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Predicting the gastrointestinal behaviour of modified-release products: Utility of a novel dynamic dissolution test apparatus involving the use of bicarbonate buffers

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ABSTRACT

The establishment of physiologically relevant *in vitro–in vivo* correlations (IV–IVCs) is key for any biorelevant dissolution test. Historically, bicarbonate buffers have produced better correlations than compendial phosphate buffered media, though such tests are usually performed at a constant pH experiment, overlooking the notion that the pH of the luminal fluids is variable and fluctuating. In this work, we have devised a dynamic dissolution test method employing a physiological bicarbonate buffer under pH conditions of the proximal gut in order to assess the dissolution behaviour of various enteric polymer-coated (gastro-resistant) prednisolone tablets. The pH of the media is modulated and controlled by an Auto pH System™ which exploits the physiological equilibria between $[H_2CO_3]$ and $[HCO_3^-]$, to match it to the aboral change in pH with transit of the dosage form through the proximal small intestine (from pH 5.6 up to 6.8). The lag time values for an accelerated release and standard EUDRAGIT® L30D-55 coated formulation (25 min and 60 min, respectively) were close to the previously reported initial tablet disintegration time data obtained *in-vivo* by γ-scintigraphy (28 min and 66 min, respectively). Dissolution of alternative delayed release coated products was also better discriminated in the dynamic buffer system. These data confirm the dynamic dissolution system provides a robust and reliable platform to predict the *in vivo* fate of oral products in a laboratory setting.

1. Introduction

Dissolution testing of oral dosage forms can serve two purposes; the first being to assess the quality of the product (i.e. using *in-vitro* dissolution testing as a means of quality control), and secondly as a prognostic tool for the performance of dosage forms in the gastrointestinal tract (i.e. predictive dissolution testing) (Dressman and Kramer, 2005).

Predictive dissolution test data may guide the early development of a new drug product by aiding rational selection of candidate formulations yielding the desired *in-vivo* dissolution characteristics, thus serving as a surrogate for clinical studies. To this end, the test method requires establishment of conditions closely reflecting the physiological environment of the gastrointestinal tract (Dressman and Kramer, 2005), albeit which is often difficult to achieve in practice.

At present, the most commonly used dissolution media are those which include phosphate species, having historically demonstrated reasonable/acceptable *in vitro–in vivo* correlations (IV–IVCs) (Sheng et al., 2009). However, the presence of phosphates in human gastrointestinal luminal fluids is otherwise insignificant, and so use of such phosphate-containing media is poorly representative of the *in vivo* environment, concerning characteristics such as ionic strength, buffer capacity, fluid volume and viscosity which also varies dramatically post-prandium (Banwell et al., 1971; Dressman et al., 1990; Fallingborg, 1999; Lindahl et al., 1997; McConnell et al., 2008; Schiller et al., 2005). These parameters are crucial to the disintegration of solid dosage forms coated with pH-sensitive polymers (Chan et al., 2001; Fadda and Basit, 2005; Ibekwe et al., 2006; McConnell et al., 2008). Equally, the composition of GI fluids *in vivo* is subject to rapid and continuous change in response to external and internal stimuli, and is not well-represented by commonly-utilized simple buffered aqueous solutions. Technological approaches such as the dynamic gastric model (DGM) and TIM-1 system may provide a more accurate simulation of the gastrointestinal tract, but there is

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Table 1
Enteric polymers used in the study.

Polymer	Brand name	Abbreviation	Grade	Soluble at or above pH	Manufacturer/supplier
Acrylic polymers					
Methacrylic acidcopolymer	EUDRAGIT®	EUD	L30D-55 L100	5.5 6	Evonik Röhm GmbH, Darmstadt, Germany
Non-acrylic polymers					
Hypromellose acetate succinate	Aqoat®	HPMCAS	MF	6	Shin-Etsu Chemical Co. Ltd., Japan
Hypromellose phthalate	–	HPMCP	HP-55	5.5	Shin-Etsu Chemical Co. Ltd., Japan
Cellulose acetate phthalate	–	CAP	–	6	Eastman Chemical Company, USA
Polyvinyl acetate phthalate	Sureteric®	PVAP	Aqueous	5	Colorcon Ltd., USA

currently little evidence to date demonstrating their added value for use in dissolution studies with pH-sensitive polymeric coatings (McAllister, 2010).

It is instead bicarbonate which functions as the main buffer species in the luminal fluids of the small intestine: dissolution media comprising physiological salt solutions predominately buffered by bicarbonate species have been shown to provide more realistic disintegration information on coated solid dosage forms as compared to compendial phosphate buffers (Boni et al., 2007; Fadda et al., 2009; Sheng et al., 2009). However, their use in dissolution media has been limited, likely due to the difficulties associated with maintaining constant pH of the media and avoiding loss of carbon dioxide (CO_2) over time, in turn leading to a consistent pH rise which the buffer cannot otherwise compensate for. Previous studies involving modified bicarbonate buffers (Liu et al., 2011; Varum et al., 2014) have also only been performed in a single-point pH experiment (e.g. pH 5.6 or 6.8) intended to represent an average pH of the duodenum or of the proximal intestine, rather than one which is subject to changes in gastrointestinal milieu. For instance, the duodenal bulb has a slightly acidic pH of 5.6 (Bratten and Jones, 2009) which then increases up to pH 6.8 in the proximal small intestine and pH 7.4 in the distal small intestine (Dressman et al., 1990; Evans et al., 1988; Fallingborg, 1999).

Recently, we have devised a dynamic pH dissolution media employing a physiological bicarbonate buffer controlled by an Auto pH System™ (Merchant et al., 2012). Another system was also introduced later to control the pH of bicarbonate buffers predicated on similar concepts (Garbacz et al., 2014). In this research, the pH of dynamic dissolution media was matched to the aboral changes in pH encountered by the dosage form en route to the small intestine following gastric emptying (from pH 5.6 to 6.8). The suitability of this media to test the dissolution of tablets coated with various enteric polymers with dissolution pH thresholds of 5.5–6 – similar to the pH of the physiological fluid of the duodenum – has been evaluated. The range of enteric polymers were selected either from aqueous polymer dispersions or organic solutions, and one accelerated-release enteric double coating formulation from Liu et al. (2009), which showed a faster drug release after the triggering pH was reached. The findings are compared with previously-reported behaviour of such coatings under static conditions of pH, and particularly with *in vivo* γ-scintigraphy data to validate the proposed system.

2. Materials and methods

2.1. Materials

The enteric polymers used in this study and their properties are listed in Table 1. Prednisolone was purchased from Aventis Pharma, Antony, France. Lactose (Pharmatose) was obtained from Ellis and Everard, Essex, UK. Cross-linked sodium carboxymethylcellulose was donated by FMC International, Cork, Ireland. Polyvinylpyrrolidone 40,000 was purchased from VWR International Ltd., Poole, UK. Magnesium stearate was purchased from Sigma–Aldrich Co. Ltd., Dorset, UK. Triethyl citrate was obtained from Lancaster Synthesis, Lancashire, UK. Sodium lauryl sulphate and triacetin were sourced from Sigma–Aldrich Co. Ltd., Dorset, UK. Talc (fine powder) was purchased from VWR International Ltd., Poole, UK. Organic solvents used were of analytical grade and were obtained from VWR International Ltd., Poole, UK (ethanol) and Fisher Scientific UK Ltd., Loughborough, UK (acetone and isopropanol). Salts for preparing buffer solutions were obtained from VWR International Ltd., Poole, UK.

2.2. Methods

2.2.1. Preparation of prednisolone tablets

The tablets were prepared using a method described previously (Liu et al., 2011), briefly, the formulation was composed of 5% prednisolone, 88.5% lactose, 5% polyvinylpyrrolidone, 0.5% cross-linked sodium carboxymethylcellulose and 1% magnesium stearate. The tablets were prepared by wet granulation and were produced using a single punch tableting machine (Manesty F3, Liverpool, UK). Cross-linked sodium carboxymethylcellulose (disintegrant) was added both intra- and extra-granularly (50:50). A biconcave 8 mm punch and die set (I Holland, Nottingham, UK) was used to obtain tablets of mass 200 mg (containing 10 mg drug) and crushing strength of 80 N.

2.2.2. Coating of prednisolone tablets

Different kinds of polymers were selected and enteric coating formulations were prepared either from aqueous polymer dispersions or organic solutions. Additionally, a double-layered enteric coating formulation (Liu and Basit, 2010; Liu et al., 2009) was incorporated to this study. The compositions of the formulations are listed in Table 2. Prednisolone tablets were coated using a Strea-1 bottom spray fluidised bed coater (Aeromatic AG, Bubendorf, Switzerland) using the method described earlier (Liu et al., 2011). After the coating process, the tablets were cured in an air-assisted oven at 40 °C for 2 h. The optimised coating parameters for each polymer formulation are briefed in Table 3. Coating levels of the polymers were determined by the amount of polymer applied per square centimetre of tablet surface (mg/cm^2), except for PVAP where percentage tablet weight gain (TWG%) was used, given that the quantitative composition of the PVAP formulation is not in the public domain. Coating levels were selected based on the optimum acid resistance (i.e. no visible signs of coat disruption and no more than 10% acid uptake after 2 h treatment with 0.1 M HCl).

2.2.3. Development of dynamic dissolution media

A physiological salt solution predominately buffered by bicarbonate ions was modulated to exhibit the aboral rise in intestinal pH following gastric emptying. The media, adapted from Hanks buffer (Liu et al., 2011), is primarily a bicarbonate buffer in which bicarbonate (HCO_3^-) and carbonic acid (H_2CO_3) co-