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An in vitro investigation into the potential for bimodal drug release from pectin/chitosan/HPMC-coated tablets

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Abstract

The influence of disintegrant on the water uptake and subsequent disintegration force developed was investigated in a simple tablet formulation. The results indicated that a reasonable correlation existed between water uptake and disintegration force for the disintegrants screened with cross linked polyvinyl pyrrolidone (PVP XL) showing a proportionally higher disintegration force for the amount of water imbibed. Two tablet formulations, intended to promote accelerated drug release in the colon, were prepared, with and without PVP XL, and film coated with a mixture of pectin, chitosan and HPMC. The two systems showed different drug release rates which were influenced by the pH of the dissolution medium. In the presence of pectinolytic enzyme, drug release was faster when compared to release in buffer alone for both systems although the mechanism differed for each. Drug release in simulated gastrointestinal conditions showed a bimodal profile with the increased drug release rate being triggered by the action of pectinolytic enzymes.

Keywords: Bimodal delivery; Chitosan; Coating; Disintegrants; Pectin

1. Introduction

Bimodal or sigmoidal drug release profiles, where release is slow in the initial stages and increases to a faster release rate at some later stage, may be of significant therapeutic benefit (Maggi et al., 1997). In disease states such as nocturnal asthma increased drug release rates may help prevent the exacerbation of symptoms caused by circadian rhythms (Lemmer, 1991). Alternatively, bimodal release profiles could be utilised so that drug release was slower in a region within the gastrointestinal tract (GIT) where absorption is good (e.g. the small intestine) and increased lower down the GIT (e.g. the colon) where drug absorption may be poor, the overall effect being to maintain therapeutic blood drug levels throughout.

Colonic microflora which release enzymes capable of degrading polysaccharide materials have been utilised in dosage forms capable of targeting the colon (Milojevic et al., 1996a,b). More recently, it has been shown that the polyelectrolyte complex (PEC) formed between pectin and chi-

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tosan has potential for use in colonic drug delivery (Fernandez-Hervas and Fell, 1998). Films manufactured from pectin/chitosan/HPMC (P:C:H) have been shown to have higher permeability to a model drug in the presence of pectinolytic enzyme than in buffer alone (Macleod et al., 1999). These films, therefore, when coated onto tablets, could be used to achieve a system capable of providing bimodal drug release.

Drug release from such systems will be influenced by many factors including film and core properties. The osmotic effect of different excipients used in core formulations is well documented (Zentner et al., 1985; Theeuwes, 1987). Gissinger and Stamm (1980) highlighted the fact that disintegrants will imbibe water to different extents. Cores formulated from materials which take up high amounts of water may give a quicker rate of release than those where the core materials imbibe less water. In addition to their ability to imbibe water, disintegrants have also been shown to swell (Kornblum and Stoopak, 1973; Gould and Tan, 1985; Faroongsarng and Peck, 1994). This swelling will result in a force being generated at different rates and to different extents by different disintegrants (Caramella et al., 1986). The force generated by the swelling core will exert a pressure on any surrounding film. The ability of the film to withstand such pressure will again influence drug release from these systems.

This paper investigates drug release from a tablet system coated with a P:C:H film. In particular, the influence of tablet core properties and pH will be considered with respect to designing a system capable of bimodal drug release.

2. Materials and methods

2.1. Materials

The materials used together with the suppliers were as follows. Pectin USP (DM 70%) (Citrus Colloids, UK); chitosan (high molecular weight, DA 86.2%) (Sigma, UK); HPMC (Methocel E4M) (Colorcon, UK); glycerol BP (Macarthy, UK); powdered cellulose (Elcema G250® and Elcema P050® USNF, both Degussa, Germany); microcrystalline cellulose USNF (PH102, FMC, USA) and croscarmellose sodium USNF (Ac Di Sol®, FMC, USA); sodium starch glycolate (Primojel, Avebe, UK); maize starch, general reagent grade (Fisons, UK); cross-linked polyvinyl pyrrolidone NF (GAF); LH 21 USNF (Shin Etsu, Japan); Tween 80®, general reagent grade (Sigma, UK); glycerol monostearate NF and triethyl citrate (Colorcon®, UK); sodium hydroxide, general reagent grade (BDH, UK); methacrylic acid copolymer USNF (Eudragit L100-55®, Rohm Pharma, Germany); magnesium stearate BP (SKF, UK); microcrystalline cellulose (Emcocel 50M USNF and dicalcium phosphate dihydrate (Emcompress USNF, both Mendell, USA); paracetamol, general reagent grade (Sigma); hydrochloric acid (Fisons); disodium hydrogen orthophosphate and potassium dihydrogen orthophosphate, both general reagent grade (BDH); Pectinex Ultra SP-L 30 925 pg/ml at pH 3.5 (Novo Nordisk Ferment, Switzerland). The Pectinex Ultra SP-L solution contains a mixture of pectinolytic enzymes (mainly polygalacturonases, pectin esterases and pectin lyases) and was used to mimic the conditions in the colon.

2.2. Tablet preparation

Initially, a simple tablet formulation, prepared using a single punch tablet machine (Manesty F3, Speke, UK; paracetamol, 10%; dicalcium phosphate dihydrate, 79%; magnesium stearate 1%; disintegrant 10%; tablet weight, 150 mg) was used to assess the influence of various tablet disintegrants on water uptake and disintegration force generation. The tablets were prepared using flat-faced, 10-mm diameter punches. The excipients were sieved through a 250-μm sieve before being mixed for 20 min on a Turbula blender prior to tablet manufacture. All the tablet batches had a similar mean tablet breaking force of 49 N measured using a Schleuniger hardness tester (Model 2E, Schleuniger, Switzerland).

It was necessary to manufacture tablets for subsequent coating studies from a formulation that would be able to withstand a prolonged tableting and coating process. For this reason the dicalcium phosphate used earlier was replaced

with a 50:50 dicalcium phosphate/microcrystalline cellulose mixture to produce a stronger tablet containing 5% cross linked polyvinyl pyrrolidone (PVP XL). The excipients were first sieved through a 250-μm sieve, then mixed for 20 min in a Turbula blender (T2C, WA Bachoven, Switzerland). Biconcave direct compression tablets (6 mm) were manufactured using a rotary tablet machine (Manesty B3B). Each batch was monitored for weight uniformity throughout the run and had similar mean tablet breaking force values of 69 N. The tablets were stored in sealed glass amber bottles prior to coating.

2.3. Water uptake

The method used was based on that outlined by Yunxia et al. (1996). A piece of filter paper (10 × 10 cm) was folded twice to give a 5 × 5-cm square. This was placed in a glass Petri dish and 4.0 ml of distilled water added. An accurately weighed tablet was placed on the moist paper for 5 min and then reweighed. Five tablets from each batch were tested. Results were expressed according to the equation below

$$\text{Water uptake (\%)} = \frac{\text{weight increase of tablet (mg)}}{\text{initial tablet weight (mg)}} \times 100$$

2.4. Disintegration force

The apparatus consisted of a teflon tablet holder with a perforated base and a freely moveable plunger. A tablet was placed in this holder with the plunger on top and the whole was immersed in water to the level of the tablet. The swelling of the tablet caused the plunger to move and the force generated by this movement was monitored by locating the plunger against a metal bar on which were mounted two strain gauges in the manner described by Reading and Spring (1984). The output from the gauges was recorded on an X–Y recorder (Servogor 210, BBC, Goerz, Austria). The metal bar was calibrated daily directly using weights.

Table 1
P:C:H coating formulation

Material	Weight
0.1 M HCl	10.6 kg
Pectin USP	109.2 g
Chitosan	36.4 g
HPMC E4M	36.4 g
Glycerol	45.5 g

2.5. Tablet coating

The formulation used to coat the tablets is shown in Table 1. Glycerol was included as a plasticiser to reduce film brittleness. A 3:1 pectin:chitosan ratio was chosen as previous work had shown this ratio to be favourable in terms of swelling and permeability properties (Macleod et al., 1999). Coating was undertaken in a 16-inch diameter stainless steel coating pan (Skermans, UK) The test tablets (200 g) were 'bulked out' with 3.0 kg of placebo tablets. Adequate mixing in the pan was achieved by the attachment of four pieces of silicone tubing to act as baffles. Drying air (inlet air) was introduced into the front of the pan approximately perpendicular to the tablet bed, and the extract was located at the top of the coating pan. The spray gun used was a Binks 460® (Binks, Bullows, UK). Table 2 gives details of the coating process parameters used. Samples were removed every hour and the mean coating weight gain calculated. Spraying was stopped after the tablets had acquired a 6.5% weight gain on coating.

To allow assessment of the coated tablet system in simulated GIT conditions a further enteric coat was applied to 100 g of the coated tablet formula-

Table 2
Coating process parameters used to apply P:C:H coating

Coating parameter	Value
Atomising pressure (bar)	3.5
Inlet temperature (°C)	64
Bed temperature (°C)	30
Pan speed (rpm)	16
Spray rate (g/min)	10–12

Table 3
Methacrylic acid copolymer coating formulation

Excipient	Weight (g)
Methacrylic acid copolymer	351.0
1 M sodium hydroxide	117.0
Distilled water	1487.0
Triethyl citrate	35.0
Glycerol monostearate	7.0
Tween 80®	3.0

tion containing no disintegrant in the core. An methacrylic acid copolymer suspension was applied to give a 15% weight gain on coating. Table 3 shows this formulation and Table 4 shows the process parameters used.

2.6. Dissolution testing

Dissolution studies were undertaken using the BP 1998 Apparatus II (Caleva® 8ST, UK) at 50 rpm. The dissolution media used were 500 ml of pH 5.0 (chosen as a compromise between the accepted pH of the colon and the maximum activity of the enzyme) or pH 7.4 Sorensen's phosphate buffer (Geigy, 1984). In the experiments to investigate the influence of pectinolytic enzyme on drug release Sorensen's phosphate buffer, pH 5.0, was used with or without addition of pectinolytic enzyme. Pectinex-Ultra® was used as a source of pectinolytic enzyme and was added at a concentration of 2 ml/l. In the experiment used to simulate GIT transit the dissolution media were 0.1 M HCl for 120 min followed by Sorensen's phosphate buffer, pH 7.4, for 120 min, and finally Sorensen's phosphate buffer, pH 5.0, with 2 ml/l of Pectinex Ultra®. The dissolution media were maintained at 37 ± 1°C throughout the experiments. Six tablets were tested and the mean percent drug release calculated in all experiments.

Table 4
Coating process parameters used to apply methacrylic acid copolymer coating

Coating parameter	Setting
Atomising pressure (bar)	3.0
Inlet temperature (°C)	61
Bed temperature (°C)	32
Pan speed (rpm)	21
Spray rate (g/min)	14
Weight gain (%)	15

3. Results and discussion

Table 5 shows the mean tablet breaking force values, water uptake and maximum force generated for the range of disintegrants tested. Fig. 1 shows there is a reasonable correlation between water uptake and maximum force developed. Of the disintegrants tested, cross-linked polyvinyl pyrrolidone exerts the maximum force relative to the amount of water uptake and was chosen for further study.

Tablets containing no disintegrant or 5% PVP XL represent systems with low water uptake and low disintegration force generation, and high water uptake and high disintegration force generation, respectively. Thus the influence of these two parameters on drug release could be determined by comparing these two systems. Visual observation of the tablets throughout the dissolution experiment showed that in all cases, in the absence of enzyme, although extensive swelling occurred, the tablets remained intact. The model developed by Korsmeyer et al. (1983), and extended by Ritger and Peppas (1987), has been used to analyse this data.

$$M_t/M_\infty = k^n \text{ for} = 0 < M_t/M_\infty < 0.6$$

where M_t, amount of drug released from time 0 to time t; M_∞, amount of drug released from time 0 to time ∞; M_t/M_∞, fraction of drug released at time t; k, kinetic constant; t, time; n, release exponent.

Table 6 shows the release exponent, n, the kinetic constant, k, and the correlation coefficient for the two tablet systems at pH 5.0 and 7.4 determined using the above model.

The results give an insight into the mechanism of release from the two different tablet formulations. For both systems the release exponent, n, lies between 0.5 and 1.0. Therefore drug release

Table 5
Results for water uptake, disintegration force and tablet hardness for various tablet disintegrants ($n = 5$, S.D in brackets)

Disintegrant (10%)	Mean breaking force (N)	Water uptake (% in 5 min)	Maximum force developed (N)
Maize starch	52.9 (2.9)	37.9 (2.6)	4.87 (1.07)
Cellulose P050®	54.9 (2.0)	19.3 (0.6)	3.29 (0.70)
LH-21®	43.1 (2.0)	124.2 (4.0)	15.06 (1.56)
Cellulose G250®	49.1 (3.9)	30.4 (2.7)	8.27 (0.94)
Sodium starch glycolate	30.4 (2.0)	198.8 (7.8)	10.03 (1.03)
Microcrystalline cellulose PH102®	62.8 (1.0)	13.4 (1.4)	2.89 (1.12)
PVP XL®	5.0 (0.2)	86.1 (3.8)	14.49 (1.39)
Croscarmellose sodium	4.5 (0.3)	126.6 (3.1)	13.80 (1.97)
None	5.8 (0.4)	7.1 (1.0)	None detected

can be described as non-Fickian or anomalous diffusion controlled. The most likely explanation is that in both systems, the rates of diffusion and swelling are similar with neither being dominant.

The release exponent, n, for the system that contains 5% PVP XL is lower than for the system with no disintegrant at both pH values (0.64 vs. 0.90 at pH 5.0 and 0.85 vs. 0.93 at pH 7.4). The drug, paracetamol, may be expected to dissolve at a faster rate in the system with 5% PVP XL which imbibes water to a greater extent (Table 5) It is possible that the dissolution of paracetamol may control the rate of drug release to a greater extent in the tablet with no disintegrant. This control will result in a higher value for n as the drug release kinetics approach the situation where release is governed by the dissolution process. In the system with disintegrant, water ingress will be higher, and so release will be controlled more by drug diffusion than dissolution so that the kinetics approach square root of time type release.

The pH of the dissolution medium has an influence on drug release from these coated tablet systems. Paracetamol will be unionised at the pH values investigated in the experiment. Therefore, pH is likely to exert its influence through its effect on the coating. The 3:1 pectin:chitosan ratio was chosen because previous work (Macleod et al., 1999) showed this to be optimal in terms of maximal interaction between the NH_3^+ groups in chitosan and COO^- groups of pectin. The increase in pH from 5.0 to 7.4 will have a significant effect on the ionisation of any amino groups that are present in excess. At pH 7.4, these excess groups will be in the unionised form; at pH 5.0, they will be partly ionised. This ionisation profile will influence the interactions between the polymers and consequently alter the swelling capacity. Increased swelling has been shown to be associated with increased permeability of the films. The result of this would be an increase in drug release. As shown in Table 6, the rate constant for drug release is higher for both the tablet systems at pH 5.0 than it is at pH 7.4.

Similarly, the release exponent, n, is greater at pH 7.4 when compared to the value at pH 5.0. If values closer to 1.0 are associated with an increase

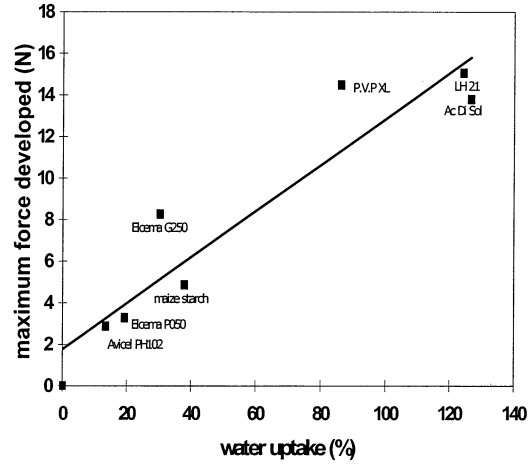

Fig. 1. The relationship between mean water uptake (%) and mean disintegrating force generated (N) for a range of disintegrants; $n = 5$.

Table 6
The diffusional release exponent, n, rate release constant, k, and correlation coefficient R^2 for the release of paracetamol from P:C:H-coated tablet cores containing no disintegrant or 5% PVP XL as disintegrant in Sorensen's phosphate buffer, pH 5.0 and 7.4

Formulation/pH	Diffusional release exponent, n	Release rate constant, k (min^{-n})	Correlation coefficient
No disintegrant, pH 5.0	0.90	0.0056	0.998
No disintegrant, pH 7.4	0.93	0.0031	0.994
5% PVP XL, pH 5.0	0.64	0.0227	0.997
5% PVP XL, pH 7.4	0.85	0.0064	0.999

in the magnitude of the non-diffusional contribution to overall drug release, then for both systems at pH 7.4, the release is less dependent on diffusion and more dependent on some other rate-controlling factor such as the dissolution of paracetamol. It is noticeable that the influence of pH on both drug release rate and the release exponent is greater in the system where the tablet core contains 5% PVP XL. The greater extent of swelling of the film, likely to occur at pH 5.0, will mean that the higher capacity for water uptake of the PVP XL will be maximised. Thus, proportionally higher rates of drug release will be observed. Similarly, the likelihood is that release will be controlled more by diffusion than dissolution, as more water is drawn into the core through the system that is more loosely connected.

Figs. 2 and 3 show that there is an increased release of drug in the presence of pectinolytic enzyme when compared to the profile in pH 5.0 buffer only. These results, together with those reported earlier (Macleod et al., 1999), indicating that P:C:H films show greater permeability to paracetamol in the presence of pectinolytic enzyme than in buffer alone, confirm that these coating systems have potential for bimodal drug delivery.

The difference between the two profiles shown in Figs. 2 and 3 is also significant. The tablets which contained 5% PVP XL as disintegrant in the core show a significant increase in drug release when enzyme is present from around 30 min onwards. A 100% drug release is achieved after around 150 min. Visual observation of these tablets during dissolution in the presence of pectinolytic enzyme showed that the coating burst during the experiment. Conversely, the tablets tested in the absence of enzyme remained intact. A force will be exerted by the PVP XL on the surrounding coating as water is taken into the tablet system. Importantly, however, it is only in the presence of pectinolytic enzyme that the exerted force exceeds the resistance afforded by the coating. The action of the pectinolytic enzyme will be to weaken the pectin:chitosan film by the breakdown of the pectin polymer chains.

The coated tablets with no disintegrant show very similar release profiles into media with and without enzyme, for the first 150 min of the experiment. At this point, approximately 45% of the total drug has been released. In the presence of enzyme this increases to around 80% release after 300 min, whereas with no enzyme only around 65% is released after 300 min. Throughout the experiment visual inspection revealed that

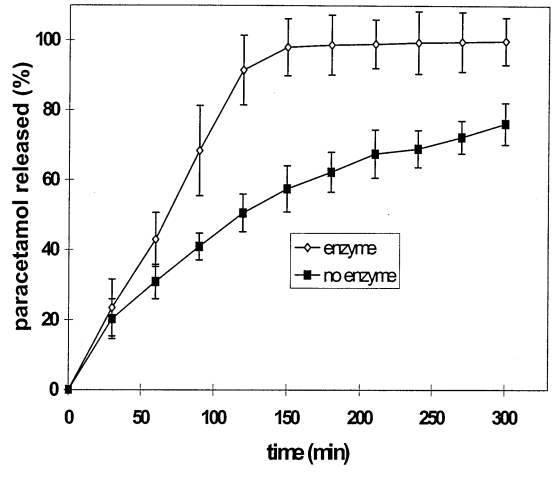

Fig. 2. Release of paracetamol (%) versus time (min) from P:C:H-coated tablets with 5% PVP XL as disintegrant; $n = 6$; error bars, $\pm$S.D.

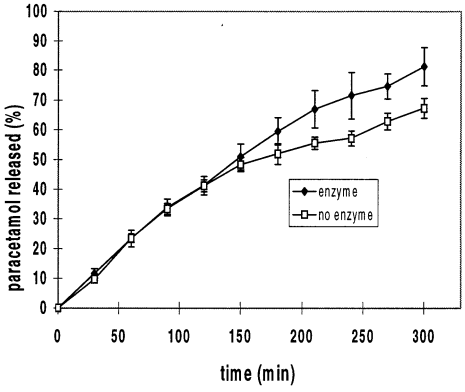

Fig. 3. Release of paracetamol (%) versus time (min) from P:C:H-coated tablets with no disintegrant; $n = 6$; error bars, $\pm$ S.D.

none of the coatings on the tablets, during dissolution testing in either media, split or burst in any way. It could be concluded, therefore, that any force exerted by these tablet cores, which would be minimal as there was no disintegrant present, was not enough to overcome the resistance afforded by the coating, even when the coating was weakened by the action of pectinolytic enzymes. Increased release of drug from the tablets with no disintegrant must be due to increased permeability of the surrounding film caused by an increase in the number of, or size of, pores. This change in porosity of the films is a result of enzymatic breakdown of the polymer chains of pectin into their smaller sub-units. The similar profiles seen both in the presence or absence of enzyme, for the first 150 min, suggests that swelling and hydration of the mixed film is necessary before enzymatic breakdown can occur.

Fig. 4 shows that a tablet system coated with a film containing a 3:1:1 ratio of P:C:H, which in turn is enteric coated with a methacrylic acid copolymer, is theoretically capable of delivering the majority of the dose to the colon. Furthermore, the system delivers no drug under in vitro conditions that simulate the stomach, commences the release of drug at low rates in conditions simulating the small intestine and accelerates the release rate in the presence of pectinolytic enzyme. Such a system would be ideal in a situation where a bimodal profile was sought.

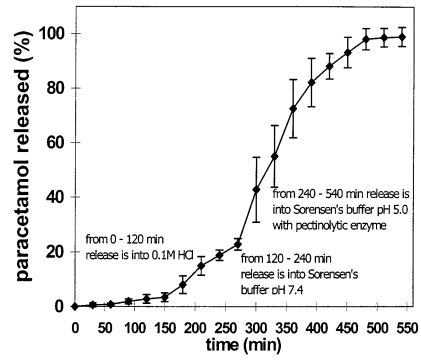

Fig. 4. Release of paracetamol (%) versus time (min) from P:C:H-coated tablets with no disintegrant in conditions intended to simulate GIT transit; $n = 6$; error bars, $\pm$ S.D.

4. Conclusion

This work has shown that tablet systems coated with films composed of pectin, chitosan and HPMC offer potential both as colonic and bimodal drug delivery systems.

It is possible by careful formulation of the tablet core to achieve different drug release profiles whereby an increase in the amount of drug released can be induced by the action of pectinolytic enzymes. By changing other variables, such as the pectin:chitosan ratio or the molecular weight of the polymers, it may be possible to produce a system with a release profile which is tailored to meet the particular requirements of any individual drug.

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