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Physiological bicarbonate buffers: stabilisation and use as dissolution media for modified release systems

Hala M. Fadda, Hamid A. Merchant, Basel T. Arafat, Abdul W. Basit*

Department of Pharmaceutics, The School of Pharmacy, University of London, 29-39 Brunswick Square, London, WC1N 1AX, United Kingdom

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ABSTRACT

Bicarbonate media are reflective of the ionic composition and buffer capacity of small intestinal luminal fluids. Here we investigate methods to stabilise bicarbonate buffers which can be readily applied to USP-II dissolution apparatus. The *in vitro* drug release behaviour of three enteric coated mesalazine (mesalamine) products is investigated. Asacol® 400 mg and Asacol® 800 mg (Asacol® HD) and the new generation, high dose (1200 mg) delayed and sustained release formulation, Mezavant® (Lialda®), are compared in pH 7.4 Krebs bicarbonate and phosphate buffers. Bicarbonate stabilisation was achieved by: continuous sparging of the medium with 5% CO_2(g), application of a layer of liquid paraffin above the medium, or a specially designed in-house seal device that prevents CO_2(g) loss. Each of the products displayed a delayed onset of drug release in physiological bicarbonate media compared to phosphate buffer. Moreover, Mezavant® displayed a zero-order, sustained release profile in phosphate buffer; in bicarbonate media, however, this slow drug release was no longer apparent and a profile similar to that of Asacol® 400 mg was observed. These similar release patterns of Asacol® 400 mg and Mezavant® displayed in bicarbonate media are in agreement with their pharmacokinetic profiles in humans. Bicarbonate media provide a better prediction of the *in vivo* behaviour of the mesalazine preparations investigated.

1. Introduction

As more sophisticated modified release oral drug delivery systems are being developed, increased emphasis is being placed on *in vitro* dissolution tests to predict the *in vivo* performance of such systems. While compendial dissolution tests rely on the use of phosphate buffers, these are not representative of physiological fluids in man (McConnell et al., 2008). Aside from pH, a number of aspects of dissolution media have been shown to affect the dissolution of ionisable polymers and compounds (Spitael and Kinget, 1979; Mooney et al., 1981; Aunins et al., 1985). It is of great importance to simulate not only the pH, but also the ionic composition and buffer capacity of gastrointestinal fluid. Small intestinal luminal fluids are buffered by bicarbonate which is secreted by the pancreas and intestinal epithelial cells. Physiological bicarbonate buffers, as dissolution media, have been shown to be more discriminative of the drug release behaviour of enteric coated formulations for ileo-colonic delivery, than compendial phosphate buffers, and gave better reflections of *in vivo* disintegration times (Ibekwe et al., 2006a,b, 2008).

A difficulty in the use of bicarbonate buffers is their progressive rise in pH due to loss of CO_2 from the solution (Perrin and Dempsey, 1974). In aqueous solutions both bicarbonate (HCO_3^-) and carbonic acid (H_2CO_3) exist (Eq. (1)).

Eq. (1) Equilibria for bicarbonate buffer systems.

$$\begin{array}{c} CO_2(g) \\ \Updownarrow \\ H_2O + CO_2(aq) \rightleftharpoons H_2CO_3(aq) \rightleftharpoons H^+ + HCO_3^-(aq) \end{array} \quad (1)$$

H_2CO_3 has a pKa of 6.4 and dissociates to yield H_2O and CO_2(aq). CO_2 evaporates from solution and therefore ionisation towards the left (protonation of HCO_3^- to yield H_2CO_3) is promoted to restore the equilibrium. When physiological buffers are used in *in vitro* cell cultures, they are maintained in a closed system equilibrated with 5% CO_2 in the gas phase to maintain the

* Corresponding author. Tel.: +44 020 7753 5865; fax: +44 020 7753 5865.
E-mail address: abdul.basit@pharmacy.ac.uk (A.W. Basit).

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pH. The use of larger scale systems such as USP dissolution baths makes bicarbonate buffer stabilisation more difficult. Sheng et al. (2009) have developed surrogate phosphate buffers equivalent to bicarbonates for the assessment of the intrinsic dissolution of weakly acidic drugs. While good equivalence has been achieved, the molarity of the phosphate buffers is drug-specific; dependent on the drug pKa and solubility. Systems equilibrated by continuously sparging with CO_2(g) have been used (McNamara et al., 2003; Fadda and Basit, 2005; Boni et al., 2007). While this has proven a reliable and reproducible method, other methods to stabilise bicarbonate buffers in a USP-II apparatus are evaluated here.

In this study we use different bicarbonate buffer stabilisation methods to compare the dissolution behaviour of three enteric coated mesalazine (mesalamine, 5-aminosalicylic acid) formulations. Mesalazine formulations with pH-responsive release mechanisms are used for the treatment of ulcerative colitis and topically act on the colonic mucosa through anti-inflammatory mechanisms. A variety of mesalazine products are available in the clinic (Basit, 2005; McConnell et al., 2009). For ease of patient compliance and evidence that treatment with higher doses of mesalazine results in greater patient improvement with no increased incidence of adverse events (Hanauer et al., 2005), a shift to the production of higher strength products has arisen (Ng and Kamm, 2008). With such a variety of doses and formulation approaches, it is important to be able to reliably discriminate between those formulations on the market, and generate realistic assessments of new formulations in the development stage. The objective of the present study was to investigate the drug release performance of two new mesalazine products (Asacol® 800 (Asacol® HD)) and Lialda® (Mezavant®) and one established formulation (Asacol® 400) in Krebs bicarbonate media and compendial phosphate buffer, and to compare the results with published *in vivo* pharmacokinetic data.

2. Materials

Asacol® 400 mg (Procter and Gamble, Surrey, UK) is a tablet formulation with an enteric coating comprising a poly(methacrylic acid methyl methacrylate) (MA-MM) (1:2) copolymer (Eudragit S) which has a dissolution pH threshold of 7.

Asacol® 800 mg (Asacol® HD in USA) (Procter and Gamble, Surrey, UK) is a tablet formulation with a double-layered enteric coating comprising MA-MM (1:2) and (1:1) (Eudragit S and L respectively) copolymers 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 (Procter and Gamble Pharmaceuticals, 2008), however, the ratio of Eudragit S and L in the outer coat is not disclosed. This particular formulation is available in the UK, Canada and USA.

Mezavant® 1200 mg (Lialda® in USA**)** (Shire Pharmaceuticals, Hampshire, UK) is a tablet formulation with a sustained release hydrophilic/lipophilic matrix core known as the Multi Matrix System® (MMX™) (Giuliani SpA, Milan, Italy) and an outer enteric coating comprising MA-MM (1:2) and (1:1) (Eudragit S and L respectively) copolymers, however, the ratio of Eudragit S and L is not disclosed. The matrix core is composed of: carmellose sodium, carnauba wax and stearic acid. Once the gastroresistant coating dissolves, an outer viscous gel mass is formed on contact of the MMX™ with fluid. This viscous gel is purported to slow diffusion of the drug from the tablet core into the colonic lumen (Lichtenstein et al., 2007).

The mesalazine preparations studied were received as gifts. All other materials were purchased from Sigma–Aldrich (Dorset, UK).

3. Methods

3.1. Dissolution media

The products were tested in pH 1.2 hydrochloric acid (0.1 M HCl) for 2 h proceeded by one of the following buffers:

Phosphate buffer (0.05 M) of pH 7.4
Composition: 50 mM KH_2PO_4 and 39.5 mM NaOH (pH adjusted with 1 M HCl/NaOH solutions).
Buffer capacity: 23 mM/L/pH unit.
Ionic strength: 0.129.
Saturation solubility of mesalazine in this medium is 6.34 mg/ml at 37 °C.

Krebs bicarbonate buffer of pH 7.4
Composition: 1.18 mM KH_2PO_4, 24 mM $NaHCO_3$, 118.07 mM NaCl, 4.69 mM KCl, 2.52 mM $CaCl_2$, 1.18 mM $MgSO_4 \cdot 7H_2O$ (pH adjusted to 7.4 using 5 M HCl for the liquid paraffin and lid stabilisation approaches and 5% CO_2 was used to adjust the pH during the gas purging approach).
Buffer capacity: 3.7 (unstabilised) and 5.45 (stabilised) mM/L/pH unit.
Ionic strength: 0.161.
Saturation solubility of mesalazine in this medium is 4.51 mg/ml at 37 °C.

3.2. Dissolution studies

Mesalazine release from the coated tablets was assessed by dissolution testing using USP-II paddle apparatus (model PTWS, Pharma Test, Hainburg, Germany) controlled by software IDIS EE 2.11.16 (Icalis Data Systems Ltd., Berkshire, UK). Tablets from within the same batch of each brand were tested. The volume of the dissolution media was 900 ml and sink conditions were attained for all the formulations (<30% saturation solubility). Dissolution media was maintained at 37 ± 0.5 °C and a paddle speed of 50 rpm was employed. Tablets ($n = 6$) were tested in 0.1 M HCl for 2 h, and then transferred to the pH 7.4 phosphate or bicarbonate buffers. The amount of mesalazine released from the dosage form was determined by an in-line UV spectrophotometer (Cecil 2020, UK) with 1 mm flow cells at 301 nm in acid and 330 nm in the pH 7.4 buffers. As UV readings were automatically taken, no loss of medium occurred throughout the duration of the dissolution run.

3.3. Stabilisation of Krebs bicarbonate buffer

Krebs bicarbonate buffer was stabilised using three different approaches:

a. Continuous sparging with 5% CO_2 throughout the duration of the dissolution run. Maintenance of CO_2(aq) prevents the decomposition of H_2CO_3 (aq) (to yield H_2O and CO_2) which in turn prevents the protonation of HCO_3^- (aq). Six polyurethane flow tubes (Freshford Ltd., Manchester, UK), one for each vessel, were connected to the regulator of the cylinder via a manifold and each tube was positioned 3 cm below the surface of its corresponding vessel.
b. Application of a layer of liquid paraffin above the dissolution media. Seventy millilitres of liquid paraffin (8.6 mm layer) was used to suppress the upward shift in pH, thus indicating the prevention of CO_2 escape.
c. A completely sealed set-up was developed for each vessel in the dissolution apparatus. A sealed lid was made in-house; this also relies on the concept of preventing the CO_2 loss. The lid is made of nylon material (Omega Services Ltd., Surrey, UK) and is impervious to gas. Its design was adapted from the conventional lids used in USP-I and -II dissolution apparatus.

In all the above procedures, stabilisation was confirmed through pH measurements. A pH electrode (H11131, Hanna Instruments Ltd., Bedfordshire, UK) attached to a pH meter (pH 211 Microprocessor pH Meter, Hanna Instruments) was used to measure the pH of the media. Through the liquid paraffin and sealed set-up approach, an equilibrium is established between $CO_2(g)$ in the liquid paraffin or below the lid and $CO_2(aq)$ in the dissolution medium. This is achieved as there is no $CO_2(g)$ escape. While with the continuous sparging approach, $CO_2(aq)$ remains at steady concentrations as the loss of $CO_2(g)$ is continuously replaced.

The pH of the Krebs bicarbonate system stabilised with $CO_2(g)$ sparging and liquid paraffin was monitored as the drug products were undergoing dissolution. This regular pH monitoring could not be performed with the completely sealed set-up as it would have impaired the experiment. Similar pH assessments were conducted in phosphate buffer. The pH of the dissolution media at the end of the experiments (phosphate and bicarbonate systems) was measured.

4. Results

The three approaches of bicarbonate stabilisation were successful at maintaining the pH of the system constant for 24 h under dissolution conditions without drug product.

All three mesalazine products were resistant to acid, showing no drug release within 2 h of exposure to 0.1 M HCl (Figs. 1–3). The dissolution of Asacol 400 mg in phosphate buffer and under the different Krebs bicarbonate stabilised systems is presented in Fig. 1. Drug release is delayed in Krebs bicarbonate media compared to phosphate buffer. After complete drug release, the pH was found to drop to 7.0 ± 0.1 in the Krebs bicarbonate media stabilised by the liquid paraffin and sealed set-up approaches, in comparison to a pH drop to 7.2 ± 0.01 in the phosphate buffer. No pH drop was observed under the continuous sparging with 5% $CO_2(g)$. Despite these pH differences, the drug release profiles were similar under all three methods of Krebs bicarbonate stabilisation; analysis of variance (ANOVA) showed statistically insignificant differences ($p > 0.05$).

Asacol 800 mg (Asacol HD) also displays a similar trend with slower drug release in Krebs bicarbonate media compared to phosphate buffer (Fig. 2). After complete drug release in Krebs bicarbonate media stabilised using liquid paraffin or the completely sealed set-up approach, the pH was found to drop to 6.7 ± 0.2. This is a larger drop than that observed for Asacol 400 mg due to the higher drug load; pH dropped to 7.1 ± 0.01 in the phosphate buffer. No drop in pH was observed under the continuous sparging with 5% $CO_2(g)$. There was no statistical difference in the release profiles between the three Krebs bicarbonate stabilisation methods (ANOVA, $p > 0.05$) (data only shown for the completely sealed stabilisation approach for clarity). A comparison of the release profiles of Asacol 800 mg and Asacol 400 mg shows the former product to have an earlier onset of drug release (Figs. 1 and 2).

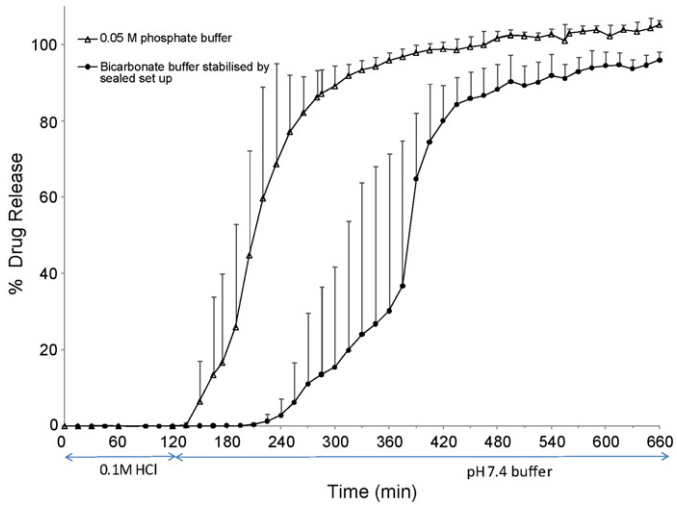

Fig. 2. Drug release profiles of Asacol® 800 mg (Asacol® HD) tablets in phosphate buffer and bicarbonate buffer stabilised by the completely sealed set-up. Drug release presented as the mean + SD.

For Mezavant (Lialda), both the lag times and drug release profiles display different behaviours in Krebs bicarbonate media compared to phosphate buffer. The zero-order, slow release which is observed in phosphate buffer is no longer apparent in Krebs bicarbonate media (Fig. 3). The observed pH drop after complete drug release was 6.4 ± 0.25 with the liquid paraffin or the completely sealed stabilisation approaches; while the drop in phosphate buffer was to 7.0 ± 0.01. No drop in pH was observed under the continuous sparging with 5% $CO_2(g)$. Again, statistically similar drug release profiles were observed under the different Krebs bicarbonate stabilisation methods (ANOVA, $p > 0.05$) (data only shown under the completely sealed stabilisation for clarity).

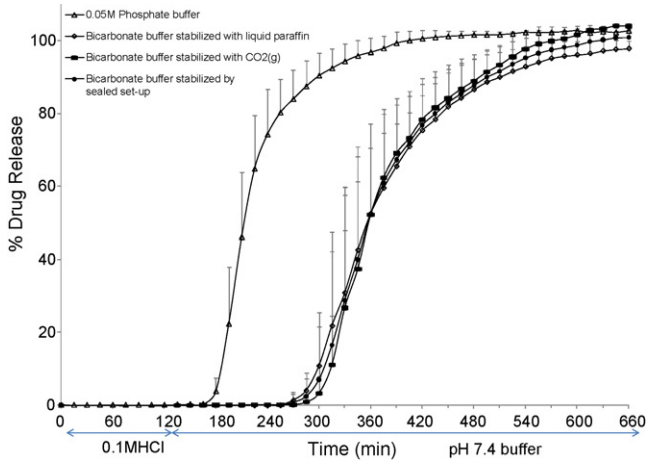

Fig. 1. Drug release profiles of Asacol® 400 mg tablets in phosphate buffer and bicarbonate buffer undergoing different methods of stabilisation. Drug release presented as the mean + SD.

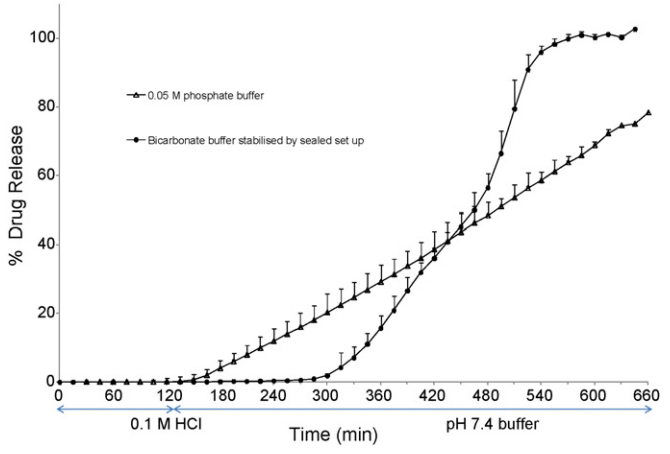

Fig. 3. Drug release profiles of Mezavant® 1200 mg (Lialda®) tablets in phosphate buffer and bicarbonate buffer stabilised by the completely sealed set-up. Drug release presented as the mean + SD.

5. Discussion

Krebs bicarbonate buffer closely resembles the electrolyte composition (Banwell et al., 1971) and buffer capacity of gastrointestinal luminal fluids of the distal small intestine. The buffer capacity of ileal fluids has been measured to be 6.4 mM/L/pH unit (Fadda and Basit, 2009). Phosphate buffer (0.05 M) and stabilised Krebs bicarbonate buffer at a pH of 7.4 have a buffer capacity of 23 and 5.45 mM/L/pH unit respectively.

The limitation of using bicarbonate buffers has been their continuous rise in pH due to evaporation of CO_2(g). Here, three different approaches were adopted to stabilise Krebs bicarbonate buffer. All methods were successful at maintaining the pH for 24 h under dissolution conditions in the absence of drug product. For each product, statistically similar drug release profiles were attained by the three different stabilisation methods. The continuous sparging with 5% CO_2(g) was the initially adopted approach and has been reported to be successful (McNamara et al., 2003; Fadda and Basit, 2005). The second approach was application of a layer of liquid paraffin above the dissolution media with 70 ml being optimum to prevent the upward drift in pH; indicative of no CO_2(g) escape. There is the limitation however for potential drug partitioning into liquid paraffin. Although this is not observed for mesalazine, it may be a concern for lipophilic molecules. The third approach investigated was the completely sealed set-up which has the advantage of easiest assembly compared to the other two methods.

Mesalazine is a zwitterion, the carboxyl group (–COOH) has a pKa value of 2.3 and the amino group [$(NH_3^+)^-$] has a pKa of 5.69 (Allgayer et al., 1985). At a buffer pH of 7.4, mesalazine reacts with the buffer species and its anionic form is produced. The hydrogen ions generated will move to drop the pH of Krebs bicarbonate medium due to the low buffer capacity of the system. This pH reduction is not observed with the continuous CO_2(g) sparging approach as bicarbonate levels are maintained constant through the $CO_2/H_2CO_3/HCO_3^-$ equilibrium. The pH of Krebs bicarbonate buffer stabilised with liquid paraffin or the completely sealed set-up, however, was found to drop on complete drug dissolution. In the case of stabilisation with liquid paraffin, the pH did not drop until drug release commenced and the decline in pH was proportional to the mesalazine dissolved. The pH changes could not be measured during the course of the experiment with the completely sealed set-up, a similar correlation, however, can be assumed. Despite this drop in pH, the drug release profiles of the mesalazine formulations are statistically similar to those in Krebs bicarbonate buffer stabilised with the continuous CO_2(g) sparging. This may be the case as the drop in pH commences following dissolution of the polymer which can be considered the rate limiting step in drug release. The anionic polymer alone is not sufficient to cause a drop in pH. This was found by estimating the amount of anionic polymer on Mezavant tablets using surface area and thickness measurements and dissolving an equivalent amount of Eudragit S or L polymers in 900 ml of Krebs bicarbonate media, stabilised using the different approaches, under dissolution conditions. No drop in pH was observed (data not shown). Therefore, a pH drop in bicarbonate media will not arise with neutral drugs formulated with anionic polymers. It can also be speculated that low doses of ionisable actives will not give rise to a substantial pH change.

Both the drug and enteric polymers in the different mesalazine products are ionisable. Eudragit S and L are poly(methacrylic acid methyl methacrylate) copolymers and dissolve through dissociation of their acid monomer units. The basic species in the dissolution media accelerate this reaction as has been described by the Bronsted catalysis law proposed by Spitael and Kinget (1977). In accordance with this theory, the pKa of the buffer salt species and its concentration in the release medium are the determining factors of polymer ionisation, hence explaining why mesalazine release from the different enteric coated products is slower in the bicarbonate media than in phosphate buffer.

The early onset of release observed for Asacol 800 mg in comparison to Asacol 400 mg may be explained by the different compositions of the gastroresistant coatings. The enteric coat of Asacol 400 mg is the Eudragit S polymer, whereas Asacol 800 mg comprises two coatings; the inner coating is a Eudragit S polymer and the outer coating is a blend of Eudragit S and L (MHRA UKPAR, 2007; Procter and Gamble Pharmaceuticals, 2008). This may have been chosen to circumvent the problem observed with Asacol 400 mg tablets passing through the gastrointestinal tract of inflammatory bowel disease patients intact (Schroeder et al., 1987; Sinha et al., 2003). While it is known that Asacol 400 mg gives rise to considerable variability in drug release (Fadda and Basit, 2005; Spencer et al., 2008), the new Asacol 800 mg (Asacol HD) formulation appears to be more variable.

The lag time of Mezavant tablets in phosphate buffer is 30 min whereas in stabilised Krebs bicarbonate buffer it is approximately 3 h (post-acid) (Fig. 3). This onset of release in bicarbonate buffer is in good agreement with the initial disintegration time of the product observed by gamma scintigraphy in humans (Wray et al., 2008). The Mezavant formulation has been designed to display both delayed and sustained release characteristics as evidenced by the profile in phosphate buffer (Fig. 3). In bicarbonate buffer, however, the zero-order slow release is no longer apparent (Fig. 3). It therefore appears that not only the drug and coating, but the matrix core of Mezavant is also susceptible to the composition of the release media. The different ionic environments can influence the tortuosity and porosity of the matrix and therefore drug diffusion. Interestingly, two recent, independent randomised trials of Asacol 400 mg and Mezavant showed these two formulations to display similar pharmacokinetic profiles in humans (Wray et al., 2008; Sandborn et al., 2008). This similarity between the two products *in vivo* is well reflected in the dissolution profiles observed in stabilised bicarbonate media and could not have been predicted from dissolution in phosphate buffer.

6. Conclusions

Physiological bicarbonate media provide a good reflection of the ionic composition and buffer capacity of human small intestinal luminal fluids. These parameters are critical when considering the dissolution behaviour of delivery systems. The three approaches explored for stabilising the Krebs bicarbonate media; continuous sparging with 5% CO_2, application of a layer of liquid paraffin and the completely sealed set-up, were all successful. Our studies with mesalazine products have shown that use of bicarbonate buffer provides improved predictions, compared to compendial phosphate buffers, of the *in vivo* behaviour of enteric coated systems for ileo-colonic delivery.

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