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Gastrointestinal release behaviour of modified-release drug products: Dynamic dissolution testing of mesalazine formulations

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ABSTRACT

The aminosalicylate mesalazine (mesalamine) forms the mainstay of treatment in ulcerative colitis (UC), a disease for which many commercial modified-release products have been developed with the aim of providing targeted gastrointestinal release. The release profiles of five of these commercial formulations were evaluated in bicarbonate buffer using a novel dissolution model that mimics the dynamic conditions of the gastrointestinal tract. Monolithic and multi-particulate mesalazine formulations with pH-dependent and/or independent release mechanisms were evaluated (Asacol® 800, Octasa®, Mezavant® XL, Salofalk®, Pentasa®), and each of the products displayed a distinctive dissolution profile. The dissolution results for Mezavant® XL (Lialda®) (lag time 290 min) demonstrated good correlation with previously reported *in vivo* disintegration times assessed by gamma-scintigraphy in humans. Octasa® showed a similar lag time to Mezavant® XL. Drug release from Asacol® 800 (Asacol® HD) showed a wide standard deviation, reflecting the great variability *in vivo*. Salofalk® displayed both delayed release and extended release characteristics. Pentasa® released more than 50% of its drug load in the stomach compartment of the model, which is attributed to the absence of a gastro-resistant coating in this product. The new dissolution method provided a realistic and discriminative *in vitro* assessment of mesalazine release from different formulations. These results demonstrate that this strategy can be used to predict intestinal release behaviour, and potentially aid the rational design of products developed to target different sites of the gut.

1. Introduction

Ulcerative colitis (UC) is one of the two main entities of inflammatory bowel disease (IBD); whereas Crohn's disease is characterised by transmural inflammation and can manifest at any membranous site along the length of the gastrointestinal (GI) tract, inflammation in UC is strictly limited to the colonic and rectal gastrointestinal mucosa. UC is also a prevalent example of a GI disorder for which oral drug delivery methods have been developed and adapted specifically with a view to minimising the risk of associated adverse drug effects, and to more specifically target the disease site(s) (McConnell et al., 2009).

Treatment strategies in UC are generally dominated by the use of aminosalicylates, with mesalazine – also known as mesalamine or 5-aminosalicylic acid (5-ASA) – as the first-line treatment indicated for UC. The exact mechanism of action of mesalazine has yet to be fully elucidated, though it is thought to act topically from the intestinal lumen to target proliferation and activity of inflammatory mediators such as prostaglandins. In this way, inflammatory "trafficking" and free radical production at disease-afflicted site(s) are considerably reduced (McConnell et al., 2009).

Following oral administration, mesalazine is normally rapidly and extensively absorbed in the upper GI tract (Lichtenstein and Kamm, 2008). Consequently, the most commonly-used dosage forms are modified-release formulations of mesalazine. These formulations employ various strategies for drug delivery by the use of pH-sensitive and/or insoluble polymers intended to allow for release of drug into the lower confines of the gut. Feagan et al. (2013) recently reported that all mesalazine formulations are safe and effective in the treatment of mild to moderate ulcerative colitis; however, there is evidence that patients who demonstrate inadequate response to one type of formulation benefit from switching to a different type (Yoshimura et al., 2013). This may be related to the fact that the various formulations display differences

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in their drug release profiles (Fadda et al., 2009; Klein et al., 2005; Schellekens et al., 2007). The choice of mesalazine therapy is also often based on trial and error, due to difficulties in tailoring individual doses to patients in addition to effective targeting of the region(s) of the gastrointestinal tract affected by disease without resulting in premature drug release (Goyanes et al., 2015a; McConnell et al., 2009).

Like all oral drug products, these mesalazine formulations are evaluated in human pharmacokinetic studies as well as clinical efficacy studies, though there is merit in developing an accurate *in vitro* model which best represents conditions in the human GI tract. Such a model would reduce both costs and development times through allowing early evaluation and comparison of the release profiles of various formulations simultaneously and in real time, as well as providing robust *in vitro–in vivo* correlations (IVIVCs).

Indeed, the design of dissolution media to accurately reflect conditions in humans and thus provide a good *in vitro* correlation to the *in vivo* situation has also been a long-standing goal for the dissolution testing of solid oral dosage forms (McAllister, 2010; Varum et al., 2013a). Compendial phosphate buffers have formed the mainstay of *in vitro* dissolution testing media over the years, though these systems is otherwise poorly representative of *in vivo* small intestinal fluid composition, leading to the rapid dissolution of enteric-coated dosage forms (Liu et al., 2009; Varum et al., 2013b). A promising alternative to the use of these standard phosphate buffers, however, are physiological bicarbonate buffers – bicarbonate being the main buffer species of human gastrointestinal luminal fluids (Fadda et al., 2009; Garbacz et al., 2013; Krieg et al., 2014) – which have been shown to better discriminate the behaviours of oral dosage forms and hence produce more accurate IVIVCs than their phosphate counterparts (Liu et al., 2011; Merchant et al., 2014).

In this work, we have evaluated a recently-developed Auto pH System™ that provides a closely-correlated representation of various human GI parameters including pH, ionic strength and buffer capacity employing a physiological bicarbonate buffer under dynamic intestinal conditions (Goyanes et al., 2015b; Merchant et al., 2012; Varum et al., 2014). We studied the feasibility of using the system to evaluate the dissolution behaviours of five commercial modified-release formulations of mesalazine. Each of the formulations, herein, features a slightly different release mechanism as intended for inflammatory bowel diseases.

2. Materials and methods

2.1. Materials

The salts for preparing the buffer solutions were obtained from VWR International Ltd. (Poole, UK) and the commercial products of mesalazine tested in this study are as follows:

Asacol® 800 mg MR tablets (Asacol® HD in USA) (Warner Chilcott UK Ltd., UK) is a tablet formulation with a double-layered enteric coating comprising Eudragit S (methacrylic acid–methyl methacrylate copolymers (1:2)) and Eudragit L (methacrylic acid–methyl methacrylate (1:1)) which have a dissolution pH threshold of 7 and 6, respectively. The inner coating is Eudragit S and the outer coating is a mixture of Eudragit S and L (Fadda et al., 2009); however, the ratio of Eudragit S and L in the outer coat is not disclosed.

Mezavant® XL 1200 mg tablets (Lialda® in USA) (Shire Pharmaceutical Ltd., UK) is a tablet formulation with a sustained release hydrophilic/lipophilic matrix core known as the Multi Matrix System® (MMX™) (Cosmo, Milan, Italy) and an outer enteric coating comprising Eudragit S and L; however, the ratio of Eudragit S and L is not disclosed.

Octasa® 800 mg MR tablets (Tillotts Pharma UK Ltd., UK) is a tablet formulation coated with Eudragit S.

Pentasa® 500 mg tablets (Ferring Pharmaceuticals Ltd., UK) are made of the compressed ethylcellulose coated granules, where drug release from granules is mediated by diffusion through the insoluble polymer coat.

Salofalk® 500 mg granules (Apriso® 0.375 g in USA) (Dr. Falk Pharma UK Ltd., UK) are gastric-resistant (Eudragit L® coated) granules, offering prolonged drug release from a matrix core centred on the pH-independent polymer, Eudragit NE.

2.2. Design and development of the physiological dynamic dissolution method

Two physiological salt solutions predominately buffered by bicarbonate ions were modulated to exhibit the physiological intestinal pH following gastric emptying. The media are primarily a bicarbonate buffer in which bicarbonate (HCO_3^-) and carbonic acid (H_2CO_3) co-exist in an equilibrium, along with CO_2 (aq) resultant from the dissociation of the carbonic acid. The pH of the buffer system can be altered by adjusting the concentration of carbonic acid (H_2CO_3) and bicarbonate (HCO_3^-), the conjugate base, according to the Henderson-Hasselbalch equation. Thus, pH can be decreased by purging CO_2 (g) in the solution, which promotes the formation of carbonic acid. Similarly, to decrease the carbonic acid (H_2CO_3) to bicarbonate (HCO_3^-) ratio, an inert gas (such as helium) is purged into the solution, which removes the dissolved CO_2 from the solution and therefore reduces the concentration of carbonic acid, reducing the pH of the media. The purging of gases is controlled by an Auto pH System™ (Merchant et al., 2012), automatically triggered by a pH feedback from the dissolution vessel (Fig. 1). The Auto pH System™ consists of a pH probe connected to a source of carbon dioxide gas (pH reducing gas), as well as to a supply of helium (pH increasing gas), controlled by a control unit. The control unit monitors changes in pH of the bicarbonate buffer and, as appropriate, feeds pH increasing and/or pH reducing gas from the supplies into the dissolution vessel. The control unit is able to provide a dynamically adjustable pH during testing (dynamic conditions) and to maintain a uniform pH value over the otherwise unstable bicarbonate buffer pH. Under dynamic conditions, the automated switching of the buffer pH between pre-defined set points allows the instrument to mimic the changing pH found in the gastrointestinal tract. Detailed information on the system can be found in Merchant et al. (2012).

A two-tiered bicarbonate-based buffer was used in this study. Initially, a modified Hanks buffer (mHanks) based dissolution media (Liu et al., 2011) (950 mL) was used, which followed the gastric phase, for the first 35 min (136.9 mM NaCl, 5.37 mM KCl, 0.812 mM $MgSO_4 \cdot 7H_2O$, 1.26 mM $CaCl_2$, 0.337 mM $Na_2HPO_4 \cdot 2H_2O$, 0.441 mM KH_2PO_4, 4.17 mM $NaHCO_3$). Subsequently, 50 mL of pre-Krebs solution (400.7 mM $NaHCO_3$ and 6.9 mM KH_2PO_4) was added to each dissolution vessel which forms an *in-situ* modified Kreb's (mKreb's) buffer (Fadda et al., 2009). These media closely resemble the ionic composition and buffer capacity of the intestinal fluids (Fadda et al., 2009; Liu et al., 2011). The buffer capacity of the physiological bicarbonate buffers representing the upper small intestine, lower small intestine and colon (3.1, 3.4 and 13 mM/L/ΔpH respectively (Fadda et al., 2009; Liu et al., 2011)), closely matches the buffer capacity of the intestinal fluids collected from the upper small intestine, lower small intestine and colon of humans (3.2, 6.4 and 13 mM/L/ΔpH, respectively (Fadda et al., 2010)).

2.3. Test conditions

The drug release from the commercial formulations was tested using a USP-II apparatus (Model PTWS, Pharmatest, Hainburg, Germany). To replicate the conditions of the GI tract the tablets or granules were initially placed for 2 h into 750 mL of 0.1 M HCl and