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Research paper

Evolution of a physiological pH 6.8 bicarbonate buffer system: Application to the dissolution testing of enteric coated products

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ABSTRACT

The use of compendial pH 6.8 phosphate buffer to assess dissolution of enteric coated products gives rise to poor *in vitro–in vivo* correlations because of the inadequacy of the buffer to resemble small intestinal fluids. A more representative and physiological medium, pH 6.8 bicarbonate buffer, was developed to evaluate the dissolution behaviour of enteric coatings. The bicarbonate system was evolved from pH 7.4 Hanks balanced salt solution to produce a pH 6.8 bicarbonate buffer (modified Hanks buffer, *m*Hanks), which resembles the ionic composition and buffer capacity of intestinal milieu. Prednisolone tablets were coated with a range of enteric polymers: hypromellose phthalate (HP-50 and HP-55), cellulose acetate phthalate (CAP), hypromellose acetate succinate (HPMCAS-LF and HPMCAS-MF), methacrylic acid copolymers (EUDRAGIT® L100-55, EUDRAGIT® L30D-55 and EUDRAGIT® L100) and polyvinyl acetate phthalate (PVAP). Dissolution of coated tablets was carried out using USP-II apparatus in 0.1 M HCl for 2 h followed by pH 6.8 phosphate buffer or pH 6.8 *m*Hanks bicarbonate buffer. In pH 6.8 phosphate buffer, the various enteric polymer coated products displayed rapid and comparable dissolution profiles. In pH 6.8 *m*Hanks buffer, drug release was delayed and marked differences were observed between the various coated tablets, which is comparable to the delayed disintegration times reported in the literature for enteric coated products in the human small intestine. In summary, the use of pH 6.8 physiological bicarbonate buffer (*m*Hanks) provides more realistic and discriminative *in vitro* release assessment of enteric coated formulations compared to compendial phosphate buffer.

1. Introduction

The application of an enteric coating to a solid dosage form is an established approach to prevent drug release in the stomach and allow release in the small intestine. It is used to preclude the degradation of acid-labile actives in the gastric environment or to protect the stomach from irritant compounds [1]. The commonly used enteric coatings employ pH-dependent polymers which contain carboxylic acid groups. These remain un-ionized in the low pH environment of the stomach and become ionized in the higher pH conditions of the small intestine, thus initiating dissolution of the coating and allowing drug release.

The *in vitro* dissolution of enteric coated products is usually assessed in compendial pH 6.8 phosphate buffer. In this medium, drug release is normally rapid [2–5]. However, neither does this reflect the *in vivo* performance of enteric coated products, nor is it sufficient to discriminate the dissolution behaviour between different enteric coatings. *In vivo* gamma scintigraphy studies have shown that there is a substantial time delay (up to 2 h) for such products to disintegrate in the human small intestine post gastric emptying, with different enteric polymer coatings exhibiting varying disintegration times [6–11]. This *in vitro–in vivo* discrepancy is not surprising considering the inadequacy of the *in vitro* test method to simulate the gastrointestinal tract in many respects such as ionic composition, buffer capacity, pH, viscosity, fluid volume, coupled with further luminal factors including motility and hydrodynamics [12–17]. Moreover, the fact that these factors are subject to considerable inter- and intra-subject variability further adds to the complexity of developing an *in vitro* model to predict the gastrointestinal behaviour of complex dosage forms such as enteric coated products [16].

The constituent buffer salts, ionic strength and buffer capacity of the dissolution media have been reported to influence drug release from pH-responsive polymer coated dosage forms [16,18–20]. Notably, the luminal fluids of the small intestine are predominantly buffered by bicarbonate (as well as other ions and luminal constituents such as bile salts, proteins, carbohydrates and food components). Hence, bicarbonate buffers would more closely resemble the environment within the intestine and provide

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a more physiological medium for the *in vitro* assessment of products designed to release in the small bowel.

We have previously shown that a pH 7.4 bicarbonate system (Krebs buffer), which simulates the luminal environment of the distal small intestine, provided better *in vitro–in vivo* correlations for a series of enteric coated products for delivery of mesalazine to the ileo-colonic region of the gastrointestinal tract [21]. The normal pH of bicarbonate buffers (Krebs or Hanks) is 7.4; however, this pH is higher than the pH in the proximal small intestine [22]. The objective of this study was to develop a pH 6.8 bicarbonate system, based on Hanks buffer. This physiological medium was then employed to evaluate the dissolution behaviour of tablets coated with a series of enteric polymers from different chemical classes in comparison with compendial pH 6.8 phosphate buffer.

2. Materials and methods

2.1. Materials

The enteric polymers used in this study and their properties are presented in Table 1. Prednisolone was purchased from Aventis Pharma., Antony, France. Lactose (Pharmatose) was obtained from Ellis & 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. Preparation of prednisolone tablets

Tablets were prepared containing 5% prednisolone, 88.5% lactose, 5% polyvinylpyrrolidone, 0.5% cross-linked sodium carboxymethylcellulose and 1% magnesium stearate. 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 (Holland Ltd., Nottingham, UK) was used to obtain tablets of mass 200 mg (containing 10 mg drug) and crushing strength of 80 N.

2.3. Coating of prednisolone tablets

Enteric coating formulations were prepared from either aqueous polymer dispersions or organic solutions. The compositions of the aqueous and organic coating formulations are presented in Table 2.

Prednisolone tablets were coated using a Strea-1 bottom spray fluidised bed coater (Aeromatic AG, Bubendorf, Switzerland). The coating conditions were optimised for each polymer formulation and are summarized in Table 3, together with the coating levels of the polymers. Coating levels 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. This is because the quantitative composition of the PVAP formulation is not in the public domain. After the coating process, the tablets were cured in an air-assisted oven at 40 °C for 2 h.

2.4. Dissolution of enteric coated tablets

2.4.1. Acid uptake

All enteric coating formulations at each coating level were evaluated for acid resistance and uptake. Six coated tablets of each formulation were weighed and subjected to dissolution conditions in 0.1 M HCl. After 2 h, the tablets were removed and excess medium was drained and blotted with filter paper from around the tablets. The tablets were weighed again, and the acid uptake by the tablet was calculated according to Eq. (1). Formulations were chosen for dissolution testing at the minimum coating level that met the criteria for acid protection, i.e., no more than 10% acid uptake and no visible signs of coat disruption after two hours acid treatment.

$$\text{Acid uptake } (\%) = \left(\frac{W_f - W_i}{W_i}\right) \times 100 \quad (1)$$

where W_f is the final tablet weight, W_i is the initial tablet weight.

2.4.2. Development of physiological bicarbonate buffer (mHanks)

Hanks balanced salt solution closely resembles the ionic composition of small intestinal milieu (Table 4); however, it has a pH of 7.4, which is too high, and a buffer capacity of 1 mmol/L/ΔpH, which is too low, compared to human jejunal fluids. Therefore, this buffer was modified to attain a pH of 6.8 and a higher buffer capacity. Hanks solution is primarily a bicarbonate buffer, in which bicarbonate (HCO_3^-) and carbonic acid (H_2CO_3) coexist, along with $CO_{2(aq)}$ resultant from the dissociation of the latter (Eq. (2)).

$$\begin{array}{c} CO_{2\,(g)} \\ \Big\downarrow\Big\uparrow \\ H_2O + CO_{2\,(aq)} \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^- \end{array} \quad (2)$$

The pH of the buffer system can be altered by adjusting the concentration of the acid (H_2CO_3) and its conjugate base (HCO_3^-) according to the Henderson–Hasselbalch equation (Eq. (3)). Purging

Table 1
Enteric polymers used in the study.

Polymer	Brand name	Abbreviation	Grade	Soluble at or above pH	Manufacturer/supplier
Methacrylic acid copolymer	EUDRAGIT®	–	L 100-55 L 30D-55 L100	5.5 5.5 6.0	Evonik GmbH, Darmstadt, Germany
Hypromellose acetate succinate	Aqoat®	HPMCAS	LF MF	5.0 6.0	Shin-Etsu Chemical Co., Ltd., Japan
Hypromellose phthalate	–	HPMCP	HP-50, HP-55	5.0, 5.5	Shin-Etsu Chemical Co., Ltd., Japan
Cellulose acetate phthalate	–	CAP	–	6.0	Eastman Chemical Company, USA
Polyvinyl acetate phthalate	Opadry® Enteric Sureteric®	PVAP	Organic Aqueous	5.0 5.0	Colorcon Ltd., USA.