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International Journal of Pharmaceutics 153 (1997) 219–224

international journal of pharmaceutics

Studies on drug release from pectin/ethylcellulose film-coated tablets: a potential colonic delivery system

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Received 10 February 1997; received in revised form 7 April 1997; accepted 14 April 1997

Abstract

Combinations of pectin and ethylcellulose, when applied as a film coat, have potential value as a colonic delivery system. Aqueous dispersions of pectin and ethylcellulose were used to film coat paracetamol tablet cores. Drug release mechanisms were assessed using flow through dissolution testing in the presence and absence of enzymes. Drug release from the coated systems was complex and depended on the nature and characteristics of the mixed film as well as the composition of the dissolution medium. Drug release profiles were compatible with a mechanism involving the formation of channels in the film caused by pectin dissolution. Channel formation was in most cases accelerated by the presence of pectinolytic enzymes showing that the pectin in the mixed film was susceptible to enzymic attack. Pectin, ethylcellulose combinations may have value as film coating preparations for colonic delivery. Formulation effects and mechanisms of drug release have been identified as a basis for further studies. © 1997 Elsevier Science B.V.

Keywords: Colonic delivery; Film coating; Pectin; Ethylcellulose; Enzymic breakdown

1. Introduction

Oral drug delivery systems designed to release drugs in the colon need to protect the drug during transit through the stomach and small intestine before allowing rapid release on entry into the colon. Bacterially degraded polysaccharides, particularly pectin, have been shown to have potential value for such systems. (Ashford et al., 1993; Rubinstein et al., 1993). One problem with the use of pectin alone is its solubility. Although pectin with a high degree of methoxylation (HM) has proved successful as a compression coat on tablets (Ashford et al., 1993), this approach is not applicable to other dosage forms.

Recently, Wakerly et al. (1996) have shown that combinations of pectin and ethylcellulose applied as a film coat may offer a potential approach to a more universal 'colonic coating'. This paper re-

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PII S0378-5173(97)00110-5

ports investigations into some factors affecting drug release in simulated colonic conditions from tablets coated with ethylcellulose/pectin mixtures.

2. Experimental

2.1. Materials

Ethylcellulose was used in the form of Surelease® and was a gift from Colorcon Ltd. (Orpington, UK); it was used as received. Pectin USP was a gift from Citrus Colloids (Hereford, UK). Paracetamol was supplied by the Sigma Chemical Company Ltd. (Poole, UK). Emdex®, a soluble direct compression material consisting of dextrose and maltodextrin, was a gift from Edward Mendell Company Inc. (Reigate, UK). Magnesium stearate was supplied by SKF (Welwyn Garden City, UK). Pectinex Ultra SP-L was supplied by Novo Nordisk Ferment Ltd. (Dittingen, Switzerland) and had an activity of 26 000 PG/ml at pH 3.5. All other materials used in the dissolution studies were of analytical reagent grade.

3. Methods

3.1. Paracetamol tablet manufacture

Tablets were prepared from a direct compression blend of paracetamol (4.54%), Emdex (95.46%) and magnesium stearate (1%). Tablet compression was performed using four stations of a 16-station rotary tablet machine (B3B, Manesty Ltd., Liverpool, UK) fitted with half-inch diameter, normal biconcave punch and die sets. Tablets of 550 mg were produced within chosen limits (<2 tablets $\pm$ 5% of mean weight, and none $\pm$ 10% of mean) and with a minimum hardness of 8 kp; tested using a Schleuniger hardness tester (Model 2E/205, Schleuniger and Co., Switzerland). Samples were taken continually throughout manufacture to ensure compliance. The resulting tablets, each containing approximately 25 mg of paracetamol, were stored in a large drum at room temperature until required. Details of the assessment of blend uniformity of the mix and content uniformity of the tablets have been given previously (Wakerly et al., 1996).

Table 1
Composition of the film coats

Component	60S:40P (%)	50S:50P (%)	40S:60P (%)
Surelease™ (S)	40.0	33.3	26.7
2% Pectin USP (P)	26.7	33.3	40.0
Distilled water	33.3	33.3	33.3

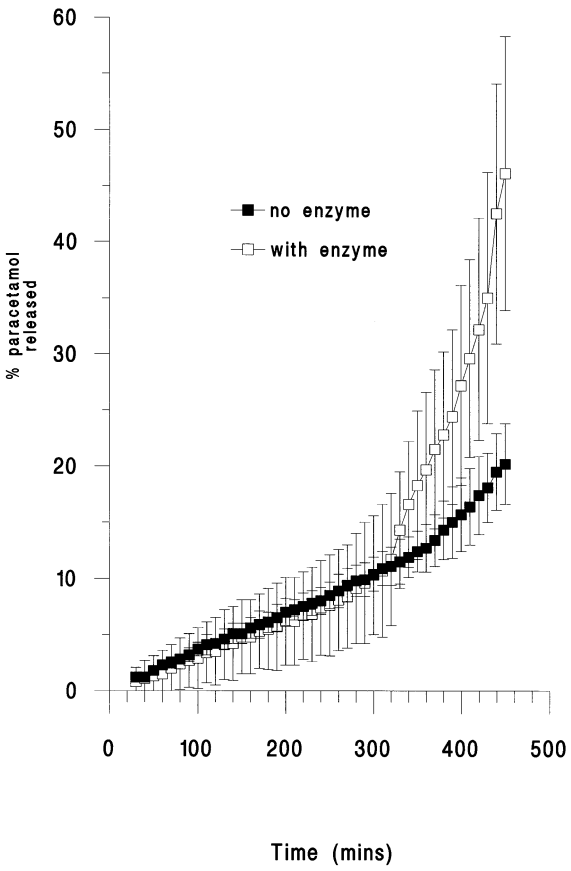

Fig. 1. Effect of Pectinex™ on release of paracetamol from 50S:50P 20 mg film-coated tablets. Mean ($n = 3$) with S.D.

3.2. Film coating

A 2% w/v solution of pectin USP in distilled water was prepared and blended with distilled water and Surelease® in various proportions, to give three coat formulations (Table 1). The tablets were coated using a fluid bed spray coater (Strea-1, Aeromatic A.G. Switzerland). The outlet temperature was set at 75°C and the coating solution was applied through a 1.1 mm spray nozzle at 2 g/min. Samples were taken periodically throughout a run to give different coating thicknesses. All tablets were stored in plastic bags at room temperature until required.

3.3. Dissolution testing

Dissolution studies were carried out at 37°C using a flow through dissolution system adapted to recirculate 1 l of dissolution fluid (Sotax, Switzerland). The fluid was recirculated to the dissolution cell (22.6 mm diam., 16 ml/min) via a flow through recording spectrophotometer set at the wavelength of maximum absorbance (243 nm). Dissolution studies were carried out in pH 6 Sorensen's phosphate buffer with or without the addition of 3 ml enzymes.

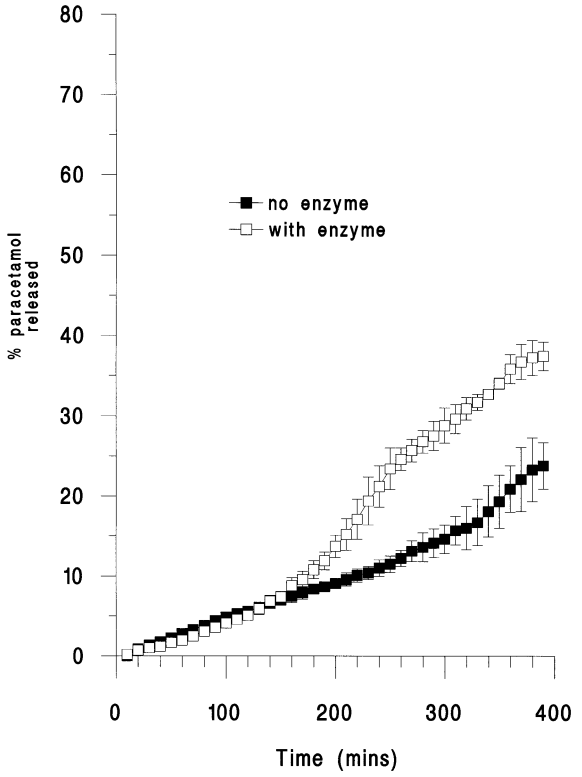

Fig. 2. Effect of Pectinex™ on release of paracetamol from 50S:50P film-coated tablets in pH 6 buffer; 14 mg coat weight. Mean ($n = 3$) with S.D.

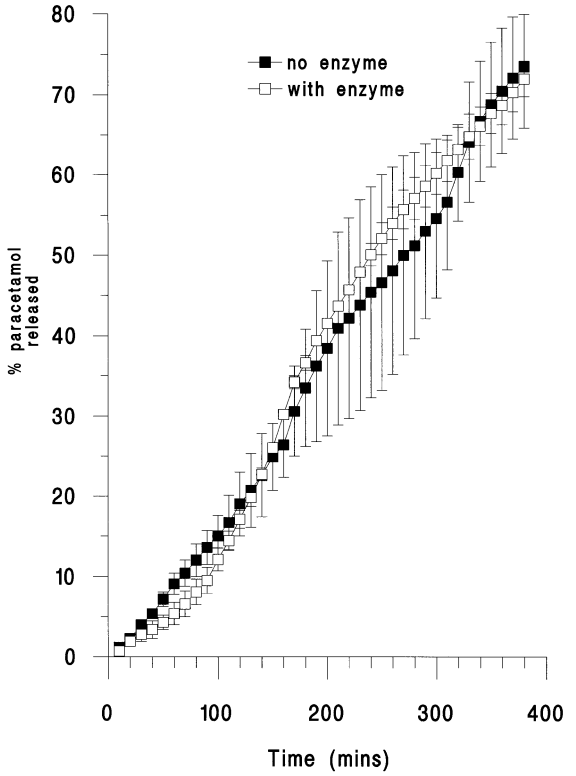

Fig. 3. Effect of Pectinex™ on release of paracetamol from 50S:50P film-coated tablets in pH 6 buffer; 10 mg coat weight. Mean ($n = 3$) with S.D.

4. Results and discussion

Release profiles from tablets tested at pH 6.0, with and without enzymes, show that Pectinex™ can degrade the pectin within the film coat, but an increase in release rate is only observed after approximately 5.5 h (Fig. 1). Several mechanisms have been proposed to explain the release of drugs from dosage forms coated with water insoluble

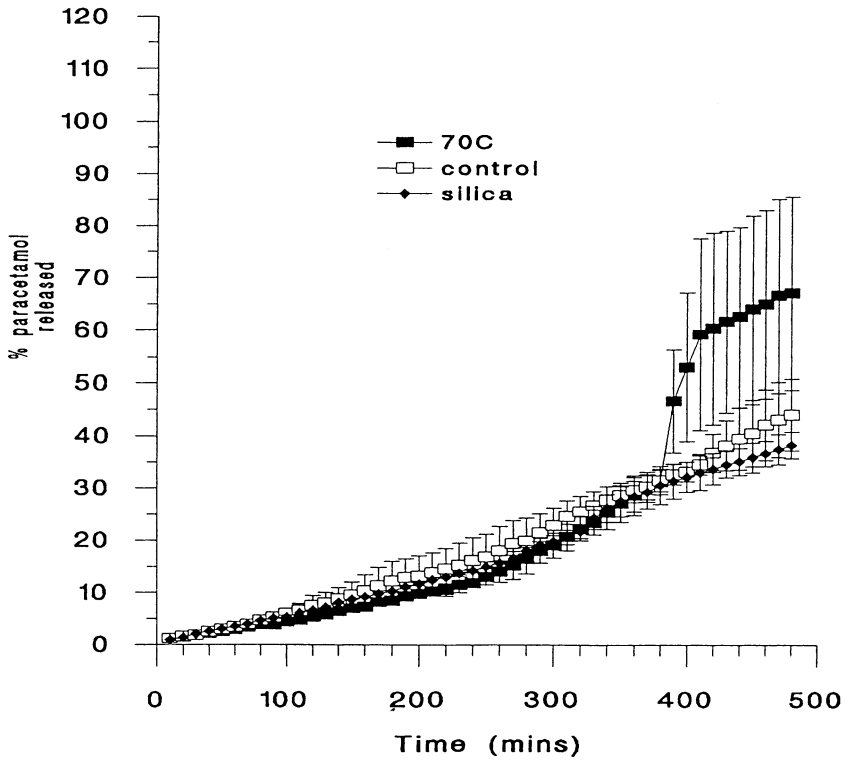

Fig. 4. Effect of storage on release of paracetamol from 40S:60P, 28 mg film-coated tablets in pH 6 buffer. Mean ($n = 3$) with S.D.

polymers. These are: diffusion through a continuous plasticised polymer phase; diffusion through plasticiser channels; diffusion through aqueous pores and osmotically driven release.

Diffusion of drug through plasticiser channels has been shown to be of little importance in these systems (Ozturk et al., 1990). Drug release from the current film-coated tablets will be complicated by the presence of pectin in the film coat. The addition of water soluble polymers such as pectin to an insoluble base can lead to the formation of aqueous pores in the film due to the polymer dissolving and leaching out into the surrounding medium (Rowe, 1985). This would lead to a gradual increase in drug release rate as the pectin dissolves. If the pectin does not dissolve, paracetamol may diffuse through ethylcellulose or pectin, and the release rate will then depend on the solubility of the drug in each polymer.

Osmotically driven release has been shown to be of major importance in dosage forms coated with ethylcellulose-based pseudolatex (Ozturk et al., 1990; Rekhi et al., 1989) and in ethylcellulose-based films containing the water soluble excipient HPMC (Miller et al., 1984). The core excipient used in the current study, dextrose and maltodextrin, will exert an osmotic pressure as it dissolves, providing the film coat remains intact. As coat integrity was observed for long periods during dissolution testing, therefore this mechanism of release is likely to be significant.

The initial stage of drug release is probably due to diffusion through the ethylcellulose phase. It is postulated that the pectin in the film dissolves slowly, as it is known to do in aqueous solution. When the pectin is fully dissolved it will leave channels through which drug can diffuse, leading to an increase in release. The dissolution of pectin is therefore rate-limiting. In addition, there is probably a significant contribution from osmotic release as the drug/excipient core gradually dissolves.

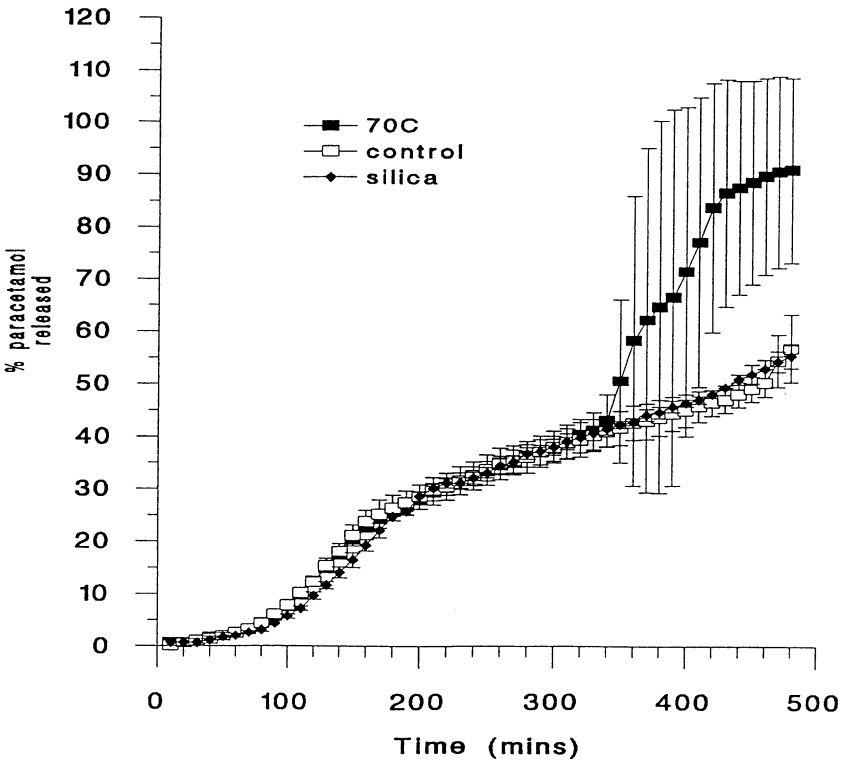

Fig. 5. Effect of storage on release of paracetamol from 40S:60P, 28 mg film-coated tablets in pH 6 buffer containing Pectinex™. Mean ($n = 3$) with S.D.

The drug release profile of the tablets in pH 6 buffer alone (Fig. 1) fits this explanation, with the rate of paracetamol release increasing towards the end of the experiment. The presence of pectinolytic enzymes simply accelerates pore formation by attacking the pectin and therefore enhancing breakdown. If this postulate is correct, dissolution rates will eventually be almost equal, as drug release will be through the same pores. Any differences in release rates will then be due to the amount of core remaining, and the osmotic pressure exerted by it.

This experiment confirms that the pectin in the mixed film coat is available for enzymatic attack. Differences in release due to enzymic breakdown should be detected sooner with thinner film coats since channels to the core caused by dissolving and degrading pectin will be formed quicker. Dissolution profiles for lower coat weights are shown in Figs. 2 and 3.

Tablets coated with 14 mg ethylcellulose/pectin film show an increase in paracetamol release in the presence of pectinolytic enzymes after approximately 80 min (Fig. 2). After about 250 min, the rate of paracetamol release levels out, and becomes similar to that seen without enzymes after 320 min (slope (% released/min) with enzymes 0.1020, without: 0.1175). This is consistent with the postulated release mechanism; diffusion through ethylcellulose while the pectin dissolves, then diffusion through channels left by the pectin. Tablets coated with 10-mg film, however, show no increase in paracetamol release in the presence of enzymes as the coat is thin enough to allow the rapid formation of pores connecting to the core (Fig. 3).

The high inter-tablet variation in release rates exhibited in these studies could be due to incomplete film formation, as noted by Lippold et al. (1989). The tablet cores were shown previously to

have uniform properties (Wakerly et al., 1996). Thermal treatment of ethylcellulose coated tablets has been shown to improve film consistency by reducing permeability (Lippold et al., 1989). The release profiles obtained for tablets stored over silica gel and cured at 70°C for 1 h are shown in Figs. 4 and 5.

Up to approximately 6 h, there were no appreciable differences either with or without enzymes, showing that drying at room temperature or storage at 70°C had little effect on the film properties. However, after 6 h the release of paracetamol from tablets cured at 70°C accelerated rapidly, correlating with the observation that some tablets had split. This lead to a wide variation in the amount of drug released. This acceleration in release is observed earlier in media containing enzymes, consistent with enzyme degradation of pectin within the film. The splitting of the film must be a reflection of instability or stress within the film and may be related to core swelling during the curing process. The thickness of tablets prior to curing was 4.86 ± 0.03 mm ($n = 10$) whereas after curing it was 4.99 ± 0.09 mm ($n = 10$). This expansion presumably places a stress on the film which leads to splitting during dissolution.

The results of this study have shown that pectin/ethylcellulose combinations, when used as film coating agents, may have value in colonic drug delivery. Potential mechanisms of drug release and enzymic attack have been identified and formulation parameters influencing these have been investigated. Further work based on these studies is in progress to fully evaluate the system.

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Acknowledgements

We wish to thank GlaxoWellcome (formerly Glaxo Group Research) for the award of a studentship to Zoë Wakerly.

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