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An in vitro investigation into the suitability of pH-dependent polymers for colonic targeting

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Summary

The effect of a pH-dependent polymer coating, Eudragit S, on its ability to protect a model drug and control its release from rapidly disintegrating tablets has been examined in vitro. Conditions were chosen to mimic those likely to occur during transit from the mouth to the colon. Dissolution was affected by coating thickness and pH. At a given pH, the nature of the buffer system dramatically affected dissolution and disintegration. Profiling experiments involving pH changes and mimicking the extremes of conditions prevailing in vivo indicated that release of drug may commence in the duodenum or not at all.

Introduction

The delivery of drugs to the colon is of value in the topical treatment of colonic diseases such as ulcerative colitis, the oral delivery of peptides and other drugs degraded in the upper gastro-intestinal tract and in the improvement of the treatment of diseases susceptible to diurnal rhythm such as asthma. To achieve successful colonic delivery, a drug needs to be protected from absorption and/or the environment of the upper gastro-intestinal tract and then be rapidly released into the proximal colon, considered to be the optimal site for colonic delivery. The use of prodrugs provides a specific approach to this problem. Sulphasalazine and olsalazine, for example, are degraded in the colon to 5-aminosalicylic acid (Peppercorn and Goldman, 1972; Lauritsen et al., 1984). However, a more universal delivery system would be more desirable.

There are numerous patents and reports within the literature in which polymers, whose integrity is dependent upon pH changes, are used as coatings to attempt to gain the required site specificity (e.g., Dew et al., 1982; Thomas et al., 1985; Rutgeerts, 1989). The use of such polymers is based on the generally held view that the pH of the gastro-intestinal tract does not exceed 7 until the distal ileum is reached. However the advent of new, more reliable, in vivo pH measuring techniques, has revealed variability of pH and a fall in

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pH from the ileum to the colon (Evans et al., 1988).

Eudragit S is a co-polymer of methacrylic acid and its methyl esters and is only soluble above pH 7. It has been chosen as a model pH-dependent polymer in this study. The ability of Eudragit S to protect an enclosed drug under acidic conditions has been investigated. The in vitro release characteristics of tablets coated with varying thicknesses of Eudragit S have been evaluated under conditions that are likely to prevail in vivo.

Materials and Methods

Tablet preparation

Rapidly disintegrating, 10 mm diameter, standard bi-convex core tablets, weight 365 mg, were prepared using a single punch tablet machine (Manesty F3; Speke; U.K.) to the following formula: salicylic acid 5% w/w; microcrystalline cellulose (Avicel PH101) 10% w/w; magnesium stearate 1% w/w, lactose (Fast flo) 84% w/w.

Tablet coating

Tablet coating was achieved using a bench pan coating system. Tablets were tumbled in a baffled glass coating pan of 1 l volume. Coating solution was sprayed onto the tablets at a flow rate of 1 ml min^{-1} using a two-fluid atomizer operating at an air pressure of 10 $lb/inch^2$. Coating thicknesses were changed by varying the coating times. The coating solution consisted of Eudragit S (Rohm Pharma, GmbH), 7% w/v, triacetin, 1.4% w/v, in isopropanol and acetone, 5:1 v/v. Once coated, the tablets were allowed to dry over night under ambient conditions and stored in the dark in airtight containers. The percentage weight increase of the tablets on coating was taken to be indicative of the coat thickness.

Assessment of fluid uptake

Six tablets of each of the coating thicknesses were weighed and incubated in 0.1 M HCl at 37°C in a shaking water bath (100 strokes/min). After 2 h, the tablets were dried, reweighed and the percentage fluid taken up by the coated tablets was calculated.

TABLE 1

Conditions employed for dissolution testing of coated tablets

% weight increase on coating	Buffer system	pH
1.7, 2.8, 4.7, 6.1, 8.2, 9.7	buffer 1	7.0, 7.2, 7.8
5.0	buffer 1	7.5
5.0	buffer 2	7.5
5.0	buffer 3	7.5

Buffer 1: prepared from 0.2 M sodium dihydrogen orthophosphate and 0.2 M disodium hydrogen phosphate; buffer 2: prepared from 0.067 M potassium dihydrogen orthophosphate and 0.067 M disodium orthophosphate (Sorensen's buffer); buffer 3: prepared from 0.067 M sodium dihydrogen orthophosphate and 0.067 M disodium hydrogen orthophosphate (modified Sorensen's buffer).

Disintegration times

These were measured following the procedure of the BP 1988. No discs were used. Disintegration testing was performed on tablets of each coat thickness. Two media were chosen as specified in Table 1; buffer 1 (0.2 M mixed sodium phosphates) and buffer 2 (Sorensen's phosphate); at pH values ranging between 7.0 and 8.0.

Dissolution studies

Dissolution rates were measured with a flow-through dissolution apparatus (Dissotest; Sotax AG; Switzerland) fitted with 12 mm cells. The dissolution media were maintained at 37°C and pumped through the apparatus and attached spectrophotometer at a flow rate of 16 ml min^{-1}. Analysis of salicylic acid released was carried out at 298 nm with readings taken every 42 s.

Experiments were carried out to assess the effect of changes in dissolution media pH, buffer system and coat thickness on the release characteristics, as detailed in Table 1. Buffers were prepared using freshly distilled water and the appropriate quantity of disodium hydrogen orthophosphate and either sodium dihydrogen orthophosphate or potassium dihydrogen orthophosphate. All the buffers were de-aerated prior to use.

In addition, tablets with a 4.7% weight increase on coating were subjected to prolonged

TABLE 2

pH profiles constructed to mimic extremes of gastro-intestinal tract conditions

Equivalent gastro-intestinal region	Time (h)	pH (low profile)	pH (high profile)
Stomach	2	1.1	1.1
Duodenum	1	6.1	7.2
Lower small intestine	2	7.0	7.8
Colon	(2)	6.5	(N/A)

dissolution studies using pH profiles based on accepted gastrointestinal transit times and the mean measured pH values within the gastrointestinal tract. The pH profiles one standard deviation higher than the mean (as reported by Evans et al., 1988) have been designated 'high profiles' and those one standard deviation below the mean have been designated 'low profiles' (see Table 2). These were constructed with two of the buffer systems specified in Table 1; buffer 1 (0.2 M mixed sodium phosphates) and buffer 2 (Sorensen's phosphate).

Results and Discussion

The ability of the Eudragit coat to protect an enclosed drug from gastric juices was elucidated by measuring the percentage weight increase, due to fluid uptake, after incubation in 0.1 M HCl for 2 h. Fluid uptake initially decreased with increasing coat thickness and became negligible after a coat thickness of approx. 50 μm. The results indicated that, assuming the extra weight was due to fluid uptake into the tablet core, there was a minimum coating thickness required to effectively protect a labile drug.

Plots of % salicylic acid released with time are shown in Figs. 1–3. These clearly show that the dissolution rate was dependent upon both the pH of the medium and thickness of the applied coat. The curves all exhibited an initial lag period characterised by limited dissolution followed by a rapid release of drug. Hence, the curves can be defined by a lag time (the intercept of the extrapolated straight line portion of the graph with the time axis) and the time for 50% dissolution ($T_{50\%}$). These values are given in Table 3. During the dissolution experiment, the coat was initially semi-permeable allowing limited release, corresponding to the lag time, before becoming sufficiently weak to allow disintegration to occur.

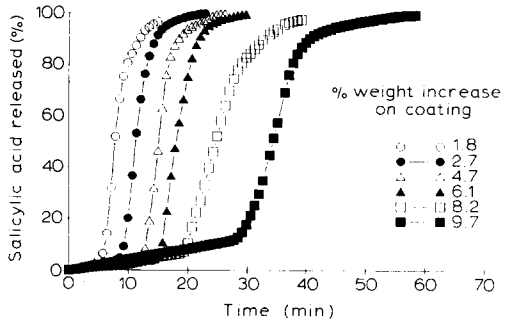

Fig. 2. The effect of coat thickness (percentage weight increase on coating) on the dissolution of tablets at pH 7.2 in buffer 1.

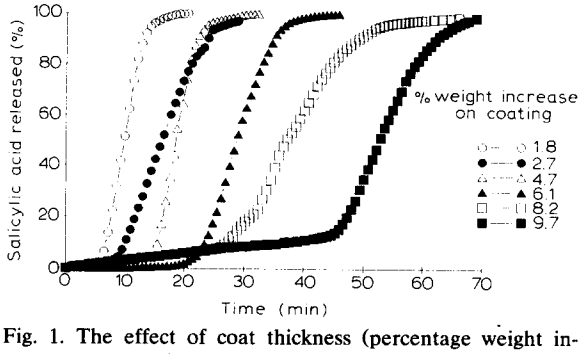

Fig. 1. The effect of coat thickness (percentage weight increase on coating) on the dissolution of tablets at pH 7.0 in buffer 1.

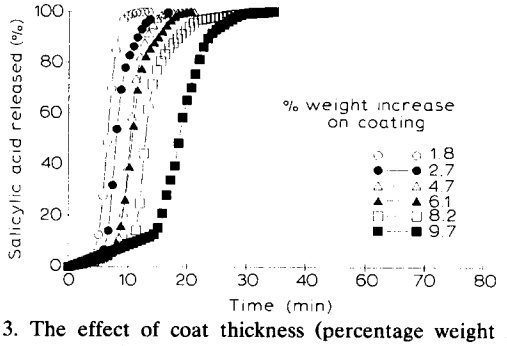

Fig. 3. The effect of coat thickness (percentage weight increase on coating) on the dissolution of tablets at pH 7.8 in buffer 1.

TABLE 3

Release characteristics (in min) as a function of pH of buffer 1 and coat thickness (percentage weight increase on coating)

% weight increase on coating	Buffer pH 7.0		Buffer pH 7.2		Buffer pH 7.8	
	Lag time	$T_{50\%}$	Lag time	$T_{50\%}$	Lag time	$T_{50\%}$
1.7	6.1	10.0	5.5	7.6	4.5	6.1
2.8	8.7	16.6	9.0	11.0	6.1	7.7
4.7	14.8	18.7	12.4	14.5	8.4	10.3
6.1	22.6	28.3	15.2	17.6	8.0	10.7
8.2	25.2	37.0	19.0	24.1	10.8	12.8
9.7	43.5	52.2	27.9	33.8	13.7	18.6

The release curves for tablets (5.0% weight increase on coating) in the three different buffer systems at pH 7.5 (mean pH of the ileum; Evans et al., 1988) are shown in Fig. 4. It can be seen that the dissolution of the tablets was dependent on the composition of the buffer and increased with increasing ionic concentration. This result is in agreement with those of Spitael and Kinget (1977) who demonstrated that the dissolution rate of pH-dependent polymer films was directly proportional to the concentration of the basic salt in the dissolution medium. These authors reported a linear relationship between the logarithm of the dissolution rate and the pK_a of the basic salts and concluded that the dissolution rate was governed by the Bronsted catalysis law.

Tablets tested in buffer 1, which has the same composition but 3-times the strength of buffer 3 (0.2 M compared to 0.067 M), have lag times and $T_{50\%}$ values of 9 and 11 min, which are 3-times

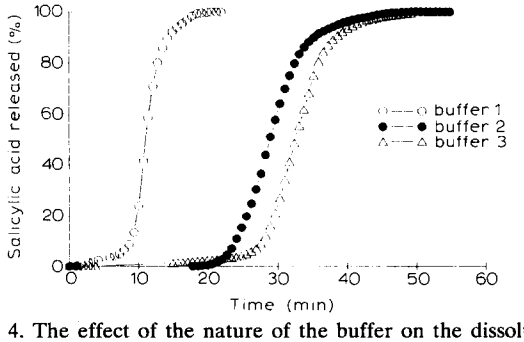

Fig. 4. The effect of the nature of the buffer on the dissolution of coated tablets (5.0% weight increase on coating) at pH 7.5

TABLE 4

Comparison of sodium and potassium composition of buffers and the gastro-intestinal tract contents

Gastro-intestinal tract region/buffer system	Sodium (mmol l^{-1})	Potassium (mmol l^{-1})	Total salt (mmol l^{-1})
Duodenum	142 ± 7 [a]	4.8 ± 0.5 [a]	147
Ileum	140 ± 6 [a]	4.9 ± 1.5 [a]	145
Buffer 1 (pH 7.5)	368		368
Buffer 2 (pH 7.5)	114	10	124
Buffer 3 (pH 7.5)	123		123

[a] From Banwell et al. (1971).

less than those in buffer 2 (27 and 33 min, respectively). Thus, the dissolution rate was directly proportional to the strength of these buffers. These results for the dissolution rate of tablets coated with a pH-dependent polymer show a good correlation with those of Spitael and Kinget (1977) obtained using free polymer films. Tablets tested in buffer 2, however, consistently showed faster dissolution than those tested in buffer 3. Both these buffers were identical in their ionic concentrations only differing in the acidic salt of the buffer. The presence of the potassium, in buffer 2, will have a small effect on the pK_a of the disodium hydrogen phosphate probably explaining the slight difference in dissolution rates in buffers 2 and 3. No direct comparison, therefore, between the strength of this buffer and dissolution rate in the mixed sodium salt buffers (buffers 1 and 3) could be made. Table 4 compares the compositions of the buffers used with the sodium and potassium levels in the gastro-intestinal tract. Buffer 2 (Sorensen's phosphate) is closest in composition to the contents of the gastro-intestinal tract. Assessment of delivery systems designed to respond to pH requires careful choice of the buffer in addition to the appropriate pH control.

Disintegration times for coated tablets decreased as the pH was increased from 7 to 8. This effect was more pronouced as the coat thickness increased. At a given pH the disintegration times were shorter in the buffer with the higher ionic concentration (buffer 1). These findings were in agreement with those from the dissolution experiments.

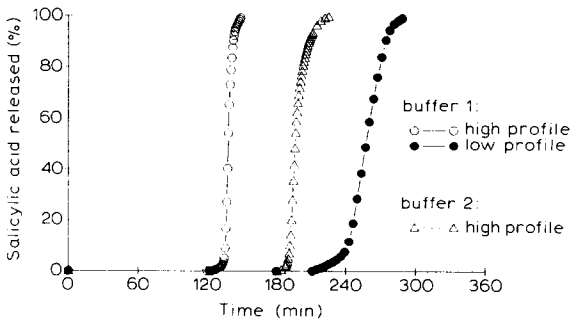

Fig. 5. Dissolution of coated tablets (4.7% weight increase on coating) during pH profiling experiments in different buffer systems.

Fig. 5 shows the dissolution of the coated tablets during the profiling experiments designed to mimic extremes of conditions likely to be found during transit from the mouth to the colon. Release occurred during the high pH profiles (see Table 2) at 140 and 190 min. At these times the tablet is likely to be in the duodenum and lower small intestine, respectively. With the lower pH profile, release occurred at 240 min in buffer I (mixed sodium phosphates buffer). This would be equivalent to release in the lower small intestine. In buffer 2 (Sorensen's phosphate), the buffer most akin to the conditions in the gastro-intestinal tract, release did not occur after 5 h at pH 7.0.

These results confirm the role of pH and buffer system on the release characteristics. More importantly they indicate that dissolution of such a dosage form coated with a pH-dependent polymer and designed to deliver to the colon, could occur as early as the duodenum or not at all. Therefore, due to variabilities in the gastro-intestinal tract conditions, pH-dependent polymers may not provide the best method of targeting to the colon.

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