# Pectin/Ethylcellulose Film Coating Formulations for Colonic Drug Delivery

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***Purpose.*** The purpose of the study was to investigate the potential of pectin, ethylcellulose combinations as a practical film coating for colonic delivery.

***Methods.*** Combinations of pectin and ethylcellulose, in the form of an aqueous dispersion, were used as coating formulations. Paracetamol cores were used as the substrate. The coatings were assessed by a flow through dissolution system simulating *in vivo* conditions by changes in pH and residence time. Pectinolytic enzymes were used to simulate the bacterial flora of the colon.

***Results.*** Drug release was controlled by the ratio of ethylcellulose to pectin in the film coat. Increasing the proportion of ethylcellulose and increasing the coat weight reduced drug release in pH1 and pH7.4 media. The addition of pectinolytic enzymes to pH6 media increased the release of drug.

***Conclusions.*** Combinations of ethylcellulose and pectin can provide protection to a drug in the upper g.i. tract while allowing enzymatic breakdown and drug release in the colon.

**KEY WORDS:** colonic delivery; pectin; ethylcellulose; film coating; enzymic degradation.

## INTRODUCTION

The potential of pectin in oral colonic drug delivery is well established. Compression coats of high methoxy pectins have been used to protect drug cores in mouth to colon transit with some success (1). However these coats are necessarily bulky and not suitable for all dosage forms. In contrast film coating is widely accepted in controlled release technology, and can be applied to a range of dosage forms. The use of pectin in film coating has not been reported; its high water solubility in comparison with traditional film forming polymers make it unsuitable for controlled release films. It may be possible, however, to combine the colon-specific properties of pectin with the protective properties of a water insoluble polymer such as ethylcellulose. This paper describes an investigation into the combined use of pectin and ethylcellulose in a film coat intended for colon-specific drug delivery.

## MATERIALS AND METHODS

### Materials

Ethylcellulose in the form of Surelease®, was a gift from Colorcon Ltd., Orpington, U.K; and was used as received. Pectin USP was a gift from H.P. Bulmer Pectin, Hereford, U.K. Paracetamol was supplied by the Sigma Chemical Company Ltd., Poole, U.K. Emdex® was a gift from Edward Mendell Company Inc., Reigate, U.K. Magnesium stearate was supplied by SKF, Welwyn Garden City, U.K. 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.

### Tablet Manufacture

Tablets were prepared on a Manesty B3B rotary tablet machine (Manesty Ltd., Liverpool, U.K.) using half inch diameter, normal biconcave punches. Direct compression blends of 4.54% paracetamol, 1% magnesium stearate, in Emdex were used. The mixtures were checked for blend uniformity prior to tableting and the tablets for content uniformity using u.v. spectroscopy. Any tablet batches having deviations of greater than ±10% of the mean were rejected. The minimum hardness of the tablets was 8kp (Schleuniger Hardness Tester, Model 2E/205, Switzerland) and the disintegration times were less than 15 min (B.P. 1988).

### Film Coating

One litre of 2% w/v solution of pectin USP (P) in distilled water was prepared and blended with distilled water and Surelease® (S) to give three coat formulations; 60S:40P; 50S:50P; 40S:60P. 1000g of paracetamol tablets were placed in a fluid bed spray granulator (Strea-1, Aeromatic A.G., Switzerland) with an outlet temperature set at 75°C. When the temperature across the tablet bed reached 70°C the coating solution was applied through a 1.1mm spray nozzle at a rate of 2g per minute using a peristaltic pump (502S, Watson Marlow Ltd., Falmouth, U.K.) and one bar atomising pressure.

Samples of approximately 30 tablets were taken periodically, weighed, and the mean coat weight calculated. When the final coat weight had been applied, the spray was turned off and the tablets dried for five minutes. All tablets were stored in plastic bags at room temperature until required.

### Dissolution Testing

Dissolution studies were carried out at 37° using a flow through dissolution system adapted to recirculate 1L of dissolution fluid. The fluid was recirculated to the dissolution cell (22.6mm dia, 16mL/min) via a flow through recording spectrophotometer set at the wavelength of maximum absorbance. Dissolution studies were carried out in 0.1M HCl and in pH 6 (with or without 3mL enzymes per litre) and pH 7.4 Sorensen's phosphate buffer.

## RESULTS

The amount of paracetamol in the core tablets was 22.7mg (S.D. 1.06, C.V. 4.7%). The tablets were compressed to a minimum hardness of 8kp to enable them to withstand the coating process, and disintegration times of 12–14 min reflected this. In 0.1M HCl, the cores released 100% paracetamol within 80 min. Tables I and II give the percentage of paracetamol released after

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**Table I.** Total Paracetamol Released After 6 Hours Dissolution Testing in 0.1 M HCl (n = 3 with SD)

| Coat Composition | % Paracetamol released |
|---|---|
| 40S:60P 14mg | 32.9 ± 3.4 |
| 40S:60P 20mg | 11.3 ± 0.6 |
| 40S:60P 28mg | 5.9 ± 0.8 |
| 50S:50P 10mg | 32.0 ± 5.3 |
| 50S:50P 20mg | 4.1 ± 1.0 |
| 50S:50P 26mg | 3.0 ± 0.9 |
| 50S:50P 32mg | 1.5 ± 0.3 |
| 60S:40P 14mg | 4.8 ± 1.4 |
| 60S:40P 20mg | 2.6 ± 0.3 |

**Table II.** Total Paracetamol Released After 6 Hours Dissolution Testing in pH 7.4 Sorensen's Phosphate Buffer (n = 3 with SD)

| Coat Composition | % Paracetamol released |
|---|---|
| 40S:60P 28mg | 27.2 ± 1.4 |
| 50S:50P 20mg | 22.9 ± 1.1 |
| 50S:50P 26mg | 13.1 ± 2.2 |
| 50S:50P 32mg | 7.4 ± 0.6 |
| 60S:40P 20mg | 5.0 ± 0.9 |

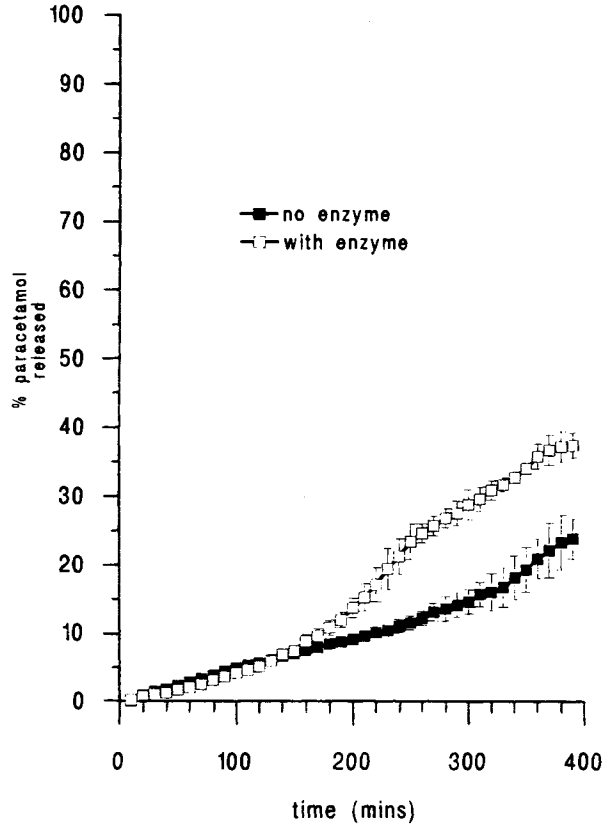


**Fig. 1.** Effect of enzymes on release of paracetamol from tablets coated with 14 mg 50S = 50P. pH 6 buffer, N = 3 with SD.

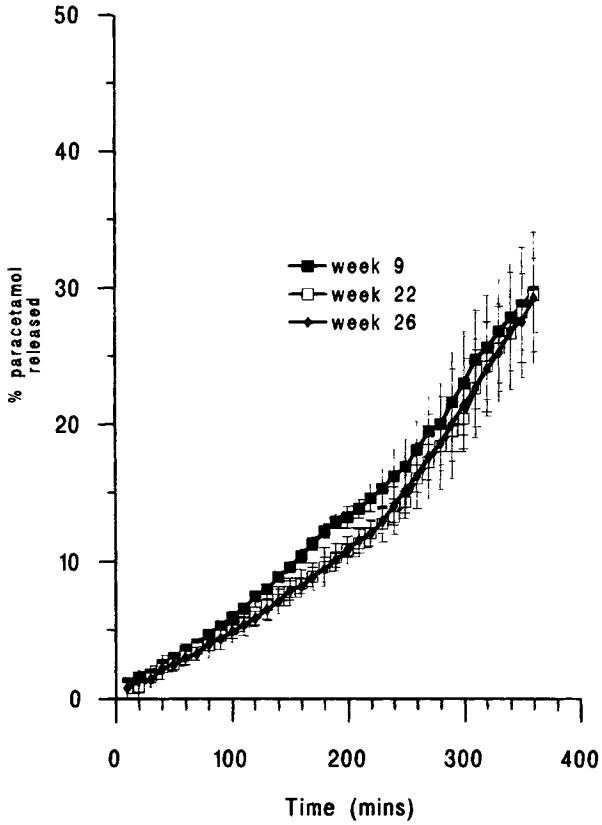


**Fig. 2.** Effect of storage time on release of paracetamol from film coated tablets. 40S:60P, 28 mg coat weight, pH 6 buffer, n = 3 with SD.

6 h in 0.1M HCl and pH 7.4 buffer respectively, for cores coated with different compositions and weights. Increasing both the proportion of ethylcellulose and the coat weight delayed release.

Figure 1 shows the release of paracetamol from coated tablets at pH 6 with and without the addition of pectinolytic enzymes to the dissolution medium. The release of paracetamol is ultimately faster in the presence of enzymes.

Figure 2 compares drug release profiles at different storage times and illustrates that storage for up to 26 weeks has little influence on drug release.

## DISCUSSION

Oral dosage forms intended to target drugs to the colon need to minimize or prevent drug release in the upper g.i. tract and be able to release the drug once the dosage form has entered the colon. The changing enzymic and pH conditions on passage through the stomach and down the small intestine make protection a significant problem. Pectin alone, if applied as a film coat, would not be able to achieve this. Indeed, Ashford *et al.*, (1) showed that a coat of considerable thickness, applied by compression, was required to achieve protection in simulated *in vivo* conditions.

The intention of combining pectin with ethylcellulose was to take advantage of the latter's insolubility over the whole pH range. Tables I and II show the amount of drug released after 6 h testing at pH 1 and pH 7.4 respectively, chosen to simulate typical pH conditions in the stomach and small intestine. The times of 6h are in excess of normal gastric residence or small

intestinal transit (2). Coats with a high proportion of pectin release significant quantities of drug. This release, however, can be minimized by changing the thickness of the coat or increasing the proportion of ethylcellulose. The ethylcellulose can thus mask the inherent solubility of the pectin and provide a coat which is relatively impermeable to the drug for a considerable period of time.

Similar results are observed when studies were carried out at pH 6, chosen to simulate the pH of the colonic contents. These studies show that ethylcellulose can effectively mask the solubility of the pectin and manipulation of proportion and coating thickness can lead to a coating system which gives limited release of drug. Drug release from dosage forms coated with ethylcellulose dispersions has been shown, in some cases, to decrease with time, corresponding with continuing film coalescence (3,4). The results from studies on tablets stored for 26 weeks (Fig. 2) show that film coalescence must have occurred soon after coating and that the coat is stable and not prone to ageing effects.

Pectin is broken down in the colon by several bacterially produced pectinolytic enzymes and simulation of this *in vitro* can be achieved by the use of commercially available enzyme mixtures (1,5). The results from these studies (Fig. 1) show that the presence of enzymes in the pH 6 buffer increases the rate of release of the paracetamol. Since these enzymes only attack pectin, the results demonstrate that the pectin within the film is available for enzymatic attack and has thus retained its colon specific properties.

## CONCLUSIONS

It has been shown previously that pectin has potential as a carrier for oral, colon-specific dosage forms. This current study has demonstrated that a combination of pectin and ethylcellulose can provide the necessary protection in the upper g.i. tract while still allowing enzymatic breakdown in the colon. The combination is suitable for the film coating of dosage forms.

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