

## Enteric coated HPMC capsules designed to achieve intestinal targeting

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### Abstract

The enteric coating of HPMC capsules containing paracetamol was investigated. Two enteric polymers, Eudragit<sup>®</sup> L 30 D-55 and Eudragit<sup>®</sup> FS 30 D were studied, which are designed to achieve enteric properties and colonic release, respectively. The capsules were coated in an Accela Cota 10, and, as shown by optical microscopy, resulted in capsules with a uniform coating. Scanning electron microscopy of the surface of the capsules illustrate that, in contrast to gelatin, HPMC has a rough surface, which provides for good adhesion to the coating. Dissolution studies demonstrated that capsules coated with Eudragit<sup>®</sup> L 30 D-55 were gastro resistant for 2 h at pH 1.2 and capsules coated with Eudragit<sup>®</sup> FS 30 D were resistant for a further 1 h at pH 6.8. The product visualisation technique of gamma scintigraphy was used to establish the in vivo disintegration properties of capsules coated with 8 mg cm<sup>-2</sup> Eudragit<sup>®</sup> L 30 D-55 and 6 mg cm<sup>-2</sup> Eudragit<sup>®</sup> FS 30 D. For HPMC units coated with Eudragit<sup>®</sup> L 30 D-55, complete disintegration occurred predominately in the small bowel in an average time of 2.4 h post dose. For HPMC capsules coated with Eudragit<sup>®</sup> FS 30 D, complete disintegration did not occur until the distal small intestine and proximal colon in an average time of 6.9 h post dose. © 2002 Elsevier Science B.V. All rights reserved.

**Keywords:** Hydroxypropylmethylcellulose capsule; Enteric coating; Eudragit<sup>®</sup>; Scintigraphic evaluation

### 1. Introduction

Enteric coated products are designed to remain intact in the stomach and then to release the active substance in the upper intestine. The rea-

sons for using enteric coated preparations are well documented (Wilding, 2000).

The polymers commonly used to achieve enteric properties are anionic polymethacrylates (copolymerisate of methacrylic acid and either methylmethacrylate or ethyl acrylate (Eudragit<sup>®</sup>), cellulose based polymers, e.g. cellulose acetate phthalate (Aquateric<sup>®</sup>) or polyvinyl derivatives, e.g. polyvinyl acetate phthalate (Coateric<sup>®</sup>).

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Colon targeting products are also designed to remain intact in the stomach but in addition intended to release the active substance further along the gastrointestinal (GI) tract, e.g. at the ileo-caecal junction or in the colon (Ashford and Fell, 1994). The site specific delivery of drugs to the colon has implications in a number of therapeutic areas (Leopold, 1999).

As previously mentioned, site specific delivery into the upper intestine has been achieved for many years by the use of pH-sensitive coatings (Healey, 1989). By applying a thicker coating and/or raising the threshold pH at which dissolution of the coating begins, colon specific delivery using enteric polymers has been achieved (Hardy et al., 1987a). Tablets containing mesalazine and coated with Eudragit<sup>®</sup> S 100, which dissolves above pH 7, are marketed in a number of countries (Asacol<sup>®</sup>, GlaxoSmithKline, UK) (Dew et al., 1983). Mesalazine tablets coated with Eudragit<sup>®</sup> L100, which dissolves above pH 6, are also commercially available (Claversal<sup>®</sup> and Salofalk<sup>®</sup>) (Hardy et al., 1987b).

The majority of the enteric and colon delivery systems are based on coated tablets or pellets which are filled into conventional hard gelatin capsules. However, during the early stages of drug development some new chemical entities (NCE's) present a challenge in testing for efficacy due to instability in gastric fluids or because of irritation in the GI tract. The limited amount of drug substance available during the early stage often precludes the development of a coated pellet or tablet formulation. Since the coating process is independent of the capsule contents, there are clear advantages resulting from the ability to coat a capsule. Thus, the oral pharmacological and/or therapeutic efficacy of the NCE can be determined without resorting to extensive formulation development studies which are expensive, time consuming and, in many instances, impossible at this point in the development of the NCE. Additionally, the capsule provides the possibility to deliver liquid or semi-solid formulations to the small or large intestine.

The most commonly used material for manufacturing capsules is gelatin. Although it is possible to coat hard gelatin capsules (Murthy et al.,

1986; Thoma and Bechtold, 1992) the process is at best very sensitive, especially if an aqueous coating system is used, and can lead to shell embrittlement and poor adhesion of the coat to the smooth gelatin surface. A pre-coating can reduce interactions between the gelatin and the enteric polymer but is time consuming and complicated.

A colonic drug delivery system, based on a starch injection moulded capsule, has been described (Watts, 1995). This system has all the advantages of a capsule described above but suffers from the disadvantage of requiring a specially designed capsule filling and sealing machine, thus narrowing the field of application of the technology.

HPMC capsules have been available commercially, mainly to the dietary supplement industry as a vegetarian alternative to gelatin, for approximately 10 years (Ogura et al., 1998). As HPMC is often used as a pre-coating material for enteric coated tablets, it may be expected that the application of enteric type polymers to a capsule made from HPMC would result in 'good polymer to polymer' adhesion and compatibility.

Gamma scintigraphy is an elegant imaging technique which allows the intestinal performance of pharmaceutical formulations to be visualized (Wilding et al., 2001; Nick, 1996). Over the last 20 years, the approach has become the technique of choice for probing the complex interaction of drug preparations/formulations with the heterogeneous environment of the human gut (Wilding and Newman, 1998).

In this paper, we describe the manufacture of two different Eudragit<sup>®</sup> coated HPMC capsules and their in vitro/in vivo performance.

## 2. Materials and methods

### 2.1. Coating materials

Two commercially available aqueous methacrylate coating dispersions (Roehm GmbH, Darmstadt, Germany) were used in this study. Eudragit<sup>®</sup> L 30 D-55 (Methacrylic Acid Copolymer Dispersion, NF), designed to achieve enteric properties, is a copolymer of methacrylic acid and

ethyl acrylate and dissolves at a pH of 5.5. Eudragit® FS 30 D is a 30% dispersion of a copolymer of methacrylic acid, methyl acrylate and methylmethacrylate. Due to the free carboxylic acid group the polymer dissolves at pH 7 or above making it particularly suitable for delivery into the colon (Gupta et al., 2001).

Excipients used for the coating dispersions were triethyl citrate, NF (Morflex Inc., Greensboro, NC, USA) as a plasticizer, Polysorbate 80 (Tween 80 V, ICI Espana, SA, Barcelona, Spain) as an emulsifier and Mono and Di Glycerides, NF (Imwitor 900, Hüls AG, Witten Germany) as a glidant. The composition of the coating dispersions and their method of preparation are given in Table 1.

In order to increase the flexibility and the adhesion of the enteric coating from methacrylic acid copolymer dispersion, the amount of plasticizer was adjusted to 20%, based on the polymer. Talc was not added as an anti sticking agent so as to avoid any discoloration of the capsule surface. Due to the lower glass transition temperature of the polymer in Eudragit® FS 30 D, a glidant was needed to reduce the tackiness. Thus 8%, calcu-

lated on the polymer, of Mono and Di Glycerides (glyceryl monostearate) was added, using polysorbate 80 as a co-emulsifier. Furthermore, in contrast to talc, GMS does not increase the brittleness of coatings due to its physico chemical properties. The solid concentration of the spray liquids was adjusted to 15%, in order to achieve as uniform a coating as possible.

## 2.2. Capsule filling and coating

Size 0 capsules (Capsugel Division of Pfizer Inc) of surface area 5.0 cm<sup>2</sup>, made from hydroxypropyl methylcellulose without colouring agent, were filled by hand with 380 mg paracetamol (Rhodia France) into which had been mixed 10 mg natural abundance samarium oxide. The capsules were sealed with the LEMS™ process (Cole, 2000) using a modified sealing fluid.

Capsule coating was carried out in an Accela Cota 10 (BWI Manesty) with a batch size of 5 kg. For each trial the pan was loaded with 4.936 kg size 1 HPMC capsules filled with 250 mg of a paracetamol formulation and 130 size 0 capsules. This size difference enabled the capsules contain-

Table 1

Composition and preparation of the coating dispersions used to coat HPMC capsules

	Enteric coating (Eudragit® L 30 D-55)	Colonic coating (Eudragit® FS 30 D)
Eudragit® Dispersion	2287.5 g = 686.2 g polymer	2287.5 g = 686.2 g polymer
Triethyl citrate	137.2 g	34.3 g
Glyceryl Monostearate	–	54.9 g
Tween 80 (33% aqueous solution)	–	65.9 g
Water	3065.2 g	2873.5 g
	5489.9 g = 823.5 g total solids	5316.1 g = 797.4 g total solids
<i>Dispersion preparation</i>	TEC added to water and homogenised Added to Eudragit® under stirring	Tween 80 added to water and heated to 63 °C with stirring GMS added and stirred for 10 min. and resulting suspensions allowed to cool to below 40 °C TEC added Added to Eudragit® under stirring

Table 2  
Operating parameters used to coat HPMC capsules with Eudragit® L 30 D-55 and Eudragit® FS 30 D

Parameter	Value
Spray gun	BWI Manesty
Nozzle diameter	1 mm
Speed of rotation	12 rpm
Atomising pressure	1.3 bar
Inlet air volume	9 m <sup>3</sup> min <sup>-1</sup>
Inlet air temperature	35 °C
Outlet air temperature	25–30 °C
Temperature of capsule bed	25–27 °C
Spray rate	4.2 g min <sup>-1</sup> kg <sup>-1</sup> per capsules
Spraying time	263 min
Drying conditions	5 min at 30 °C

ing samarium oxide to be sampled from the bulk capsules. At various time intervals, during capsule coating, samples were taken corresponding to a theoretical coating thickness of 6, 8 and 10 mg cm<sup>-2</sup>. At the end of the coating process the capsules had received 12 mg cm<sup>-2</sup> of polymer substance. The operating parameters used during the coating process are provided in Table 2. As the mechanical properties of hydrophilic polymers are influenced by the residual moisture, any drying by pre-heating or high process temperatures must be avoided. Due to the low minimum film-forming temperatures of the coating dispersions, the temperature of the capsules could be kept between 25 and 27 °C during spraying. By using such mild process conditions any drying of the capsule shells or spray drying of the atomised mist can be avoided. After the coating process the capsules were dried on trays for 2 h at 30 °C.

### 2.3. *In vitro* dissolution studies

To select the appropriate coating thickness for the capsules to be evaluated in the *in vivo* scintigraphic studies dissolution testing on the size 0 capsules was undertaken using USP Apparatus 2 at 50 rpm, in 900 ml of medium at 37 °C with a wire sinker. Due to the small number of capsules available only limited *in vitro* testing was possible.

For the enteric capsules 2 h of exposure in 0.1 N hydrochloric acid (pH 1.2) was followed by

testing in 0.05 M phosphate buffer of pH 6.8. The colonic capsules were tested for 2 h at pH 1.2, followed by 1 h at pH 6.8 and finally in phosphate buffer of pH 7.4. Paracetamol concentrations were determined by UV spectrophotometry at a wavelength of 300 nm.

### 2.4. Scanning electron microscopy (SEM)

To characterise the surface properties of HPMC capsules the SEM (Jeol JSM 35) technique was used. As a comparison, the surface of a gelatin capsule was also examined. In an attempt to characterise the interface between HPMC and the coat a coated capsule was cleaved. The sample was prepared as a mechanically cleaved cross-section.

### 2.5. Optical microscopy

Low Resolution optical microscopy (Nikon Labophot 2A) was used to document the uniformity of film thickness on the domed area of an HPMC capsule and also on the junction where the cap and body meet. The capsule cross-section was prepared by encapsulating the whole capsule in a slow-setting resin which was allowed to set for 24 h. The sample was then cut with a diamond saw and ground and polished to achieve the desired longitudinal cross-section.

### 2.6. *In vivo* evaluation

The product visualisation technique of gamma scintigraphy was used to establish the *in vivo* disintegration properties of the coated HPMC capsules in a group of eight healthy volunteers. The objectives of the scintigraphic evaluation were to establish both the intestinal site and time of initial/complete capsule disintegration following fasted dosing.

This was a two way randomized crossover study in eight healthy male or non-pregnant female volunteers. All subjects received either the Eudragit® L 30 D-55 or Eudragit® FS 30 D coated HPMC capsules in randomized order after an overnight fast. The Clinical Protocol for the study was approved by the Quorn Research Re-

view Committee and all volunteers provided written Informed Consent to participate in the study.

Neutron activation methods can be used to radiolabel dosage forms for scintigraphic studies. These techniques require the addition of a stable non-radioactive isotope within a formulation; subsequent irradiation in a neutron source converts the isotope into a gamma emitting radionuclide (Digenis and Sandefer, 1991; Kenyon et al., 1995). In order to validate this technique, the irradiation process must be shown to have no significant effect on the formulation, i.e. the preparation must behave in a similar manner both prior to and following the irradiation procedure. Coated capsules were irradiated for 4.5 min in a neutron flux of  $10^{12} \text{ n cm}^{-2} \text{ s}^{-1}$ . In vitro dissolution tests showed that the neutron activation process did not adversely affect the performance of the dosage form.

The volunteers arrived at the study site having fasted from midnight. Anterior anatomical markers containing 0.1 MBq  $^{99\text{m}}\text{Tc}$  were taped to the skin, where the mid-clavicular line meets the right costal margin so that they lay in approximately the same transverse plane as the pylorus. Each subject received a single preparation radiolabelled with 1 MBq  $^{153}\text{Sm}$  on each of two occasions. The preparations were administered at approximately 08.00. Subjects remained fasted until 4 h post-dose at which time a standard lunch was provided. An evening meal was also provided at 9 h post-dose.

Anterior scintigraphic images were recorded at frequent intervals for 12 h post-dose, using a gamma camera (General Electric Maxicamera) with a 40 cm field of view and fitted with a low energy parallel hole collimator. Images were recorded at approximately 10 min intervals until 8 h post-dose and at approximately 20 min intervals until 12 h post-dose. The times provided for the transit and disintegration properties of the two enteric coated formulations are the mid-point values of the two images either side of the intestinal event. Return visits were made to the clinical unit at 24 h post-dose to allow the acquisition of a further scintigraphic image. Acquired images were initially of 50 s duration. The volunteers remained moderately active throughout the study period

and all images were acquired with the subjects standing in front of the gamma camera.

### 3. Results and discussion

#### 3.1. Microscopy of uncoated and coated capsules

Coatings on gelatin capsules often suffer from insufficient adhesion between the shell and the coating. Thus previous workers in the area of enteric coating have found it necessary to pre-coat gelatin capsules with, for instance, a cellulose derivative, either to promote adhesion of polymers to the capsule shell (Murthy et al., 1986) or to improve gastro-resistance (Plaizier-Vercammen et al., 1992). A procedure recommended for coating gelatin capsules (Roehm Technical Brochure, 1994) also involved pre-coating with Eudragit® L 30 D-55 plasticized with glycerol to improve adhesion and storage stability. When the capsule itself is made of a cellulose derivative it would be expected, based on the experience with enteric coating of tablets with a pre-coating of HPMC, that a pre-coating step could be eliminated.

Gelatin capsules have a very glossy surface due to the fact that the amount of regular reflection from the surface is high and the amount of diffuse reflection is low. In contrast, HPMC capsules have a visually matt surface with a greater amount of diffuse reflection, suggesting a more irregular surface. SEM's of the surface of HPMC and gelatin capsules are shown in Fig. 1 where this difference is clearly visible. During the coating process the temperature of the capsule bed reaches 25–27 °C. At this temperature HPMC is soluble and will start to dissolve in the aqueous based film providing a strongly adhesive surface. Gelatin, on the other hand, is only slightly soluble at this temperature and its surface characteristics will remain virtually unchanged. Fig. 2 shows a SEM of the cross-section of a cleaved surface through a capsule coated with  $10 \text{ mg cm}^{-2}$  Eudragit FS 30 D. The contours of the coating material are seen to follow the irregular surface of the HPMC capsule. During the cleaving process it was observed that the strength of the interface was superior to that of either the substrate or the

coating material. It is suggested that the high strength of the bond between HPMC and the film is a combination of the irregular surface and the tackiness of the partially dissolved surface.

In contrast to tablets, capsules are of much lower density, which could result in capsules sticking together to give a non-uniform coating. Fig. 3 shows a cross-section through a domed end of an

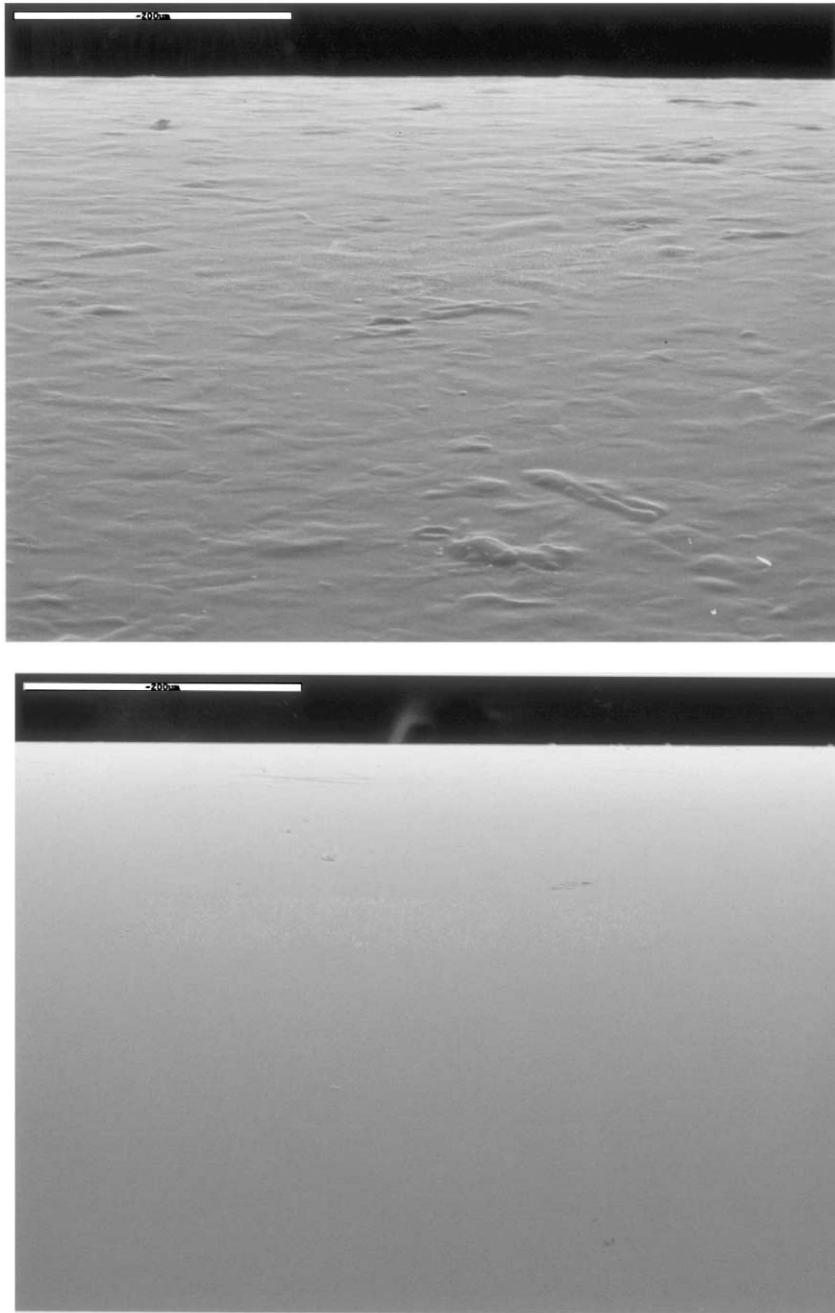


Fig. 1. Scanning electron micrographs of the surface of HPMC and gelatin capsules.

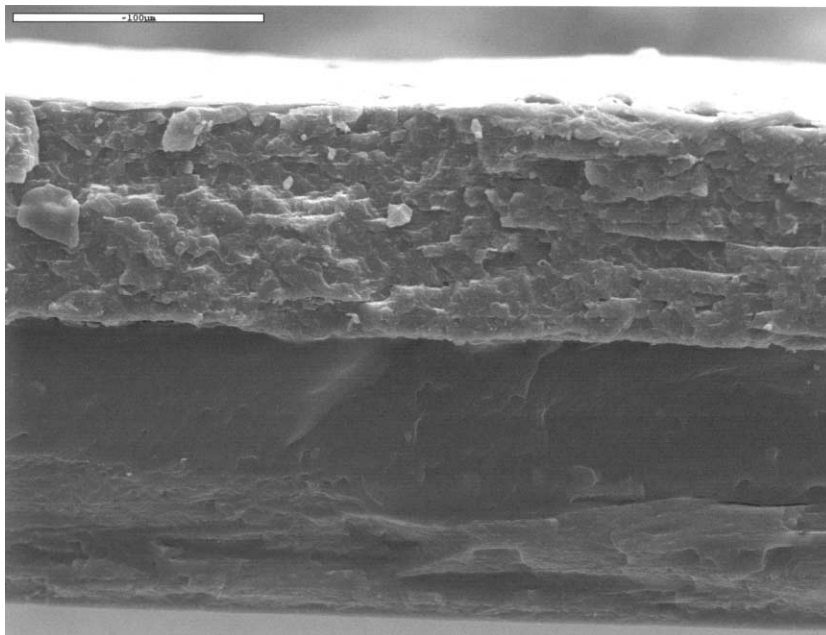


Fig. 2. Scanning electron micrograph of the cross-section of a cleaved surface through an HPMC capsule coated with  $10 \text{ mg cm}^{-2}$  Eudragit® FS 30 D.

HPMC capsule coated with  $10 \text{ mg cm}^{-2}$  Eudragit® L 30 D-55 and a longitudinal cross-section of a capsule coated with  $6 \text{ mg cm}^{-2}$  Eudragit® L 30 D-55. These micrographs confirm that a uniform coating thickness around the curved surface of the capsule as well as along the flat surface was achieved. No pores or cracks can be observed, due to the well controlled coating process. In addition, the critical area of overlap between the cap and body of the capsule is covered with polymer ensuring gastric integrity.

During the coating process no significant loss of coating material was observed as was demonstrated by good agreement between the actual and theoretical weight of the coated capsules. This is confirmation of the excellent compatibility between the HPMC capsule and the anionic methacrylate dispersions.

### 3.2. *In vitro* dissolution

The dissolution profiles from the capsules coated with Eudragit® L 30 D-55 and Eudragit® FS 30 D are shown in Fig. 4. No paracetamol was released

over 2 h at pH 1.2 from the capsules coated with 6 and  $8 \text{ mg cm}^{-2}$  Eudragit® L 30 D-55. At pH 6.8 release of paracetamol was rapid, with very little difference between the two coating thicknesses. In order to ensure *in vivo* gastric integrity, the capsules coated with  $8 \text{ mg cm}^{-2}$  Eudragit® L 30 D-55 were selected for evaluation in the scintigraphic study.

No release of paracetamol was detected at pH 1.2 over 2 h or at pH 6.8 over the subsequent 1-h period for the capsules coated with Eudragit® FS 30 D. At pH 7.4 the capsules coated with 6, 8 and  $10 \text{ mg cm}^{-2}$  all opened rapidly and release of paracetamol commenced. Incomplete release of paracetamol was due to the inclusion of drug by pockets of polymer which did not dissolve under the gentle conditions of the dissolution test. It was considered that the minimum coating to achieve a 3 h *in vitro* lag time (2 h at 1.2 and 1 h at 6.8) would be suitable to achieve *in vivo* capsule opening either in the terminal ileum or colon; therefore, the capsule formulation coated with  $6 \text{ mg cm}^{-2}$  of Eudragit® FS 30 D was selected for *in vivo* evaluation.

Tablets coated with a monolayer of enteric polymer will show small amounts of drug release, usually around 1–2% per h, when tested at a pH

below that of the solubility of the polymer due to diffusion through the film. At these pH values no release of paracetamol was detected from either

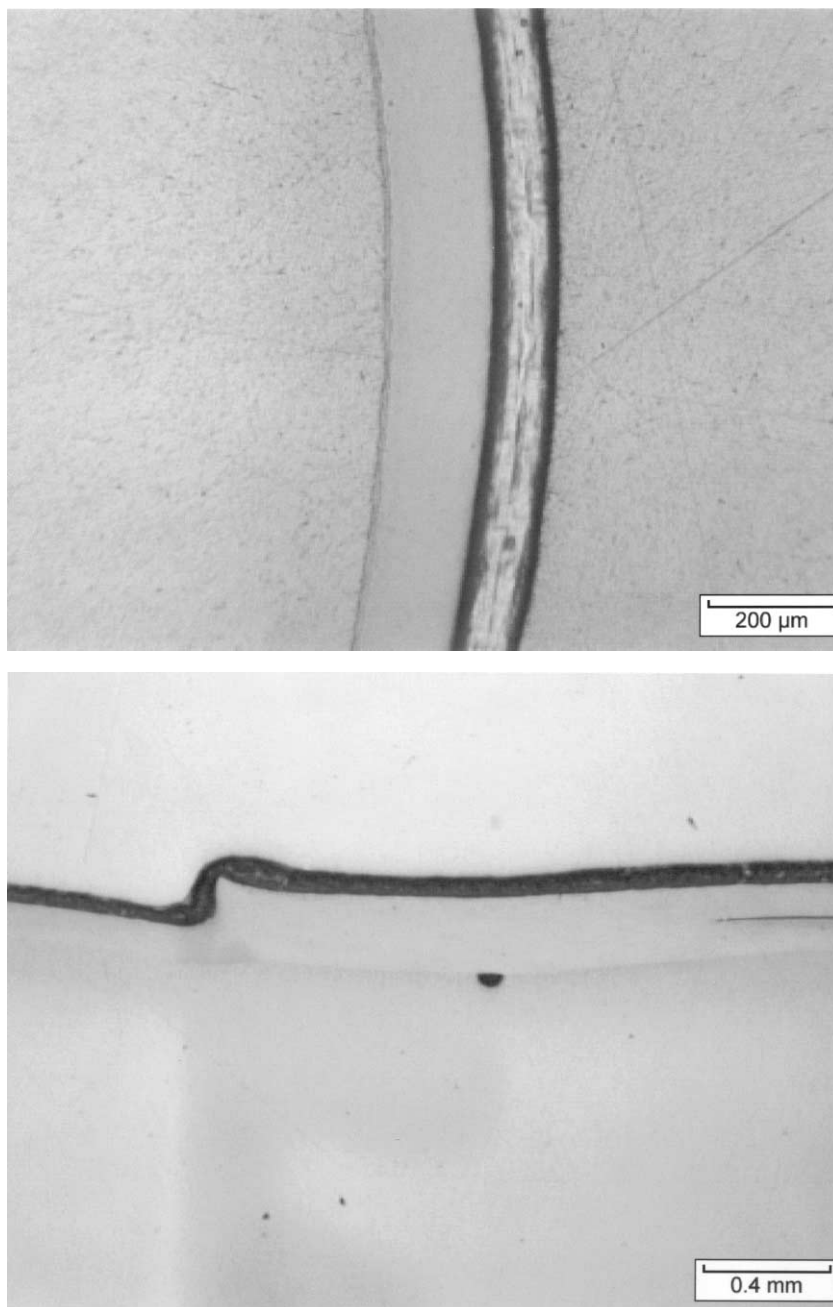


Fig. 3. Optical micrographs of HPMC capsules coated with Eudragit<sup>®</sup> L 30 D-55. (Top) Cross-section of domed end of capsule coated with  $10 \text{ mg cm}^{-2}$  Eudragit<sup>®</sup> L30 D-55. (Bottom) Longitudinal cross-section through a capsule coated with  $6 \text{ mg cm}^{-2}$  Eudragit<sup>®</sup> L30 D-55.

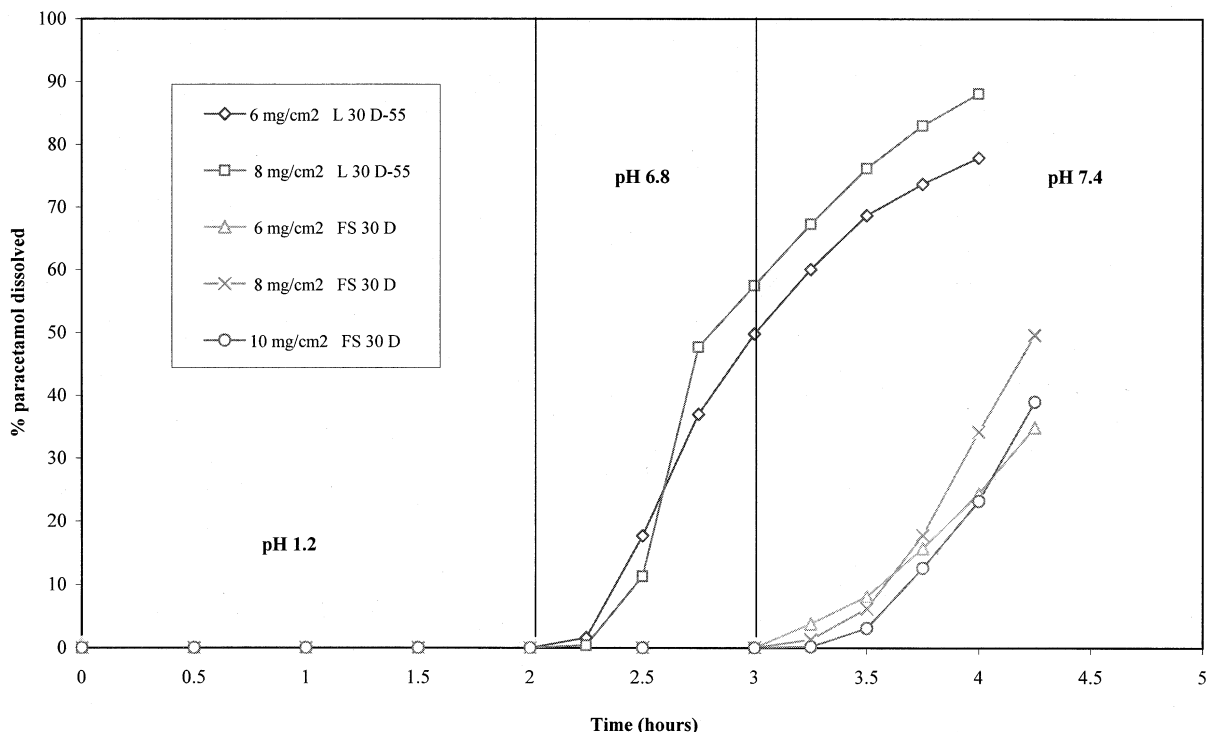


Fig. 4. Dissolution of paracetamol from HPMC capsules coated with Eudragit<sup>®</sup> L 30 D-55 and Eudragit<sup>®</sup> FS 30 D.  $N = 3$ .

capsule system demonstrating that the HPMC capsule provides a system of low permeability and a good barrier to drug diffusion at the pH, where protection is required.

As can be seen from Fig. 4 variation in coating levels had little influence on the dissolution profiles of paracetamol confirming the robustness of the formulation and the good compatibility between HPMC and the polymethacrylate films.

### 3.3. Human product visualisation

Time-lapse photography of intestinal performance was assessed by obtaining scintigraphic images at frequent intervals for approximately 12 h post-dose. Analysis of the images provided detailed information on the GI transit and in vivo disintegration of the Eudragit<sup>®</sup> L 30 D-55 (Table 3) and Eudragit<sup>®</sup> FS 30 D (Table 4) coated capsules.

The major factor influencing the gastric emptying of oral dosage forms is whether they are

administered with or without food. In the fasted state, stomach residence time is predominantly controlled by the frequency of the phase III housekeeper wave, which occurs approximately every 2 h. Therefore, not surprisingly, gastric emptying of the capsules occurred within this time interval for the majority of subjects.

Both capsule types remained intact in the stomach which confirmed the gastro-resistant properties of the Eudragit<sup>®</sup> L 30 D-55 and Eudragit<sup>®</sup> FS 30 D polymers. In addition, the interaction of the polymer and underlying capsule substrate was strong in vivo, providing excellent evidence of enteric protection for the coated units.

Following gastric emptying, the site and time of disintegration were strongly correlated with the choice of Eudragit<sup>®</sup> polymer. For the HPMC units coated with Eudragit<sup>®</sup> L 30 D-55, complete disintegration occurred in the small bowel (Fig. 5) in all but one subject confirming that once gastric emptying has occurred, the capsule disintegrates relatively rapidly within the small intestine.

In contrast, the HPMC capsules coated with the relatively new polymer, Eudragit® FS 30 D, were more resistant to *in vivo* dissolution with complete disintegration occurring lower down the GI tract in the mid to distal small intestine and proximal colon (Fig. 6). Enteric coatings that dissolve at relatively high pH values have been used previously to target drug delivery to the colon (Watts and Illum, 1997).

A number of researchers have concluded that a change in luminal pH cannot be used reliably

and routinely as a mechanism to deliver drugs specifically to the colon (Ashford and Fell, 1994). However, the data from this study demonstrate that in seven of the eight subjects dosed with the FS 30 D coated units, initial and complete capsule disintegration occurred between the mid to distal small intestine and proximal colon suggesting that the subject's intestinal pH was sufficient to dissolve the coating on this formulation and thereby provide for distal intestinal targeting.

Table 3

Transit and disintegration of the Eudragit® L 30 D-55 coated HPMC capsules (h)

Subject	Gastric emptying	Colon arrival	Initial disintegration		Complete disintegration	
			Time	Site	Time	Site
1	2.0	–	2.8	PSB	3.2	MSB
2	0.2	–	1.4	MSB	1.9	MSB
3	0.4	–	1.5	MSB	1.9	MSB
4	0.9	–	1.3	PSB	1.3	PSB
5	0.8	2.6	1.9	DSB	3.2	AC
6	0.1	–	2.5	PSB	3.6	DSB
7	0.4	–	1.3	PSB	1.6	MSB
8	1.5	–	2.0	DSB	2.5	DSB
Mean	0.8	–	1.8		2.4	
S.D.	0.7	–	0.6		0.9	
<i>n</i>	8	–	8		8	

PSB, proximal small bowel; MSB, mid small bowel; DSB, distal small bowel; AC, ascending colon.

Table 4

Transit and disintegration of the Eudragit® FS 30 D coated HPMC capsules (h)

Subject	Gastric emptying	Colon arrival	Initial disintegration		Complete disintegration	
			Time	Site	Time	Site
1	2.5	–	2.7	PSB	5.0	MSB
2	0.5	–	3.6	MSB	5.6	DSB
3	2.3	4.0	3.5	DSB	10.0	AC
4	0.6	4.1	3.8	DSB	7.0	AC
5	0.7	2.6	3.0	AC	6.5	AC
6	0.3	2.8	3.7	AC	4.7	HF
7	2.5	–	4.3	MSB/DSB	6.0	DSB
8	2.9	4.0	9.0	AC	10.0	AC
Mean	1.5	3.5	4.2		6.9	
S.D.	1.1	0.8	2.0		2.1	
<i>n</i>	8	5	8		8	

PSB, proximal small bowel; MSB, mid small bowel; DSB, distal small bowel; AC, ascending colon; HF, hepatic flexure.

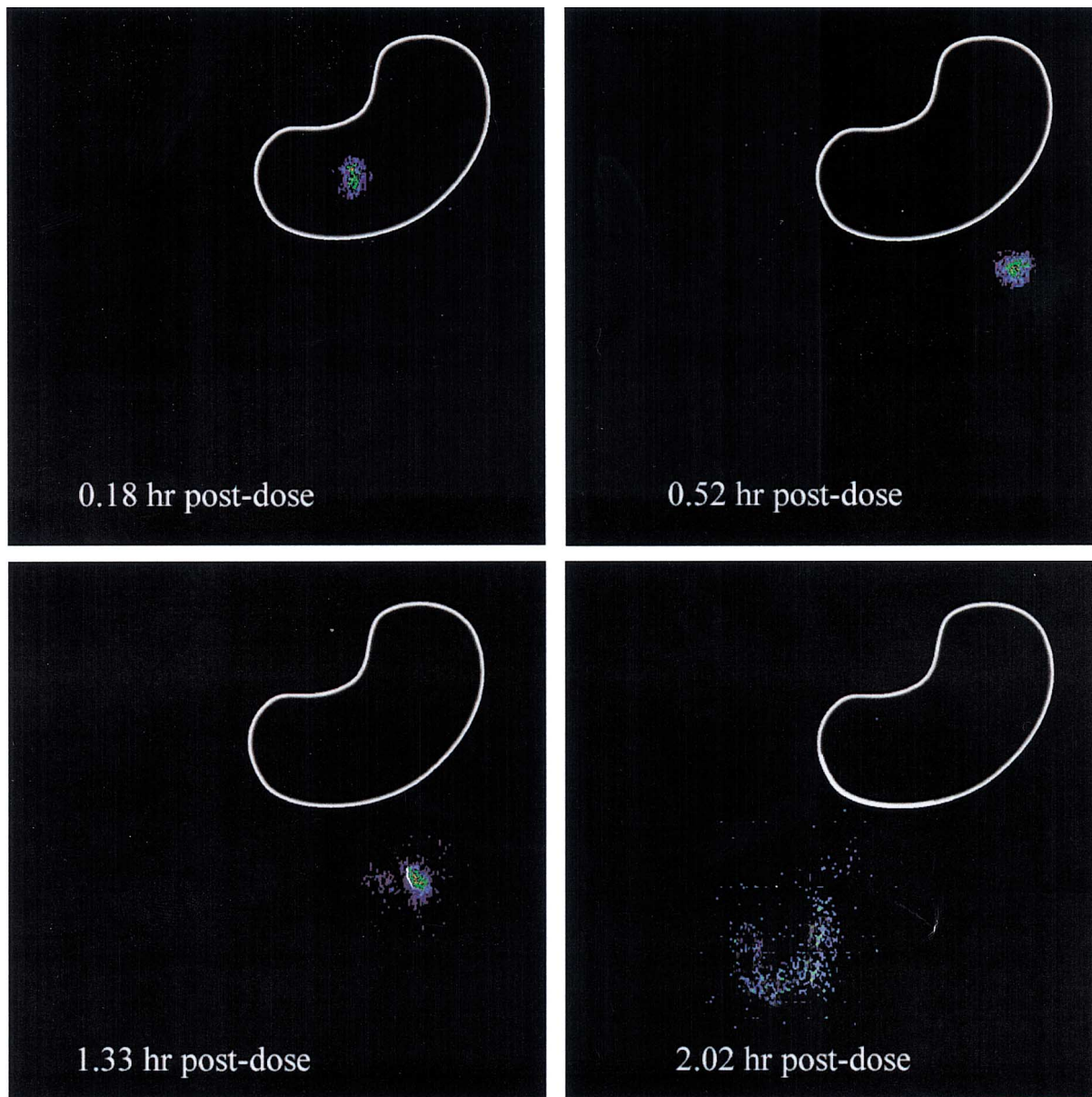


Fig. 5. Time lapse drug delivery from the Eudragit® L 30 D-55 HPMC capsules in subject 7.

#### 4. Conclusion

The investigations described demonstrate that the enteric coating of HPMC capsules is an industrially viable process. The matt surface of the capsule provides a good substrate for adhesion of the coating material, which results in an all round

uniform film, providing gastric integrity. Scintigraphic techniques demonstrated that in the case of Eudragit® L 30 D-55, disintegration of the capsule was relatively rapid within the small intestine. The capsules coated with Eudragit® FS 30 D, however, disintegrated lower down the GI tract towards the distal small intestine and proximal colon.

Enteric coated HPMC capsules can thus be considered to provide a good container for drugs during the early development phase providing the possibility of drug release either in the small intestine or towards the colon.

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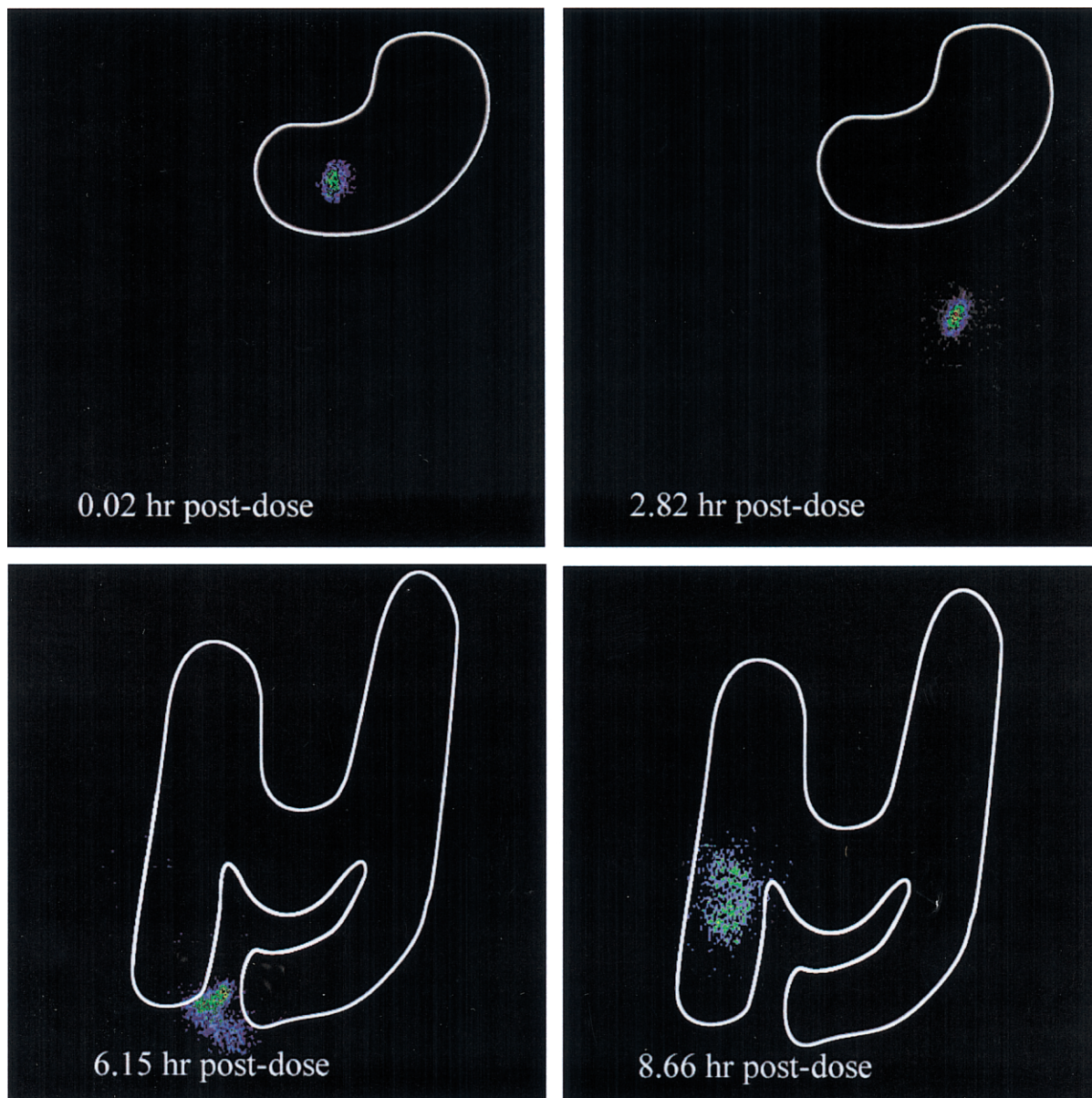


Fig. 6. Time lapse drug delivery from the Eudragit<sup>®</sup> FS 30 D HPMC capsules in subject 7.

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