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Application of the Dynamic Gastric Model to evaluate the effect of food on the drug release characteristics of a hydrophilic matrix formulation

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ABSTRACT

Characterisation of the effect of food on the bio-performance of modified and extended release dosage forms can be very challenging due to the need to replicate the dynamic biochemical conditions of the human gut as well as the complex physical processing modalities under fed state. Classical compendial methods are useful for testing the quality of pharmaceutical dosage forms but typically have limitations in the accurate prediction of food-effect *in-vivo*. Preliminary evaluation of the Dynamic Gastric Model (DGM) shows that it can provide substantially more detailed mechanistic information on dosage form properties compared to conventional compendial testing. The potential effect of food on the drug release and physical properties of a hydrophilic matrix formulation containing a model drug, hydrochlorothiazide, was studied using compendial methods, bio-relevant media and the DGM (in combination with an off-line intestinal model). Whilst the compendial methods with biorelevant media provided good correlation with the dissolution rates observed using the DGM/intestinal model under simulated fasted state, the quantification of simulated fed state performance changes was much more challenging using the compendial methods. Classical compendial studies using biorelevant FeSSIF and FaSSIF media could not readily discern differences in dissolution performance under fasted and fed states; however, the DGM could detect significant changes in both physical properties as well as drug release performance under fed state processing.

1. Introduction

Hydrophilic matrix technology has been widely used for the controlled delivery of orally active pharmaceuticals for many years. The advantages of this technology are that it provides ease of formulation, cost-effective manufacture, wide regulatory acceptance of the polymer systems, and flexibility in the control of the drug release profiles. One of the challenges associated with hydrophilic matrices, however, is the potential for food-effect, especially for drugs with low water solubility, which could result from sub-optimal formulation design and/or physical incompatibility between the active and the polymeric matrix. In these cases, there is scope for premature erosion of the formulation matrix to occur often as a consequence of the intense gastric processing under fed state. Premature matrix erosion gives rise to a "positive" food-effect that manifests as an increase in drug exposure in the initial phase of absorption or in rare instances, a sudden complete release of the drug payload, a phenomenon known as dose-dumping (Abrahamsson et al., 1998).

Hydroxypropylmethyl cellulose (HPMC) is the most commonly used polymer for controlled release hydrophilic matrix systems (Tiwari and Rajabi-Siahboomi, 2008). When a hydrophilic matrix dosage form is exposed to the gastro-intestinal (GI) fluid, the polymer on the surface of the dosage form hydrates and swells, creating a protective gel layer from which the active is gradually and continuously released over time, either by diffusion through the polymeric gel layer, by erosion of the gel layer, or by a combination of the mechanisms above. The principal mode of drug release for aqueous soluble actives is diffusion and for poorly aqueous soluble actives erosion can be more dominant. The key optimal formulation design premise for hydrophilic matrix systems is the creation of a robust gel structure on hydration which enables the active to be released consistently irrespective of the changes in the environment of the GI-tract and especially under the influence of food, which can impart significant increases in shear forces on the dosage form.

A strategy to reduce the susceptibility for food-effect for hydrophilic matrices is the use of a drug release retardant polymer at an optimum concentration (Levina and Rajabi-Siahboomi, 2004;

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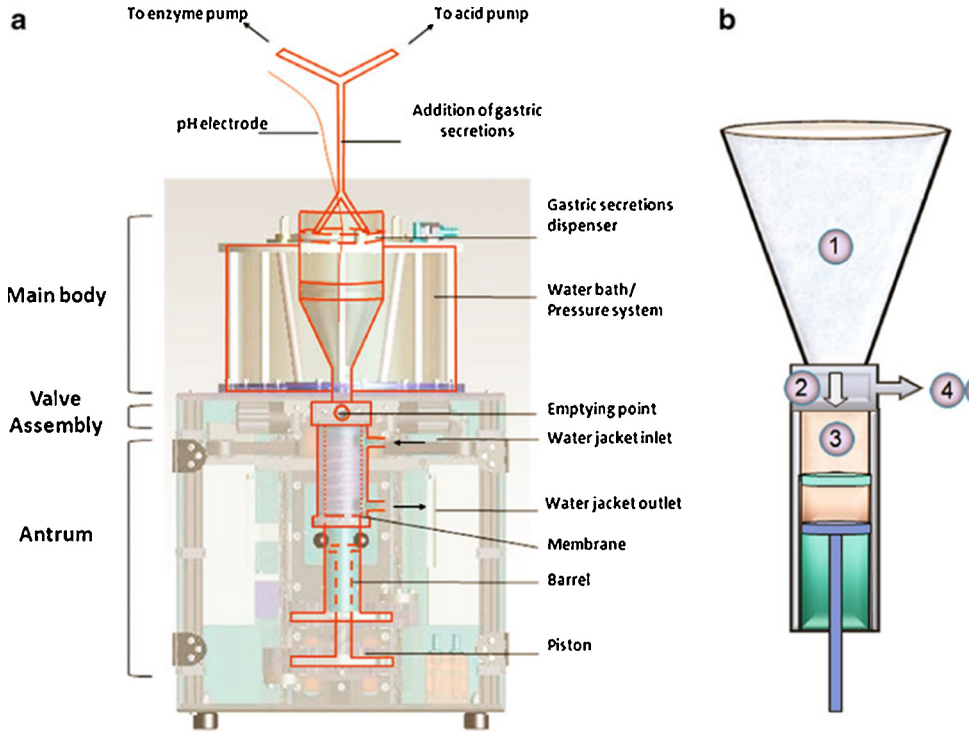

Fig. 1. Schematic representations of the dynamic gastric model, depicting the main components of the DGM (a), and illustrating the mechanism of the mechanical digestion (b). For (b), the number notations refer to the following: (1) The meal/gastric content within the main body of the stomach inhomogeneously mixed with the gastric secretions through application of pulsatile contractions. (2) The content's transit into the model antrum through the valve assembly. The inlet valve opens during the process allowing reflux and mixing between the main body and the model antrum. (3) The chyme processed mechanically by the movement of the piston and barrel, and forced through an annular membrane. (4) The chyme emptied from the antrum and collected for analysis.

Levina and Rajabi-Siahboomi, 2006), as well as excipients such as fillers or binders which can moderate gel-layer erosion (Levina and Rajabi-Siahboomi, 2004). It has been found that by adding pre-gelatinised starch (Starch 1500®) to hydrophilic matrices, the erosion of the formulation can be significantly minimised (Vandecruys and Jans, 2003). Whilst the effect of food on the bio-performance of hydrophilic matrix systems has been established for many years, its avoidance has been problematic due to a lack of predictive bio-relevant *in-vitro* models that can fully replicate the dynamic biochemical conditions as well as the complex contractility mode of the human stomach. Efforts to address the changes in biochemical conditions, for instance under simulated fasted and fed states using simulated fasted state media (FaSSIF) and simulated fed state media (FeSSIF provide some partial resolution but in the main, such approaches do not reflect the changing (dynamic) chemical and biochemical nature of the gut (Dressman et al., 1998; Galia et al., 1998). In addition, these approaches do not replicate the complex mixing, the break-up of food and the repetitious high shear-action that takes place under fed state. For this reason, a number of alternative non-compendial and new *in-vitro* models have been developed with the aim of improving *in-vitro*/*in-vivo* correlation (McAllister, 2010).

The Dynamic Gastric Model (DGM) developed by the Model Gut group, is an *in-vitro* model of the human stomach which seeks to accurately replicate three important facets of gastric function *viz.* (1) storage and gentle mixing in the main body of the stomach (fundus), (2) functional shear and turbulent flow in the distal part of the stomach (antrum), and (3) calorie-dependent gastric processing and pulsatile emptying from the distal stomach.

The DGM apparatus comprises essentially two main parts: an upper part made by a flexible cone immersed in a water bath kept at the body temperature of 37 °C (the main body of the stomach at lower agitation) and a lower stainless steel part consisting of two cylinders and a piston, which simulates the antral part of the stomach – the region that is responsible for the physical break-down of food material (Fig. 1). While in the main body gentle contractions applied at 3 cycles per minute allow the gentle and non-homogeneous mixing between the material inside the stomach and the gastric secretions, the model antrum is designed to apply antral shear forces analogous to those produced during digestion. The gastric secretions are added continuously during digestion over time, mimicking the *in-vivo* physiological conditions. pH electrodes directly immersed within the DGM content monitor the pH changes within the "meal" over time and control the rate and amount of acid addition through a controlled feedback mechanism. All the DGM processes are controlled by a specialised software that permits monitoring of all parts in real time (Mercuri et al., 2008; Wickham et al., 2009; Mercuri et al., 2011; Vardakou et al., 2011; Wickham et al., 2012). Material emptied from the DGM can be then processed within a simulation of the small intestine.

The aim of this study was to evaluate the suitability of the DGM for assessing the food-effect of an experimental hydrophilic matrix formulation, containing a model active, hydrochlorothiazide (HCTZ). Starch 1500®, a well-established filler and functional excipient in hydrophilic matrix systems, is included in the formulation to confer resistance to the food-effect. In this preliminary evaluation of the DGM apparatus, without the availability of human pharmacokinetic data, the focus of the study is to characterise the dissolution performance and physical properties of the dosage form under simulated fasted and fed in comparison to the dissolution data obtained from conventional compendial (United States Pharmacopeia – USP) dissolution methodologies, in standard aqueous buffer and in bio-relevant (FeSSIF, FaSSIF, Ensure® Plus) dissolution media. The DGM was used in conjunction with an off-line intestinal model, comprising a low-volume stirred mix of bile salts and digestive enzymes to