Article

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.

Keywords: 5- aminosalicylic acid; 5-ASA; colonic delivery; enteric coatings; biorelevant dissolution; physiological bicarbonate buffers.

Introduction

Ulcerative colitis (UC) is one of 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 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.

Materials and Methods

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® 0.375g 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.

Methods

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. 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 (Figure 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 $MgSO_4.7H_2O$, 1.26 mM $CaCl_2$, 0.337 mM $Na_2HPO_4.2H_2O$, 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)).

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 subsequently into 950 mL of modified Hanks based dynamic physiological dissolution medium for 35 min (pH 5.6 to 7); then in mKrebs buffer (pH 7 to 7.4 and then to 6.5). The 2 h acid stage simulates the gastric residence time, the 3.5 h in bicarbonate buffer at pH 5.6 to 7.4 represents the transit time through the small intestine, followed by a drop in buffer pH (6.5) which represents the colonic environment. These conditions were selected based on literature data to represent conditions for intestinal transit of pharmaceutical dosage forms and pH values in different segments of the GI tract in a "typical" fasted individual (Davis et al., 1986; Evans et al., 1988; Freire et al., 2011; Ibekwe et al., 2008a; McConnell et al., 2008a; Nugent et al., 2001).
The paddle speed was fixed at 50 rpm and the tests were conducted at 37 $\pm$ 0.5 °C (n=6). The amount of mesalazine released from commercial formulations was determined using an in-line UV spectrophotometer (Cecil 2020, Cecil Instruments Ltd., Cambridge, UK) at the wavelength of 310 nm for samples from the acid media and of 330 nm for those in bicarbonate buffer media. Data were processed using Icalis software (Icalis Data Systems Ltd, Berkshire, UK).

Results and discussion

The physiological bicarbonate based dynamic dissolution media showed a high control of the pH (±0.01 pH units) using the Auto pH System™. The pH was controlled within the range of pH 5.6 to 7.4, and it was subsequently decreased to a value of pH 6.5 in order to simulate the dynamic pH conditions of the small and large intestines. Figure 2 shows a real-time pH profile achieved with the use of the Auto pH System™ at the various set points to modulate the pH of the media to resemble a typical fasted state GI transit and pH profile.

The drug release performance of the mesalazine products is depicted in Figure 3. All four enteric coated formulations were resistant to acid, showing no drug release after 2 h of exposure to 0.1 M HCl. In the intestinal phase of the test, release from the enteric coated products was dependent on the nature of the pH-dependent coating material. The physiological pH trigger of the Salofalk® product under the test conditions is 7.2. For the Asacol®, Octasa® and Mezavant® products the pH trigger is 7.4, but the lag times for release differ for each product. For all the enteric coated products, drug release is initiated in the small intestinal phase of the test and then continues in the colonic compartment of the test (after 330 mins). In contrast to the enteric coated formulations, in the case of Pentasa more than 50% of the drug load was released after 2 h of exposure to acid.

Though limited by their inability to simulate complex aspects of GI physiology, there is much merit in developing effective and accurate *in vitro* models for the purpose of mimicking physiological conditions in human for mesalazine products. The true value of these models also lies in enabling extrapolation of real-time data on dissolution and distribution kinetics to inform both preclinical and clinical studies – information otherwise not readily derived from other techniques such as gamma scintigraphy, pharmacokinetic studies and gut mucosal biopsies (Lichtenstein and Kamm, 2008).
As such, the dynamic dissolution system has successfully discriminated the intestinal release behavior of the five mesalazine products. In the case of Mezavant® XL, the dissolution results using bicarbonate buffer under the dynamic mode correlated closely with the *in vivo* disintegration times of the same product from Wray et al. (2008), as assessed by gamma-scintigraphy in humans. The *in vitro* lag time under the dynamic conditions for Mezavant® XL in this study was 290 min, which correlates well with the initial tablet disintegration time of the same formulation *in vivo* (lag time 285 min). The gastroresistant coating of Mezavant® XL– which is a mixture of Eudragit S and L polymers – is designed to allow dosage form transportation to the lower gut by circumventing the harsh acidic conditions of the stomach. It is the core of Mezavant® XL which is purported to extend release of drug by formation of an outer viscous gel mass on contact of the exposed core to fluid following dissolution of the coating. However, our results have shown that the release profile of mesalazine from this formulation was similar to that of the other pH 7-coated tablets with no apparent evidence of superior sustained release characteristics. This phenomenon was also demonstrated in a study by Fadda et al, (2009) whereupon both the lag times and drug release profiles for Mezavant® XL were shown to display different behaviours in Krebs buffer as compared to phosphate buffer, with no slow release in Krebs bicarbonate media.

By comparison, the formulations Asacol® and Octasa® showed slightly different lag times - 240 and 330 min respectively (Figure 3). The early onset of release observed for Asacol® by comparison to Octasa® may be explained by the difference in composition of the their gastro-resistant coatings. The enteric coat of Octasa® is the Eudragit S polymer, which dissolves at pH 7. By contrast, Asacol® comprises two enteric coatings; the inner coating is an Eudragit® S polymer, whereas the outer coating is a blend of Eudragit® S and L (Fadda et al., 2009). The high standard deviation of Asacol® also indicates an expected high variability *in vivo* (eMC-Asacol). Overall, according to the drug dissolution profiles for these products

obtained under these standard fasted state conditions, release *in vivo* would take place in the last part of the small intestine and continue into the colon.
An issue with these, and similar preparations, is that a failure to disintegrate has been reported with some dosage forms *in vivo*. This dosage form failure might be expected in inflammatory bowel disease patients (IBD) in whom the colonic pH may be lower. pH values of 4.7 ± 0.72 were measured in the right colon of ulcerative colitis patients (Nugent et al., 2000), and a fall in colonic pH to <5.5 was found in 2 out of 6 patients studied (Fallingborg et al., 1993). In one case, a proximal colonic pH as low as 2.3 was detected in an ulcerative colitis patient (Fallingborg et al., 1993). However, the failure to disintegrate was also observed in healthy volunteers (McConnell et al., 2009). This led to the suggestion that pH-responsive dosage forms are influenced by more than just pH (Ibekwe et al., 2008b), but also by residence time at the ileocaecal junction and feeding states. Gastrointestinal fluid composition is also important as the mechanism of enteric polymer dissolution in aqueous fluids is complex and influenced by a multitude of factors (Narasimhan and Peppas, 1997; Nguyen and Fogler, 2005). Hydrogen ions are generated at the polymer-solution interface during polymer dissociation (Nguyen and Fogler, 2005) and contribute to a pH drop near the surface of the dissolving carboxylic polymer (Harianawala et al., 2002). Removal of these hydrogen ions at the interface increases the polymer dissolution rate, and can be facilitated by reacting with proton acceptors (buffer species) depending on their buffer capacities, which also directly linked to the pKa of the buffering species. The rank order in the dissolution of these products can be explained by the determinant factors for enteric coating dissolution; that is, polymer pKa and chemical structure (Ozturk et al., 1988). Polymers with higher pKa values reflected by higher dissolution pH thresholds include the Eudragit® S100 coated product, Octasa® 800, which had slower drug release.

To circumvent some of the issues above, other approaches to pH-responsive drug delivery to the distal gut include using polymers that have a lower pH threshold. In this respect for Salofalk® 500mg granules, the release of drug begins in the small intestine after 195 min – much earlier than for the other aforementioned products (Figure 3). This is supported by pharmacokinetic data where Salofalk® product displays a shorter time to maximum plasma concentration - 4- 5 h (eMC-Salofalk) - than the other enteric products, Asacol® 4-12 h (eMC-Asacol) or Mezavant® 9-12 h (eMC-Mezavant). The shorter lag time is attributable to the fact that the coating of Salofalk® is based on the polymer Eudragit L, which has a theoretical pH threshold of 6. At this value, no release occurs, but instead only begins with a lag time delayed until pH 7.2 is achieved (~175 mins). Salofalk® is thus advantageous in potentially overcoming the “pass-through” effects noted with the other comparable formulations. However, enteric coated pellets have also been observed to pass through the gut intact (McConnell et al., 2008b). Although this approach of delayed and sustained drug release throughout small and large intestine is not very efficacious in targeting colon in ulcerative colitis but can be advantageous in patients with inflamed sites spread across the gut.
In contrast to the pH dependent release systems, the Pentasa® product is manufactured with a pH independent polymer (ethylcellulose), in consequence, the Pentasa® formulation evaluated in this study showed distinctly different behaviour in terms of its drug release as compared with the others formulations. Pentasa® 500 mg tablets are comprised of compressed ethylcellulose-coated granules that degranulate rapidly in the acid stage. The drug release mechanism in this case is by diffusion through this insoluble polymer, allowing for more than 50% of drug release to take place during the acid stage with the subsequent 50% releasing throughout the entire small intestine and colon (Figure 3). Interestingly, the mucosal concentrations of mesalazine in the sigmoid colon is lower from this type of pH independent formulations compared to those receiving pH dependent formulations (D'Inca et al., 2013).
The physiologic dissolution system evaluated in this study can be theoretically modified to mimic different situations (real-life) such as transit time, fluid volumes and pH values; and it could be further improved by the addition of other luminal compounds including

acetate/maleate and short chain fatty acids which are found in the last part of the gut. It may also be possible to mimic the environment of different disease states that we know have different GI profiles to otherwise “normal” healthy individuals. Indeed, this can be crucial for the drug release from dosage forms designed to dissolve at a specific pH value which may only be maintained in the gut for a short amount of time in a given individual, and thus be potentially insufficient to allow for complete drug release. Such variations may also be apparent in disease states such as IBD, manifesting as diarrhoea and affecting the performance of modified release formulations. Whereas, altering various parameter values of the *in vitro* physiologic model – including pH and residence times – may also render it possible to evaluate robustness of these different products under different conditions.

Conclusions

The dynamic dissolution system provides a realistic in vitro simulation of the gastrointestinal tract. This system provided discriminative *in vitro* assessment for various commercial modified-release mesalazine formulations all run under an identical set of standard conditions reflecting typical *in vivo* transit and pH conditions. We have shown that the release profiles of five commercial formulations of mesalazine – Asacol® 800 mg tablets, Mezavant® XL 1200 mg tablets, Octasa® 800 mg tablets, Pentasa® 500 mg tablets and Salofalk® 500 mg granules - differ considerably. These differences can be attributed to the different mechanisms used to control/modified the release of mesalazine, but owing to the highly variable physiological conditions of the GI tract, suggests that the release of drug may equally be compromised by factors such as inter-individual variability. One of the main highlights of the study was identifying good correlation (both *in vitro* and *in vivo* lag times) for drug release from the Mezavant® XL product specifically, supporting the notion that the novel dissolution testing approach can be used as a predictive tool of *in vivo* results. Altering the settings of the *in vitro* physiologic model – including pH and residence times – may also render it possible to evaluate robustness of these different products under different conditions, for instance simulating disease states such as IBD, manifesting as diarrhoea and affecting the performance of modified release formulations.

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Figure captions

Figure 1. Schematic design of the Auto pH System™ used to modulate and maintain the pH of a bicarbonate buffer in a conventional USP-II apparatus. Figure adapted from Merchant et al., 2012.

Figure 2. A real-time pH profile of a bicarbonate based dissolution media simulating the dynamic pH conditions of the gut in a conventional USP-II apparatus employed for dissolution testing. The pH was modulated and maintained using the Auto pH™ System.

Figure 3. Drug release from the commercial formulations in 0.1M HCl for 2h followed by physiological bicarbonate buffer under dynamic pH conditions (pH ramp from 5.6 to 7.4 followed by a drop to pH 6.5) controlled by the Auto pH System™. Red line shows real-time pH dissolution values.

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