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A comparative in vitro assessment of the drug release performance of pH-responsive polymers for ileo-colonic delivery

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Abstract

The aim of this study was to investigate the in vitro dissolution characteristics of pH-responsive polymers in a variety of simulated fluids. Prednisolone tablets were fabricated and coated with the following polymer systems: Eudragit S (organic solution), Eudragit S (aqueous dispersion), Eudragit FS (aqueous dispersion) and Eudragit P4135 (organic solution). Dissolution tests were conducted using a pH change method whereby tablets were transferred from acid to buffer. Three different buffer media were investigated: two compendial phosphate buffers (pH range 6.8–7.4) and a physiological buffer solution (Hanks buffer) with very similar ionic composition to intestinal fluid (pH 7.4). There was considerable drug release from tablets coated with Eudragit P4135 in acid, prompting discontinuation of further investigations of this polymer. Eudragit S (organic solution), Eudragit S (aqueous dispersion) and Eudragit FS on the other hand prevented drug release in acid, though subsequent drug release in the buffer media was found to be influenced by the duration of tablet exposure to acid. At pH 7.4 drug release rate from the polymer coated tablets was similar in the two compendial media, however in the physiological buffer, they were found to differ in the following order: Eudragit S (aqueous dispersion) > Eudragit FS > Eudragit S (organic solution). The results indicate that the tablets coated with the newer Eudragit FS polymer would be more appropriate for drug delivery to the ileo-colonic region in comparison to the more established Eudragit S. More importantly, however, dissolution in the physiological buffer was found to be markedly slower for all the coated tablets than in the two compendial buffers, a result akin to reported slower dissolution of enteric coated tablets in vivo. There is therefore the need to adequately simulate the ionic composition of the intestinal fluid in the dissolution media.

Keywords: Colonic delivery; Ileal delivery; Enteric coating; Eudragit; Organic coating; Aqueous coating; Bicarbonate buffers

1. Introduction

The colon has secured prominence as a target for drug delivery, primarily because of the therapeutic benefits to be gained from topical treatment of local disorders such as inflammatory bowel disease, irritable bowel disease and carcinoma. The colon has also been proposed as a more favourable target site for systemic absorption of therapeutic peptides because of its lower peptidase activity, as well as for other drugs that would otherwise be inactivated in the upper gastrointestinal regions. The inherent lag time in mouth to colon transit can also be exploited to achieve delayed drug release in the therapy of conditions that display a diurnal rhythm such as nocturnal asthma and arthritis.

The functional requirement of an oral colonic drug delivery system is twofold: a robustness of form to prevent drug release in the upper gastrointestinal regions and sensitivity to the trigger mechanism to ensure prompt drug release in the colon. While the former is relatively simple to achieve, the difficulty comes in ensuring that drug release occurs promptly and completely once the dosage form arrives in the colon (Basit, 2005). Such dosage forms have relied on a unique physiological feature of the colon to act a trigger for drug release, and those investigated so far include pH gradient (Dew et al., 1983; Ashford et al., 1993a,b; Cole et al., 2002), colonic bacterial enzymes (Ofori-Kwakye et al., 2004; Tuleu et al., 2002; Wilson and Basit, 2005), gastrointestinal transit time (Gazzaniga et al., 1994; Steed et al., 1997) and pressure arising from intestinal contractions (Takaya et al., 1995).

The pH dependent approach for colonic drug delivery is based on the pH differential along the gastrointestinal tract with values

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increasing from about 1 to 2.5 in the stomach through 6.6 in the proximal small bowel to a peak of about 7.5 in the terminal ileum followed by a fall in pH to 6.4 in the colon (Evans et al., 1988). This concept utilises polymeric carriers that are insoluble in the low pH media of the upper gastrointestinal tract, but dissolve at the higher, near neutral pH of the distal gut. In effect, such polymers will begin to dissolve in the ileum and as such are more appropriately defined as ileo-colonic delivery systems. The most commonly used pH-responsive polymer to facilitate drug delivery to the ileo-colonic region is the methacrylic acid and methyl methacrylate ester copolymer marketed as Eudragit S and which is soluble at pH >7.0 (Rohm Pharma, Darmstadt, Germany). The ratio of methacrylic acid to methyl methacrylate is 1:2. Eudragit S has been traditionally applied as a film coating from a solution in organic solvents, but environmental and health concerns with the use of organic solvents have led to an interest in the use of aqueous-based coating preparations. An aqueous dispersion of Eudragit S can be prepared by a partial neutralisation of the methacrylic acid group of the polymer. Recently, a methacrylic acid, methyl acrylate and methyl methacrylate copolymer Eudragit P4135 has been developed (ratio of the functional groups 25:10:65) (Hu et al., 1999). An aqueous dispersion derivative of this copolymer, Eudragit FS30D is now also commercially available. These new polymers are reported to have similar pH dissolution thresholds as Eudragit S; however, the drug carrier performance of these newer polymer preparations has yet to be fully investigated.

The in vitro assessment of drug release from pH-responsive dosage forms is usually by sequential dissolution testing in compendial acid and near neutral pH buffer systems. While these simple dissolution media systems are routinely used to represent the pH conditions in the stomach and small intestine, respectively, they do not fully reflect the complex nature of the gastrointestinal fluid (Lindahl et al., 1997). Furthermore, lumenal fluids of the small intestine are buffered by bicarbonate. Aside from pH, a number of aspects of the dissolution media have been shown to affect drug release from enteric coated dosage forms and include buffer capacity (Ashford et al., 1993a), ionic strength (Kararli et al., 1995), and the constituent buffer salts (Chan et al., 2001; Fadda and Basit, 2005). However, despite supporting evidence of the influence of electrolyte composition of dissolution media on drug release from enteric dosage forms, simple two-phase buffer media containing potassium and sodium phosphate salts continue to be used routinely in dissolution testing. Recent work to more closely simulate the gastrointestinal fluid in both the fasted and fed states has focused on biological surfactants rather than ionic composition (Dressman et al., 1998; Rudolph et al., 2001).

This study was therefore conducted to compare drug (prednisolone) release from tablet dosage forms coated with a range of pH-responsive polymers potentially suited for drug delivery to the ileo-colonic region: Eudragit S (in the form of an organic solution and aqueous dispersion), Eudragit P4135 (organic solution) and Eudragit FS (aqueous dispersion). Drug release was also assessed in different media of varying electrolyte composition.

2. Materials and methods

2.1. Materials

Prednisolone Eur. Ph. was obtained from Aventis Pharma SA (Antony, France). Lactose was obtained from Ellis and Everand, Essex, UK. Eudragit S100, P4135 and Eudragit FS30D were kindly donated by Röhm GmbH (Darmstadt, Germany). Triethyl citrate was a gift from Alfa chemicals (Bracknell, UK). Glyceryl monostearate (Imwitor 900) was obtained from Hüls AG (Witten, Germany). All other excipients and reagents were purchased from Sigma–Aldrich chemicals and were of analytical grade.

2.2. Preparation of prednisolone tablets

Bi-convex tablet cores, 8 mm in diameter, 200 mg nominal weight, were prepared according to the following wet granulation formula: prednisolone 5%, lactose 89%, polyvinyl pyrollidone 5% and magnesium stearate 1% (added extragranularly), using a single punch tablet machine (Manesty, Speke, UK). The dose of prednisolone in each tablet was 10 mg. The weight uniformity of the tablets was 199 ± 5 mg. The crushing strength was 70 N and the friability 0.28%. Complete drug release occurred within 30 min in pH 1.2 acid.

2.3. Preparation of coating solutions and dispersions

2.3.1. Glyceryl monostearate dispersion

A fine dispersion of glyceryl monostearate (GMS) was used as a glidant in the coating of all the polymers and has proven advantages over talc (Petereit et al., 1995). An aqueous suspension of GMS was prepared by emulsification in water using polysorbate 80. Glyceryl monostearate (15 g) and polysorbate 80 (6 g) were dispersed in 279 g water and stirred while heating to 70 °C. The resulting fine dispersion was then allowed to cool under continued gentle stirring.

2.3.2. Eudragit S aqueous coating dispersion

Eudragit S aqueous dispersion was prepared by dispersing Eudragit S 100 granules in water under high speed stirring followed by a drop-wise addition of 1 N ammonia, to effect a partial neutralisation (theoretically 15%) of the acid functional groups in the polymer (Table 1). Addition of the ammonia resulted in a change in appearance of the dispersion from a coarse dispersion to a milky latex. Stirring was continued for an hour, after which triethyl citrate (50% on dry polymer substance) was added and stirring continued for at least a further hour. The GMS dispersion (5% on dry polymer substance) was added to the final coating dispersion as a glidant.

2.3.3. Eudragit S organic coating solution

Eudragit S 100 was dissolved in 96% ethanol under high speed stirring until a clear solution was obtained. Triethyl citrate (10% on dry polymer) was added as a plasticizer and GMS (5% on dry polymer) as a glidant (Table 1).

Table 1
Basic formulation for polymer coating preparations

	Eudragit S organic solution	Eudragit P4135 organic solution	Eudragit S aqueous dispersion	Eudragit FS 30% aqueous dispersion
Polymer (g)	25	25	50	50 (30% polymer)
Water (g)	–	–	277	35
96% Ethanol (g)	350	–	–	–
1 N ammonia (g)	–	–	25	–
Acetone (g)	–	285	–	–
Isopropyl alcohol (g)	–	190	–	–
Triethyl citrate (g)	2.5	–	25	–
Glyceryl monostearate (g)	1.25	1.25–10	2.5	0.75

2.3.4. Eudragit FS aqueous coating dispersion

Eudragit FS30D is commercially available as a 30% aqueous dispersion and was diluted to 15% dispersion with water before use. GMS (5% on dry polymer) was added as a glidant, but due to the inherent flexible nature of the polymer and the low minimum film forming temperature, no plasticizer was required (Table 1).

2.3.5. Eudragit P4135 organic coating solution

Eudragit P4135 granules were milled to fine particles and then dissolved in a solvent mixture containing acetone and isopropyl alcohol (60:40). Like Eudragit FS, Eudragit P4135 does not require the addition of plasticizer. Increasing amounts of GMS was added as a glidant (5–40% on dry polymer) (Table 1).

2.4. Film coating

The tablets were coated using Strea-1 bottom spray fluidised bed spray coater (Aeromatic AG, Bubendorf, Switzerland). The coating parameters were optimised for each polymer preparation and film thickness measured as the total weight gain by the tablets (%TWG). After each coating run, tablets were fluidised for a further 10 min before checking the weight gain and then subsequently cured in an air-assisted oven at 40 °C for 24 h. To assess the optimal polymer film thickness, the tablets were coated to several total weight gains by varying the coating time and hence the amount of coating applied. A weight gain of 5% corresponds to a coating thickness of 84 ± 4 μm. Cured tablets were stored in an airtight container until tested.

2.5. In vitro drug release testing

Prednisolone release from the coated tablets was assessed by dissolution testing using a USP XXIV type II paddle dissolution apparatus (model PTWS, Pharma Test, Hainburg, Germany). The tests were conducted in triplicates, at a paddle speed of 100 rpm in 900 ml dissolution medium maintained at 37.0 ± 0.5 °C. Tablets were tested first in 0.1 N hydrochloric acid (pH 1.2) for 30 min or 2 h to simulate gastric residence and then for 6 h in buffer media of varying pH and ionic composition, akin to small intestinal pH conditions. Prednisolone release was assessed at pH 6.8–7.4 in two compendial buffer media: 0.067 M mixed sodium and potassium phosphate (Sorensen's) buffer and 0.05 M potassium phosphate buffer as well as in a pH 7.4 multi-electrolyte salt solution (Hanks) buffer which is similar in ionic composition to intestinal fluid. The electrolyte composition of the different pH 7.4 buffers in relation to known values in the small intestine is depicted in Table 2. All the buffers were freshly prepared with de-ionised water and de-aerated by sparging with helium prior to use. The amount of prednisolone released from the dosage form was determined at 5 min intervals by an in-line UV spectrophotometer at a wavelength of 240 nm and results expressed as cumulative drug release versus time profile. The

Table 2
Comparison of the electrolyte concentrations and characteristics of the pH 7.4 tested buffer media and small intestinal fluid (Sorensen's buffer ($Na_2HPO_4 \cdot 7H_2O/KH_2PO_4$), potassium phosphate buffer (KH_2PO_4/NaOH) and Hanks physiological buffer)

Ions	Sorensen's buffer	Potassium phosphate buffer	Hanks buffer	Small intestine (Banwell et al., 1971; Phillips and Giller, 1973; Kalantzi et al., 2003)
Na^+ (mM)	107.3	39.5	141.7	140
K^+ (mM)	13.07	50	5.8	4.9
Cl^- (mM)	–	–	142.9	125
Ca^{2+} (mM)	–	–	1.3	4.2
Mg^{2+} (mM)	–	–	0.8	2.8
HCO_3^- (mM)	–	–	4.2	30
HPO_4^{2-} (mM)	53.65	39.5	0.3	–
SO_4^{2-} (mM)	–	–	0.8	–
$H_2PO_4^-$ (mM)	13.07	10.5	0.4	–
Osmolality (mOsm/kg)	306	228	295	292
Ionic strength	0.174	0.129	0.155	0.139
Buffer capacity (mmol/L/pH unit)	28.1	23.0	1.0	5

lag time and $T_{50\%}$ representing the time during which there is limited drug release in the dissolution media and the time to release 50% of drug content, respectively, were also calculated for comparison of the test polymers in the different media.

2.6. Solubility of prednisolone

Solubility of prednisolone in the three different buffers at pH 7.4 was determined by adding excess prednisolone to the buffer and leaving it for 24 hours in a shaking water bath at 37 °C. The excess prednisolone was then filtered and UV absorbance of the solution measured. Solubility was found to be the same (2.23×10^{-1} g/L) in the different buffer media studied.

3. Results and discussion

The tablet cores were satisfactorily coated with Eudragit S (aqueous dispersion), Eudragit S (organic solution) and Eudragit FS (aqueous dispersion) to coating thicknesses ranging from 3 to 9% TWG. However, coating with the polymer system, Eudragit P4135 (organic solution) was problematic. Significant tablet agglomeration was noted during the coating process because of the thermoplastic and tacky nature of the coating system. A variety of formulation parameters (e.g. type/concentration of organic solvents and glidants) and processing factors (e.g. spray rate, atomising pressure, bed temperature, etc.) were investigated in an attempt to improve coating, but it was only possible to achieve a 5.7% TWG with a high level of GMS (40% GMS on dry polymer substance). No such difficulties in coating were noted with Eudragit FS30D, which is an aqueous dispersion variant of Eudragit P4135.

No drug release was observed from tablets coated with Eudragit S organic solution, Eudragit S aqueous dispersion and Eudragit FS for up to 6 h in acid. In contrast, tablets coated with Eudragit P4135 were highly permeable in the acid media with 40% drug release occurring within 2 h. This can be attributed to the aforementioned difficulties in coating and the need for a high proportion of GMS in the formulation, which results in a weak and permeable coat structure. Further work with this coating system was therefore discontinued. There are recent reports in the literature on the use of Eudragit P4135 for seal coating (Hu et al., 1999) and microencapsulation applications (Jeong et al., 2001), but the present study would suggest that its use as a spray coating polymer is limited.

The influence of coating thickness on drug release rate was investigated in compendial buffers at pH range 6.8–7.4, following acid exposure for 2 h (unless otherwise stated). Fig. 1 shows the influence of coating thickness on drug release from Eudragit FS coated tablets in pH 7.2 Sorensen's buffer. As expected, increasing the coating thickness decreases the rate of drug release. Furthermore, the pH of the dissolution medium has a major role to play in the dissolution of the coating; increasing the pH of the dissolution fluid accelerates the rate of dissolution (Fig. 2). Similar trends were observed with the Eudragit S (aqueous) and Eudragit S (organic) polymer coated tablets. These initial experiments show that a coating equivalent to 5% TWG on the tablets (corresponding to a coating thickness of 84 ± 4 μm) provide sufficient retardation of drug release in the upper intestinal region; hence, further detailed drug release studies were carried out at this coating thickness for all the polymers. Table 3 summarises the drug release results (lag time and $T_{50\%}$) for the coated tablets in the tested buffer media.

The pre-test time in acid was varied to elucidate any possible effects of gastric residence time, known to be variable for monolithic dosage forms, on subsequent drug release from the coated tablets in the intestinal media. Drug release from the coated tablets was observed to be slower for tablets pre-tested in acid for 2 h compared to 0.5 h (Figs. 3 and 4, respectively), and was of the same order for the different polymer systems. The slower dissolution rate for tablets tested in acid for 2 h could be due to the ingress of low pH acid into the film coat thus delaying the neutralising action of the alkaline buffer media on subsequent testing in near neutral pH buffer. The result demonstrates a possible effect of gastric residence time of the tablets on the subsequent disintegration in the intestine. However, this effect is not readily apparent from previous in vivo results (Ashford et

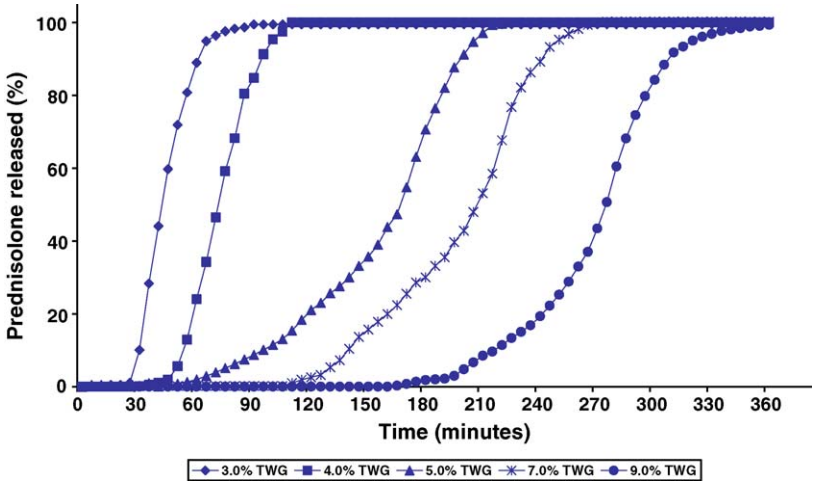

Fig. 1. In vitro dissolution profiles for Eudragit FS coated tablets in pH 7.2 Sorensen's buffer following a 2 h exposure to acid as a function of coating thickness (TWG).

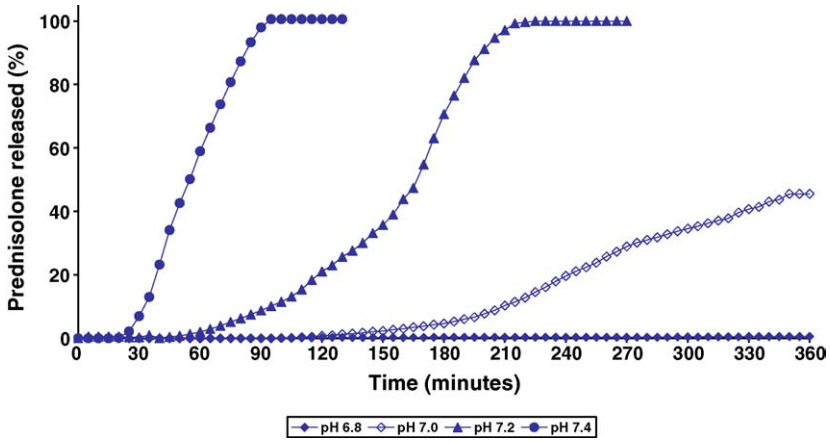

Fig. 2. In vitro dissolution profiles for Eudragit FS coated tablets (5% TWG) in pH 6.8–7.4 Sorensen's buffer following a 2 h exposure to acid.

Table 3
Lag time and $T_{50\%}$ (min) of the polymer coated tablets (5% TWG, coating thickness 84 ± 4 μm) as a function of pH and dissolution media following a 2 h exposure to acid

Buffer	pH	Eudragit S (aqu)		Eudragit S (org)		Eudragit FS	
		Lag	$T_{50\%}$	Lag time	$T_{50\%}$	Lag time	$T_{50\%}$
Sorensen's buffer	6.8	–	–	–	–	–	–
	7.0	70	130	185	352	170	–
	7.2	30	65	110	185	60	167
	7.4	25	52	35	68	25	55
Potassium phosphate buffer	6.8	–	–	–	–	–	–
	7.0	175	247	–	–	–	–
	7.2	50	97	150	252	70	232
	7.4	35	57	65	112	45	90
Hanks buffer	7.4	95	197	130	305	120	245

(–) indicates limited dissolution within the 6 h time-frame.

al., 1993b; Cole et al., 2002), which is not surprising given that inter-subject variability in intestinal pH and transit time through the small intestine, would also contribute to the actual time and site of disintegration.

Drug release from Eudragit S aqueous coated tablets occurred completely at pH 7.0 Sorensen's buffer (Table 3), while for tablets coated with Eudragit S (organic) and Eudragit FS, drug release was very slow (lag time > 3 h) and incomplete over 6 h. At pH 7.2, however, drug release occurred readily from all the coated tablets albeit after a polymer-dependent variable lag time (Table 3). The drug release rates of the different polymer coated systems is of the order Eudragit S (aqueous) > Eudragit

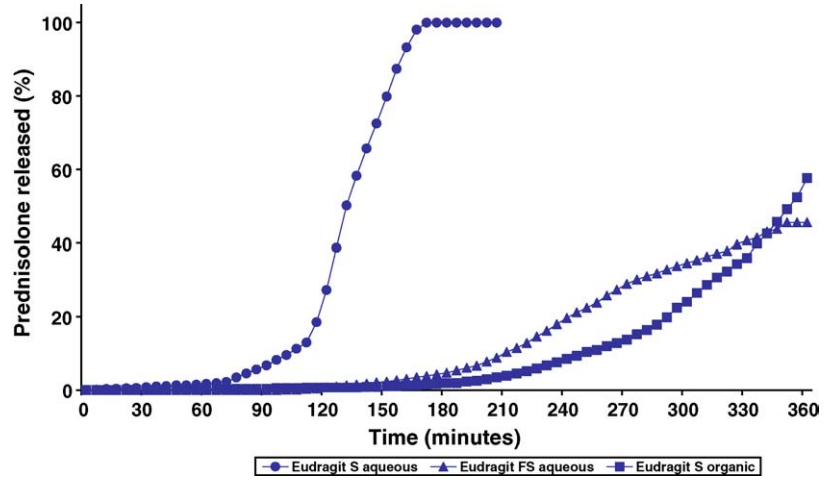

Fig. 3. In vitro dissolution profiles for Eudragit S aqueous, Eudragit FS and Eudragit S organic coated tablets (5% TWG) in pH 7.0 Sorensen's buffer following a 2 h exposure to acid.

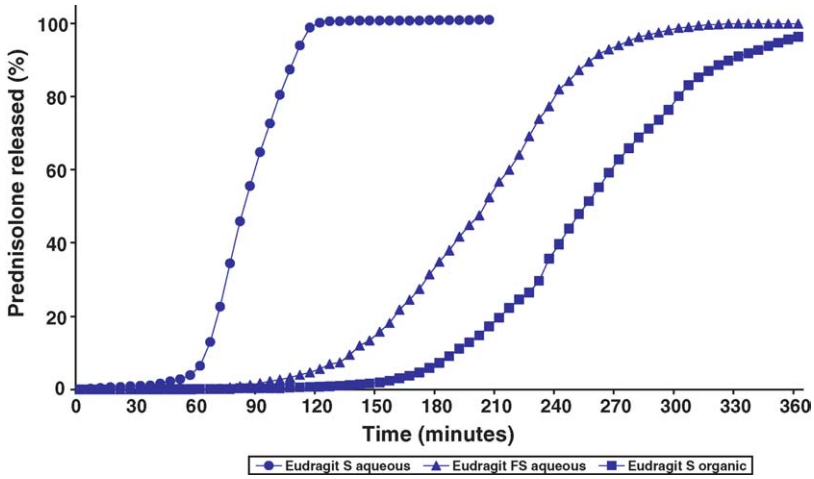

Fig. 4. In vitro dissolution profiles for Eudragit S aqueous, Eudragit FS and Eudragit S organic coated tablets (5% TWG) in pH 7.0 Sorensen's buffer following a 0.5 h exposure to acid.

FS > Eudragit S (organic), and the trend is the same in all the tested media. The faster dissolution rate of tablets coated with Eudragit S aqueous dispersion compared to Eudragit S from an organic solution, is in agreement with previous results (Rudolph et al., 2001) and attributable to the partial neutralisation of the methacrylic acid units, responsible for the pH dependent solubility of the polymers, during the re-dispersion process. Drug release from Eudragit FS coated tablets occurs at pH >7.0, and is quicker in comparison to tablets coated with Eudragit S (organic).

A major concern with the performance of Eudragit S coated dosage forms has been its high dissolution pH threshold. The reported physiological pH values in man is 6.6 ± 0.5 in the proximal small intestine, 7.4 ± 0.4 in the mid small intestine and 7.5 ± 0.5 in the terminal ileum, with a drop to 6.4 ± 0.6 in the ascending colon (Evans et al., 1988). However, the gastrointestinal pH in some healthy subjects falls short of pH 7.0 (Fallingborg et al., 1989), while intestinal pH may also be lower in certain disease states such as ulcerative colitis as has been found by Raimundo et al. (1992) and Fallingborg et al. (1993). Nugent et al. (2000) have found a fall in colonic pH to less than 5.5 in two out of six patients with active ulcerative colitis. Not all studies, however, have identified a reduction in pH; a study in five patients with moderate or severe disease did not detect a change in pH (Ewe et al., 1999), while others have detected a rise in pH (Press et al., 1998). In a comprehensive review of the area, Nugent et al. (2001) concluded that caecal and right colonic pH is reduced in some, but not all patients with ulcerative colitis.

Comparing lumenal pH values to the dissolution pH threshold of the polymer coated tablets in phosphate buffers indicate that drug release in vivo could be very variable depending on the residence time of the tablets in the different gastrointestinal regions. In the timescale of normal transit through the intestine and reported pH values in this region, the site of drug release from the coated tablets could range from the mid to distal small intestine, to a possible failure of the tablet to disintegrate in the course of gastrointestinal transit, as has been reported in in vivo studies with Eudragit S organic (Ashford et al., 1993b; Wilding, 1999).

As for Eudragit S (aqueous) coated tablets, drug release occurs much more readily in simulated intestinal media and may well occur proximal to the ileo-colonic region. On the other hand, tablets coated with Eudragit FS offer a compromise between the two formulations exhibiting a dissolution profile suited for delivery to the ileo-colonic region. In addition to the advantages of aqueous polymeric coating preparations and its particular ease of use, it could prove a better alternative to the Eudragit S. However, Eudragit FS polymer coating was observed to exhibit a pH dependent permeability to aqueous media, with some degree of moisture uptake across the entire pH range employed in the dissolution tests and swelling around the tablet core prior to eventual drug release at pH >7.0.

Drug release from the polymer coated tablets was consistently faster in Sorensen's buffer compared to potassium phosphate buffer up to pH 7.2 (Table 3). At pH 7.4, drug release was very rapid, showing no difference between the different polymer systems in Sorensen's buffer (Fig. 5). In contrast, drug release from Hanks buffer (Fig. 6) was considerably slower than in the compendial buffers and also discriminated between the different polymer coatings. The much slower drug release in the physiological buffer is in agreement with previous results with Eudragit S whereby dissolution was conducted in Hanks and Krebs buffers (Fadda and Basit, 2005). It is noteworthy that the observed differences in drug release in the three buffers investigated are attributable to the polymer coating rather than the drug since the solubility of prednisolone was found to be the same in different buffers.

Kararli et al. (1995) have reported that an increase in ionic strength of the dissolution media increases drug release from Eudragit S coated dosage forms. However, while this may explain the faster drug release in Sorensen's buffer compared to potassium phosphate buffer at lower pHs of up to 7.2 it does not justify the slower release in Hanks physiological buffer comparative to potassium phosphate buffer despite their similar ionic

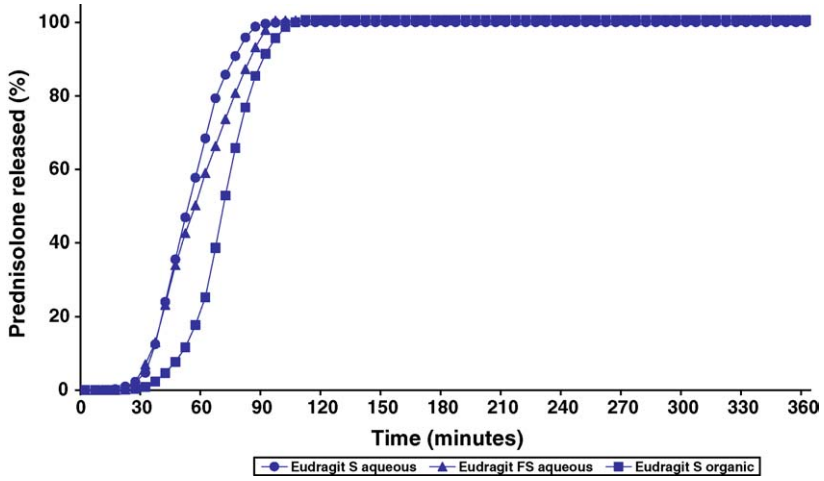

Fig. 5. In vitro dissolution profiles for Eudragit S aqueous, Eudragit FS and Eudragit S organic coated tablets (5% TWG) in pH 7.4 Sorensen's phosphate buffer following a 2 h exposure to acid.

strengths. The release profiles in the different buffers can be explained by buffer capacity in agreement with the theories discussed in earlier work by Ozturk et al. (1988). However, buffer capacity is not the only determinant of dissolution rate as the identity of the buffer salts is also of importance as has been show by our group (Fadda and Basit, 2005). Spitael and Kinget (1977) reported that the dissolution of enteric polymers is affected by the pK_a of the basic component of the dissolution medium. The pK_a of the dissolution medium while being dependent on the ionic strength concentration of buffer salts is however modulated by the ionic species present in the medium. Hence, there is a need to ensure that the ionic composition of the dissolution media is representative of intestinal fluid. Hanks buffer provides a better simulation of small intestinal lumenal fluids compared to phosphate buffers as shown in Table 2. Most importantly, it is buffered by bicarbonate, as are intestinal fluids. Furthermore, its buffering capacity is similar to that of gut lumenal fluids. Kalantzi et al. (2003) found the buffer capacity of lumenal fluids in the fasted state to be approximately 5 mmol/L/pH unit.

A limitation, however, to the use of the physiological buffer media is its pH instability arising from the breakdown of the bicarbonate salt constituent and a subsequent rise in pH of the media. Though it should be noted that even as the pH rises, one would expect the dissolution rate of the coating to increase, but this has not been the case, lending further credibility to the role played by factors other than mere pH on the dissolution of enteric polymers.

It is indeed a generally agreed fact that the in vivo lag time before drug release from enteric coated dosage forms is significantly longer than is predicted by in vitro drug release tests employing compendial buffers. Several gamma scintigraphic studies in human volunteers have shown prolonged initial disintegration times of enteric coated tablets. A study by Ashford et al. (1993b) of rapidly disintegrating Eudragit S coated tablets in healthy volunteers showed prolonged onset of drug release in the range of 5–15 h. This delayed disintegration of enteric coated tablets is better reflected in physiological buffers. From the drug release results in the physiological buffer media, it is reasonably conceivable that the disparity between in vitro and in vivo drug

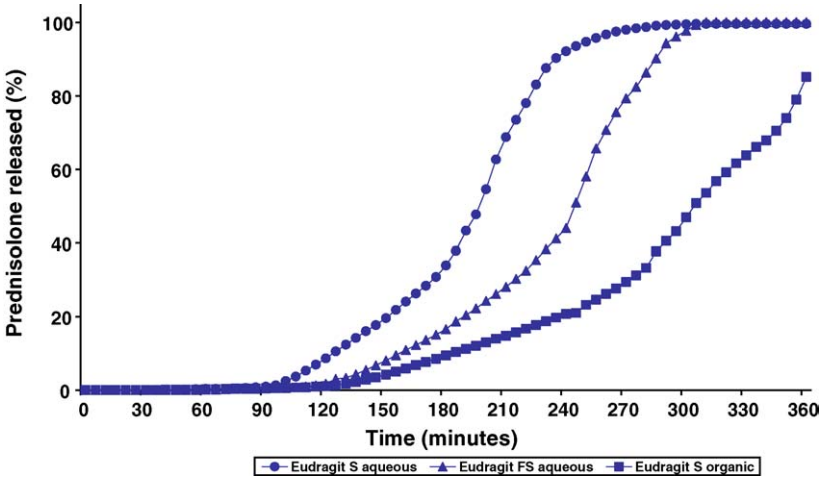

Fig. 6. In vitro dissolution profiles for Eudragit S aqueous, Eudragit FS and Eudragit S organic coated tablets (5% TWG) in pH 7.4 physiological salt solution (Hanks buffer) following a 2 h exposure to acid.

release characteristics is attributable, inter alia, to the inadequacy of the in vitro dissolution media in simulating intestinal fluid. It is to be noted also that the compendial media at pH 7.4 were not able to discriminate between the different polymer coated dosage forms, whereas this was possible with the physiological buffer media, and of course, the ability to discriminate between different formulations is an essential requirement of any in vitro tests in dosage form development.

4. Conclusion

Drug release from the polymer coated tablets is shown here to be different for the three tested polymers. While dissolution of Eudragit S aqueous coated tablets is likely to occur proximal to the ileo-colonic region, tablets coated with Eudragit S organic solution may however fail to dissolve at the physiological pH within the time frame of intestinal transit, especially in certain patient groups in whom intestinal pH is known to be lower. Tablets coated with the newer Eudragit FS polymer on the other hand, have been shown to exhibit a dissolution profile appropriate for ileo-colonic drug delivery.

The results also show that in addition to the intestinal pH conditions, drug release is additionally dependent on the ionic composition of the dissolution media, and must be considered alongside other aspects of in vitro drug release testing, in performance assessments of enteric polymer coated dosage form. The observed effects of different exposure times in acid on drug release, though not directly corroborated in vivo, does in the least, highlight the benefit of exposing enteric dosage forms to acid prior to testing in buffer.

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