European Journal of Pharmaceutics and Biopharmaceutics 107 (2016) 234–248

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

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

Review article

Fed-state gastric media and drug analysis techniques: Current status and points to consider

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ARTICLE INFO

Article history:
Received 14 April 2016
Revised 7 June 2016
Accepted in revised form 11 July 2016
Available online 12 July 2016

Keywords:
Fed state
Gastric
Biorelevant media
Drug analysis
Dissolution
Bioavailability

ABSTRACT

Gastric fed state conditions can have a significant effect on drug dissolution and absorption. *In vitro* dissolution tests with simple aqueous media cannot usually predict drugs' *in vivo* response, as several factors such as the meal content, the gastric emptying and possible interactions between food and drug formulations can affect drug's pharmacokinetics. Good understanding of the effect of the *in vivo* fed gastric conditions on the drug is essential for the development of biorelevant dissolution media simulating the gastric environment after the administration of the standard high fat meal proposed by the FDA and the EMA in bioavailability/bioequivalence (BA/BE) studies. The analysis of drugs in fed state media can be quite challenging as most analytical protocols currently employed are time consuming and labour intensive. In this review, an overview of the *in vivo* gastric conditions and the biorelevant media used for their *in vitro* simulation are described. Furthermore an analysis of the physicochemical properties of the drugs and the formulations related to food effect is given. In terms of drug analysis, the protocols currently used for the fed state media sample treatment and analysis and the analytical challenges and needs emerging for more efficient and time saving techniques for a broad spectrum of compounds are being discussed.

Contents

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http://dx.doi.org/10.1016/j.ejpb.2016.07.013
0939-6411/

1. Introduction

In vitro dissolution studies are an integral part of quality control and drug development processes. During drug development, they are used as a tool for the selection of the appropriate excipients and the most suitable formulation type [1] and also as an *in vitro* surrogate for *in vivo* performance [2]. In quality control, they are used to ensure the batch-to-batch consistency [3–5]. Dissolution tests, as dictated by the Pharmacopoeias, cannot always provide information about the *in vivo* behaviour of the drugs, even though there are cases in which these tests can provide good *in vitro–in vivo* correlations (IVIVC). The dissolution media described in Pharmacopoeia monographs are mainly used for quality control purposes, and are not often able to predict *the in vivo* behaviour of poorly soluble drugs for which the fat content and the bile salt concentration in the gastrointestinal environment will affect their solubility and dissolution rate [6,7]. Due to the limited ability of the simple aqueous media suggested by the Pharmacopoeias to simulate the characteristics of the gastrointestinal (GI) tract, the need for media simulating the GI physiological environment in the fasted and fed states (usually called biorelevant media) arose; in these media the physicochemical properties of the GI contents (pH, osmolality, surface tension, buffer capacity) are taken into account and physiological components such as bile salts and lecithin are incorporated [2]. Use of biorelevant media during the drug development process enables the assessment of drug's biopharmaceutic characteristics and the prediction of *in vivo* performance [2,8].

While the fasted state gastric environment has been well studied, the more complex conditions of the fed state stomach have made the prediction of food effect a challenging task. Several *in vitro* biorelevant gastric media have been used for the simulation of the gastric fed state environment and as far as the sample treatment is concerned, there is no specific protocol available and sample treatment and drug analysis are developed on a case by case basis. A good understanding of the *in vivo* conditions of the fed state stomach could lead towards the development of a suitable medium being able to simulate the gastric content and ideally overcoming the extensive treatment before the analysis that is needed with the current gastric fed state media [9,10]. The dependence of the drug food effect on the meal content, the role of the fat content in the solubilisation of drugs, the gastric emptying rate and the interaction with certain formulations [11] as well as the binding of drugs with metal ions and meal components are some of the parameters which have rendered the *in vitro* prediction of food effect extremely complicated.

In the current review, initially we describe the available information for the characterisation of the *in vivo* gastric fed state conditions after the administration of standard meals with an aim to provide an understanding of the effect of drug's physicochemical parameters on its *in vivo* behaviour. Then, the standard meals and the gastric biorelevant media currently being used and their interaction with drugs of different physicochemical properties are presented. In the last part the analytical techniques used *in vitro* for sample treatment and quantification of the drug along with their challenges are discussed.

2. *In vivo* gastric conditions in the fed state

Gastric conditions in fasted state have been characterised in terms of pH, osmolality, surface tension, buffer capacity and protein content [12–14]. In the fed state, the determination of absolute values is more complicated than in the fasted state. The food type is an additional factor on top of other parameters responsible for the interindividual variation of the above properties such as the individual's age [15] and administered medication [16]. The role of several physicochemical parameters of the contents of the fed state stomach on drug's dissolution and absorption is reviewed.

2.1. Gastric secretions in the fed state

The main components of the gastric juice are hydrochloric acid (HCl), pepsinogens, mucus and water; pepsinogen is the inactive form of pepsin, activated by the presence of HCl [17]. Pepsin content is higher in the fed state stomach than in the fasted state (fasted state values = 0.11–0.22 mg/mL). Samples of gastric antrum content of twenty healthy volunteers after administration of Ensure Plus®, demonstrated pepsin values within a range from 0.26 to 0.58 mg/mL in a time period from 30 to 210 min after administration of the liquid meal [13]. Gastric lipase is also present in the stomach. It is the enzyme responsible for the digestion of fat in the upper gastrointestinal tract. Its role involves the hydrolysis of exogenously administered triglycerides to di-glycerides and fatty acids [18]. Gastric lipase has been reported to account from 10 to 30% of the total hydrolysis of triglycerides contained in a meal [19,20] with the activity of the enzyme measured at 11.4–43.9 U/mL [21]. Its total output after administration of a liquid meal was 22.6 ± 8.1 mg (concentration 16.7 ± 0.7 μg/mL) after administration of a liquid meal in human subjects [19].

2.2. Bile salts in gastric contents in the fed state

Bile salts can increase the dissolution of poorly soluble drugs by decreasing the energy barrier between the drug and the medium, by increasing the active surface area, or via micellar solubilisation [22]. Bile salt concentration in the stomach is much smaller than in the small intestine, where the bile salts are released by the gall bladder, with their concentration in the intestinal environment in the fasted state demonstrating an approximate four fold decreased value in comparison with the fed state (1–4 mM and 10–20 mM, respectively) [23,24]. In the gastric fed state (after administration