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Use of the Dynamic Gastric Model as a tool for investigating fed and fasted sensitivities of low polymer content hydrophilic matrix formulations

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ABSTRACT

The Dynamic Gastric Model (DGM) is an *in-vitro* system which aims to closely replicate the complex mixing, dynamic biochemical release and emptying patterns of the human stomach. In this study, the DGM was used to understand how the polymer content of hydrophilic matrices influences drug release in fasted and fed dissolution environments. Matrices containing a soluble model drug (caffeine) and between 10 and 30% HPMC 2208 (METHOCEL® K4M CR) were studied in the DGM under simulated fasted and fed conditions. The results were compared with compendial USP I and USP II dissolution tests. The USP I and II tests clearly discriminated between formulations containing different polymer levels, whereas the fasted DGM test bracketed drug release profiles into three groups and was not able to distinguish between some different formulations. DGM tests in the fed state showed that drug release was substantially influenced by the presence of a high fat meal. Under these conditions, there was a delay before initial drug release, and differences between matrices with different polymer contents were no longer clear. Matrices containing the typical amount of HPMC polymer (30% w/w) exhibited similar release rates under fed and fasted DGM conditions, but matrices with lower polymer contents exhibited more rapid drug release in the fasted state. In both the fasted and fed states erosion mechanisms appeared to dominate drug release in the DGM: most likely a consequence of the changing, cylindrical forces exerted during simulated antral cycling. This is in contrast to the USP tests in which diffusion played a significant role in the drug release process. This study is one of the first publications where a series of extended release (ER) formulations have been studied in the DGM. The technique appears to offer a useful tool to explore the potential sensitivity of ER formulations with respect to the gastric environment, especially the presence of food.

1. Introduction

Extended release (ER) oral dosage forms remain an important strategy for improving clinical outcomes by facilitating more stable drug plasma concentrations and reducing dosing frequency, in addition to extending the product life-cycle (Wilson and Crowley, 2011). However, the development of ER dosage forms is complicated by the challenges of predicting *in-vivo* performance from *in-vitro* drug release testing. Prediction is more difficult than for immediate release dosage forms, because of the extended time period and the different environments the ER dosage form encounters as it traverses the GI tract (Zahirul and Khan, 1996). The *in-vivo* testing of multiple formulations is costly and time intensive, prompting a move to improve the bio-relevance of *in-vitro* test methods. The many recent publications in this field (Garbacz and Klein, 2012; Mcallister, 2010, Kostewicz et al., 2014; Koziolek et al., 2013) include the use of biorelevant media (Markopoulos et al., 2015; Dressman, 2014; Jantratid et al., 2008; Galia et al., 1998), the USP III (Bio-Dis) Apparatus (Fotaki et al., 2009; Klein et al., 2008; Asare-Addo et al., 2013), the dissolution stress tester (Garbacz et al., 2008; Garbacz et al., 2014), and models that simulate the GI tract, such as TIM (an artificial

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digestion system) (Souliman et al., 2007; Brouwers et al., 2011; Blanquet et al., 2004) and the Dynamic Gastric Model (Chessa et al., 2014; Mann and Pygall, 2012), the focus of this paper.

A diagram of the Dynamic Gastric Model (DGM) is shown in Fig. 1. It is designed to replicate the complex mixing, temporal biochemical release and cyclical muscular contractions of the fundal and antral regions of the stomach. It is one of the few *in-vitro* models that can accommodate real food items. The DGM has been built from *in-vivo* data, typically MRI studies, in healthy and ileostomised subjects, to ascertain the physiological processing parameters of the upper gastrointestinal tract under different feeding states. The up and downward movement of the piston forces the food to pass a flexible annulus during every stroke, which simulates the rhythmic peristaltic contractions of the human stomach, and exerts shear stress on the antral contents. Gastric sieving is simulated due to a "dead volume" between the barrel and the piston, which is maintained during sample ejection to allow large, dense particles to remain in the antrum and undergo further processing cycles. At the end of simulated digestion, any material remaining in this dead volume is ejected to simulate the phase III contraction (housekeeper wave) which fully empties the stomach at the end of gastric digestion. The volumes and duration of processing are tailored to the specific meal used (Wickham et al., 2012; Wickham and Faulks, 2013; Vardakou et al., 2011a; Thuenemann et al., 2015).The DGM was originally developed to investigate food processing by the stomach, but in recent years it has been used for the *in-vitro* testing of pharmaceutical products. Initial studies utilised agar beads of a specific fracture strength (0.53-0.90 N) to investigate how forces exerted on oral products within the DGM compare with those in a compendial USP II test (Vardakou et al., 2011a). They found forces were much greater in the DGM. All beads broke up within 2 h of gastric processing in the presence of high and low viscosity meals whereas only 15% of beads broke up in the USP II test at the highest paddle speed (100 RPM) in a high viscosity meal. A comparison with *in-vivo* MRI data showed that DGM fracture strength results were comparable with the human stomach (Marciani et al., 2001). Another study, which recorded the rupture time of capsule shells, showed how the DGM could closely mimic *in-vivo* human measurements that included gamma scintigraphy and plasma profiling (Vardakou et al., 2011b). The above suggests the DGM may be useful for investigating the sensitivity of dosage forms to the mechanical stresses of the *in-vivo* stomach. It should be noted that the DGM, whilst sophisticated in its design features, is still a mechanical representation of the human gut and does not take into account the control of the peristatic action, including the dynamic gastric emptying profile, under the control of the human humoral system. The DGM is not able to replicate the exact GI motility, but is one of the few available *in-vitro* tools that in some way mimics the dynamic processing that occurs in the stomach.

In one of the first published studies of pharmaceutical formulations (Mann and Pygall, 2012), the DGM was used to investigate why USP II dissolution testing had failed to predict the non-bioequivalence under *in-vivo* conditions between a

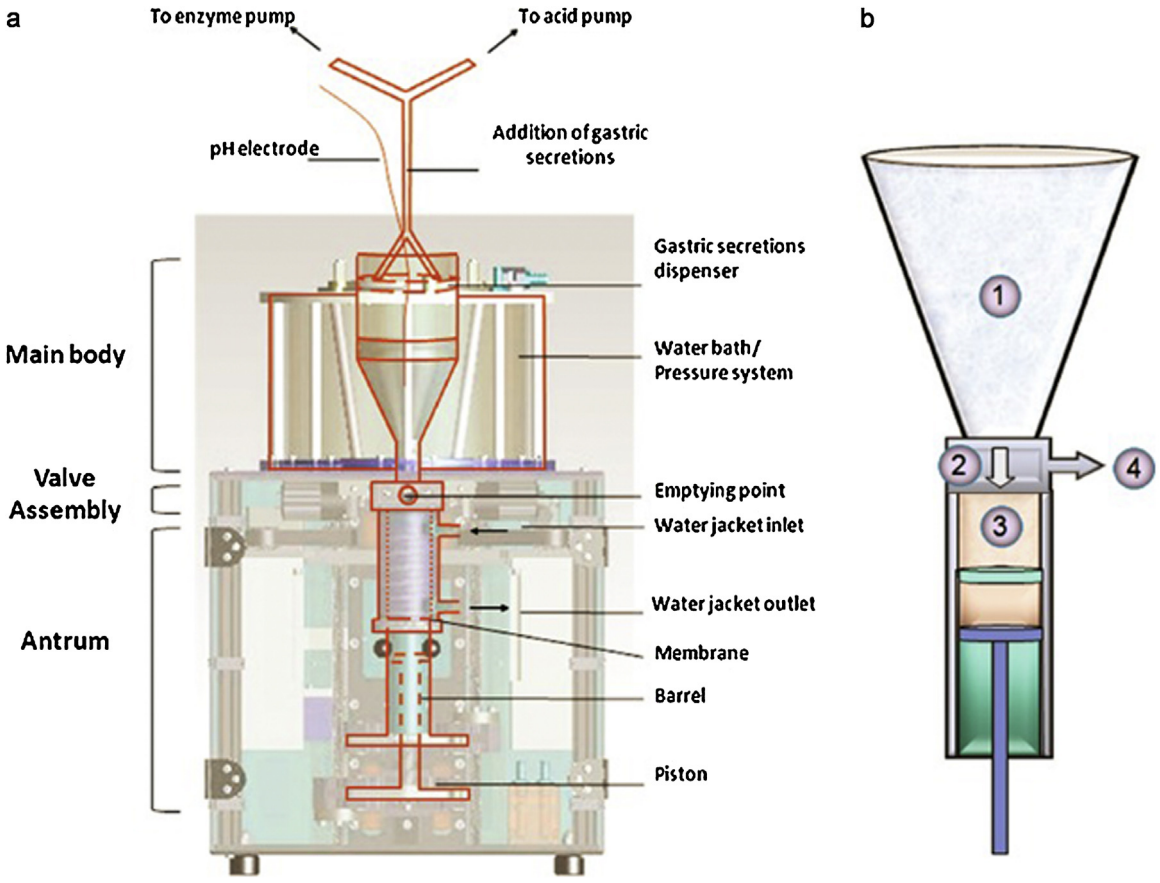

Fig. 1. Schematic representations of the dynamic gastric model. Diagram (a) depicts the main components of the DGM whilst diagram (b) illustrates the principal mechanisms of the mechanical digestion in which the number notations refer to the following: (1) The main body of the stomach where the gastric contents are mixed inhomogeneously with gastric secretions through the application of pulsatile contractions. (2) The transit of gastric contents into the model antrum through the valve assembly. The inlet valve opens during this process, allowing reflux and mixing between the main body and the model antrum. (3) The chyme being processed mechanically by the movement of the piston and barrel, and through being forced through an annular membrane. (4) The chyme being emptied from the antrum and collected for analysis. From (Vardakou et al., 2011a), permission granted from Springer RightsLink.