Received: 14 March 2018 | Revised: 15 February 2019 | Accepted: 20 February 2019

DOI: 10.1002/bdd.2176

ORIGINAL PAPER

WILEY

Evaluation of food effect on the oral absorption of clarithromycin from immediate release tablet using physiological modelling

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Abstract

Background: Food may affect the oral absorption of drugs. Purpose: The aim of the present study was to investigate the influence of food on the oral absorption of clarithromycin by evaluating the effect of media parameters, such as pH, bile secretions and food composition, on the release of the drug from immediate release tablets, using *in vitro* and *in silico* assessments. Method: The solubility, disintegration and dissolution profiles of clarithromycin 500 mg immediate release tablets in compendial media with/without the addition of a homogenized FDA meal as well as in biorelevant simulated intestinal media mimicking fasting and fed conditions were determined. These *in vitro* data were input to GastroPlus™, which was used for developing a physiological absorption model capable of anticipating the effect of food on clarithromycin absorption. Level A *in vitro–in vivo* linear correlations were established using a mechanistic absorption modelling based deconvolution approach. Results: The pH of the media has a profound effect on clarithromycin solubility, tablet disintegration and drug release. Clarithromycin has lower solubility in biorelevant media compared with other media, due to complex formation with bile salts. Clarithromycin tablets exhibited prolonged disintegration times and reduced dissolution rates in the presence of the standard FDA meal. The simulation model predicted no significant food effect on the oral bioavailability of clarithromycin. The developed IVIVC model considered SIF, acetate buffer and FaSSIF media to be the most relevant from the physiological standpoint. Conclusion: The intake of a standard FDA meal may have no significant effect on the oral bioavailability of clarithromycin immediate release tablet.

KEYWORDS

biorelevant media, clarithromycin, drug release, food effect, physiological modelling

1 | INTRODUCTION

Food may alter the pharmacokinetics of drugs and produce positive, negative or no effect on drug absorption (Fleisher, Li, Zhou, Pao, & Karim, 1999; Welling, 1996). A positive food effect, i.e. the extent of drug absorption (AUC and C_{max}) is increased by 25% or more when administered with food, may produce clinically significant consequences and increase the risk of drug toxicity (Gu et al., 2007). Several mechanisms have been proposed to explain the observed positive food effect on BCS class II drugs, which include: prolonged residence time, reduced gastric emptying, improved solubility in the presence of high fat meal and bile salts, increased lymphatic uptake, altered

pre-systemic metabolism and increased splanchnic blood flow (Fleisher et al., 1999).

The Food and Drug Administration (FDA) has recognized the potential of food on the bioavailability of drugs and developed a guidance that requires food-effect bioavailability (BA) and fed bioequivalence (BE) studies to be conducted for a large majority of drugs during investigational new drug applications (INDs). This FDA guidance does not accept waivers for *in vivo* BA and BE studies under fed conditions. According to the FDA guidance, a high-fat and high-calorie meal is the recommended test meal for fed BA and BE studies since it can provide the greatest impact on GI physiology. An example test meal would be two eggs fried in butter, two slices of toast with butter, four ounces of hash brown potatoes and eight ounces of whole milk (US Department of Health and Human Services, 2002).

Various approaches have been described in the literature for predicting a food effect on drug absorption, which include: *in silico*, *in vitro* and *in vivo* animal methods. The Biopharmaceutics Classification System (BCS) is one approach, which classifies the potential for a drug to demonstrate a food effect based on the solubility and the permeability data (Amidon, Lennernäs, Shah, & Crison, 1995).

In vitro dissolution testing is considered a vital tool in predicting the *in vivo* performance of drugs. Since *in vivo* BA and BE studies are expensive and invasive, dissolution could be used as a surrogate for BE studies, especially for BCS class I and III drugs when they exhibit rapid or very rapid dissolution (CDER, 2000). Various physiologically relevant media were proposed to simulate the gastric and intestinal fluids under fasted and fed conditions. These biorelevant media were superior to compendia media in predicting the effect of food on the pharmacokinetic profiles of BCS class II drugs. These biorelevant media were suggested as an alternative to the homogenized standard meal and considered factors such as media pH, osmolality, surface tension, bile salts, lipolytic enzymes and phospholipids contents (Klein, 2010). However, the effect of a standard FDA meal composition and dietary components on drug release was not well defined.

Physiologically based pharmacokinetic modelling (PBPK) has been applied in predicting a food effect using *in silico* simulation software packages, such as: GastroPlus™, SimCyp, PKsim and Stella. Some published literatures have suggested the coupling of *in silico* modelling with *in vitro* predictive dissolution testing for better prediction of food effect on drug performance (Andreas et al., 2017; Heimbach, Xia, Lin, & He, 2013; Ilić, Kovačević, & Parojčić, 2015; Jones, Parrott, Ohlenbusch, & Lavé, 2006; Parrott, Lukacova, Fraczkiewicz, & Bolger, 2009; Radwan, Zaid, Jaradat, & Odeh, 2017; Shono et al., 2009). Despite the many successful examples of food-effect predictions using *in silico* tools, health authorities are still critical of the utility of PBPK modelling in predicting the clinical food effect on the oral absorption of drugs. A previous study has evaluated the predictive performance of PBPK as a useful tool for the prospective prediction of the food effect in 48 cases. In this study, PBPK modelling described 50% of the observed food effect within a predefined boundary of 25%. The successful application of PBPK modelling in food-effect predictions requires model verification against *in vivo* clinical data (Li, Zhao, Pan, & Wagner, 2018).

Clarithromycin is a broad-spectrum antibiotic, belonging to the macrolide group. It can be used in the treatment of lower respiratory tract infection, sinusitis, pharyngitis and skin infections (Hardy, Guay, & Jones, 1992). Clarithromycin is rapidly absorbed and has an oral bioavailability of 50 to 55% due to first-pass metabolism. Clarithromycin is metabolized in the liver by cytochrome P-450-III to one active metabolite: 14-hydroxy clarithromycin. About one third of the oral dose of clarithromycin is excreted unchanged or as an active metabolite in the urine, while the remainder is excreted via the biliary route (Davey, 1991; Rodvold, 1999). Clarithromycin is stable in the pH range 3–8, but undergoes rapid degradation in acidic pH conditions in the stomach with a degradation half-life of 17 minutes (Nakagawa, Itai, Yoshida, & Nagai, 1992). Clarithromycin can be classified as BCS class II due to its low solubility and good permeability (Morakul, Suksiriworapong, Leanpolchareanchai, & Junyaprasert, 2013).

Literature data on food effect on the oral bioavailability for clarithromycin is contradictory. A preclinical study in dogs demonstrated a pronounced decrease in C_{max} and AUC values in the fed state compared with the fasted state. On the other hand, an *in vivo* human study reported an increase in the bioavailability of clarithromycin by 25% upon co-administration of clarithromycin immediate-release tablets with food, however, this increase was considered to be not clinically significant (Chu, Deaton, & Cavanaugh, 1992a; Chu, Park, Locke, Wilson, & Cavanaugh, 1992b). They concluded that immediate-release clarithromycin could be taken with or without food. On the other hand, several studies have demonstrated a significant positive-food effect on the rate and extent of absorption of clarithromycin 500 mg extended release tablet (Alkhalidi, Tamimi, Salem, Ibrahim, & Sallam, 2008; Guay et al., 2001; Gurule, Monif, Verma, & Khuroo, 2009).

The main objectives of this work were: (1) to understand the underlying mechanism of food effects on the oral absorption of clarithromycin from immediate release formulations using a PBPK approach and *in vitro* dissolution testing, (2) to study the influence of dissolution media key parameters that control clarithromycin release such as food composition, bile salts concentration and media pH, furthermore, (3) to develop a correlation between the *in vitro* dissolution and *in vivo* PK data, which will help in selecting the most suitable dissolution media that could be used as a surrogate for *in vivo* bioavailability testing.

In an attempt to achieve these objectives, *in vitro* dissolution and disintegration studies in simple compendial buffers as well as media simulating the gastric and intestinal environments under both prandial conditions were conducted. The effect of media pH on the release and disintegration behaviour of clarithromycin formulations was evaluated using compendial media of different pH (1.2, 4.5, 6.8). Moreover, the impact of bile salts concentrations in the small intestine under both fasted and fed states on the absorption of clarithromycin was investigated using biorelevant media (FaSSIF and FeSSIF) and comparing the results with blank buffers. Additional dissolution testing was used to investigate the influence of dietary composition on the release behaviour of the clarithromycin tablet using media with an added real homogenized FDA meal and comparing the results with blank buffers.

Furthermore, simulation technology was used to develop a physiological absorption model for clarithromycin that is capable of predicting the *in vivo* performance of the drug. PBPK modelling was used to predict the food effect for clarithromycin from immediate release formulation by integrating the *in vitro* solubility and dissolution data in the model. In this study, GastroPlus™ can be used with a high level of confidence to describe the food effect on clarithromycin absorption since the model can be validated with the pre-existing i.v. and p.o. pharmacokinetics data (already available in the literature).

2 | MATERIALS AND METHODS

2.1 | Materials and dosage form

Hydrochloric acid, glacial acetic acid (Frutarom), monobasic potassium phosphate, sodium acetate, phosphoric acid (Frutarom), methanol HPLC-grade (Lab-Scan, Ireland), sodium hydroxide, sodium hydroxide (pellets), sodium chloride, sodium phosphate monobasic monohydrate (Sigma-Aldrich), acetonitrile HPLC-grade (Sigma-Aldrich) and biorelevant media powder (Biorelevant Company, UK) were used during the study. Claricare® 500 mg immediate release tablets were purchased from local pharmacies. Clarithromycin API was obtained as a gift sample from Pharmacare Company, Palestine.

2.2 | Media composition

Various types of study media with different pH were used to simulate the fasted state:

- Simulated gastric fluid (SGF) (USP) without pepsin, which has a pH of 1.2, was prepared by diluting 9.7 ml of 32% HCl in 1 L of distilled water.
- Acetate buffer (pH = 4.5) (USP) was prepared by mixing 2.99 g of sodium acetate, and 1.66 g of glacial acetic acid, then distilled water was added up to 1 L, the pH adjusted to 4.5.
- Simulated intestinal fluid (SIF) (USP), which has a pH of 6.8, was prepared by dissolving 6.8 g monobasic potassium phosphate and 0.896 g sodium hydroxide in 1000 ml distilled water.
- The FDA standard breakfast was prepared to investigate the effect of food composition on the *in vitro* release of clarithromycin. The FDA standard meal was selected as a test meal since it is the food recommended to be administered to healthy volunteers in fed bioequivalence and fed bioavailability studies. The FDA food was prepared by mixing: two strips of hot dogs (44 g), two eggs fried in butter, two slices of toast with butter, eight ounces of whole milk (226.8 g), four ounces of hash brown potato (113.39 g) and 240 ml of tap water in a mixer until homogenized. Then, 100 ml of this homogenized meal was mixed thoroughly with 800 ml of the different buffers (SGF, acetate buffer, SIF) using a mixer.
- Biorelevant media (FaSSIF and FeSSIF) were prepared, according to the manufacturer's instruction (Biorelevant.com, Croydon, Surrey, UK). FaSSIF (pH = 6.5) was prepared in two steps. In the first step, phosphate buffer was prepared by dissolving 3.95 g of $NaH_2PO_4{}^*H_2O$ (monohydrate), 0.42 g sodium hydroxide (pellets) and 6.19 g of sodium chloride in 0.9 L of purified water. The pH was adjusted to 6.5 with either 1 N HCl or 1 N NaOH. Purified water was added to make up the volume to 1 L. The second step entailed dissolving 2.24 g of FaSSIF powder in 500 ml of the buffer, and stirring until the powder had dissolved and the volume was made up to 1 L. FaSSIF was left to stand for 2 hr before being used.
- FeSSIF media (pH = 5), was prepared using acetate buffer, in which 8.65 g of glacial acetic acid, 4.04 g of sodium hydroxide (pellets) and 11.87 g of sodium chloride were dissolved in 0.9 L of purified water. The pH was adjusted to the desired value (pH = 5). Purified water was added to make the volume up to 1 L. 11.2 g of the powder was then added to 500 ml of the acetate buffer, and stirred until all the powder had dissolved, then the volume was made up to 1 L with purified water.

2.3 | pH measurements

All measurements of pH values of the different media were determined using a pH meter (Jenway 3510).

2.4 | Degradation of clarithromycin in acidic medium

The impact of acidic pH on the degradation of clarithromycin in aqueous medium was studied by HPLC assay of clarithromycin standard aqueous solution at pH 1.2 over a period of 2 hours. The study was conducted by dissolving 10 mg of clarithromycin standard drug in 10 ml of acetonitrile before adding 100 ml of 0.1 N HCl (pH = 1.2). The samples were withdrawn from the solution over a period of 2 hours, filtered and assayed for clarithromycin concentrations using HPLC. The concentrations of clarithromycin in the samples were determined by comparing the peak areas with the response of the standard curve.

2.5 | Solubility study

The flask shake method was used to determine the equilibrium solubility of clarithromycin in the different media. Clarithromycin powder was added in an excess amount to 10 ml of the investigated media in test tubes, which were kept in a shaker (Memmert, Germany) at 37°C for 48 h. Thereafter, the samples were centrifuged, filtered and analysed by HPLC. Samples containing the homogenized FDA meal were treated by the same method used for dissolution testing. The measurements were made in triplicate.

2.6 | Rheological measurements

The rheological behaviour of the diluted FDA meal was characterized using a rotational rheometer (Brookfield DV1 viscometer) spindle 7,

within a shear rate range of 0–100 rpm. The measurements were made in triplicate at 37 °C.

2.7 | Disintegration study

Tablet disintegration rates in the different media were determined using a tablet disintegration tester (μP, 1901) at 37 °C. All the tests were carried out according to the USP, in 800 ml of the various media, using six tablets, one per vessel, for each test. Individual disintegration times were measured and mean ± SD reported.

2.8 | Drug release study

Clarithromycin release from the IR tablets was determined using apparatus type II (BTC – 9100, Hsiang Tai Machinery Industry Co, Ltd) with a paddle rotating at a speed of 50 rpm. The tests were conducted in 500 ml dissolution media at 37 °C. Five ml samples were withdrawn at predetermined time intervals: 0, 5, 10, 15, 30, 45, 60, 90 and 120 min, filtered using a 0.45 μm PTFE syringe filter and assayed for clarithromycin concentrations using HPLC. Samples containing the FDA meal were treated before further analysis in order to precipitate protein. Five ml samples were centrifuged at 4000 rpm for 5 min to separate food components. One ml of the supernatant layer was removed and further treated with acetonitrile. Different amounts of acetonitrile were tried in an attempt to determine the proper concentration required to precipitate any remaining proteins in the 1 ml sample. 100 μl of acetonitrile was the lowest volume that produced clear samples and precipitated most of the proteins. After which, the sample was centrifuged again at 15000 rpm for 10 min. The supernatant layer was filtered before being taken for analysis, and subsequently analysed using HPLC. Dissolution testing in biorelevant media was performed according to the recently approved testing from Orbito (Mann et al., 2017).

2.9 | HPLC analysis

The HPLC analysis of clarithromycin in the various samples was performed using a Waters HPLC system, equipped with Waters 1525 binary pump and a Waters 2998 photodiode array detector. The chromatographic separation of clarithromycin was achieved using a stainless steel column (25 cm × 4.6 mm) packed with base-deactivated octadecylsilyl silica gel chromatography (5 μm). The mobile phase was prepared by mixing methanol and 0.067 M monobasic potassium phosphate (650:350), then the pH was adjusted to 4 by phosphoric acid. The mobile phase was filtered using a 0.45 μm microporous filter and was degassed by sonication for 5 min prior to use. A wavelength of 210 nm was used. The flow rate was set at 1.1 ml/min and the injection volume was 20 μl. The standard solution was prepared by dissolving 150 mg of accurately weighed clarithromycin in 50 ml acetonitrile, then diluted with water up to 100 ml (USP). The retention time for clarithromycin was 8 min. The concentrations of clarithromycin in the unknown samples were determined by comparing the peak areas with that of a standard curve.

2.10 | Drug release and statistical analysis

Drug release data in the different media were assessed using similarity and difference factors (f_2 and f_1) respectively as reported in Equations (1) and (2). The f_2 factor measures the closeness between two profiles while f_1 measures the difference between the two profiles:

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

$$f_1 = \left\{\left[\sum_{t=1}^{n}|R_t-T_t|\right]/\left[\sum_{t=1}^{n}R_t\right]\right\}*100 \quad (2)$$

Where R_t and T_t are the percentages of drug dissolved at each time point for the reference and test products, respectively. An f_1 value greater than 15 indicates non-similarity, and an f_2 value greater than 50 indicates significant similarity between the two analysed products.

2.11 | *In silico* simulation using Gastroplus™

GastroPlus™ software (version 9.0, Simulations Plus Inc., Lancaster, CA) was used for building an absorption model for clarithromycin under fasted and fed states. This software is based on the advanced compartmental absorption and transit (ACAT) model and is composed of three modules: compound, physiology and pharmacokinetics. For the compound module, the input parameters were either determined experimentally or taken from the literature. The summary of the input parameters used in the simulation is given in Table 1. The experimental values for clarithromycin solubility at the different pH and biorelevant media were incorporated in the model. The effective permeability of clarithromycin (P_{eff}, 20×10^{-4} cm/s) was estimated using GastroPlus™, based on the reported intestinal permeability of the drug in rat jejunum (1.20×10^{-3} cm/s) (Zakeri-Milani et al., 2014). The default values for precipitation time (900 s), particle density (1.2 g/ml) and particle size (25 μm) were used.

In the physiology module, the simulations were conducted using the GastroPlus™ single simulation mode. The human physiology fasted mode was selected for predicting the absorption profile under the fasted state, while the human physiology fed mode was used when conducting the simulations upon the concomitant intake of FDA meal. All the physiological parameters were fixed at default values in both states. The water content was 10% in the colon and 40% in the small intestine.

In the pharmacokinetic module, clarithromycin follows the one compartment model. The PK parameters (volume of distribution and clearance) used to establish the model were obtained from an (i.v./p.o.) crossover study, which was performed to investigate the absolute bioavailability of clarithromycin tablets compared with the i.v. infusion (Chu et al., 1992). The volume of distribution (V_d = 1.8 L/kg), total body clearance (CL = 29 L/h) and the fraction unbound to plasma

TABLE 1 Input data for simulation

Parameter	Value
Molecular weight (g/mole)	747.95[a]
Log D	1.7 at pH 7.4[a]
pKa	8.9[b]
Dose (mg)	500
Formulation	Tablet
Dose volume (ml)	250[c]
Precipitation time (s)	900[c]
Particle density (g/ml)	1.2[c]
Particle size (μm)	25[c]
Human P_{eff} (cm/s)	20×10^{-4}[d]
Solubility (mg/ml)	Fasted: 1.04 (pH = 4.5), 0.8 (pH = 6.8), 1.43 (FaSSIF) Fed: 1.5 (pH = 4.6), 4.5 (pH = 6.7), 1.07 (FeSSIF)[e]
Chemical degradation rate vs. pH (%/h)	100% (pH 1.0) 80% (pH = 1.2) 20% (pH = 1.5) 0% (pH = 3)[f]
Total body clearance (L/h)	29[g]
Volume of distribution (L/kg)	1.8[g]
First-pass extraction ratio (%)	23%[h]
f_{un}	30%[i,j]
Bioavailability (F)	55%[h,i,j]

[a]Fernandes et al, 1989.

[b]Drug Bank.

[c]Gastroplus default value.

[d]See text.

[e]Experimental solubility test data.

[f]Fujiki et al., 2011.

[g]Chu et al., 1992.

[h]See text.

[i]Davey, 1991.

[j]Rodvold, 1999.

protein (f_u = 30%) derived from i.v. data were used in model development. Clarithromycin is known to undergo first-pass metabolism. The percentage first-pass extraction was calculated by using the following Equation (3):

$$\%\text{First Pass Extraction} = \frac{CL_H}{Q_H} * 100\% \quad (3)$$

Where CL_H is the hepatic blood clearance 21.3 L/hr (Chu et al., 1992b) and Q_H is the hepatic blood flow (90 L/hr).

The model was verified by comparing the simulations with the observed data generated from other clinical studies. The *in vivo* concentration–time profile of the product (Claricare®) obtained from Pharmacare Ltd was used to verify the model under the fasted state. Whereas, the *in vivo* data for clarithromycin taken from the Chu et al. (1992b) study was used to verify the model under the fed state (Chu et al., 1992b). The model was built to describe the fasted state, which was then implemented to simulate the fed state. The observed C_{max}, AUC, $T_{1/2}$ and T_{max} under the fasted state were compared with the predicted values to verify the model. Simulation of the fed state was performed using the human physiology fed mode and introducing the solubility data under fed conditions. The simulations were conducted using the z factor (Takano) as a dissolution model in an attempt to integrate the *in vitro* dissolution data at various pH conditions. The z factor values for media simulating the fasted state of different pH were used as an input function for building the model under the fasted state. Whereas the z factor values for media simulating the fed state were incorporated in building the fed model.

The 'IR tablet mode' was used to refer to immediate (IR)-release tablets. Clarithromycin may undergo decomposition under low pH conditions. Additional simulations were conducted to account for the loss of clarithromycin due to acid-induced degradation, using an input table of the observed degradation rates vs. pH. The decomposition rate constants under various pH were obtained from the report of Fujiki et al. (Fujiki, Iwao, Kobayashi, Miyagishima, & Itai, 2011).

Furthermore, parameter sensitivity analysis (PSA) was conducted to investigate the impact of some key parameters on the rate and extent of clarithromycin absorption under both fasted and fed conditions.

The predictability of the simulation was measured by the percent prediction error (% PE) between the predicted and *in vivo* observed data, which can be calculated using the following Equation (4):

$$\%PE = \frac{PK_{\text{predicted}} - PK_{\text{observed}}}{PK_{\text{observed}}} * 100\% \quad (4)$$

2.11.1 | Virtual population simulations

Virtual BE trials were conducted in a crossover design in 25 healthy subjects randomly selected by GastroPlus™ using the population simulator mode to investigate food effect on the bioavailability of 500 mg clarithromycin IR tablet. All selected physiological and PK parameters are randomly sampled from log-normal distribution with a defined coefficient of variance CV% of 20–30%. The population simulation can estimate 90% CI of C_{max}, AUC_{0-inf} and the mean plasma concentration. The virtual tests were conducted after a single dose under fasted and fed state.

2.12 | *In vitro in vivo* correlation/relationship (IVIVC/R)

An IVIVR was developed using the IVIVC Plus Module™ integrated within the GastroPlus™ software. The *in vivo* fraction of clarithromycin absorbed under both fasted and fed conditions was estimated using the mechanistic absorption deconvolution approach. The fraction of drug absorbed at specific time points was plotted against the percentage of drug dissolved *in vitro* at the same time points. The IVIVR were established between the *in vivo* PK data under the fasted state and the

in vitro dissolution data in media mimicking fasting conditions (SGF, SIF, acetate buffer and FaSSIF). Whereas, in the fed state, the IVIVR were evaluated using the fed absorption profile and the *in vitro* release data in media simulating fed conditions (FeSSIF, FDA containing media). Regression analysis was used to evaluate the obtained correlations.

3 | RESULTS

3.1 | Clarithromycin degradation study

A degradation study of clarithromycin standard solution was carried out in 0.1 N HCl at room temperature for 2 hours. The degradation rate of clarithromycin was found to be 50% within 1 hour. These findings are in agreement with previous reports that investigated the effect of media acidity on the stability of clarithromycin from immediate release tablets. Clarithromycin was shown to be stable at a pH range of 3–8 in aqueous solution, but it rapidly degrades at gastric pH (1–2) with a decomposition half-life of 10.4 minutes (Fujiki et al., 2011; Manani, 2014). Similarly, Manani (2014) reported a degradation rate of 64% of clarithromycin active ingredient within 1 hour at pH = 1.2 (Nakagawa, Itai, Yoshida, & Nagai, 1992).

3.2 | Solubility study

The results of the solubility determinations of clarithromycin in the different media are presented in Table 2.The solubility of clarithromycin was shown to be pH independent within the physiological range. Clarithromycin is a weak base with a pKa of 8.8, which is available in the ionized form within the pH range (1.5–7.5). The drug demonstrated not much difference in the solubility values at pH 6.8 and 4.5. The solubility at pH 1.2 was not determined since clarithromycin undergoes rapid degradation under acidic conditions.

Food has an apparent effect on clarithromycin solubility. The solubility of clarithromycin in the presence of food was greater when comparing results in buffer media alone. The high fat content in the FDA meal would play a crucial role in enhancing the solubility of lipophilic drugs, such as BCS class II drugs. It was possible to measure the clarithromycin solubility in SGF with FDA meal (pH = 1.4) since the decomposition rate was much lower than at pH 1.2. The decomposition rate constant at pH 1.5 (k_{dec} = 3.66 × 10^{-2} min^{-1}) was reported to be much slower than at pH 1.2 (k_{dec} = 1.04 × 10^{-1} min^{-1}) (Fujiki et al., 2011). However, clarithromycin still undergoes decomposition at pH = 1.4, which makes the reliability of these measurements questionable.

Interestingly, the solubility of clarithromycin in FeSSIF was lower than that in FaSSIF, despite the higher bile salts content in this medium, which would be expected to aid solubility of this lipophilic drug.

TABLE 2 The solubility of clarithromycin and the Z-factor values for the different dissolution media

Media	pH	Solubility (mg/ml)	SD	Z-factor (ml/mg/s)
SGF	1.2	*	*	3.83 *10^{-5}
SGF with FDA meal	1.4	1.8	0.95	6.06 × 10^{-5}
Acetate buffer	4.5	1.04	0.22	2.79 × 10^{-4}
Acetate buffer with FDA meal	4.6	1.5	0.05	4.38 × 10^{-4}
SIF	6.8	0.8	0.15	2.03 × 10^{-3}
SIF with FDA meal	6.7	4.5	0.77	2.83 × 10^{-4}
FaSSIF	5	1.43	0.09	2.83 × 10^{-4}
FeSSIF	6.5	1.07	0.16	2.03 × 10^{-5}

*The solubility of the drug could not be determined at pH 1.2 due to its decomposition at that pH.

• The test was conducted three times (n = 3).

3.3 | Rheological measurements

The viscosity of the buffer media (SGF, acetate buffer and SIF) was shown to follow Newtonian behaviour (0.8 mPa.s). The rheogram of the diluted FDA meal (in acetate buffer and SIF) at different shear rates is shown in (Figure 1). The rheological behaviour of this food is pseudo-plastic, i.e. the viscosity decreases with an increase in the shear rate. At low shear rate (0.3 rpm), the viscosity was 13330 mPa.s. As the shear rate increased the viscosity decreased to 40 mPa. Elevated viscosity within the GI tract would be expected to reduce drug release and delay tablet disintegration. The rheograms for the FDA meal in both SIF and acetate buffer were superimposed. However, the viscosity of the homogenized FDA meal (pH = 1.2) was lower than that at pH = 4.5 and 6.8 at the various shear rates. This viscosity–pH dependent behaviour is in line with previous reports that demonstrated reduced viscosity of polymeric solutions and soups at low pH (Cvijić, Parojčić, & Langguth, 2014; Radwan et al., 2017).

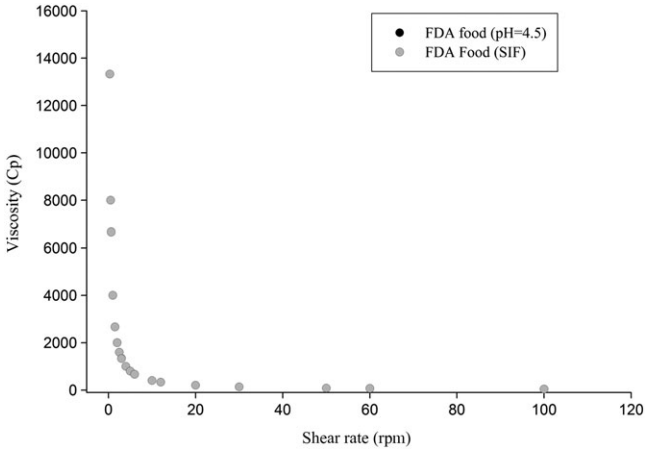

FIGURE 1 The rheogram of the diluted FDA meal (in acetate buffer and SIF) at the different shear rates (the rheological profiles for the FDA meal in acetate buffer and SIF are superimposed)

3.4 | Disintegration study

The average disintegration times of the clarithromycin tablets in the different media are shown in Figure 2. The media pH showed a significant effect on tablet disintegration. In acidic media, clarithromycin tablets exhibited longer disintegration times compared with more alkaline media. The mean disintegration times were increased from an average value of 0.8 and 3 min in SIF and acetate buffers to 33.4 min in SGF media. These findings are in agreement with a previous report, which reported a delay in the *in vitro* disintegration of clarithromycin tablet in media of acidic pH. This delay in tablet disintegration in acidic media was attributed to gel formation on the tablet surface (Fujiki et al., 2011). Inclusion of the FDA meal in the different buffers delayed tablet disintegration. Prolonged disintegration times in media containing FDA food reflect the high viscosity of the media.

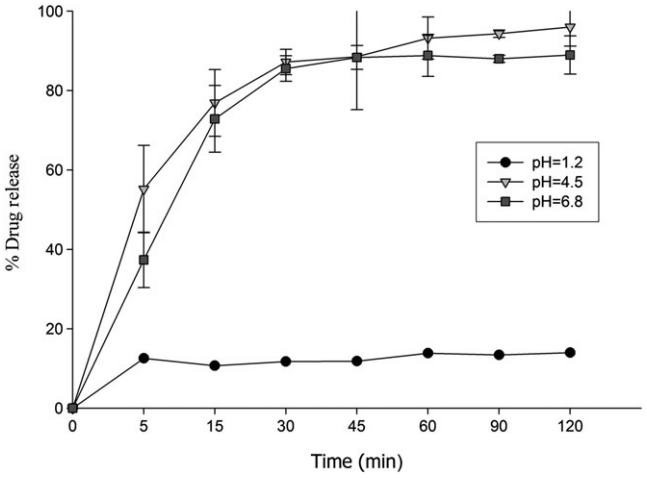

FIGURE 3 *In vitro* dissolution profile for clarithromycin immediate release tablet (500 mg) in compendial buffers

3.5 | Drug release study

3.5.1 | The effect of media pH on the release of clarithromycin

The *in vitro* release of clarithromycin from immediate release tablet was investigated in media with different pH (1.2, 4.5 and 6.8). The effect of media pH on drug release profiles is shown in Figure 3. The dissolution rate of the clarithromycin was higher than 88% in SIF (pH =6.8) and almost complete in the acetate buffer (pH = 4.5). However, in SGF (pH = 1.2), the apparent amount of clarithromycin released was less than 15% within 120 minutes while the remaining fraction (85%) was protected within the tablet by the gel layer formed on the its surface. These findings are in agreement with Fujiki et al. (2011), who reported rapid decomposition and slow dissolution of clarithromycin with no more than 20% of the API being dissolved at pH 1.2 (Fujiki et al., 2011). These observations can be explained by the acid-catalysed decomposition of clarithromycin and delayed tablet disintegration under acidic condition due to the gelling tendency of the tablet ingredient at pH 1.2.

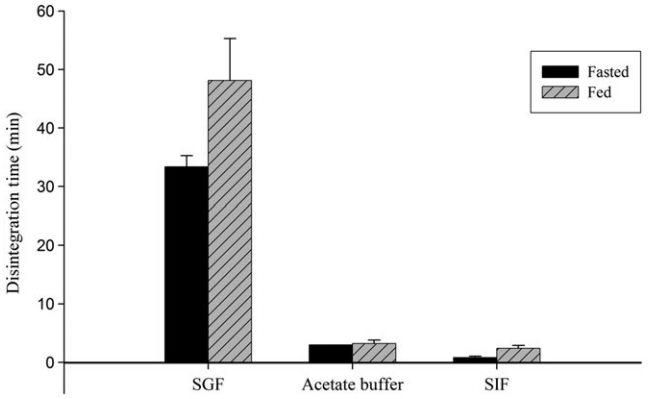

FIGURE 2 The average disintegration times of clarithromycin tablets in the different media

3.6 | Effect of FDA food on the release of clarithromycin

The presence of FDA food in the media was shown to have a marked effect on clarithromycin release. A great difference was obvious between the *in vitro* drug release profiles under fed conditions at the various pH. In SGF under the fed state, the percentage of clarithromycin released (after addition of the FDA meal to SGF) was higher compared with that in the fasted state, because of the slower degradation rate (Figure 4a). However, at higher pH (pH = 4.5 and 6.8), the release of the drug in the presence of the FDA meal was negatively affected as can be shown in Figure 4b,c. The amount of dissolved clarithromycin in the dissolution medium with added FDA diet did not reach 60% or 74% of the total tablet content of the drug at pH 4.5 and 6.8, respectively. This delay in dissolution rates reflects the slower disintegration.

3.7 | Effect of bile salts on clarithromycin release

Clarithromycin release from immediate release tablets was determined in biorelevant media and compared with that in compendial buffers. The percentages of drug released in FaSSIF and FeSSIF were lower than that in blank buffers. In FaSSIF (pH = 6.5), 60% of the drug was dissolved within 120 minutes compared with 88% in SIF (pH = 6.8). Obviously, there is a great difference between the release profiles of the drug in FaSSIF and SIF, despite the small change in the pH between FaSSIF and SIF (difference in pH = 0.3). In FeSSIF (pH = 5), the dissolution rate was very poor, i.e., only 10% of the drug dissolved within 120 minutes (Figure 5). The f_1 and f_2 value were calculated for each media, where the fasted state

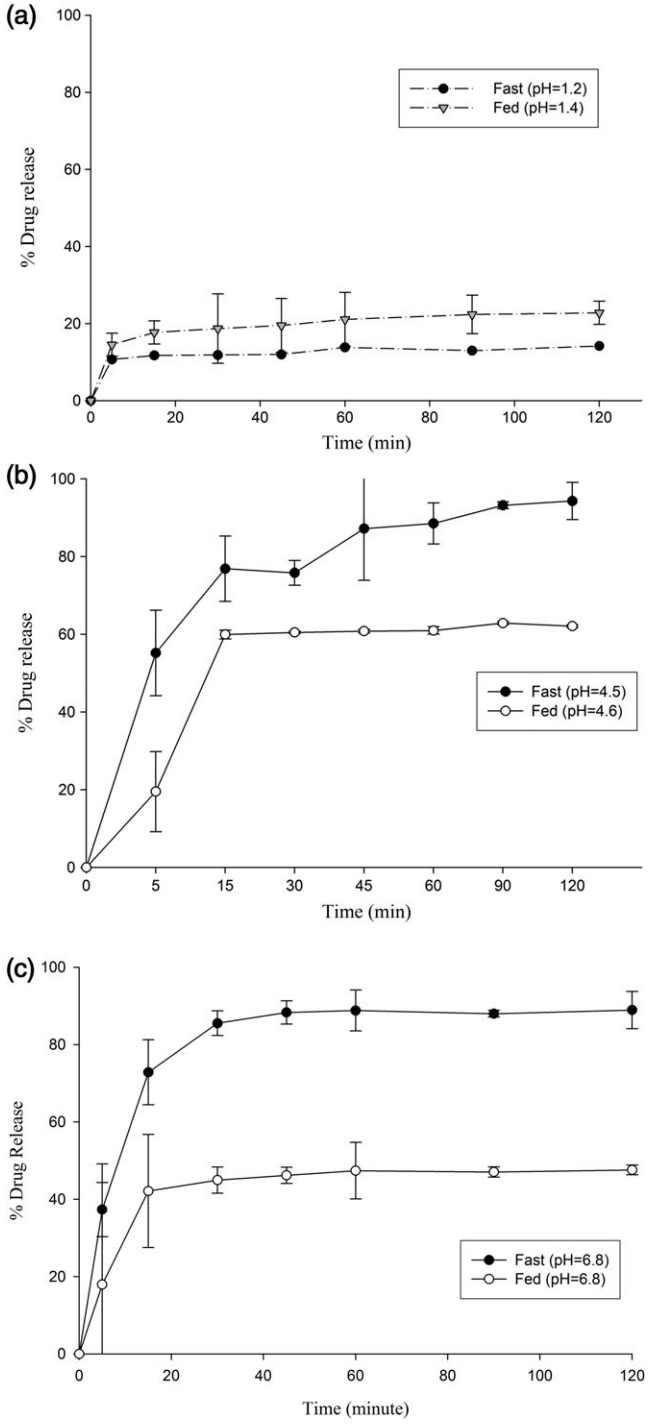

FIGURE 4 (a) *In vitro* dissolution profile for clarithromycin immediate release tablet (500 mg) in SGF (fasted) vs. SGF media containing FDA meal (fed). (b) *In vitro* dissolution profile for clarithromycin immediate release tablet (500 mg) in acetate buffer (fasted) vs. acetate buffer media containing FDA meal (fed). (c) *In vitro* dissolution profile for clarithromycin immediate release tablet (500 mg) in SIF (fasted) vs. SIF media containing FDA meal (fed)

in each buffer was the reference and the fed state was the test media. The results of similarity were lower than 50 at the various dissolution conditions.

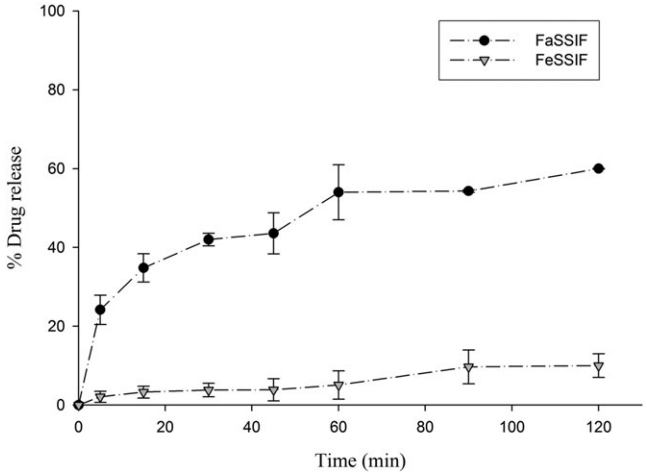

FIGURE 5 *In vitro* dissolution profile for clarithromycin immediate release tablet (500 mg) in biorelevant media (FaSSIF vs. FeSSIF)

3.8 | Gastrointestinal simulation

3.8.1 | Z-factor dissolution modelling of clarithromycin

The Z-factor was introduced in this study to reflect the impact of media pH on the *in vivo* PK profiles of clarithromycin. The Z-factor values for clarithromycin in the different media are shown in Table 2. These Z-factor values were used as the input function to evaluate the effect of dissolution behaviour at different pH on the *in vivo* performance of the drug.

3.9 | Drug absorption simulation

The results of the *in silico* single simulation for clarithromycin using GastroPlus™ are shown in Figure 6. The simulated plasma concentration–time profile was in good agreement with the *in vivo* absorption curve following the intake of 500 mg oral dose clarithromycin immediate release tablet under fasting conditions. The simulated pharmacokinetic parameters and those observed *in vivo* are presented in Table 3. The percent prediction errors obtained were not much higher than 10% for the pharmacokinetic parameters, indicating good predictability. The simulated absorption profile predicted a prolonged T_{max} in the fed state compared with that observed *in vivo* under the fasted state. This can be attributed to the delay in the gastric emptying rate. Clarithromycin is reported to be rapidly and well absorbed from the GI tract (Cvijić et al., 2014). GastroPlus™ predicted 91.6% of the dose to be absorbed under the fasted state and complete (100%) absorption under the fed state (Figure 7). However, no significant changes in the $AUC_{(0\text{-infinity})}$ values were associated with clarithromycin administration with the FDA meal (Figure 6).

The effect of pH-induced degradation on the oral bioavailability of clarithromycin was examined. Figure 6 shows the simulated plasma concentration profile considering the acidic decomposition of clarithromycin. The predicted C_{max} and AUC values were lower compared with those where degradation was not accounted for

TABLE 3 *In silico* predicted and *in vivo* observed pharmacokinetics parameter

	C_{max} (μg/ml)			AUC_{0-t} (μg h/ml)			$_{max}T$		Fa	
Study	Observed	Simulated	%PE	Observed	Simulated	%PE	Observed	Simulated	Observed	Simulated
Fasted	2.48	2.46	0.8	14.16	13.28	6.2	2	1.2	N/A	99.0
Fasted (degradation)	2.48	2.26	8.8	14.16	12.22	13.7	2	1.2	N/A	91.7
Fed	2.51	2.21	11.9	16.18	16.95	4.54	2	2.2	N/A	84.9

*N/A: Data are not available.

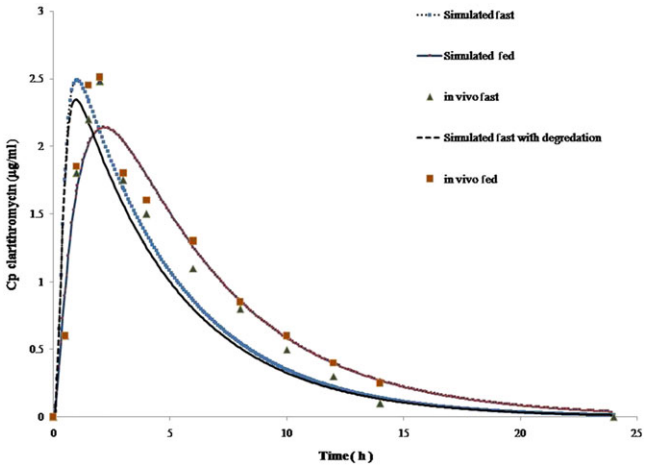

FIGURE 6 The simulated and observed plasma concentration–time profile for clarithromycin after a single oral dose (500 mg) IR tablet under fasting (with/without acid induced degradation consideration) and fed conditions. The black triangles represent *in vivo* data for Claricare® obtained from Pharmacare Ltd. Black squares represent the observed data (Chu et al., 1992b)

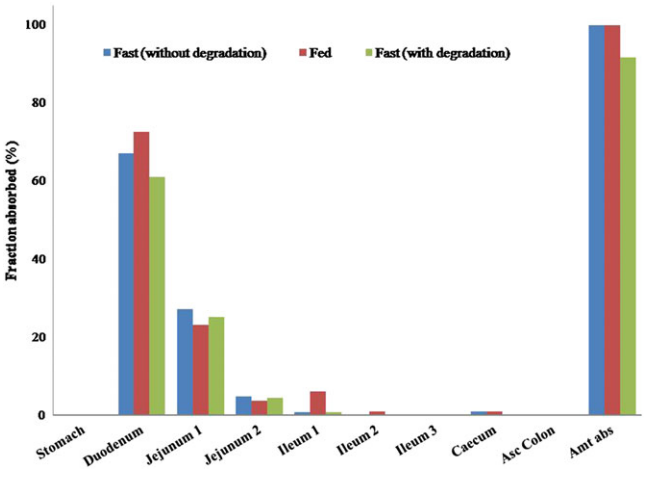

FIGURE 7 The regional absorption distribution simulated by GastroPlus™ under fasted vs. fed conditions (with and without consideration of acidic decomposition)

(Table 3). Clarithromycin instability under the gastric pH may reduce the fraction of drug available for absorption.

The regional absorption distribution simulated by GastroPlus™ under fasted conditions (with and without consideration of acidic degradation) is shown in Figure 7. In the fasted state, the majority of clarithromycin is shown to be absorbed in the duodenum (67.1%), while 27.1% of the dose in the jejunum. In the fed state, clarithromycin is completely absorbed, with the fraction of dose absorbed in the duodenum increased to 73.7% due to the enhanced bile reuptake, while 22.1% of the dose was absorbed in the jejunum. Clarithromycin instability under the gastric pH may reduce the fraction of drug available for absorption. The total fraction of clarithromycin absorbed decreases to 91.6%, when presystemic degradation is accounted for.

3.10 | Parameter sensitivity analysis

Parameter sensitivity analysis (PSA) was conducted to assess the impact of some key parameters on the clarithromycin absorption process under both fasted and fed conditions. The selected parameters for PSA included: solubility, permeability, gastric emptying, GI pH, GI transient time, total body clearance, gut and liver first-pass effect (FPE). The results of PSA are presented in Figure 8. According to the PSA outcomes: CL, liver FPE and gut FPE were found to have a significant effect on the predicted PK parameters (C_{max} and AUC). However, varying the input of solubility, permeability, GI pH, had no profound effect. Under the fed state, PSA analysis suggested that C_{max} is impacted by the gastric empting rate. A reduction in C_{max} will be observed by a long gastric residence time. However, C_{max} is not much sensitive to the changes in GER under fasted conditions. Similarly, extensive liver metabolism and gut FPE may lead to a substantial decrease in the PK parameters (C_{max}, and AUC). The enhanced hepatic blood flow associated with meal intake may reduce the hepatic extraction ratio and increase drug bioavailability. The PSA revealed that a decrease in drug solubility and permeability would not affect the extent of drug absorption.

3.11 | Virtual BE simulations

The virtual simulation results showed no clinically significant food effects on the rate and extent of clarithromycin bioavailability. The mean plasma concentration–time curves of the clarithromycin tablet under fed and fasted states fall in the 90% CIs (Figure 9). The population trials showed that food did neither significantly alter the C_{max} nor the AUC of clarithromycin. As shown in Table 4, the 90% CIs of the geometric mean ratios (fed vs. fasted) for C_{max} and AUC were within

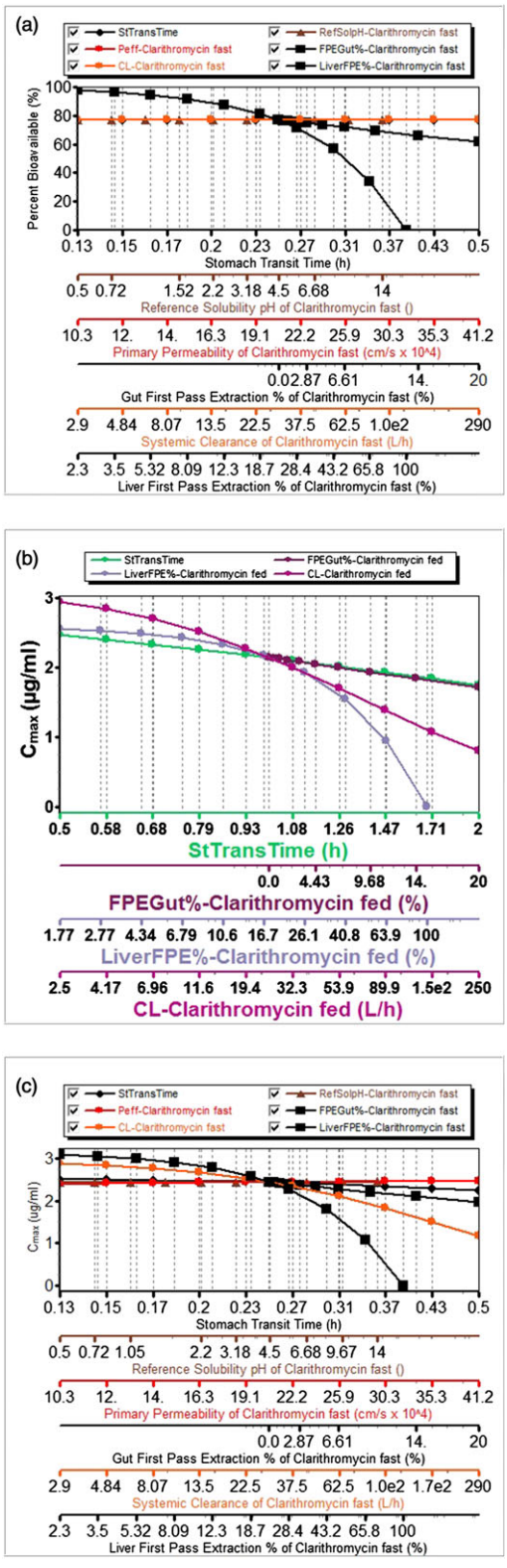

FIGURE 8 (a) Parameter sensitivity analysis for solubility, permeability, gastric emptying time, CL, liver FPE and gut FPE on % drug on C_{max} under fasting conditions, (b) Parameter sensitivity analysis for solubility, gastric emptying time, CL, liver FPE and gut FPE on % drug on C_{max} under fed conditions, (c) Parameter sensitivity analysis for solubility, permeability, gastric emptying time, CL, liver FPE and gut FPE on % drug on drug bioavailability under fasting conditions

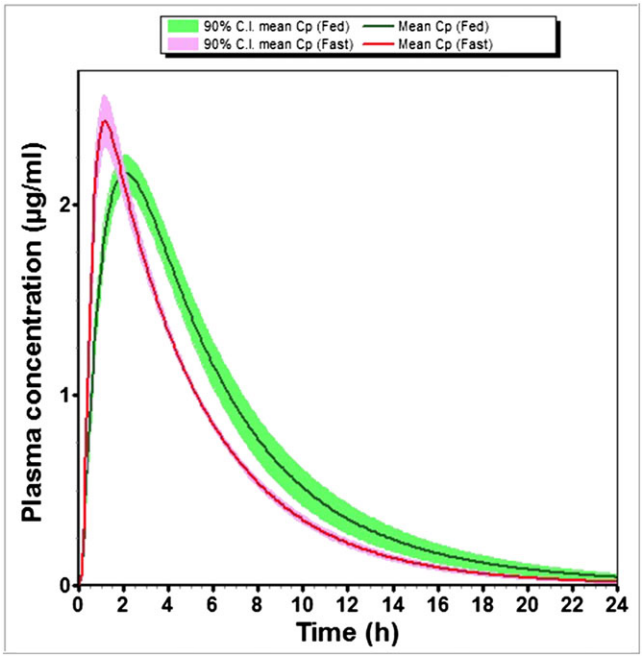

FIGURE 9 Human plasma concentration profile with 90% confidence interval (CI) after a single dose of clarithromycin (500 mg) in the fasted state and the fed states using virtual trial simulations

the requested bioequivalence (80–125%) limits for a sample size sample of 25.

3.12 | *In vitro–in vivo* correlation

GastroPlus™ was used to explore the possibility of establishing an *in vitro–in vivo* relationship using a mechanistic absorption model based on the deconvolution approach to correlate the *in vitro* dissolution data and the corresponding *in vivo* plasma concentration under both prandial states. Table 5 shows that an *in vivo* relationship was successfully established in SIF, acetate and FaSSIF media, since the value of the correlation coefficient (r^2) was close to 1. The correlation value (r^2) showed that using the HCl medium resulted in a low correlation coefficient (r^2 = 0.3). Whereas, in the fed state, the *in vitro* dissolution data were not well correlated with *in vivo* values in the different media.

4 | DISCUSSION

In the present work, the underlying mechanisms behind the food effect on the oral bioavailability of clarithromycin from immediate release tablet have been investigated using *in silico* and *in vitro* techniques. *In silico* modelling was employed to build a model describing the *in vivo* performance of clarithromycin under both fasted and fed conditions. Furthermore, the impact of media parameters, such as pH, bile salts and food composition on the oral absorption of clarithromycin is highlighted.

Media pH (pH > 3) had no significant effect on clarithromycin stability and release from the formulations. The cumulative amount of

TABLE 4 Virtual food effect study for clarithromycin

	Fasted (values)		Fed (values)		
Parameter	Mean	90% CI	Mean	90% CI	Fed vs. fasted (ratio)
C_{max} (μg/ml)	2.42	[2.32, 2.59]	2.14	[2.04, 2.24]	0.88
AUC_{0-inf} (μg × h/ml)	13.71	[12.95, 15.15]	16.33	[15.31, 16.70]	1.19
t_{max} (h)	1.22	[1.19, 1.27]	2.19	[2.11, 2.31]	1.79

TABLE 5 Statistical parameters of the obtained IVIVR

Media	a Value	r^2 Value
SGF	1.451	0.346
Acetate buffer	1.445	0.721
SIF	0.889	0.942
FaSSIF	1.694	0.927
FeSSIF	0.026	0.093
SGF with FDA meal	4.974	0.548
Acetate buffer with FDA meal	1.616	0.673
SIF with FDA meal	1.573	0.559

drug released at pH = 4.5 and pH = 6.8 was more than 94% and 88%, respectively. The acidic environment dominating in the stomach (pH from 1 to 3) had a profound effect on the stability, disintegration and dissolution of clarithromycin from immediate release tablets and reduced the fraction of the drug available for absorption. These findings are in agreement with a previous report (Fujiki et al., 2011). A small decrease in media pH (from pH 1.5 to 1.2) could significantly accelerate the decomposition and reduce the dissolution and disintegration rates of clarithromycin. Drug release at pH 1.2 was less than 20% compared with 80% at pH 1.5 within the first 10 minutes. Similarly, clarithromycin tablets were completely disintegrated within 10 min at pH (1.5–3.0). However, the disintegration time was as long as 1 hour at pH 1.2.

Prolonged tablet disintegration under acidic condition can be attributed to the formation of a transparent gel on the surface of the clarithromycin tablet, as a result of the reaction between clarithromycin molecule and hydrochloric acid under low pH conditions. Clarithromycin can be considered as a supramolecular gelator that undergoes gelation in solvents under acidic conditions by entrapping the solvent in a three-dimensional network structure created by entanglement of noncovalent interactions. The abundant concentrations of chloride anions and protons under acidic conditions are responsible for the formation of the three-dimensional network structure, which entrap water within (Fujiki et al., 2011). This gel layer, formed on the surface of the tablet, is stable at the intensely acidic pH found in the stomach but rapidly dissolves in alkaline conditions. Formation of this transparent gel may reduce the penetration rates of gastric fluid in the tablet, resulting in delayed tablet disintegration rates and provide a controlled release of clarithromycin by a time-independent mechanism, as well as protecting clarithromycin from acid decomposition.

At gastric pH, a small fraction of the clarithromycin dose was released while the remaining fraction (85%) was protected within the dosage form by the gel layer. Clarithromycin is an acid labile drug that undergoes rapid degradation in acidic conditions. However, the prolonged tablet disintegration time as well as the short residence time in the fasted stomach (15–30 min) will allow only a minor fraction of the drug to be lost by acid decomposition. Upon reaching the neutral pH of the small intestine, this gel layer will dissolve and the tablet will undergo rapid disintegration that will efficiently enhance clarithromycin release. Therefore, clarithromycin tablets remain stable under low-pH gastric conditions and exhibit *in vivo* antibacterial activity, even if the clarithromycin molecule itself is susceptible to rapid decomposition, which explains the activity of the drug when taken on an empty stomach. On the other hand, at the luminal pH (> 3), clarithromycin is presumably stable and did not undergo degradation.

Biorelevant systems contain bile salts in a concentration within the physiological range. Bile salts are responsible for the solubilization of lipid soluble drugs and their transport. In contrast to expectation, clarithromycin release in the presence of bile salts was much lower than that in compendial media. This can be attributed to the complexation interaction between macrolide antibiotic and bile salts. Clarithromycin was reported to strongly bind to bile acids cholate and deoxycholate micelles, which form a complex of low solubility and diffusivity but faster uptake through the body (Glanzer et al., 2015). This complex formation between the compound with bile decreases the release of the drug, but bile re-uptake increases the fraction of clarithromycin that enters the blood. Therefore, similar permeability values were used for the simulations in both prandial states, especially, no permeability data are available in the literature under the fed state (Glanzer et al., 2015).

The available biorelevant models simulating the fed state have considered parameters such as volume, pH, osmolality, phospholipids and bile salts concentration; however, the effect of dietary components and the composition of a standard test meal were not well characterized. Yet, *in vitro* dissolution models containing a real standard meal have not been described due to their complexity. In this work, the effect of the composition of the FDA standard meal, normally given to healthy volunteers in clinical trials, on drug release was investigated. These findings revealed that FDA food-containing media have a considerable effect on drug release and dosage form disintegration. In medium simulating the fed gastric conditions, the dissolution rate

of the clarithromycin was enhanced. In fact, the FDA meal has a neutralization capacity for the acidic secretions of the stomach. Postprandial elevation in gastric pH could reduce clarithromycin degradation in the stomach and enhance its dissolution rate. Based on this, clarithromycin bioavailability is expected to increase when dosed in the fed state. On the other hand, at the luminal pH (pH = 4.5, 6.8), the homogenized FDA meal caused a marked reduction in drug dissolution and prolonged tablet disintegration rates compared with that in the fasted state. These observations can be explained by the high viscosity of the medium that contains an FDA meal. These results are in line with previous reports, which ascribed the reduced disintegration and dissolution rates in various types of beverages, soups and FDA food to the elevated viscosity, slow water uptake rates into tablets and film precipitation on tablets (Abrahamsson, Albery, Eriksson, Gustafsson, & Sjöberg, 2004; Brouwers et al., 2011; Radwan, Amidon, & Langguth, 2012; Radwan, Wagner, Amidon, & Langguth, 2014). Obviously, the presence of the FDA meal in the dissolution medium has a considerable effect on drug release and dosage form disintegration, in spite of the low concentrations (100 ml of homogenized meal with 800 ml of blank buffer) used. The use of a higher concentration of FDA meal in the media would be more biorelevant and produce an intense effect. However, sample analysis becomes complex and difficult. The FDA meal media used in this study are not physiologically representative of the postprandial GI composition and pH. The physiological gastric pH following food intake was reported to rise rapidly from an initial value of 1.2 under the fasted state to about 3–7 which is much higher than the pH of the FDA meal containing media (pH = 1.4–1.5) (Dressman et al., 1990). Therefore, the possibility of acid induced degradation of clarithromycin in the fed stomach is unlikely at the elevated pH. Similarly, the small amounts of lipids, carbohydrates and proteins in food media may lead to an underestimation of the actual effect of these dietary components on the absorption process. The difference in dissolution results between media containing FDA meal and biorelevant media may be due to variations in the pH and bile salts concentration.

Gastrointestinal simulation was used to build an absorption model for predicting the *in vivo* performance of clarithromycin from immediate release tablet under fasted and fed states. The simulated concentration–time profiles matched well with the *in vivo* observed data. The calculated percent prediction error values for the *in silico* data indicates good predictability. The *in vivo* data have reported no significant clinical effects of the co-administered meal on the extent of clarithromycin absorption but a delay in the onset of action. The AUC remained constant in the fed state, the C_{max} value increased by about 24%, the peak time was prolonged from 2 to 2.5 hours due to delayed gastric emptying and increased residence time in the presence of food (Chu et al., 1992b). The simulated pharmacokinetic parameters in the fed state (AUC and T_{max}) agreed well with the *in vivo* data. However, the predicted model underestimated the observed increase in C_{max} in the fed state, despite being considered as a statistically non-significant effect (C_{max}-fed/C_{max}-fasted less than 25%). This can be due to the fact that the fed simulations were developed based on the (fasted state) model, which neglected drug loss due to acid induced decomposition in the gastric fluid. However, elevation of gastric pH under fed conditions would reduce the possibility of drug degradation and increase the available fraction for absorption, which might lead to an increase in the observed CLM C_{max}.

In vitro data can be used to explain the mechanisms behind the lack of food effect. The *in vitro* results suggest that the acidic conditions dominating in the fasted stomach would prolong tablet disintegration and reduce drug release by gel layer formation. Despite, the poor stability of clarithromycin under acidic conditions, only a minor fraction of the released drug may undergo decomposition. The short gastric transient time for the tablet in the fasted state (15–30 min) as well as delayed tablet disintegration (33 min) will reduce drug exposure to acid degradation. But when the drug enters the intestinal lumen, improved drug stability and complete tablet disintegration as well as drug dissolution would increase the fraction available for absorption. These *in vitro* findings are consistent with the *in silico* prediction that about 91.6% of dose was absorbed under the fasted state.

On the other hand, the elevation in gastric pH following food intake may improve clarithromycin stability and reduce presystemic clearance. Moreover, the longer gastric residence time under fed state (2 hours) may allow more time for drug dissolution but expose the drug to the less acidic condition of the fed stomach. The postprandial increase in hepatic blood flow would tend to decrease the extraction ratio. The reduced liver FPE, gut FPE and total clearance of clarithromycin under fed conditions compared with the fasted state would contribute to the increase in the oral bioavailability of the drug. However, the increased concentration of bile salts in the small intestine would reduce the dissolution rate of clarithromycin due to complex formation, leading to incomplete absorption under fed conditions. The net effect of the above mentioned mechanisms seems to lead to similar fraction of drug absorbed under both fasted and fed states.

A level A linear correlation was established between the actual *in vivo* and the *in vitro* dissolution data under fasted conditions. The developed IVIVR model under fasted conditions considered SIF, acetate and FaSSIF buffer media to be relevant from the physiological standpoint, whereas, SGF medium is not. In the fed state, no clear IVIVR relationship has been established for the different fed media, indicating the difficulty in correlating *in vitro* results with *in vivo* behaviour under fed conditions.

5 | CONCLUSION

The present study describes the use of *in silico* and *in vitro* tools to predict the food effect on the oral absorption of clarithromycin from an immediate-release tablet. Furthermore, the impact of media parameters, which include: media pH, bile salts content, viscosity and food composition, on the disintegration and dissolution behaviour of clarithromycin was investigated. The food effect is most likely to be as a result of combination of these factors.

PBPK modelling and *in vitro* dissolution testing were successfully applied to simulate the food effect on clarithromycin. Food may retard

the *in vitro* disintegration and dissolution rates of drug products containing clarithromycin, but enhance drug stability and increase the uptake through bile. These findings suggested that *in vitro* and PBPK approaches can be considered as reliable tools for the prediction of food effect on certain oral drugs without the need to conduct expensive and time consuming clinical studies during development of new generic solid products, especially as biowaivers for food effect studies are not readily accepted for any BCS class drugs.

FUNDING STATEMENT

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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How to cite this article: Radwan A, Jayyousi R, Shraim N, Zaid AN. Evaluation of food effect on the oral absorption of clarithromycin from immediate release tablet using physiological modelling. *Biopharm Drug Dispos*. 2019;40:121–134. https://doi.org/10.1002/bdd.2176