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European Journal of Pharmaceutics and Biopharmaceutics 53 (2002) 65–73

European Journal of Pharmaceutics and Biopharmaceutics

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Research paper

In vitro evaluation of pectin–HPMC compression coated 5-aminosalicylic acid tablets for colonic delivery

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Received 17 May 2001; accepted in revised form 23 August 2001

Abstract

In this study, we report pectin–HPMC compression coated core tablets of 5-aminosalicylic acid (5-ASA) for colonic delivery. Each 100 mg core tablet contained 5-ASA and was compression coated at 20 kN or 30 kN using 100% pectin, 80% pectin–20% HPMC, or 60% pectin–40% HPMC, at two different coat weights as 400 or 500 mg. Drug dissolution/system erosion/degradation studies were carried out in pH 1.2 and 6.8 buffers using a pectinolytic enzyme. The system was designed based on the gastrointestinal transit time concept, under the assumption of colon arrival times of 6 h. It was found that pectin alone was not sufficient to protect the core tablets and HPMC addition was required to control the solubility of pectin. The optimum HPMC concentration was 20% and such system would protect the cores up to 6 h that corresponded to 25–35% erosion and after that under the influence of pectinase the system would degrade faster and delivering 5-ASA to the colon. The pectin–HPMC envelope was found to be a promising drug delivery system for those drugs to be delivered to the colon.

Keywords: Colonic delivery; 5-Aminosalicylic acid; Pectin; HPMC; Compression coating; Pectinase

1. Introduction

Colonic delivery of drugs has attracted a lot of attention and many different approaches were discussed in the literature. Kopecek et al. [1] reported new hydrogels with azoaromatic crosslinks that were sensitive to azoreductases for colonic delivery of peptides such as insulin. Ashford et al. [2] studied a pH dependent system using Eudragit S to deliver salicylic acid to the colon and concluded that pH dependent systems may not be the best approach. Ashford et al. [3] reported the use of compression coated pectin on core tablets for colonic delivery and they reported that pectin USP was the correct choice among the other pectin grades and a minimum coat weight of 700 mg would be required for a dosage form to reach the colon based on mouth to colon transit time concept. Another study concentrating on azo polymers was reported by Mooter et al. [4] and it was concluded that the degree of swelling of hydrogels affected the azo bonds. Gazzaniga et al. [5] reported the use of HPMC either by press coat or spray coat techniques applied to active cores for colonic delivery based on the gastrointestinal (GI) transit time concept. According to Steed et al. [6] beclomethasone could be delivered to the colon in a HPMC matrix coated with an enteric polymer. Calcium pectinate was suggested by Rubinstein and Radai [7] for colonic delivery. Amylose coated 5-aminosalicylic acid (5-ASA) cores was reported by Milojevic et al. [8] they combined water insoluble polymers to the coat to control drug release. A pectin–ethylcellulose combination as a coating material was reported by Wakerly et al. [9]. Sriamornsak [10] reported calcium pectinate gel beads for oral delivery of proteins to the colon. Macleod et al. [11] reported mixed films of pectin chitosan and HPMC, Turkoglu et al. [12] suggested a pectin–HPMC compression coat system for colonic drug delivery. Lauroyldextran and crosslinked galactomannan were reported as new coating materials for site-specific drug delivery by Hirsch et al. [13].

The purpose of this study was to develop and evaluate a drug delivery system in vitro based on a compression coated tablet containing 5-ASA as the core and a pectin HPMC mixture as the coat layer based on the GI transit time concept. The main reason for selecting pectin was its biodegradation in the colon by colonic flora. On the other hand, high molecular weight HPMC increases the mechanical strength of the tablet wall around a drug core during its transportation in the gastro-intestinal tract. Hence, it was

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0939-6411/02/$ - see front matter
PII: S0939-6411(01)00225-9

Table 1
Experimental list for compression coated 5-ASA tablets

Formulation code	Pectin–HMPC (%)	Coating force (kN)	Coating weight (mg)
F1	100–0	20	400
F2	100–0	30	400
F3	80–20	20	400
F4	80–20	30	400
F5	60–40	20	400
F6	60–40	30	400
F7	100–0	20	500
F8	100–0	30	500
F9	80–20	20	500
F10	80–20	30	500
F11	60–40	20	500
F12	60–40	30	500

our hypothesis that with the positive contribution of HPMC, pectin would be a good candidate for designing a colonic delivery system.

2. Materials and methods

2.1. Materials

5-Aminosalicylic acid (5-ASA) was donated by Dr Falk GmbH, Germany, Batch # 0499040, pectin USP 100 was obtained from Copenhagen Pectin, Denmark, hydroxy propyl methyl cellulose HPMC (Metolose SR, Type 90SH, 100000 cP) was a gift from Shin-Etsu Chemicals Ltd., Japan, Pectinex 3XL (3000 FDU/ml) and Ultra SP-L (26000 FDU/ml) were obtained from Novo Nordisk Ferment Ltd, Switzerland. All other materials were of reagent grade.

2.2. Methods

2.2.1. Preparation of 5-ASA core tablets

5-ASA was dry mixed with PVP (K 29-32) and water was added to granulate. Wet granules were sieved through 1 mm screen and dried overnight at 40°C. After adding 0.25% magnesium stearate as a lubricant tablets that contain 100 mg drug were compressed using a laboratory size single station tablet press (Korsch EKO) with 6 mm flat faced punches. Tablet quality control tests such as weight variation, crushing strength, friability, thickness, and dissolution were performed on the core tablets.

2.2.2. Compression coating of core tablets

5-ASA core tablets were placed in 10 mm die cavity of a laboratory hydraulic press. Depending on the design 100% pectin, 80% pectin–20% HPMC, 60% pectin–40% HPMC combinations were used for the outer shell compression coating. Coating pressures were either 20 or 30 kN, and the coat weights were either 400 or 500 mg. Tablet quality control tests such as weight variation, crushing strength, friability, thickness, dissolution/erosion rates in different media were performed on the compression coated tablets. The experimental design is summarized in Table 1.

2.2.3. Test method for pectin–HPMC coat erosion

After compressing the tablets a erosion study was performed. First medium was 500 ml 0.1 N HCl solution. The USP XXIII dissolution apparatus 2 was used at 50 rpm at 37°C. The test was continued for 2 h, at the end of the time period the medium was discarded and refilled with USP pH 6.8 buffer solution and the test was continued for additional 6 h. After 6 h, depending on the design 3 ml Pectinex was added to the dissolution vessels and the test was continued until for a pre-determined time depending on the study design. Tablets were dried overnight at 45°C in an oven (Memmert, Germany) and the remaining tablet mass was determined gravimetrically (Shimadzu AX120, Japan). In the case of drug dissolution 5-ASA concentration was determined spectrophotometrically at 303 nm (Shimadzu UV 2100, Japan).

2.2.4. Statistical analysis

The effect of compression force, coat weight, and pectin–HPMC ratio on the dissolution erosion rate with ($t_{50\%\ \text{pectinase}}$) and without pectinase ($t_{50\%}$), difference between enzyme and no enzyme cases at the last sampling point ($\Delta\%$) were tested using a factorial ANOVA model, specifically *a three-way analysis of variance* (3-way ANOVA) procedure for the main effects (SPSS for Windows 9.0).

3. Results and discussion

3.1. Results of tablet characteristics

The physical properties of 5-ASA core tablets and pectin–HPMC compression coated tablets were given in Table 2. All tablets were high quality and complied with pharmaceutical standards.

Table 2
Physical properties of 5-ASA core and pectin–HPMC compression coated tablets

Code	Weight (mg)	Crushing strength (*N*)	Thickness (mm)	Friability (%)
Core	100 ± 1.55	75.7 ± 6.6	2.76 ± 0.01	0.18
F1	505 ± 1.74	> 200	4.85 ± 0.03	0.05
F2	519 ± 2.17	> 200	4.78 ± 0.02	0.04
F3	505 ± 2.70	> 200	4.75 ± 0.02	0.03
F4	508 ± 2.70	> 200	4.67 ± 0.02	0.03
F5	503 ± 3.40	> 200	4.66 ± 0.01	0.02
F6	503 ± 1.63	> 200	4.58 ± 0.06	0.02
F7	603 ± 3.55	> 200	5.70 ± 0.08	0.04
F8	605 ± 3.32	> 200	5.60 ± 0.04	0.03
F9	605 ± 4.96	> 200	5.73 ± 0.02	0.03
F10	609 ± 2.67	> 200	5.56 ± 0.02	0.03
F11	604 ± 3.79	> 200	5.68 ± 0.05	0.02
F12	613 ± 1.13	> 200	5.60 ± 0.04	0.02

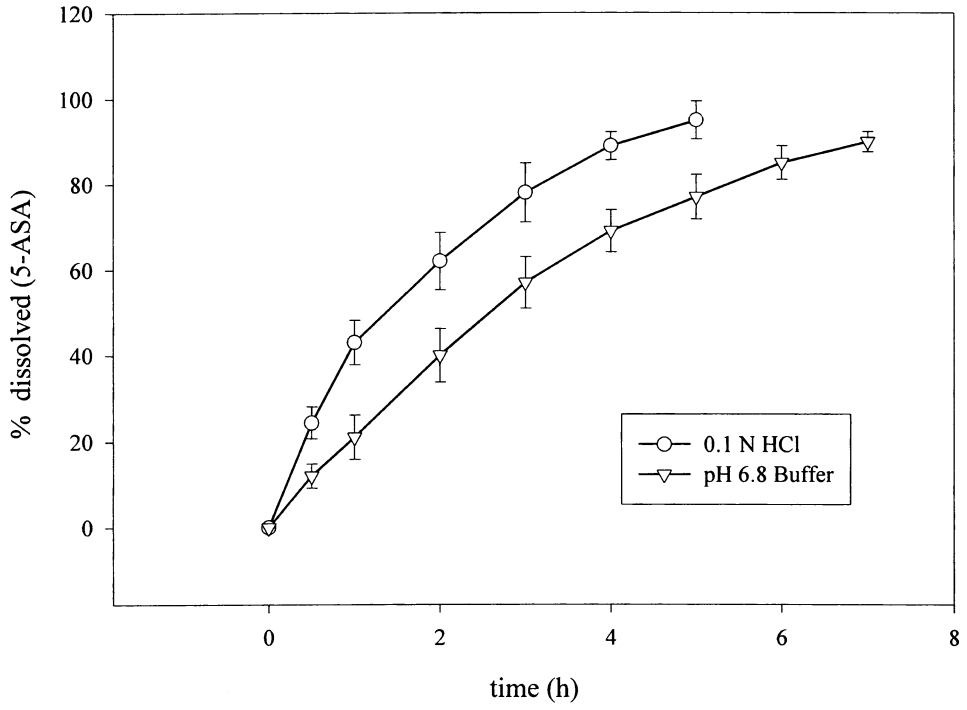

Fig. 1. Dissolution profiles of 5-ASA core tablets in 0.1 N HCl and pH 6.8 buffer solutions (USP Appartus 2 and 50 rpm).

3.2. Solubility and dissolution results of 5-ASA core tablets

The core tablets containing 100 mg 5-ASA were tested in 0.1 N HCl and pH 6.8 USP phosphate buffer solutions for their dissolution rates. Also the solubility of 5-ASA was investigated. The solubility of 5-ASA was found to be 8.65 mg/ml in 0.1 N HCl and 3.94 mg/ml in pH 6.8 buffer at 37°C. Fig. 1 shows the dissolution results of core tablets. 5-ASA core tablets dissolved faster in 0.1 N HCl and reached 100% in 5 h and dissolution rate was slower in pH 6.8 buffer and

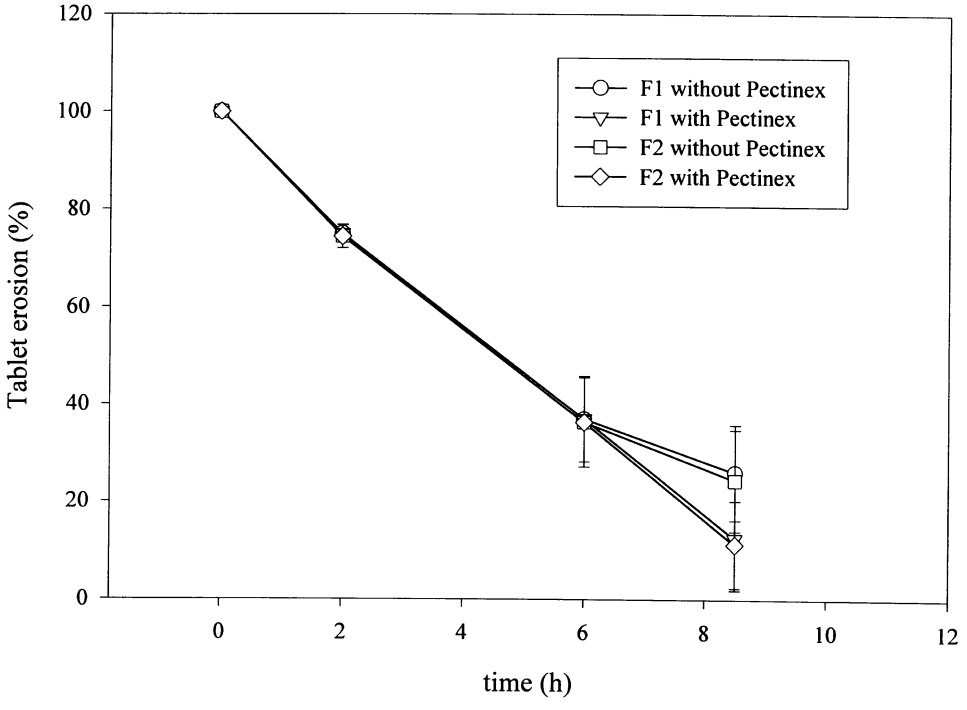

Fig. 2. Percent erosion vs time plot of 100% pectin coated tablets at 20 and 30 kN compression forces and 400 mg coat weight (n = 6 with standard deviation bars).

Table 3
Experimental list and observed erosion parameters for compression coated 5-ASA tablets[a]

Formulation	t_{50} (with pectinase) (hour)	t_{50} (without pectinase) (hour)	Δ%[b]
F1	4.1	4.1	13
F2	4.2	4.2	12
F3	7.5	7.7	9
F4	7.7	8.0	15
F5	9.5	21.0	24
F6	9.6	26.0	21
F7	5.5	5.5	8
F8	5.0	5.0	9
F9	7.5	8.4	17
F10	7.4	8.6	19
F11	11.0	27.0	17
F12	10.0	24.5	20

[a] All values are the mean values obtained from regression analysis $*t_{50\%\,(pectinase)}$; $**t_{50\%}$.
[b] Average percent weight difference between tablets with and without enzyme at the last sampling point.

100% drug release was reached in 8 h due to high compression pressures and not using any disintegrant.

3.3. Erosion results of pectin–HPMC coated tablets

When 100% pectin was used for coating material at two levels for 5-ASA cores, 20 and 30 kN compression forces were studied. These experimental runs are listed as F1, F2, F7, F8 in Table 1. Fig. 2 shows the percent remaining of the tablets with and without enzyme addition for F1–F2, and Fig. 5 shows the dissolution of 100% pectin coated tablets at the higher coat level (F7–F8). The $t_{50\%}$ values and the average difference (Δ%) between the remaining tablet weights in the case of enzyme and no enzyme dissolution studies were given in Table 3. At the 6th hour point where pectinase was added to the dissolution medium, the tablets of F1–F2, F7–F8 had already lost more then 50% of their weight. For 100% pectin coated tablets it was found that at 2 h 5-ASA release could be observed from the system (Fig. 8) that corresponded to 25% erosion rate for studied tablets.

In Table 1, F3, F4 and F9, F10 contained 80% pectin 20% HPMC as the coat material. Table 3 summarized the $t_{50\%}$ and Δ% values for those batches. Figs. 3 and 6 show the erosion profiles for F3, F4, and F9, F10 respectively. For 80% pectin-20% HPMC coated tablets it was found that at the 6th hour 5-ASA release could be observed from the system (Fig. 8) that corresponded to 25–35% erosion rate depending on the standard deviation.

Among all batches the slowest erosion pattern was observed with 60% pectin–40% HPMC combinations (F5-F6 and F11-F12). Figs. 4 and 7 show the profiles. The effect of pectinase addition at the 6th hour resulted in the highest Δ% values as 24–21% for F5–F6 and 17–20% for F11–F12. This combination was found too slow for the GI transit time concept and was not evaluated any further.

To determine the critical time point that would correspond to a certain percent erosion from compression coated systems a study was carried out using 100% pectin coated and 80–20% pectin HPMC coated tablets. At the 2 h sampling point 5-ASA was detected for 100% pectin

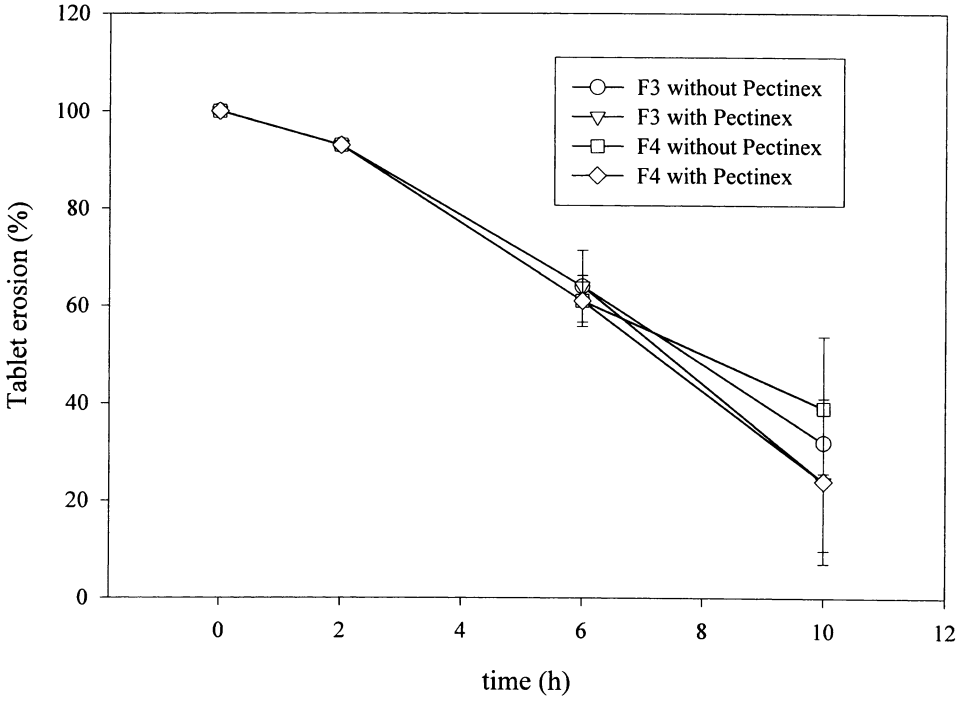

Fig. 3. Percent erosion vs time plot of 80–20 pectin–HPMC coated tablets at 20 and 30 kN compression forces and 400 mg coat weight (n = 6 with standard deviation bars).

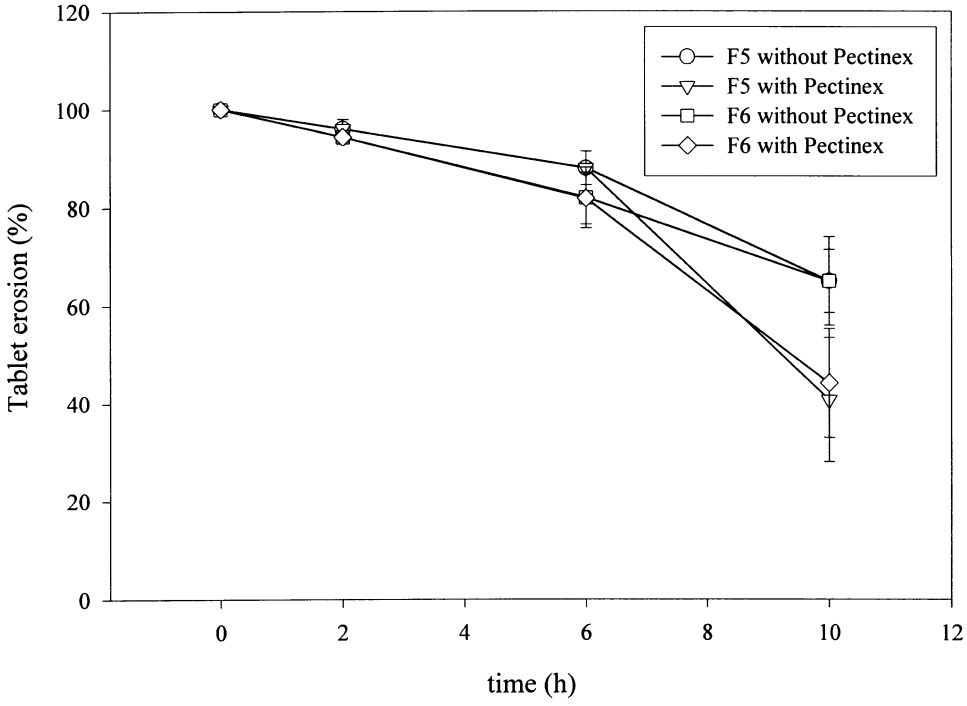

Fig. 4. Percent erosion vs time plot of 60–40 pectin–HPMC coated tablets at 20 and 30 kN compression forces and 400 mg coat weight (n = 6 with standard deviation bars).

batch. The remaining drug was released in a sigmoidal pattern up to 14 h depending on the dissolution erosion rate. In Fig. 8, one can observe that 80–20 coating system did not release any drug up to 6th hour point where enzyme addition was made and acid medium was replaced with the USP pH 6.8 phosphate buffer. Between 6 and 14 h the remaining drug was released following a zero order pattern. So it was concluded that the critical value for the compression coated tablets was 25–35% coat erosion for the studied tablets.

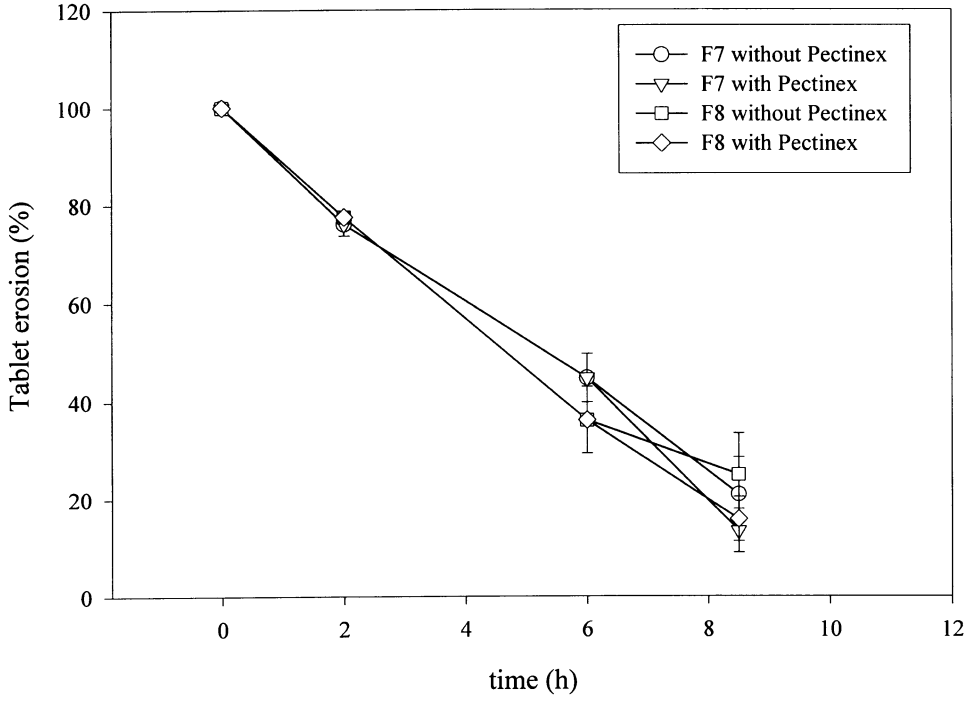

Fig. 5. Percent erosion vs time plot of 100% pectin coated tablets at 20 and 30 kN compression forces and 500 mg coat weight (n = 6 with standard deviation bars).

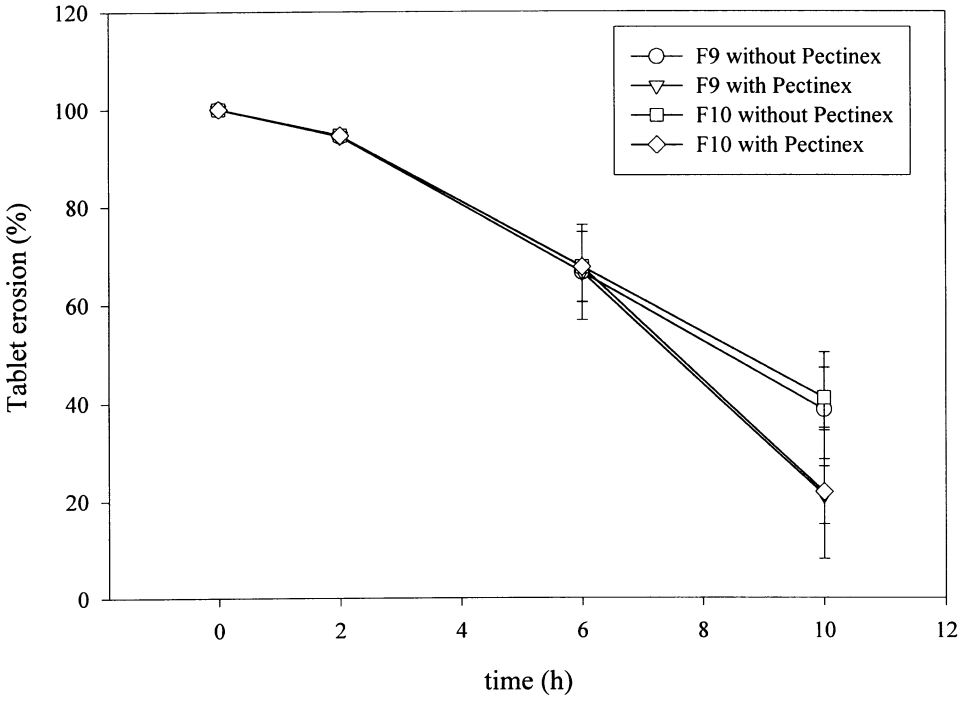

Fig. 6. Percent erosion vs time plot of 80–20 pectin–HPMC coated tablets at 20 and 30 kN compression forces and 500 mg coat weight (n = 6 with standard deviation bars).

3.4. Statistical evaluation and comments on erosion study

In this study we used a high molecular weight HPMC to enforce the mechanical resistance of the tablet during its transit in the gastro-intestinal tract and to partially modify the high solubility of pectin. Among the studied factors were: Pectin–HPMC ratio, compression coat pressure, and the amount of coating mixture. This design resulted in 12 batches and it was summarized in Table 1.

The dependent variables that were the parameters to char-

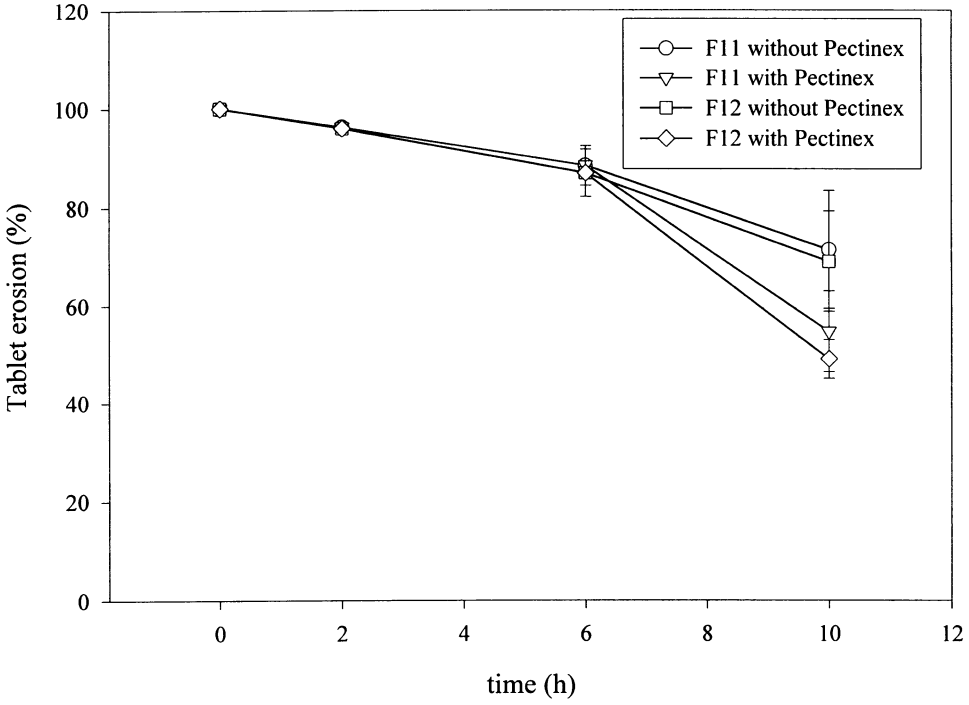

Fig. 7. Percent erosion vs time plot of 60–40 pectin–HPMC coated tablets at 20 and 30 kN compression forces and 500 mg coat weight (n = 6 with standard deviation bars).

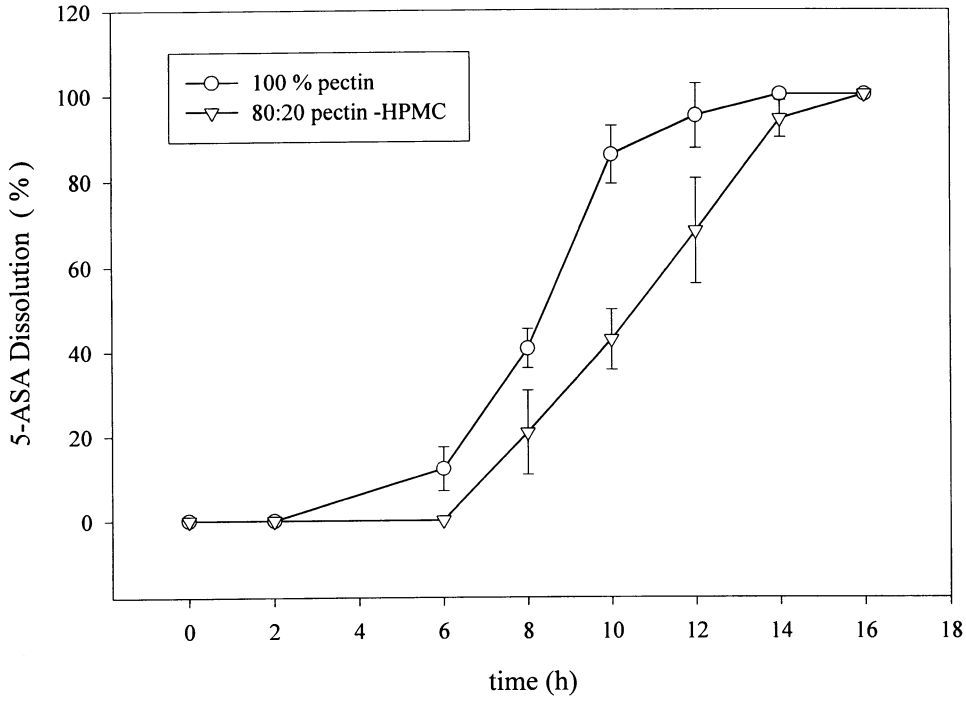

Fig. 8. 5-ASA dissolution profiles from 100% pectin and 80–20 pectin–HPMC compression coated tablets (n = 6 with standard deviation bars and pectinase addition at 6th hour).

acterize coat erosion such as $t_{50\%\ \text{pectinase}}$, $t_{50\%\ \text{without pectinase}}$, and $\Delta\%$. Tables 4 and 5 summarized the results of statistical analysis.

In three-way ANOVA, the main effects model was found significant for all dependent variables and the adjusted R^2 values were presented in Tables 4 and 5. Pectin–HPMC ratio was found to be a significant factor on dependent variables. The mean t_{50} values that correspond to dissolution studies without pectinase addition were 4.7 h, 7.5 h, and 10 h for 100% pectin, 80–20 pectin–HPMC mixture, and 60–40 mixtures respectively. In the case of pectinase addition to dissolution medium at the 6th hour, $t_{50\ \text{pectinase}}$ values were found to be 4.7 h, 8.1 h, and 24.6 h for the above mentioned formulations.

Compression force was not found to be a significant factor on none of the measured responses. Increased coating level from 400 to 500 mg did not affect the dissolution/erosion rates significantly, the only exception was $t_{50\ \text{pectinase}}$ that was found to be borderline significant ($P = 0.048$).

Table 4
Results of 3-way ANOVA for the main factors

Factor		N
Pectin–HPMC	60:40	4
	80:20	4
	100	4
Compression force	20	6
	30	6
Coat weight	400	6
	500	6

Pectin and HPMC are hydrophilic materials. The systems made from a mixture of these polymers will swell and form a hydrogel layer when they are placed in an aqueous medium. The relaxation of the polymer chains occur too fast and an increase in compression force from 20 to 30 kN was not influential on the hydration rates. Therefore, compression pressure would not be a reliable release modifying factor for compression coated tablets of pectin–HPMC.

Since the die diameter was constant, increasing coat weight from 400 to 500 mg the volume increase occurred axially and the side wall thickness stayed the same around the cores. When erosion proceeded drug exposure from the sides were indistinguishable between two coating levels.

The pure pectin coat was found insufficient to protect 5-ASA cores until the 6th hour where pectinase was added based on the time delivery concept. Pectin is water soluble and its mechanical properties are poor. Therefore, there is always a need to incorporate another polymer to produce a pharmaceutically acceptable film or a coating layer. The 80–20 pectin–HPMC coating mixture provided an intermediate erosion pattern for the colonic delivery of 5-ASA tablets. The 6th h time point for 80% pectin–20% HPMC system corresponded to 25–35% erosion rate. If one evaluates the 60–40 pectin–HPMC system 25% erosion occurs at about 9 h without enzyme and at the 8th h in the presence of enzyme. Hence, it was concluded that 6–40 system was too slow for drug delivery purposes.

Table 5
Results of 3-way ANOVA for the main factors

Source	Dependent variable	Type III SS[a]	df[b]	F[c]	Significance
Model	$t_{50\%\ pectinase}$	718.188	5	683	0.0001*
	$t_{50\%}$	2787.142	5	235	0.0001*
	$\Delta\%$	3028.667	5	46	0.0001*
Pectin–HPMC	$t_{50\%\ pectinase}$	56.782	2	135	0.0001*
	$t_{50\%}$	906.245	2	191	0.0001*
	$\Delta\%$	200.667	2	8	0.0170*
Compression force	$t_{50\%\ pectinase}$	0.120	1	0.571	0.475
	$t_{50\%}$	0.563	1	0.237	0.641
	$\Delta\%$	5.333	1	0.409	0.543
Coat weight	$t_{50\%\ pectinase}$	1.203	1	5.724	0.048*
	$t_{50\%}$	5.333	1	2.247	0.178
	$\Delta\%$	1.333	1	0.102	0.759

Model = pectin–HPMC + Compression force + coat weight
Adjusted $R^2 = 0.996$ $t_{50\%\ pectinase}$
Adjusted $R^2 = 0.990$ $t_{50\%}$
Adjusted $R^2 = 0.950$ $\Delta\%$

[a] Type III SS = Sum of squares.
[b] df = Degrees of freedom.
[c] F = Table value of the F distribution.

To determine the effect of pectinolytic enzyme, dissolution studies were carried out with and without the enzyme (Pectinex Ultra SP). The enzyme was added at the 6th h to simulate the colon arrival time under normal conditions. Drug release from hydrophilic polymers occurs through diffusion from the gel layer and erosion of the gel layer. When there is an enzyme in the environment dissolution rate changes due to increased destruction of pectin chains, hence, increasing erosion rate. In our experiments erosion curves significantly deviated starting from 6th h for 80–20 (Figs. 3–6) and 60–40 sytems (Figs. 4–7) after the addition of pectinase. Due to its fast solubility at the 6th h, only 35% of the coat had remained for 100% pectin coated tablets. The effect of pectinase was optimum after only a sufficient polymer hydration stage.

4. Conclusion

5-ASA containing core tablets were compression coated with a pectin–HPMC mixture. In vitro test results suggested that an optimum system for colonic delivery would be obtained using 20% HPMC (100.000 cP) and 80% pectin USP 100 mixture as coating material for 6 mm core tablets that had a 2 mm coat thickness on the side walls in a 10 mm die. Such system would have a $t_{50\%}$ value of 7.5 h and no drug release would be expected from such a system up to 6 h. Under the influence of pectinase which is found in the colon the coat erosion/degradation would be faster than in the small intestines and 5-ASA or any other candidate drug could be delivered to the colon.

Acknowledgements

The authors would like to acknowledge the genereous donations of Dr Falk GmbH, Germany, Copenhagen Pectin, Denmark, Novo Nordisk Ferment Ltd, Switzerland, and Shin-Etsu Chemicals Ltd., Japan.

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