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Research paper

Lauroyldextran and crosslinked galactomannan as coating materials for site-specific drug delivery to the colon

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Abstract

Lauroyldextran (LD) and crosslinked galactomannan (XGM) were investigated as microbiologically degradable film coating materials for site-specific drug delivery to the colon. LD was used with degrees of substitution between 0.12 and 0.40, and swelling in aqueous media between 195 and 50%, XGM-batches showed swelling between 309 and 520%. Theophylline tablets were coated in a Hüttlin Kugelcoater® with coating quantities of 4–17 mg/cm^2. Sprayable coating formulations were obtained with 4% aqueous dispersions of XGM or 4% dispersions of LD in a 1:1 mixture of 1-propanol and water with 10% glycerol (based on the polymer) as a plasticizer. Theophylline dissolution was monitored in a USP XXIII paddle dissolution apparatus with buffer pH 5.5. After 4 h, which is an average small intestine transit time, colon conditions were simulated by adding galactomannanase or dextranase, respectively. Results showed similar dissolution rates for all XGMs and high-swelling LDs during the first 4 h and a relatively quick disintegration after enzyme addition. Both parameters decreased with increasing coating quantities. Dissolution from low-swelling lauroyldextrans was very low but no disintegration was observed after enzyme addition. The disintegration rate was found to be proportional to the square root of the enzyme activity. All swollen materials exhibited low mechanical stability. XGM coatings, especially at higher coating quantities, showed small transient ruptures at the edges not caused by enzyme addition. This behaviour was explained by internal stress due to the high degree of swelling. In principle, materials of both types proved to be suitable as degradable coating materials. The ideal zero-dissolution before and quick disintegration after enzyme addition, however, was not realized with the present materials. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Colonic drug delivery; Film coating; Lauroyldextran; Crosslinked galactomannan; Microbiologically degradable coating excipients; Hüttlin Kugelcoater

1. Introduction

The local treatment of colonic diseases, e.g. ulcerative colitis [1] or colon cancer [2], is one of the applications of site-specific drug delivery to the colon. Furthermore, peptide-drugs like insulin [3] and vasopressin [4] may be absorbed from the large intestine when protected against the proteolytic enzymes of the small intestine.

A site-specific drug delivery to the colon may be achieved by different principles. One of those principles is a combination of site-specific and time-controlled release. Site-specificity is assured by an enteric coating, release is then delayed for a predetermined time during transit through the small intestine. This time-controlling system can be a slowly dissolving hydroxypropylmethylcellulose coating [5] or an inert capsule with a swelling hydrogel plug that is ejected at a predetermined degree of swelling [6]. Those systems still depend on reliable small intestinal transit times.

Real site-specificity has to make use of unique physiological properties of the colon, such as the enormous microflora with its reductive capacity and the ability to hydrolyze many polysaccharides and glycosides that are not attacked in the small intestine [7].

Prodrugs like sulfasalazin [8] or coating materials with

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Table 1

Results of coating and dissolution experiments of theophylline tablets coated with lauroyldextran and crosslinked galactomannan

Batch-no. of coated tablets[d]		Coating material		Coating quantity (mg/cm^2)	Coating thickness (mm, mean ± SD, $n = 5$) at position				Dissolution rate[a] (mg/h, mean ± SD)	Failures[a,c] (%)	Disintegration time[b] (min) with an enzyme activity of					
		DS	SI		a	b	c	d			15 DU/g		150 DU/g		750 DU/g	
Theo-LD	A1	0.123	1.95	5.09	55 ± 5	50 ± 0	44 ± 4	34 ± 4	10.15 ± 0.13	0			30	60	30	30
	A2			10.17	104 ± 6	96 ± 6	77 ± 8	50 ± 0	6.40 ± 0.25	0			90	90	40	60
	A3			15.00	152 ± 5	143 ± 7	108 ± 8	81 ± 6	4.73 ± 0.17	0			180	180	90	90
	B1	0.143	1.37	5.47	52 ± 6	48 ± 5	42 ± 5	30 ± 0	8.28 ± 0.56	0			–	150	90	60
	B2			10.94	113 ± 5	104 ± 6	76 ± 2	55 ± 4	5.80 ± 0.39	0			–	–	120	–
	B3			15.00	150 ± 0	141 ± 10	100 ± 12	76 ± 9	4.51 ± 0.32	0			–	–	–	–
	C1	0.233	0.80	4.71	44 ± 2	43 ± 5	42 ± 3	28 ± 8	8.28 ± 0.80*	0*	–	180	90	–	–	–
	C2			9.41	95 ± 7	85 ± 10	71 ± 7	54 ± 6	4.65 ± 0.22*	0*	–	–	–	–	–	–
	C3			15.00	144 ± 13	130 ± 14	112 ± 13	89 ± 9	2.63 ± 0.24	0			–	–	–	–
	D1	0.397	0.50	4.94	44 ± 6	40 ± 7	35 ± 6	25 ± 5	8.84 ± 1.41	0			–	–	–	–
	D2			10.21	102 ± 14	89 ± 7	74 ± 11	50 ± 10	3.60 ± 1.25	0			–	–	–	–
	D3			15.00	138 ± 18	132 ± 11	135 ± 14	104 ± 15	1.28 ± 0.19	0			–	–	–	–

Table 1 (continued)

Results of coating and dissolution experiments of theophylline tablets coated with lauroyldextran and crosslinked galactomannan

Batch-no. of coated tablets[d]		Coating material		Coating quantity (mg/cm^2)	Coating thickness (mm, mean ± SD, n = 5) at position				Dissolution rate[a] (mg/h, mean ± SD)	Failures[a,c] (%)	Disintegration time[b] (min) with an enzyme activity of		
		DS	SI		a	b	c	d			100 VHCU/g	1000 VHCU/g	10 000 VHCU/g
Theo-XGM	A1	n.d.	3.09	4.32	50 ± 7	54 ± 5	22 ± 4	24 ± 9	9.21 ± 0.82	0			41 ± 1
	A2			8.64	94 ± 9	86 ± 9	56 ± 15	40 ± 12	6.53 ± 1.46	17			80 ± 17
	A3			12.96	138 ± 15	130 ± 12	98 ± 15	82 ± 4	4.78 ± 0.31	33			125 ± 10
	A4			17.28	160 ± 19	162 ± 15	114 ± 26	102 ± 18	3.91 ± 0.73	50			155 ± 19
	B1	n.d.	5.20	4.34	54 ± 5	50 ± 7	36 ± 5	22 ± 4	8.12 ± 0.57$^+$	0$^+$	235 ± 41	70 ± 12	23 ± 8$^+$
	B2			8.68	88 ± 13	76 ± 11	50 ± 12	48 ± 13	5.13 ± 0.30	33			40 ± 0
	B3			13.01	106 ± 9	102 ± 4	82 ± 4	60 ± 0	4.26 ± 0.37	50			65 ± 6
	B4			17.35	160 ± 7	152 ± 8	108 ± 11	70 ± 14	3.62 ± 0.67	17			103 ± 12
	C1	n.d.	4.09	4.37	34 ± 9	40 ± 0	38 ± 4	26 ± 5	8.17 ± 0.51	0			20 ± 0
	C2			8.73	88 ± 8	76 ± 5	58 ± 4	42 ± 8	5.51 ± 0.27	50			45 ± 10
	C3			13.10	122 ± 4	114 ± 9	82 ± 4	62 ± 4	4.37 ± 0.18	67			80 ± 8
	C4			17.47	156 ± 9	144 ± 5	116 ± 9	88 ± 11	3.05 ± 0.20	33			125 ± 10
	D1	n.d.	3.57	4.41	34 ± 5	36 ± 5	36 ± 5	22 ± 4	9.52 ± 0.66	0			20 ± 0
	D2			8.82	76 ± 5	66 ± 5	68 ± 13	42 ± 8	6.21 ± 0.70	33			45 ± 10
	D3			13.23	116 ± 11	110 ± 10	108 ± 11	74 ± 9	4.47 ± 0.24	67			85 ± 13
	D4			17.64	148 ± 11	128 ± 11	128 ± 11	92 ± 11	3.47 ± 0.45	83			125 ± 10

[a]The dissolution rate and the percentage of failures were determined with n = 6 (*n = 8, ^+n = 18) samples.
[b]With Theo-LD-batches the disintegration time of both samples is given, with Theo-XGM values are mean ± SD of n = 4 (^+n = 6) samples. –, No disintegration within 4 h.
[c]'Failures' means the percentage of samples of a batch that was not stable in enzyme-free medium.
[d]The batch number of the coated tablets includes the drug ('Theo' for theophylline), the coating material (XGM A-D or LD A-D) and the coating quantity (1–3 or 1–4, in the order of increasing coating quantity).

azo-bonds [3,9] use the azo-reductive capacity of the colonic microflora. Glycosidic prodrugs are also capable of releasing a drug in the colon [10]. Prodrugs have the disadvantage that every drug needs its own prodrug.

Many systems have been realized using the polysaccharidase activity, e.g. matrix tablets consisting of crosslinked chondroitinsulfate [11], crosslinked dextran [12] and calcium pectinate [13,14]. However, a faster disintegration should be achieved by having an enzymatically degradable coating rather than a whole matrix tablet.

Our goal is to develop polysaccharide-based coating materials for oral dosage forms that are stable in the upper gastrointestinal tract and degraded by polysaccharidases of the colonic microflora [15]. Currently two materials are under investigation: crosslinked galactomannan [16] and lauroyldextran [17].

This paper presents data on coating experiments with crosslinked galactomannan and lauroyldextran characterized by different swelling behaviour. Tablet cores containing theophylline as a model drug are used. From dissolution experiments dissolution rates of theophylline, stability of the coated tablets in enzyme-free medium and the enzymatic disintegration of the coatings are determined.

2. Materials and methods

Unless stated otherwise, materials were supplied by Merck KGaA, D-64271 Darmstadt.

2.1. Preparation and characterization of coating materials

2.1.1. Lauroyldextran (LD)

Dextran 200 (mol.wt. 200 000–300 000, Boehringer Ingelheim, D-69115 Heidelberg, Germany) was modified with varying amounts of lauric acid chloride in formamide and pyridine at room temperature [17,18]. The polymer was precipitated with demineralized water and purified by washing with water and acetone (Carl Roth GmbH + Co., D-76185 Karlsruhe). The four products LD A-D were characterized by the average degree of substitution DS (number of substituted hydroxy groups per glucose unit, maximum value 3), determined by HPLC analysis after hydrolysis [18], and the swelling index in the buffer pH 5.5 used in the dissolution experiments. With DS ranging between 0.12 and 0.40 a swelling index between 1.95 and 0.50 was obtained (Table 1, column 2 and 3).

2.1.2. Crosslinked galactomannan (XGM)

Galactomannan (locust bean gum Rexer BCL 610, Burben S.A., Valencia, Spain) was crosslinked with butanediol-diglycidylether (Ciba Spezialitätenchemie, D-79662 Wehr) in aqueous medium [19]. The four materials XGM A-D used in the coating experiments had a swelling index between 3.09 and 5.20 (Table 1, column 3).

2.1.3. Determination of the swelling index (SI)

Films were cast by means of a spin casting device consisting of an internally Teflon-coated cylindric rotor with film-strips being formed on the inner surface. An outer thermostated jacket allows the evaporation of the solvents. Films of 10–20 mg/cm^2 were cast at a temperature of 55°C with the same dispersions as in the coating experiments. Pieces of 25 mg were immersed in buffer pH 5.5 at 37°C and weighed after swabbing buffer from the surface. After 1 h the water uptake has reached an equilibrium stage of swelling. The swelling index (SI) was calculated by $SI = (mass_{swollen} - mass_{dry})/mass_{dry}$, with $mass_{dry}$ being the mass of the dry film without plasticizer.

2.2. Cores

Biconcave 9 mm-cores with 100 mg theophylline (Knoll AG, D-67061 Ludwigshafen) as a model drug, 147 mg Ludipress® (93% α-lactose-monohydrate, 3.5% povidone K 30, 3.5% crospovidone, BASF AG, D-67056 Ludwigshafen, Germany) and 3 mg magnesiumstearate (Bärlocher GmbH, D-80992 München) were prepared by direct compression on a rotary tablet press. The surface area was calculated to 1.82 cm^2 per core.

2.3. Coating

Dispersions of 4% (w/w) lauroyldextran in a 1:1 (w/w) mixture of 1-propanol and water were prepared by simple stirring. As a plasticizer glycerol (Carl Roth GmbH + Co., D-76185 Karlsruhe) was added in a concentration of 10% (w/w) based on the lauroyldextran mass.

Four percent aqueous dispersions of crosslinked galactomannan without the addition of plasticizers were prepared by a 20 min homogenization with an Ultra-Turrax (Jahnke und Kunkel, D-79217 Staufen, Germany).

The approximate size of the swollen XGM particles was 10 mm, as microscopically determined. LD-dispersions coagulated without stirring so that the determination of particle size was not possible.

Cores with a mass of 150 g were coated in a Hüttlin Kugelcoater® HKC 005 (BWI Hüttlin GmbH, D-79585 Steinen, Germany) to theoretical polymer masses per surface area (coating quantities) of 5, 10 or 15 mg/cm^2 lauroyldextran and 4.3, 8.7, 13.0 or 17.4 mg/cm^2 XGM, respectively. Inlet air temperature was 38–45°C and core temperature was 28–34°C. The continuously stirred coating dispersions were sprayed at 20 g/min per m^2 with a 1 mm nozzle at an atomization pressure of 0.25×10^5 Pa.

2.4. Microscopic determination of the coating thickness

Cross-sections were prepared by cutting the coated tablets with a scalpel. The thickness of the coating in four different positions a, b, c and d, opposite to the cutting side was microscopically determined from the cross section of

five coated tablets from each batch at a magnification of 50 or 200 (Fig. 1) using an ocular micrometer.

2.5. Enzymes

For dissolution testing of the tablets coated with LD and XGM two corresponding enzyme solutions were used.

2.5.1. Dextranase

Dextranase 50 L (kindly provided by Novo Nordisk, Bagsvaerd, Denmark) is an endo-dextranase produced by *Penicillium lilacinum*. It is standardized to 50 000 dextranase units/g. One dextranase unit (1 DU) is that enzyme activity which is able to produce reducing sugar ends equivalent to 1 mg maltose/h.

2.5.2. Galactomannanase

Gamanase® 1.0 L (kindly provided by Novo Nordisk, Bagsvaerd, Denmark) is an endo-galactomannanase produced by *Aspergillus niger*. It is standardized to 1 000 000 viscosity hemicellulase units/g (VHCU/g). The enzyme activity of Gamanase® is determined by measuring the decreasing effect on the viscosity of a locust bean gum solution compared with a standard enzyme [20].

2.6. Dissolution

Dissolution tests were carried out according to a modified USP XXIII paddle method (DT D-6, DT 6 and DT, Erweka GmbH, D-63130 Heusenstamm, Germany) with 300 ml buffer pH 5.5 (citric acid 43.08 mmol/l, Na_2HPO_4 113.91 mmol/l) with regard to economic use of the enzymes, 37°C, at a paddle speed of 50 min^{-1}. After 4 h enzyme solution was added leading to the declared activity. The pH of 5.5 in our dissolution experiments was chosen as a compromise between human physiology and the pH optima of the enzyme solutions. Control experiments without enzyme addition were carried out. Drug release was monitored by taking samples of the dissolution liquid through 0.22 mm membrane filters. After appropriate dilution the UV-absorption at 272 nm was measured with a UV/VIS Spectrophotometer (Perkin Elmer Lambda 11, Bodenseewerk Perkin-Elmer, D-88662 Überlingen, Germany) against corresponding blank solutions. In Figs. 2 and 3, individual dissolution curves are shown.

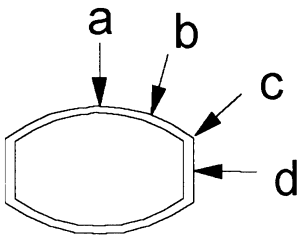

Fig. 1. Determination of the coating thickness at four positions a–d from the cross-section of a coated tablet.

3. Results

3.1. Coating with lauroyldextran

The development of an applicable coating preparation led to 4% dispersions in a 1:1 mixture of 1-propanol and water. Coagulation and sedimentation of those dispersions was prevented by simple stirring. Water, 2-propanol and acetone, and mixtures of these solvents were not suitable for the preparation of sprayable dispersions due to the insufficient dispersion of particles or insufficient film-forming properties. The brittleness of cast lauroyldextran films demonstrated the need for a plasticizer. Lipophilic plasticizers such as triethylcitrate or glyceroltriacetate were not compatible with lauroyldextran, whereas hydrophilic plasticizers such as sorbitol and glycerol led to soft, clear films. Glycerol was preferred due to the better reproducibility. The concentration of 10% (based on the polymer) was sufficient to prevent visible cracks and did not lead to sticky tablet surfaces. By comparing the mass of the coated versus the uncoated tablets, no losses of the sprayed dispersions were observed as a consequence of the bottom spray technique of the Hüttlin Kugelcoater®. Coating thickness at the edges at position d was half of those at position a and b (Table 1). Spraying of 1 mg/cm^2 lauroyldextran and 10% glycerol, i.e. 1.1 mg/cm^2, led to a thickness of 9 mm at position b.

3.2. Dissolution of theophylline from lauroyldextran coated tablets

During the in vitro dissolution experiments the obligatory gastric resistance was not studied, as it can be achieved with conventional enteric coatings. Theophylline dissolution in buffer pH 5.5 was monitored for 4 h as an average small intestine transit time. After 4 h the passage to the caecum was simulated by adding different amounts of dextranase to the dissolution medium ($n = 2$ for each dextranase concentration), whereas other samples served as enzyme-free control experiments ($n = 2$).

Swelling of the coating led to penetration of dissolution medium into the core and to subsequent diffusion of theophylline. With all the samples an almost linear dissolution was obtained in the first 4 h (Fig. 2). The dissolution rate was determined by linear regression of the data between 7 and 20 mg released theophylline (Table 1). The dissolution rate decreased with increasing coating quantity and increasing degree of substitution.

Dextranase activity in human caecostomy effluent samples was reported to be 650 DU/ml, equivalent to 30 U/ml measured in conventional enzyme units [21], and 15 DU/g equivalent to 0.69 U/g in human fecal samples [12]. In order to cover this range of activities the dextranase activity in the dissolution medium was adjusted to 15, 150 or 750 DU/g.

After addition of dextranase the coatings with a lower degree of substitution began to disintegrate at the edges with a subsequent increase in dissolution rate. The approx-

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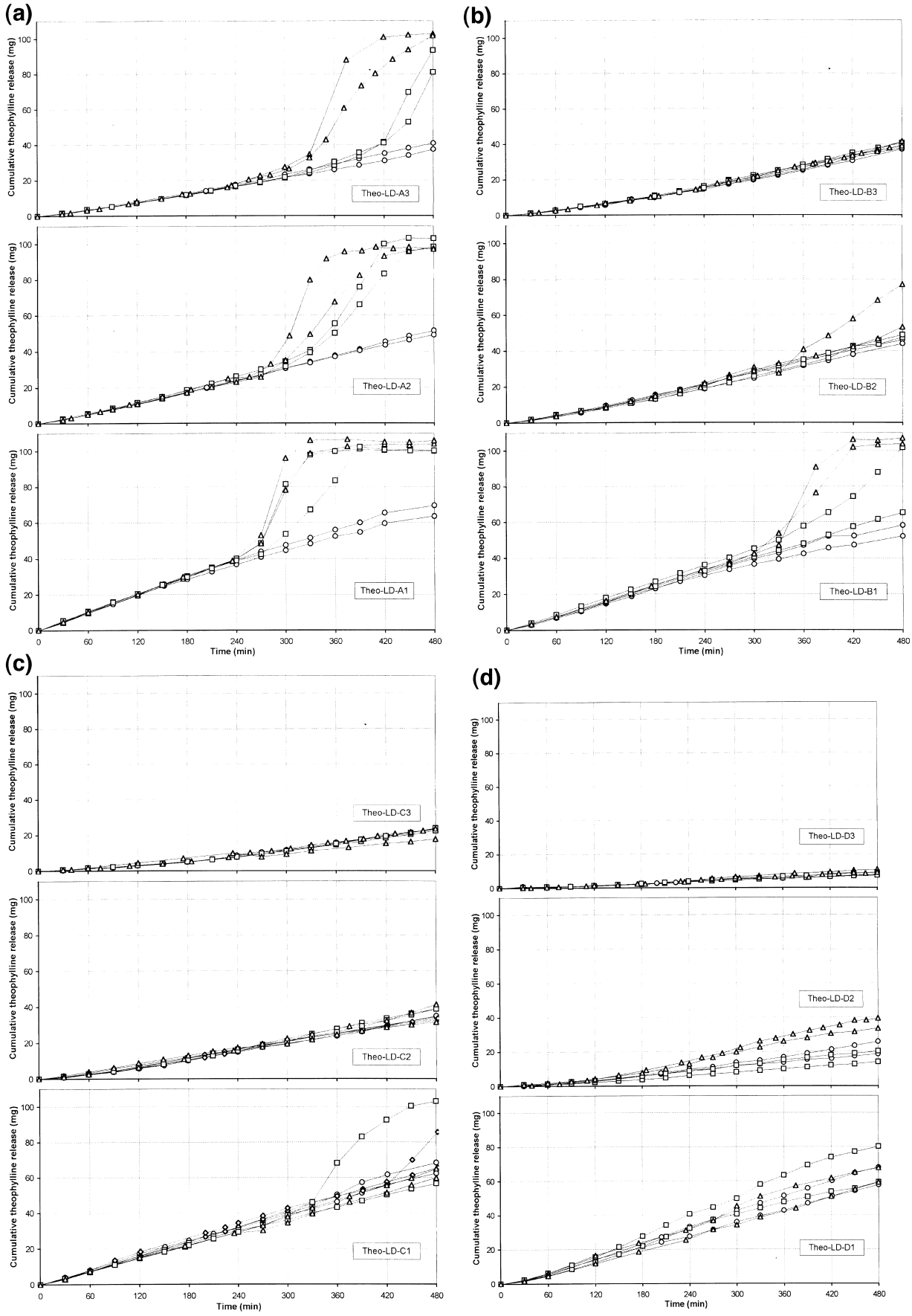
(a)
(b)
(c)
(d)
Cumulative theophylline release (mg)
Time (min)
Theo-LD-A3
Theo-LD-A2
Theo-LD-A1
Theo-LD-B3
Theo-LD-B2
Theo-LD-B1
Theo-LD-C3
Theo-LD-C2
Theo-LD-C1
Theo-LD-D3
Theo-LD-D2
Theo-LD-D1

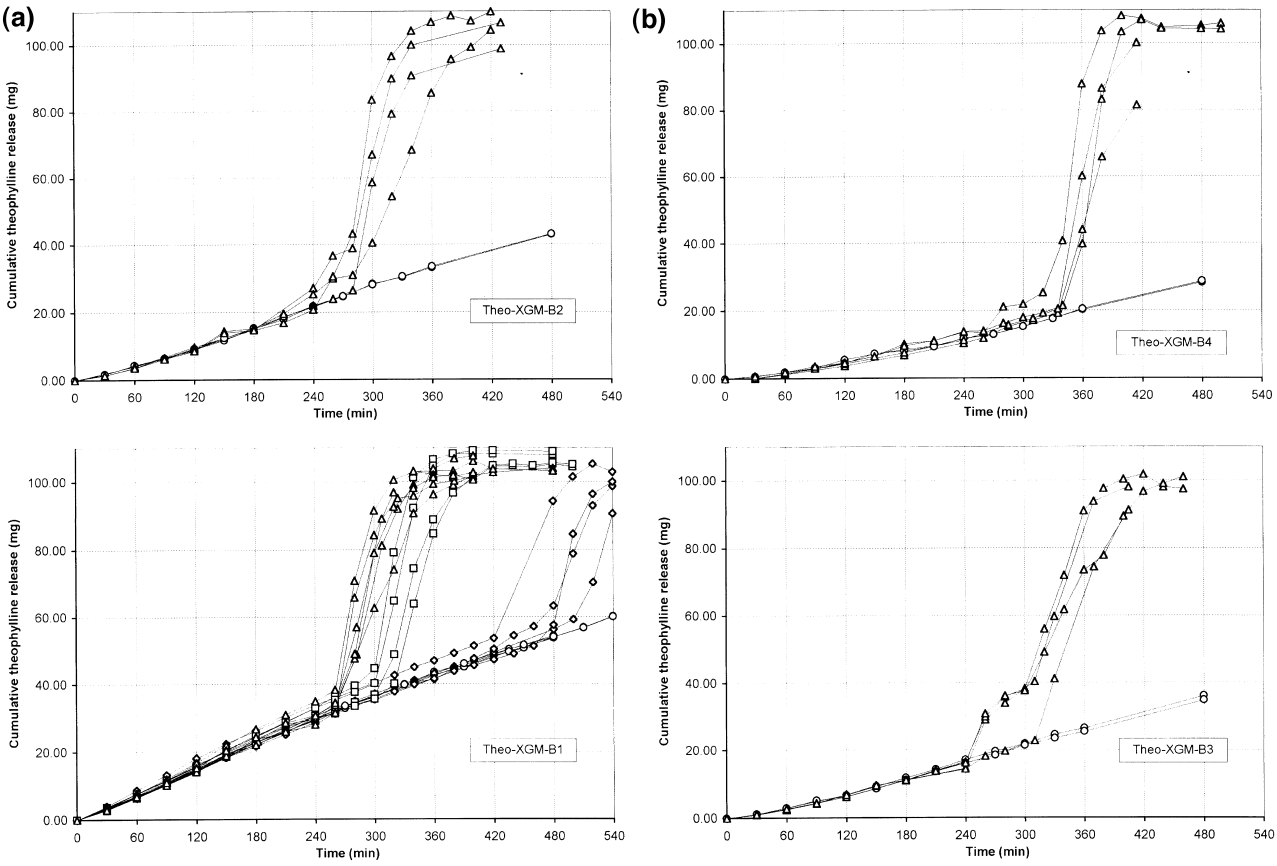

Fig. 3. Theophylline dissolution in buffer pH 5.5 from Theo-XGM-B1 to Theo-XGM-B4, 100 mg theophylline tablets coated with varying coating quantities of crosslinked galactomannan XGM B. After 240 min galactomannanase was added leading to enzyme activities of 100 (-◇-), 1000 (-□-) or 10 000 VHCU/g (-Δ-). Two samples served as enzyme-free control experiments (-○-).

imate lag time between enzyme addition and disintegration (disintegration time) was determined (Table 1). The disintegration time decreased with increasing enzyme activity and increased with increasing DS and increasing coating quantity. No reproducible disintegration was observed within 4 h after enzyme addition with a DS of 0.2332 and higher. In the control experiments without addition of enzyme no disintegration of the coated tablets occurred within 8 h.

3.3. Coating with crosslinked galactomannan

Four percent aqueous dispersions homogenized with an Ultra-Turrax are suitable coating formulations for crosslinked galactomannans. No plasticizer was added, as the coatings did not show any sign of brittleness. More than 4% solids content, both with XGM- and LD-dispersions, often occluded the spraying nozzle. As with the lauroyldextrans the mass gain of the coated versus the uncoated tablets revealed no losses of spraying dispersion and the coating thickness at the edges was half of that at position b (Table 1). Coating of 1 mg/cm^2 was equivalent to a coating thickness of 8–9 mm at position b.

3.4. Dissolution of theophylline from crosslinked galactomannan coated tablets

Dissolution experiments with crosslinked galactomannan coated tablets were carried out with the same parameters as with the lauroyldextran tablets. After 4 h in buffer pH 5.5 varying amounts of galactomannanase were added ($n = 4$ for each enzyme concentration, except from $n = 6$ with Theo-XGM-B1 at 10 000 VHCU/g). Some of the samples continued as enzyme-free control experiments ($n = 2$). Since the dissolution curves of the XGM-tablets only showed quantitative variations, just the representative curves of Theo-XGM-B-tablets are given in Fig. 3. In the first 4 h almost linear dissolution of theophylline was

Fig. 2. Theophylline dissolution in buffer pH 5.5 from all Theo-LD-batches, 100 mg theophylline tablets coated with varying coating quantities of the lauroyldextrans LD A-D. After 240 min dextranase was added leading to enzyme activities of 15 (-◇-), 150 (-□-) or 750 DU g^{-1} (-Δ-). Two samples served as enzyme-free control experiments (-○-).

observed. The dissolution rate was determined by linear regression of the data between approximately 5 and 15 mg released theophylline (Table 1). Generally the dissolution rate decreased with increasing coating quantity.

Galactomannanase activity of human fecal samples and pig caecum samples was determined to be in the range of 100 VHCU/g [18]. With Theo-XGM-B1, tablets coated with 4.34 mg/cm^2 XGM B, dissolution experiments with 100, 1000 and 10 000 VHCU/g showed lag times from enzyme addition to beginning disintegration of 4, 1 and 0.5 h, respectively. In order to induce a disintegration after enzyme addition within 4 h, for all other experiments an activity of 10 000 VHCU/g was chosen.

In contrast to the LD-coated tablets some XGM-coated tablets, especially those with a higher coating quantity, showed mechanical instability not directly caused by enzymatic action. Their coatings were perforated in distinct small areas at the edges and closed again to finally disintegrate with the other tablets of this lot. This led to a characteristic parallel shift in the dissolution curves.

4. Discussion

4.1. Mechanical stability without enzymatic degradation

In aqueous media both lauroyldextrans and crosslinked galactomannans were swelling. In the case of the lauroyldextrans the hydrated films were soft and formed a very flexible sack around the slowly dissolving tablet core.

XGM coatings in the swollen state, however, showed an elasticity comparable to rubber balls. As mentioned above, unfortunately during dissolution testing some of them failed by releasing a small amount of drug for some minutes without enzymatic degradation. The frequency of those failures increased with increasing coating quantity except from two samples (Fig. 4). This behaviour may be explained by a simple model (Fig. 5). Coatings of crosslinked galactomannan consist of internally crosslinked small particles,

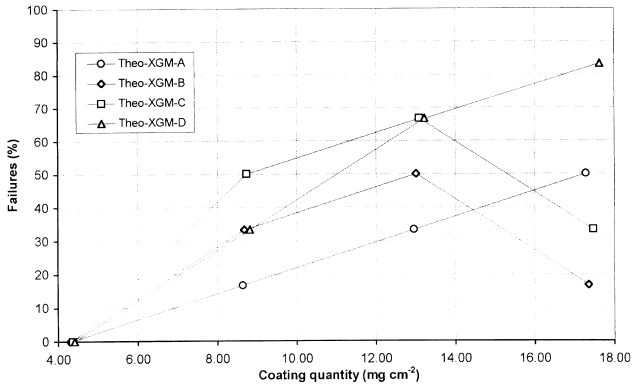

Fig. 4. Percentage of Theo-XGM-samples unstable without enzymatic degradation as a function of the coating quantity (n = 6, Theo-XGM-B1: n = 18).

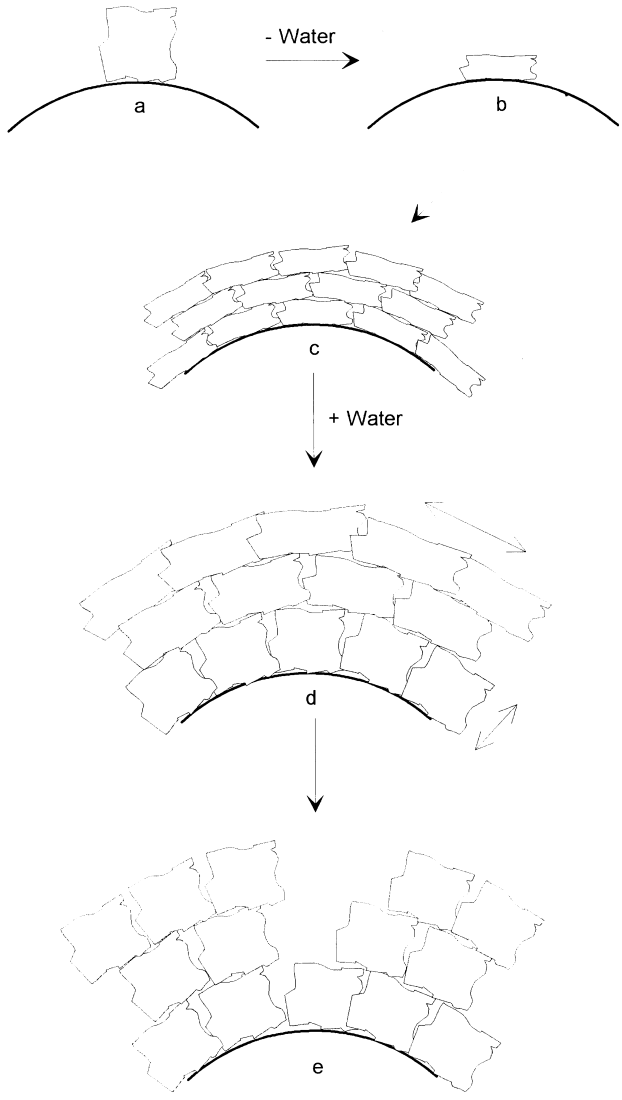

Fig. 5. Model for the mechanical instability of swollen XGM-coatings (explanations see Section 4.1).

whereas, binding between particles is probably achieved by hydrogen bonds and interpenetration of the outer polymer chains. During the coating process the particles swollen homogeneously in all three dimensions are sprayed onto the tablet surface (Fig. 5a). Adhesion to the tablet surface leads to a mainly vertical drying (Fig. 5b). Now the next swollen particles hit upon a dry surface and by repetition of this process a consistent film is formed (Fig. 5c). During rehydration all single particles tend to regain their initial dimensions. Due to the curvature of the tablet surface the upper layers of XGM-particles are now stressed (Fig. 5d) and the film may split (Fig. 5e). With increasing coating quantity the tension in the upper layers and consequently the probability of a failure increases.

The problem described above is a basic problem of films that consist of crosslinked particles with a high degree of swelling. It may not occur when the swelling of the materi-

als is lower or the interparticle binding forces are stronger. The problem can also be minimized by choosing a sphere as tablet geometry due to the homogeneous distribution of internal stresses in the coating.

4.2. Dissolution rate of theophylline

As an unwelcome consequence of swelling the drug intended to be released in the colon diffused through the coating prior to enzymatic degradation. Due to the low solubility there is a saturated solution of theophylline inside the coating leading to a zero order dissolution. The dissolution rates of all Theo-XGM- and Theo-LD-tablets are plotted in Fig. 6 as a function of the coating quantity. The dissolution rates of the Theo-XGM-tablets do not differ to a great extent, whereas the theophylline dissolution rate through lauroyldextrans especially at the highest coating quantity is exactly in the order of increasing SI and decreasing degree of substitution.

The further analysis of this data, according to Fick's law of diffusion, is possible when the thickness and the surface area of the swollen coating is known. Measurements of those parameters is difficult at intact swollen tablets. However, thickness and surface area can be calculated from the swelling index assuming degrees of vertical and horizontal swelling. The explanation of those calculations is beyond the scope of this paper and given in Ref. [18]. By neglecting the lower coating thickness at the edges a diffusion coefficient of 5×10^{-6}cm^2/s for theophylline in swollen XGM coatings was calculated. With lauroyldextran coatings, diffusion was assumed to occur only in the water moiety of the swollen coating which sufficiently explained the differences in the dissolution rates. A common diffusion coefficient of about 1×10^{-6} cm^2/s was calculated for theophylline diffusion in the water moiety of swollen lauroyldextran coatings. These values suggest an almost unhindered diffusion in swollen XGM coatings, whereas theophylline permeation through swollen lauroyldextran coatings is hindered on the one hand by a lower diffusion coefficient and on the other hand, by a smaller moiety of the film accessible to diffusion. The overall similar dissolution rates for XGM and low-DS-lauroyldextran coatings are explained by lower swelling, also leading to lower thickness of the swollen coating that again enhances permeation.

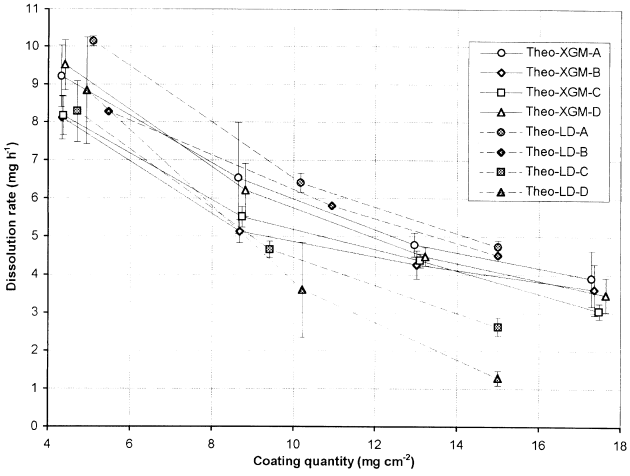

Fig. 6. Dissolution rate of theophylline during the zero-order release in the first 4 h as a function of the coating quantity. Values represent mean ± SD of $n = 6$ samples (for exceptions see Table 1).

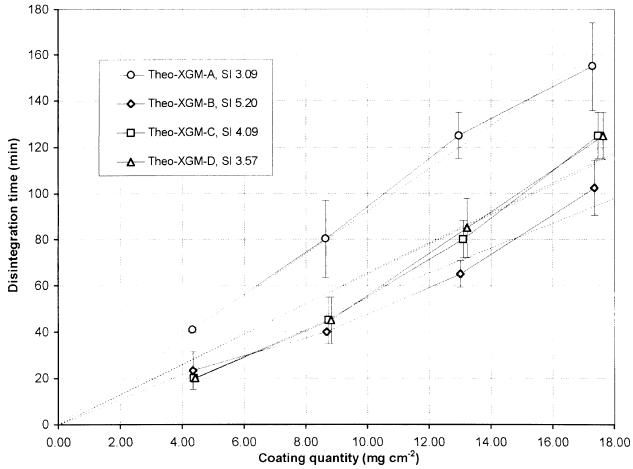

Fig. 7. Disintegration time of Theo-XGM-samples after addition of 10 000 VHCU/g galactomannanase as a function of the coating quantity. Values represent mean ± SD of $n = 4$ samples (for exceptions see Table 1). The dotted lines represent linear regressions through zero.

4.3. Enzymatically induced disintegration

The disintegration of the coatings is influenced by coating quantity and enzyme activity. For the following discussion the disintegration time is defined as the time between enzyme addition and the beginning disintegration of the coatings marked by increasing theophylline dissolution. The data of the XGM tablets at an enzyme activity of 10 000 VHCU/g (Fig. 7) allow the assumption of proportionality between coating quantity and disintegration time. The inverse slope of the linear regression through zero is defined as disintegration rate. The disintegration rate depends on the swelling index SI of each XGM-material (Fig. 8). The stronger crosslinked and less swelling materials are obviously degraded more slowly. An explanation may be that with a stronger crosslinked material more cleavages are necessary to disintegrate the film. A second explanation may be the slower penetration of large molecules such as enzymes in the more narrow-meshed network.

The disintegration rate also depended strongly on the enzyme activity, as was shown with samples from Theo-XGM-B1. Here the disintegration rate, calculated by dividing the coating quantity by the disintegration time, was empirically found to be proportional to the square root of the enzyme activity (Fig. 9).

With all lauroyldextran coated tablets the disintegration of two samples was examined at dextranase activities of 150

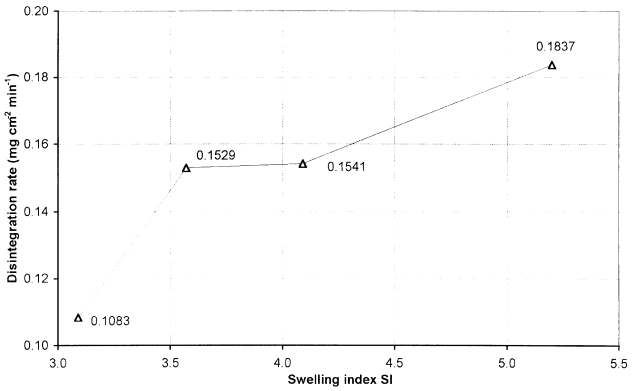

Fig. 8. Disintegration rate of XGM-coatings at an enzyme activity of 10 000 VHCU/g as a function of the swelling index SI.

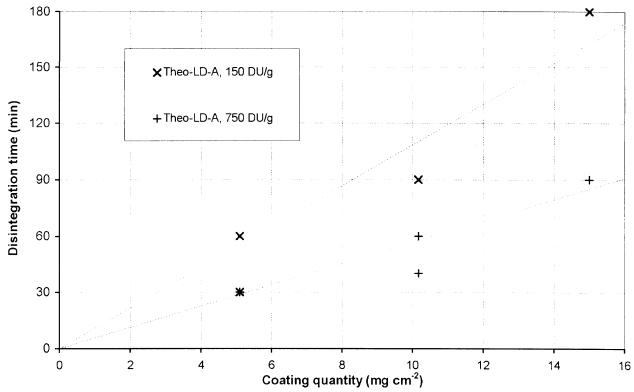

Fig. 10. Disintegration time of Theo-LD-A-samples after addition of 150 and 750 DU/g dextranase as a function of the coating quantity. Both values are given (may be identical) for each coating quantity and enzyme activity. The dotted lines represent linear regressions through zero for both enzyme activities.

and 750 DU/g, with Theo-LD-C1 and -C2 also at 15 DU/g. No disintegration within 4 h was observed with lauroyldextrans C (SI 0.80) and D (SI 0.50). This only allowed the calculation of a maximum disintegration rate from the minimal coating quantity and the 4 h at an enzyme activity of 750 DU/g not leading to disintegration. This maximum disintegration rate was 0.02 mg/cm^2 per min for both materials.

With only two values the calculation of disintegration rates for the other lauroyldextrans was less accurate as for the crosslinked galactomannans. The disintegration time of Theo-LD-A was plotted as a function of the coating quantity (Fig. 10). The disintegration rate was calculated from a linear regression through zero. With Theo-LD-B only the samples with the lowest coating quantity examined at the highest enzyme activity showed a reproducible disintegration. A disintegration rate of 0.073 mg/cm^2 per min was calculated. Fig. 11 illustrates the strong dependence of the disintegration rates on the swelling index.

In further studies also the influence of factors kept constant in this study should be considered. Those factors are the differentiation in ‘endo-’ and ‘exo-’enzyme activity, the coating thickness at the weakest region of the coating and the mechanical stress by stirring in the dissolution device.

5. Conclusion

The evaluation of crosslinked galactomannans and lauroyldextrans as coating materials for colonic drug delivery revealed several factors that need further optimization. Disintegration rates and dissolution rates of crosslinked galactomannans and high-swelling lauroyldextrans were similar. Low-swelling lauroyldextrans exhibited low dissolution rates but showed no degradability under the experimental conditions.

Dissolution followed the laws of diffusion so that with more water-soluble drugs higher dissolution rates prior to enzymatic degradation can be expected. For the evaluation of the enzymatic degradation more data on enzyme activ-

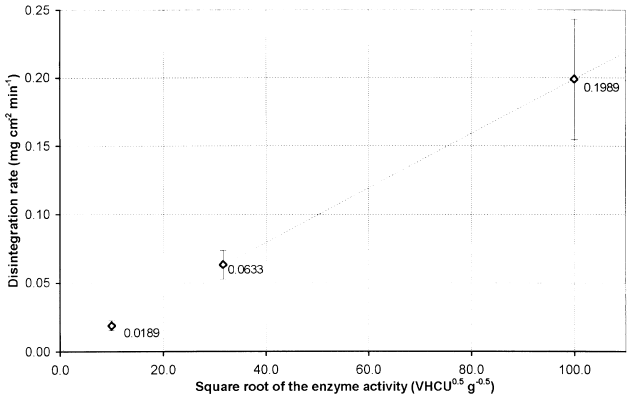

Fig. 9. Disintegration rate of Theo-XGM-B1 as a function of the square root of the enzyme activity. Values and error bars represent the mean ± SD (n = 4 samples with 100 and 1000 VHCU/g, n = 6 samples with 10 000 VHCU/g). The dotted line represents a linear regression through zero of the mean disintegration rates (n = 3, R = 0.99997).

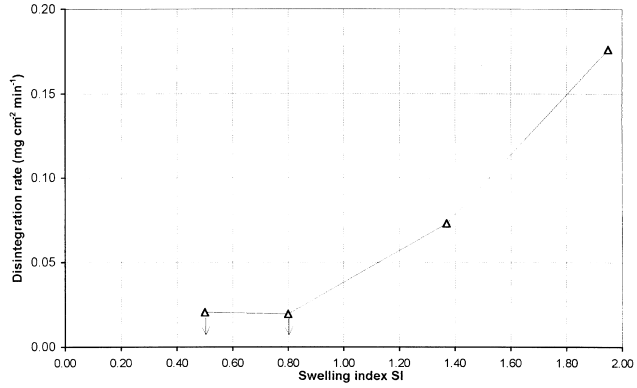

Fig. 11. Disintegration rate of LD-coatings at an enzyme activity of 750 DU/g as a function of the swelling index SI. Values with arrows are maximum disintegration rates where no disintegration occurred within the observation time.

ities in the colon and on optimum degradation conditions are needed. As a last critical aspect the mechanical stability of the films, especially with crosslinked galactomannan, became obvious.

In principle materials of both types proved to be suitable as degradable coating materials. The ideal zero-dissolution before and quick disintegration after enzyme addition, however, was not realized with the present materials.

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