained from LGC Promochem (Wesel, Germany). Potassium dihydrogen phosphate and hydrochloric acid (Sigma–Aldrich Ltd., Germany) were used to prepare dissolution media during the dissolution test of Ciprinol® 500 mg film-coated tablets (KRKA, Slovenia).

2.2. Dissolution test

In vitro food–drug interaction study on CPFX was carried out with a paddle apparatus (Hanson SR8-Plus Dissolution Test Station, Hanson Research Corp., Chatsworth, CA, USA) prescribed by the United States Pharmacopeia. The dissolution of CPFX from Ciprinol® 500 mg film-coated tablets was analyzed at three different pH values (pH 1.2, 4.5 and 6.8) – according to the pH conditions of the gastrointestinal tract – in the presence of various food or food components (low-fat milk, calcium, casein). The tests were conducted using 500 ml of dissolution medium. Dissolution media were prepared by the use of hydrochloric acid solution, potassium dihydrogen phosphate solution or potassium dihydrogen phosphate added to sodium hydroxide solution with the pH values 1.2, 4.5 and 6.8, respectively, according to Ph. Eur 5. CPFX containing film-coated tablet was dropped into the dissolution fluid thermostated at 37 ± 0.5 °C and at the same time 250 ml – 'one FDA glass' – of either water or calcium/casein enriched water or low-fat milk was added into the dissolution vessel. The stirring speed of the paddle was 50 rpm. Aliquots (1.00 ml) were taken at the following sampling times: 5, 10, 15, 30, 45, 60, 90 and 120 min from the release medium and were not replaced by equal volume of the receptor medium. All measurements were carried out in nine parallels; data are given as average ± S.D.

2.3. Dissolution efficiency (DE)

To characterize drug release profiles dissolution efficiency (DE) parameter was used [33] and defined as the area under the dissolution curve up to a certain time t, expressed as a percentage of the area of the rectangle arising from 100% dissolution in the same time. DE can be calculated by the following equation:

$$\mathrm{DE} = \int \frac{y\,\mathrm{d}t}{100t}$$

where y is the drug percent dissolved at time t. In this paper, all dissolution efficiencies were obtained with t equal to 120 min.

The areas under the curve (AUC) were calculated for each dissolution profile by the trapezoidal rule implemented on Microsoft Office Excel 2003 for Windows.

2.4. Sample preparation

2.4.1. Stock solutions

1.0 mg/ml stock solution of CPFX was prepared by dissolving 25.0 mg CPFX in 25.0 ml water; 5.0 mg ARI, as internal standard was dissolved in 50.0 ml methanol for the preparation of stock internal standard solution with a concentration of 0.1 mg/ml. SPE and HPLC–MS methods were developed and optimized using the above-mentioned stock solutions.

2.4.2. Low-fat milk

Low-fat milk was prepared by dispersing the milk powder in distilled water. Low-fat milky medium was prepared from 90.0 g milk powder and 850.0 ml distilled water according to the package instructions. The prepared milky media were stored for 24 h at +4 °C temperature in refrigerator, in order to get a homogeneous system.

2.4.3. Milk analyses

Because of the diversity between the traded milk goods, in order to standardize the biological matrix we used freeze-dried milk from the same batch dissolved in distilled water instead of fresh milk. Milk samples were analyzed with a Milko-Scan 130-Series (Type 10900, Foss Electric, Hillerod, Denmark) Flow System & Infrared System. Fat, protein and lactose – contents of low-fat milk, used as dissolution medium-components in the dissolution test – were analyzed by Milko-Scan 130. The determined fat, protein and lactose contents for low-fat milk were 0.12 ± 0.005 g/100 ml, 3.13 ± 0.1 g/100 ml and 4.91 ± 0.1 g/100 ml, respectively. Before analyses milk samples were preheated to 40 °C in water bath in order to get a homogenous system.

2.4.4. Calcium enriched water

Calcium enriched water was prepared to study the effect of milk calcium on the dissolution profile of CPFX. According to the USDA National Nutrient Database for Standard Reference [34] calcium content of milk was taken as 204 mg calcium in 100 g low-fat milk solution. Thus, 250 g calcium enriched water, containing the same amount of calcium as the same volume of low-fat milk, was prepared by adding 2.79 g calcium chloride hexahydrate (equivalent to 510 mg calcium) to the appropriate amount of distilled water.

2.4.5. Casein enriched water

Casein enriched water was prepared to study the effect of milk proteins on the dissolution profile of CPFX. The casein concentration was chosen on the basis of our milk analysis results (3.13 g protein in 100 g low-fat milk). The whole protein amount of the milk was replaced by casein; thus, for the experiments 7.83 g casein was added to 242.17 g distilled water at 30 °C and after that was kept in refrigerator for 24 h.

2.4.6. Solid phase extraction methods

The clean up procedure was carried out with Supelco Discovery 100 mg/1 ml C_{18} endcapped SPE Cartridges (Sigma–Aldrich Ltd., Steinheim, Germany). After placing the column on a vacuum elution manifold (Supelco Visiprep™ 24, Sigma–Aldrich Ltd., Steinheim, Germany), it was conditioned with 2.0 ml methanol and 2.0 ml water. 250 μl samples were passed through the cartridges. Several methods were tested for rinsing and elution of the CPFX and ARI, and the following method was the most successful: the cartridge was washed with 2.0 ml water–methanol (80:20, v/v) mixture and CPFX and ARI were eluted with 6.0 ml acetonitrile containing 1% TFA. 1.0 ml of the eluate was evaporated to dryness at 50 °C under a stream of nitrogen (TurboVap® LV Evaporator, Zymark Corporation, Hopkinton, MA, USA). The residue was dissolved in 100 μl mixture of ammonium-acetate solution (0.02 M) (pH 2.5 adjusted with formic acid) and acetonitrile (80:20, v/v). 20.0 μl samples were injected to the HPLC–MS system.

2.5. High performance liquid chromatography and mass spectrometry method

Quantitative analysis of CPFX was carried out on an Agilent 1100 series HPLC-MS instrument (Agilent 1100 Series LC/MSD SL, Agilent Technologies Inc., Santa Clara, CA, USA) equipped with Hewlett-Packard ChemStation software (version A. 10.02). Supelco Discovery C_8 analytical column (150 mm × 4.6 mm, 5 μm) (Sigma–Aldrich Ltd., Steinheim, Germany) was used. A gradient program was developed by mixing eluent A (acetonitrile) and eluent B (0.02 M ammonium-acetate solution adjusted to pH 2.5 with formic acid according to Ballesteros et al. [35]) as follows: 0–8.5 min 80% B, 8.5–8.7 min 40% B, 8.7–17.5 min 40% B, 17.5–17.7 min 80% B and 17.7–23 min 80% B. The flow rate was 0.5 ml/min. The column temperature was set at 30 °C. Aripiprazole a quinolone derivative antipsychotic agent was proven to be the ideal internal standard because of its structural similarity to CPFX. Fig. 1 shows the chromatographic separation of CPFX and the internal standard with gradient elution.

Mass spectrometer (MSD SL, Agilent Technologies Inc., Santa Clara, CA, USA) equipped with electrospray ion source (ESI) was used to analyze CPFX after HPLC elution. The mass spectrometer worked in positive ion mode with selected-ion monitoring (SIM). In SIM-mode *m*/*z* values for CPFX and ARI were 332.1 and 448.1 Da for the protonated molecular ion (MH+), respectively. Nitrogen gas was applied as nebulizer and drying gas. The MS parameters during the measurements were as follows: drying gas flow, 13 l/min; nebulizer pressure, 60 psi; drying gas temperature, 350 °C; capillary voltage, 4.0 kV; fragmentor voltage, 70 V. The previously described method [32] which was developed and validated for the determination of CPFX in low- and high fat milk media was used throughout the present work.

3. Results and discussion

The CPFX-dissolution tests were conducted using 500 ml of dissolution medium, simulating the total fluid available in stomach/intestine during gastric/intestinal residence of the drug [36]. As in pharmacokinetic studies the volume of co-administered fluid, used to take in a tablet or a capsule is ~200–250 ml, we used a volume of 'one FDA glass', 250 ml, to simulate the real amount of co-administered food or food components [37]. Knowing that CPFX gets absorbed only from the stomach and the duodenum, thus only from a 20 to 30 cm long part of the gastrointestinal tract, and the relevant resident time for the absorption window is ~120 min, the samples were taken out throughout 120 min in our experiments, too [38,39]. pH values used in our study represent various parts of the gastrointestinal tract. The median pH of the stomach in fasted state has been usually reported to lie in the pH range 1.5–1.9 [40–42], although a few subjects may have pH values as low as below pH 1 or as high as pH 5–6 [39]. From the duodenum to the jejunum pH values of 4.4–7.4 are characteristic, thus pH 4.5 and 6.8 used in the present dissolution study simulating the pH conditions in the small intestine [43]. The addition of 250 ml low-fat milk/calcium enriched water/casein enriched water to the dissolution medium can have an impact on the pH of the system. It was found, that in case of pH 4.5 and 6.8 dissolution systems, the addition of 250 ml co-administered fluid does not significantly alter the original pH value. At pH 1.2 the addition of low-fat milk (with a pH 6.55) increases the pH value of the dissolution fluid to pH ~1.60.

Studying the dissolution of CPFX in aqueous media at three different pH values it can be observed that with increasing pH values the amount of free CPFX – at a given time – is decreasing (Fig. 2). For the sake of comparison, at pH 1.2 the half of the CPFX amount of the tablet (250 mg) is dissolved at about 15 min, while at pH 4.5 and 6.8 the appropriate values are ~35 and ~45 min, respec-

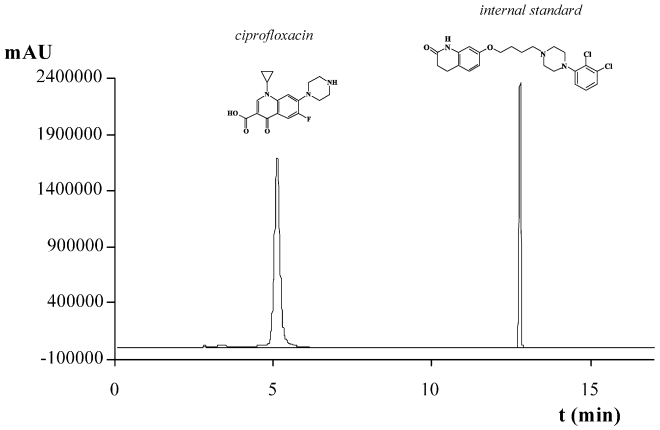

Fig. 1. Selected-ion monitoring chromatogram of ciprofloxacin and aripiprazole (internal standard); *m*/*z* = 332.1 and 448.1 Da, respectively.

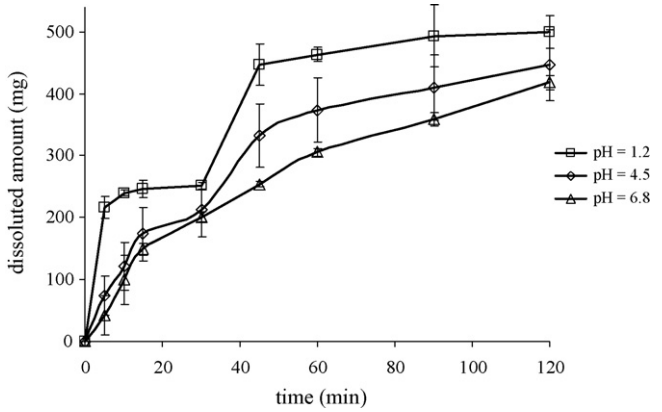

Fig. 2. Dissolution profile of ciprofloxacin at three different pH values with the addition of 250 ml water to the dissolution medium (*n* = 9).

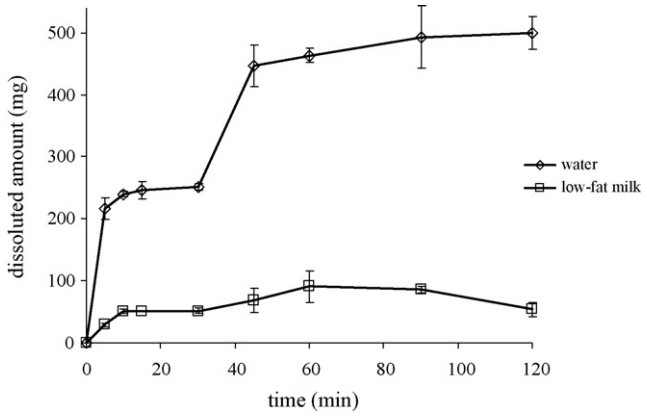

Fig. 3. Comparing the dissolution profiles of ciprofloxacin co-administrated with water and low-fat milk at pH 1.2. The shapes of the dissolution profiles derived at the two highest pH values are similar to those determined at pH 1.2 ($n = 9$).

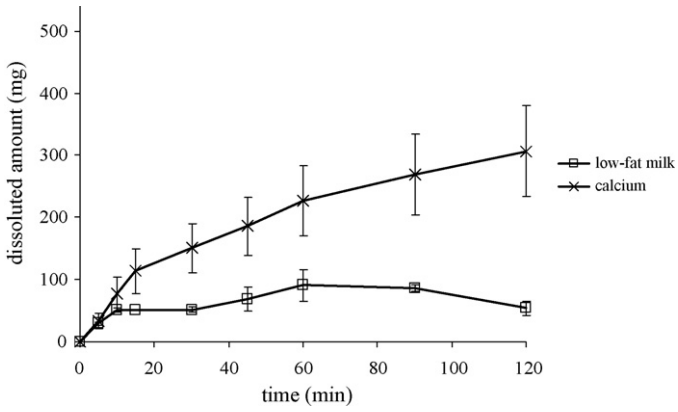

Fig. 4. Comparing the dissolution profiles of ciprofloxacin co-administrated with low-fat milk and calcium enriched water at pH 1.2. The shapes of the dissolution profiles derived at the two highest pH values are similar to those determined at pH 1.2 ($n = 9$).

tively. Furthermore, observing the dissolution profiles at pH 1.2 and 4.5 break-points are present in the curves at ~30 min. This can be explained with the special coating of the Ciprinol® 500 mg tablets. In 120 min 500 mg, 100% of the active ingredient is liberated.

Investigating the effect of low-fat milk on the dissolution of CPFX, it can be stated, that at each pH value examined – at each sampling time – the amount of dissolved CPFX is significantly decreased in comparison to the CPFX amounts measured in the aqueous dissolution media (Fig. 3). The shapes of the dissolution profiles derived at the two highest pH values are similar to those determined at pH 1.2, and they are not shown here.

Dissolution efficiency values – listed in Table 1 – make possible a convincing comparison. The dissolution efficiency values gained in the appropriate aqueous medium taking as 100%, at pH 1.2 only 17.1% of the reference amount is present in the low-fat milky medium, while at pH 4.5 and 6.8 the values are 58.8% and 19.5%, respectively. One can address the question why the shapes of the dissolution curves in milky medium are depending on pH values. At pH 4.5 the amount of dissolved CPFX as a function of time is continuously increasing. However, at pH 1.2 and 6.8 maximum value(s) can be observed. Regarding the experimental uncertainty the lack of continuous increase in the amount of dissolved CPFX is interesting. It can only be explained by the presence of a complicated balance in the system studied. Physico-chemical interactions between CPFX and the milky matrix studied can result in the decrease of free CPFX amount caused by complexation with metal ions being present in the milk and/or by adsorption at the surface of protein components. In order to evaluate the background of milk-CPFX interaction and to decide whether complexation and/or adsorption cause the decrease in the amount of bioavailable CPFX, the main components of milk were separately studied. The metal ion components of milk potentially playing a role in the complexation were modeled by calcium – using calcium enriched water to the dissolution studies – while the protein components as potential adsorption surfaces were modeled by casein – using casein enriched water.

Although a clinically relevant interaction between a fluoroquinolone and a metal cation was first described more than 20 years ago the biopharmaceutical mechanism of this interaction is still not known, it is thought to involve the formation of non-absorbable chelates [44]. The interaction of CPFX with metal ions (calcium, magnesium, aluminum, etc.) was investigated by various analytical methods, such as elemental and thermal analysis, FT-IR, spectral and electrical conductivity, X-ray diffraction and thermogravimetric analyses [45–49]. The results suggest a strong or slight complexation between calcium and CPFX-depending on the applied circumstances (pH, calcium concentration, etc.). The solubility results clearly show that the metal cations either do not effect or even increase the solubility of fluoroquinolones [50]. Thus they do not seem to influence the bioavailability of FQs by decreasing their solubility. Similarly to the earlier observations the present milk–CPFX *in vitro* interaction study confirms that 510 mg calcium – being present in the aqueous dissolution medium – has different effect on the released amount of CPFX, depending on the pH of the medium. At pH 1.2 the DE value determined for calcium-fortified medium is only 51%, while at pH 4.5 the appropriate value of DE is 92% (Table 1). It is consistent with the observation [30] that the acidic milieu leads to a more effective complexation between FQ and cations. Although calcium cations reduced the amount of free CPFX, the bioavailability reducing effect (Fig. 4) was not so expressed as in the case of milk (Fig. 3). The shapes of the dissolution profiles derived at the two highest pH values are similar to those determined at pH 1.2, and they are not shown here.

Supposing that calcium does not reduce the bioavailable CPFX amount in the same extent as milk, one can arise the question, which milk component can be taken responsible for the decreasing effect. Casein is the main protein component of the milk, being present in a concentration of ~84% of total proteins [36]. The total amount of milk protein was modeled by casein.

At lower pH values (pH 1.2 and 4.5) the casein enriched dissolution media come almost to term with the profiles observed for the

Table 1
Dissolution efficiency values (DE, %) determined for ciprofloxacin dissolution in low-fat milk, in calcium enriched water and in casein enriched water on the basis of AUC values. The dissolution efficiency determined for the appropriate aqueous systems is taken as reference (100%).

pH 1.2			pH 4.5			pH 6.8		
Dissolution medium	AUC	DE (%)	Dissolution medium	AUC	DE (%)	Dissolution medium	AUC	DE (%)
Water	47,889	100	Water	38,276	100	Water	32,931	100
Low-fat milk	8168	17.1	Low-fat milk	22,518	58.8	Low-fat milk	6419	19.5
Casein	7805	16.3	Casein	25,777	67.3	Casein	12,676	38.5
Calcium	24,546	51.3	Calcium	35,392	92.5	Calcium	22,537	68.4

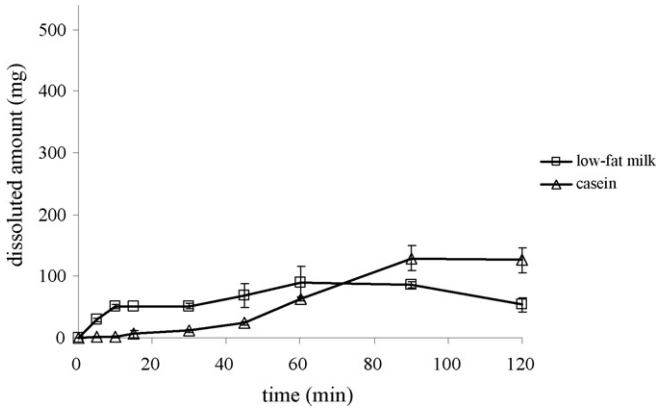

Fig. 5. Comparing the dissolution profiles of ciprofloxacin co-administrated with low-fat milk and casein enriched water at pH 1.2. The shapes of the dissolution profiles derived at the two highest pH values are similar to those determined at pH 1.2 ($n = 9$).

low-fat milky media (Table 1). Only 0.76% and 8.51% differences are between the DE values determined for the above-mentioned media at pH 1.2 and 4.5. However, at pH 6.8 the DE decreasing effect of casein (DE = 38.5%) is much lower than that of low-fat milk (DE = 19.5%). The difference between the DE values for casein enriched water and low-fat milk is 19.0% (Table 1). The exact mechanism of the DE decreasing effect in case of casein is still not known; but it is presumable that there is a connection with the interfacial properties of the protein. The interfacial properties and the structure of the adsorbed layers of a natural block copolymer, casein, are extensively studied by ellipsometry, surface force measurements, and neutron reflectivity measurements as well as by applying a specific proteolytic enzyme, endoproteinase Asp-N. Casein is a highly surface active protein forming brush like structures at interfaces depending on the surface properties and the ionic strength and salt composition [51]. It can be supposed that pH also has an impact on the adsorption properties of casein and it could give explanation for the observed differences of CPFX release profiles at various pH values in casein enriched water. Although the DE values determined for casein enriched water–CPFX system at the three pH values examined are different, the shapes of the dissolution profiles derived at all the three pH values are similar to that determined at pH 1.2 (the dissolution curves at pH 4.5 and 6.8 are not shown here) (Fig. 5).

Comparing the amount of bioavailable CPFX in the presence of casein or calcium enriched water, it can be concluded that casein has a more pronounced effect on the absorbable amount of the antibiotic – at each pH value studied, than calcium (Table 1). It means that *e.g.* at pH 1.2 taking a 500 mg CPFX tablet in casein enriched water only a maximum of 81.5 mg (DE = 16.3%) CPFX is bioavailable, while for calcium enriched water the appropriate absorbable CPFX amount is 256.3 mg (DE = 51.3%). According to the *in vivo* data [52] taking a 500 mg CPFX tablet with 200 ml of drinking water, the relative bioavailability for CPFX is 78.7%. The presence of milky components – according to our *in vitro* data – has a significant decreasing effect on the bioavailability of CPFX.

4. Conclusions

Our previously validated LC–ESI-MS analytical method appears to be suitable for studying the molecular background of the milk–CPFX interaction. In the case of concomitant intake of CPFX film-coated tablet and milk or other dairy products not only the complexation with calcium, but also the adsorption of CPFX on the surface of proteins decreases the absorbable amount of CPFX. Our results give evidence, that the presence of milk protein has a more pronounced effect on the CPFX-dissolution and bioavailability, than the complexation of CPFX with multivalent ions, *e.g.* calcium being present in the milky medium, thus highlighting the fact that protein-rich diet may have an impact on the CPFX bioavailability, too. This fact raises the inevitable need of reevaluation of the – until now – commonly accepted explanation (complexation is the main factor being responsible for the decreased bioavailability of CPFX) for the CPFX–milk interaction.

Acknowledgements

Authors thank the Agromilk Ltd. the kind support for the Milko-Scan 130 milk analyzer and the Hungarian Dairy Research Institute for the milk calibration standards.

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