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Pectin/chitosan mixtures as coatings for colon-specific drug delivery: an in vitro evaluation

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Abstract

The ability of a multiple-unit dosage form to reach the colon intact has been investigated, in vitro, using conditions chosen to simulate the pH and times likely to be encountered during transit to the colon. Small tablets were coated with either pectin USP or pectin in a 1:10 mixture with chitosan. Indomethacin and paracetamol were used as model drugs to represent poorly soluble and soluble compounds. Pectin alone was able to protect the cores from premature release, but only when a substantially thick coat was present. Pectin/chitosan mixtures achieved better protection at a lower coat weight. The use of pectinolytic enzymes to simulate breakdown in the colon showed that the pectin/chitosan mixture was susceptible to enzymic breakdown and allowed drug release to occur. The importance of pre-exposure of the tablets to conditions in the upper gastro-intestinal tract prior to exposure to the enzyme was noted.

Keywords: Colonic drug delivery; Pectin; Chitosan; Enzymic breakdown

1. Introduction

Site-specific targeting of drugs to the colon has been attempted by several different approaches (Ashford and Fell, 1994). Of these, utilisation of the bacterial population, existing almost exclusively in the colon, as a means of targeting offers considerable promise (Rubinstein et al., 1993; Milojevic et al., 1996). Multiple-unit systems have been shown to spread out on entry to the colon (Hardy et al., 1989) and this may give improvements in drug absorption and local treatment. Additionally, the higher surface area of multiple unit systems should lead to a more rapid release of drug due to more rapid bacterial breakdown. The transit of dosage forms in the upper gastrointestinal tract is also a consideration in colonic delivery as delays expose the material to longer periods of time in a harsh environment. In

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this regard also, multiple-unit systems may empty from the stomach and traverse the ileo-caecal junction in a more reproducible manner than single units.

The potential of pectin as a carrier for colonic drug delivery has been demonstrated previously (Ashford et al., 1993). The use of high-methoxy pectin or cross-linking with calcium have been investigated as methods for reducing the inherent solubility. An alternative approach is to form an interpolymer complex with chitosan in a similar manner to that investigated by Meshali and Gabr (1993).

Chitosan itself has been shown to be of value in colonic delivery. Enteric-coated chitosan capsules (to prevent solubility at low pH) have been used to enhance the delivery of insulin. Chitosan is degraded by the colonic microflora, allowing release of the active principle (Tozaki et al., 1997). An interpolymer complex of pectin and chitosan may thus prove valuable both in restricting drug release in the upper gastro-intestinal tract and allowing rapid release in the colon.

This paper reports an in vitro investigation of the potential of pectin/chitosan mixtures in colonic drug delivery using compression coated 'mini' tablets as a model for a multiple-unit system.

2. Materials and methods

2.1. Materials

The following materials were obtained from the indicated sources. Pectin USP (DM 70%) (Citrus Colloids UK); chitosan (Practical Grade, Sigma Chemical Co., UK), sieved to obtain a 180–250-μm fraction; lactose, magnesium stearate, potassium dihydrogen orthophosphate, disodium orthophosphate (all BDH Chemicals, UK); indomethacin and paracetamol (Sigma); Pectinex Ultra SP-L, 30925 PG/ml at pH 3.5 (Novo Nordisk Ferment, Switzerland). The final material was a mixture of pectinolytic enzymes obtained from *Aspergillus niger* and used to mimic conditions in the colon.

2.2. Preparation of compression-coated tablets

Core tablets of 3 mm diameter were prepared using flat-faced punches from 10 mg of powder mixture under a compression force of 1000 kg using a hydraulic press (Beckman, model 16, UK). The composition of the cores is given in Table 1. To prepare the coated tablets, half the quantity of the coat formulation was placed in a 5-mm die. The core tablet was carefully positioned in the centre of the die and the remaining coat material added. The coat was compressed around the core using normal concave punches at a compression force of 3000 kg. The compositions of the different coating formulations are shown in Table 2. The thicknesses of the cores and the final coated tablets was measured to 0.001 mm using a micrometer.

2.3. Dissolution testing

Dissolution testing was carried out on single tablets under conditions chosen to simulate the gastrointestinal tract. Testing was carried out using the BP (1993) apparatus 2 (Caleva 8ST, UK), with 700 ml medium, maintained at 37° and using a paddle speed of 50 rpm. The media used were: 0.1 M HCl, pH 1.1; Sorensen's phosphate buffer, pH 7.4; Sorensen's phosphate buffer, pH 6, in the absence or presence of 1 ml pectinolytic enzymes. The results are the mean of six determinations.

3. Results and discussion

Dissolution studies were carried out in pH 1.1 for 2 h, immediately followed by pH 7.4 for 3 h to

Table 1
Composition of the core tablets

Materials	Formulation 1 (mg)	Formulation 2 (mg)
Indomethacin	7.43	—
Paracetamol	—	3.37
Lactose	2.47	6.53
Magnesium stearate	0.10	0.10

Table 2
Composition of the coated tablets

Coat type	Drug type	Ratio, core:coat	Coat thickness (mm)
Pectin USP	Indomethacin	1:5	1.75 ± 0.04
Pectin USP	Indomethacin	1:8	2.43 ± 0.007
Pectin USP	Indomethacin	1:10	3.51 ± 0.007
Chitosan/pectin (1:10)	Indomethacin	1:5	1.59 ± 0.08
Chitosan/pectin (1:10)	Paracetamol	1:5	1.48 ± 0.16

simulate the transit times and pH conditions pertaining in the upper gastrointestinal tract. Indomethacin was used to represent a relatively insoluble drug, and paracetamol a relatively soluble one. The results for pectin-coated indomethacin tablets are given in Fig. 1. During the testing of these tablets it was observed that, in the batches with the two lower core/coat ratios, disintegration of the coat took place, although the low solubility of the indomethacin limited the drug release. The tablets made with the highest coat thickness remained intact throughout the testing period and exhibited the lowest release. These results are in agreement to those obtained earlier with larger tablets (Ashford et al., 1993). The problem with this successful formulation is the high coat weight required to protect the core. Meshali and Gabr (1993) investigated the interaction between pectin and chitosan and showed that a maximum interaction occurred at a weight ratio of 10 pectin/1 chitosan. This mixture was used to coat both indomethacin and paracetamol cores, the latter used to provide a more stringent test of the coat's protective ability. Little release of indomethacin was detected at any core/coat ratio. The results shown in Fig. 2 are for paracetamol and indicate that the mixed polymer coat, relative to pectin at the same coat thickness, substantially retards drug release.

Chitosan is a polysaccharide prepared from the chitin of crabs and lobsters by *N*-deacetylation with alkali. Chitosan is ionised ($pK_a = 6.0$) at pH 1.1 as, to some extent, is pectin ($pK_a \approx 3.0$). Both materials are soluble at this pH and an interaction would be expected between the carboxyl groups of the pectin and the amino groups of the chitosan (Meshali and Gabr, 1993). In basic medium, the protection offered by the coat should be mainly due to the pectin as chitosan is insoluble at this pH. However, this does not take into account that, under conditions pertaining in the gastro-intestinal tract, a gel would be formed at lower pH values, with the pectin/chitosan interaction occurring, and this may behave differently at higher pH

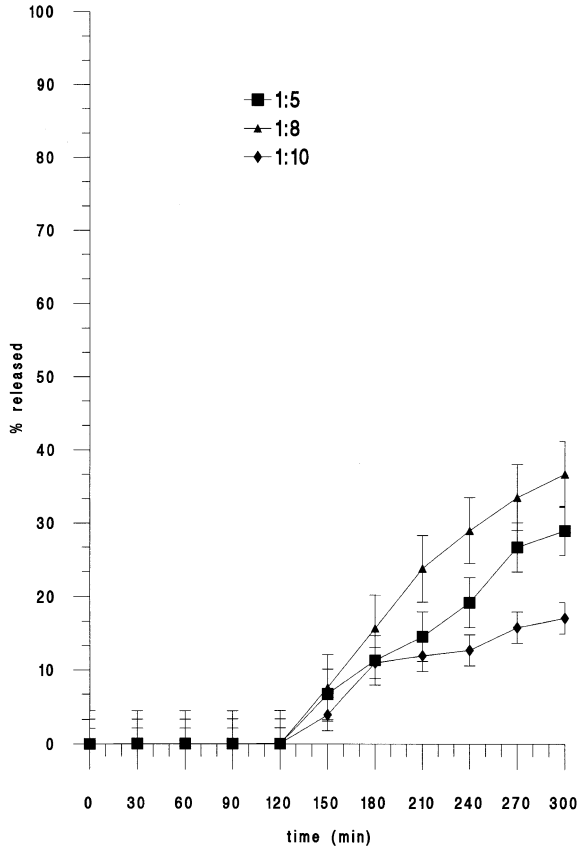

Fig. 1. The release of indomethacin from tablets coated with different pectin weights (pH 1.1, 2 h; pH 7.4, 3 h; core to coat ratios, 1:5, 1:8, 1:10).

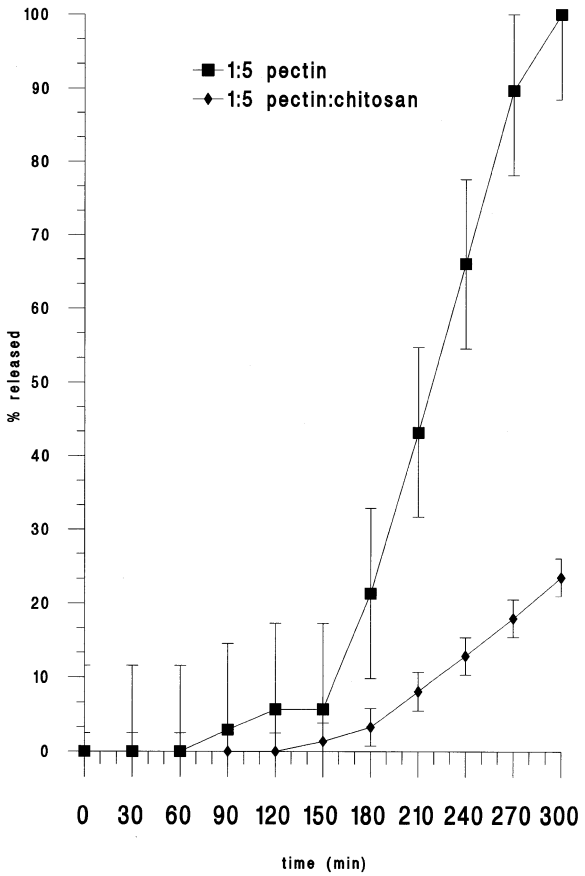

Fig. 2. The release of paracetamol from tablets coated with pectin and a pectin/chitosan mixture (core/coat ratio, 1:5).

values than if the dry coat is subjected directly to a higher pH. Dissolution testing to examine the behaviour in the colon must take this into account.

Fig. 3 shows the drug release profiles from experiments where the tablets were subjected to 2 h at pH 1.1, 3 h at pH 7.4 and then placed in pH 6 buffer containing pectinolytic enzymes. The protection of indomethacin from early release can again be noted, followed by a marked acceleration in release when the tablets are exposed to enzyme. This implies that the pectin is available for degradation in the mixed coat and that breakdown of the coat allows enhanced drug release. A similar effect is seen for paracetamol, except that the higher solubility of this drug allows substantial release in the absence of enzymic degradation. The importance of allowing exposure of the tablets to conditions similar to those in the upper gastro-intestinal tract prior to testing with enzymes can be seen from Fig. 4. This shows release of indomethacin at pH 6 in the presence of enzymes, with and without preconditioning. The higher release rate in the presence of enzymes after preconditioning stresses the importance of hydration for enzyme activity and highlights that the coat protects the drug from premature release and is converted to a system that is readily attacked by enzymes.

4. Conclusions

Pectin/chitosan compression-coated tablets offer a greater degree of protection from premature drug release in the upper GI tract than pectin

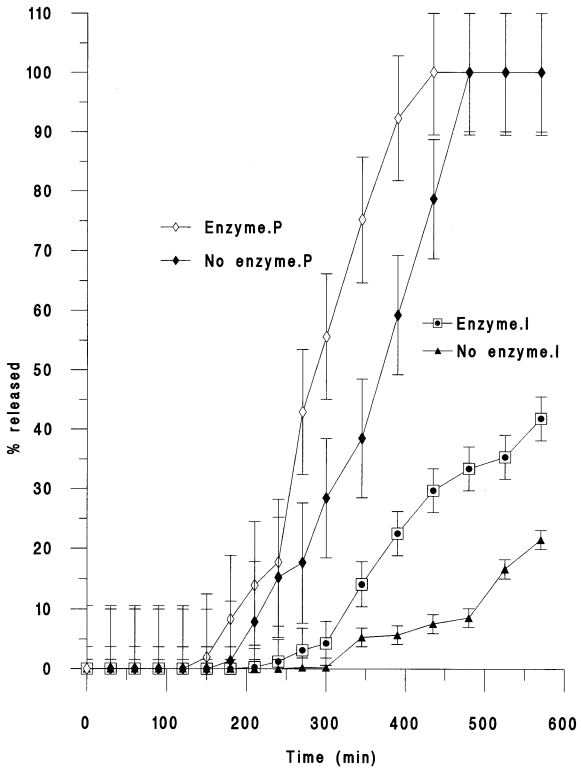

Fig. 3. The release of indomethacin (I) and paracetamol (P) in conditions simulating gastro-intestinal transit (pH 1.1, 2 h; pH 7.4, 3 h; pH 6, with and without pectinolytic enzymes; core/coat ratio, 1:5 (pectin/chitosan coat)).

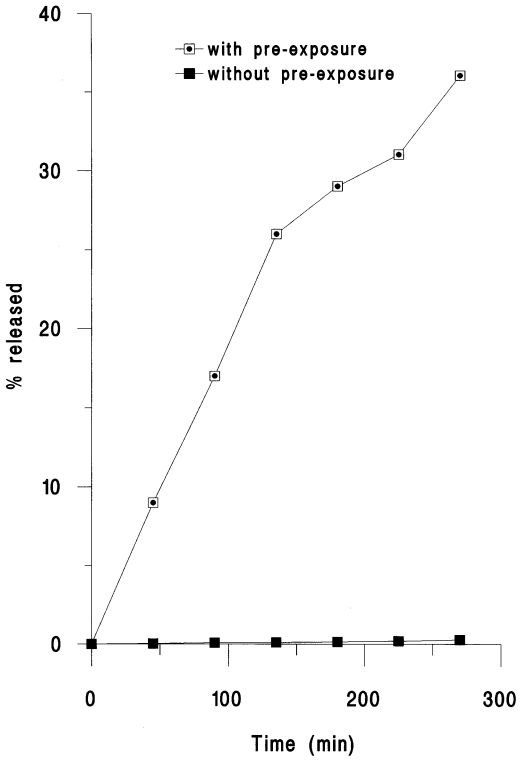

Fig. 4. The release of indomethacin at pH 6 in the presence of enzymes with and without pre-exposure (core/coat ratio, 1:5 (pectin/chitosan coat)).

alone. The pectin is still available for enzymic degradation which allows greater drug release under conditions that may be expected to pertain in the colon. The coat is successful at protecting and then releasing relatively insoluble compounds, soluble materials show premature release in conditions analogous to those in the upper gastrointestinal tract.

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