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Studies on Amidated Pectins as Potential Carriers in Colonic Drug Delivery

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Abstract

Amidated pectins have been assessed, in-vitro, for their potential value in colonic drug delivery. The monitoring of the release of a model soluble drug, paracetamol, gives a sensitive indication of the behaviour of the pectins under simulated gastrointestinal conditions.

Inclusion of calcium as a cross-linking agent increased the viscosities of amidated pectin gels to a maximum value. Further addition of calcium reduced gel viscosity and for pectin with a high extent of amidation this led to a reduction in drug release. Release was faster for pectin with less amidation in the presence of calcium; this could be related to matrix erosion.

The results of the study suggest that the materials might be of value in colonic delivery either alone or in combination, possibly in the form of a coating.

Several studies have established that pectin might be a potentially valuable material in the formulation of an oral dosage form designed for release in the colon (Ashford et al 1993; Rubinstein et al 1993).

The changing conditions encountered in the gastrointestinal tract place demands on the tolerance of any material used to achieve colonic delivery. For pectin these demands can to some extent be met by using a high-methoxy pectin or by forming the calcium salt.

Amidated pectins are pectins in which the galacturonic acid units are either methoxylated or amidated. The extent to which this occurs can be varied and is expressed by the degree of methoxylation or amidation, this being the average number of substituent groups per 100 galacturonic acid units. The two substituents confer different properties on the pectins; amidated pectins are perhaps the more tolerant to pH variations and fluctuations in calcium levels. They are also susceptible to enzymatic breakdown (Wakerly 1995). They might, therefore, be of value in colonic delivery. This paper reports the results of a study designed to investigate the potential of amidated pectins for colonic delivery. The release of a model drug, paracetamol, from matrix tablets under conditions mimicking mouth-to-colon transit is assessed and analysed in terms of the water uptake by the tablets and the rheological properties of the pectins.

Materials and Methods

Materials

Citrus pectins type 920 and 4200 were a gift from Citrus Colloids, Hereford, UK. Pectin type 920 has a degree of amidation of 24% and a degree of methoxylation of 24%; pectin type 4200 has a much lower degree of amidation (13%). Paracetamol was from Sigma (Poole, UK) and calcium chloride was from BDH (Poole, UK). All other materials were of laboratory reagent grade.

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Matrix tablets

Tablets (300 mg) were compressed individually in a 12-mm die using flat-faced punches at 4000 kg. The tablets contained the appropriate pectin, paracetamol (20 mg) and, where necessary, 10 mg Ca^{2+} (g pectin)$^{-1}$.

Rheology

Gels containing 2% w/v amidated pectin and increasing amounts of calcium chloride were prepared in pH 6 Sørensen's phosphate buffer by mixing all the components overnight by use of a magnetic stirrer. The apparent viscosity of each gel was measured at room temperature using a bob-and-cylinder viscometer (Contraves Rheomat RM135, Contraves, Switzerland). Viscosity was measured at nine increasing shear rates each held for 6 s.

Dissolution studies

The release of paracetamol from the matrix tablets was studied at 37°C using a flow-through dissolution system (Sotax, Switzerland) adapted to re-circulate 1 L of dissolution fluid. Drug release was monitored by use of a spectrophotometer programmed to record the UV absorbance at the wavelength of maximum absorption (243 nm).

Hydration studies

The increase in weight of tablets individually placed on wire mesh supports in distilled water (pH 5·6) was monitored with time. At suitable intervals, the tablets were removed from the water, blotted dry and weighed.

Results and Discussion

Figs 1 and 2 show the relationship between apparent viscosity and calcium levels at different shear rates, for the two amidated pectins. Pectin 920, with the greater degree of amidation,

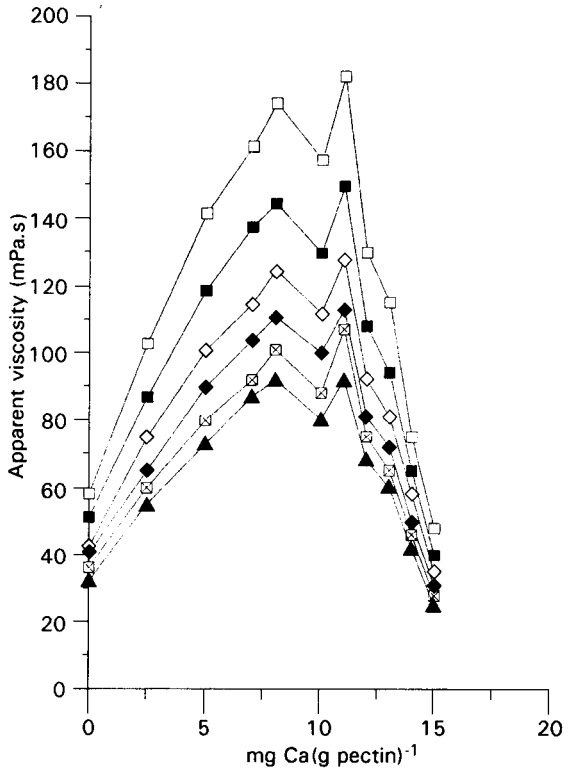

FIG. 1. Effect of calcium on apparent viscosity of 2% pectin 920 gels in pH 6 Sørensen's phosphate buffer at different shear rates (s^{-1}). □ = 44·5, ■ = 55·6, ◇ = 66·7, ◆ = 77·8, ☒ = 88·9, ▲ = 100.

formed the stronger gels. In both cases the addition of calcium increased the strength of the gels up to a maximum at approximately 12·5 mg Ca^{2+} (g pectin)$^{-1}$. Further calcium resulted in a reduction in strength. The optimum amount of calcium for maximum gel strength was similar to that found by Ashford et al (1994) for non-amidated pectin with a similar level of free carboxyl groups. Calcium causes low methoxy pectins to gel by cross-linking the carboxyl groups on adjacent pectin chains, resulting in the so called 'egg box' structure (Grant et al 1973). Increasing amounts of calcium will lead to a greater degree of cross-linking and aggregation of the initial dimers giving a higher gel strength. Excess calcium causes a phenomenon known as pre-gelation where localized areas of solidified pectin are formed in a watery matrix. This is reflected in the current studies by a reduction in apparent viscosity.

The release of paracetamol from the pectin/drug matrices in pH 6 buffer is shown in Figs 3 and 4. Calcium delays the release of drug from pectin 920 matrices (Fig. 3) but accelerates it from pectin 4200 matrices (Fig. 4). For matrices without calcium, the release of drug is faster from the pectin matrix with the higher degree of amidation.

Drug release from hydrophilic matrices such as those used in the current study will be controlled by the rate of hydration of the matrix and the properties of the gel formed on hydration, which influence drug diffusion and gel erosion. Although the rheological studies performed on the pectin solutions are not sufficiently comprehensive for full characterization of the structure (Talukdar et al 1996), there are clear enough differences between the materials and between calcium levels to

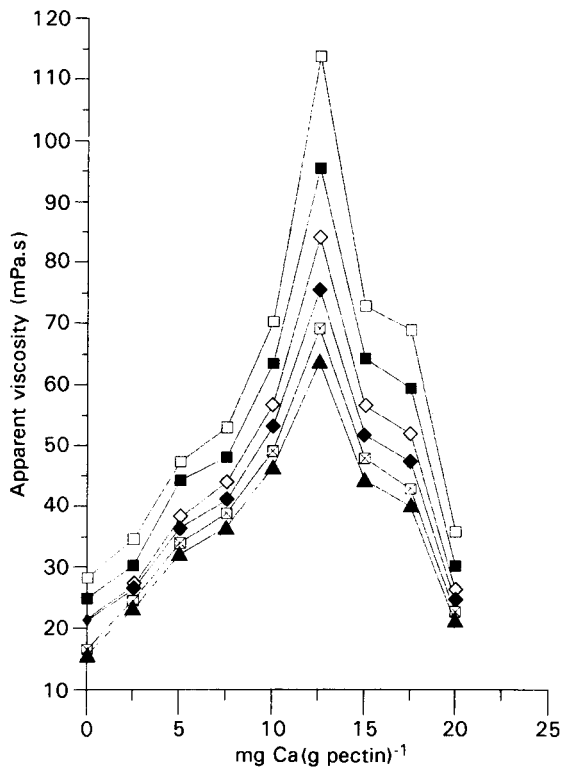

FIG. 2. Effect of calcium on apparent viscosity of 2% pectin 4200 gels in pH 6 Sørensen's phosphate buffer at different shear rates (s^{-1}). □ = 44·5, ■ = 55·6, ◇ = 66·7, ◆ = 77·8, ☒ = 88·9, ▲ = 100.

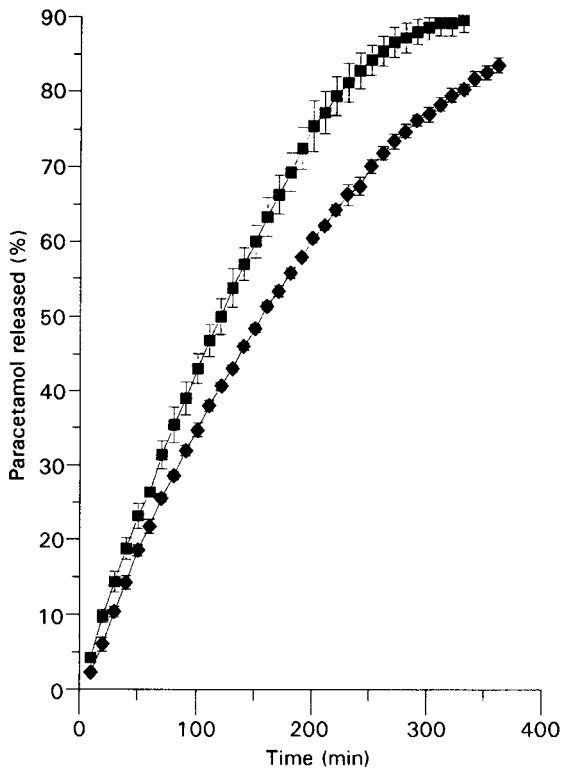

FIG. 3. Effect of calcium on release of paracetamol from pectin 920 drug matrices in pH 6 Sørensen's phosphate buffer (bars indicate s.d.; n = 3). ■ = no calcium, ◆ = calcium.

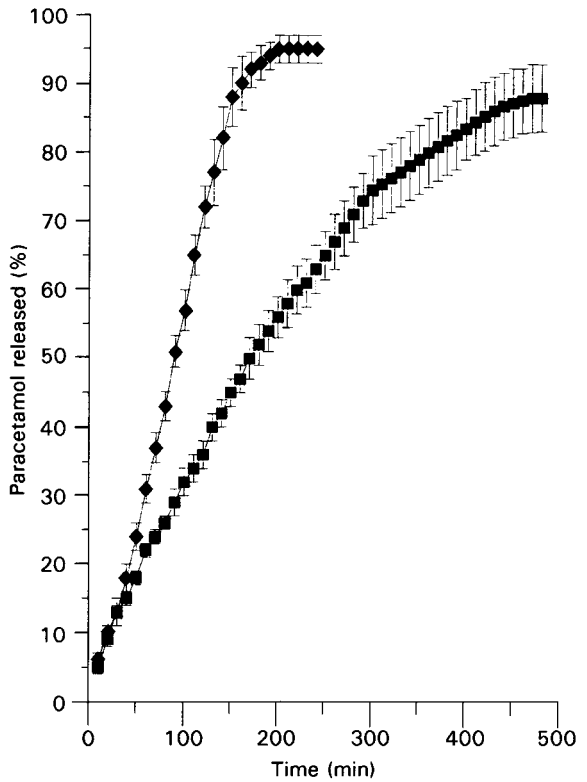

FIG. 4. Effect of calcium on release of paracetamol from pectin 4200 drug matrices in pH 6 Sørensen's phosphate buffer (bars indicate s.d.; n = 3). ■ = no calcium, ◆ = calcium.

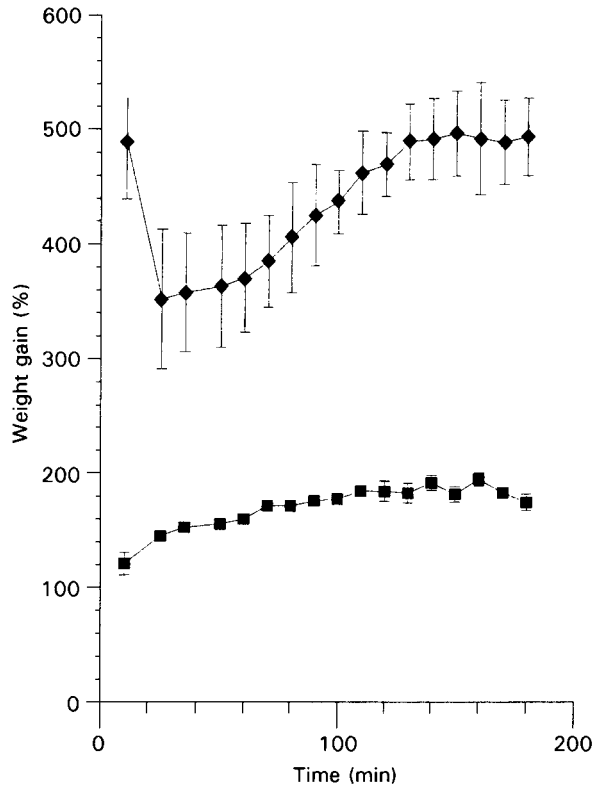

FIG. 5. Effect of calcium on hydration of pectin 920 matrices in distilled water (bars indicate s.d.; n = 3). ■ = no calcium, ◆ = calcium.

imply a relationship between drug release and the apparent viscosity of the gels. This is indeed so for the materials without calcium where the pectin with the higher degree of amidation (producing gels of higher viscosity) releases the drug more slowly than pectin 4200. It is also true for pectin 920 with calcium added at a level sufficient to achieve an optimum increase in gel viscosity; drug release is retarded from these matrices. The argument does not hold for the pectin 4200 matrices with calcium; for these, despite the higher viscosity, drug release is faster.

The other factor involved in controlling drug release is the rate of hydration of the matrices. The hydration rates are shown as graphs of weight gain (%) against time in Figs 5 and 6. Rapid hydration is required to establish the gel layer and prevent the release of an initial burst of drug. Thereafter, the thicker the gel layer, the longer is the diffusional path for the drug molecules, and the stronger the gel the less will be its susceptibility to erosion. The changes in weight shown in Figs 5 and 6 are a result of a combination of swelling and erosion. Pectin 920 hydrates rapidly, particularly in the presence of calcium, to form a viscous gel which does not visibly erode. Pectin 4200 hydrates to a similar extent, but in the presence of calcium erosion of the matrix is observed; this accounts for the higher release of drug from these matrices.

Drug release into 0·1 M HCl (to simulate the acidic conditions of the stomach) is shown in Figs 7 and 8. Calcium increases drug release from both because pre-gelation of the pectin causes cracking and erosion of the matrices.

The experiments described in this paper used release from matrices as an indicator of the behaviour of the amidated

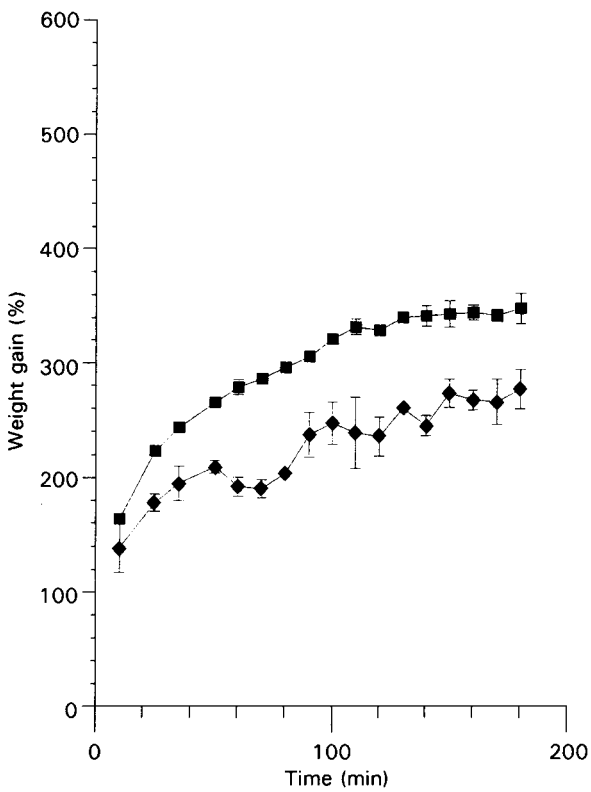

FIG. 6. Effect of calcium on hydration of pectin 4200 matrices in distilled water. (bars indicate s.d., n = 3). ■ = no calcium, ◆ = calcium.

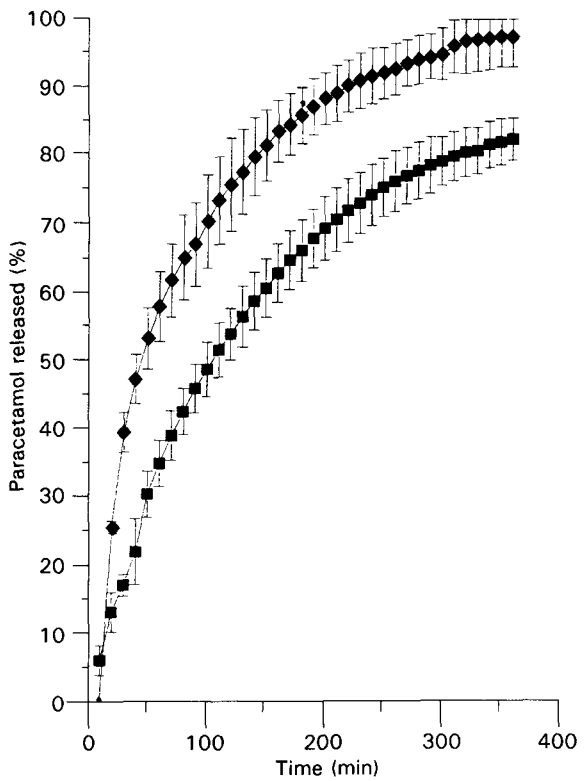

FIG. 7. Effect of calcium on release of paracetamol from pectin 920 drug matrices in 0·1 M HCl (bars indicate s.d.; n = 3). ■ = no calcium, ◆ = calcium.

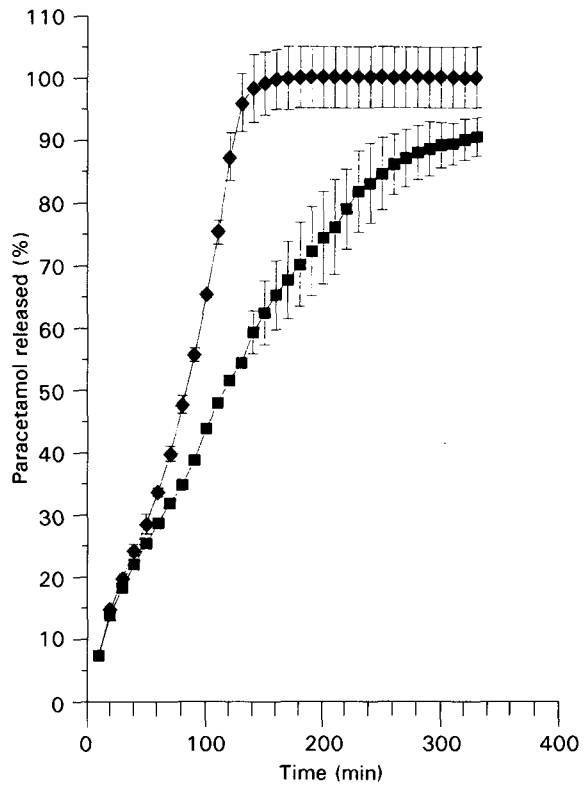

FIG. 8. Effect of calcium on release of paracetamol from pectin 4200 drug matrices in 0·1 M HCl (bars indicate s.d.; n = 3). ■ = no calcium, ◆ = calcium.

pectins under conditions likely to be encountered in the gastrointestinal tract. The matrices are not suitable for colonic delivery because they would result in too high a level of drug release before entry into the colon. The two pectins investigated have different properties and different susceptibilities to calcium added to aid gelation. Pectin 920 forms strong gels, aided by the addition of calcium, which have drug release retarding properties. This pectin might, therefore, be useful either alone or in combination with other materials as a compression coat to achieve a colon-specific dosage form.

Acknowledgements

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References

Ashford, M., Fell, J., Attwood, D., Sharma, H., Woodhead, P. (1993) An evaluation of pectin as a carrier for drug targeting to the colon. J. Contr. Rel. 26: 213–200

Ashford, M., Fell, J., Attwood, D., Sharma, H., Woodhead, P. (1994) Studies on pectin formulations for colonic drug delivery. J. Contr. Rel. 30: 225–232

Grant, G. T., Morris, E. R., Rees, D. A., Smith, P. J. C., Thom, D. (1973) Biological interactions between polysaccharides and divalent cations. The egg box model. FEBS Lett. 32: 195–198

Rubinstein, A., Radai, R., Ezra, M., Pathak, S., Rokem, J. S. (1993) In-vitro evaluation of calcium pectinate: a potential colon-specific drug-delivery carrier. Pharm. Res. 10: 258–263

Talukdar, M. M., Vinekier, I., Moldenaers, P., Kinget, R. (1996) Rheological characterization of xanthan gum and hydroxypropylmethyl cellulose with respect to controlled-release drug delivery. J. Pharm. Sci. 85: 537–540

Wakerly, Z. (1995) An Investigation into Citrus Pectins for Colonic Drug Delivery. PhD Thesis. University of Manchester