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Film-forming polymers for colonic drug delivery: I. Synthesis and physical and chemical properties of methyl derivatives of Eudragit S

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Summary

Several methylated derivatives of Eudragit S with different degrees of substitution were prepared for evaluation as potential coatings for colon delivery. Water vapor transmission, in vitro dissolution and stability in function of pH were investigated using the technique of isolated films. The data presented demonstrate relative differences in physico-chemical characteristics due to differences in degree of substitution. The relationship of degree of substitution and dissolution pH is direct and inverse for moisture diffusion rate. In the second part of the in vitro study the coating properties of the methyl substitutes of Eudragit S were investigated after application on hard gelatin capsules. The disintegration time of the coated capsules and the release of caffeine at pH 7.5 were in very good agreement with the results obtained with isolated films.

Introduction

In many situations it is desirable to coat an active substance in such a way that it is released only after a predetermined time interval or a change in environment. It has been particularly advantageous in medicine to be able to administer orally a medicament which is coated so that it passes through the stomach and is released only when the coated material reaches the small intestine. Such coatings are called enteric coatings and are nowadays quite easy to formulate taking advantage of different polymers which do not dissolve in the acid stomach contents but in the alkaline intestinal fluids.

A harder task is to provide a coated medicament which will survive both the stomach and the small intestine and will release the active ingredient only when the material reaches the large intestine or colon. Many diseases of the colon could be better treated if site-specific delivery of the therapeutic agent could be effected. Therapeutic agents mainly include corticosteroids, laxatives, cytostatics and compounds for the treatment of ulcerative colitis or Crohn's disease. Other drugs such as peptides may also benefit from such a form of release depending on their absorption characteristics.

A number of approaches have been suggested for site specific release into the colon. The strategies followed are sumarized in Table 1. The goal

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is always to provide a mechanism that has region specific release characteristics.

The aminosalicylic acid prodrugs such as sulphasalazine have been known for a considerable time. More recently, glycoside derivatives of steroids (Friend and Chang, 1984) were found to be poorly absorbed in the stomach and the small intestine but were released in the large intestine through microbial hydrolysis. A coating (Saffran et al., 1986) has been proved to be able to protect peptide drugs such as insulin and vasopressin from digestion in the stomach and small intestine and to allow their release in the large intestine by the action of the endogeneous microflora. Knowing that azoaromatic compounds are susceptible to cleavage by the colonic bacteria, they synthesized copolymers of styrene and hydroxyethylmethacrylate cross-linked with divinylazobenzene. The study of Saffran et al., although not clearly demonstrating the possible effect of drug leaching through the ruptured membrane coat on the delayed pharmacological response, represents the first attempt to fabricate a generally applicable controlled delivery system for the colon. Their approach offers a pharmaceutical film-forming polymer with site affinity properties which allows, without special pretreatment or chemical modification, delivery of almost any drug to the colon. However, the slow degradation of the coat when incubated in fecal content is an important problem in their approach. This factor may explain the non-negligible intra- and intersubject variability between the results obtained. For use in man, the aspect of toxicity of the azopolymer cannot be ignored. In this respect, a copolymer, polyurethane-oligosaccharide, which was recently synthesized (Bauer, 1990), looks more promising for the future.

Besides low-molecular-weight prodrugs, a similar approach is based on the use of macromolecular carriers and 5-ASA has been azo-linked to polymer backbones (Lapique and Dellacherie, 1986; Kopeckova and Kopecek, 1990).

Hence, this investigation was undertaken in order to reveal whether chemical modification of polymers used for enteric coating can prevent their dissolution in the gastrointestinal tract.

The polymers used for gastroresistance are commonly acrylic acid or cellulose derivatives such as cellulose acetate phtalate and hydroxypropyl-

TABLE 1

Review of approaches and mechanisms applied for colon drug delivery

Approach	Mechanism	Application
Prodrug synthesis	enzymatic reduction of azo bonds	ASA prodrugs bioadhesive polymeric carrier (Kopeckova and Kopecek, 1991)
	enzymatic hydrolysis of β- glycoside bond	drug glycosides (Friend and Chang, 1984) polysaccharide carriers (Lapique and Dellacherie, 1986)
Coating	pH-dependent dissolution	polymethylmethacrylates (Lehmann, 1975; Dew et al., 1982; Bogentoft et al., 1983; Van Saene et al., 1986; Mardini et al., 1987)
	enzymatic hydrolysis of β-glycoside bonds	ethylcellulose coat + Avicel (Zeitorn and Brisard, 1988)
	enzymatic reduction of azo bonds	azopolymer (Saffran et al., 1986)
	enzymatic hydrolysis	polyurethane-oligosaccaharide (Bauer, 1990)
Hydrogel matrix	pH-dependent swelling + reduction of azo crosslinks	azo crosslinked copolymers (Pradny and Kopecek, 1990)

methylcellulose phthalate. The polymethylmethacrylates form the largest group. Eudragit L or S and Eudragit RL or RS (Röhm Pharma) are well-known copolymers of methacrylic acid and methylmethacrylic ester. These products are available as granules soluble in organic solvents or as dispersions in water.

Eudragit RL and RS are used to release the drug as a retarded form to the gastrointestinal tract while Eudragit L and S release their drug in the small intestine. The difference between Eudragit L and S, and that between Eudragit RL and RS, concerns the ratio of the amount unsubstituted to substituted carboxylic groups. These compounds have been extensively used, sometimes in combination with other products, by several investigators (Table 1) as film-forming agents in order to prevent drug release until the dosage form reaches the colon.

On the basis of Eudragit S being characterised by having the highest pH of dissolution (Spitael and Kinget, 1979), chemical modification of this polymer appears to be the most suitable means of obtaining a coating that releases its content in the large intestine.

Materials and Methods

General chemistry

The degree of substitution of the modified polymer formed was calculated indirectly by titration of the remaining carboxylic groups. Approx. 1 g was dissolved in acetone containing 3% H_2O and titrated with 0.5 N NaOH in the presence of phenolphthalein as indicator. The acid value was calculated using the following formula:

$$\text{acid value} = \frac{28.05x}{m} \qquad (1)$$

where x denotes the volume (ml) of 0.5 N NaOH and m is the sample weight (g).

^{1}H-NMR spectra were determined on a Jeol FX 90 Q Fourier Transform NMR spectrophotometer and 10 mg product was therefore dissolved in acetone-d_6 (C3D6O) 99.5 atom% D (Janssen Chimica).

Preparation of methylated derivatives of Eudragit S

Methylation of the carboxylic groups of EuS (Eudragit S, Rohm Pharma, Darmstadt, Germany) was carried out with diazomethane prepared (De Boer and Backer, 1954) using diazald (99%, Aldrich Chemie) dissolved in ether. The diazomethane solution obtained was titrated with 0.1 N NaOH after the addition of an accurately measured quantity of benzoic acid. Phenolphthalein was used as indicator.

An exactly known quantity of about 10 g EuS was dissolved in 25 ml acetone, ether or tetrahydrofuran. A calculated amount of diazomethane solution depending on the required acid value was added to the solution which was then mixed at room temperature with a magnetic stirrer.

The reaction product was precipitated in ether. The filtered precipitate was firstly air dried and then further in a vacuum oven at 50°C. The different methylated products (EuSMe) were named according to their acid value; e.g., EuSMe 100 corresponds to the copolymer of methacrylic acid and methylacrylate, methylated to attain an acid value of 100.

Preparation of isolated films

Cast films were prepared from 10% solutions in acetone using a film casting knife (Gardner Multicator type 411) on a degreased glass plate according to specifications given elsewhere (Spitael and Kinget, 1979). The thickness of the dried film was measured with a Lorentzen & Wettres micrometer.

Water vapor permeability procedure

Procedure B of ASTM-E 96-66 was followed to measure water vapor transmission. Through the use of Payne permeability cups and controlled humidities on both sides of the film, the water vapor transmission could be determined. The cup covered with the film was filled with 10 ml demineralised water and placed at room temperature in an exsiccator filled with silica gel. The loss in weight of the cup was measured at about 24, 48, 72 and 96 h. The American Society for Testing Materials suggests the following formula

for calculation of the water vapor transmission (WVT).

$$\text{WVT}\left(\text{g m}^{-2}\ (24\ \text{h})^{-1}\right) = \frac{24\ g}{A \cdot t} \qquad (2)$$

where g is the weight gain or loss (in g), A represents the exposed area (in m^2), t is the time (in h) during which g was observed and 24 is a factor used to convert the actual measuring time (t) to the time basis of 24 h.

From the water vapor transmission the permeance (P_e) can be calculated using the formula

$$P_e[\text{WVT/mmHg}] = \text{WVT/dp} \qquad (3)$$

where dp is the difference in mmHg ($= S(R_1 - R_2)$), S denotes the saturation water vapor pressure (in mmHg), at test temperature, and R_1 and R_2 are the relative humidities at the source and at the sink, respectively.

Dissolution pH procedure

Dried cast films of the methylated derivatives of Eudragit S were cut in pieces of 3 by 1 cm. About 20 mg of the film was placed into test tubes. 10 ml of buffer solution of varying pH was added to each tube. The tubes were rotated for 30 min followed by a rest interval of 30 min. After 4 h of contact with the solvent the experiment was stopped. Dissolution pH was determined by noting the lowest pH at which the film dissolved completely.

Determination of the pH stability of isolated films

For the pH stability studies, isolated films were mounted in a diffusion cell of which the donor compartment was filled with a solution (15 g/l) of caffeine. The amount permeated was determined by measuring continously the absorbance in the acceptor compartment at 272 nm. A sudden steep increase in the permeability of an isolated film was considered to indicate the onset of dissolution and disintegration of the film.

Coating of capsules

Capsules were coated on laboratory scale using the apparatus shown in Fig. 1. It consists of a small conical glass container of which the top and bottom are closed with a metal sieve. The coating solution was applied using a spraying nozzle which also imparts an upward and downward movement to the capsules. The degree of coating corresponding to the amount (mg) of coating per unit surface area (cm) provides a measure of the efficiency of the process.

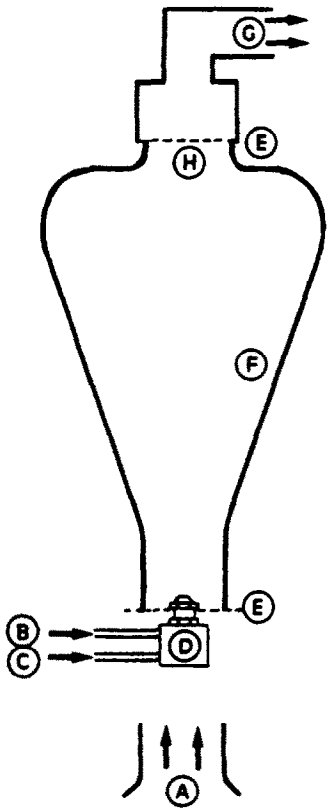

Fig. 1. Apparatus for capsules coating on laboratory scale. (A) Dry air; (B) inlet of pressured air; (C) inlet of coating solution; (D) spray nozzle; (E) sieve; (F) conical glass container; (G) air aspiration; (H) input of capsules.

Disintegration of the coated capsules

Disintegration times of the coated capsules were measured using the apparatus as described in the European Pharmacopeia test procedure. The capsules were maintained firstly for 2 h in simulated gastric fluid. For the purpose of this study, a phosphate buffer of pH 7.5 was used in lieu of simulated intestinal fluid.

Release of a tracer molecule from coated capsules

The release from coated capsules of the tracer molecule caffeine was studied at pH 7.5 using the

USP paddle method. The experimental conditions were the same as for the disintegration test. The concentration of the caffeine in the dissolution fluid was continuously measured spectrophotometrically at 272 nm.

Results and Discussion

Characteristics of the methylated derivatives (EusMe) of Eudragit S

Acid value Table 2 summarizes the acid values obtained for the methylated compounds prepared in three different solvents. Less diazomethane had to be added when the reaction takes place in solution (acetone, tetrahydrofuran) than in suspension (ether). The NMR spectra (Fig. 2) do not show any major difference between the products obtained except for the amount of solvent remaining. This can be reduced by prolonging the vacuum drying time.

Solubility EuSMe derivatives are soluble in a concentration of at least 10% in acetone, ethanol, isopropanol and methylene chloride.

Toxicity In initial toxicity studies, after oral application of methylated derivative EuSMe 100 to 10 mice at a dose of 10 mg/kg no mortality or abnormal symptoms were observed (Simon Laboratories, 1990).

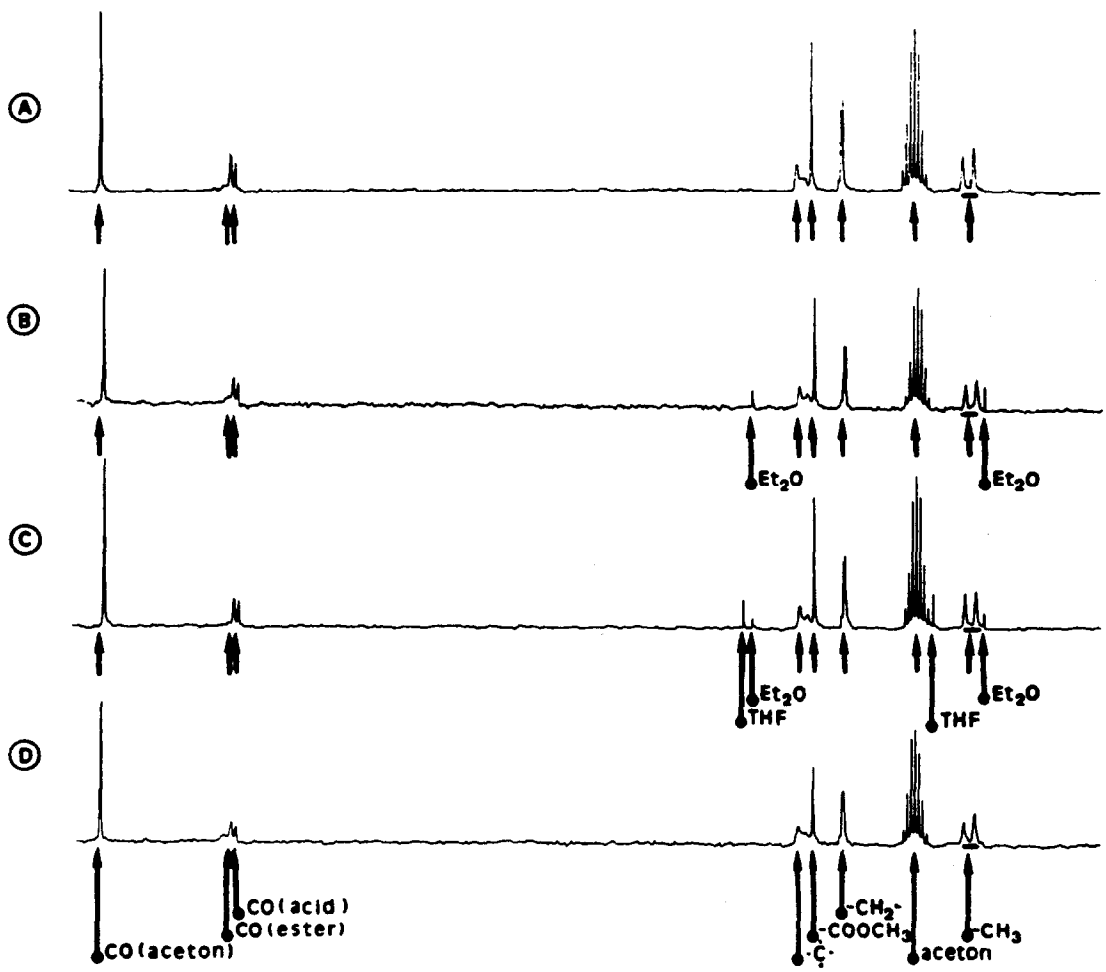

Fig. 2. NMR spectra of EusMe 100 prepared in ether (A), acetone (B) or THF (C) and of EuS (D).

TABLE 2

Acid value obtained after methylation of 10 g Eudragit S in different solvents

Solvent	Volume of diazomethane solution (ml)	Acid value of the methylated product
Acetone	50	73.3
Tetrahydrofuran	50	74.7
Ether	50	97.1
	20	148.5
	70	62.0

Characteristics of isolated films

Water vapor transmission The water vapor transmission of EuSMe 100 and 110 has been determined by the procedure outlined in Materials and Methods. The values obtained for WVT and permeance of the two methylated polymers (Table 3) were about 50% of those determined for the starting polymer Eudragit S. Polymers such as Eudragit S which contain several hydrophilic groups attract water molecules and allow them to penetrate more readily as compared to those with a greater content of lipophilic groups, e.g., EuSMe 100.

In the context of a coating designed to deliver drugs to the colon, low water permeability is a desirable property for a film-coating agent as the content of the tablet or capsule should be protected from degradation by water for a much longer period.

Dissolution pH Table 4 summarizes the results on the dissolution behavior of the cast films at different pH values as a function of the acid value of methylated Eudragit S. With decreasing acid value, the threshold dissolution pH increased and at a limit value of about 70 EuSMe became practically insoluble even at high pH values.

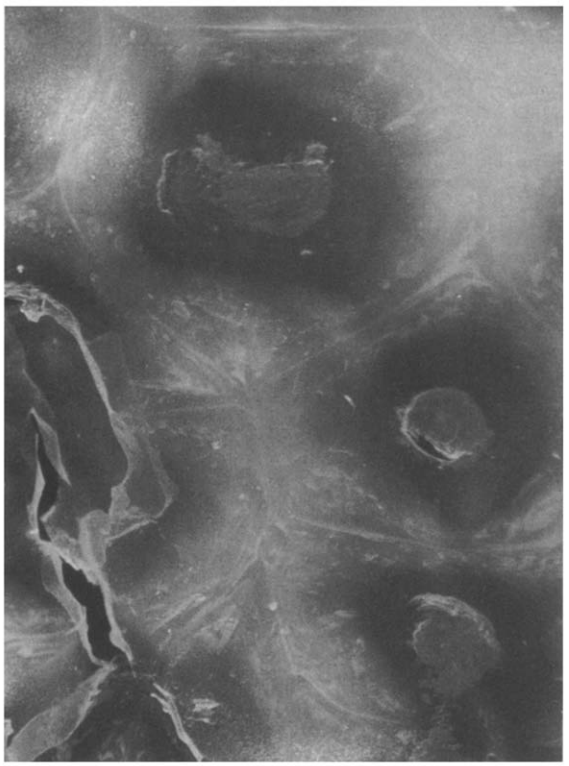

Fig. 3. Microscopic picture of a cast film of EuSMe 110 after a period of 400 min at pH 7.5 (magnification, 10×).

In Figs 3 and 4, the onset of dissolution of the films after contact with the alkaline buffer solution is clearly visible.

Influence of pH on the pH stability of isolated films of EuSMe The above-described experiments clearly demonstrate that, depending on the acid value which corresponds to a different methyl content, the modified polymers show a different dissolution pH profile. As the acid value is correlated with the free carboxylic groups, their amount

TABLE 3

Water vapor permeability of EuSMe 100 and 110 compared to Eudragit S

Polymer	EuS			EuSMe 100			EusMe 110		
Film thickness (μm)	49	23.5	26	39	35	34	31	31	40
WVT (g m^{-2} (24 h)$^{-1}$)	456	347	534	128	237	161	176	176	151
P_e (WVT/mmHg)	19.3	14.6	22.5	5.4	10.0	6.8	7.4	7.4	6.4

will determine the onset of dissolution. In order to investigate this process more carefully, which is macroscopically invisible, the pH stability of EuSMe coatings was studied following the permeation of a low-molecular-weight non-ionic substance, caffeine, through an isolated film at different pH values.

Fig. 5 shows the increase as a function of time of the optical absorbance in the acceptor compartiment of the diffusion cell for isolated films of Eudragit S at pH 7.5. The value obtained after extrapolation of the vertical straight line given by the very sharp rise of the absorbance is defined as the break-through time of the film.

Table 5 lists the values of the break-through time for isolated films of different EuSMe derivatives. From the values reported, it appears that for an acid value of 80 the film remained impermeable even at the highest pH and that an acid value of 100–120 provides an acceptable compromise between sufficient resistance at lower alkaline pH values and rapid onset of disintegration at the high pH values at the ileocaecal junction and in the colon.

TABLE 4

Dissolution of cast films of methyl derivatives of Eudragit S as a function of pH and acid value

Acid value	Time (h)	pH				
		7.0	7.4	8.0	8.3	8.5
187	2	+	+	+	+	+
	4	+	+	+	+	+
148	2	−	+	+	+	+
	4	−	+	+	+	+
120	2	−	+	+	+	+
	4	−	+	+	+	+
110	2	−	−	+	+	+
	4	−	−	+	+	+
96	2	−	−	+	+	+
	4	−	−	+	+	+
89	2	−	−	+	+	+
	4	−	−	+	+	+
69	2	−	−	−	/	/
	4	−	−	−	/	/

+, dissolved; −, not dissolved; /, not tested.

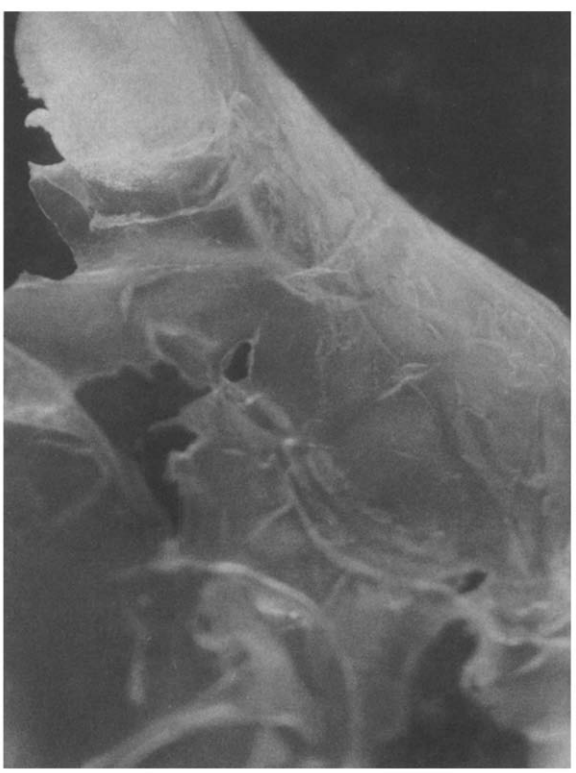

Fig. 4. Microscopic picture of a cast film of EuSMe 110 after a period of 60 min at pH 8 (magnification, 10×).

A film with an acid value of 100 and thickness of approx. 30 μm resisted pH 8 for a duration of 225 min, while a film with an acid value of 90 and comparable thickness needed about 12 h to become highly permeable at the same pH.

Influence of the thickness on the disintegration of isolated films of EuSMe Isolated films of various thickness were tested in different pH media.

Figs 6 and 7 show the results obtained for Eudragit S and EuSMe 100, respectively. For both polymers, the influence of film thickness was more pronounced at the lower pH values. For isolated films of Eudragit S, a steeper increase in the break-through time with increasing thickness was found at pH 7 than at pH 7.5. A similar pattern was obtained for EuSMe 110 for which dissolution became independent of film thickness from pH 8.

In vitro disintegration of coated placebo capsules The coating equipment and process were tested by making placebo capsules gastroresistant

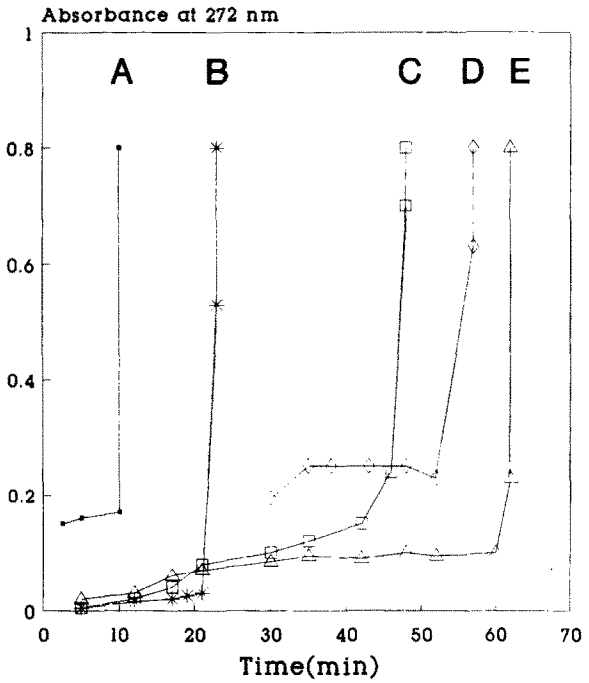

Fig. 5. Time course of permeation of caffeine at pH 7.5 through Eudragit S films of varying thickness (μm); (A) 21; (B) 52; (C) 90; (D) 95; (E) 103.

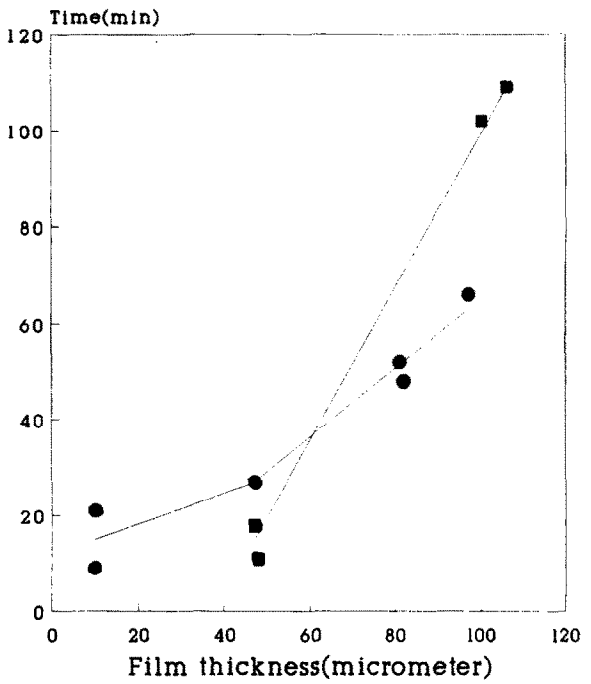

Fig. 6. Break-through time of Eudragit S films as a function of thickness and pH; (■) 7; (●) 7.5.

with a 10% solution of hydroxypropylmethylphthalate (HP 55) in acetone/ethanol (1 : 1 v/v).

10 batches of placebo capsules coated in the laboratory apparatus were tested for gastric resistance and disintegration in simulated intestinal fluid of pH 7.5. Table 6 lists the results obtained. All capsules with a coating density above 3.3 mg/cm^2 complied with the pharmacopoeial requirements for gastric resistance except one capsule from batch 9. These results concur with published recommendations (Lehmann, 1989; Ter

TABLE 5

Break-through times of methyl derivatives of Eudragit S as a function of pH and film thickness

Acid value	Film thickness	pH 7.0	Film thickness	pH 7.5	Film thickness	pH 8.0	Film thickness	pH 8.5
120	27 μm	10.0 h	28 μm	144 min	39 μm	30 min	26 μm	33 min
	38 μm	13.5 h	43 μm	225 min	56 μm	86 min	47 μm	54 min
110	32 μm	[a]	20 μm	210 min	23 μm	57 min	18 μm	60 min
	30 μm	[a]	33 μm	413 min	46 μm	102 min	45 μm	80 min
100		/	30 μm	12 h	28 μm	180 min	29 μm	75 min
			31 μm	225 min	34 μm	108 min		
97		/	36 μm	7.5 h	30 μm	108 min	39 μm	66 min
			42 μm	7.5 h			44 μm	78 min
90		/	25 μm	[a]	28 μm	8.25 h	26 μm	180 min
					35 μm	12.0 h	29 μm	225 min
80		/	25 μm	[a]	30 μm	[a]	28 μm	[a]
							12 μm	[a]

[a] No permeation after 18 h. /, not tested.

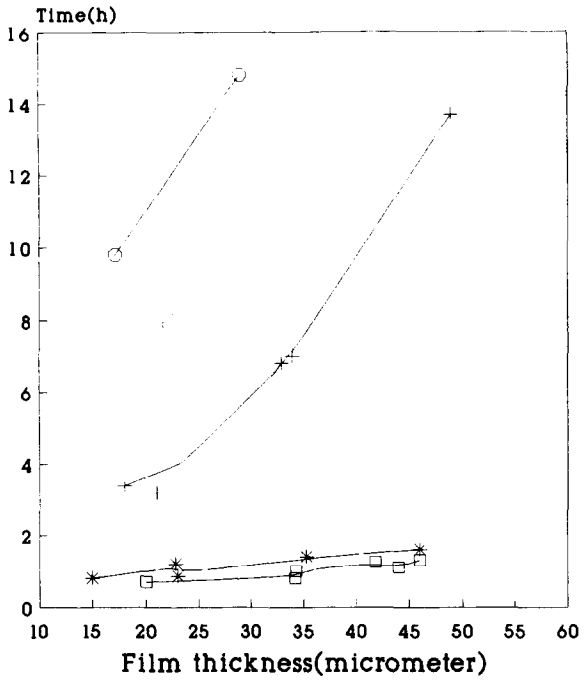

Fig. 7. Break-through time of EuSMe 110 films as a function of thickness and pH; (○) 7; (+) 7.5; (*) 8; (□) 8.4.

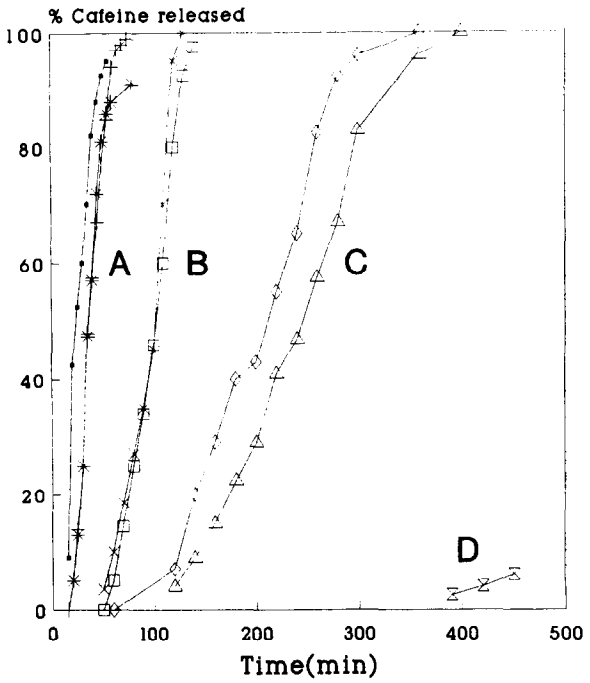

Fig. 8. Time course of the release (pH 8) of caffeine from capsules coated with an EuSMe film of 40 μm, as a function of the acid value of the coating polymer; (A) EuSMe 120; (B) EuSMe 97; (C) EuSMe 90; (D) EuSMe 80.

Horst et al., 1989) which also require this coating level for sufficient gastroresistance.

Release of caffeine from coated capsules Fig. 8 shows the release pattern of caffeine from capsules covered with an EuSMe coating of approx. 40 μm. Experiments A–C were repeated three and two times, respectively. For fast film disintegration (Expts A and B), the reproducibility of the experiment was found to be very satisfactory. In the case where disintegration needed more time, e.g., EuSMe 90 (Expt C), somewhat larger variability was observed. Compared to isolated films of the same thickness, the break-through times at pH 8 were about the same. For EuSMe 120 the values were 20 and 30 min, respectively, for EuSMe 97 100 and 108.

TABLE 6

Number of disintegrated out of six capsules, as a function of the density of the HP 55 coating

Batch no.	Coating density (mg/cm^2)	Simulated gastric juice	Buffer pH 7.5
1	10.0	0	6
2	7.0	0	6
3	2.6	4	2
4	5.5	0	6
5	3.3	1	5
6	2.9	3	3
7	8.0	0	6
8	6.4	0	6
9	5.7	0	6
10	5.0	1	5

Conclusion

This investigation was undertaken to develop a pharmaceutical coating which might be used to control the release of drugs upon reaching a specific intestinal pH, namely the colonic pH. A procedure is described for the preparation of methylated derivatives of Eudragit S, a copolymer of methacrylic acid and methylmethacrylate. Various derivatives with different degrees of substitu-

tion were prepared. They form clear, colorless films.

Relative differences in chemical properties between these compounds were demonstrated by measurement of the dissolution pH, water vapor transmission and permeability as a function of pH with cast films. Disintegration and permeability of films were also determined after application of the methylated polymers as coating on capsules. Significant correlations were found between these characteristics and the degree of substitution. Dissolution or disintegration of isolated or applied films of certain methyl derivatives of Eudragit S can be retarded till they reach the high pH values present at the ileocaecal junction and in the colon (Evans et al., 1988).

The results can provide a logical basis for the selection of the appropriate degree of substitution which is capable of delaying 'in vivo' the release of a drug up to the colon and which does not limit dissolution upon arrival at the large bowel. It will then become possible to transport in concentrated form medicaments such as 5-ASA, vermicides, corticosteroids and cytostatics and to deliver them locally in the colon, so as to eliminate or at least diminish their systemic effects.

Acute toxicity studies indicated that these products are as safe as other polymethacrylates for use as pharmaceutical coatings. Additional in vivo studies on the utility of these compounds are forthcoming.

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