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Food effect: The combined effect of media pH and viscosity on the gastrointestinal absorption of ciprofloxacin tablet

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ABSTRACT

Background: The clinical implications of food-drug interactions may have to be taken seriously into account with oral drugs administration in order to minimize variations in drug bioavailability. Food intake may alter physiological changes in the pH and viscosity of the gastrointestinal lumen, which could affect the oral absorption of drugs.
Purpose: The aim of the present study was to have an insight on the effect of media parameters: viscosity and pHon the oral absorption of ciprofloxacin HCl from solid formulations using a model food: *Corchorus olitorius* (Jute) Soup.
Methods: In vitro disintegration and dissolution rates of ciprofloxacin tablet were evaluated using compendia buffer media in the presence/absence of *C. olitorius* leaves. These *in vitro* data were then input to GastroPlus™ to predict ciprofloxacin absorption profiles under fasted and fed states.
Results: The present study demonstrated the significance of luminal pH and viscosity on the dissolution and disintegration of solid formulations following postprandial ingestion of the viscous soup. The tablets showed prolonged disintegration times and reduced dissolution rates in this soup, which could be attributed to the postprandial elevation in media viscosity and reduced solubility at elevated gastricpH. The predicted model under fed state showed no impact on AUC but prolonged T_{max} and a decrease in C_{max}.
Conclusion: Concomitant intake of *C. olitorius* soup with ciprofloxacin might have negative effect on the rate of drug release from conventional immediate release tablets.

1. Introduction

Food-drug interaction is one of the major factors that affect the efficacy and safety of drugs. In fact, concomitant food intake may alter the systemic availability of many drugs, which may impact their therapeutic effectiveness. Food may have positive, negative or no effect on drug absorption. Negative food effect is of special importance for active pharmaceutical ingredients (API) with narrow therapeutic index, where impaired drug absorption may lead to a risk of treatment failure, whereas, positive food effect may increase the risk of drug toxicity (Fleisher et al., 1999).

The negative food effect on the drug absorption can be mediated through several mechanisms, including: Postprandial changes in the GI physiology (pH, motility, transient times, and viscosity), complexation interactions of the API with food components, reduced drug diffusivity and solubility, delayed dosage form disintegration and drug release under fed conditions (Abrahamsson et al., 2004; Kalantzi et al., 2005; Parojčić et al., 2008; Radwan et al., 2012, 2013 and 2014; Reppas et al., 1998).

Tablet disintegration and drug dissolution are critical steps in the process of drug absorption. Any delay in one of these steps will affect the overall release of the active ingredient. The *in vitro* dissolution and disintegration tests are recognized as valuable means for predicting drug bioperformance under fast and fed conditions.

Media viscosity was identified as one of the key parameters affecting drug release (Parojčić et al., 2008; Radwan et al., 2012). The viscosity of the gastric juice in the fasted state lies in the range 0.01–2 mPa·s. Ingestion of food leads to an elevation in the digesta viscosity, which was reported to be in the range of 300–4000 mPa·s (Marciani et al., 2001). The *in vivo* flow patterns within the GI tract are laminar and very low. The average gastric flow velocity was estimated to be 3 mm/s with the Reynold's numbers in the range of 0.01 to 30 (Abrahamsson et al., 2005 and Pal et al., 2004). Postprandial elevation in the luminal viscosity was shown to delay tablet disintegration and to reduce the dissolution of poorly permeable drugs with an absorption window in the proximal intestine (Radwan et al., 2012 and 2014). Previous reports have shown prolonged tablet disintegration times in different polymeric solutions, soups and beverages, which was explained in part by impaired water ingress into tablets under viscous conditions as well as film formation on the surface of the dosage form (Abrahamsson et al., 2004; Brouwers et al., 2011; Radwan et al., 2012 and 2014).

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Ciprofloxacin is a broad-spectrum fluoroquinolone that has an *in vitro* activity against a wide range of gram-negative and gram-positive microorganisms. It exhibits *in vitro* minimum inhibitory concentration (MIC) of 1 μg/ml or less against susceptible strains of microorganisms, however, more than 4 μg/ml is required against resistant strains (Cipro Labeling Revision, 2009). Ciprofloxacin can be classified as BCS class IV drug due to its low permeability and low solubility (Breda et al., 2009). Ciprofloxacin is known for its interactions with food rich in multivalent ions. Formation of insoluble metallic complex is a possible mechanism. Casein and calcium present in dairy products were reported to reduce the absorption of ciprofloxacin. Concomitant administration of milk with ciprofloxacin reduced C_{max} and AUC by 36% and 30%, respectively (Neuvonen et al., 1991). The intake of calcium-fortified juices has been demonstrated to reduce the bioavailability of ciprofloxacin (Akinleye et al., 2007; Neuhofel et al., 2002). Similarly, Frost et al. have reported a significant reduction in ciprofloxacin bioavailability (both C_{max} and AUC) when co-administered with antacid preparations containing aluminium hydroxide and calcium carbonate (Frost et al., 1992). In rabbits, concurrent administration of *Corchorus olitorius* soup reduced the bioavailability of ciprofloxacin by 43%, with a delay in T_{max} and a reduction in C_{max} by 33% (Radwan et al., 2016). However, the overall absorption of ciprofloxacin was not affected by concomitant intake of a standard breakfast except for an increase in the time to reach C_{max} (Ledergerber et al., 1985).

Corchorus olitorius is a member of the Tiliaceae plant family that is found in the Mediterranean region. It is also referred to as long-fruited jute, molokhia, tossa jute, jute mallow, and jew's mallow. *Corchorus olitorius* is rich in vitamins and mineral such as, potassium, calcium, phosphorous, iron, and carotene (Idirs et al., 2009). The leaves of this plant have diuretic, antipyretic, analgesic, antimicrobial, antitumor and antioxidants activity. It is known as “food of kings”, since the Egyptian pharaohs drank it since ancient times to recover from illnesses.

The green leaves of *C. olitorius* are used as an ingredient for a famous viscous soup in many countries and especially in Middle Eastern countries. The leaves of this plant are rich in mucilage polysaccharides and hydrocolloids that explain the slimy consistency of this soup. The viscosity of *C. olitorius* hydrocolloids was reported to surpass that of guar gum and locust bean gum at the same conditions (0.25–1%, at 25C°) (Yamazaki et al., 2008 and 2009).

Gastrointestinal simulation is considered as an important tool for predicting the *in vivo* behavior of drugs. *In silico* modeling is valuable for simulation of food drug interactions. In a previous study, an *in silico* absorption model has been developed for simulating ciprofloxacin HCl interactions with metallic compounds (Stojkovic et al., 2014).

The aim of this study was to have an insight on food effect on ciprofloxacin tablet disintegration and dissolution as well as to evaluate the effects of media parameters, such as viscosity and pH on the oral absorption of ciprofloxacin HCl. *C. olitorius* (Jute) soup was selected as a test meal, since the leaves of this plant are rich in dietary fibers, mucilage and polysaccharides that upon intake may elevate the luminal viscosity by several orders of magnitudes. The viscosity of *C. olitorius* hydrocolloids was shown to surpass that of other natural gums. Therefore, the effect of the viscosity of this soup on tablet disintegration and drug release was tested. Moreover, simulation technology was used to develop a drug-specific *in silico* absorption model under fasted and fed states.

1.1. Study design

In vitro dissolution and disintegration studies in buffer solutions without/with the addition of *C. olitorius* leaves were performed in order to predict the *in vivo* behavior following a postprandial administration of ciprofloxacin solid dosage forms. In addition, a drug specific absorption model for ciprofloxacin is built to predict the *in vivo* performance of ciprofloxacin HCl under fasted and fed states based on the experimental *in vitro* dissolution data in the different media.

In this study, predictions of the *in vivo* behavior can be conducted based on the *in vitro* dissolution data by applying modeling and simulation techniques. This approach can be facilitated using prediction software such as GastroPlus™, which has been reported to accurately predict the oral Pharmacokinetic (PK) profile of small drug-like molecules. GastroPlus™ modeling and simulation can be employed using *in vitro* data to predict PK profiles. Previous reports demonstrated the feasibility of adequately predicting plasma-concentration-time profiles with *in silico* derived as well as *in vitro* measured parameters and hence predicting PK profiles with minimal data.

2. Materials and methods

2.1. Materials and dosage form

Ciprofloxacin hydrochloride immediate release (IR) tablets (Ciprocare® 500 mg, Pharmacare, Palestine) were used in this study. Ciprofloxacin hydrochloride salt was kindly donated by Pharmacare, Palestine. HPLC grade solvents of acetonitrile (ACN) and methanol (MeOH) were purchased from Carlo Erba (DASIT GROUP); orthrophosphoric acid and triethylamine were purchased from Merck; High purified water was prepared by using a Millipore Milli-Q plus water purification system. All other reagents were analytical grade. *C. olitarious* leaves were obtained from local market.

2.2. Study media

Various types of test media were used:

- Buffers solutions: USP HCl buffer pH 1.2, and simulated intestinal fluid (SIF) pH 6.8 was prepared by dissolving 6.8 g KH_2PO_4, 0.098 g NaOH in 1000 ml distilled water. Both solutions were used as reference media to simulate the fasted conditions in the different gastrointestinal regions.
- *C. olitorius* soup was prepared in different concentrations (2.5%, 5%, 7.5%) to investigate the effect of food viscosity on the disintegration and the dissolution of ciprofloxacin. The fresh leaves of *C. olitorius* were cut and mixed thoroughly with 1 L media (SIF or 0.1N HCL) using mixer and heated until boiling.

2.3. Rheological measurements

Rheological measurements of the different media were measured using a rotational rheometer (Brookfield, Germany). All measurements were made in triplicate at 37 °C. The viscosity of the soup was determined within the shear rate range (0–100 rpm).

2.4. Disintegration study

Tablet disintegration tests were carried out in a disintegration apparatus (ERWEKA ZT 221, Germany) without disks. All tests were carried out in 800 ml of the investigated media at 37 °C using six tablets, one per vessel, for each test.

2.5. Drug release study

Drug release from the tablets was determined according to Ph. *Eur.* using a rotating paddle apparatus II (Erweka dt70, Germany). All tests were conducted in 900 ml dissolution media at 37 °C with a paddle rotating speed of 50 rpm. 4 ml samples were withdrawn at predetermined time intervals, and filtered using a0.45-μm PTFE syringe filter and assayed for ciprofloxacin HCl concentrations using HPLC.