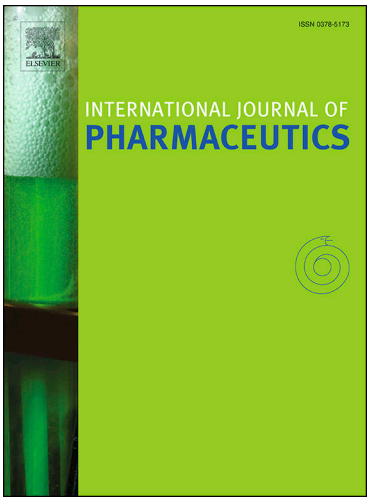
Journal Pre-proofs



OPTICORE™, an innovative and accurate colonic targeting technology

Felipe Varum, Ana Cristina Freire, Roberto Bravo, Abdul W. Basit

PII: S0378-5173(20)30356-2
DOI: https://doi.org/10.1016/j.ijpharm.2020.119372
Reference: IJP 119372

To appear in: *International Journal of Pharmaceutics*

Received Date: 6 February 2020
Revised Date: 21 April 2020
Accepted Date: 22 April 2020

Please cite this article as: F. Varum, A. Cristina Freire, R. Bravo, A.W. Basit, OPTICORE™, an innovative and accurate colonic targeting technology, *International Journal of Pharmaceutics* (2020), doi: https://doi.org/10.1016/j.ijpharm.2020.119372

OPTICORE™, an innovative and accurate colonic targeting technology

Felipe Varum[1,2*], Ana Cristina Freire[2a], Roberto Bravo[1], Abdul W. Basit[2]

[1]Tillotts Pharma AG, Baslerstrasse 15, CH-4310 Rheinfelden, Switzerland
[2]UCL School of Pharmacy, University College London, Brunswick Square WC1N 1AX, London

[a]Current address:
Aptuit, an Evotec Company
115 Innovation Drive
Milton Park, Abingdon
Oxfordshire OX14 4RZ
England, UK

***Corresponding author**

Felipe Varum, PhD
Tillotts Pharma AG
Baslerstrasse 15
CH-4310 Rheinfelden
Switzerland
Phone: +41 61 935 26 75
Email: felipe.varum@tillotts.com

Abstract

Inflammatory bowel disease (IBD) is a debilitating condition, estimated to affect 7 million people worldwide. Current IBD treatment strategies are substandard, relying on colonic targeting using the pH gradient along the gastrointestinal tract. Here, we describe an innovative colonic targeting concept, OPTICORE™ coating technology. OPTICORE™ combines two release triggers (pH and enzyme: Phloral™) in the outer layer, with an inner layer promoting a release acceleration mechanism (Duocoat™). The technology comprises an inner layer of partially neutralized enteric polymer with a buffer agent and an outer layer of a mixture of Eudragit® S and resistant starch. 5-aminosalicylic acid (5-ASA) tablets were coated with different inner layers, where the type of polymer, buffer salt concentration and pH of neutralization, were investigated for drug release acceleration. Buffer capacity of polymethacrylate neutralized polymer significantly contributes to the buffer capacity of the inner layer formulation, while buffer salt concentration is a major contributor to dispersion buffer capacity in the case of hypromellose enteric polymers. An interplay between buffer capacity, pH and ionic strength contributes to an accelerated drug release. Resistant starch does not impact the enteric properties but allows for drug release mediated by colonic bacterial enzymes, ensuring complete drug release. Therefore, OPTICORE™ technology is designed to offer significant advantages over standard enteric coatings, particularly for accurate colonic drug delivery in ulcerative colitis patients.

Keywords

Gastro resistant film coatings , Colonic drug delivery systems, Colon targeted oral drug products, Gut microbiome, Intestinal microbiota triggered drug release, Mesalazine

1 Introduction

Enteric coatings are the mainstream formulation approach widely used to delay drug release to the distal gastrointestinal tract. Delaying drug release serves multiple purposes, including protection of acid-labile drugs and protection of the stomach from irritating compounds (Goyanes *et al.* 2015a, Goyanes *et al.* 2015b). Colonic targeting offers great potential for the delivery and systemic absorption of molecules that undergo degradation and/or are poorly absorbed in the upper gastrointestinal tract (Lee *et al.* 2020). This is due to the low levels of luminal and mucosal metabolic enzymes found in the colon, in comparison to the small intestine (Basit *et al.* 2002, Wang *et al.* 2015a, Wang *et al.* 2015b, Yadav *et al.* 2016a), which are favorable for the delivery of sensitive therapeutic drugs such as peptides and proteins (Mackay *et al.* 1997, Rubinstein *et al.* 1997, Luppi *et al.* 2008, Wang *et al.* 2015a, Bak *et al.* 2018) and drugs which are substrates for intestinal CYPs and efflux transporters (Tubic-Grozdanis *et al.* 2008, McConnell *et al.* 2009). The metabolic potential of the human gut microbiota also has a significant impact on disposition of drugs taken orally (Clarke *et al.* 2019, Zimmermann *et al.* 2019a, Zimmermann *et al.* 2019b).

Enteric coating dissolution in the gastrointestinal tract relies on pH gradients along the gut which, along with other physiological characteristics, exhibit significant inter- and intra-individual variability (Fallingborg *et al.* 1989). It is well established that pH sharply increases from the stomach to the duodenum due to the secretion of bicarbonate in the upper small intestine and gradually increases until the distal small intestine. However, a luminal pH drop occurs at the ileocaecal junction due to the production of short chain fatty acids – a degradation product from polysaccharide fermentation produced by colonic bacteria (Evans *et al.* 1988). This halts the continuous pH increase observed in the small bowel and results in challenges to the triggering of pH-sensitive dissolution systems in the colon. To allow the complete drug

release in the colon, rapid coating dissolution and sufficient residence time are required once the release trigger is activated. This may be further complicated by other factors such, feeding regimen (Koziolek *et al.* 2019), low fluid volumes (dispersed in water pockets) in the small intestine and particularly in the colon (Schiller *et al.* 2005), viscosity of the luminal fluid and variability in buffer capacity (Fadda and Basit 2005, Fadda *et al.* 2010, Vertzoni *et al.* 2010, Hatton *et al.* 2015) to name a few. Additionally, in certain disease conditions, such as in ulcerative colitis (Yadav *et al.* 2016b, Hatton *et al.* 2018, Stillhart *et al.* 2020), the pH in the colon is often lower than a healthy individual (Fallingborg *et al.* 1993, Nugent *et al.* 2001) and transit time through the colon may be accelerated (Hebden *et al.* 2000, Haase *et al.* 2016). This presents a challenge for the timely dissolution of enteric coated dosage forms in the colon, particularly single-unit dosage forms (Varum *et al.* 2010, Goyanes *et al.* 2015c) with reported cases of occasional excretion of intact tablets (Schroeder *et al.* 1987, Ibekwe *et al.* 2006, Ibekwe *et al.* 2008a, McConnell *et al.* 2008b).

Alternative approaches to accelerate drug release from enteric coated dosage forms have been described in the literature (Maroni *et al.* 2017, Foppoli *et al.* 2019, Ma *et al.* 2019). Double-layer systems comprising of an inner layer of partially neutralized enteric polymer and an outer enteric layer (Duocoat®) have shown significant drug release acceleration when targeting the proximal small intestine or the ileo-colonic region, both *in vitro* (Liu *et al.* 2009a, Liu *et al.* 2009b, Liu *et al.* 2010, Varum *et al.* 2014) and in humans (Liu and Basit 2010, Varum *et al.* 2013). Buffer capacity of the dissolving inner layer and ionic strength play a significant role on the drug release acceleration mechanism as described by Liu and co-authors (Liu *et al.* 2009a). Also, inclusion of swellable agents, such as sodium starch glycolate, into enteric coatings (Colopulse®) have been proposed to facilitate drug release from enteric coated dosage forms designed to release in the colon (Schellekens *et al.* 2008, Schellekens *et al.* 2009, Maurer *et al.* 2013, Maurer *et al.* 2016).

Although an accelerated drug release will occur in the case of Duocoat® and Colopulse® coatings (only pH-sensitive) when the relevant pH is reached, if the pH is not high enough to initiate dissolution of the enteric coating, risk of failure to disintegrate persists. Therefore, triggering drug release using an additional physiological trigger, such as colonic bacterial enzymes can be of benefit (Tuleu *et al.* 2002, Siew *et al.* 2004, McConnell *et al.* 2008a, Karrout *et al.* 2009, Karrout *et al.* 2015, Fadda 2020, Varum *et al.* 2020). Ibekwe and co-workers proposed the combination of a pH trigger and enzymatic trigger in a single coating system (Phloral™). The bacterial enzymatic trigger, provided by the presence of a polysaccharide in the coating (high amylose starch, resistant to bacterial degradation in the small intestine) acts as a fail-safe mechanism in case the pH is not high enough for a sufficient period of time to allow dissolution of the enteric polymer (Eudragit® S), which is designed to dissolve at pH 7.0 (Ibekwe *et al.* 2008b).

The aim of the work described here was to develop a new colon targeting drug delivery system, OPTICORE™, comprising an outer layer with dual trigger (Phloral™) and a suitable alkaline inner layer able to accelerate drug release as soon as the pH trigger is activated or alternatively when the starch in the outer coating is digested by bacterial enzymes in the colon.

2 Materials and methods

2.1 Materials

Different enteric polymers (polymethacrylates and hypromellose derivatives) were explored (see Table 1) for their potential to accelerate drug release from Eudragit® S coated tablets. These were used to produce neutralized coating dispersions in order to assess buffer capacity and viscosity of the resultant dispersions. Lactose monohydrate was obtained from Meggle, Wasserburg Germany. Povidone (K25) was acquired from Boai NKY Pharmaceuticals Ltd, Jiaozuo, China, and sodium starch glycolate was obtained from JRS Pharma, Rosenberg,

Germany. Magnesium stearate was provided by Peter Greven GmbH & Co. KG, Bad Münstereifel, Germany. Talc was obtained from Ferdinand Kreuzter Sabamühle GmbH, Nürnberg, Germany. Hydroxypropylmethyl cellulose (HPMC, Methocel E5) was kindly provided by Colorcon. Triethyl citrate (TEC) was supplied by Lancaster Synthesis, Lancashire, UK. Glyceryl monostearate (GMS) and polysorbate 80 (Tween 80) were purchased from Sigma-Aldrich Co. Ltd., Dorset, UK. Talc (micronized) and sodium hydroxide were obtained from VWR International Ltd, Poole, UK. Maize starch (Amylo-N-400, formerly known as Eurylon 6) was donated by Roquette, Lestrem, France. Magnesium sulphateheptahydrate and calcium chloride hexahydrate were obtained from VWR, UK. Sodium bicarbonate was obtained from Sigma Aldrich, UK, while haemin, L-cysteine HCl, vitamin K and resazurin were obtained from Sigma Life Sciences, UK. Bile salts were from Fluka Analytical, UK and FlukaChemika, UK respectively. Buffer salts for dissolution buffers preparation, trifluoroacetic acid, were obtained from Sigma-Aldrich Co. Ltd., Dorset, UK. Sodium chloride and di-potassium hydrogen phosphate were obtained from Fisher Chemical. Magnesium sulphateheptahydrate and calcium chloride hexahydrate were obtained from VWR, haemin, L-cysteine HCl, vitamin K and resazurin were obtained from Sigma Life Sciences, UK. Bile salts were from Fluka Analytical, UK.

2.2 Preparation of neutralized enteric polymer coating dispersions (inner layer)

Coating dispersions comprising of an enteric polymer were prepared based on supplier guidelines/recommendations for standard enteric coatings (single coating). Coating formulations differ between themselves not only in the enteric polymer used but also in the type and concentration of anti-tacking agent (talc or GMS) and concentration of plasticizer (TEC). These small differences are not likely to have a major effect on the buffer capacity of the dispersions, but their impact cannot be completely excluded.

The composition of different coating formulations, with or without a buffer agent (KH_2PO_4) neutralized to pH 8 are presented in Table 2 and Tables S2 and S3 (see Supplementary information). Briefly, TEC and buffer agent (when specified) are dissolved in water under mechanical stirring at room temperature for 15 minutes. Polymer was dispersed into the above solution and neutralized to pH 8 using 1N NaOH and stirring continued for further 60 minutes. Anti-tacking agent, talc (30-50%, based on polymer) or GMS (10%, based on polymer) was added and mixed for 15 minutes. In the case of HP50 and HP55, a fraction of the total NaOH required to neutralize the polymer was used to increase the pH of the aqueous dispersion and allow complete polymer dissolution before completing the neutralization process.

2.2.1 Buffer capacity measurements

The equivalent quantity of coating dispersion (ready to use) to 2.5 g of enteric polymer was weighed. With a pH meter dipped into the coating dispersion, 0.1N HCl was added dropwise until a difference of 1 unit of pH was reached. Buffer capacity (β) was calculated using the following formula:

$$\beta = \frac{mmol\ (0.1NHCl)/2.5g}{\Delta pH}$$

2.2.2 Viscosity measurements

Viscosity measurements of neutralized coating dispersions prepared as described above, with or without buffer agents were measured using a rotational rheometer (Bohlin Instruments, Cirencester, UK) equipped with 50 mm base plate and a 2º cone plate (gap 70 µm). A 2 mL sample of coating dispersion was placed on the stationary plate and a constant shear rate of 200 1/s was applied for 120 s. All measurements were performed at 25ºC, controlled by a thermostated system. The measurements were performed in triplicate. Viscosity value (cP) at

the end of the measurements (15 s) were used for comparison purposes.(viscosity values remained mostly constant for all samples during the acquisition time).

195

2.3 Tablet manufacture

Tablet cores (520 mg) containing 400 mg 5-ASA (5-aminosalicylic acid; mesalazine) were kindly provided by Tillotts Pharma AG. Besides 5-ASA, tablet cores contain lactose monohydrate, povidone, sodium starch glycolate, talc and magnesium stearate. Quantitative
200 composition of the tablet cores is not disclosed.

2.4 Tablet Coating

2.4.1 Isolation layer

An isolation layer coating formulation of hydroxypropyl methylcellulose (HPMC, Methocel
205 E5) was prepared containing 10% TEC as plasticizer. Briefly, HPMC was dissolved in water under magnetic stirring and then TEC was added to form a coating preparation. The coating preparation was sprayed onto 50 g of 400 mg 5-ASA tablet cores using a fluid bed bottom-spray coater (Strea-1, Aeromatic AG, Bubendorf, Switzerland) to achieve a coating amount of 3 mg polymer/cm^2. The coating parameters were as follows: spray rate 3.1 g/min/kg tablet
210 cores, atomizing pressure 0.2 bar, and inlet air temperature 40 °C.

2.4.2 Inner layer

The inner layer coating suspension was prepared using different enteric polymers as listed in Table 1. Additionally, one batch (F7) was prepared using HPMC as a film-forming polymer
215 (Table 3). A brief method description using Eudragit® S as an example is described next. Potassium dihydrogen phosphate (10% based on polymer) and TEC (50% based on polymer)

were dissolved in distilled water, followed by dispersion of the Eudragit® S under mechanical agitation. The pH of the dispersion was then adjusted to pH 8 with 1M NaOH and left mixing for 1 hour. The GMS dispersion (10% based on polymer) was added and the final preparation was coated on 50 g of 400 mg 5-ASA tablet cores, using a fluid bed coater (Strea-1, Aeromatic AG, Bubendorf, Switzerland) until 5 mg polymer/cm^2 was achieved. The coating parameters were as follows: spraying rate 20 ml/min/kg tablets, atomizing pressure 0.2 bar and inlet air temperature 40 °C.

2.4.3 Outer layer/single layer Eudragit® S

The coating layer containing Eudragit® S was applied as an organic coating composition. Briefly, 20% TEC (based on polymer weight) was dissolved in 96% ethanol followed by Eudragit® S under mechanical stirring. The GMS emulsion was added at a concentration of 10% w/w (based on Eudragit S). The final coating solution was coated on to 50g of the 5-ASA tablet cores previously coated with the inner layer or as a single layer (comparator), using a fluid bed spray coater (Strea-1, Aeromatic AG, Bubendorf, Switzerland) to achieve a coating amount of 5 mg polymer/cm^2. The coating parameters were as follows: spraying rate 16 ml/min/kg tablets, atomizing pressure 0.2 bar and inlet air temperature 40 °C.

2.4.4 Outer layer/single layer Phloral™

High-amylose starch (Amylo N-400) dispersions were prepared in a butanol aqueous solution by heating to boiling and left to boil for 3 minutes, followed by cooling to room temperature under stirring overnight. Eudragit® S was dissolved in 96% ethanol under magnetic stirring. The starch dispersion was then added dropwise to the Eudragit® S solution to obtain a ratio of starch:Eudragit® S of 30:70. Then, 20% TEC and 5% GMS (both based on total polymer weight) were added and mixed for further 2 hours. The final preparation was coated on to 50 g

of 400 mg 5-ASA tablet cores, previously coated with the inner coating layer or as a single layer, using a fluid bed coater (Strea-1, Aeromatic AG, Bubendorf, Switzerland) until 5 mg Eudragit® polymer/cm^2 was obtained. The coating parameters were as follows: spraying rate 16 ml/min/kg tablets, atomizing pressure 0.2 bar and inlet air temperature 40 °C.

245

2.5 Scanning Electron Microscopy (SEM)

The morphology of the surface and cross-sectioned coated tablets was evaluated by SEM. Samples were placed on SEM stubs and fixed using carbon discs before being gold coated using an EMITEC K 550 sputter coater for three minutes at 40 mA. The samples were then transferred
250 to a Phillips XL20 Scanning Electron Microscope for imaging.

2.6 Drug release in pH 6.8 mHanks buffer with and without pancreatin

Drug release was assessed in pH 6.8 mHanks buffer, as described elsewhere (Liu *et al.* 2011) (composition described in Table S3) using a USP type II paddle apparatus (Model PTWS,
255 Pharmatest, Hainburg, Germany) The tests were conducted at least in triplicate, in 900 ml dissolution medium maintained at 37 ± 0.5 ºC. A paddle speed of 50 rpm was used throughout the experiments. The tests were conducted under sink conditions. The amount of 5-ASA released in pH 6.8 mHanks buffer from the coated tablets was determined by an in-line UV spectrophotometer at a wavelength of 330 nm (buffer stage). Drug release in pH 6.8 mHanks
260 buffer was assayed after 2 hours pre-exposure of coated tablets to 0.1N HCl using the same dissolution apparatus and instrumental parameters as described above. The pH was kept constant at pH 6.8 by means of constant CO_2 purging into the medium throughout the dissolution run as described elsewhere (Liu *et al.* 2011). To evaluate the robustness to pancreatin enzymatic digestion, during passage through the small intestine, OPTICORE™

coated tablets (e.g. F14) were also assessed in pH 6.8 mHanks buffer containing 1% (w/v) porcine pancreatin (8 USP). In this case the amount of 5-ASA released after 4 hours (small intestinal transit) was quantified using an in-house developed isocratic HPLC method (Agilent technologies 1200 Series) using a LichroCart 250-4 column (Merck Chemicals) and with a UV detection set at 228 nm. The mobile phase was composed of 95% Water, 5% Methanol and 0.05 % trifluoreacetic acid (TFA) set at 1 mL /min. A column temperature of 40 °C was used.

2.7 Drug release in pH 7.4 Krebs buffer

Drug release was assessed in pH 7.4 Krebs buffer, as described elsewhere (Fadda *et al.* 2009) (composition described in Table S3) using a USP type II paddle apparatus (Model PTWS, Pharma Test, Hainburg, Germany). The tests were conducted at least in triplicate, in 900 ml dissolution medium maintained at 37 ± 0.5 ºC. A paddle speed of 50 rpm was used throughout the experiments. The tests were conducted under sink conditions. The amount of 5-ASA released from the tablets was determined using an in-line UV spectrophotometer at a wavelength of 301 nm (acid stage) and 330 nm (buffer stage). Data were processed using Icalis software (Icalis Data Systems Ltd., Berkshire, UK). Drug release from coated tablets was assessed using physiologically relevant Krebs buffer pH 7.4 (with pre-exposure to 0.1N HCl for 2 hours using the same dissolution apparatus and instrumental parameters as described above). The pH was kept constant at pH 7.4 by means of constant CO_2 purging into the medium throughout the dissolution run.

2.8 Drug release in pH 6.8 human faecal slurry

The bacteria (enzymatic) triggered drug release was assessed in faecal slurry prepared from human faeces (Yadav *et al.* 2013, Sousa *et al.* 2014) and adjusted to pH 6.8. Briefly inside an

anaerobic workstation (Electrotek 500TG workstation, Electrotek, West Yorkshire, UK) maintained at 37 °C and a relative air humidity of 70%, fresh faecal samples of 3 different healthly donors were homogenized (Ultra Turrax (IKA T18 Basic) in 0.1M phosphate buffer saline pH 6.8 to obtain a slurry at 40% w/w. The homogenized medium was sieved through an open mesh fabric (SefarNitex™, pore size 350 mm) to remove any unhomogenised fibrous material. This medium was then diluted to 20% w/w faecal contents with a nutrient rich medium (Hughes *et al.* 2008) . After adjusting the pH to 6.8, the tablets were added to faecal slurry in individual containers with 210 mL faecal slurry which were left under anaerobic conditions and under continuous shaking and samples were collected hourly. Tablets were encased in small baskets made of a flexible mesh type material (SEFAR NITEX™ mesh size of 2000 µm). Further pH adjustment were made each 30 minutes in the event of pH drop. Faecal slurry samples (1.5 mL) were collected hourly up to 9 hours and a last sample was colleted after 24 hours. Samples were then centrifuged at 13,000 rpm for 10 minutes. The supernatant was collected from the eppendorfs using 1mL syringes and filtered through 0.22 µm filters (Millex GP syringe-driven filter units, Millipore, Ireland). Thereafter, 100 µl of the filtered supernatant was transferred using a micropipette (Gilson, Inc., USA) into labeled 2 mL amber glass HPLC vials and diluted with 900 µl of mobile phase (95% Water, 5% Methanol and 0.05 % TFA). The samples were analysed for 5-ASA content by High Pressure Liquid Chromatography (Agilent technologies 1200 Series) using a LichroCart 250-4 column (Merck Chemicals) and with a UV detection set at 228 nm. The mobile phase (95% Water, 5% Methanol and 0.05 % TFA) was set at 1 mL /min and the temperature was set at 40 °C.

3 Results and Discussion

3.1.1 Development of the inner layer – polymer selection

Due to small differences in the composition of neutralized enteric coating formulations, in terms of plasticizer and anti-tacking agent levels, buffer capacity measurements were performed considering a predetermined quantity of enteric polymer (Table 2). Clearly, the Eudragit® L30D-55 neutralized dispersion showed the highest buffer capacity among the enteric polymers tested (Table 4). This pattern is maintained when a buffer agent is incorporated (2% and 10%). In contrast, the lowest buffer capacity was found in the case of the HP50 dispersion. Therefore, the effect of the incorporation of 2% buffer agent was much more pronounced in the HP50 and HP55 formulations than in Eudragit® polymer dispersions. Increasing the concentration of buffer agent to 10% (based on polymer weight) in the methacrylate polymer dispersions resulted in a further increasein buffer capacity (Table 4), however of lower magnitude in comparison to the effect seen with HPMCAS-LF, HP50 and HP55 dispersions. An increase in buffer agent in the hypromellose–based enteric polymers significantly increased buffer capacity by several orders of magnitude in comparison to the equivalent dispersions without buffer salts, highlighting the major role of the buffer agent on the overall buffer capacity of the neutralized coating dispersions prepared with these excipients. These enteric polymers are weakly acidic polymers which increase their ionized fraction as pH increases. The lower density of acidic groups, in comparison to Eudragit L30D-55 in hypromellose based enteric polymers associated with the lower pKa (Barbosa *et al.* 2019) results in higher extent of ionization at pH 8, in a region where buffer capacity is much lower (more than 2 units higher than pKa). The Eudragit L30D-55 dispersion when neutralized to pH 6 showed the highest buffer capacity (Table 4) since the balance between ionized and nonionized groups are closer to an equilibrium.

The buffer capacity determination of the neutralized enteric polymer formulations can be an useful tool to design an inner coating formulation that is able to accelerate the dissolution of

the outer coating composed of enteric polymers and ultimately accelerate drug release. Additionally, the higher the buffer capacity the higher the quantity of NaOH that is required for the neutralization step, which results in an increased ionic strength and osmotic pressure due to in situ salt formation (Liu *et al.* 2009a). Buffers with higher buffer capacity and ionic strength contribute to faster polymer dissolution (Kararli *et al.* 1995). The higher osmotic pressure contributes to a faster drug release from dosage froms coated with semi-permeable membranes, such as suitained release coatings (Marucci *et al.* 2007, Kallai *et al.* 2010, Kallai-Szabo *et al.* 2014). The effect of increased osmotic pressure alone on delayed release coatings could however not be demonstrated in a related enteric double-coating system (Liu *et al.* 2009b). However, the film-forming properties of the neutralized formulation and its viscosity are also critical properties in order to achieve a fast and robust coating process.

Among the methacrylate polymers, Eudragit® L30D-55 neutralized formulations had the highest viscosity and Eudragit® S the lowest viscosity (Table 5). This may be linked to the higher density of carboxylic acids in Eudragit® L30D-55 and to the different ester group, ethyl acrylate in the case of Eudragit L30D-55 and methyl methacrylate in the case of Eudragit S, which may result in slower chain disentanglement and dissolution. When neutralized to lower pH 6, the viscosity was even higher than at pH 8, demonstrating that a lower ionization extent of the carboxylic groups results in higher viscosity (Figure 5). Neutralized HP55 and HP50 dispersions had comparable viscosity to the neutralized Eudragit® S formulation. The proportion of acidic groups are comparable between HP55 and Eudragit® S but the latter has a higher pKa. (Barbosa *et al.* 2019). Interestingly, an increase in the concentration of buffer agent to 10% in the HPMCAS-LF and Eudragit® L30D-55 formulations resulted in a lower viscosity. This may result from the effect of the buffer salt in neutralizing further the enteric polymer allowing polymer chain disentanglement and dissolution. This reduction in viscosity canprovide an additional advantage, in addition to the higher buffer capacity, in terms of coating processing

Further investigations were carried out to establish correlations between the buffer capacity, displayed by different neutralized enteric polymers, containing a buffer agent, and drug release acceleration in Krebs buffer pH 7.4.

Surprisingly, when Eudragit® L30D-55 was used as the inner layer (F4), it failed to provide significant acceleration of drug release (Fig. 2 and Table 6) since lag times in pH 7.4 Krebs buffer are comparable with a standard single layer system (Table 6). For comparison purposes, the release profile of Eudragit® S single coated 400 mg 5-ASA cores (F1) is included. Neutralized Eudragit® S (with 10% buffer) formulation (F3) showed a lower buffer capacity than neutralized Eudragit® L30D-55, however it was able to accelerate drug release from coated tablets very efficiently. This suggests that buffer capacity alone is not the main driver of drug release acceleration. The higher buffer capacity is reflected by the presence of proton-carriers at the interface polymer/bulk buffer or polymer/inner layer which is able to accelerate proton diffusion and increase the solubility of the polymer (Nguyen and Fogler 2005, Barbosa *et al.* 2019). When HP55 (F6) was used as the inner layer, no drug release acceleration compared to the single coating (F1) was noticed. These results would be expected, as the buffer capacity of this formulation was the lowest. However, drug release was comparable to F4, which showed the highest buffer capacity (Fig. 2).

An inner layer composed of Eudragit® L100, neutralized to pH 8 with 10% buffer was not possible. After coating, the inner layer was brittle and after drying at 40 ºC, the coating peeled off the tablets, therefore this polymer was excluded from the scope of this research. Since buffer capacity is higher when pH of the bulk solution is closer to the pKa of the polymer, an inner layer composed of Eudragit L30D-55 and 10% KH_2PO_4, neutralized to pH 6 was applied on 400 mg 5-ASA cores and an outer coating of Eudragit® S (organic) was applied (F5). Neutralization of Eudragit® L30D-55 to pH 6 increased buffer capacity ($\beta = 13.38$), compared to the coating dispersion neutralized to pH 8 ($\beta = 5.64$) as described in Table 4. However, the

lag time in Krebs buffer pH 7.4 occurred even later when the neutralization pH was set to 6 (F5) as can be seen in Fig. 2. The fact that the pH of the inner coating is lower than the pH threshold of the outer coating may explain the results, despite the higher buffer capacity attained at this lower pH. Similar observations were also made during the development of a Duocoat® system for drug release in the proximal small intestine (Liu *et al.* 2009a). Additionally, tablets containing an inner layer made of soluble neutral polymer, hydroxypropyl methylcellulose (Methocel E5) adjusted tp pH 8.0 and 10% KH_2PO_4 also failed to provide a significant drug release acceleration (F7, Table 6) as described in Fig. 2. These results suggest that the mechanisms responsible for polymer dissolution acceleration and consequently drug release acceleration are complex and that an interplay between buffer capacity and pH of the dissolving inner layer may also contribute to the overall drug release acceleration effect.

3.1.2 Additional development steps

Additional development steps were conducted in order to assess if drug release could be further accelerated from tablets comprising an inner layer made of Eudragit® S. Among the parameters investigated were the concentration of buffer agent, the coating level and incorporation of an isolation layer between the tablet core (acidic) and the alkaline inner layer. In agreement with the buffer capacity results (Table 4), in the case of neutralized Eudragit® S formulations, the addition of a buffer salt (up to 10%) plays only a minor role and thereby decreasing the concentration of buffer salt in the formulation resulted in only a minor impact on drug release acceleration effect (Fig. 3). Since, most of the buffer capacity of the inner layer composition is provided by the neutralized Eudragit® S, the buffer salt contribution is rather limited.

Due to the acidic nature of the tablet core (high proportion of 5-ASA), the alkaline inner layer effectiveness in accelerating outer layer polymer dissolution may be negatively affected due to interactions at the interface core-inner layer. Thereby, the effect of an isolation layer of neutral

polymer (HPMC) between the tablet core and the inner layer was assessed. The inclusion of an isolation layer (F11) resulted in a further drug release acceleration in comparison to tablets coated without an isolation layer (F3), confirming that indeed an isolation layer can protect the functionality of the inner layer in promoting drug release acceleration (Fig. 4). The negative effect of acidic drugs or excipients present on dosage form cores on delayed drug release was also reported by others (Crotts *et al.* 2001, Varum *et al.* 2011). Reducing the amount on neutralized Eudragit® S inner coating from 5 mg/cm^2 to 3 mg/cm^2 (F12) resulted in an increase in the lag time to release (Fig.4). This may be explained by the lower availability of the proton-carrier species, both neutralized polymer and buffer agent, thereby, decreasing the overall acceleration mechanism efficiency. Additionally, the acidic drug in the tablet core (5-ASA) can also compete for the buffer species in the inner layer, decreasing its functionality in promoting a faster dissolution of the enteric polymer in the outer coating. In contrast, further increasing the quantity of neutralized inner layer to 7 mg/cm^2 (F13) did not resulted in a further drug release acceleration (Fig. 4), indicating that 5 mg/cm^2 of neutralized Eudragit® S provides an optimal drug release acceleration.

3.1.3 OPTICORE™ coating - Combining a two-trigger outer layer with accelerated release properties

Tablets containing a double layer coating of Eudragit® S (F3) exhibited a smooth coating surface due to the organic coating, in which the enteric polymer is fully soluble. In cross-sectioned tablets a clear distinction between the inner layer and the Eudragit® S outer layer is not possible from the SEM micrographs (Fig. 5). On the other hand, in the case of OPTICORE™ coated tablets (F14), the outer layer clearly reveals a more rough surface due to the presence of starch granules which are not fully gelatinized. Moreover, a clearer distinction between the inner alkaline layer and the Phloral™ outer layer is seen due to the different coating

densities caused by the presence of starch in the outer coating (Fig. 6). The details of the two-trigger system (Phloral™) have been previously described (Ibekwe *et al.* 2008b, Dodoo *et al.* 2017, Allegretti *et al.* 2019, Varum *et al.* 2020).

The inclusion of starch in the outer coating does not impact the *in vitro* robustness of the coated tablets to simulated upper gastrointestinal luminal fluid. Coated tablets did not show any release after 2 hours in 0.1N HCl and were fully resistant for more than four hours (expected small intestinal transit time) in pH 6.8 mHanks buffer which closely resembles the luminal composition of small intestinal fluid (Liu *et al.* 2011, Krieg *et al.* 2014, Al-Gousous *et al.* 2019). Even when pancreatin was added to the bicarbonate buffer no drug release has been observed, demonstrating that the starch embedded into the coating is not enzymatically degraded by amylases from pancreatin extract (data not shown).

Inclusion of starch into Eudragit® S coating does not affect the gastric resistance of the coated tablets. Similarly, by replacing the outer Eudragit® S coating (F3) with a mixture of resistant starch and Eudragit® S (F14) resulted in the same onset of drug release (Fig. 7). The combination of an alkaline inner layer with drug release acceleration properties with an outer layer combining both pH-sensitive polymer (Eudragit® S) and enzymatic-sensitive polysaccharide (starch) has the potential to provide more efficient and accurate colonic targeting than standard Eudragit® S and Phloral™ coatings. This is due to an acceleration of drug release, even in the scenario of low luminal pH in the colon and/or fast transit time, when the enzymatic trigger would serve as a back-up to initiate drug release. As described in Fig. 4, if an isolation layer is applied between the acidic tablet core and the alkaline inner layer, a further drug release acceleration would be expected also in the case of OPTICORE™ coated tablets.

In the event that pH is not high enough or colonic transit is too fast, a drug release acceleration in the target region of the gastrointestinal tract is also desirable. As described in Fig. 8, in an *in*

vitro model of the human colon using faecal material from healthy donors (Basit *et al.* 2002, McConnell *et al.* 2008a, Sousa *et al.* 2014, Wang *et al.* 2015a, Wang *et al.* 2015b, Yadav *et al.* 2016a), drug release was again initiated earlier in the case of OPTICORE™ coated tablets (F14) in comparison to single layer Phloral™ coated tablets (F2). Tablets coated with a single layer of Eudragit® S (F1) did not disintegrate at pH 6.8 faecal inoculation while tablets containing an inner layer of neutralized Eudragit® S (F3) showed a late disintegration, showing an added benefit but of limited extent under these conditions. These results demonstrate that drug release from OPTICORE™ coated tablets can be initiated rapidly when either the correct pH is reached or bacterial enzymes start the digestion process when pH is not high enough such as in the conditions of testing. Additionally, the drug release acceleration mechanism provided by the inner layer is also effective below the pH at which Eudragit® S dissolves (pH 7.0). As the outer layer starts to dissolve or to be digested by bacterial enzymes, the fluid ingress through the weakened coating towards the core contributes to the dissolution of the inner layer, generating a micro-environmental region of high buffer capacity and high ionic strengthat the interface inner-outer layer. This results in a promotion of a faster ionization and dissolution of Eudragit® S in the outer layer (Kararli *et al.* 1995, Varum *et al.* 2011, Varum *et al.* 2013). This is particularly important for drug release in the colon where fluid volumes are low and in situations where a fast transit time may limit full exposure of the mucosa to the delivered active pharmaceutical ingredient.

A novel 1600 mg 5-ASA drug product comprising the OPTICORE™ technology showed a good safety profile and efficacy in a Phase III clinical trial (D'Haens *et al.* 2017), which resulted in its market approval and launch and is currently available for UC patients in multiple worldwide regions.

4 Conclusions

OPTICORE™ coating technology was successfully developed by combining an alkaline inner layer with an outer enteric layer with embedded pH and enzymatic triggers. The coating system comprises an inner layer of partially neutralized enteric polymer and buffer agent and an outer layer of a mixture of Eudragit® S and resistant starch. Buffer capacity of polymethacrylate-neutralized polymer significantly contributes to the overall buffer capacity of the formulation, while buffer salt concentration plays a major role in the case of hypromellose derivative enteric polymers. However, other factors, such as viscosity and ionic strength also contribute to the overall effect in terms of drug release acceleration. The inclusion of an isolation layer between the core and the inner layer further accelerates drug release. The inclusion of resistant starch to the Eudragit® S coating formulation does not impact coating robustness and the enteric properties but is designed to allow an accelerated drug release when the pH of the luminal fluid is above 7 (as in Krebs buffer pH 7.4) or below 7 (as in faecal slurry pH 6.8). Therefore, OPTICORE™ coating technology offers significant advantages, particularly for accurate drug delivery in the colon of ulcerative colitis patients even when using single-unit dosage forms, such as tablets.

Declaration of interest

OPTICORE™ coating technology is patented by Tillotts Pharma AG. Felipe Varum and Roberto Bravo do not hold any commercial rights on the use of the technology. Phloral™ technology has been developed and is proprietary technology of UCL School of Pharmacy.

Acknowledgments

The authors would like to acknowledge David McCarthy (UCL) for the SEM imaging. Helen Wüthrich and Raphael Laoun are acknowledged for the revision of the manuscript.

Funding

This work was supported by funding from Tillotts Pharma AG.

Trademark statement

The rights to the OPTICORE™ technology, including the rights to the trademark, are owned by Tillotts Pharma AG in various countries. The rights to the Phloral™ technology, including the rights to the trademark, are owned by UCL School of Pharmacy in various countries.

5 References

Al-Gousous, J., Ruan, H., Blechar, J. A., Sun, K. X., Salehi, N., Langguth, P., Job, N. M., Lipka, E., Loebenberg, R., Bermejo, M., Amidon, G. E. and Amidon, G. L. 2019. Mechanistic analysis and experimental verification of bicarbonate-controlled enteric coat dissolution: Potential in vivo implications. Eur. J. Pharm. Biopham. 139 47-58. https://doi.org/10.1016/j.ejpb.2019.03.012

Allegretti, J. R., Fischer, M., Sagi, S. V., Bohm, M. E., Fadda, H. M., Ranmal, S. R., Budree, S., Basit, A. W., Glettig, D. L., de la Serna, E. L., Gentile, A., Gerardin, Y., Timberlake, S., Sadovsky, R., Smith, M. and Kassam, Z. 2019. Fecal microbiota transplantation capsules with targeted colonic versus gastric delivery in recurrent Clostridium difficile Infection: A comparative cohort analysis of high and low dose. Dig. Dis. Sci. 64 (7), 2059-2059. https://doi.org/10.1007/s10620-019-05527-4.

Bak, A., Ashford, M. and Brayden, D. J. 2018. Local delivery of macromolecules to treat diseases associated with the colon. Adv. Drug Deliv. Rev. 136 - 137 2-27. https://doi.org/10.1016/j.addr.2018.10.009

Barbosa, J. A. C., Abdelsadig, M. S. E., Conway, B. R. and Merchant, H. A. 2019. Using zeta potential to study the ionisation behaviour of polymers employed in modified-release dosage forms and estimating their pKa. Int. J. Pharm.: X 100024. https://doi.org/10.1016/j.ijpx.2019.100024

Basit, A. W., Newton, J. M. and Lacey, L. F. 2002. Susceptibility of the H2-receptor antagonists cimetidine, famotidine and nizatidine, to metabolism by the gastrointestinal microflora. Int. J. Pharm. 237 (1), 23-33. https://doi.org/10.1016/S0378-5173(02)00018-2

Clarke, G., Sandhu, K. V., Griffin, B. T., Dinan, T. G., Cryan, J. F. and Hyland, N. P. 2019. Gut reactions: Breaking down xenobiotic–microbiome interactions. Pharmacol. Rev. 71 (2), 198-224. https://doi.org/10.1124/pr.118.015768

Crotts, G., Sheth, A., Twist, J. and Ghebre-Sellassie, I. 2001. Development of an enteric coating formulation and process for tablets primarily composed of a highly water-soluble, organic acid. Eur. J. Pharm. Biopharm. 51 (1), 71-76. http://dx.doi.org/10.1016/s0939-6411(00)00129-6

D'Haens, G. R., Sandborn, W. J., Zou, G., Stitt, L. W., Rutgeerts, P. J., Gilgen, D., Jairath, V., Hindryckx, P., Shackelton, L. M., Vandervoort, M. K., Parker, C. E., Muller, C., Pai, R. K., Levchenko, O., Marakhouski, Y., Horynski, M., Mikhailova, E., Kharchenko, N., Pimanov, S. and Feagan, B. G. 2017. Randomised non-inferiority trial: 1600 mg versus 400 mg tablets of mesalazine for the treatment of mild-to-moderate ulcerative colitis. Aliment. Pharmacol. Ther. 46 (3), 292-302. https://doi.org/10.1111/apt.14164

Dodoo, C. C., Wang, J., Basit, A. W., Stapleton, P. and Gaisford, S. 2017. Targeted delivery of probiotics to enhance gastrointestinal stability and intestinal colonisation. Int. J. Pharm. 530 (1), 224-229. https://doi.org/10.1016/j.ijpharm.2017.07.068

Evans, D. F., Pye, G., Bramley, R., Clark, A. G., Dyson, T. J. and Hardcastle, J. D. 1988. Measurement of gastrointestinal pH profiles in normal ambulant human subjects. Gut 29 1035-1041. https://doi.org/10.1136/gut.29.8.1035

Fadda, H. M. 2020. The route to palatable fecal microbiota transplantation. AAPS PharmSciTech 21 (3), 114. https://doi.org/10.1208/s12249-020-1637-z

Fadda, H. M. and Basit, A. W. 2005. Dissolution of pH responsive formulations in media resembling intestinal fluids: bicarbonate versus phosphate buffers. J. Drug Deliv. Sci. Technol. 15 (4), 273-279. http://dx.doi.org/10.1016/S1773-2247(05)50049-2

Fadda, H. M., Merchant, H. A., Arafat, B. T. and Basit, A. W. 2009. Physiological bicarbonate buffers: stabilisation and use as dissolution media for modified release systems. Int. J. Pharm. 382 (1), 56-60. https://doi.org/10.1016/j.ijpharm.2009.08.003

Fadda, H. M., Sousa, T., Carlsson, A. S., Abrahamsson, B., Williams, J. G., Kumar, D. and Basit, A. W. 2010. Drug solubility in luminal fluids from different regions of the small and large intestine of humans. Mol. Pharm. 7 (5), 1527-1532. https://doi.org/10.1021/mp100198q

Fallingborg, J., Christensen, L., Jacobsen, B. and Rasmussen, S. 1993. Very low intraluminal colonic pH in patients with active ulcerative colitis. Dig. Dis. Sci. 38 (11), 1989-1993. https://doi.org/10.1007/bf01297074

Fallingborg, J., Christensen, L. A., Ingeman-Nielsen, M., Jacobsen, B. A., Abildgaard, K. and Rasmussen, H. H. 1989. pH-profile and regional transit times of the normal gut measured by a radiotelemetry device. Aliment. Pharmacol. Ther. 3 (6), 605-613. https://doi.org/10.1111/j.1365-2036.1989.tb00254.x

Foppoli, A., Maroni, A., Moutaharrik, S., Melocchi, A., Zema, L., Palugan, L., Cerea, M. and Gazzaniga, A. 2019. In vitro and human pharmacoscintigraphic evaluation of an oral 5-ASA delivery system for colonic release. Int. J. Pharm. 118723. https://doi.org/10.1016/j.ijpharm.2019.118723

Goyanes, A., Buanz, A. B. M., Hatton, G. B., Gaisford, S. and Basit, A. W. 2015a. 3D printing of modified-release aminosalicylate (4-ASA and 5-ASA) tablets. Eur. J. Pharm. Biopharm. 89 157-162. https://doi.org/10.1016/j.ejpb.2014.12.003

Goyanes, A., Chang, H., Sedough, D., Hatton, G. B., Wang, J., Buanz, A., Gaisford, S. and Basit, A. W. 2015b. Fabrication of controlled-release budesonide tablets via desktop (FDM) 3D printing. Int. J. Pharm. 496 (2), 414-420. https://doi.org/10.1016/j.ijpharm.2015.10.039

Goyanes, A., Hatton, G. B., Merchant, H. A. and Basit, A. W. 2015c. Gastrointestinal release behaviour of modified-release drug products: Dynamic dissolution testing of mesalazine formulations. Int. J. Pharm. 484 (1–2), 103-108. http://dx.doi.org/10.1016/j.ijpharm.2015.02.051

Haase, A. M., Gregersen, T., Christensen, L. A., Agnholt, J., Dahlerup, J. F., Schlageter, V. and Krogh, K. 2016. Regional gastrointestinal transit times in severe ulcerative colitis. Neurogastroenterol. Motil. 28 (2), 217-224. https://doi.org/10.1111/nmo.12713

Hatton, G. B., Madla, C. M., Rabbie, S. C. and Basit, A. W. 2018. All disease begins in the gut: Influence of gastrointestinal disorders and surgery on oral drug performance. Int. J. Pharm. 548 (1), 408-422. https://doi.org/10.1016/j.ijpharm.2018.06.054

Hatton, G. B., Yadav, V., Basit, A. W. and Merchant, H. A. 2015. Animal Farm: Considerations in animal gastrointestinal physiology and relevance to drug delivery in humans. J. Pharm. Sci. 104 (9), 2747-2776. https://doi.org/10.1002/jps.24365

Hebden, Blackshaw, Perkins, Wilson and Spiller 2000. Limited exposure of the healthy distal colon to orally-dosed formulation is further exaggerated in active left-sided ulcerative colitis. Aliment. Pharmacol. Ther. 14 (2), 155-161. http://dx.doi.org/10.1046/j.1365-2036.2000.00697.x

Hughes, S. A., Shewry, P. R., Gibson, G. R., McCleary, B. V. and Rastall, R. A. 2008. In vitro fermentation of oat and barley derived β-glucans by human faecal microbiota. FEMS Microbiol. Ecol. 64 (3), 482-493. https://doi.org/10.1111/j.1574-6941.2008.00478.x

Ibekwe, V., Fadda, H., McConnell, E., Khela, M., Evans, D. and Basit, A. 2008a. Interplay between intestinal pH, transit time and feed status on the in vivo performance of pH responsive ileo-colonic release systems. Pharm. Res. 25 (8), 1828-1835. https://doi.org/10.1007/s11095-008-9580-9

Ibekwe, V. C., Khela, M. K., Evans, D. F. and Basit, A. W. 2008b. A new concept in colonic drug targeting: a combined pH-responsive and bacterially-triggered drug delivery technology. Aliment. Pharmacol. Ther. 28 (7), 911-916. https://doi.org/10.1111/j.1365-2036.2008.03810.x

Ibekwe, V. C., Liu, F., Fadda, H. M., Khela, M. K., Evans, D. F., Parsons, G. E. and Basit, A. W. 2006. An investigation into the in vivo performance variability of pH responsive polymers

for ileo-colonic drug delivery using gamma scintigraphy in humans. J. Pharm. Sci. 95 (12), 2760-2766. https://doi.org/10.1002/jps.20742

Kallai-Szabo, N., Luhn, O., Bernard, J., Kallai-Szabo, B., Zelko, R. and Antal, I. 2014. Comparative dissolution study of drug and inert isomalt based core material from layered pellets. J. Pharm. Biomed. Anal. 98 339-344. https://10.1016/j.jpba.2014.06.005

Kallai, N., Luhn, O., Dredan, J., Kovacs, K., Lengyel, M. and Antal, I. 2010. Evaluation of drug release from coated pellets based on isomalt, sugar, and microcrystalline cellulose inert cores. AAPS PharmSciTech 11 (1), 383-391. https://10.1208/s12249-010-9396-x

Kararli, T. T., Kirchhoff, C. F. and Truelove, J. E. 1995. Ionic strength dependence of dissolution for Eudragit S-100 coated pellets. Pharm. Res. 12 (11), 1813-1816. https://doi.org/10.1023/a:1016202814109

Karrout, Y., Dubuquoy, L., Piveteau, C., Siepmann, F., Moussa, E., Wils, D., Beghyn, T., Neut, C., Flament, M. P., Guerin-Deremaux, L., Dubreuil, L., Deprez, B., Desreumaux, P. and Siepmann, J. 2015. In vivo efficacy of microbiota-sensitive coatings for colon targeting: a promising tool for IBD therapy. J. Control. Release 197 121-130. https://doi.org/10.1016/j.jconrel.2014.11.006

Karrout, Y., Neut, C., Wils, D., Siepmann, F., Deremaux, L., Dubreuil, L., Desreumaux, P. and Siepmann, J. 2009. Colon targeting with bacteria-sensitive films adapted to the disease state. Eur. J. Pharm. Biopharm. 73 (1), 74-81. https://doi.org/10.1016/j.ejpb.2009.04.003

Koziolek, M., Alcaro, S., Augustijns, P., Basit, A. W., Grimm, M., Hens, B., Hoad, C. L., Jedamzik, P., Madla, C. M., Maliepaard, M., Marciani, L., Maruca, A., Parrott, N., Pávek, P., Porter, C. J. H., Reppas, C., van Riet-Nales, D., Rubbens, J., Statelova, M., Trevaskis, N. L., Valentová, K., Vertzoni, M., Čepo, D. V. and Corsetti, M. 2019. The mechanisms of pharmacokinetic food-drug interactions – A perspective from the UNGAP group. Eur. J. Pharm. Sci. 134 31-59. https://doi.org/10.1016/j.ejps.2019.04.003

Krieg, B. J., Taghavi, S. M., Amidon, G. L. and Amidon, G. E. 2014. In vivo predictive dissolution: Transport analysis of the CO2, bicarbonate in vivo buffer system. J. Pharm. Sci. 103 (11), 3473-3490. https://doi.org/10.1002/jps.24108

Lee, S. H., Bajracharya, R., Min, J. Y., Han, J.-W., Park, B. J. and Han, H.-K. 2020. Strategic approaches for colon targeted drug delivery: An overview of recent advancements. Pharmaceutics 12 (1), 68. https://doi.org/10.3390/pharmaceutics12010068

Liu, F. and Basit, A. W. 2010. A paradigm shift in enteric coating: achieving rapid release in the proximal small intestine of man. J. Control. Release 147 (2), 242-245. https://doi.org/10.1016/j.jconrel.2010.07.105

Liu, F., Lizio, R., Meier, C., Petereit, H. U., Blakey, P. and Basit, A. W. 2009a. A novel concept in enteric coating: a double-coating system providing rapid drug release in the proximal small intestine. J. Control. Release 133 (2), 119-124. https://doi.org/10.1016/j.jconrel.2008.09.083

Liu, F., Lizio, R., Schneider, U. J., Petereit, H. U., Blakey, P. and Basit, A. W. 2009b. SEM/EDX and confocal microscopy analysis of novel and conventional enteric-coated systems. Int. J. Pharm. 369 (1-2), 72-78. https://doi.org/10.1016/j.ijpharm.2008.10.035

Liu, F., Merchant, H. A., Kulkarni, R. P., Alkademi, M. and Basit, A. W. 2011. Evolution of a physiological pH 6.8 bicarbonate buffer system: application to the dissolution testing of enteric coated products. Eur. J. Pharm. Biopharm. 78 (1), 151-157. https://doi.org/10.1016/j.ejpb.2011.01.001

Liu, F., Moreno, P. and Basit, A. W. 2010. A novel double-coating approach for improved pH-triggered delivery to the ileo-colonic region of the gastrointestinal tract. Eur. J. Pharm. Biopharm. 74 (2), 311-315. https://doi.org/10.1016/j.ejpb.2009.11.008

Luppi, B., Bigucci, F., Cerchiara, T., Mandrioli, R., Di Pietra, A. M. and Zecchi, V. 2008. New environmental sensitive system for colon-specific delivery of peptidic drugs. Int. J. Pharm. 358 (1-2), 44-49. https://doi.org/10.1016/j.ijpharm.2008.02.009

Ma, C., Battat, R., Dulai, P. S., Parker, C. E., Sandborn, W. J., Feagan, B. G. and Jairath, V. 2019. Innovations in oral therapies for inflammatory bowel disease. Drugs 79 (12), 1321-1335. https://doi.org/10.1007/s40265-019-01169-y

Mackay, M., Phillips, J. and Hastewell, J. 1997. Peptide drug delivery: colonic and rectal absorption. Adv. Drug Deliv. Rev. 28 253-273. https://doi.org/10.1016/S0169-409X(97)00076-8

Maroni, A., Moutaharrik, S., Zema, L. and Gazzaniga, A. 2017. Enteric coatings for colonic drug delivery: state of the art. Exp. Opin. Drug Deliv. 14 (9), 1027-1029. https://doi.org/10.1080/17425247.2017.1360864

Marucci, M., Ragnarsson, G. and Axelsson, A. 2007. Evaluation of osmotic effects on coated pellets using a mechanistic model. Int. J. Pharm. 336 (1), 67-74. https://doi.org/10.1016/j.ijpharm.2006.11.032

Maurer, J. M., Hofmana, S., Schellekens, R. C., Tonnis, W. F., Dubois, A. O., Woerdenbag, H. J., Hinrichs, W. L., Kosterink, J. G. and Frijlink, H. W. 2016. Development and potential application of an oral ColoPulse infliximab tablet with colon specific release: A feasibility study. Int. J. Pharm. 505 (1-2), 175-186. https://doi.org/10.1016/j.ijpharm.2016.03.027

Maurer, J. M., Schellekens, R. C. A., van Rieke, H. M., Stellaard, F., Wutzke, K. D., Buurman, D. J., Dijkstra, G., Woerdenbag, H. J., Frijlink, H. W. and Kosterink, J. G. W. 2013. ColoPulse tablets perform comparably in healthy volunteers and Crohn's patients and show no influence of food and time of food intake on bioavailability. J. Control. Release 172 (3), 618-624. http://dx.doi.org/10.1016/j.jconrel.2013.09.021

McConnell, E. L., Liu, F. and Basit, A. W. 2009. Colonic treatments and targets: issues and opportunities. J. Drug Target. 17 (5), 335-363. https://doi.org/10.1080/10611860902839502

McConnell, E. L., Murdan, S. and Basit, A. W. 2008a. An investigation into the digestion of chitosan (noncrosslinked and crosslinked) by human colonic bacteria. J. Pharm. Sci. 97 (9), 3820-3829. https://doi.org/10.1002/jps.21271

McConnell, E. L., Short, M. D. and Basit, A. W. 2008b. An in vivo comparison of intestinal pH and bacteria as physiological trigger mechanisms for colonic targeting in man. J. Control. Release 130 (2), 154-160. https://doi.org/10.1016/j.jconrel.2008.05.022

Nguyen, D. A. and Fogler, H. S. 2005. Facilitated diffusion in the dissolution of carboxylic polymers. AIChE J. 51 (2), 415-425. https://doi.org/10.1002/aic.10329

Nugent, S. G., Kumar, D., Rampton, D. S. and Evans, D. F. 2001. Intestinal luminal pH in inflammatory bowel disease: possible determinants and implications for therapy with aminosalicylates and other drugs. Gut 48 (4), 571-577. https://dx.doi.org/10.1136/gut.48.4.571

Rubinstein, A., Tirosh, B., Baluom, M., Nassar, T., David, A., Radai, R., Gliko-Kabir, I. and Friedman, M. 1997. The rationale for peptide drug delivery to the colon and the potential of polymeric carriers as effective tools. J. Control. Release 46 (1–2), 59-73. http://dx.doi.org/10.1016/S0168-3659(96)01582-9

Schellekens, R. C., Olsder, G. G., Langenberg, S. M., Boer, T., Woerdenbag, H. J., Frijlink, H. W., Kosterink, J. G. and Stellaard, F. 2009. Proof-of-concept study on the suitability of 13C-urea as a marker substance for assessment of in vivo behaviour of oral colon-targeted dosage forms. Br. J. Pharmacol. 158 (2), 532-540. https://doi.org/10.1111/j.1476-5381.2009.00302.x

Schellekens, R. C., Stellaard, F., Mitrovic, D., Stuurman, F. E., Kosterink, J. G. and Frijlink, H. W. 2008. Pulsatile drug delivery to ileo-colonic segments by structured incorporation of disintegrants in pH-responsive polymer coatings. J. Control. Release 132 (2), 91-98. https://doi.org/10.1016/j.jconrel.2008.08.008

Schiller, C., Frohlich, C. P., Giessmann, T., Siegmund, W., Monnikes, H., Hosten, N. and Weitschies, W. 2005. Intestinal fluid volumes and transit of dosage forms as assessed by magnetic resonance imaging. Aliment. Pharmacol. Ther. 22 (10), 971-979. https://doi.org/10.1111/j.1365-2036.2005.02683.x

Schroeder, K. W., Tremaine, W. J. and Ilstrup, D. M. 1987. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N. Engl. J .Med. 317 (26), 1625-1629. https://doi.org/10.1056/NEJM198712243172603

Siew, L. F., Man, S. M., Newton, J. M. and Basit, A. W. 2004. Amylose formulations for drug delivery to the colon: a comparison of two fermentation models to assess colonic targeting performance in vitro. Int. J. Pharm. 273 (1-2), 129-134. https://doi.org/10.1016/j.ijpharm.2003.12.015

Sousa, T., Yadav, V., Zann, V., Borde, A., Abrahamsson, B. and Basit, A. W. 2014. On the colonic bacterial metabolism of azo-bonded prodrug sof 5-aminosalicylic acid. J. Pharm. Sci. 103 (10), 3171-3175. https://doi.org/10.1002/jps.24103

Stillhart, C., Vučićević, K., Augustijns, P., Basit, A. W., Batchelor, H., Flanagan, T. R., Gesquiere, I., Greupink, R., Keszthelyi, D., Koskinen, M., Madla, C. M., Matthys, C., Miljuš, G., Mooij, M. G., Parrott, N., Ungell, A.-L., de Wildt, S. N., Orlu, M., Klein, S. and Müllertz, A. 2020. Impact of gastrointestinal physiology on drug absorption in special populations – An UNGAP review. Eur. J. Pharm. Sci. 147 105280. https://doi.org/10.1016/j.ejps.2020.105280

Tubic-Grozdanis, M., Hilfinger, J. M., Amidon, G. L., Kim, J. S., Kijek, P., Staubach, P. and Langguth, P. 2008. Pharmacokinetics of the CYP 3A substrate simvastatin following administration of delayed versus immediate release oral dosage forms. Pharm. Res. 25 (7), 1591-1600. https://doi.org/10.1007/s11095-007-9519-6

Tuleu, C., Basit, A. W., Waddington, W. A., Ell, P. J. and Newton, J. M. 2002. Colonic delivery of 4-aminosalicylic acid using amylose–ethylcellulose-coated hydroxypropylmethylcellulose capsules. Aliment. Pharmacol. Ther. 16 (10), 1771-1779. https://doi.org/10.1046/j.1365-2036.2002.01327.x

Varum, F., Freire, A. C., Fadda, H., Bravo, R. and Basit, A. W. 2020. A dual pH and microbiota-triggered coating (Phloral™) for fail-safe colonic drug release Int. J. Pharm. Accepted for publication

Varum, F. J., Hatton, G. B., Freire, A. C. and Basit, A. W. 2013. A novel coating concept for ileo-colonic drug targeting: proof of concept in humans using scintigraphy. Eur. J. Pharm. Biopharm. 84 (3), 573-577. https://doi.org/10.1016/j.ejpb.2013.01.002

Varum, F. J., Merchant, H. A. and Basit, A. W. 2010. Oral modified-release formulations in motion: The relationship between gastrointestinal transit and drug absorption. Int. J. Pharm. 395 (1–2), 26-36. https://doi.org/10.1016/j.ijpharm.2010.04.046

Varum, F. J., Merchant, H. A., Goyanes, A., Assi, P., Zboranova, V. and Basit, A. W. 2014. Accelerating the dissolution of enteric coatings in the upper small intestine: evolution of a novel pH 5.6 bicarbonate buffer system to assess drug release. Int. J. Pharm. 468 (1-2), 172-177. https://doi.org/10.1016/j.ijpharm.2014.04.019

Varum, F. J. O., Veiga, F., Sousa, J. S. and Basit, A. W. 2011. Mucoadhesive platforms for targeted delivery to the colon. Int. J. Pharm. 420 (1), 11-19. http://dx.doi.org/10.1016/j.ijpharm.2011.08.006

Vertzoni, M., Goumas, K., Soderlind, E., Abrahamsson, B., Dressman, J. B., Poulou, A. and Reppas, C. 2010. Characterization of the ascending colon fluids in ulcerative colitis. Pharm. Res. 27 (8), 1620-1626. https://doi.org/10.1007/s11095-010-0158-y

Wang, J., Yadav, V., Smart, A. L., Tajiri, S. and Basit, A. W. 2015a. Stability of peptide drugs in the colon. Eur. J. Pharm.Sci. 78 31-36. https://doi.org/10.1016/j.ejps.2015.06.018

Wang, J., Yadav, V., Smart, A. L., Tajiri, S. and Basit, A. W. 2015b. Toward oral delivery of biopharmaceuticals: An assessment of the gastrointestinal stability of 17 peptide drugs. Mol. Pharm. 12 (3), 966-973. https://doi.org/10.1021/mp500809f

Yadav, V., Gaisford, S., Merchant, H. A. and Basit, A. W. 2013. Colonic bacterial metabolism of corticosteroids. Int. J. Pharm. 457 (1), 268-274. http://dx.doi.org/10.1016/j.ijpharm.2013.09.007

Yadav, V., Varum, F., Bravo, R., Furrer, E. and Basit, A. W. 2016a. Gastrointestinal stability of therapeutic anti-TNF α IgG1 monoclonal antibodies. Int. J. Pharm. 502 (1–2), 181-187. http://dx.doi.org/10.1016/j.ijpharm.2016.02.014

Yadav, V., Varum, F., Bravo, R., Furrer, E., Bojic, D. and Basit, A. W. 2016b. Inflammatory bowel disease: Exploring gut pathophysiology for novel therapeutic targets. Trans. Res. https://doi.org/10.1016/j.trsl.2016.04.009

Zimmermann, M., Zimmermann-Kogadeeva, M., Wegmann, R. and Goodman, A. L. 2019a. Mapping human microbiome drug metabolism by gut bacteria and their genes. Nature 570 (7762), 462-467. https://doi.org/10.1038/s41586-019-1291-3

Zimmermann, M., Zimmermann-Kogadeeva, M., Wegmann, R. and Goodman, A. L. 2019b. Separating host and microbiome contributions to drug pharmacokinetics and toxicity. Science 363 (6427), eaat9931. https://doi.org/10.1126/science.aat9931

Figure Captions

Fig. 1. Schematic representation of the OPTICORE™ coating technology designed for colonic targeting.

Fig. 2. Effect of different neutralized enteric polymers and neutral polymers in the inner layer of a double-coating system on dissolution in pH 7.4 Krebs buffer after pre-exposure to 0.1N HCl for 2 hours (data not represented). Data represented as average and standard deviation of triplicate samples. F1) Single layer coating (control), F3) Eudragit® S, F4) Eudragit® L30D-55 (pH 8), F5) Eudragit® L30D-55 (pH 6), F6) HP-55, F7) HPMC.

Fig. 3. Effect of buffer agent concentration in the inner layer on drug release acceleration. F1) Single layer coating (control), F3) 10% KH_2PO_4, F8) 0% KH_2PO_4, F9) 2% KH_2PO_4, F10) 4% KH_2PO_4. Data represents the dissolution from coated tablets in pH 7.4 Krebs buffer (n=3) after pre-exposure to 0.1N HCl for 2 hours (data not represented).

Fig. 4. Effect of an isolation layer and amount of enteric polymer in the inner layer on drug release acceleration. F1) Single layer coating, F3) no isolation layer, F11) with isolation layer and 5 mg/cm inner layer, F12) with isolation layer and 3 mg/cm inner layer, F13) with isolation layer and 7 mg/cm inner layer. Data represents the average dissolution and standard deviation from coated tablets in pH 7.4 Krebs buffer (n=3) after pre-exposure in 0.1N HCl for 2 hours (data not represented).

Fig. 5. Scanning electron micrographs of the surface and cross-section of double layer Eudragit® S tablets coated tablets (F3).

Fig. 6. Scanning electron micrographs of OPTICORE™ (F14) surface and cross-sectioned tablets.

Fig. 7. Effect of Phloral™ outer layer on drug release from double layer coated tablets (OPTICORE™). F1) Single layer Eudragit® S coating, F3) Inner layer neutralized Eudragit® S and outer layer Eudragit® S, F14) Outer layer Phloral™ (OPTICORE™). Data represents the average dissolution and standard deviation from coated tablets in pH 7.4 Krebs buffer (n=3) after pre-exposure to 0.1N HCl for 2 hours (data not represented).

Fig. 8. Drug release in human faecal slurry pH 6.8 from coated tablets. F1) Single Eudragit® S coating, F2) Phloral™ coating, F3) Eudragit® S double coating, F14) OPTICORE™ coating. Values and error bars on graph represent the average and the standard deviation of three individual measurements.

Table Captions

Table 1. Summary of enteric polymers.

Table 2. Composition of neutralized (to pH 8) enteric polymer coating dispersions with 10% buffer agent (KH_2PO_4), based on dry polymer weight.

Table 3. Formulation summary.

Table 4. Buffer capacity (mmol 0.1N HCl/g polymer/ΔpH) measurements of neutralized (to pH 8) enteric polymer coating dispersions.

Table 5. Viscosity (cp) of neutralized (to pH 8) enteric polymer coating dispersions.

Table 6. Summary of lag times in pH 7.4 Krebs buffer of 5-ASA 400 mg double-coated formulations with different neutralized enteric polymers and neutral polymer used as the inner layer. Outer layer composed of organic formulation of Eudragit® S.