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Research paper

The impact of reduced gastric acid secretion on dissolution of salts of weak bases in the fasted upper gastrointestinal lumen: Data in biorelevant media and in human aspirates

Chara Litou [a], Maria Vertzoni [a], Wei Xu [b], Filippos Kesisoglou [b], Christos Reppas [a,*]

[a] Department of Pharmacy, School of Health Sciences, National and Kapodistrian University of Athens, Zografou, Greece
[b] Pharmaceutical Sciences and Clinical Supply, Merck & Co., Inc., Kenilworth, NJ, USA

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ABSTRACT

Purpose: To propose media for simulating the intragastric environment under reduced gastric acid secretion in the fasted state at three levels of simulation of the gastric environment and evaluate their usefulness in evaluating the intragastric dissolution of salts of weak bases. To evaluate the importance of bicarbonate buffer in biorelevant in vitro dissolution testing when using Level II biorelevant media simulating the environment in the fasted upper small intestine, regardless of gastric acid secretions.
Methods: Media for simulating the hypochlorhydric and achlorhydric conditions in stomach were proposed using phosphates, maleates and bicarbonates buffers. The impact of bicarbonates in Level II biorelevant media simulating the environment in upper small intestine was evaluated so that pH and bulk buffer capacity were maintained. Dissolution data were collected using two model compounds, pioglitazone hydrochloride and semifumarate cocrystal of Compound B, and the mini-paddle dissolution apparatus in biorelevant media and in human aspirates.
Results: Simulated gastric fluids proposed in this study were in line with pH, buffer capacity, pepsin content, total bile salt/lecithin content and osmolality of the fasted stomach under partial and under complete inhibition of gastric acid secretion. Fluids simulating the conditions under partial inhibition of acid secretion were useful in simulating concentrations of both model compounds in gastric aspirates. Bicarbonates in Level III biorelevant gastric media and in Level II biorelevant media simulating the composition in the upper intestinal lumen did not improve simulation of concentrations in human aspirates.
Conclusions: Level III biorelevant media for simulating the intragastric environment under hypochlorhydric conditions were proposed and their usefulness in the evaluation of concentrations of two model salts of weak bases in gastric aspirates was shown. Level II biorelevant media for simulating the environment in upper intestinal lumen led to underestimation of concentrations in aspirates, even when bicarbonate buffer was used.

1. Introduction

Reduced gastric acid secretion is observed in certain population groups including the Japanese [1], the elderly [2], and users of proton pump inhibitors (PPIs) or histamine-2 receptor antagonists (H_2-RAs).

Simultaneous use of PPIs or H_2-RAs with drugs that treat other diseases is very common and it has been suggested that the alteration of intraluminal dissolution rates, due to reduced gastric acid secretion, is the main cause for the impaired drug absorption and, therefore, therapeutic effect in patients treated with PPIs or H_2-RAs [3]. The development of in vitro/in silico methods for evaluating drug/drug product performance under these conditions is probably a necessity and it is considered of high importance by regulatory agencies worldwide [4].

To date, in vitro methods for the preclinical investigation of relevant scenarios involve the use primarily of Level 0 biorelevant media (Fig. 1) and the USP Apparatus II [5–8]. In relevant attempts, the choice of dissolution medium pH for simulating the reduced gastric acid secretion was made on a case-by-case basis depending on the pH-solubility profile of the compound; the pH value ranged from 3.9 to 6.8 and was achieved by employing diluted HCl solution, compendial acetate buffer or compendial phosphate buffer.

* Corresponding author at: Department of Pharmacy, School of Health Sciences, National and Kapodistrian University of Athens, Panepistimiopolis, 157 71 Zografou, Greece.
E-mail address: reppas@pharm.uoa.gr (C. Reppas).

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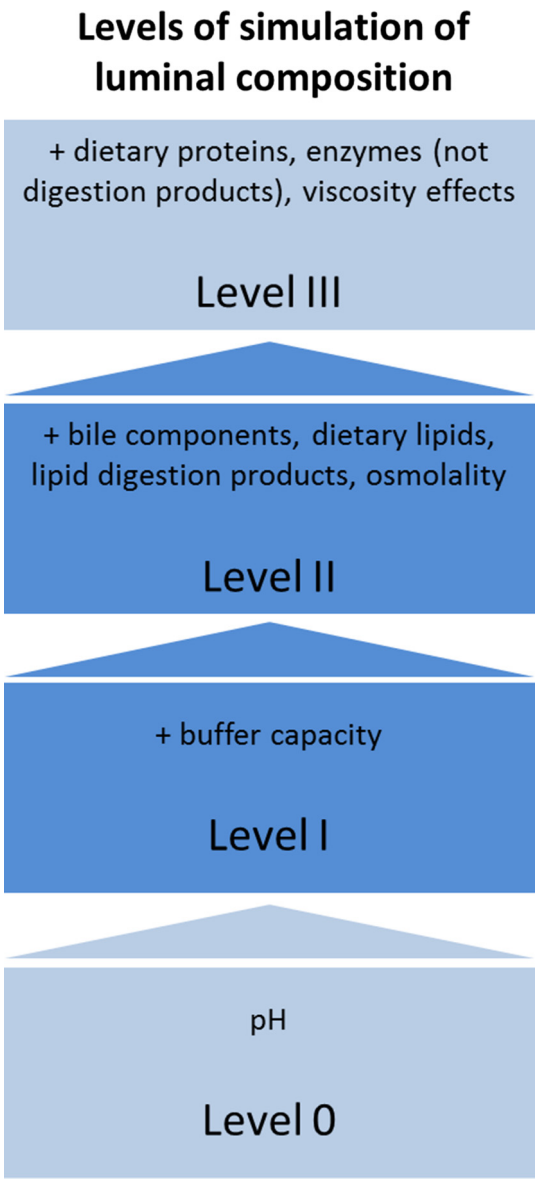

Fig. 1. An overview of the four levels of biorelevant media recommended for the simulation of the luminal environment during development of oral formulations (reproduced from Markopoulos et al. [14]).

It is interesting to note that the usefulness of relevant approaches in predicting human data has been shown in only one case in which HCl solution with very low buffer capacity had been employed [6].

Non – compendial gastrointestinal transfer systems have also been utilized for evaluating the drug product performance in upper gastrointestinal (GI) lumen, under conditions of reduced gastric acid secretion [9–12]. In such approaches, Level II and Level III biorelevant media (Fig. 1) were also considered. The pH value employed for simulating the reduced gastric acid secretion in stomach varied from 4.5 to 6. The pH values applied in the intestinal compartment range from 6.0 to 6.5 [9,10,12] or it was not specified [11]. It is interesting to note that a qualitative comparison of in vitro data with plasma data in humans was made only with the approach of Dickinson et al. [11], i.e. exposure was increased broadly proportionally with increasing dose both in vitro (using the TNO TIM-1 model) and in humans. Interestingly, the approach of Dickinson et al. was the most complex and the only one which employed bicarbonates for managing pH values.

The present investigation had three objectives. The first was to propose media for simulating the intragastric environment under reduced gastric acid secretion in the fasted state, according to luminal data in humans collected in a recent clinical study [13] and by using various buffer systems. The second objective was to evaluate the usefulness of biorelevant media in predicting the impact of reduced gastric acid secretion on intragastric drug dissolution based on dissolution data collected ex vivo in human aspirates. The third objective was to evaluate the importance of bicarbonate buffer in dissolution testing when using Level II biorelevant media simulating the contents of upper small intestine under conditions of reduced acid secretion in stomach. Level II biorelevance is the most frequently considered when dissolution in upper small intestine is of interest from the absorption point of view [14]. Although an increase of about 0.7 pH units in upper small intestine was observed 15–30 min post-water administration under achlorhydric conditions [13], it is not clear if the increase is drug specific or is due to the achlorhydric conditions in stomach [13] whereas it was not observed early after water administration. Therefore, in the present investigation the fasted state simulating intestinal fluid (FaSSIF, [15] and the fasted state simulating intestinal fluid version 3 (FaSSIF-V3, [16] were used as basis for evaluating the importance of bicarbonates on drug dissolution.

Since salts of weak bases are frequently considered for mitigating the impaired drug absorption due to elevated gastric pH [17], pioglitazone hydrochloride and semifumarate cocrystal of Compound B were selected as model compounds. Pioglitazone (5-[[4-[2-(5-ethylpyridin-2-yl)ethoxy]phenyl]methyl]-1,3-thiazolidine-2,4-dione) is indicated as second or third line treatment of type 2 diabetes mellitus (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000285/WC500021386.pdf), it is a BCS Class II drug [18] with molecular weight of 356.33 g/mol, clogP 3.2–3.3, and two pkas, one basic (5.6) and one acidic (6.7) (www.drugbank.ca/drugs/DB01132 accessed 28 August 2016). Compound B is a MSD BCS Class II compound under development, with molecular weight of 447.52 g/mol, clogP 2.87, logD 1.9, and two basic pKas (<2.0 and 4.42) (data in file).

2. Materials and methods

2.1. Materials

Pioglitazone Hydrochloride was from Matrix Scientific, Columbia, and semifumarate cocrystal of Compound B, was from Merck & Co., Inc., Kenilworth, NJ, USA. Acetonitrile and water of HPLC-grade were from Sigma-Aldrich® (Chemie GmbH, Steinheim, Germany). Maleic acid, sodium dihydrogen phosphate dihydrate, sodium chloride and sodium hydroxide were of analytical grade and purchased from Sigma-Aldrich® (Chemie GmbH, Steinheim, Germany). Pepsin from porcine gastric mucosa (15.8% protein) was purchased from Sigma Aldrich (Saint Louis, U.S.A.). Sodium hydrogen carbonate was of analytical grade and purchased from Pancreac, Quimica SA (Barcelona, Spain). FaSSIF/FeSSIF/FaSSGF powder and FaSSIF-V3 powder were kindly donated by biorelevant.com.

2.2. Evaluation of physicochemical characteristics of media simulating hypochlorhydric and achlorhydric gastric conditions

Buffer capacity was measured by dropwise addition of HCl solutions. Osmolality was measured by using the freezing point depression technique (semimicro osmometer Typ Dig L; Knauer, Berlin, Germany). Surface tension was measured according to the Du Nouy ring method (KSV Sigma 70, KSV Instruments, U.S.A.) at 37 °C.