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Research paper

# Immersion coating of pellet cores consisting of chitosan and calcium intended for colon drug delivery

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ABSTRACT

Biopolymers such as pectin, alginate, and chitosan have a great potential in colon drug delivery. The aim of this study was to produce pellets with calcium and chitosan in the core and then by an interfacial complexation reaction coat the cores with pectin or alginate in combination with calcium or chitosan. Pellets with calcium in the core acted as a reference. The drug release was investigated in environments mimicking the stomach and the small intestine.

The morphology of the coatings indicated a more wrinkled and irregular structure for coatings composed of pectin or alginate in combination with chitosan compared to the coat consisting of alginate in combination with calcium. The results from the drug release experiments showed that all the investigated coatings, especially with alginate, slowed down the drug release compared to the uncoated cores. The release from the chitosan-containing pellets was higher than the reference. The swelling studies revealed a high degree of swelling of the core consisting of chitosan. This probably explains the higher drug release from the coated chitosan pellets.

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## 1. Introduction

Colon drug delivery has been an important research topic for many years. Nevertheless, a perfect universal formulation able to deliver the drug directly to the colon without any drug leakage to the stomach or the small intestine has not been developed. Many challenges must be overcome to be able to deliver a drug to the colon, such as the harsh environment and the variable transit time of the stomach, and the shift in the pH value when going from the stomach to the small intestine [1]. Numerous approaches have been tried to obtain colon delivery; from a pH-dependant drug release to a time-dependant drug release [2,3]. The most promising approach for delivering drugs to the colon appears to be a formulation consisting of biopolymers that will be degraded by enzymes specific to the colon [4].

Pectin and alginate are naturally occurring biopolymer. These polymers can be found in the cell wall of almost all higher plants and in brown seaweeds, respectively [5,6]. The polymer backbone of pectin mainly consists of galacturonic acid, while the backbone of alginate is composed of guluronic and mannuronic acid [7,6]. The p*K*a value of both pectin and alginate is close to 3.5 [8,9].

Chitin is also a biopolymer, found widely in nature especially in shell, crabs, shrimps and krill [10]. The aminoacetyl groups of chitin are hydrolyzed to form chitosan. Chitosan has a backbone that consists of repeating units of glucosamine. Chitosan will have a positive charge at a pH below the p*K*a value, of about 6.2–7.0 [11].

All the three biopolymers have been tried as vehicles for delivering drugs to the colon. Since the three polymers are hydrophilic in nature, they will, when used alone in a formulation, start to swell when entering the stomach or the gastrointestinal tract. To solve this problem, two possible opportunities exist. The polymers may be modified hydrophobically. However, this turns the polymer into a new molecule that has to be tested for toxicity before it may be used in drug formulations. Another approach is to combine two oppositely charged polymers for example pectin and chitosan or alginate and chitosan. These polymers will at certain pH values create a polyelectrolyte complex (PEC), which has lower solubility properties than the mother molecule [12,6].

Attempts have been made to use pectin and chitosan for film-coated tablets [13–15], beads [16], and hydrogels [17]. Hydrogels beads [18], microparticles [19] and nanoparticles [20] of alginate and chitosan have also been investigated. However, the leakiness of the drug formulation is still too high. Improvement may be obtained by using other types of pectin, alginate or chitosan or other combination ratios. To coat pellets with pectin or alginate and subsequent with calcium or chitosan has been feasible by an interfacial complexation technique, i.e. immersion coating [21,22]. In this procedure, pellets with calcium in the core are placed in a solution of pectin or alginate, and the build-up of a complex is achieved [23]. A further strengthening of the network is accomplished by placing the pectin/alginate-coated pellets in a solution of calcium or chitosan.

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In our previous study, the minimum amount released was 17% over a period of 5 h for a combination of calcium in the core, a pectin coating (1 wt.%) and strengthening the coating with a final chitosan layer (0.1 wt.%) [21]. To further strengthen the coating a possibility might be to introduce the chitosan at an earlier stage of the coating process, i.e. by including chitosan in the pellet cores. Since chitosan is soluble at acidic pH, this alteration to the formulation will lead to an increased swelling and release for the uncoated cores. However, the possibility exists that when coated with pectin, pectin will prevent this effect and instead form a less swellable and soluble coat since pectin is not soluble under acidic condition. In addition, there might be a chance, that when coated with both pectin and chitosan, the PEC formation (between chitosan and pectin) will be fast enough to form a strong network with improved release characteristics.

The aim of this study was to produce pellets with calcium and chitosan in the core and then immersion coat the cores with pectin or alginate in combination with calcium or chitosan. By placing chitosan in the core of the pellets, the network may be strengthened both from the inside of the coating and from the outside. To our knowledge, this principle has not been studied previously.

The pellets without chitosan in the core were produced and immersion coated as a reference. Both types of coated pellets were evaluated with respect to the morphology of the coat, the amount of drug release and the swelling of both the core and the coat.

## 2. Materials and methods

### 2.1. Materials

The pellet cores consisted of microcrystalline cellulose (MCC) as an extrusion aid (Avicel PH101, FMC Biopolymer, Ireland), calcium acetate (Sigma–Aldrich, Germany) as the complexation agent, and riboflavin (Merck, Norway) as the model drug. In some of the pellets, chitosan (Chitoclear, degree of N-deacetylation (Dda) of 95%, Primex, Iceland) [24] was added with a corresponding reduction in the amount of MCC. Distilled water was used as granulation liquid.

In the first immersion solution, either low-methoxylated pectin (Pectin Classic CU701, degree of methoxylations (DM) of 36%, Herbstreith & Fox GmbH, Germany) or sodium alginate (Protanal LF 10/60, FMC Biopolymer, USA) was used. In the second immersion solution, either chitosan HCl (Seacure CL214, Dda of 89%, Pronova Biopolymer, Norway) or calcium chloride-dihydrate (Merck, Germany) was used as the external cross-linker. Distilled water was used as solvent in all the coating solutions.

### 2.2. Methods

#### 2.2.1. Preparation of the pellets

The composition of the two different types of pellets may be found in Table 1. Granulation was performed by the addition of 47% w/w water to the two different powder mixtures. For a detailed procedure for the production of the pellets see a previous article by Hiorth et al. [21]. The fraction of pellets with the size of 0.7–1.0 mm were collected and used in the further studies.

**Table 1**
The content of the two different types of pellets.

| Content | Calcium pellets (%) | Calcium–chitosan pellets (%) |
|---|---|---|
| MCC | 89 | 79 |
| Calcium acetate | 10 | 10 |
| Riboflavin | 1 | 1 |
| Chitosan | 0 | 10 |

#### 2.2.2. The preparation of the polymer solutions

Separate pectin or alginate 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).

#### 2.2.3. The immersion coating

The immersion coating process was a modified version of the method reported by Sriamornsak and co-workers [23]. In short, the pellets cores were first immersed in a solution of either pectin or alginate for 10 min, washed and subsequently introduced to a second coating solution consisting of either chitosan or calcium before a final washing procedure. A thorough description of the method can be found in a previous article by Hiorth et al. [21]. The encapsulation efficiency was estimated by measuring the amount of riboflavin in 200 uncoated pellets. The pellets were dissolved in 0.1 M HCl, and the absorbance was measured at 444 $\lambda$. Then, the amount of riboflavin in 200 coated pellets was measured. The encapsulation efficiency in % was estimated by taking (the amount of riboflavin in the coated pellets/the amount of riboflavin in the uncoated pellets) $*$ 100.

#### 2.2.4. The experimental design

The experimental setup was a fractional factorial design without center-points with respect to the polymer factors, whereas the concentration-factors were only varied for selected polymers (and combinations). For details see Table 2 and 3. The factors investigated were the following: (1) the type of pellets, i.e. with or without addition of chitosan to the core, (2) the type of polymer used in the first immersion solution (pectin or alginate 1%) and the concentration of pectin (1% and 2%), and (3) the counter ion employed in the second immersion solution (chitosan or calcium 5%) and the concentration of chitosan (0.1% and 1%) The complete design amounted to 16 experiments.

#### 2.2.5. Tensile strength of the pellets

The crushing strength, cs, of 50 pellets was measured by a TA-XT2 (Stable Micro Systems, UK). The method has previously been described by Schröder and Kleinebudde [25]. The punch was moved with a speed of 1 mm/s. The tensile strength, ts, of the pellets was calculated by the equation: $ts = (4 * cs)/(\pi * d^2)$, where $d$ = the height of the pellets [26].

#### 2.2.6. Release studies

The method can be found in a previous article by Hiorth et al. [21]. The parameters 1 h in 0.1 M HCl followed by 3 h in phosphate buffer pH 6.8 will be referred to as standard conditions.

#### 2.2.7. Swelling studies

Dry and coated pellets were placed in a Petri dish, and 0.1 M HCl or 0.125 M phosphate buffer pH 6.8 was added. These mediums should mimic the environment of the release studies. Pictures of

**Table 2**
The experimental design.

| Factors | Levels | |
|---|---|---|
| | Low | High |
| Chitosan in the core | Yes | No |
| 1. Immersion<br>Polymer type and concentration | Pectin (1–2%) | Alginate (1%) |
| 2. Immersion<br>Counter ion and concentration | Chitosan (0.1–1%) | Calcium (5%) |

**Table 3**
The complete design and the results from the release studies under standard conditions.

| Type of pellet | Polymer | Polymer concentration (%) | Counter ion | Counter ion concentration (%) | Release after 4 h (%) |
|---|---|---|---|---|---|
| Calcium | Pectin | 1 | Chitosan | 0.1 | 33.0 |
| Calcium | Pectin | 1 | Chitosan | 1 | 34.6 |
| Calcium | Pectin | 1 | Calcium | 5 | 42.7 |
| Calcium | Pectin | 2 | Chitosan | 0.1 | 34.3 |
| Calcium | Pectin | 2 | Chitosan | 1 | 35.2 |
| Calcium | Pectin | 2 | Calcium | 5 | 40.2 |
| Calcium | Alginate | 1 | Chitosan | 0.1 | 26.4 |
| Calcium | Alginate | 1 | Calcium | 5 | 29.2 |
| Calcium–chitosan | Pectin | 1 | Chitosan | 0.1 | 55.4 |
| Calcium–chitosan | Pectin | 1 | Chitosan | 1 | 73.6 |
| Calcium–chitosan | Pectin | 1 | Calcium | 5 | 69.9 |
| Calcium–chitosan | Pectin | 2 | Chitosan | 0.1 | 65.1 |
| Calcium–chitosan | Pectin | 2 | Chitosan | 1 | 71.5 |
| Calcium–chitosan | Pectin | 2 | Calcium | 5 | 62.3 |
| Calcium–chitosan | Alginate | 1 | Chitosan | 0.1 | 47.2 |
| Calcium–chitosan | Alginate | 1 | Calcium | 5 | 47.2 |

the dry pellets were taken immediately and 60 min after addition of solution. The area (A) of the pellets/core was calculated. The percentage swelling of the core and the degree of swelling of the coating layer were calculated from the following equations:

$$\%\ \text{Core swelling} = ((A_{\text{core 60 min}} - A_{\text{pellet 0 min}})/A_{\text{pellet 0 min}}) * 100$$

$$\text{Degree of coat swelling } (\text{mm}^2) = A_{\text{total 60 min}} - A_{\text{core 60 min}}$$

*2.2.8. Multivariate analysis*

Due to the unbalanced design, partial least square regression (PLS) was primarily used (The Unscrambler, Camo ASA, Norway) to evaluate the results and for identification of the most important factors with respect to reduction in the drug release in both 0.1 M HCl and phosphate buffer pH 6.8. In addition, the different swelling properties of both the pellet cores and the coating layers were evaluated multivariate. The variation of each variable was scaled to unit variance (1/SD). The models were calculated using full cross-validation. Jack-knifing was used to estimate the uncertainty of the PLS regression coefficients [27]. In addition, Principal Component Analysis (PCA) was used for looking at some of the factors and the different responses.

## 3. Results

Both the calcium pellets and the calcium–chitosan pellets were successfully produced, see Fig. 1. There was almost no difference in the crushing strength between the two types of pellets. The calcium pellets had a crushing strength of 28 N/mm$^2$ (SD: 3.5) and the calcium–chitosan pellets had a crushing strength of 26.9 N/mm$^2$ (SD: 3.2). The drug release from the uncoated cores was tested under standard conditions. The drug release from the calcium pellets showed a sustained release, see Fig. 2. After 15 min only 14% was released, and after 4 h 46.1% of the model drug was released. This was in contrast to the calcium–chitosan pellets. By replacing 10% MCC with 10% chitosan in the core, the drug re-

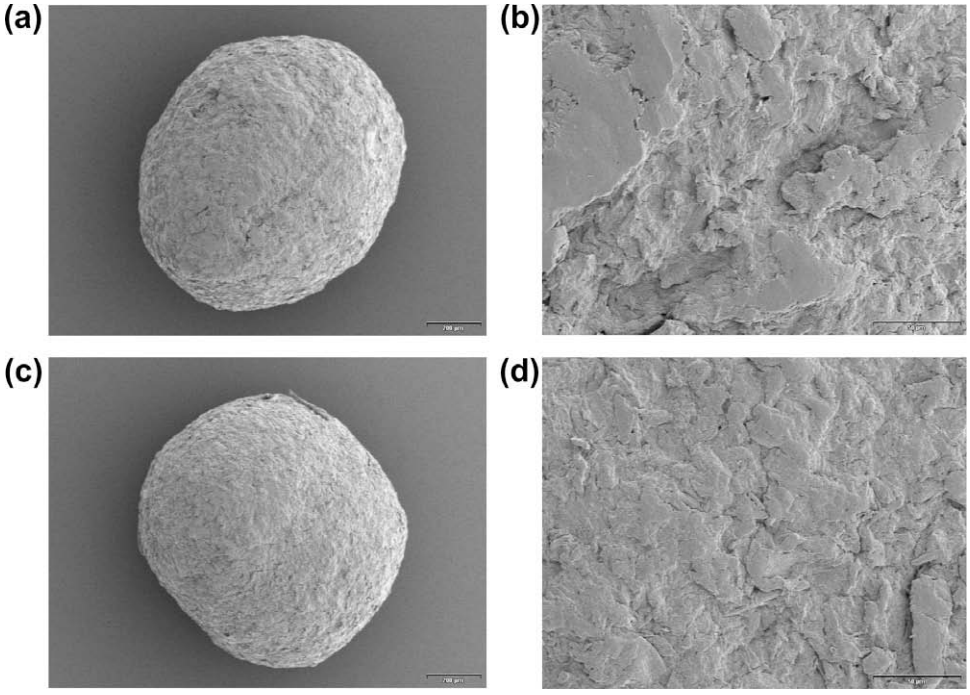


**Fig. 1.** The two different types of pellets, (a) and (b) the calcium–chitosan pellet and (c) and (d) the calcium pellet. Scale = 200 and 50 μm, respectively.

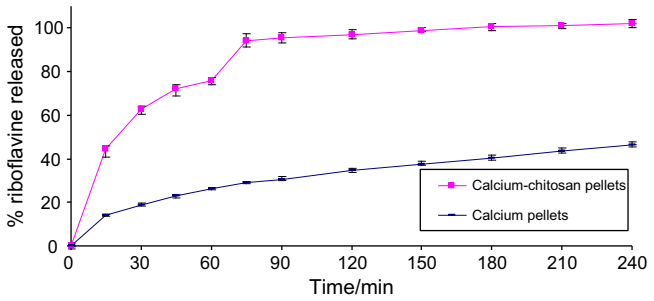


**Fig. 2.** The drug release from the uncoated cores of both calcium pellets and calcium–chitosan pellets. Max and min values ($n = 3$) are indicated in the plot. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

lease was dramatically increased. After only 15 min 44% riboflavin was released, and after 1 h in 0.1 M HCl almost 80% of the drug was released. In addition, when the release medium was changed from 0.1 M HCl to phosphate buffer pH 6.8, a further increase in the drug release was observed. After 75 min, the drug release for the calcium–chitosan pellets was completed.

Both types of pellets were successfully coated. Although the calcium–chitosan pellets started to swell during the immersion coating process, the interfacial complexation reaction and the deposition of a coating at the surface of the core seemed to protect the pellets from disintegrating. During pre-testing of the coating procedure, pellets containing only MCC and chitosan were produced, i.e. without calcium. These pellets started to disintegrate as soon as they were placed in the first immersion solution, and no coating at the surface of these pellets was formed. This type of pellet was consequently not included in the design.

The encapsulation efficiency was tested for one of the coating combination: 2% pectin in combination with 5% $CaCl_2$. The encapsulation efficiency was close to 70% for both types of pellets. 67% for the calcium pellets and 73% for the calcium–chitosan pellets. The SEM pictures, Fig. 3, indicate that the microstructure of the various coatings seems to differ. The coatings consisting of pectin or alginate in combination with chitosan displayed an irregular structure. The coat consisting of alginate in combination with calcium appeared to have a smoother surface that may indicate a more regular structure.

### 3.1. Drug release, all samples

Modeling (PLS1) the amount released after 4 h under standard conditions, the only significant factor ($p < 0.05$) found was the type of pellets although the type of polymer was close to being

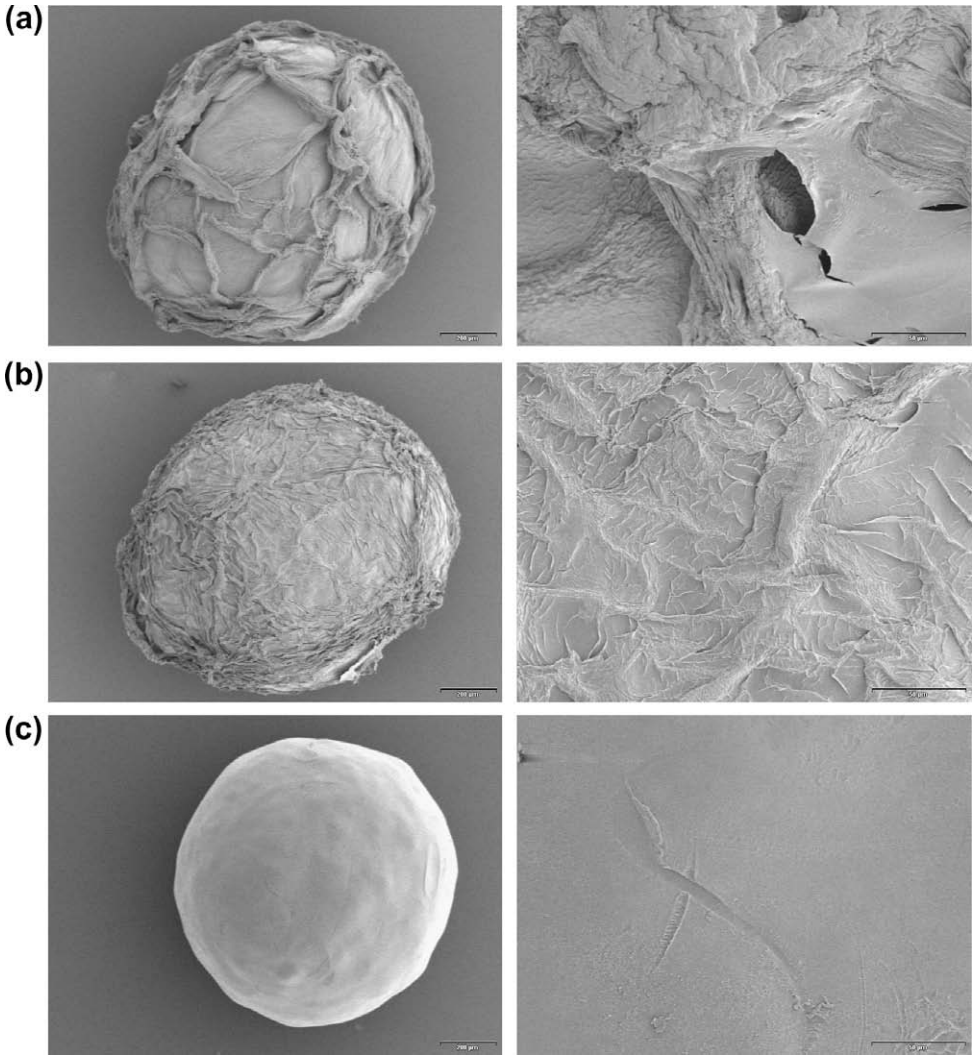


**Fig. 3.** The coated calcium–chitosan pellets: (a) alginate in combination with chitosan, (b) pectin in combination with chitosan, and (c) alginate in combination with calcium.

significant, see Fig. 4. The explained *Y*-variance of the model was 90%. The model revealed that the coated calcium pellets had a much slower drug release than the coated calcium–chitosan pellets. It was therefore decided to model the two different types of pellets separately.

### 3.2. The drug release from the calcium–chitosan pellets

Fig. 5 shows the drug release from the coated calcium–chitosan pellets. It is clear that coating the cores reduces the drug release dramatically compared to the uncoated cores. For the uncoated cores, the drug release was complete after 75 min, whereas the coated cores displayed drug release from the different combinations in the range of 15.4–40.2% after 75 min. The only significant factor in the PLS1 analysis of amount released after 4 h under standard conditions was the type of polymer used in the first immersion solution. The lowest drug release was obtained by using alginate instead of pectin.

A previous study had revealed that chitosan in the second immersion solution was more effective than calcium in slowing down the drug release [21]. For the calcium–chitosan pellets, however, the counter ion had no significant impact on the drug release.

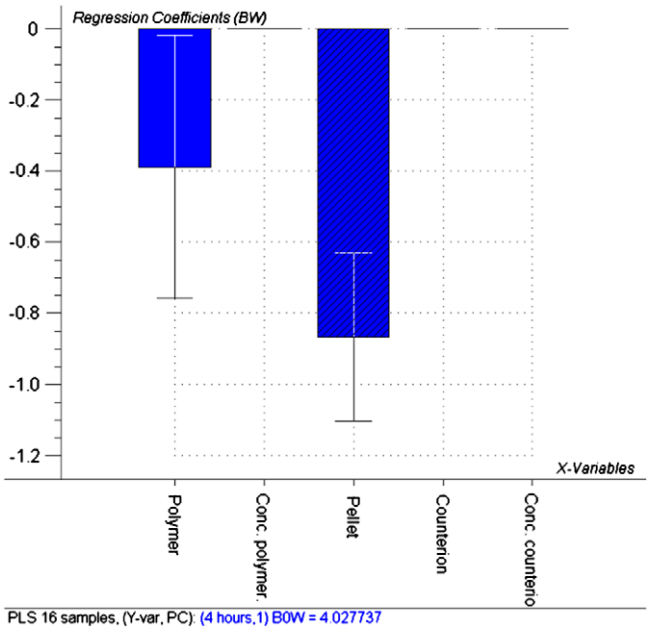


**Fig. 4.** The regression coefficient plot when modeled on all the samples. Only the type of pellets was significant ($p < 0.05$) using the jack-knife. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

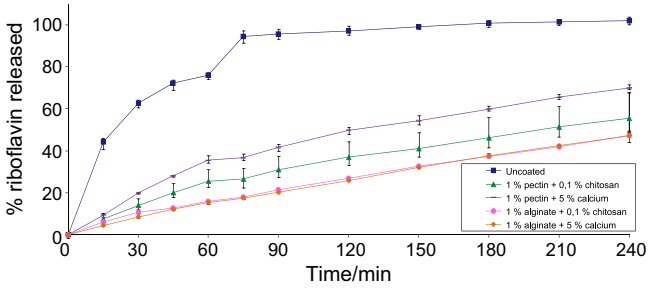


**Fig. 5.** The drug release from some of the coated calcium–chitosan pellets. Max and min values ($n = 3$) are indicated in the plot. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

It was interesting to note that the drug release from the alginate pellets was almost linear and independent of the pH of the release medium. The slope for the drug release was 0.18%/min ($r^2 = 0.995$) and 0.17%/min ($r^2 = 0.996$) for the two different combinations with alginate. The drug release from the pellets coated with pectin was pH dependant, and the slope for the drug release was significantly higher (*t*-test $p < 0.05$) in 0.1 M HCl pH 1 than in phosphate buffer pH 6.8.

### 3.3. The drug release from the calcium pellets

Fig. 6 shows the drug release from the coated calcium pellets. By comparing the drug release from the coated pellets with the uncoated cores, it is obvious that by coating the cores the drug release was reduced. The drug release was dependant on the coating composition and was in the range of 23–42.7% riboflavin after 4 h. The drug release appeared to be fairly linear during the first 3–4 h. A PLS1 analysis of drug released after 4 h under standard conditions for the coated calcium pellets resulted in a model with 1 PC and two significant factors with an explained *Y*-variance of 93%. The analysis showed that alginate in the first immersion solution significantly reduced the release rate compared to pectin and that chitosan in the second solution significantly reduced the release compared to calcium ($p < 0.05$).

### 3.4. Swelling studies of the cores and coating

A PLS model showed no significant factors for the swelling of the uncoated cores in phosphate buffer pH 6.8 but in 0.1 M HCl, the type of pellets was significant (*t*-test, $p < 0.05$). The test revealed that the calcium–chitosan pellets swelled more than the calcium pellets.

In addition, the swelling of some of the coated pellets was tested in acid 0.1 M HCl and phosphate buffer pH 6.8, see Table 4. Overall, the swelling of the coatings in phosphate buffer pH 6.8 was much higher than in 0.1 M HCl pH 1 as can be seen by looking at Fig. 7. A PLS model revealed no significant factors for explaining the observed differences in swelling of the coatings in 0.1 M HCl.

A PLS model of the swelling of the coatings in phosphate buffer pH 6.8 had an explained *Y*-variance of 99%. The model revealed two significant factors ($p < 0.05$) namely the type of polymer as well as the type of pellets. Highest degree of swelling was obtained for the coatings composed of pectin, and in contrast to the release studies, the coatings on the calcium pellets swelled more than the coatings on the calcium–chitosan pellets.

Finally, a PCA model was made by including all the factors and responses to try to illustrate, which factors that dominate the drug release. The PCA loading plot, Fig. 8, showed that the swelling of

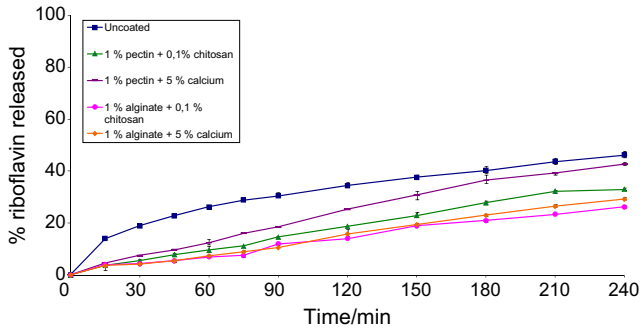


**Fig. 6.** The drug release from some of the coated calcium pellets. Max and min values ($n = 3$) are indicated in the plot. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

**Table 4**
The results from the swelling studies.

| A | B | C | Medium | Pellet area 0 min ($mm^2$) | Core area 60 min ($mm^2$) | Degree of coat swelling 60 min ($mm^2$) | Core swelling after 60 min (%) |
|---|---|---|---|---|---|---|---|
| Ca | 1% P | 0.1% Chit | Acid | 0.88 | 1.03 | 1.56 | 17.31 |
| | | | Buffer | 1.06 | 1.23 | 4.77 | 17.30 |
| Ca | 2% P | 1% Chit | Acid | 0.85 | 1.04 | 1.69 | 21.62 |
| | | | Buffer | 0.96 | 1.08 | 4.70 | 12.68 |
| Ca | 1% A | 0.1% Chit | Acid | 1.32 | 1.42 | 1.80 | 7.28 |
| | | | Buffer | 1.11 | 1.14 | 3.99 | 3.20 |
| Ca–Chit | 1% P | 0.1% Chit | Acid | 0.90 | 1.47 | 2.37 | 62.00 |
| | | | Buffer | 0.85 | 0.87 | 4.10 | 1.99 |
| Ca–Chit | 1% A | 0.1% Chit | Acid | 1.01 | 1.38 | 1.61 | 37.65 |
| | | | Buffer | 0.87 | 0.96 | 3.19 | 10.66 |
| Ca–Chit | 1% A | 5% Ca | Acid | 0.80 | 1.20 | 1.33 | 51.04 |
| | | | Buffer | 0.87 | 1.06 | 3.34 | 21.63 |

A: The type of pellets, Ca = calcium pellets, Ca–Chit = calcium–chitosan pellets.
B: The concentration and the type of polymer, P = pectin, A = alginate.
C: The concentration and the type of counter ion, Chit = chitosan, Ca = calcium.

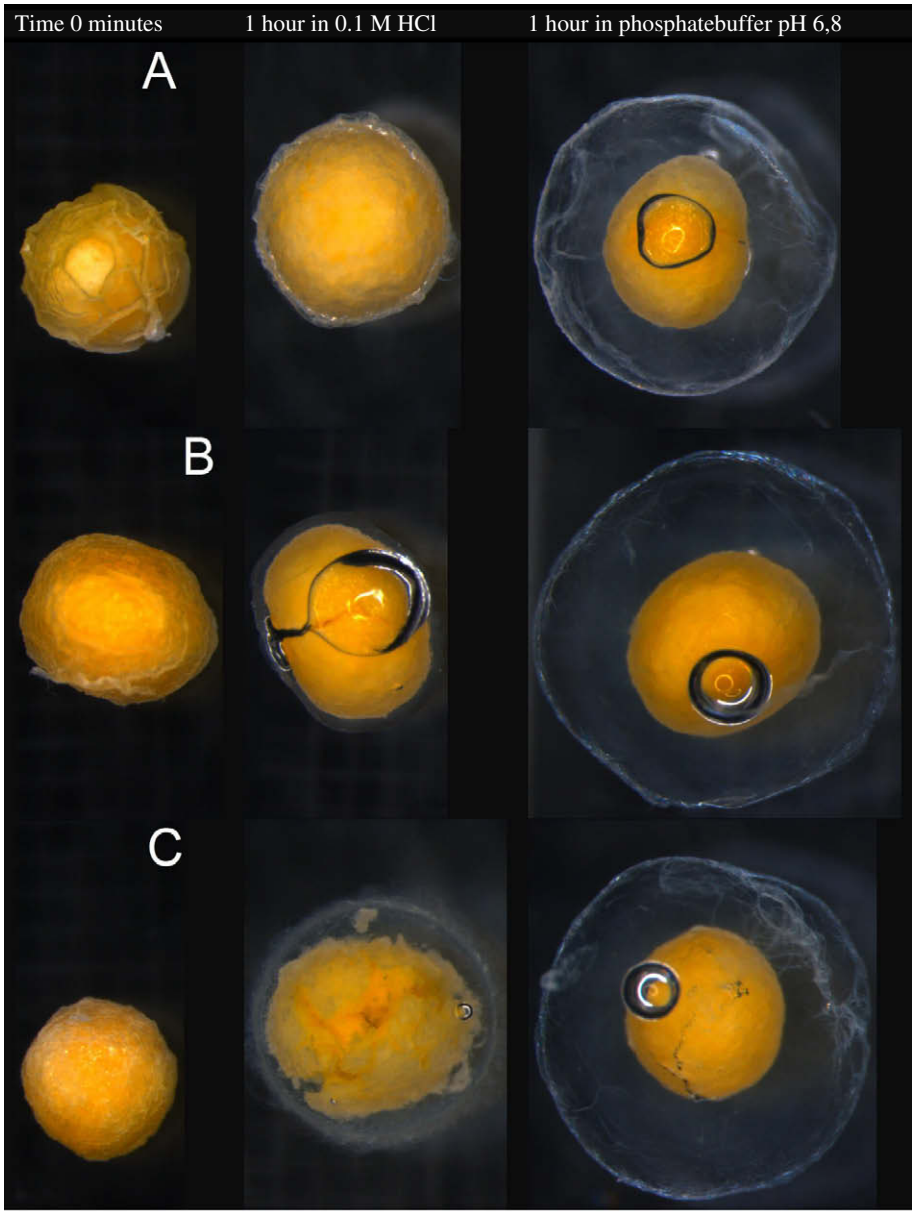


**Fig. 7.** Swelling of some of the different coatings A = calcium–chitosan pellet with 1% alginate and 0.1% chitosan, B = calcium pellet with 1% pectin and 0.1% chitosan, C = calcium–chitosan pellet with 1% pectin and 0.1% chitosan. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

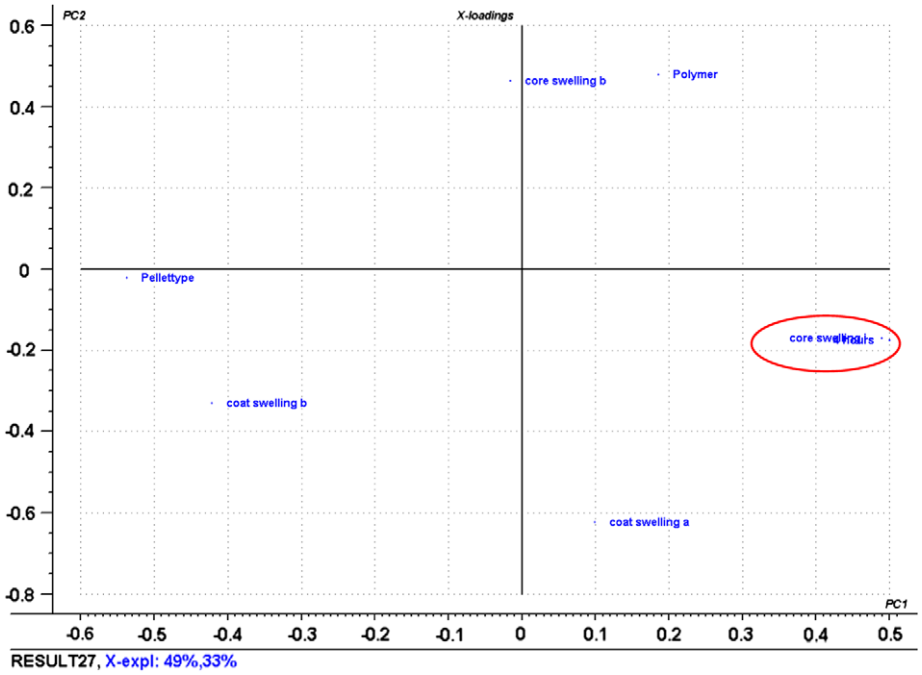


**Fig. 8.** PCA loading plot for some of the different factors and responses investigated. In the oval to the right both release after 4 h and core swelling in 0.1 M HCl can be found. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

the core in 0.1 M HCl was correlated to the drug release as well as the type of pellets. This indicates the properties of the core are decisive for the release and that the drug release consequently will be highest for the calcium–chitosan pellets due to the high degree of core swelling in 0.1 M HCl.

### 3.5. Drug release in pure phosphate buffer pH 6.8

It was decided to include one new experiment to investigate the drug release from the coated pellets in pure phosphate buffer pH 6.8. The drug release from both types of pellets coated with 2% pectin and 0.1% chitosan was tested in phosphate buffer pH 6.8. The results (Fig. 9) indicate that by excluding the first hour in 0.1 M HCl the drug release from the two different types of pellets becomes almost identical.

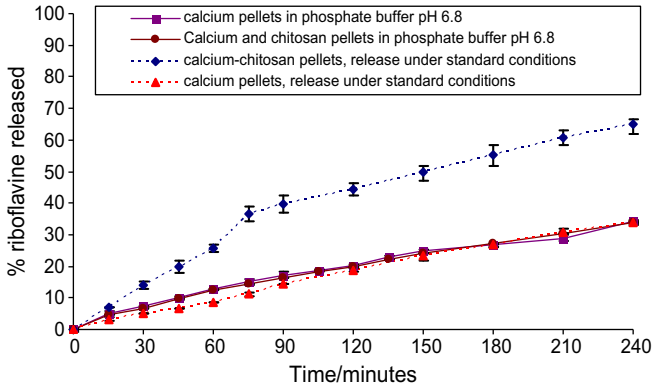


**Fig. 9.** The drug release from the calcium pellets and the calcium–chitosan pellets in phosphate buffer pH 6.8 coated with 2% pectin and 0.1% chitosan. Max and min values ($n = 3$) are indicated in the plot. As a reference the corresponding curves for the release under standard conditions are indicated (dotted lines). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

## 4. Discussion

The framework for this study was colon drug delivery. The hope was that by immersion coating the two different types of pellets important factors for formulations with potential as a colon drug delivery system would be revealed.

As reported for pre-testing of the coating procedure, it turned out to be impossible to coat pellets without calcium acetate in the core. This indicates how important calcium is for a quick start of the complexation reaction [28] and for protecting the chitosan-containing pellets from disintegration. Chitosan alone in the pellets is not capable of forming a polyelectrolyte complex with pectin or alginate fast enough to prevent disintegration of the pellets. The immersion coating method was successful in coating the two chosen types of pellets in the selected experimental region, and the encapsulation efficiency was quite high.

The morphology of the coatings indicated differences between the coatings with alginate/pectin in combination with calcium and the coatings with alginate/pectin in combination with chitosan (see Fig. 3). This is supported by a study by Xu et al. [18] where the morphology of gel beads composed of alginate and chitosan was investigated. The more alginate and less chitosan the smoother was the surface. There were lots of wrinkles in the beads with a mass ratio of alginate–chitosan 5:5 and 7:3. This is probably due to the formation of a random fibrillar network explained by Lai et al. [29]. Since alginate and pectin are reacting with calcium in a regular egg-box structure [30,31], this combination might form a more homogenous structure and a smoother surface.

Even though the uncoated calcium–chitosan pellets had a high drug release, our theory was that by including chitosan in the core of the pellets a PEC may be formed on the surface of the core in addition to the calcium complexes when immersion coating with pectin or alginate. This would hopefully provide a sufficient retardation of the release.

The results from the drug release experiments of the uncoated cores displayed different release patterns for the two different types of pellets. The calcium pellets provided a sustained release

while the calcium–chitosan pellets completed the drug release within 75 min. A previous study by Santos et al. on the release of diclofenac sodium from chitosan pellets, where chitosan was included in the range of 0%, 4% and 16%, showed a fast release with a complete drug release after 30–60 min in phosphate buffer pH 7.4 [32]. The results from our study revealed a somewhat slower drug release even though a release medium of pH 1 would be expected to provide a faster drug release than a medium of pH 7.4. The slower release in our study may be explained by the partly substitution of MCC with lactose or other fillers in the study by Santos (50% MCC and 16–34% lactose). The MCC level in our study was almost 80%, and other fillers were not used. Furthermore, the water solubility of riboflavin is much lower than diclofenac sodium, and the concentration of diclofenac was higher, 10% compared to 1% riboflavin in our study.

The drug release from the calcium pellets showed a sustained release with only 46% of the model drug released within 4 h. This is in good agreement with other studies of pellets composed of MCC. It is well known that MCC is an excellent excipient in the pelletization process [33], but if the pellets do not disintegrate, the release profile of low soluble drugs from MCC pellets will be retarded [34,35].

The drug release from the coated cores revealed that the calcium pellets were most successful in slowing down the drug release under standard conditions. When comparing the two types of pellets especially the drug release in 0.1 M HCl was responsible for the high drug release from the calcium–chitosan pellets. This was illustrated by the final drug release experiment (Fig. 9) that proved the two types of pellets equal when the 1 h in 0.1 M HCl was excluded from the release studies.

This difference in drug release from the coated cores may probably be explained by looking at the results from the swelling studies, Fig. 7. Here, a high degree of swelling, fragmentation and dissolution of the cores consisting of calcium and chitosan in 0.1 M HCl is observed. This is probably due to the p*K*a value of chitosan. Chitosan will be charged in 0.1 M HCl, and the polymer chains will start to repulse each other and swell. Drug release from porous swellable formulations is dependant of water penetrating the network leading to the dissolution of the drug and thereby diffusion of the drug in water-filled pores. The penetration of water also leads to swelling and this will change the structure and the diffusion length for the drug to be released. The drug release will be dependant of a combination of these two processes [36]. In hydrated coatings, the drug release is often increased by an increased degree of swelling [37]. Our result is supported by a study from Sriamornsak et al. where gel beads composed of calcium, pectin and chitosan had a much higher drug release when the beads where pre-treated in SGF than if the beads were only tested in SIF [38].

For both types of pellets, alginate was indicated as the most promising candidate for reduction in the drug release. Alginate and pectin are both polysaccharides quite similar in structure. Both types of polysaccharides react with divalent ions such as calcium causing an egg-box-like structure. When alginate and pectin react with cationic polymers, e.g. chitosan, a polyelectrolyte complex (PEC) is formed [12]. Different studies have revealed chitosan in combination with polysaccharides as a promising candidate in slowing down the drug release [39–43]. This is probably caused by a low solubility of the complex between chitosan and alginate/pectin. Our study indicates that alginate and chitosan probably make up a tighter PEC complex than pectin and chitosan. This is indicated by the higher degree of swelling for the coating composed of pectin compared to the coating composed of alginate. The lowest drug release was obtained for the complexes of alginate. These coatings turned out to swell the least. As mentioned earlier, there is always a competition between water solubility and swelling and the way the drug must diffuse through the swelled coating. The results obtained in this study seem to indicate that the higher swelling and thereby higher water solubility will lead to a higher drug release. In this system, the increased diffusing pathway for the drug is consequently less important.

The calcium pellets coated with chitosan instead of calcium in the second immersion solution was most effective in slowing down the drug release. This was in contrast to the calcium–chitosan pellets where no significant difference could be found. These results may indicate that chitosan in the pellet core react with pectin or alginate in the first immersion solution and thereby strengthen the network form the inside. This seems to be more important than which counter ion that is used for strengthening the network from the outside. The complexation reaction with chitosan in the core is probably slow since, as described earlier, having only chitosan in the pellets without any calcium, no complexation reaction was achieved. The complexation reaction may also take place when the pellets are exposed to the release media.

Another proof for the possible network strengthening by chitosan from the inside of the core is that the coatings on the calcium pellets swelled more in buffer than the coatings on the calcium–chitosan pellets. A PEC complex between the two polysaccharides possibly swells less than the complex between calcium and the polysaccharides. It is important to notice that even though the coatings on the calcium pellets are swelling more than the calcium–chitosan pellets, the swelling of the core is most important for determining the drug release.

The different concentrations of the polymers were not found significant. This was unexpected since a previous study by the authors had shown this parameter to be important [21].

This study has shown that the calcium pellets coated with alginate in combination with chitosan have the highest potential as a colon drug delivery system. Even though the calcium pellets had a lower drug release than the calcium–chitosan, it is interesting to note that the calcium–chitosan pellets coated with the best alginate combination had an almost linear drug release independent of the pH. Although beside the scope of this study, it should be mentioned that this might be an advantage, for example for the delivery of drugs to the small intestine, where the residence time is quite small (approximately 4 h).

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