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Development of Polysaccharide Gel Coated Pellets for Oral Administration:
Swelling and Release Behavior of Calcium Pectinate Gel.

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Keywords: polysaccharide; pectin; calcium pectinate; pellets; controlled release;
swelling
ABSTRACT

The aim of this study was examine the rehydration, swelling and drug release behavior of spherical pellets containing theophylline and coated with two different calcium pectinates. The spherical pellets were prepared by an extrusion-spheronization method and then coated with calcium pectinate using the diffusion-controlled interfacial complexation technique, which provides a defect-free and uniform coating on solid cores. The effect of pellet size, pectin type, pectin concentration and dissolution medium on the swelling and drug release behavior was investigated by a multi-level factorial design approach. Theophylline release from the pellets was slowed by the application of the coatings. The time to release 50% of the payload (i.e. T_{50}) in an acidic medium was 7 minutes from uncoated small pellets and was 55 minutes after an amidated calcium pectinate coat was applied; a comparable coat on large pellets showed a T_{50} of 93 minutes. Drug release profiles of dry coated pellets showed a lag time (all less than 20 minutes) when the gel coat hydrated and swelled, followed by a zero-order release. It was found that the release rate was controlled by the pellet size, pectin type, pectin concentration and dissolution medium.
INTRODUCTION

Pectin is a naturally occurring water-soluble polysaccharide that is found in the cell wall of most plants. It is largely composed of linear chains of (1→4)-linked α-D-galacturonic acid residues, some of which are naturally presented as methyl esters and some of which may be amidated by reaction with ammonia. The degree of esterification (DE) and the degree of amidation (DA) are both expressed as a percentage of the total carboxyl groups that are either esterified or amidated. Both the DE and DA are important criteria used to classify the pectins. Low methoxy pectins (DE < 50%) form gels through the action of calcium ions or other suitable cations, that are generally thought to form cross-links between the rigid and buckled galacturonic acid regions forming a so-called egg-box structure. Low methoxy amidated pectins also form gels through the action of calcium ions. The chemistry, general properties and gel formation properties of pectin have been reviewed previously.\(^1,2\)

The potential of pectin to be cross-linked by calcium ions has been used to manufacture controlled release dose-forms and various food products. Numerous oral delivery systems based on calcium pectinate gels (mainly matrix gel beads) have been investigated.\(^3-5\) However, the method of using drug entrapped in gel beads as a sustained release drug delivery system has suffered from rapid release in-vitro. An approach to solve this disadvantage by the application of a gel coating was described,\(^6\) refined for use with spherical pellets\(^7\) and compared with gel bead systems.\(^8\) A few studies have examined the potential and the physico-chemical properties of calcium gels of pectin as a membrane coating for controlled release systems.\(^7,9,10\) Although, the effect of formulation factors (polysaccharide concentration, type and the cross-
linking time) on the drug release profiles were investigated, direct comparison between different coatings is needed before a more comprehensive understanding of the diffusion process can be obtained. This will be critical to optimize the systems for the purpose of drug delivery.

The aims of this paper are to present the results of multi-level factorial design experiments to determine the effect of the pectin type, pectin concentration, size of core pellets and dissolution medium on the swelling and release parameters of the calcium pectinate gel coated pellets.

MATERIALS AND METHODS

Materials

Low methoxy pectin with DE of 28% was obtained from two sources. A commercial pectin (LMA) with DA of 20% (GENUpectin type LM-104 AS-FS) was the generous gift of CP Kelco (Lille Skensved, Denmark), and potassium salt of esterified pectin from citrus fruit (LMC) was purchased from Sigma Chemical Co. (St Louis, USA). Theophylline (TPL, 150-300 μm), polyvinylpyrrolidone (average MW 360 000), calcium acetate (300-355 μm) (Sigma Chemical Co., St Louis, USA) and microcrystalline cellulose (45-106 μm) (Avicel PH101, FMC Corp., Philadelphia, USA) were used as received without further purification. All other chemicals were of reagent grade and used as supplied. Deionized water was prepared by reverse osmosis throughout all experiments.

Manufacture of calcium pectinate gel coated pellets

Core pellets (containing 40% wt/wt TPL, 50% wt/wt microcrystalline cellulose and 10% wt/wt calcium acetate) were manufactured by extrusion-
spheronization (using model 25 extruder and model 120 spheronizer, G.B. Caleva, Sturminster Newton, England) as previously described. They were dried on a tray in an air dryer (Clayson Laboratory Apparatus, Brendale, Australia) at 50 °C for 24 h.

Pectin solutions were prepared by dissolving the pectins in water with stirring and then leaving them undisturbed overnight in sealed containers to allow the air bubbles to rise. Five grams of pellets in the size fractions of 0.85–1.0 and 1.4–1.7 mm, were dispersed in 300 g of 1–4% wt/wt aqueous solutions of the pectins by stirring using a 5-cm diameter turbine stirrer at a speed of 400 rpm for 10 min. This allowed the calcium in the pellets to dissolve, diffuse to the surface and cross-link with the pectin to form a water-insoluble calcium gel film around the pellet. Further film formation occurred by diffusion of calcium ions through the (hydrated) calcium gel film already formed. Coated pellets were rinsed in water, stirred in 0.34 M CaCl₂ for 5 min, rinsed in water and then stirred in ethanol for 5 min. The coated pellets were filtered, dried at 40 °C for 48 h and stored in glass bottles in a desiccator over silica gel until required. The physico-mechanical properties of both the uncoated and coated pellets have been reported previously.

Swelling studies

Dry coated pellets were placed in a vial to which 10 mL of the different dissolution media (water, 0.1 M hydrochloric acid (HCl), simulated gastric fluid USP without pepsin (SGF) or 0.1 M sodium chloride (NaCl)) were added. The vials were then shaken in an orbital mixer incubator (Ratek Instruments, Boronia, Australia) at a constant temperature of 37 °C. The agitation technique ensured that water penetration and swelling occurred 3-dimensionally. After 24 h, the equilibrium-swollen pellets were observed and photographed (using transmitted light) with the aid of a

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microscope (Olympus SZ-40, Olympus Co., Japan) with 35mm camera attachment. Printed photographs were scanned and the image files were assessed by image analysis (Image-Pro Plus v4.1, Media Cybernetics, Maryland, USA). The Feret diameter of the swollen pellet ($d_{\text{out}}$) and its core ($d_{\text{in}}$) was taken from pellet images on each photograph. The coat thickness was then calculated as shown in Equation 1.

$$\text{Coat thickness} = \frac{d_{\text{out}} - d_{\text{in}}}{2}$$

(1)

The swelling kinetics of some coated pellets in 0.1 M NaCl was also investigated by the same method, except that the pellets were photographed at specific time intervals.

**In-vitro drug release studies**

An automated USP dissolution apparatus type 1 (Model VK7000, Vankel, Cary, USA), was linked to 6×0.1 cm flow-through UV cells in a UV spectrophotometer (Model Cary 1E, Varian Australia Pty. Ltd., Melbourne, Australia) by a peristaltic pump (Model 17-2300, Vankel, Cary, USA) under control of Cary WinUV software (Varian Australia Pty. Ltd., Melbourne, Australia), was used to measure drug release. The temperature was 37 °C, the volume of dissolution media (water, 0.1 M HCl, SGF or 0.1 M NaCl) was 1000 mL and the baskets were rotated at 100 rpm. The analytical wavelengths were 273 nm (water), 270 nm (0.1 M HCl and SGF), 271 nm (0.1 M NaCl) and Beer’s law was obeyed over the range of 0-100 mg/L. Drug release was measured from accurately weighed amounts of both uncoated and coated pellets such that 100 mg of TPL was present in each dissolution pot. All dissolution runs were performed in triplicate.
**Statistical design and analysis**

The effect of the pellet size, pectin type and concentration and dissolution medium on the swelling and release behaviour of the pellets was investigated using a multi-level factorial design approach (Table 1). For swelling and drug release experiments, a $2^4$ complete factorial design was used. The four factors tested were 2 sizes of pellet, 2 types of pectin, 2 concentrations of pectin and 2 different media (i.e. water and 0.1 M HCl). The effect of dissolution medium on release characteristics was studied extensively in 0.1 M NaCl and SGF in a $2 \times 2 \times 4$ factorial design; the factors are 2 sizes of pellet, 2 types of pectin and 4 dissolution media. Similarly, the effect of concentration of LMA was also investigated by a $2 \times 4 \times 2$ factorial design (2 sizes of pellet, 4 concentrations of LMA and 2 dissolution media).

Analysis of variance (ANOVA) and Levene’s test for homogeneity of variance were performed using SPSS version 10.0 for Windows (SPSS Inc., Chicago, USA). Post hoc testing ($p<0.05$) of the multiple comparisons was performed by either the Scheffé or Games-Howell test depending on whether Levene’s test was insignificant or significant, respectively.¹¹

**RESULTS AND DISCUSSION**

**Swelling behavior of calcium pectinate gel coated pellets**

Optical microscopy was used to investigate the hydration and swelling of pellets coated with dried calcium pectinate. All the hydrated coats of calcium pectinates were slightly turbid or translucent. Figure 1 shows optical photomicrographs of 2% wt/wt LMA coats that have been allowed to rehydrate in water, 0.1 M HCl, SGF and 0.1 M NaCl. The appearance of the other hydrated pellets
was similar. It has been suggested that signs of turbidity are indicative of molecular aggregates\textsuperscript{12}, and it is likely that in this case, the aggregates are calcium polygalacturonate junction zones.

The extent of swelling at equilibrium of small pellets coated with the pectins in 0.1 M HCl and water is shown in Figure 2. Although there was a statistically significant increase in swelling as the concentration of LMA was increased, an increase in the concentration of LMC (from 1 to 2% wt/wt) did not influence swelling. Although the swelling of LMA was significantly greater in water than in the 0.1 M HCl, the swelling of the LMC coats was not significantly influenced by the pH of the medium. The equilibrium swelling of LMA was significantly higher than LMC. This was probably due to the presence of amide groups in the LMA, and consequently a decrease in the free carboxyl groups,\textsuperscript{13} which would decrease the availability of anionic groups for cross-linking by calcium ions. The swelling of the calcium pectinate coats in water, 0.1 M HCl and SGF were greater than calcium alginate coats.\textsuperscript{14}

The effect of all the media on the equilibrium thickness of hydrated coats on both small and large pellets is shown in Figure 3. Although the effect of medium was similar for the two pellet sizes, the two pectins were affected differently by the media. The LMA coats always swelled more than the LMC, and notably the difference was greater in water and 0.1 M NaCl. The large swelling in the 0.1 M NaCl was caused by the exchange of the cross-linking calcium ions with the non-gelling sodium ions and the partial formation of soluble sodium pectinate which induced water uptake into the dry coats. Although the amount of calcium remaining in the swollen gel coats after 4 h in 0.1 M NaCl was only about 10-30% of the original amount present,\textsuperscript{15} this was
apparently sufficient to maintain gel coat integrity for 24 h. A recent report has suggested that one calcium ion can stabilize up to 18 dimeric poly galacturonate units.\textsuperscript{16} Compared to water, the 0.1 M NaCl has relatively less influence on the LMA than LMC and this may be due to hydrogen bonding between the amide groups that provides a mechanism of association between the chains that is independent of the calcium ion. Previous findings showed that rehydrated LMA gel films are stronger than LMC films.\textsuperscript{10}

In the acidic media, the swelling of LMA-coated pellets were significantly less than in water. However, the acidic media did not significantly affect the LMC coats. The low swelling of pectin coats in acidic media was probably due to proton-calcium exchange that formed insoluble pectinic acid domains within the gel coats. In the acidic media, the pectin coats were slightly turbid suggesting the formation of polymer aggregates whose size is of the order of the wavelength of light.\textsuperscript{12} Such aggregation of LM pectins in acidic media has been confirmed.\textsuperscript{17} This aggregation may be a further source of gel stabilization, which could reduce the swelling in low pH systems, compared to in water. In a previous report, it was shown that although LMA films rehydrated in acidic media or water were stronger than LMC films, the acidic media caused a greater relative improvement (LMA compared to LMC) than water alone.\textsuperscript{10}

\textit{In-vitro drug release studies}

\textit{Drug release from uncoated pellets}

Drug release from the uncoated pellets in the different media is shown in Figure 4. Although the release of theophylline (TPL) was affected by pellet size, it was unaffected by the pH or ionic strength of the media, as was shown previously.\textsuperscript{14}
TPL has two $pK_a$ values\textsuperscript{18}, namely $\approx 3.5$ and 8.6, and the saturation solubility in water and 0.1M HCl at 37 °C are 11.8 and 12.5 g L$^{-1}$ respectively.\textsuperscript{15} Although TPL will range from cationic to predominantly unionized, its solubility does not alter substantially and this would account for the observed lack of effect of pH on the release of TPL from the uncoated pellets. The drug release was essentially complete release within 30 min for small pellets (0.85-1.0 mm) and 60 min for large pellets (1.4-1.7 mm). Previous studies have shown that the release of TPL from uncoated pellets was found to agree with the diffusion controlled release model (drug release linearly related to square root of time).\textsuperscript{7,14} The results here show a significantly faster release of active than was shown for similar (uncoated) pellets; this may be largely due to the lower solubility of the model drug (riboflavin) used in that study.\textsuperscript{19}

Overview of drug release from coated pellets

Figures 5 and 6 show the percentage of TPL released from calcium pectinate coated pellets versus time. The gel coats prolonged the duration of drug release compared to the uncoated pellets. The release from coated pellets is essentially constant until about 80-90% of the payload has been released, and the duration of constant release was about 2-4 h for small coated pellets and about 4-6 h for large coated pellets. As expected, statistically significantly slower release was observed when the pellet size was increased as illustrated in Table 2 and Figure 5. Similar findings have been observed in other studies and are thought to be due to the increased diffusional pathlength and reduced surface area in the large pellets.\textsuperscript{7}

TPL release from calcium pectinate gel coated pellets showed drug release profiles similar to calcium alginate coated pellets.\textsuperscript{14} During the initial 2-3% release, the rate of release increased non-linearly as the calcium pectinate membrane hydrated,
swelled and increased in permeability. This was followed by a predominant, 80-90% zero-order release, also described as the steady state or equilibrium release phase.

During the final 5-10% of release, there was a non-linearly decreasing release rate.

The percentage of the drug released as a function of time may be expressed as:

$$\frac{M_t}{M_\infty} = k \cdot t$$  \hspace{1cm} (2)

where $M_t/M_\infty$ is the percentage released at time $t$, and $k$ is a release constant which is influenced by the thickness of the membrane, permeability coefficient, concentration of drug inside the pellet, and also the surface area of the sphere. In order to see the effect of pellet size, pectin type, pectin concentration and dissolution medium on drug release from coated pellets, three release parameters were described. The parameters are (a) $T_{50}$ (i.e. the time for 50% release of TPL), (b) zero-order release rate constant (i.e. $k$ from Equation 2), and (c) the lag time ($T_L$) which is the time required for a drug to establish a uniform concentration gradient within the rehydrated gel film. The lag time can be estimated from the intercept of the linear (i.e. steady state) portion of the release plots extrapolated back to the time axis. It should be noted that the $T_{50}$, although a very useful parameter from a therapeutic perspective, is less useful in developing a mechanistic understanding of the release process, because $T_{50}$ depends on both the lag time and the release rate. Products with short lag time and slow release rate or long lag time and rapid release rate, could present similar values of $T_{50}$.

**Effect of pectin type on drug release from coated pellets**

The pectin type directly influenced the gel properties and the release behavior of the drug. The pellets coated with LMA and LMC gave comparable values of $T_{50}$ (Table 2), probably due to the composite nature of $T_{50}$ as discussed above. The release
rate of LMC is greater than LMA, but the $T_L$ of LMC is generally shorter than LMA (Table 2). Therefore LMC was more permeable and hydrated more rapidly than LMA. The flux of TPL across the LMA coats may have also been reduced because of the greater equilibrium swelling of the LMA (Figures 1 and 2). Racape and co-workers\textsuperscript{20} suggested that the amide groups (in LMA) allowed other modes of chain association (e.g. hydrogen bonding), in addition to simple cross-linking between carboxyl group of galacturonic acid residues and calcium ions. Therefore, although it is likely that such associations contribute to the reduced permeability and slower hydration of the LMA coats, they did not ultimately reduce the extent of LMA swelling. The hydrogen bonding present in LMA may promote molecular flexibility and physical elasticity that allows extensive swelling during hydration. Previous experience with LMA (both as a coating and a free-standing gel) shows, that in comparison to LMC, the LMA is more robust and elastic.\textsuperscript{9,10} This has also been confirmed in other studies with LMA-like pectins.\textsuperscript{2,13} It is possible that the greater equilibrium swelling of the LMA contributed to the reduced flux of TPL because of the increased diffusional path-length.\textsuperscript{7}

In comparison to previous results,\textsuperscript{14} it is apparent that both types of pectin gave faster drug release rate, shorter $T_L$ and $T_{50}$ than the types of alginate studied. This may be due to the difference in molecular structure of alginate and pectin. The galacturonic acid units in pectin are epimers of guluronic acid units in alginate and the gel cross-linking mechanism are generally thought to be very similar.\textsuperscript{1} Although there have been many parallels drawn between the calcium-induced gelation of alginate and pectin (e.g. reference 21), there are some notable differences including the anomaly mentioned above\textsuperscript{16} and the insertion of rhamnose residues which interrupt the pectin
chains that would probably cause differences in gel formation and properties. In particular, the pectin gels may not form as densely as the alginate gels. Comparison of Figures 1-3 with previous results, shows that the pellets coated with pectin swelled more than the pellets coated with alginate. Therefore, the porosity of the pectin gel coat would probably be greater and this could contribute to the faster release of drug from pectin coated pellets.

Effect of pectin concentration on drug release from coated pellets

Changing the concentration of the pectin coating solution influenced the release characteristics (Table 2). From the statistical analysis, it was found that increased concentrations of LMC (i.e. 0% (uncoated pellets), 1% and 2%) and of LMA (i.e. 0%, 1%, 2%, 3% and 4%) significantly slowed release. In general, the $T_{50}$ was increased, the $T_L$ prolonged and the release rate was decreased by an increase in the pectin concentration. It is likely that an increase in pectin concentration would lead to an increase in the number of cross-links and to a reduction in the pore size within the gels. It has been previously shown that the increase in pectin concentration lead to an increase in the dry coat thickness (from 40 – 80 micrometers) and also lead to an increase in the crushing strength of the coated pellets. The former would translate to an increase in the swollen thickness of the rehydrated coats and the latter is indicative of increased gel density and cross-linking.

Effect of dissolution medium on drug release from coated pellets

The rate of drug release from coated pellets was considerably higher and the $T_L$ and $T_{50}$ were shorter in 0.1 M HCl than in water. The faster drug release in the acid could be explained by a calcium-proton ion exchange mechanism as described for calcium alginate gel coated pellets. Negligible calcium remained in calcium
pectinate gel films after only 5 min exposure to 0.1 M HCl. The reduced cross-linking in the pectinic acid domains would allow greater flexibility of the polysaccharide chains and this would provide reduced impediment to drug diffusion and would also be expected to be followed by greater solvent penetration into the hydrogel network. However, the coats appeared to swell less in 0.1 M HCl than in water and a thin gel membrane was present at the end of the release period, for both LMA and LMC. This observation showed that the diffusion pathlength was less for the acid compared to water and would also explain why the drug release proceeded much faster in acid medium.

The release behavior of pectin coated pellets in SGF showed that the release rate was significantly lower and the $T_L$ was shorter than in the 0.1 M HCl (see Table 3). It should be noted that, except for the water, all dissolution media have similar ionic strength ($\mu = 0.1$) to reduce the influence of ionic strength alone on the gel properties and release behaviors of the gel coated systems. It is expected that the behavior is driven by the calcium-sodium/proton exchange phenomenon. There was no significant difference in the release rate, $T_{50}$ or $T_L$ between the calcium pectinate (LMA or LMC) gel coated pellets, when tested in SGF.

The statistical analyses showed that the rate of drug release from coated pellets was significantly lower and the $T_L$ and $T_{50}$ were longer in 0.1 M NaCl than in the acidic media and water (Table 3 and Figure 6). This is in contrast to calcium alginate coated pellets, where the drug release was faster in 0.1 M NaCl than in water. The $pK_a$ of pectin varies with the DE, and for the polysaccharides employed in this study, it is likely to be in the range 3.6 – 4.1. Since the $pK_a$ values of manuronic and guluronic acids are about 3.4 and 3.7 respectively, although the $pK_a$ of sodium...
alginate will depend on the composition, it is similar to the pKₐ of the pectin. The increased degree of ionization of the polysaccharides above pH 4 will contribute to the greater swelling that was observed in 0.1M NaCl compared to the acidic media. However, at near-neutral pH, although the polysaccharides will be polyanionic, the TPL will be predominantly un-ionized and no coulombic interactions are expected between TPL and the polysaccharides.

Therefore the different behaviors of the alginate and pectinate CaPG in 0.1M NaCl might be due to differences in the molecular structure of the alginates and pectinates and also the relative affinity of pectin or alginate for sodium ions and protons. The calcium alginate coated pellets swelled extensively during the release testing in the 0.1 M NaCl solution due to the calcium-sodium ion exchange within the hydrogels. The partial formation of soluble sodium alginate induced water uptake into the gel network and would increase the mobility of the polysaccharide chains. Recently, it has been reported that exposure of calcium alginate gel fibers or spheres to dilute solutions of counter-gelling ions (e.g. sodium) expands the gel network sufficiently to allow uptake of high molecular weight proteins into the gel.

Unlike the pellets coated with alginate, the calcium pectinate gel coated pellets showed a slower release rate in 0.1 M NaCl than in water. The likely reason was that the pectin coat swelled more in 0.1 M NaCl than in water, and this increased the drug diffusional pathlength. Although the calcium exchange by sodium ions occurred to a greater extent in LMA, compared to alginates, the LMA displayed a slower drug release. This may be due to the multiple modes of chain association mentioned previously.
Given the low toxicity of pectin, the relative ease of application of the coats and the demonstrated mucoadhesive qualities of a range of pectins (including an LMA-like material)$^{26}$, calcium pectinate gel coats may show some potential in the design of sustained release oral dosage forms with utility in both the stomach and the intestine.

CONCLUSIONS

The application calcium pectinate gel coats on to spherical pellets containing theophylline markedly slowed the drug release (compared to uncoated pellets) and the release profiles were influenced by the pellet size, pectin type, pectin concentration and dissolution medium. Drug release profiles of dry coated pellets showed a lag time when the gel coat hydrated and swelled, followed by a zero-order release. The use of large pellets (1.4-1.7mm diameter), an increase in the pectin concentration or the use of an amidated low methoxy pectin all significantly slowed the release rate of theophylline.

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REFERENCES


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Figure 2  Equilibrium swelling of small pellets coated with pectin (mean ± SD; n=10).

Figure 3  Effect of media on equilibrium swelling of pectin-coated pellets (mean ± SD; n=10).

Figure 4  Effect of dissolution media on release of uncoated theophylline pellets. (Means plotted, n=3; SD are within the point size.)

Figure 5  Theophylline release from small and large pellets coated with 2% LMA. (Means plotted, n=3; SD are within the point size.)

Figure 6  Effect of dissolution medium on theophylline release from pellets coated with 2%LMA. (Means plotted, n=3; SD are within the point size.)
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Table 1  Summary of the experimental design.

Table 2  Drug release parameters for theophylline from small and large pellets coated with different pectins (mean ± SD; n=3).

Table 3  Drug release parameters for theophylline from pellets coated with 2% pectins (mean ± SD; n=3).
Figure 1
Figure 2
Figure 3
Figure 4
Figure 5
Figure 6

[Graph showing the percentage of theophylline released over time for different conditions.]

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Table 1

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<th>Level 3</th>
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<td>SGF</td>
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¹ LMC = low methoxy pectin, conventional (from Sigma Chemical, USA),
LMA = low methoxy pectin, amidated (from CP Kelco, Denmark)
² N/A = not applicable
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<th>Release rate (%/min) ± SD</th>
<th>Lag time (min) ± SD</th>
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<td>4% LMA</td>
<td>67.2 ± 0.93</td>
<td>92.8 ± 1.65</td>
<td>0.812 ± 0.012</td>
</tr>
<tr>
<td>Large</td>
<td>Core</td>
<td>13.1 ± 0.38</td>
<td>14.7 ± 0.10</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>1% LMC</td>
<td>80.8 ± 2.14</td>
<td>123.1 ± 1.33</td>
<td>0.659 ± 0.012</td>
</tr>
<tr>
<td></td>
<td>2% LMC</td>
<td>86.1 ± 0.81</td>
<td>126.9 ± 1.20</td>
<td>0.599 ± 0.004</td>
</tr>
<tr>
<td></td>
<td>1% LMA</td>
<td>79.6 ± 0.96</td>
<td>105.4 ± 2.28</td>
<td>0.649 ± 0.006</td>
</tr>
<tr>
<td></td>
<td>2% LMA</td>
<td>92.5 ± 1.25</td>
<td>128.2 ± 0.56</td>
<td>0.566 ± 0.006</td>
</tr>
<tr>
<td></td>
<td>3% LMA</td>
<td>105.5 ± 1.40</td>
<td>147.0 ± 0.54</td>
<td>0.501 ± 0.007</td>
</tr>
<tr>
<td></td>
<td>4% LMA</td>
<td>114.9 ± 1.97</td>
<td>164.3 ± 2.64</td>
<td>0.467 ± 0.008</td>
</tr>
</tbody>
</table>
Note: N/A = not applicable; LMC = low methoxy pectin, conventional (from Sigma Chemical, USA); LMA = low methoxy pectin, amidated (from CP Kelco, Denmark)
Table 3

<table>
<thead>
<tr>
<th>Pellet size</th>
<th>Medium</th>
<th>T$_{50}$ (min) ± SD</th>
<th>Release rate (%/min) ± SD</th>
<th>Lag time (min) ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2% LMC</td>
<td>2% LMA</td>
<td>2% LMC</td>
</tr>
<tr>
<td>Small</td>
<td>Water</td>
<td>64.7 ± 0.73</td>
<td>72.7 ± 1.08</td>
<td>0.884 ± 0.011</td>
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<tr>
<td></td>
<td>0.1 M HCl</td>
<td>47.0 ± 0.49</td>
<td>54.6 ± 1.05</td>
<td>1.151 ± 0.011</td>
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<tr>
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<td>SGF</td>
<td>53.5 ± 0.85</td>
<td>64.9 ± 0.09</td>
<td>0.949 ± 0.020</td>
</tr>
<tr>
<td></td>
<td>0.1 M NaCl</td>
<td>70.6 ± 0.95</td>
<td>96.3 ± 2.31</td>
<td>0.809 ± 0.017</td>
</tr>
<tr>
<td>Large</td>
<td>Water</td>
<td>126.9 ± 1.20</td>
<td>128.2 ± 0.56</td>
<td>0.439 ± 0.004</td>
</tr>
<tr>
<td></td>
<td>0.1 M HCl</td>
<td>86.1 ± 0.81</td>
<td>92.5 ± 1.25</td>
<td>0.599 ± 0.004</td>
</tr>
<tr>
<td></td>
<td>SGF</td>
<td>98.0 ± 0.50</td>
<td>98.4 ± 0.71</td>
<td>0.521 ± 0.005</td>
</tr>
<tr>
<td></td>
<td>0.1 M NaCl</td>
<td>139.0 ± 3.25</td>
<td>142.0 ± 1.20</td>
<td>0.386 ± 0.002</td>
</tr>
</tbody>
</table>

Note: LMC = low methoxy pectin, conventional (from Sigma Chemical, USA); LMA = low methoxy pectin, amidated (from CP Kelco, Denmark)