Development and description of controlled release formulations for use in powder detergents
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6 WATER-INSOLUBLE COATINGS

6.1 Introduction

In this chapter the results are discussed of reservoir devices with a water-insoluble core surrounding a spherical water-soluble core. Because of the concentration gradient over the coating, water will diffuse into the core increasing the volume of the core. The resulting stress on the coating will eventually cause mechanical failure of the coating and release of the contents of the microcapsule.

Similar formulations have been developed by Schultz and Kleinebudde [1, 2] and have been discussed in chapter 2. The difference with the aforementioned articles is that in this chapter the emphasis is laid on formulations with a release cycle completed in less than one hour and furthermore that a mathematical model is presented to predict the moment of release. Moreover, the influence of several properties of the core (shape, size distribution and incorporation of a swelling agent) are investigated and the physical properties (mechanical and diffusion characteristics) of the coating were determined.

6.2 Materials & Methods

Materials

One of the water-insoluble coatings used in the experiments is ethylcellulose (EC), a cellulose derivative. It is available as an aqueous polymer dispersion also referred to as pseudo-latex (Aquacoat ECD-30, FMC corporation, USA) which makes it possible to coat without the use of organic solvents.

The dispersion is called pseudo-latex because it is manufactured from the polymer itself and, not as with true latexes, from the monomer. The polymer particle size in a pseudo-latex is reduced by a physical process. Aquacoat, for example, is produced by dissolving ethylcellulose in an organic solvent and emulsifying the solution in an aqueous continuous phase. When the organic solvent is removed the polymer remains in the aqueous phase as fine polymer particles (smaller than 1 µm, figure 6.1). Aquacoat ECD-30 contains 30 w/w%
solids and 70 w/w% water. The solid phase consists of 87 w/w-% ethylcellulose, 9 w/w-% cetyl alcohol, 4 w/w% sodium laurylsulphate and a small amount of food grade anti-foam [3]. The cetyl alcohol and sodium lauryl sulphate act as stabilizers to prevent flocculation and sedimentation of the particles.

Another water-insoluble coating used in the experiments is a copolymer of methyl metacrylate and methacrylic acid, Eudragit RS30D (Eudragit RS30D, Röhm Pharma, Germany). In contrast with the Eudragit L30D55 used in chapters 4 and 5 this coating is insoluble at any pH of the dissolution medium. It is also available in the form of an aqueous latex.

The change from a heterogeneous aqueous dispersion to a transparent homogeneous film is a complex physical process. The film formation process has been a continuous source of research over the last 40 years and still even nowadays the mechanism is not completely elucidated. A short description of the process is given below.

**Figure 6.1** SEM photograph of a freeze-dried Ethylcellulose pseudo latex

The film formation can generally be divided in 6 stages, which can be grouped in three major steps [4-7] (figure 6.2).

A. Water evaporation:
   1. The evaporation of the bulk of the water with concentration of the particles until the first particles reach their critical particle distance.
   2. Particles near the surface reach their critical particle distance and flocculate; water from the bottom of the film will percolate through the top layer until all the particles are flocculated.

B. Particle deformation:
   3. The polymer particles become densely packed.
   4. The traces of water in the interstices of the matrix of densely packed particles will evaporate and the particles will deform. The particles will deform into a polyhedral structure forming a compact layer.
C. Autohesion:

5. The last water present in the particle boundaries will diffuse towards the surface and evaporate. Polymer chains will diffuse over the separate particle surfaces and the particles will lose their identity.

6. A homogeneous film will be formed.

---

Figure 6.2 Schematic representation of the film formation of aqueous dispersions.

Several theories have been developed to predict the evaporation rate of water from a film (step A) [8, 9]. These theories find however no application in fluid bed coating because they all have been developed for films that are applied as a liquid layer on a stagnant substrate. In the fluid bed coating process the coating is applied in successive thin layers formed when the substrate passes the nozzle and thus these theories might not apply. Moreover it is suggested that even in the case of a liquid layer applied on a stagnant substrate the three major steps in film formation always occur simultaneously rather than in discrete several stages.

Also for the second step (B) a lot of research has been done and several theories have been developed to describe the formation of the film [10-12]. All these models give different physical reasons for the same process: the coalescence of polymer particles during film formation. Therefore each model has its own conditions for film formation, i.e. the conditions at which a continuous clear film is formed instead of a powdery non-transparent film. However, a general observation is that when the latex particles have a smaller diameter the film is easier to form. This is due to the increased capillary forces between two particles with decreasing particle diameter. Also when the polymer has a lower elastic modulus (i.e. the latex particles are easier to deform) it will form films more easily.
A very important step for the final properties of the polymer film, especially mechanical properties, is the autohesion or inter-diffusion step (step C). After the particles have coalesced the boundaries between the particles are still visible. During aging of the coating or subjecting the coating to higher temperatures preferably above its glass transition temperature (curing) the polymer chains will diffuse through the boundaries into the latex particles. Therefore the (hydrophilic) boundaries between the latex particles become less pronounced because the polymer chains are able to interact which each other through these boundaries. This will have a positive effect on the mechanical properties of the film [13] and also the diffusion properties of the film will be affected [14].

**Core production**

Cores were produced using a wet high-shear pelletization a Gral 10 high-shear mixer (Machines Collette, Wommelgem, Belgium) (see also paragraph 3.2.1). After 5 minutes of premixing a precisely determined amount of binder liquid was added to a mixture of 37.5-w/w% microcrystalline cellulose and 62.5-w/w% sodium chloride and the mass was kneaded for 5 minutes. Subsequently, the wall-addition was scraped from the wall, and the mass was kneaded for another 15 minutes. The total processing time was 25 minutes (including 5 minutes premixing). During the whole experiment, the impeller speed was set at 400 rpm. The chopper speed was set at 3000 rpm during the liquid addition and the first four minutes of the kneading stage; the chopper was turned off during the last 15 minutes of kneading stage. All pellets were tray-dried at 50°C for 24 hours. For the coating process a sieve fraction of 600-710 µ was taken.

Cores were also prepared by melt pelletization (paragraph 3.2.2) in the Gral 10 high-shear mixer. The cores consist of 62-w/w% lactose 450 mesh, 22-w/w% PEG4000, 10-w/w% swelling agent and 5-w/w% sodium chloride. The pelletization procedure was as follows: after premixing the mixture for 5 minutes in a bowl at room temperature hot water was pumped through the (double walled) bowl to melt the PEG. When the bowl had reached the desired temperature the mixture was kneaded for a certain amount of time. The final pellets were obtained by cooling the mixture outside of the apparatus. During the whole experiment the impeller and chopper speed were set on 600 and 3000 rpm respectively.

Although it is possible to produce particles with a narrow particle size distribution with high-shear granulation we also needed particles which were even more uniform in size and shape. With these particles the influence of size and shape on the release properties were investigated. A technique for the production of almost perfectly spherical cores is atomizing a molten stream of polyethyleneglycol (PEG) into molten droplets and cool them in cold paraffin oil. The droplets solidify and form spherical cores (paragraph 3.2.3).
droplets used in our experiments consist of 80-w/w% PEG 4000, 10-w/w% sodium chloride (all particles smaller than 45 micron) and 10-w/w% swelling agent (polyvinylpolypyrrolidone, (PVPP), Fluka chemicals, Germany). The sodium chloride and PVPP particles were suspended in the molten PEG by stirring.

Coating

The cores were coated in a Uniglatt fluid bed, equipped with a bottom-spray Schlick pneumatic nozzle (see also chapter 3.3). The process conditions were the following:

- Inlet temperature: 60°C
- Product temperature: 35-40°C
- Batch size: 300 g
- Atomizing pressure: 1 bar
- Spraying rate: 2 g/min
- Fluidizing air flow: 60 m³/hr

The experimental procedure was as follows: the plasticizer was added to the polymer latex and this mixture was stirred overnight to ensure that all the plasticizer is diffused into the polymer. The coating is than applied in the fluid bed and the coated pellets are dried in an oven at 60°C for 12 hours. Immediately after drying the release properties were measured.

Release measurements

The release of the contents from the coated pellets was measured with a conductivity meter (Knick Konduktometer 703, Knick GmbH Germany). Two types of measurement were performed; release experiments with a large number of pellets and single pellet release measurements. In release experiments with a large number of pellets 3 g of pellets were suspended in 1 liter of water in a stirred vessel at a constant temperature (25 ± 0.2°C). The release was monitored with a normal sensitivity conductivity electrode (Mettler Toledo 950-K19/120, Mettler Toledo Inc. Switzerland). In a single pellet experiment the release of one single pellet was measured in 10 ml of water in a stirred vessel at a constant temperature. A high sensitivity conductivity electrode (Knick ZU6985, Knick GmbH, Germany) was used to monitor the release.

Water sorption measurements

Free films of the coatings were prepared with a casting apparatus (RK print-coat instruments ltd, Royston, UK). Small pieces from these free films were cut out and the thickness (Digimatic micrometer, Mitutoyo, Japan) and surface area (Digimatic Caliper, Mitutoyo, Japan) were measured. The water sorption characteristics of these free films were determined gravimetrically.
with the use of a Surface Measurement Systems Dynamic Vapour Sorption apparatus (DVS-1000, SMS Ltd., England).

The pure water uptake of EC films was determined by immersing free films in water of 25 °C which were weighed periodically with removal of adhered water to the surface of the film.

The water sorption characteristics of the core materials were also determined gravimetrically with the DVS-1000 with the materials in powder form.

**Swelling measurements**

The swelling of a coated pellet when immersed in water was determined by measuring the increase in diameter of the coated pellets with a microscope (Nikon SMZ-U, Nikon, Japan) a digital camera (Sony DYC-151P, Sony, Japan) and imaging analysis software (Sigma Scan Pro 3.0, Jandel Scientific, USA).

**Particle size and shape measurements**

The size and shape of the cores were determined with image analysis software (Quantimet 520, Cambridge Instruments Ltd., England) and a PC.

**Density/Porosity**

The densities of the coatings were determined in two ways: with a pycnometer (multi-pycnometer MVP-1, Quantachrome, USA) and by calculating the volume through surface area and thickness measurements of a piece of film. The densities were then calculated by dividing the mass of the film by the measured volume.

The porosity of the cores was determined by counting a number of pellets (50) of a known diameter and determining the total weight of the pellets. It was found that the cores prepared by wet high shear pelletization had a very low porosity of 3 ± 0.5 %.

**Tensile tests**

To determine the tensile properties of the ethylcellulose coating free films were prepared by spraying the pseudo-latex onto a rotating glass cylinder. The film was removed from the glass cylinder and test pieces were cut out of the film. After preparation the films were cured for 19 hours at 50 °C. The tensile properties were determined in a dry and wet state. The dry films were tested immediately after curing. The wet films were tested after they had a constant weight after immersing them in water of 25 °C. The tensile tests were performed on a Zwick tensile tester 1445 (Zwick GmbH, Germany). The test conditions are given in table 6.1. The thickness of each test piece was measured at 10 different places with a micrometer.
Table 6.1 Tensile test parameters.

<table>
<thead>
<tr>
<th>Temp.</th>
<th>tensile speed</th>
<th>pre-force</th>
<th>Film length</th>
<th>film width</th>
</tr>
</thead>
<tbody>
<tr>
<td>°C</td>
<td>mm/min</td>
<td>N</td>
<td>Mm</td>
<td>mm</td>
</tr>
<tr>
<td>25 ± 1</td>
<td>1</td>
<td>0.005</td>
<td>15</td>
<td>10</td>
</tr>
</tbody>
</table>

Surface characterization

SEM photographs (JEOL 6301, Japan) of the cores and the coated cores were taken, to evaluate the surface roughness and coating quality.

6.3 Theory: Mathematical model to predict the lag-time

The description of the water uptake of the coating is similar to the method used in chapter 5 (paragraph 5.2.2). We use the Maxwell-Stefan transport equations and fit concentration dependent diffusion coefficients from the water sorption experiments. We use these diffusion coefficients to calculate the concentration profile in the film. The difference is that we are in this case not so much interested in the water concentration in the coating but in the water concentration in the core. If the water concentration in the core is known than the total volume of water diffused into the core is known. If we then know the maximum extension at break of the coating, and thus the maximum increase of volume of the core the coating can withstand, we can predict the release time. The water concentration in the core can be estimated by using mass balance of the core. In this way the flux of the water from the film into the core and the increase in volume of the core can be calculated.

We assume the coating to be a Hookean material, which is allowed considering the low strains at break for the materials used. Furthermore we neglect the compressibility of air present in the core and we neglect any swelling of materials present in the core under influence of the increasing water concentration. Also we assume that the resistance for mass transfer lies completely in the coating.

6.4 Experimental results

6.4.1 Results release experiments

Release experiments with a large number of pellets

The release profiles of the formulations discussed in this chapter are given in figures accompanying the text. To be able to make an easy comparison the characteristics of the formulations are given in the next table, which is similar to table 4.2 (chapter 4). In this table the properties of the cores
and coatings, the most important release characteristics and the number of the figure in which the profile is depicted are given.

<table>
<thead>
<tr>
<th>Code</th>
<th>Figure number</th>
<th>Core code (see table 6.3)</th>
<th>Avg. core size (mm)</th>
<th>Eudragit (µm)</th>
<th>EC coating (µm)</th>
<th>t&lt;sub&gt;10%&lt;/sub&gt; (min)</th>
<th>t&lt;sub&gt;50%&lt;/sub&gt; (min)</th>
<th>t&lt;sub&gt;90%&lt;/sub&gt; (min)</th>
<th>Lag efficiency (min/µm)</th>
<th>Form factor (-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C40I</td>
<td>6.3 + 6.4</td>
<td>DP2</td>
<td>1.4</td>
<td>16</td>
<td>5.5</td>
<td>10.2</td>
<td>17.0</td>
<td>0.34</td>
<td>0.32</td>
<td></td>
</tr>
<tr>
<td>C40II</td>
<td>6.3 + 6.4</td>
<td>DP2</td>
<td>1.4</td>
<td>22</td>
<td>10.0</td>
<td>16.0</td>
<td>22.5</td>
<td>0.45</td>
<td>0.44</td>
<td></td>
</tr>
<tr>
<td>C40III</td>
<td>6.3 + 6.4</td>
<td>DP2</td>
<td>1.4</td>
<td>26</td>
<td>20.0</td>
<td>30.2</td>
<td>44.0</td>
<td>0.77</td>
<td>0.45</td>
<td></td>
</tr>
<tr>
<td>C41II</td>
<td>6.4</td>
<td>G75</td>
<td>0.68</td>
<td>27</td>
<td>6.7</td>
<td>16.0</td>
<td>33.0</td>
<td>0.25</td>
<td>0.20</td>
<td></td>
</tr>
<tr>
<td>MC7</td>
<td>6.6</td>
<td>MP24</td>
<td>0.65</td>
<td>19</td>
<td>1.2</td>
<td>2.5</td>
<td>4.7</td>
<td>0.06</td>
<td>0.26</td>
<td></td>
</tr>
<tr>
<td>MC8</td>
<td>6.6 + 6.7 + 6.8</td>
<td>MP24</td>
<td>0.65</td>
<td>20</td>
<td>5.0</td>
<td>9.0</td>
<td>13.5</td>
<td>0.25</td>
<td>0.37</td>
<td></td>
</tr>
<tr>
<td>MC9c</td>
<td>6.6</td>
<td>MP29</td>
<td>0.65</td>
<td>10</td>
<td>2.1</td>
<td>4.2</td>
<td>7.2</td>
<td>0.21</td>
<td>0.29</td>
<td></td>
</tr>
<tr>
<td>MC9b</td>
<td>6.7 + 6.8</td>
<td>MP29</td>
<td>0.65</td>
<td>20</td>
<td>2.5</td>
<td>5.2</td>
<td>8.7</td>
<td>0.28</td>
<td>0.29</td>
<td></td>
</tr>
<tr>
<td>MC142</td>
<td>6.7 + 6.8 + 6.20</td>
<td>MP34</td>
<td>0.65</td>
<td>11</td>
<td>7.5</td>
<td>14.2</td>
<td>22</td>
<td>0.68</td>
<td>0.34</td>
<td></td>
</tr>
<tr>
<td>MC144</td>
<td>6.7 + 6.8 + 6.10</td>
<td>MP34</td>
<td>0.65</td>
<td>21</td>
<td>14.4</td>
<td>26.5</td>
<td>39.0</td>
<td>0.69</td>
<td>0.44</td>
<td></td>
</tr>
<tr>
<td>MC5</td>
<td>6.10</td>
<td>MP14</td>
<td>0.65</td>
<td>29</td>
<td>52</td>
<td>100</td>
<td>250</td>
<td>1.79</td>
<td>0.21</td>
<td></td>
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<tr>
<td>C56</td>
<td>6.10</td>
<td>MP34</td>
<td>0.65</td>
<td>10</td>
<td>25</td>
<td>43.5</td>
<td>69</td>
<td>2.50</td>
<td>0.36</td>
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</tr>
<tr>
<td>C57I</td>
<td>6.10</td>
<td>MP34</td>
<td>0.65</td>
<td>10</td>
<td>9.5</td>
<td>19</td>
<td>31.5</td>
<td>0.96</td>
<td>0.30</td>
<td></td>
</tr>
<tr>
<td>C57II</td>
<td>6.10</td>
<td>MP34</td>
<td>0.65</td>
<td>20</td>
<td>18.8</td>
<td>30</td>
<td>46</td>
<td>0.94</td>
<td>0.41</td>
<td></td>
</tr>
<tr>
<td>C58I</td>
<td>6.10</td>
<td>MP34</td>
<td>0.65</td>
<td>20</td>
<td>6.5</td>
<td>14.2</td>
<td>23.5</td>
<td>0.65</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>C58II</td>
<td>6.10</td>
<td>MP34</td>
<td>0.65</td>
<td>20</td>
<td>7.5</td>
<td>15.3</td>
<td>25.5</td>
<td>0.38</td>
<td>0.29</td>
<td></td>
</tr>
<tr>
<td>MC141</td>
<td>6.20</td>
<td>MP34</td>
<td>0.65</td>
<td>5</td>
<td>3.8</td>
<td>9</td>
<td>15.5</td>
<td>0.76</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>MC143</td>
<td>6.20</td>
<td>MP34</td>
<td>0.65</td>
<td>16</td>
<td>12.2</td>
<td>20.2</td>
<td>30</td>
<td>0.76</td>
<td>0.41</td>
<td></td>
</tr>
</tbody>
</table>

Table 6.2  Overview characteristics coating experiments. More detailed description of the properties of the cores in table 6.3. Lag efficiency is defined as the time up to 10 % release (the lag-time) divided through the thickness of the EC coating. Form factor is defined as the time needed to reach 10 % release divided through the time needed to reach 90 % release.

<table>
<thead>
<tr>
<th>Code</th>
<th>Production method</th>
<th>Particle size distribution (mm)</th>
<th>Composition (percentages are weight percentages)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DP2</td>
<td>drop pelletization</td>
<td>1.36 ± 0.07</td>
<td>80 % PEG, 10 % NaCl, 10 % PVPP</td>
</tr>
<tr>
<td>G75</td>
<td>high shear melt pelletization</td>
<td>0.68 ± 0.12</td>
<td>18 % PEG, 10 % PVPP, 5 % NaCl, 67% Lactose</td>
</tr>
<tr>
<td>MP24</td>
<td>high shear wet pelletization</td>
<td>0.6-0.71</td>
<td>24 % Lactose, 29 % NaCl, 37 % MCC, 10 % PVPP</td>
</tr>
<tr>
<td>MP29</td>
<td>high shear wet pelletization</td>
<td>0.6-0.71</td>
<td>24 % Lactose, 29 % NaCl, 37 % MCC, 10 % PVPP</td>
</tr>
<tr>
<td>MP14</td>
<td>high shear wet pelletization</td>
<td>0.6-0.71</td>
<td>62.5 % NaCl, 37.5 % MCC</td>
</tr>
<tr>
<td>MP34</td>
<td>high shear wet pelletization</td>
<td>0.6-0.71</td>
<td>62.5 % NaCl, 37.5 % MCC</td>
</tr>
</tbody>
</table>

Table 6.3  Properties of the cores used for the coating experiments in table 6.2. PEG denotes polyethylene glycol, MCC microcrystalline cellulose and PVPP polyvinylpyrrolidone.
Proof of principle

In figure 6.3 the result is given obtained with a formulation of cores prepared with drop pelletization, coated with different levels of ethylcellulose. It is seen that this formulation is quite successful in inducing a lag-time at low levels of coating, when compared to water-soluble (chapter 4) or partly water-soluble (chapter 5) coatings.

![Figure 6.3 Influence coating thickness on the release properties from a formulation with cores prepared with drop pelletization (average particle diameter 1363 micron, consisting of 80-w/w% PEG 4000, 10-w/w% NaCl and 10-w/w% PVPP, codes: C40I, C40II, C40III). Coating contains 25-w/w% dibutylsebacate as a plasticizer.](image)

Influence particle size distribution and shape core

The results in figure 6.3 are for a formulation with cores that are almost perfectly spherical and have a very narrow particle size distribution. We can compare these results with a formulation consisting of cores prepared by melt pelletization which are less spherical and have a wider particle size distribution. SEM photos revealed that the two types of cores have very smooth surfaces and are thus comparable in surface roughness. The dimensionless release times \((t/t_{50\%})\) of the formulations from figure 6.3 and a formulation with a core prepared by melt pelletization are compared in figure 6.4. The particle size and shape is given in table 6.4. The shape factor is defined by equation 6.1, in which \(A\) is the area and \(O\) is the perimeter of the core.
Water-insoluble coatings

\[
\text{shape factor} = \frac{4\pi \cdot A}{O^2}
\]  \hspace{1cm} (6.1)

<table>
<thead>
<tr>
<th>type of pelletization</th>
<th>average core size (mm) ± s.d.</th>
<th>Shape factor ± s.d.</th>
</tr>
</thead>
<tbody>
<tr>
<td>drop pelletization</td>
<td>1.36 ± 0.07</td>
<td>1.17 ± 0.04</td>
</tr>
<tr>
<td>melt pelletization</td>
<td>0.68 ± 0.12</td>
<td>1.25 ± 0.09</td>
</tr>
</tbody>
</table>

Table 6.4 Particle size data for cores for which the release properties are given in figure 6.5 (s.d. denotes standard deviation).

It is seen that the particles with the narrower particle size distribution have a more pulse-like release than the cores prepared by melt pelletization. This means that particles that are more uniform in shape and have a narrower particle size distribution have a more reproducible release mechanism. This is discussed in more detail in the paragraph on single pellet releases.

The formulation with cores prepared by drop pelletization and the thinnest coating (16 µm) has a release curve in-between the other curves. This probably indicates that less coating gives a bigger chance on coating defects; more coating defects give a less reproducible release mechanism. This gives a larger deviation in the lag-times of individual pellets and thus a less pronounced pulse-release.

\[\text{Figure 6.4} \quad \text{Influence particle size distribution and shape of the cores on the release properties. Open symbols (codes: C40I, C40II, C40III) are the drop pelletization cores, closed circles (code C41II) are the melt pelletization cores. The coating is ethylcellulose plasticized with 25-w/w\% DBS. Error bars denote standard deviation in three independent experiments.}\]
Influence surface roughness

We can determine the influence of the surface roughness by applying a water-soluble sub-coating on the core surface before the actual ethylcellulose coating is applied. In this way the roughness of the core is reduced (see figure 6.5) and a comparison can be made to particles without a sub-coating. The cores were prepared by wet high-shear pelletization and the sub-coating is a water-soluble methacrylic acid copolymer, Eudragit L30D55. The results of the release experiments are shown in figure 6.6.

From figure 6.6 it is clear that the sub-coating alone does not have a large influence on the release properties. However when an ethylcellulose coating is applied on a core with or without sub-coating the influence of the sub-coating is quite large. The coating thickness of the insoluble layer can be reduced by half and still the lag-time of the formulation with the sub-coating is longer. Thus applying a sub-coating before the EC layer increases the efficiency in terms of amount of EC coating and lag-time considerably. As will be seen from the mathematical model the Eudragit coating has a large resistance for mass transfer and therefore has a large influence on the release properties.

Figure 6.5 SEM photos of a core without coating (left); a water-soluble sub-coating (middle) and the final water-insoluble layer (right).
Water-insoluble coatings

Figure 6.6 Results of release experiments on formulations MC7, MC8 and MC9C: influence of applying a sub-coating on the release properties.

### 6.4.2 Influence swelling agent in the core

With the cores produced by wet high shear pelletization a comparison was made between cores with and without swelling agent. The polymer polyvinylpolypyrrolidone, which swells approximately 2.7 times [15] its own volume when brought into equilibrium with water, was incorporated into the pellets and subsequently coated.

The reason to incorporate a swelling agent was that when the release of coated pellets without a swelling agent was monitored under a microscope it was seen that the release is started when the coating bursts at a certain point in time. However, the coating does not totally fall apart but only a large crack or hole is developed (figure 6.7). The pressure inside the pellet will decrease when the coating is ruptured and thus there is no driving force to open the coating further. This might cause a delay of the dissolution of the components in the core. To induce a further swelling of the core when the coating is ruptured, and thus induce a more pulse-like release, a swelling agent was added to the core. The idea was that the swelling agent would take up water and increase in volume and therefore provide a sustained driving force to open the coating further when the coating was ruptured.
The incorporation of a swelling agent in the core decreases the lag-time achieved with a certain coating thickness (figure 6.8). However the release profile is not improved (i.e. a more pulse-like release) when a swelling agent is incorporated, this is illustrated in figure 6.9. In this graph the time is made dimensionless by dividing with the time necessary to reach 50% release. All the release profiles coincide and thus the swelling agent does not improve the release characteristics. The pressure on the coating is increased by the swelling agent and decreases the lag-time but the release rate after failure of the coating is not enhanced. This is further discussed in the paragraph where an attempt is made to predict the lag-time.
Figure 6.8 Results release experiments MC8, MC9b, MC142, MC144: influence of 10-w/w% swelling agent (PVPP) in the core on the release properties of formulations with a Ethylcellulose coating thickness of 10 and 20 µm. All cores are 0.6-0.7 mm in diameter and have a 20 µm thick sub-coating.

Figure 6.9 Influence of swelling agent in the core on the release properties: release versus dimensionless time (t/t_{50%}).
Influence of adding brittle-inducing additives to the coating on the release

As mentioned in paragraph 6.2 there is a curing step involved in giving the Ethylcellulose coating its final properties. This curing step is necessary for the coalescence of the latex particles and the inter-diffusion of the polymer chains into adjacent latex particles. If the curing temperature is higher the inter-diffusion will be more complete. This is illustrated in figure 6.10 in which the difference in release behaviour between a coating cured at 50 °C and at 80 °C is given (the lines with the solid squares and solid circles respectively). The main reason for this large difference in release properties is the difference in the mechanical properties. A coating cured at 80 °C is more elastic and has a higher strain at failure (see paragraph 6.4.3) consequently more water can diffuse through the coating before the coating bursts.

A fully cured coating has as an advantage that its mechanical properties are constant, i.e. the release properties will not change anymore due to curing during drying or storage. However, as shown in figure 6.10, the release properties of a fully cured coating are inferior to a not fully cured coating in terms of the form-factor, i.e. a pulse release is not achieved. The ideal coating would be brittle and in a fully cured state.

One way of producing a coating with more desirable properties is the addition of brittle-inducing materials. It is known that mineral additives make polymers more brittle [16] because the numerous fine particles introduced in the film will act as sites at which fractures can be induced. Apart from making the coating more brittle it is also known from the literature that mineral additives make the coating more permeable to water [17].

An attempt was made to add a mineral to the coating to produce a coating cured at 80 °C with a release behaviour equal to that of a coating cured at 50 °C. As a mineral Aerosil 200 (colloidal silicon dioxide) was chosen because of its high specific surface area. Release profiles of EC coatings in which Aerosil 200 is dispersed are given in figure 6.10 (next page).

Adding 10 w/w% Aerosil 200 already improves the release profile considerably for a fully cured coating compared to the formulation without Aerosil. The addition of 20-w/w% Aerosil is sufficient to give the coating the same release properties cured at 80 °C as the coatings cured at 50 °C. At higher levels of Aerosil (30 w/w-%) the lag-times become very short and almost independent of the coating thickness. Doubling the coating thickness from 10 µm to 20 µm has only a small effect on the lag-time.

From figure 6.10 there is evidence that the coating has to be brittle in order to reach the desired release characteristics with a water-insoluble coating, i.e. the coating has to have a small extension to break. We can illustrate this further with comparing the previous release profiles to results obtained with the water-insoluble Eudragit RS30D coating. From the literature
it is known that Eudragit RS30D coatings have extensions at break about a factor 100 larger [18] than Ethylcellulose films.

We found that the Eudragit RS30D coating gave a slow release profile instead of a pulse-release profile (figure not shown), most of the coated pellets did not burst but remained intact over the release cycle. From this and the results in figure 6.10 we can conclude that only water-insoluble film-formers with a low extension at break will give a pulse-release.

**Single pellet release**

All the release profiles shown in the previous paragraphs were release profiles of a large number of pellets. In order to achieve a better insight in the release mechanism of the formulations release experiments were conducted on single pellets. In figure 6.11 a release experiment on single pellets is presented for an experiment with a swelling agent incorporated in the core, in figure 6.12 for an experiment without a swelling agent incorporated in the core and in figure 6.13 for experiments with mono-sized pellets.
Figure 6.11  Single pellet measurements experiment MC8b. Formulation: cores consist of 29-w/w% NaCl, 37.5-w/w% MCC, 23.5-w/w% Lactose 200 mesh and 10 w/w% PVPP and are 0.6-0.7 mm in diameter. Coating: 20 µm sub-coating, 20 µm EC coating.

Figure 6.12  Single pellet measurements experiment MC144. Formulation: cores consist of 37.5-w/w% NaCl, 62.5-w/w% MCC, and are 0.6-0.7 mm in diameter. Coating: 20 µm sub-coating, 20 µm EC coating.
Figure 6.13  Single pellet measurements on experiment C39II. Formulation: cores consist of 80-w/w% PEG 4000, 10-w/w % NaCl and 10-w/w% swelling agent and 1.6 mm in diameter. Coating: 35 µm EC coating

It is clear from figure 6.11 and 6.12 that the deviation in lag-time between the individual pellets is rather large (see also table 6.5). This has as a consequence that although most of the individual pellets have release profiles close to a perfect pulse release the release profile of 6 grams of pellets has a somewhat lower slope.

The data for single pellet experiments with particles with different particle size distributions are given in table 6.5. To compare the three experiments the release characteristics (the average time necessary for the individual pellets to reach 10, 50 and 90 % release and the standard deviation in these times) of the single pellet experiments are given.

From table 6.5 it is seen that the pellets with the narrowest particle size distribution have the lowest variation in the release times between the pellets. These results correspond to the difference in release characteristics found in figure 6.5 between mono-sized pellets and pellets with a wider particle size distribution.
Table 6.5 Release characteristics of the single pellet experiments for three experiments with cores with different particle size distributions and shapes. s.f. denotes shape factor of the core and p.s.d. denotes particle size distribution of the cores.

<table>
<thead>
<tr>
<th>fig. #</th>
<th>% deviation in s.f.</th>
<th>% deviation in p.s.d.</th>
<th>t_{10%} (min) avg.</th>
<th>t_{50%} (min) Avg.</th>
<th>t_{90%} (min) avg.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>s.d.</td>
<td>s.d. %</td>
<td>s.d.</td>
</tr>
<tr>
<td>6.11</td>
<td>8</td>
<td>10</td>
<td>4.9</td>
<td>1.6 33</td>
<td>7.2</td>
</tr>
<tr>
<td>6.12</td>
<td>8</td>
<td>10</td>
<td>10.1</td>
<td>3.8 38</td>
<td>15.8</td>
</tr>
<tr>
<td>6.13</td>
<td>2.5</td>
<td>5</td>
<td>13.4</td>
<td>3.3 25</td>
<td>19.5</td>
</tr>
</tbody>
</table>

Table 6.6 Results tensile tests at different water contents of the film.

The results of the tensile test experiments can be divided into two parts: dry films and wet films. The tensile tests were conducted on dry films, and films brought to equilibrium with pure water at 25 °C. The results are given in table 6.6, the results are an average of 15 measurements. The wet films were dried and weighed after the tensile tests to make sure that no plasticizer had diffused out of the coating during the time they were immersed in water (see also the paragraph on water diffusion/sorption free films).

The water present in the film changes the mechanical properties of the film. The most important parameter for the mathematical model is the extension at break. This parameter determines how much the coating can be stretched before it breaks and thus how much the core can increase in volume before the coating fails mechanically.

<table>
<thead>
<tr>
<th>extension at break (%)</th>
<th>E-modulus (MPa)</th>
<th>tensile strength (MPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>average</td>
<td>s.d.</td>
<td>average</td>
</tr>
<tr>
<td>Dry</td>
<td>5.2</td>
<td>0.7</td>
</tr>
<tr>
<td>Wet</td>
<td>1.4</td>
<td>0.2</td>
</tr>
</tbody>
</table>

We have investigated the extension at break in greater detail by measuring the swelling of coated pellets under a microscope. The results of several swelling measurements are given in figure 6.14. It is seen that all the pellets show the same swelling behaviour: first a slow increase in diameter followed by a fast increase in diameter. It was seen that the start of the fast increase in diameter is always accompanied with a large crack in the coating (figure 6.7). This means that the moment of the fast increase in diameter coincides with the start of the release. Therefore, we can give an estimate of the maximum extension in the coating at the start of the release. We found a value of 1.5 ± 0.5 % (n=10) for the maximum extension, which corresponds to the
extension at break found for the wet free films. This is an indication that at the moment of release the mechanical properties of the coating are similar to the mechanical properties of *wet* free films.

![Swelling characteristics of the pellets](image)

*Figure 6.14  Swelling characteristics of the pellets used for the single pellet releases in figure 6.12. Each line represents the swelling of one pellet.*

There are several publications [13, 18-22] on the mechanical properties of ethylcellulose films. If we compare the strain at break measured in our experiments with the ones found in the literature we see that the results are comparable. Arwidsson [13] found a strain at break in tensile tests of 1.3 and 4.6 % of a spray cast Aquacoat-ECD30 film with 12 and 22-w/w% triethylcitrate plasticizer respectively. Parik et al [19] found strain at break values of 1-5 % for DBS plasticized Surelease films. Sun et al. [22] found values in the order of 1 % for spray cast DBS plasticized ethylcellulose films.

Bodmeier and Paeratakul [18] investigated the difference in mechanical properties of dry and wet ethylcellulose films with puncture tests. Although the absolute values of the experiments cannot be compared to our results because of the difference in testing methods, Bodmeier et al also found a decrease in strength when the films were wet. Furthermore Bodmeier et al also found that films prepared from an ethylcellulose latex plasticized with DBS were very brittle with maximum strain values smaller than 1 %.
6.4.4 Water diffusion/sorption free films

Water sorption

The water sorption curve for an ethylcellulose film plasticized with 15-w/w% DBS and a Eudragit L30D55 film plasticized with 10-w/w% TEC at 25 °C are given in figure 6.15.

![Water sorption curve](image)

Figure 6.15 Water uptake at different temperatures for an EC film plasticized with 15-w/w% DBS.

It should be noted that in the experiments in which the pure water uptake of ethylcellulose was determined the weight of a film starts to decrease after it has reached equilibrium (figure 6.16). When films are immersed in water for a longer time (17 hours) and subsequently dried and weighed the decrease in weight is 12 ± 0.3-w/w%. This corresponds approximately to the amount of plasticizer present in the film and thus it is likely that the plasticizer diffuses out of the coating over prolonged period of times. However, during the short period that the weight is constant the loss in weight in the films after drying is negligible (< 1-w/w%) and thus no or only a small amount of plasticizer has diffused out of the coating when equilibrium is reached. This result is confirmed by Lippold et al [20] who found that DBS remains in an Aquacoat-ECD 30 film during a five-hour period in water.

Sun et al [22] found a large difference in the permeability of spray cast films in comparison to cast films. This is of importance regarding our results because we prepared the films for the sorption experiments by a casting
method (with the exception of the film used for pure water uptake). This was done because it was not possible to produce thin films (thickness < 0.1 mm) with the spray cast method. Films of this thickness have to be used in the sorption experiments to prevent extreme long experimental times. Sun showed that the porosity of spray cast films is much higher than the porosity of films prepared by a casting method and therefore a much higher permeability for the spray cast films was measured. The difference in densities Sun found was approximately 725 kg/m³ for a spray cast film (25-w/w% DBS) and 950 kg/m³ for a cast membrane. Based on the densities of the pure materials (ethylcellulose 1140 kg/m³, DBS 937 kg/m³) an air free film should have a density of 1089 kg/m³. We found a density of 1088 ± 2 kg/m³ (n=8) for our spray cast films plasticized with 15-w/w % DBS. The calculated density for this film is 1120 kg/m³. Since the difference between the calculated and measured density is much smaller for our experiments than for the experiments of Sun we assume that there is no difference in permeability for a spray cast and a cast film.

![Water uptake against time for an ethylcellulose film plasticized with 15-w/w% DBS immersed in pure water at 25 ºC.](image)

The sorption properties of the core materials are depicted in figure 6.17. It is seen that the swelling agent PVPP takes up more water than MCC or sodium chloride. Above a relative humidity of 75.3 % r.h. (25 ºC) the deliquescence point of sodium chloride is reached to give a saturated solution of sodium chloride.
Diffusion coefficients of water in the coatings

The diffusion coefficients of water in ethylcellulose were calculated analogue to the calculation in chapter 5 on the UV crosslinked Eudragit coatings.

The diffusion coefficients fitted from the water sorption data as function of the mole fraction water in the coating are given in figure 6.18. It is seen that the diffusion coefficient for ethylcellulose is fairly constant over the activity range (denoted next to the markers) 0.2 to 0.95. The diffusion coefficients are lower and higher when the outside activity is very low or very high respectively. We have no explanation for the low diffusion coefficient at the low water activity. The increase in the diffusion coefficient at a water activity of one, which is a factor two higher than the average diffusion coefficient over the activity range 0.1 to 0.9, could be due to a small amount of swelling of the material at this high water activity.

The diffusion coefficients for Eudragit L30D55 (the water-soluble sub-coating) are depicted in the same figure. They remain fairly constant over the whole activity range. Since the polymer is water-soluble the diffusion coefficient of water in the coating at a water activity equal to one is assumed to be equal to the self-diffusion coefficient of water: $2 \cdot 10^{-9}$ m$^2$/sec.
Figure 6.18  Maxwell Stefan diffusion coefficients of water as function of the mol fraction water in an EC film plasticized with 15-w/w% DBS and a Eudragit L30D55 film plasticized with 10-w/w% TEC. The numbers next to the markers denote the water activity at which the mole fraction water on the x-axis is present in the film. Error bars denote standard deviation in 4 measurements with 4 different films.

**6.4.5 Prediction lag-time**

We chose the formulations with the cores produced by wet high shear pelletization for testing the mathematical model. Since we now know the relation between diffusion coefficients and mole fraction water in the film we can use the model to predict the concentration profile in the film and the flux of water from the coating into the core. We also know the water uptake properties of the core and thus we can calculate the increasing water concentration in the core as a function of time.

If a sub-coating is applied before the final ethylcellulose coating we have a system with three regions: an outer water-insoluble ethylcellulose coating, a water-soluble coating of the copolymer of methacrylate and ethyl acrylate and a core consisting of MCC and NaCl. A typical calculated concentration profile for this system is given in figure 6.19. One must keep in mind that the driving force for diffusion is given by the difference of water activities in the materials rather than differences in water concentration as with the Fick diffusion theory. This explains why water can diffuse through the coating despite the
fact that the water concentration is higher in the Eudragit coating than in the EC coating.

Since we know how much the coating can be extended before it breaks we know the volume of water which has to diffuse into the core before the coating breaks. This corresponds to a certain water concentration in the core. If we calculate the water concentration in the core as a function of time with the mathematical model we can give an estimate of the lag-time.

In figure 6.20 the release profiles for four formulations with a sub-coating and increasing amounts of EC coating are given, in figure 6.21 the predicted release time intervals for the different coating levels are given. Also in figure 6.21 the predicted release time for three formulations without sub-coating are given.
Water-insoluble coatings

Figure 6.20  Release profiles for cores coated with a 20 µm thick Eudragit L30D55 coating and varying EC coating levels. Error bars denote standard deviation in two coating experiments.

Figure 6.21  Experimental lag-times compared to calculated lag-times for a formulation with a sub-coating and a formulation without a sub-coating.
The predicted lag-time was calculated for the lower and upper boundaries of the particle size distribution of the cores. If we assume that all the cores receive an equal amount of coating in terms of mass this will give a different coating thickness for smaller and larger pellets. We calculate the coating thickness around the cores by assuming that the volume of the applied coating is evenly distributed around spherical pellets; this volume corresponds to a certain coating thickness. The experimental lag-time is defined as the moment in time when 10% of the total release is completed.

The prediction for the lag-time is reasonable for the formulations without sub-coating. The formulation with the thinnest coating (20 µm) has a somewhat shorter lag-time than the lag-time predicted by the model. This is probably caused by coating defects, which are more likely to occur at low coating levels. Coating defects will decrease the lag-time; the model assumes a defect-free homogeneous coating and thus the predicted lag-time is longer. This is confirmed by plotting the dimensionless \( \frac{t}{t_{50\%}} \) against the release (figure not shown). The \( \frac{t}{t_{50\%}} \) release profiles of the formulations with the higher coating levels coincide, but the lowest coating level gives an entirely different \( \frac{t}{t_{50\%}} \) release profile. This is an indication that the release mechanism is not controlled by the mechanical failure of the coating but by diffusion through defects in the coating already present at the beginning of the release cycle.

The prediction of the lag-times for the formulations with a sub-coating is less satisfactory especially at low EC coating levels. The predicted lag-times are too high at low EC coating levels. Also here coating defects caused by the low level of coating could decrease the lag-time. This is confirmed by plotting the \( \frac{t}{t_{50\%}} \) against the release (figure not shown) as explained in the previous paragraph. However the experimental data shows that a formulation with an EC coating thickness of 0 µm the lag-time is close to 0 min. The model however still predicts a lag-time when there is no EC coating present. This means that apart from the effect of coating defects in the EC layer also the influence of the sub-coating is not yet well implemented in the model; the influence of the sub-coating is overestimated. The most probable reason for this is that the Eudragit layer is not homogeneous. The surface roughness for cores without a coating is quite high. Therefore the Eudragit layer is probably not homogeneous in thickness. As can be seen from figure 6.19 the mass transfer resistance of the Eudragit layer is considerable. This means that if the sub-coating is thin at some places this could have a large influence on the mass transfer resistance and thus on the lag-time. The consequence would be that although the surface roughness is reduced by the Eudragit layer its influence on the lag-time is reduced by these thin spots in the coating.

The prediction of the lag-times from the model is also not satisfactory when calculations are done on a formulation with a swelling agent.
incorporated in the core. As seen from figure 6.17 the swelling agent (PVPP) can take up much more water than MCC or NaCl at low water activities. This effect is also found in the results of the model: the lag-time is reduced when the water activity data of the swelling agent is incorporated in the core in comparison to a core without swelling agent. However the reduction in the lag-time is only a fraction of the reduction of the lag-time found experimentally (experimental: three fold reduction lag-time, model: 1.5 fold reduction in lag-time). This can be explained with the fact that there is an increased force on the coating caused by the swelling of the swelling agent. The volume of the core does not only increase because of diffusion of water into the core but also because of the increase in volume due to relaxation of the polymer chains. The model does not account for this effect and thus the prediction of the lag-time is not satisfactory.

It must be noted that MCC also has minor swelling properties (1.4 times its own volume at equilibrium with water [15]) when immersed in water. Considering that the swelling of the swelling agent is of major importance on the results of the model this could also influence the results of the model depicted in figure 6.21.

### 6.5 Conclusions Chapter 6

Formulations with a water-insoluble coating are more efficient in inducing the desired release profile than the formulations with a water-soluble or partly water-soluble coating. The term efficient is defined as the amount of coating applied compared to the achieved lag-time.

The water-insoluble coating has to be brittle, i.e. it has to have a low extension at break, otherwise no pulse release is obtained. This is also shown by tensile tests on free films of the coating material; low extensions at break were found for dry and wet films of the materials that give a pulse release profile.

To achieve an optimum pulse-like release profile the cores of the formulation should be uniform in shape and size. Incorporation of a swelling agent in the core decreases the time to mechanical failure of the coating, however the release mechanism is not changed; i.e. the size of the crack in the coating is not increased.

Single pellet experiments showed that there is a large deviation in the moment of release of individual pellets. As a consequence the slope of the release of a large amount of pellets is lower than that of the individual pellets.

The mathematical model gives a satisfactory prediction of the lag-time with a formulation without sub-coating. The prediction on a formulation with a sub-coating is less satisfactory at low coating levels.
The model breaks down when the lag-time of a core in which a swelling agent is incorporated has to be predicted.

6.6 References

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