

Pectin/chitosan/Eudragit® RS mixed-film coating for bimodal drug delivery from theophylline pellets: Preparation and evaluation

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Pellets containing theophylline as a model drug and microcrystalline cellulose, in a ratio of 6:4, were prepared by the extrusion-spheronization method. The pellets were coated with Eudragit® RS aqueous dispersions, containing various amounts of pectin-chitosan complex and different coating mass gains, using a fluidized-bed apparatus. Twelve formulations were developed, which differed in two factors: coating mass gain (10, 15 and 20%, *m/m*) and the amount of pectin-chitosan complex (5, 10, 15 and 20%, *m/m*). Drug release studies were conducted using the USP apparatus I (basket) in dissolution media, mimicking the conditions prevailing in the stomach, small intestine or colon. Studies have shown that the drug release rate and pattern were dependent on both of the two mentioned factors. Some formulations showed bimodal and burst drug release, being triggered in the colonic medium by the action of pectinolytic enzymes. In formulations with 15 or 20% (*m/m*) of coating mass gain and 5 or 10% (*m/m*) of pectin-chitosan, the burst drug release was eliminated and replaced by the lag phase of drug release. In the case of burst drug release in the colonic medium, formulations with 20% (*m/m*) of coating mass gain and 15 or 20% (*m/m*) of pectin-chitosan were found to be better than the other formulations. Studies on the surface SEMs of uncoated and coated pellets show that after coating, coated pellets become smoother and exposure to pectinolytic enzymes in the colonic medium may result in surface erosion.

Keywords: bimodal drug delivery, burst release, chitosan, Eudragit® RS, mixed-film coating, pectin, pellet

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Multiple-unit dosage forms are based on subunits such as granules, pellets, or mini-tablets and they are usually delivered in hard gelatin capsules (1). The recent interest in multiple-unit dosage forms is a result of the advantages they offer over the single-unit systems (*e.g.*, tablets). Multiple-unit forms offer more predictable gastric emptying, less

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dependent on the state of nutrition, less variance in transit time through the gastrointestinal tract (GIT), a higher degree of dispersion in the digestive tract, less absorption variability, and a lesser risk of dose dumping than single-unit dosage forms (2).

Bimodal or sigmoidal drug release profiles, where release is slow in the initial stages and increases to a faster release rate in some later stages, may be of significant therapeutic benefit (3). In disease states such as nocturnal asthma, increased drug release rates may help prevent the exacerbation of symptoms caused by circadian rhythms (4). Bimodal release profiles could be utilized so that drug release is slower in a region within the GIT where absorption is good, *i.e.*, small intestine and the lower GIT where drug absorption may be poor, *i.e.*, the colon. The overall effect being to maintain therapeutic blood drug levels throughout (5).

Natural or modified polysaccharides such as gelatin, dextran, chondroitin sulphate, calcium pectinate, pectin and chitosan have been used as potential carriers for the oral delivery of drugs to the colon because they are safe, biodegradable and widely available (6).

Among these polymers, pectin and chitosan have shown particular promise, since they are able to form a polyelectrolyte complex (PEC). Complexation of pectin with chitosan allows control over drug release while maintaining the pectin ability to be degraded by colonic bacteria, thus potentially achieving bimodal delivery (5).

The major problems encountered with polysaccharides such as pectin and chitosan are their high water-solubility and swelling properties in aqueous media. Films consisting of pectin and chitosan are unable to prevent fast drug release during its transit through the stomach and small intestine. However, incorporation of hydrophilic degradable polysaccharides in water-insoluble film-forming polymers such as cellulosic or acrylic polymers could provide a promising alternative. The integrity of such a mixed-film could be better controlled by preventing fast swelling and solubilization of pectin and chitosan during the transit from mouth to colon. On the other hand, the film degradability is maintained by the pectinolytic enzymes of the colonic flora, which is expected to generate pores for drug release or coating disintegration during the colonic transit (7).

The objective of this paper was to develop and evaluate the potential of Eudragit® RS, containing various amounts of pectin-chitosan complexes (as coating material) and different coating mass gains, intended for bimodal or sigmoidal drug release from a multiple-unit of theophylline pellets. *In vitro* dissolution studies have been carried out in simulated GIT media on coated theophylline pellets. Influence of the pectin-chitosan amount, coating mass gain, the presence of pectinolytic enzymes in the simulated colonic medium and acidic dissolution environment on the drug release was also investigated. Theophylline was used as a model drug, since it is known to be well absorbed from the wide regions of the gastrointestinal tract (8).

EXPERIMENTAL

Materials

Theophylline anhydrous was supplied by BASF (Germany), Eudragit® RS and Eudragit® L100-55 were kindly provided by Röhm Pharma GmbH (Germany). Microcrys-

talline cellulose (Avicel® PH 101) was supplied by FMC Corp. (USA). Pectin HM (High Methoxylated) from citrus fruit and chitosan [low molecular mass, 84.7% deacetylated, viscosity 1% (*m/V*) solution in acetic acid 1% (*V/V*) is 34 mPas] were purchased from Sigma-Aldrich (UK). Pectinex® Ultra SP-L (pectinolytic enzymes extracted from *Aspergillus niger*) was kindly donated by Novo Nordisk Ferment (Switzerland). According to the Pectinex® producer, it has a standard activity of 26000 pg mL⁻¹ (pH 3.5). The Pectinex® Ultra SP-L solution contains a mixture of pectinolytic enzymes, mainly polygalacturonases, pectin esterases and pectin lyases and was used to mimic the conditions in the colon. The other materials were of pharmaceutical or analytical grade, and were used as received.

Methods

Preparation of theophylline pellets. – Theophylline pellets were prepared by the extrusion-spheronisation method (laboratory unit, Gabler GmbH, Germany). A 100-g batch of theophylline anhydrous and microcrystalline cellulose (Avicel® PH 101), in a mass ratio of 6:4, was mixed in a plastic bag for 10 min, kneaded with 95 mL of deionized water and loaded into the extruder (extruder type E-35, Gabler). Wet mass extrusion was carried out shortly after moistening to avoid any water loss, using an axial type, single-screw extruder provided with a 1.0-mm screen (for both the orifice diameter and screen thickness). The extruder rotation speed was kept constant at 90 rpm. The extrudates were immediately transferred to a spheronizer (spheronizer type R-250, Gabler) equipped with a crosshatch plate and processed at 1000 rpm rotating speed for 15 min. Pellets were collected and dried in a hot air oven at 50 °C for 12 h.

Preparation of the polyelectrolyte complex (PEC) and coating dispersion. – In this study, due to formulation of pectin and chitosan as biodegradable coating materials, first a complex between two polymers was formed and then the complex was incorporated in Eudragit® RS films, since pectin-chitosan itself has no film-forming properties. Eudragit® RS is a copolymer of acrylic acid and methacrylic esters with a low content of quaternary ammonium groups. It was chosen as film-former because it gives water-insoluble, pH-independent, low permeable films, which are inert to endogenous digestive secretions and enzymes (9).

Chitosan was dissolved in 0.1 mol L⁻¹ acetic acid and pectin was dispersed in distilled water. The chitosan solution was slowly added to the pectin aqueous dispersion. Then, the pH of the mixture was adjusted to 5.4 with 0.1 mol L⁻¹ HCl or 0.1 mol L⁻¹ NaOH and allowed to react under mechanical stirring for 1 hour. After mixing, it was filtered and the filter cake was washed with 0.1 mol L⁻¹ acetic acid to remove free chitosan and then washed with warm water until the filtrate became neutral. After being dried at 50–60 °C, the PEC was dispersed in formic acid (10%, *V/V*). Then, appropriate amounts of the pectin-chitosan complex suspension were added to the aqueous dispersion of Eudragit® RS30D. Eudragit® RS30D was previously mixed for 30 min with triethyl citrate (TEC) as a plasticizer (10%, *m/m*, related to the solid content of Eudragit® RS30D).

Eudragit® RS requires addition of 10–20% of plasticizers in order to lower the minimum film forming temperature (MFT) below 30 °C (9). The compositions of different coating dispersions are presented in Table I.

Table I. Composition of formulations F₁–F₁₂

Formulation code	Eudragit® RS (solid content, g)	Eudragit® RS30D (g)	Pectin-chitosan complex (g)	Triethyl citrate (g)	Water ad (g)	Pectin-chitosan complex in film (% <i>, m/m</i>)	Theoretical CMG (% <i>, m/m</i>) ^a	Actual CMG (% <i>, m/m</i>) ^b
F ₁	9.50	31.67	0.5	0.95	285	5	10	9.8 ± 0.2
F ₂	9.00	30.00	1.0	0.90	270	10	10	9.5 ± 0.1
F ₃	8.50	28.33	1.5	0.85	255	15	10	8.7 ± 0.6
F ₄	8.00	26.67	2.0	0.80	240	20	10	8.9 ± 0.4
F ₅	14.25	47.50	0.75	1.42	427.5	5	15	14.1 ± 0.2
F ₆	13.50	45.00	1.5	1.35	405	10	15	13.5 ± 0.8
F ₇	12.75	42.50	2.25	1.27	382.5	15	15	13.8 ± 0.5
F ₈	12.00	40.00	3.0	1.20	360	20	15	13.3 ± 0.2
F ₉	19.00	63.33	1.0	1.90	560	5	20	18.6 ± 0.1
F ₁₀	18.00	60.00	2.0	1.80	540	10	20	18.1 ± 0.9
F ₁₁	17.00	56.67	3.0	1.70	510	15	20	19.0 ± 0.3
F ₁₂	16.00	53.33	4.0	1.60	480	20	20	17.9 ± 1.2

^a CMG: coating mass gain.

^b Mean ± SD, *n* = 3.

Coating processes. – Known masses of pellets (100 g) of 25-mesh were transferred into a fluidized-bottom spray coating system assisted by a Wurster column (Uni-Glatt, Glatt GmbH, Germany) and then coated with each dispersion medium (Table I). During the coating operations, the aqueous dispersions were continuously stirred in order to prevent sedimentation of the insoluble materials. The operating conditions during the coating process can be described as follows: inlet and outlet temperatures of drying air were of 48–50 °C and 30–32 °C, respectively. Pneumatic spraying pressure and spraying rate were set correspondingly at 1.5 bar and 10 mL min⁻¹. After coating, the resulting coated pellets were cured at 60 °C for 24 hours.

Drug content determination. – The drug contents of uncoated and coated pellets were determined by HPLC analysis (10). The HPLC (LC1445 model, GBC Scientific Equipment, Australia) consisted of a pump (LC1150 model) set at a constant flow rate of 2 mL min⁻¹, a variable UV detector (LC1205 model) set at 280 nm, and Eurospher®-100 C18 (4.6 × 250 mm) reversed-phase column, 5 µm. The eluant solution consisted of a mixture of acetonitrile and acetate buffer solution pH 4.5 (7:93). After determination of the drug content, hard gelatine capsules No. 2 were filled manually with an appropriate amount of coated pellets (equivalent to 200 mg of theophylline) for each formulation. Then, the capsules were enteric-coated by alcoholic solution of Eudragit® L100-55 polymer in a conventional coating pan (approximately 100 mg of polymer for each capsule).

Drug release study. – Drug release studies were conducted using the USP basket method (apparatus I) at 100 rpm and 900 mL of dissolution fluid at 37 ± 0.5 °C. Three en-

teric-coated capsules of each formulation were tested individually in 0.1 mol L⁻¹ HCl (pH 1.5) for the first two hours, phosphate buffer pH 7.4 for the second three hours and phosphate buffer pH 6.0 containing pectinolytic enzymes (4 mL L⁻¹) for the third five hours. These media were chosen to mimic the conditions in the stomach, small intestine and colon, respectively. At predetermined time intervals, 5 mL of medium was sampled and replaced by an equal volume of fresh medium. Samples were filtered, diluted and analyzed. The amount of drug released was assayed spectrophotometrically at λ_{\max} = 270.5, 271.8 and 271.7 nm for the first to third medium, respectively.

Determination of size distribution of pellets. – Pellet size distribution was determined using the sieve analysis method. Approximately 50 g of coated pellets were placed on the top sieve in the sieve shaker (AS200 digit model, Retsch®, Germany) equipped with 10, 14, 18, 25, 35, 45 and 60-mesh US standard sieves and were shaken for 10 min. Orifice sizes of the aforementioned sieves were 2000, 1410, 1000, 710, 500, 350 and 250 μm , respectively. Finally, the mass of each fraction was measured.

Scanning electron microscopy (SEM). – Surface morphology views of both uncoated and coated pellets, before and after the dissolution test, were photographed using a scanning electron microscope (MV2300 model, Obducat CamScan Ltd, UK). Prior to examination, samples were gold sputter-coated to render them electrically conductive.

RESULTS AND DISCUSSION

Both uncoated and coated theophylline pellets were successfully produced using the extrusion-spheronization and fluidized bed bottom spray coating systems, respectively. In Table I, the actual coating mass gain (% *m/m*) of each formulation of coated pellets was calculated taking into account the relative decrease of drug content in coated pellets compared to the initial drug content in uncoated pellets. The drug content in three batches of coated pellets (F₁) was found to be 98.4 ± 2.4%, indicating that the manufacturing process was quite reproducible.

Size distribution of the coated pellets (F₁ formulation) was determined by the sieve analysis method (Fig. 1). Approximately 60% (*m/m*) of the pellets were in size range of 710–1000 μm , and 31% (*m/m*) were between 1000 to 1410 μm . The mean size (d_{mean}) of 880 μm (880 ± 17) was obtained.

In the present investigation, pectin HM (as a polyanionic polymer) was complexed with chitosan (as a polycationic polymer). The PEC formed between them reduced the ionic charge, hydrophilicity and the swelling properties of both pectin and chitosan. It was reported that the optimum pectin/chitosan ratio for PEC formation was somewhere between 2:1 and 3:1 (11). Our findings from the viscosity studies suggest that 2:1 is closer to the optimal ratio for PEC formation at pH 5.4 (data not shown). Thus, in the current study, the pectin/chitosan ratio was kept constant at 2:1 for all formulations (F₁–F₁₂).

In our study, isolated films of the pectin-chitosan complex were prepared by the solvent casting method in Teflon® Petri dishes and immersed in the following media: acidic medium (0.1 mol L⁻¹ HCl, pH 1.5), phosphate buffer pH 7.4 and phosphate buffer pH 6.0. These media simulate gastric, small intestine and colonic media, respectively. It was

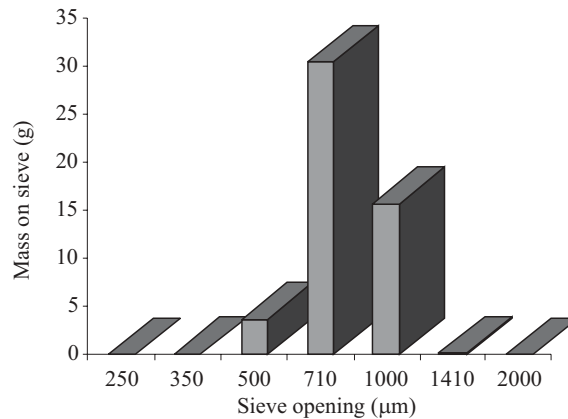


Fig. 1. Histogram plot of the size distribution of a coated theophylline pellet (F₁).

observed that the films dissolved easily after about 10 min in acidic medium, while they swelled rapidly without any dissolution in the other two media. It was assumed that pectin-chitosan complex in the mixed ternary blends (pectin/chitosan/Eudragit® RS) could be dissolved and leached from the mixed-film; hence, an additional outer enteric-coating is necessary to prevent this undesired effect. After capsule filling with coated pellets, capsules were enteric-coated by the alcoholic solution of Eudragit® L100-55 polymer in a conventional coating pan. None of the enteric-coated formulations showed any drug release in the first 2 hours in the simulated gastric environment.

Influence of the coating mass gain and pectin-chitosan content on the theophylline release from coated pellets. – Effects of the mentioned factors on the drug release profiles were investigated in the F₁–F₁₂ formulations.

The theophylline release profiles obtained from enteric-coated F₁–F₄ formulations (compositions shown in Table I) with 10% (*m/m*) of theoretical coating mass gain and different amounts of pectin-chitosan (5–20%, *m/m*, relative to the total amount of film) are presented in Fig. 2a. It can be observed that, after an almost constant lag time of about 120–130 min, drug release happened due to the protective effect of the enteric coating. The drug release rates were different, depending on the amount of pectin-chitosan incorporated in the film coatings. Drug release rates in phosphate buffer pH 7.4 (simulated small intestine) were in the order F₄ > F₃ > F₂ > F₁. It was found that the higher were the amounts of pectin-chitosan, the more drug was released. This effect was due to the swelling-hydration ability of the pectin-chitosan complex. After 300 min, phosphate buffer pH 7.4 was replaced by phosphate buffer pH 6.0 and 3.6 mL of pectinolytic enzymes in 900 mL of the medium was added. This commercially available mixture of specific enzymes with pectinolytic activity has shown to be closely correlated with that of the *Bacteroides ovatus*, the main colon producer of pectinolytic enzymes (12). After 10 min of drug release in the colonic medium, the rate of drug release from formulations was highly increased, which was probably caused by the degradation of pectin with pectinolytic enzymes. It seems that a fast biodegradation and erosion process occurred within the pectin-chitosan complex, which is in agreement with the results of release studies

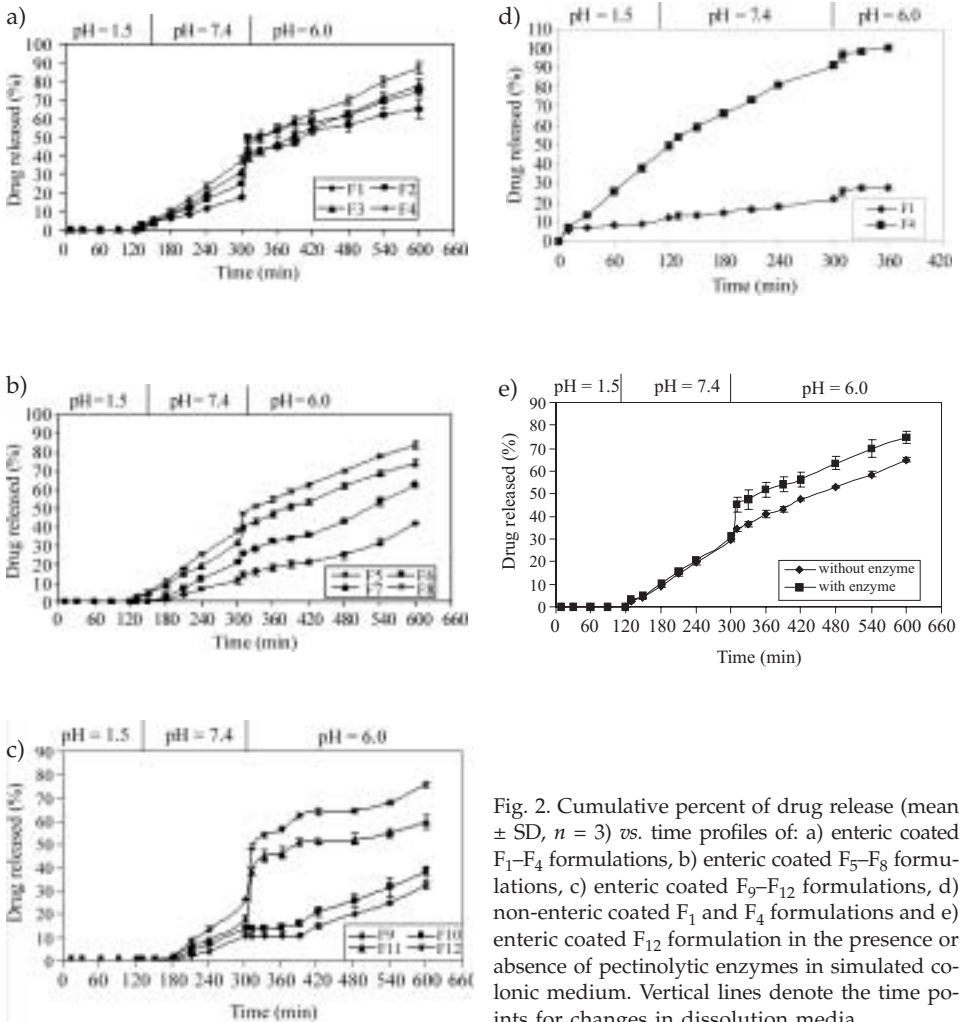


Fig. 2. Cumulative percent of drug release (mean \pm SD, $n = 3$) vs. time profiles of: a) enteric coated F₁-F₄ formulations, b) enteric coated F₅-F₈ formulations, c) enteric coated F₉-F₁₂ formulations, d) non-enteric coated F₁ and F₄ formulations and e) enteric coated F₁₂ formulation in the presence or absence of pectinolytic enzymes in simulated colonic medium. Vertical lines denote the time points for changes in dissolution media.

causing a marked increase in the release rate. F₁-F₄ formulations deliver no drug under *in vitro* conditions that simulate the stomach (pH 1.5), commence the release of drug at moderate rates under conditions simulating the small intestine (pH 7.4) and accelerate the release rate in the presence of pectinolytic enzymes (colonic medium, pH 6.0). Such a system would be proper in the situation where a bimodal or sigmoidal drug release profile is sought.

Fig. 2b shows the curves of theophylline release from enteric-coated F₅-F₈ formulations (compositions in Table I). As can be seen, these release profiles are different from those depicted for F₁-F₄ formulations in Fig. 2a. Contrary to F₇ and F₈, there is no dis-

tinct increase in the drug release after 300 min in F₅ and F₆ formulations. The lower amounts of pectin-chitosan in the F₅ and F₆ formulations compared to F₇ and F₈ formulations may be responsible for this difference. Drug release from F₅ and F₆ formulations is not bimodal and a little burst drug release can be observed for F₇ and F₈ formulations.

Fig. 2c illustrates the drug release profiles from enteric-coated F₉–F₁₂ formulations. The dissolution profiles of F₉ and F₁₀ formulations are characterized by an initial latency phase of almost no or very slow drug release in the period of 120–180 min and a second lag phase from 300 to 360 min. These lag time periods depend on the pectin-chitosan content and may be attributed to the time required for the dissolution media to diffuse and stabilize the hydrodynamic exchanges across the mixed-films. After the lag phases, the drug release from F₉ and F₁₀ formulations is linear as a function of time. Fig. 2c also shows that F₁₁ and F₁₂ formulations have only one lag phase at 120–150 min and after 300 min; their drug release profiles follow a burst and bimodal release pattern. Owing to the considerable burst drug release, the F₁₁ and F₁₂ formulations were found to be better than the other formulations and they were selected as optimal formulations.

Chemical degradation is the most important mechanism for the biodegradation of polymers. By introducing hydrolyzable functional groups into the polymer backbone, polymer chains become labile to an aqueous environment and thus, chemical degradation initiates polymer erosion (13). Pectinex® Ultra SP-L used as a pectinolytic enzyme in this research is capable of hydrolytic breakdown of pectin substrate (14). During polymer degradation, the polymer breaks down into oligomers and monomers. Degradation is the most important part of erosion (13, 15). The release of degradation products leads to mass loss, which is a characteristic of erosion. The above-mentioned explanation may help understand the possible reason for the burst drug release observed in this study.

Drug release mechanism for optimal formulations. – The release data for F₁₁ and F₁₂ were fitted into various release equations and kinetic models [first-order (16), zero-order, Higuchi (17) and Korsmeyer and Peppas (18)]. As indicated by the value of R^2 , the zero-order and Higuchi model were found to be efficient in describing the kinetics of drug release from F₁₁ and F₁₂ in the small intestine and colonic media, respectively. To explore the release pattern, results of the release data of the aforementioned formulations were also fitted to the Korsmeyer and Peppas equation [$M_t/M_\infty = k t^n$, where M_t/M_∞ is the fraction of drug released after time t relative to amount of drug released at infinite time, k is the rate constant and n is the diffusional exponent characterizing the transport mechanism (19)]. The n values for F₁₁ and F₁₂ in the simulated small intestine medium were equal to 2.7328 and 2.5102, respectively, indicating that the drug release was governed by super case-II transport. In colonic medium, n values were equal to 0.3854 and 0.402 for F₁₁ and F₁₂, respectively, pointing to Fickian diffusion.

Influence of acidic dissolution medium on the drug release from coated pellets. – In the previous section, it was mentioned that the isolated film of pectin-chitosan dissolved rapidly in acidic medium, while they swelled and showed no dissolution in the two phosphate buffer media. F₁ and F₄ (the former has 5%, *m/m* and the latter has 20%, *m/m* of pectin-chitosan complex) as two example formulations were chosen for the dissolution study under acidic conditions (Fig. 2d). Neither of the two formulations showed a bimodal release profile and a linear drug release pattern was observed for them. This observation may be explained by the pores (channels) formation mechanism whereby solu-

tes are transported through the film. When the coated pellets were exposed to the acidic medium, the pectin-chitosan moiety dissolved and was removed from the film, and consequently the film became porous. After exposure to acidic medium, due to the higher amount of pectin-chitosan incorporated in F_4 vs. F_1 , the film porosity and drug release rate from F_4 will be higher than for F_1 .

Influence of pectinolytic enzymes on the theophylline release from coated pellets. – Studies of Semd  *et al.* (20) on theophylline pellets coated with Eudragit® RS containing pectin

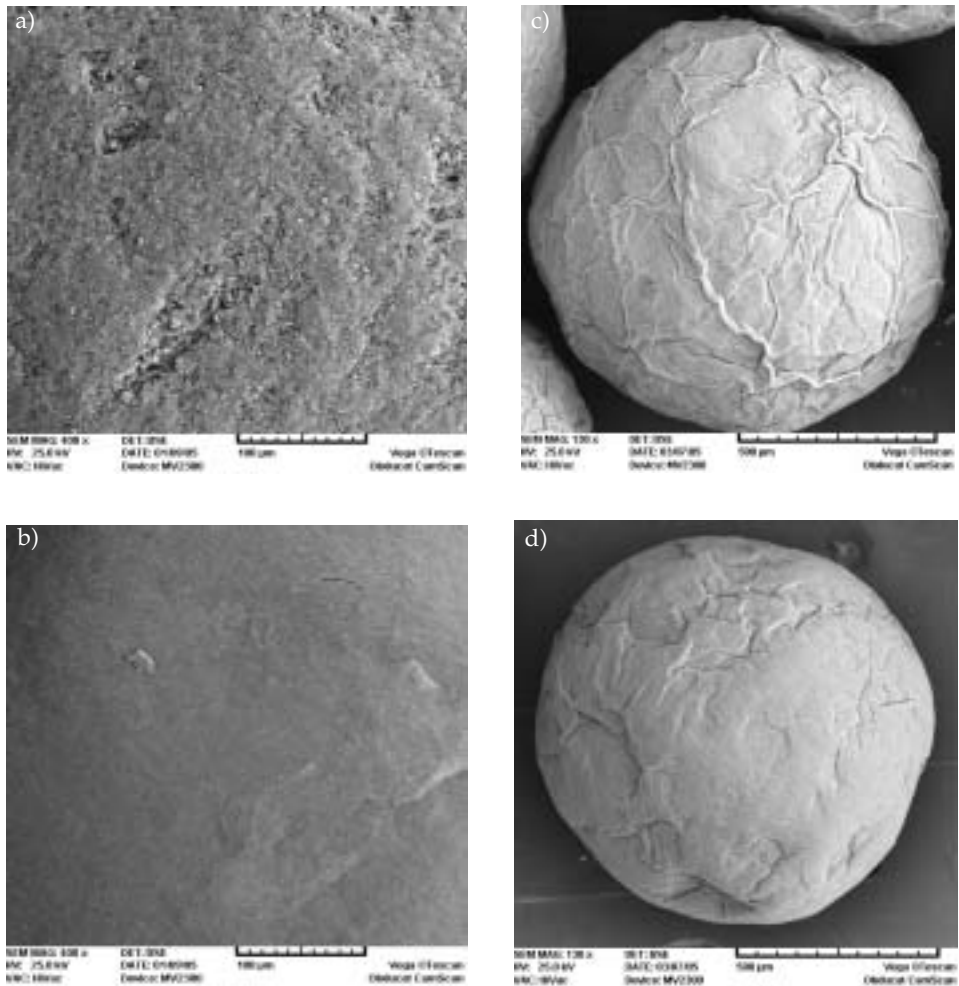


Fig. 3. Scanning electron microscopy of the surface of: a) uncoated theophylline pellet, b) coated theophylline pellet (F_{12} formulation, before dissolution), c) after 3 h dissolution in phosphate buffer solution pH 7.4, d) after 3 h dissolution in phosphate buffer pH 7.4 and then 15 min in phosphate buffer pH 6.0 with pectinolytic enzymes. Magnification: 400x for a and b, 130x for c and d.

HM or calcium pectinate gave unsatisfactory results. Their investigations showed that the presence of pectinolytic enzymes in dissolution media resulted in decreased drug release rate. Nevertheless, our study showed that the presence of pectinolytic enzymes in the colonic dissolution medium resulted in an increase of the drug release from most formulations. Fig. 2e displays the drug release rate from the enteric-coated F₁₂ formulation. A significant difference ($p < 0.001$) was recorded for the drug release rate in the presence *vs.* absence of pectinolytic enzymes.

Scanning electron microscopy. – Figs. 3a and 3b show the SEMs of the surface of uncoated and coated pellets (F₁₂ formulation), respectively. As can be seen, the uncoated pellet surface became smoother after coating. Fig. 3c depicts the surface SEM of F₁₂ coated pellets after 3 h dissolution in phosphate buffer pH 7.4 (simulated small intestine). Fig. 3d exhibits the surface SEM of that formulation after 3 h in phosphate buffer pH 7.4 and then 15 min dissolution in the colonic medium. Bimodal drug release obtained in the dissolution study agrees with the microscopic changes of coated pellets in the two mentioned media. As can be seen in Fig. 3c, the surfaces of coated pellets at pH 7.4 are very rough, probably due to film swelling. In the simulated colonic environment, the pellets surfaces erode, which may be caused by the action of pectinolytic enzymes.

CONCLUSIONS

The optimal formulations for bimodal drug delivery were made up of theophylline pellets having approximately 20% (*m/m*) of coating mass gain and 15 or 20% (*m/m*) of pectin-chitosan. Zero-order was found to be a better fitting model for optimal formulations in the simulated small intestine medium. In the simulated colonic medium, drug release followed the Fickian diffusion transport or the Higuchi model.

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S A Ž E T A K

Film-ovojnica smjese pektina, kitozana i Eudragita® RS za bimodalno oslobađanje lijeka iz peleta s teofilinom: Priprava i evaluacija

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Pelete s teofilinom kao modelnim lijekom i mikrokristaliničnom celulozom u omjeru 6:4 pripravljeni su metodom ekstruzije i sferonizacije. Pelete su presvučene vodenom disperzijom Eudragita® RS koja sadrži različite količine kompleksa pektina i kitozana i različite mase ovojnice, koristeći uređaj za fluidizaciju. Pripravljeno je 12 peleta koje se razlikuju po masi ovojnice (10, 15 i 20%, *m/m*) i udjelu kompleksa pektina i kitozana (5,

10, 15 i 20%, *m/m*). Oslobođanje lijekovite tvari proučavano je u USP aparaturni I (s košaricama) u medijima koji odgovaraju pH probavnog sustava. Dobiveni rezultati ukazuju da brzina i način oslobađanja lijeka ovisi o oba spomenuta parametra. Iz nekih pripravaka oslobađanje je bimodalno, a posljedica je djelovanja pektinolitičkih enzima iz kolona. U pripravcima u kojima je udio ovojnice 15 ili 20% (*m/m*), a udio pektin-kitozana 5 ili 10% (*m/m*) oslobađanje je bilo polagano. Najbolji pripravci za naglo oslobađanje u pH mediju područja kolona sadržavali su 20% (*m/m*) ovojnice i 15 ili 20% (*m/m*) pektin-kitozana. Proučavanje obloženih i neobloženih peleta SEM metodom pokazuje da obložene pelete imaju glatkiju površinu, koja erodira uslijed djelovanja pektinolitičkih enzima.

Ključne riječi: bimodalna isporuka lijekova, naglo oslobađanje, kitozan, Eudragit® RS, film-ovojnica, pektin, peleta

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