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Letter to the Editor

The effect of milk components, especially of casein, on the bioavailability of ciprofloxacin tablets cannot be evaluated by dissolution testing

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In a recently published paper Pápai et al. [1] are dealing with the broader issue of fluoroquinolone interactions with food and drugs containing metal cations. It is a fact that the biopharmaceutical mechanism of the interaction, which was first described in 1985 by Höffken et al. [2] has not yet been fully explained and the long period of time with relatively few studies relevant to the mechanism of the interaction, may make it harder for researchers to keep in mind all the known facts. It must also be stressed that research of a neglected interaction, which is important for the therapeutic success or failure of antimicrobial therapy with fluoroquinolones as well as for the evolution of antimicrobial resistance, is highly commendable. Unfortunately, Pápai et al. [1] used dissolution testing of ciprofloxacin tablets in media containing different milk components at different pH values to evaluate the influence of milk components on the bioavailability of ciprofloxacin from tablets.

The science of the biopharmaceutical classification system (BCS) clearly explains that drug dissolution is not the only parameter affecting its bioavailability. For low permeability drugs (BCS classes 3 or 4) like ciprofloxacin a lack of correlation between the "in vitro" dissolution and "in vivo" bioavailability should be expected [3], thus the use of the term "bioavailability" in the title and in the conclusions of the paper by Pápai et al. [1] is clearly incorrect. Furthermore, a work by Wallis et al. showed that the decreased bioavailability of norfloxacin in dogs is caused by several different metal cations including calcium. The animals were given norfloxacin with and without metal cations dissolved in 0.01 M HCl via a stomach tube. Clearly, drug dissolution in the intestinal lumen could not be relevant for this interaction [4].

Pápai et al. have envisioned a simulation of the gastrointestinal conditions by dissolution testing at three different pH values to approximately emulate the conditions in the stomach, duodenum and the jejunum. However, they have failed to acknowledge a simple fact that casein (a protein) would be digested already in the stomach and in the duodenum. The proteins active surface, which might bind ciprofloxacin "in vitro" is thus not relevant at the site of absorption "in vivo". At most, it might be interesting to see if there is any binding of dissolved ciprofloxacin on the pancreatic digest of casein, but then there would be no active surface for the fluoroquinolone to bind to.

It is also worth mentioning that the results of early clinical studies of interactions between fluoroquinolones and calcium or food were indeed conflicting as it is described by Pápai et al. [1]. However, it is now clear that this interaction is clinically important, but can quite easily be avoided by spacing the administration of fluoroquinolones and calcium containing food or medicines as it was reviewed by Lomaestro and Bailie [5] in 1995.

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Response

In the recently published article entitled "*In vitro* food–drug interaction study: which milk component has a decreasing effect on the bioavailability of ciprofloxacin?" [1], we showed that under static circumstances the dissolved amount of ciprofloxacin (CPFX) was lowered by low-fat milk. Comparing the dissolution efficiency values for various dissolution media (calcium- and casein enriched water), casein as the main milk protein component can be taken as being responsible for the decreasing effect to the highest extent. Results were obtained by the quantitative determination of the free CPFX amount in the dissolution medium by an LC–MS method after SPE sample preparation.

In a *Letter to the Editor*, Žakelj claimed that "unfortunately Pápai et al. . . . used dissolution testing of ciprofloxacin tablets in media containing different milk components at different pH values to evaluate the influence of milk components on the bioavailability of ciprofloxacin".

In vitro dissolution testing is a widely used method for forecasting the oral absorption of drugs [2], for studying *in vitro* food and drug interactions [3] and "for predicting bioavailability" [4]. According to Žakelj "for low permeability drugs (BCS classes 3 or 4) like ciprofloxacin a lack of correlation between the "in vitro" dissolution and "in vivo" bioavailability should be expected."

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However, biopharmaceutical classification is more complex for CPFX. Wu and Benet [5] described CPFX as an interesting example, which is listed in Classes 2 and 3 with intermediate properties and also listed as Class 4. According to Amidon et al. [6] limited or no correlation can be expected for BCS 3 and 4 drugs. Moreover, our hypothesis was that the dissolution of CPFX is limited in the presence of milk components; therefore *in vitro* dissolution test may be predictive. In our study the importance of permeability is not disputed, however, we intended to investigate the factors having an impact on the *in vitro* dissolution of CPFX, meanwhile focusing not primarily on the rate of dissolution under various circumstances, but on the quantitative determination of the amount of released free (not-complexed, not adsorbed but available for absorption) CPFX. As liberation and adsorption are key steps in the LADME-system, and only the free, non-complexed/not-adsorbed form of the API molecules can be absorbed from the gastrointestinal tract (GIT), the amount of the free form of CPFX present in the dissolution medium (and also present *in vivo* in the various parts of the GIT) should be correlated with its bioavailability.

From this point of view the interaction of casein or calcium should be considered as a factor limiting the dissolution of the drug and hence reducing the amount of freely dissolved CPFX which is alone available for absorption. The results of the present *in vitro* dissolution tests are concordant with previously published *in vivo* observations of Neuvonen et al. which showed that at ½ h the plasma CPFX concentration was lowered by 70%, while the extent of bioavailability was reduced by 30% in the presence of milk [7]. Furthermore, Žakelj discommends that "casein would be digested already in the stomach and in the duodenum". The dissolution of CPFX was carried out in the presence of milk or a selected milk component under static circumstances avoiding the addition of any digesting enzymes. Since static circumstances were chosen to investigate and detect the interaction with casein in relevant terms the main protein component of the milk. Casein is "considered to be slow-digested protein" [8], as the lengths of the dissolution tests were 2 h, chosen according to the time interval covering the absorption window of CPFX, and the amounts of free CPFX in most cases studied reached their maximum values within 90 min. Obviously further *in vivo* studies are required to determine within what time period is the slow-digesting casein responsible for limiting dissolution and absorption.The results of earlier clinical studies are contradictory. The co-administration of 500 mg CPFX tablets and milk or yoghurt reduced the plasma peak concentrations by 36% and 47%, and the bioavailabilities by 30% to 36%, respectively [7]. Similarly to the observations of Neuvonen et al. there was a mean reduction of 40% in C_{max} and 43% in AUC when calcium carbonate was administered with CPFX, compared with ciprofloxacin alone [9]. However, with standard breakfast and antacids *no reducing effect* was observed on the extent of absorption and bioavailability of ciprofloxacin and ofloxacin [10] and on the pharmacokinetics of ciprofloxacin co-administered with high fat/high calcium breakfast [11]. Shah et al. reported that in either a fasted or fed state, there were no significant differences between C_{max} or $AUC_{0-\infty}$ values for CPFX [12]. The effect of milk on CPFX bioavailability, described by Neuvonen et al. [7], is in line with our *in vitro* data [9,10].

We agree that the interaction is clinically important and that it has to be taken into consideration to avoid the co-administration of fluoroquinolones and milk. In our recent article our goal was to put the possible role of casein in addition to that of calcium into spotlight; this had not been published before.

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