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Immersion coating of pellets with calcium pectinate and chitosan

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Abstract

This study has investigated the potential of immersion coating calcium containing pellet cores first with pectin, and then with two different cross-linkers, calcium or chitosan. The interaction between pectin and calcium, and between pectin and chitosan, are believed to slow down the drug release, and thereby, the coated pellets might possibly be used for colon specific drug delivery. Both the calcium coated pellets and the chitosan coated pellets had a reduced drug release compared to uncoated pellets in 0.1 M HCl (1 h) and phosphate buffer pH 6.8 (4 h). The most successful combination had a drug release of only 17% during the entire test period in comparison to the uncoated pellets that had a drug release of 80%. When chitosan was used as a cross-linker, a higher reduction in drug release was obtained than by using calcium as the cross-linker. For the pellets coated with pectin in combination with chitosan, the type of pectin with a degree of methoxylation (DM) of 35 was superior to the pectin type with DM 17. The drug release was further slowed down by choosing a type of chitosan with a high degree of deacetylation (Dda) 89% and by coating at low concentrations (0.1%) in the immersion solution.

Keywords: Pectin; Chitosan; Interfacial complexation; Colon delivery; Multivariate analysis

1. Introduction

Pectin is a natural non-toxic biopolymer found in cell walls of plants. Pectin consists mainly of linearly connected α-(1-4)-D-galacturonic acid residues partially esterified with methanol. The degree of methoxylation (DM) is used to classify the pectins as high methoxyl pectins (DM > 50) and low methoxyl pectins (DM < 50) (Sakai et al., 1993; Thakur et al., 1997).

Low methoxyl pectins gels in the presence of divalent cations such as calcium. Intermolecular cross-links are formed between the calcium ions and the negatively charged carboxyl groups of the pectin molecules. This bridging of chains builds up the well-known egg-box structure (Grant et al., 1973) first by dimerization and then by subsequent aggregation. The lower the DM of the pectin the more sensitive the pectin is to calcium as a gelling agent (Thakur et al., 1997).

Due to this complexation and the formation of calcium pectinate, pectin and calcium have been investigated in many different formulations intended for colon drug delivery. This combination has been reported in the literature both for matrix tablets (Sungthongjeen et al., 1999; Ahrabi et al., 2000) and gel beads (Munjeri et al., 1997a; Sriamornsak and Nunthanid, 1998). Formulations based on calcium pectinate have potential as drug delivery systems for poorly water-soluble drugs. Unfortunately, the release of water-soluble drug is not slowed down sufficiently through networks of calcium pectinate (Liu et al., 2003).

Sriamornsak and co-workers have reported a method for immersion coating of pellets. In this system, pectin is expected to interact with calcium ions in an interfacial complexation reaction (Sriamornsak et al., 1997). The drug release from these coated pellets was strongly reduced but is still too high to achieve colon delivery.

Chitosan is also a non-toxic biopolymer, extracted among other sources, from crab-shells. Chitosan consist of *N*-acetylglucosamin and is classified according to the degree of acetylation (or deacetylation, Dda).

Combinations of pectin and chitosan form a polyelectrolyte complex (PEC) at pH values in the range of 3–6 (Meshali and Gabr, 1993; Macleod et al., 1999a), hence this combination is expected to reduce the release of drug in the upper GI tract. In addition to the formation of a PEC, pectin and chitosan also interact by hydrogen bindings at low pH values (Nordby et al., 2003). Mixtures of the two polymers have been studied as exipients in colon drug delivery devices for example in press-coated tablets

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(Fernández-Hervás and Fell, 1998), hydrogel beads (Munjeri et al., 1997b) and as film coating in combination with HPMC (Macleod et al., 1999b) and without HPMC (Hiorth et al., 2003).

The aim of the current study was to investigate the potential of coating pellets with calcium pectinate and calcium pectinate in combination with chitosan by an interfacial complexation reaction and to determine important formulation factors. The main purpose was to investigate how different cross-linkers, i.e. calcium and chitosan affected the release of a low soluble drug in environments mimicking the stomach and the small intestine.

2. Materials and methods

2.1. Materials

Low methoxylated pectin with different degrees of DM was investigated. DM 35% pectin Pectin Classic CU701, batch 0811754 was used in Design 1 and batch no. 0903185 was used in Designs 2 and 3. DM 17% pectin (Pectin Classic CU-L 050/01, batch no. 0106215) and DM 5% pectin (Pectin Classic AU-L 049/01, batch no. 0106214) was used in Design 1. All the pectin types were from Herbstreith & Fox GmbH (Germany). Chitosan with two different Dda were used: Seacure CL214, batch no. 607-783-08 (Dda 89%) and Seacure CL211, batch no. 707-771-10 (Dda 60%) from Pronova Biopolymer (Norway). Distilled water was used as solvent in all coating solutions. Calcium chloride dihydrate (Merck, Germany) solved in water was used as the external calcium cross-linker.

The pellet cores consisted of microcrystalline cellulose as an extrusion aid (Avicel PH101, Philadelphia, USA), calcium acetate (BDH Laboratory supplies, UK) in different amounts (5, 10 and 20% (w/w)) as complexing agent and 1% (w/w) riboflavin from Sigma-Aldrich (Norway) as model drug. Distilled water was used as granulation liquid.

2.2. Preparation of pellets

Granulation was performed by addition of 54% (w/w) water to the powder mixture. Pellets were prepared by feeding the moist granulate into a basket extruder (NICA model E140, Sweden) with a mesh size of 1.2 mm. Extrusion was performed at constant agitation and the extrudate was spheronized (NICA model S320, Sweden) for 5 min at 800 rpm. The pellets were dried for 48 h at room temperature.

2.3. Preparation of polymer solutions

Separate pectin and chitosan solutions (450 g) were prepared by dissolving the appropriate type and amount of polymer in distilled water. The solutions were stirred for 2 h at high temperature (approximately 70 °C).

2.4. Immersion coating

The immersion coating process was a modified version of the method reported by Sriamornsak et al. (1997).

7.5 g pellets with calcium in the core with a size of 0.7–1.7 mm were first immersed in a hot pectin solution (72 °C) for 10 min; filtrated and washed with distilled water (Fig. 1). Then the pellets were immersed either in a cold $CaCl_2$ or in a hot chitosan solution (72 °C) for 5 min; filtrated and washed with distilled water. Finally, the pellets were immersed in an ethanol solution for 5 min; filtrated and washed in distilled water. Finally, the pellets were dried. The pellets were protected against light during the whole process.

2.5. Release studies

0.5 g pellets were tested in a USP paddle apparatus: 37 °C at 100 rpm, for 1 h in 750 ml 0.1 M HCl. The pH of the medium

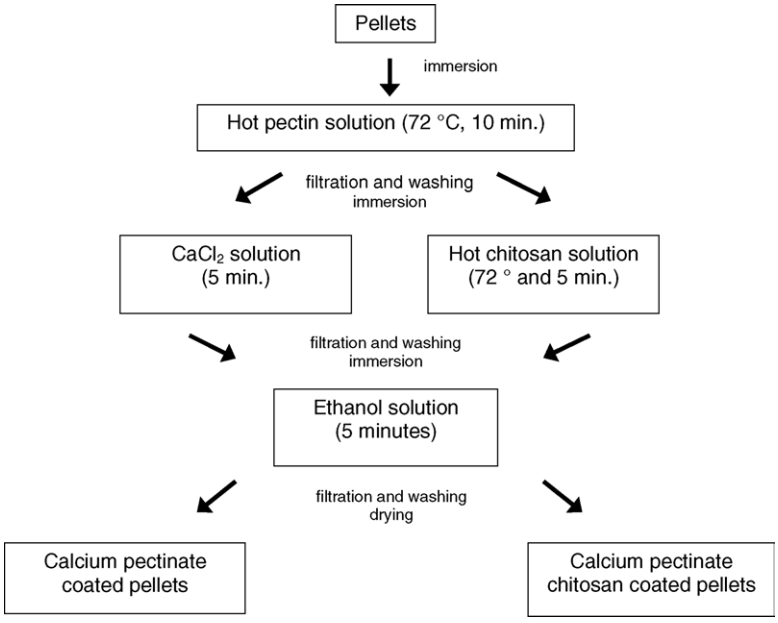

Fig. 1. Float scheme for the immersion coating of pellets.

Table 1
The experimental Designs 1–3

Factors	Levels			
Design 1 (cross-linker concentration of calcium constant at 10%, 24 experiments)				
Pectin type	DM 5	DM 17	DM 35	
Immersion coating time (min)	10	20		
Calcium concentration in the core (%)	10	20		
Pectin concentration in the immersion solution (%)	2	4		
Design 2 (pectin DM 35, coating time 10 min, calcium concentration in the core 10%, six experiments)				
Cross-linker concentration of calcium in the immersion solution (%)	1	5	10	
Pectin concentration in the immersion solution (%)	1	3		
Design 3 (31 experiments)				
Pectin concentration in the immersion solution (%)	1	2	3	
Pectin type	DM 17	DM 35		
Chitosan type	Dda 60	Dda 89		
Chitosan concentration in the immersion solution (%)	0.1*	1	1.5	2
Calcium concentration in the core (%)	5	10		

* Only DM 35 was tested at this concentration.

was then changed to 6.8 by adding 250 ml 0.2 M sodium phosphate, and the test was continued at this pH value for 4 h. Samples of 3 ml were drawn every 15 min. In order to determine the total amount of drug, the pellets were crushed and a final measurement of the total concentration of riboflavin in the pellets was measured after 12 h. The amount of model substance (riboflavin) released was determined spectrophotometrically ($\lambda = 444$ nm). Each test was repeated three to six times. During the whole study, the pellets were protected against light.

2.6. The experimental design

This study has been divided into three parts; Designs 1 and 2 is a study on calcium pectinate-coated pellets, and Design 3 is a study on calcium pectinate–chitosan-coated pellets. The response for all the designs is the amount of riboflavin released, given as percentage of the total drug content.

2.6.1. The calcium pectinate-coated pellets, Designs 1 and 2

Both Designs 1 and 2 are full factorial designs with calcium used as cross-linker. In Design 2, one pectin type (DM 35) was subjected to further studies. All factors and levels are given in Table 1.

2.6.2. The calcium pectinate–chitosan-coated pellets, Design 3

In Design 3 chitosan was used as cross-linker. This was a D-optimal design. Factors and levels are given in Table 1.

2.7. Multivariate analysis

Partial least square regression (PLS) was used (The Unscrambler, Camo ASA, Norway) to evaluate the results and for identification of the most important factors for reducing the drug release in both 0.1 M HCl and phosphate buffer pH 6.8. The variation of each variable was scaled to unit variance (1/S.D.). The models were calculated using systematic cross-validation. Jack-knifing was used to estimate the uncertainty of the PLS regression coefficients (Martens and Martens, 2000). The interpretation of PLS values and plots (graphs, score plots and loading plots) can be found elsewhere (Martens and Naes, 1989; Esbensen et al., 1998).

3. Results

3.1. Screening for appropriate pectin types

All tested types of low methoxylated pectin (DM 5, DM 17 and DM 35) were successful in forming a coating by an interfacial complexation reaction with calcium ions as the cross-linker. The pellets aggregated to some degree in doublets and triplets, but approximately 50% of the coated pellets remained as single entities (Fig. 2).

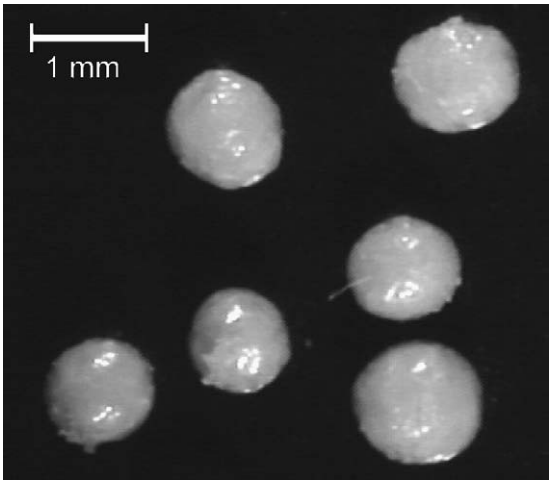

Fig. 2. Pellets coated with 3% DM 35 pectin in the immersion solution and 5% cross-linker concentration of calcium in the immersion solution.

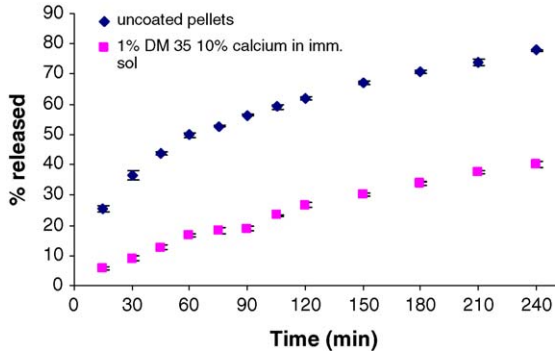

Fig. 3. Drug release profiles for the uncoated pellets (♦) and for pellets coated with 1% DM 35 pectin and 10% cross-linker concentration of calcium in the immersion solution (■).

3.2. Influence of coating on drug release (uncoated versus coated pellets)

Fig. 3 represents a typical example of the difference in drug release between uncoated and coated pellets. Uncoated pellets released 40–50% of the riboflavin load during the first hour in 0.1 M HCl. The release from the coated pellets was only 5–20% of the total drug load. In the subsequent test in phosphate buffer pH 6.8 (4 h) an equal amount of drug was released, leading to a total release of 80% of the riboflavin load during the entire test. In comparison, the coated pellets released 20–40% riboflavin within the entire test period. The exact amount of drug released was depending on the composition of the coating formulation.

3.3. Pellets coated with calcium pectinate

3.3.1. Design 1

A PLS analysis of drug released after 1 h in 0.1 M HCl and 4 h in phosphate buffer pH 6.8 from pellets coated with calcium pectinate and calcium as the cross-linker had an explained *Y*-variance of 69% and an explained *X*-variance of 19% using one principal component (PC). The regression coefficient plot revealed only one significant factor, the interaction between the coating time and the calcium concentration in the pellet core. The positive term indicate that the drug released was increased when the coating time was long and the calcium concentration was high. The trends of the non-significant factors indicated that a reduced drug release might be obtained for pectin with high DM (DM 35) and that the concentration of pectin in the immersion solution should be high. The coating time should preferably be long, except for pellets with a high concentration of calcium in the core (20%). Twenty percent calcium ions in the core seemed to be too high. The quality of these pellets were poorer; the cores were brittle and calcium had precipitated on the surface of the pellets.

3.3.2. Design 2

Pectin type DM 35 was studied more closely in Design 2. A PLS model had an explained *Y*-variance of 98% and an explained *X*-variance of 55% using two PCs. This model showed that the pectin concentration as well as the square of the cross-linker concentration of calcium and the interaction between pectin concentration and cross-linker concentration of calcium was correlated to the amount of drug released after 5 h ($p < 0.05$) (Table 2). A surface plot (Fig. 4) shows the interaction between the cross-linker concentration of calcium and pectin concentration. It indicates that the optimal cross-linker concentration of calcium is 5% or below. The optimal combination of the calcium pectinate pellets had a drug release of 22% during the entire test. This was the combination of 3% pectin and 5% $CaCl_2$ in the immersion solution.

Table 2
Significant regression coefficients ($p < 0.05$) for a PLS model on the amount of drug released after 1 h in 0.1 M HCl and 4 h in phosphate buffer pH 6.8 for the calcium pectinate-coated pellets Design 2

Factor	Significant regression coefficients (weighted)
Pectin concentration	−0.39
Pectin × $CaCl_2$ concentration	−0.38
($CaCl_2$ concentration)^2	0.59

3.4. Pellets coated with calcium pectinate in combination with chitosan

3.4.1. Design 3

Fig. 5 shows the significant regression coefficients of a PLS analysis based on the experiments with chitosan as the cross-linker. The model had an explained *Y*-variance of 57% and an explained *X*-variance of 30% using two PCs. All main factors, except Dda of the chitosan, were significant ($p < 0.05$). The regression coefficient plot indicates, among other things that pectin type DM 35 is slowing down the drug release more than DM 17. Several interactions occur in the model and the DM grade seems to be involved in many of them. Consequently, chitosan seems to relate differently to the two pectin types, it was therefore decided to model DM 35 and DM 17 separately.

A PLS model calculated on the pellets coated with pectin DM 35 and chitosan had an explained *Y*-variance of 60% and an explained *X*-variance of 53% using two PCs. Three of the main factors were significant: pectin concentration, the Dda of the chitosan and the concentration of chitosan in the immersion solution (Fig. 6). In order to reduce drug release pectin concentration should preferably be low and the concentration of chitosan with a high Dda should be low.

The PLS model calculated for the pellets coated with pectin, DM 17 in combination with chitosan displays the opposite effect of chitosan concentration compared to DM 35 for the tested concentrations. The explained *Y*-variance of the model was 57% and the explained *X*-variance was 58% using three PCs. The model shows that the drug release is decreased with 10% calcium in the core and a high concentration of chitosan in the immersion solution (Fig. 6).

The best combination of the pellets coated with calcium pectinate in combination with chitosan had a drug release of only 17% during the entire test period. This combination consisted of a high concentration of pectin DM 35 in the immersion solution in combination with a low concentration of chitosan Dda 89 in the immersion solution.

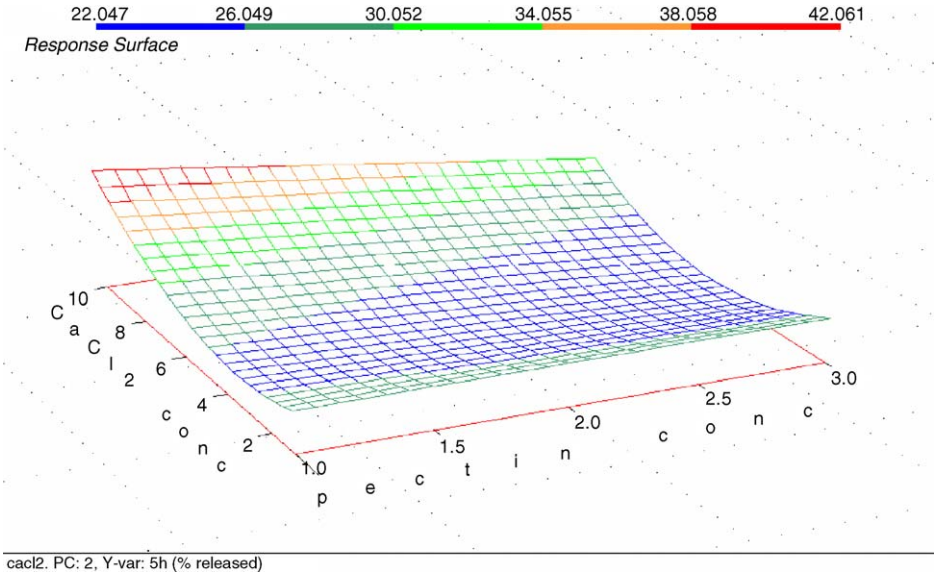

Fig. 4. Response surface plot from a PLS model showing the interaction between pectin concentration and cross-linker concentration of calcium, for the calcium pectinate-coated pellets Design 2.

3.5. Calcium versus chitosan as cross-linker

Pellet cores containing 10% calcium coated with a combination of 1% DM 35 pectin and 5% $CaCl_2$ released a total amount of $26.2 \pm 1.0\%$ riboflavin. The slope of the buffer phase was 0.082 ± 0.005 (%/min). In comparison, the combination of 1% DM 35 pectin and 1% Dda 60 chitosan released a total amount of $20.4 \pm 0.9\%$ riboflavin. The slope of the buffer phase was 0.065 ± 0.003 (%/min). Based on these data it seems like the drug release is slightly slower when the pellets are coated with calcium pectinate combined with chitosan compared to a coating with calcium as the cross-linker.

To further investigate this hypothesis a PLS analysis was performed on results from pellet cores containing 10% calcium coated with pectin DM 35 and both types of cross-linker. The explained *Y*-variance was 59% using three PCs and the explained *X*-variance was 65%. The regression coefficient showed that Dda and type of cross-linker is negatively correlated to the amount of drug released ($p < 0.05$). Since calcium is coded at the low level, this means that chitosan as cross-linker reduces the drug release to a higher extent than calcium. Chitosan Dda 89 would be preferable in order to reduce the drug release.

Another approach to verify the difference is employing the two PLS models obtained for the coatings with different type

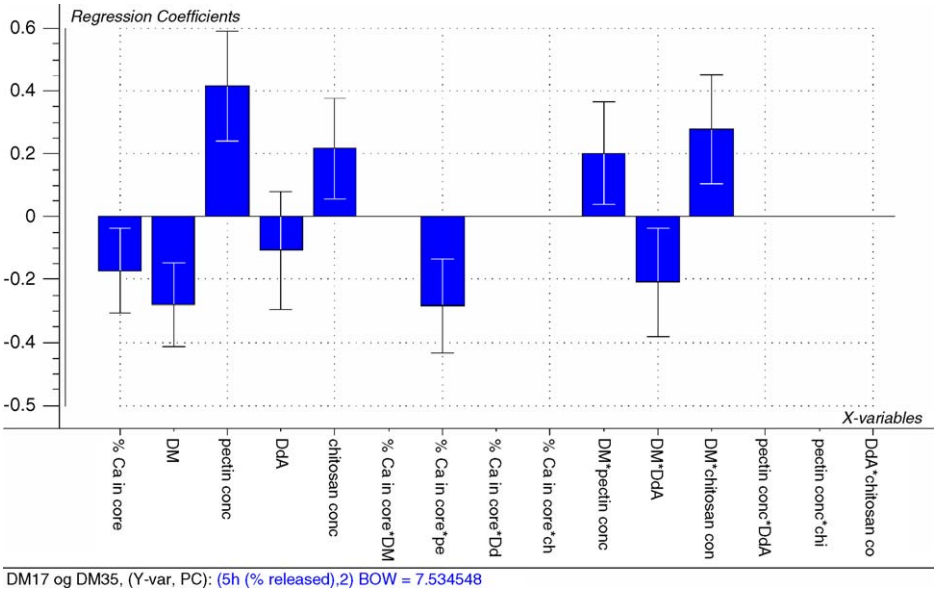

Fig. 5. Significant regression coefficients ($p < 0.05$) for a PLS model on the amount of drug released after 1 h in 0.1 M HCl and 4 h in phosphate buffer pH 6.8 for the pellets coated with calcium pectinate in combination with chitosan Design 3, both DM 17 and DM 35.

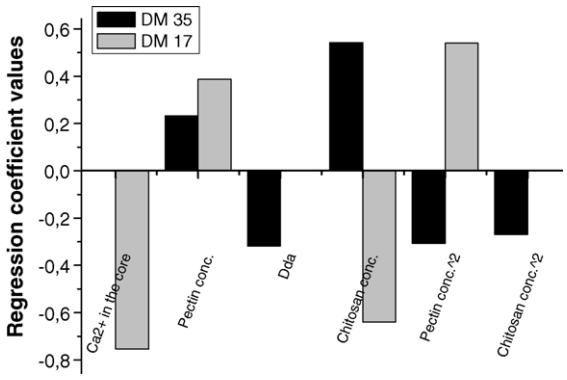

Fig. 6. Significant regression coefficients ($p < 0.05$) for a PLS model on the amount of drug released after 1 h in 0.1 M HCl and 4 h in phosphate buffer pH 6.8 for both the pellets coated with calcium pectinate (DM 35 ■) in combination with chitosan and the pellets coated with calcium pectinate (DM 17 □) in combination with chitosan Design 3.

of cross-linker to predict the drug release. From the model presented in Fig. 4 the drug release after 1 h in 0.1 M HCl followed by 4 h in phosphate buffer pH 6.8 was predicted to be within the range 25–40% for the calcium pectinate–calcium pellets. The corresponding predicted release for the calcium pectinate–chitosan-coated pellets was predicted by the use of the same model as presented in Fig. 6 to be within the range 14–27%. Even though the two ranges overlap, the predicted values for the drug release also indicate that the drug release is lower from the pellets coated with calcium pectinate in combination with chitosan than from the calcium pectinate-coated pellets.

4. Discussion

The method described by Sriamornsak et al. (1997) allows application of multiple layers by subsequent immersion into different solutions. Consequently, this method also provides a good alternative for coatings consisting of polymers of opposite charge that would otherwise be unsuitable due to phase separation and precipitation by mixing. This includes the application of pectin and chitosan as film coatings.

Pellets coated in this study contain 5, 10 or 20% (w/w) calcium acetate in the core. The calcium ions are expected to dissolve and migrate to the surface of the pellets when the pellets are immersed into the pectin solution (Bhagat et al., 1991). Due to ionic interaction between pectin and calcium, a complexation reaction will take place at the pellet solution interface. The formed calcium pectinate gel layer will grow as calcium ions diffuse through the pectin network and interact with pectin chains further from the core. The layer nearest to the core will probably have many calcium ions bound to the pectin chains and the amount of bound calcium will decrease with the distance from the core. A subsequent immersion in a calcium solution will strengthen the gel from the outside as the calcium ions can penetrate into the network and form additional binding sites. When calcium pectinate-coated pellets are immersed in a chitosan solution instead of the calcium solution, the chitosan chains will form a PEC, with the pectin chains due to ionic interactions as described in the literature (Yao et al., 1997). It is important to note that the pectin layer nearest to the pellet core will also be cross-linked with calcium ions from the core. The complexation between pectin and chitosan will take place at the external surface of the calcium pectinate gel. Chitosan may compete with calcium for the interaction sites or interact with unbound pectin. The pellets coated with pectin in combination with chitosan are therefore expected to consist of a network of calcium pectinate and a network of pectin and chitosan.

The first part of the present study was dedicated to a thorough study of calcium as the cross-linker. A long coating time was shown to be favourable for a low drug release within the test time except when the calcium concentration in the core was high. This result is probably due to the fact that a longer immersion time results in a longer interaction time, and consequently, a higher amount of pectin added to the pellet and thereby a thicker coating layer. Unfortunately, long immersion time is also associated with a higher degree of elution of model drug from the core. It was decided to keep the coating time at 10 min in further experiments due to higher drug encapsulation efficiency. The type of pectin with a DM of 35 gave lower release of drug than DM 17 and DM 5. This was a bit surprising since pectin with a low DM was expected to interact more strongly with calcium due to higher amount of free carboxylic acid groups available for cross-linking. But the low methoxylated pectins are prepared by hydrolytic demethylation of pectin of higher degree of methoxylation and this reaction is known to attack the chain lengths and thereby reduce the molecular weight (M_w) of the pectin. Shorter chain length of the polymer in combination with a higher water solubility may result in a more unstable network and thereby a higher drug release (Thakur et al., 1997).

As pectin DM 35 was found to be most promising in Design 1, this pectin type was subjected to more thorough investigations in Design 2. The result from the PLS analysis of Design 2 revealed that the calcium concentration in the immersion solution was very important. The gel strength of calcium pectinate gels is known to be highly dependant on the amount of calcium present (Ashford et al., 1994). In the present study, immersion solution of 5% calcium produced the strongest gel. A certain level of cross-links is necessary in order to reduce the drug release, but a further increase in the amount of calcium ions produced a weakened gel. This may be explained by excessive cross-linking by calcium ions and hence the formation of a non-homogenous gel at high concentrations.

In experiments using chitosan as the cross-linker (Design 3) different effects were found depending on the pectin type chosen. When analysing the result with pectin DM 35 a low chitosan concentration in the immersion solution was found to be favourable for reducing the drug release. This may seem a bit odd since one would believe that a higher concentration of polymer in the immersion solution leads to a thicker coat and thereby a lower drug release. However, the drying time might be an important factor. The drying time was much longer for the pellets coated with the low concentration of chitosan than for the pellets coated with a high concentration of chitosan. Longer drying time probably provides the polymer chains time to rearrange and thereby produce a tighter network.

In addition, at low chitosan concentration the amount of chains that reach the pellets and stick to them will be rather low per time unit. This might provide the pectin chains time to diffuse into the network and form junction zones, which connect the pectin chains and the chitosan chains and thereby producing a network consisting of pectin and chitosan. At high chitosan concentration lots of chitosan chains will stick to the pellet surface thereby producing an outer network consisting mainly of chitosan. This hypothesis is supported by preliminary swelling studies where pellets with low concentrations of chitosan does not seem to swell while the pellets with high concentration of chitosan swell both in 0.1 M HCl and phosphate buffer pH 6.8 (unpublished results).

The calcium concentration of the core was also identified to have some importance for the pellets coated with DM 17 and chitosan. A high calcium concentration (10%) gave the lowest drug release. This indicates that there is an optimal concentration of calcium needed to make the strongest interaction between pectin and calcium and that 5% is probably too low. Twenty percent is too high due to poor quality of the core.

Comparing the release reducing effect of calcium and chitosan as cross-linkers revealed that the amount of drug released was lowest through the pellets coated with chitosan. It is known from the literature that diffusion of drugs through films is dependant both of the thickness of the dry coating layer and the degree of swelling of the film (Bhagat et al., 1991). In the study by Bhagat et al. calcium tablets were coated with alginate. The lowest drug release was observed for the tablet with the highest weight gain and hence the tablet with the thickest coat. In the present study, it was not suitable to use weight gain as an indicator for film thickness since the variation in the pellet size was rather large (the sieve fraction 0.7–1.7 mm was used) and there is a weight loss from the pellets during the immersion coating. In addition, the process produced a rather small amount of pellets pro batch (3.5 g). But it is reasonable to assume that addition of an extra layer of polymer would lead to a thicker coat. Besides there is no doubt that the structure of network consisting of calcium pectinate and calcium pectinate in combination with chitosan should be different. The slope of the dissolution profile from calcium pectinate-coated pellets in phosphate buffer pH 6.8 is steeper than that of the pellets coated with calcium pectinate in combination with chitosan, indicating differences in the network (pore size) or the swelling ability. The swelling of a calcium pectinate coat in 0.1 M HCl are not very high since the carboxyl groups of the pectin chains are not dissociated. In buffer pH 6.8, pectin is dissociated and the carboxyl groups of pectin will repel each other leading to an increased swelling. Increased swelling will open up the network allowing more riboflavin to diffuse out. The coat consisting of calcium pectinate in combination of chitosan, on the other hand, will swell to a certain degree in 0.1 M HCl because of the charged amino groups of chitosan. When the pH is changed to 6.8 both chitosan and pectin will be charged to some degree and the formation of a PEC will decrease the ability of swelling. Pectin will have the highest number of charged groups so an increase in the amount of pectin to chitosan may lead to an increased swelling (Yao et al., 1996). A correct ratio between pectin and chitosan is therefore probably important to suppress swelling.

5. Conclusion

This study has confirmed that it is possible to use the interfacial complexation technique to coat pellets with calcium pectinate as well as calcium pectinate in combination with chitosan. All the types of low methoxylated pectin tested were successful in forming film coatings in combination with calcium. The pellets coated with calcium pectinate in combination with chitosan showed a lower drug release than pellets coated with calcium pectinate. The best combination in order to obtain a low drug release was to use a low concentration (0.1%) of the chitosan type Dda 89 in the immersion solution in combination with a low concentration (1%) of the pectin type DM 35. The optimal combination of pellets consisting of calcium pectinate in combination with chitosan had a drug release of only 17% during the entire test period, and may have potential as a colon specific drug delivery device.

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