Development and description of controlled release formulations for use in powder detergents
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SEMI-SOLUBLE COATINGS

5.1 Introduction

In this chapter the results are discussed of reservoir devices that have a coating which is only partly water-soluble or forms a gel when immersed in water. The partly water-soluble coating or gelled coating does not dissolve totally when immersed in water over prolonged periods of time.

5.2 Crosslinking of water-soluble coatings

5.2.1 Physical crosslinking

Calcium-alginate coatings

Introduction

The properties of the film-former alginate are discussed in paragraph 4.2.2. It is possible to alter the water solubility of this natural polymer by exchanging the sodium ion in the water-soluble sodium alginate for a multivalent cation such as calcium or barium. The multivalent ion will move in-between the guluronate structures and bind the alginate together (see figure). This leads to a decreased water-solubility and swelling behaviour in water. Because the crosslinking is not chemical but physical the process can be reversed, for example if the calcium alginate is brought into a warm dilute alkali solution the calcium alginate is transformed back into sodium alginate [1].

The aim was to investigate if a calcium alginate coating can induce a lag-time by coating pellets consisting of 37.5-w/w % MCC and 65.5-w/w % sodium chloride (diameter range: 0.71-0.85 mm) with a low viscosity grade of sodium alginate (Protanal LF 10/60, Orffa b.v., the Netherlands). The cores were prepared by wet high shear pelletization, the coating was applied in a fluid bed. The physical crosslinking was done after the coating process by bringing the pellets into a solution of calcium chloride.

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Experimental

Release measurements

The release of the contents from the coated pellets (for all the formulations in this chapter) 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 experiments

To characterize the water sorption characteristics of coating and core materials in this and the next chapter gravimetric water sorption experiments were carried out. The apparatus used for the water sorption experiments is a Dynamic Vapour Sorption system (DVS-1000, manufactured by Surface Measurement Systems ltd., London, United Kingdom). A schematic presentation of the Dynamic Vapour Sorption configuration is shown in figure 5.1.

The DVS system has a Cahn D200 microbalance capable of measuring changes in sample mass lower than 1 part in 10 million. This type of microbalance has a good long-term stability and is therefore suited to the measurement of vapour sorption phenomena that may take days. The microbalance was calibrated by a certified 100 mg calibration weight (100 mg ultra Class s/s weight, Troemner inc.), each month or when the temperature of the incubator is changed. The main instrument is housed in a precisely controlled constant temperature incubator.

Mixing dry and water vapour saturated nitrogen gas flows in the correct proportions using mass flow controllers generates the required humidity’s. Humidity and temperature probes are situated just below the sample and reference holders to give verification of the system performance.
For each temperature the generated humidity was checked by a salt validation procedure. This validation method relies on the principle that the partial vapour pressure of water above a saturated salt solution in equilibrium with its surroundings is a constant at a particular temperature. The validation method involves making up saturated solutions of the salt, and measuring the relative humidity above the solution at the desired temperature using a standard method for the DVS instrument. For each salt solution, the humidity is linearly ramped from above the literature value to below and then back again. At the point where the generated RH is equal to the RH above the saturated salt solution, the rate of change of mass with RH of the salt solution is zero. This point is compared with the literature value and the target RH should be within one percent of this value.

**Results physically crosslinked alginate coating**

In figure 5.2 the release curves are given for a formulation coated with 14.5-w/w% sodium alginate. It is seen that the release is very fast when the formulation is immersed in pure water. It is also seen that the release in a 0.01 M CaCl₂ solution is very fast. This means that the crosslinking has no effect on the release properties or that the dissolution of the coating is faster than the crosslinking process of the coating.

To investigate if the dissolution process of the coating is faster than the crosslinking process the coating was crosslinked beforehand in a solution of calcium chloride in ethanol. Because sodium alginate is insoluble in ethanol in this way the coating is crosslinked without dissolving the coating. However, the coating crosslinked in alcohol also resulted in a release profile without a lag-time.
Figure 5.2 Results of release experiments with pellets (0.71-0.85 mm in diameter, 37.5-w/w% MCC and 65.5-w/w% NaCl) coated with 14.5-w/w% sodium alginate (corresponding to a 20 to 24 µm thick coating), influence physical crosslinking on release.

When the release mechanism of the coated pellets is observed more closely under the microscope it is seen that the sodium alginate coatings without crosslinking dissolve very fast. The crosslinked calcium alginate coatings (crosslinked in water as well as in ethanol) do not dissolve but take up water and swell in a short period of time and stay intact. SEM pictures (figure 5.3) of crosslinked coatings revealed that the coating stays intact even after drying. Therefore it became clear that the alginate coatings are very permeable to water because they can contain a high percentage of water. This is confirmed by gravimetric water sorption experiments which also showed that the crosslinked calcium alginate coatings take up more water at a high relative humidity than the sodium alginate coatings (figure 5.4).

The release mechanism of these coatings is controlled by the transport of water through the coating. This process is very fast because of fast dissolution of the coating (sodium alginate) or fast swelling of the coating (calcium alginate). This makes alginate not a suitable film-former for a pulse release mechanism.
Figure 5.3  SEM photographs of pellets coated with sodium alginate, before crosslinking, (left), after crosslinking with calcium chloride and drying for 12 hrs at 60 °C (right).

Figure 5.4  Water sorption behaviour of sodium alginate and calcium alginate films.

5.2.2 Chemical crosslinking induced by UV radiation

In this part an attempt is made to alter the solubility properties of water-soluble polymers by inducing covalent bindings between the polymer molecules (crosslinking) or by creating an interpenetrating network between
the polymer molecules of the coating. The crosslinking reactions are induced by ultraviolet light.

**UV crosslinked copolymers of metacrylic acid and ethyl acrylate**

**Introduction**

The copolymer of metacrylic acid and ethyl acrylate has been discussed in paragraph 4.2.4. They are available as a latex with a low viscosity and give very smooth coatings at high spray rates (short production times). The copolymer is an enteric film-former i.e. it dissolves only above pH 6-7. The pH of the release medium used in our experiments (demineralised water) is above the pH at which the copolymer dissolves and thus no or only a small period of time in which the release is delayed can be obtained. The dissolution rate of the coating can be decreased by creating a semi-interpenetrating network (semi-IPN) of the copolymer and another polymer. A semi-interpenetrating network is a material containing two polymers from which one polymer is in a crosslinked form [2]. A semi-IPN has the property that it swells in solvents but it does not dissolve.

To create a semi-IPN a poly-functional molecule is incorporated to form a network in-between the molecules of the copolymer. The reaction between the poly-functional molecules is initiated by a photo-initiator that is activated by UV light at a wavelength of 365 nm.

**Experimental**

**Materials**

The cores of the formulation consisted of microcrystalline cellulose (Pharmacel ph102, DMV, The Netherlands) and milled sodium chloride (NaCl USP powder, Mallinckrodt, USA) and were prepared by wet high shear pelletization.

The coating used was a 30-w/w% copolymer of methacrylic acid and ethyl acrylate latex in water (Eudragit L30D55, Röhm Pharma, Germany), plasticized with 10-w/w% (based on dry polymer content) triethylcitrate (TEC, Merck, Germany). The poly-functional molecule or crosslinker used is the tri-functional acrylic monomer pentaerythritol triacrylate (PET, Sigma-Aldrich, USA) and the photo-initiator 2,2-dimethoxy-2-phenyl-acetophenone (DMPA, Sigma-Aldrich, USA), the weight percentages added based on dry polymer content were 10 and 5 respectively. The coating was performed in a fluidized bed.

The cross-linking reaction is initiated by the decomposition of DMPA into a radical. Sander and Decker [3] suggested the following reaction scheme depicted in figure 5.5.
Both the benzoyl and the methyl radicals may initiate the crosslinking; the mechanism of the crosslink-reaction itself is yet unknown.

The experimental procedure was as follows: the photo-initiator and crosslinker were dissolved in the plasticizer to give a clear solution and were then added to the polymer latex. This mixture was stirred overnight to ensure that all the plasticizer (and the compounds dissolved in the plasticizer) was diffused into the polymer. The coating was applied in a fluid bed at 60 °C and the coated pellets were dried in an oven at 60 °C for 12 hours. The crosslinking reaction was initiated by exposing the pellets to an UV lamp (Uvaspot 400, Dr. Höhle GmbH, Germany) emitting UV light with an average wavelength of 365 nm and an intensity of approximately 30 mW/cm². To ensure that the coating on the pellets was evenly crosslinked the pellets were kept in a fluidized state under the UV lamp by vibration.

**Water sorption measurements**

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

The uptake of pure water of the crosslinked films was determined by immersing free films in water of 25 °C. After fixed time intervals the films were removed from the water and weighed after carefully removing water adhered to the surface of the films with a paper tissue.

**Swelling measurements**

The swelling of the coating as function of the water content was determined by bringing a free film at equilibrium at a certain given outside water activity. The outside water activities were established using saturated salt solutions. Subsequently the increases in thickness and surface area of the film were measured with a microscope (Nikon SMZ-U, Nikon, Japan) a digital
camera (Sony DXC-151P, Sony, Japan) and imaging analysis software (Sigma Scan Pro 3.0, Jandel Scientific, USA).

**Glass transition temperature**

The glass transition temperature (Tg) of the coating was measured as function of the water content by means of modulated differential scanning calorimetry (DSC 2920 Modulated DSC, TA Instruments, USA). The Tg was determined in the first run, the sample size used was approximately 6 mg, the heating rate 2 °C/min, and the modulation temperature rate 1 °C/min. The Tg was determined by the midpoint method.

![SEM photographs of dry pellets coated with 154-w/w% cross-linked polymethacrylate coating (percentage coating based on core weight). Figure c: a photograph of pellets with 154 w/w% coating immersed in water after the release cycle was completed (45 minutes). The transparant part is the coating, the white part the core.](image)

**Figure 5.6**
Results

Coating characterization

The crosslinking changes the solubility behaviour of the coating. The untreated coatings disintegrate fast but the crosslinked coatings swell to a hydrogel-like state. This hydrogel did not dissolve, disintegrate or fail mechanically during the release experiments. This is illustrated in figure 5.6c (previous page) where a photograph of pellets with 154-w/w% coating immersed in water for 45 minutes is shown. Almost all the pellets show a swollen but intact coating.

Also shown in the same figure are two SEM photographs (figure 5.6a and 5.6b) of two pellets with an equal amount of coating as the pellets in figure 5.6c but in a dry state. The coatings are defect free, no major cracks or pinholes can be detected on the photographs.

The amount of material (polymer, crosslinker or plasticizer) that diffuses out of the coating during a release cycle was determined by measuring the weight loss of a free film before and after immersion in water. The time that the film was immersed was equal to the time needed to complete the release cycle for that coating thickness. It was found that the amount of material diffusing out of the coating in that period is negligible (< 0.5 ± 0.3-w/w%, weight loss determined of 5 free films) for a film with a thickness of 150 µm. This weight loss increases to 10 ± 2-w/w% after 2 days immersion in water. The coating totally dissolves when immersed in a 0.5 M NaOH solution of 70 °C for 16 hours.

Release experiments

The influence of the coating thickness on the release properties is given in figure 5.7. The release properties of the formulation are satisfactory: the formulation is able to induce a lag-time and the release has a pulse profile. The level of UV curing determines the lag-time until a certain maximum lag-time is reached; this is shown in figure 5.8.

In some of the release experiments the pH was monitored during the release cycle of the pellets. It was seen that the pH does not change significantly from neutral during the release cycle. Also the release of the formulation with 154-w/w% coating was measured in a 0.05 M Na₂HPO₄/KH₂PO₄ buffer (pH = 6.8) which gave the same result as the release experiments in demineralised water. This shows that the release is not controlled by a pH change during the release experiments.

To achieve a better insight into the deviation of the release of individual pellets the release profiles of several individual pellets were determined. The result is given in figure 5.9, which shows that the release mechanism is reproducible and only shows a small variation in the lag-time. Also the slope of the release curves is equal for all the pellets.
Semi-soluble coatings

Figure 5.7  Release profiles for 3 grams of NaCl/MCC pellets (0.6-0.7 mm) coated with different levels of Eudragit L30D55 and crosslinked with UV light of 365 nm for 10 minutes. Weight percentages coating are based on the weight of the core. Error bars denote standard deviation in two independent coating experiments.

Figure 5.8  The influence of the UV curing time on the release for a formulation with 70-w/w% or 90 µm thick Eudragit L30D55 coating.
Figure 5.9 Single pellet release measurements compared to the release of 3 g of pellets. Measurements for a formulation with 105-w/w% or 115 µm thick UV crosslinked Eudragit L30D55 coating.

Water sorption measurements

In figure 5.10 the water uptake is given as function of the water activity. It is seen that above a water activity of 0.9 the water uptake increases dramatically.

Swelling and DSC measurements

In figure 5.11 the relative swelling of the coating is given as function of the water content of a crosslinked coating. The relative swelling is calculated by equation 5.1.

\[
\text{relative increase volume} = 1 + \frac{\text{volume wet} - \text{volume dry}}{\text{volume dry}}
\]  

(5.1)

As with the sorption measurements it is seen that the major part of the swelling takes place at the higher water activities.
Semi-soluble coatings

Figure 5.10  Equilibrium water uptake for a crosslinked Eudragit L30D55 coating, water-percentage based on dry polymer weight. Error bars denote standard deviation in the water uptake from five independent sorption experiments.

Figure 5.11  Equilibrium swelling as a function of the water content of a crosslinked Eudragit L30D55 film.

In Table 5.1 the glass transition temperature as function of the water activity is given. It is seen that the largest decrease in Tg is above a water activity of 0.9.
In conclusion it can be stated that above an outside water activity of approximately 0.9, corresponding to a mole fraction water in the film of approximately 0.67, the glass transition temperature drops below room temperature. As a result the polymer takes up more water and starts to swell.

<table>
<thead>
<tr>
<th>a (-)</th>
<th>Tg (°C)</th>
<th>±</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>102</td>
<td>1</td>
</tr>
<tr>
<td>0.75</td>
<td>49</td>
<td>0.3</td>
</tr>
<tr>
<td>0.80</td>
<td>44</td>
<td>0.4</td>
</tr>
<tr>
<td>0.90</td>
<td>29</td>
<td>1</td>
</tr>
<tr>
<td>0.95</td>
<td>-1</td>
<td>0.5</td>
</tr>
<tr>
<td>1.0</td>
<td>-1</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Table 5.1  Glass transition temperature as function of the water activity (a) for a crosslinked Eudragit L30D55 film. Tg is average of measurements on three independent films.

Mathematical model to predict the release time.

Since the formulation with UV crosslinked Eudragit coatings meets the requirements for a pulse release formulation we developed a mathematical model to predict the release time.

The release mechanism of this formulation depends on the swelling of the coating. From the literature [4] it is known that the diffusivities of penetrants are low in non-swollen or glassy polymers. As the swelling of the polymer increases (e.g. by a temperature increase) the diffusivities increase with order of magnitudes. This can be visualized by the free volume theory that originally has been used to describe diffusional properties of simple liquids. Diffusion of penetrants is said to take place only through the available free volume in the polymer [5]. Thus for small values of the free volume (when the polymer is in its glassy state) the diffusion of penetrants is slow. When the free volume is increased (e.g. by increasing the temperature, or swelling induced by a penetrant) the diffusion will become faster. Above a certain free volume the diffusivity increases rapidly, at this point there is a transition of the polymer from a glassy state into a rubbery state. Therefore the diffusion coefficient of the penetrant in the coating depends on the water concentration especially above the glass transition temperature.

We can calculate these concentration dependent diffusion coefficients by using data gathered from water sorption experiments. In the sorption experiments the outside water activity or relative humidity was increased in small steps. If it is assumed that the diffusion coefficient is constant for each of these small increases in the water activity we can calculate diffusion coefficients for each increase in the water activity.

The diffusion coefficients are calculated on the basis of the second law of Fick and the Maxwell-Stefan transport equations. Fick’s law results in
algebraic equations, while the Maxwell-Stefan transport equation results in a numerical model. Both diffusion laws are used and the results are compared.

**Description of the moisture uptake**

A mass balance describes the uptake of moisture by a polymeric film. The general mass balance of a one-dimensional uptake is given by:

\[
\frac{\partial c_i}{\partial t} = -\frac{\partial N_i}{\partial z}
\]  

(5.2)

Here \(c_i\) is the concentration of the permeating component, \(t\) the time, \(N_i\) the molar flux and \(z\) the direction of permeation. The molar flux is given by:

\[
N_i = c_i v_i
\]  

(5.3)

Here \(v_i\) is the species velocity of the permeating component. In order to describe the permeation of a component, the species velocity has to be calculated on the basis of a diffusion theory.

**Calculating diffusion coefficients with the second law of Fick**

Fick assumed that the diffusion of a component is proportional to the concentration gradient of the component. According to the first law of Fick the diffusive flux is given by:

\[
J_i = c_i (v_i - v_{mix}) = -D \frac{\partial c_i}{\partial z}
\]  

(5.4)

Here \(J_i\) is the diffusive flux, \(v_{mix}\) the drift velocity of the mixture, and \(D\) the Fick diffusion coefficient of the component. When the swelling of a polymer is neglected, the drift velocity of the mixture becomes zero and the diffusive flux becomes equal to the molar flux. The one-dimensional mass balance rearranges to the second law of Fick:

\[
N_i = J_i \Rightarrow \frac{\partial c_i}{\partial t} = \frac{\partial}{\partial z} \left( D \frac{\partial c_i}{\partial z} \right)
\]  

(5.5)

The second law of Fick can be solved if a constant diffusion coefficient is assumed. A solution is given by equation 5.6 for a polymeric film of thickness \(d\) placed in an infinite bath of diffusant [6].

\[
\frac{C}{C_\infty} = 1 - \frac{4}{\pi} \sum_{n=0}^{\infty} \frac{(-1)^n}{2n+1} \exp \left[ -\frac{D(2n+1)^2 \pi^2 t}{d^2} \right] \cos \left[ \frac{(2n+1)\pi x}{d} \right]
\]  

(5.6)
The boundary conditions for this equation being zero initial concentration of diffusant at \( t = 0 \) and the concentration at both surfaces being instantaneously established at a concentration \( C_s \) at any time. Integrating equation 5.6 over the thickness of the film to obtain the absorbed mass as a function of time yields:

\[
\frac{M_t}{M_{\infty}} = 1 - \sum_{n=0}^{\infty} \frac{8}{(2n+1)^2 \pi^2} \exp\left(-\frac{D(2n+1)^2 \pi^2 t}{d^2}\right)
\]  
(5.7)

where \( M_t \) is the sorbed mass in the film at time \( t \) and \( M_{\infty} \) the sorbed mass at equilibrium. For the initial water uptake \((M_t / M_{\infty}) \leq 0.5\) equation 5.7 can be written as:

\[
\frac{M_t}{M_{\infty}} = 4 \left( \frac{D}{\pi} \right)^{1/2} t^{1/2}
\]  
(5.8)

For longer periods of time equation 5.7 can be written as:

\[
\frac{M_t}{M_{\infty}} = 1 - \frac{8}{\pi^2} \exp\left(-\frac{D \pi^2 t}{d^2}\right)
\]  
(5.9)

For the initial water uptake (“penetration”) the diffusion coefficient is determined by measuring the slope of the absorption curve \((M_t / M_{\infty})^2\) against \( t \). For longer periods of time (“steady state”) the diffusion coefficient is determined by measuring the slope of the curve \( \ln(1- M_t / M_{\infty}) \) against \( t \).

**Calculating diffusion coefficients with the Maxwell-Stefan mass transfer theory**

The Maxwell-Stefan mass transfer theory takes a starting point that differs considerably from Fick’s law. The main idea of the Maxwell transport equations is that the driving forces on each individual component in a mixture are balanced by the friction forces exerted on that component (-driving forces on component \( i \) = friction forces on component \( i \)).

In the sorption experiments the driving force is the gradient of the chemical potential, the friction force with the other component (the polymer) balances this driving force. Equation 5.10 gives the one-dimensional (direction \( z \)) Maxwell-Stefan equation for component \( i \). In this equation \( D_{ij} \) is the inverse friction coefficient between component \( i \) and \( j \) or the Maxwell-Stefan diffusion coefficient. Furthermore is \( \mu_i \) the chemical potential of component \( i \), \( R \) the gas constant, \( T \) the absolute temperature, \( v \) the component velocity and \( x_j \) the mole fraction of component \( j \).
The chemical potential $\mu_i$ of component $i$ is given by equation 5.11, in which $\gamma_i$ is the activity coefficient of component $i$.

$$
\mu_i = \mu_i^0 + RT \ln(\gamma_i x_i)
$$

(5.11)

The Maxwell-Stefan equation contains differences in species velocity; i.e. it contains relative velocities. To calculate the absolute species velocity of a single component a so-called bootstrap relation is required. In this case the bootstrap relation is that we assume that the total volume flux is equal to zero. In this way the swelling of the polymer is incorporated in the description. When water diffuses in the film, an equal amount (by volume) of polymer has to move in an opposite direction. The zero volume flux is obtained by:

$$
x_w V_w v_w + x_p V_p v_p = 0
$$

(5.12)

Here $V_w$ is the partial molar volume of water and $V_p$ the partial molar volume of the polymer.

The one-dimensional mass balance, the Maxwell-Stefan transport equation and the zero volume flux equation can be used to describe the concentration profile in the film. This set of equations is in fact a partial differential equation, which has to be solved numerically. The partial differential equation (mass balance) is transformed into a set of ordinary differential equations when the directional derivative is written as a finite difference for a number of grid-points inside the polymeric film:

$$
\frac{\partial N_i}{\partial z} = \frac{N_{z+1/2} - N_{z-1/2}}{z_{z+1/2} - z_{z-1/2}}
$$

(5.13)

Here the subscript $z_{z+1/2}$ indicates the flux and the position between two grid-points. This is illustrated in figure 5.12.
Over each individual set of grid-points equations 5.10 and 5.11 are integrated with a 4th order Runga-Kutta method [7]. The concentration profile is then optimized to fit the experimental sorption curve of water in the polymer film by changing the diffusion coefficient. The fit procedure used to determine the diffusion coefficients is the Levenberg-Marquardt method [7].

In order to be able to perform the numerical method some calculations have to be done on the data obtained from the water sorption experiments. First the wet mass fractions and mole fractions of water in the film as function of the outside water activity are calculated. The mole fraction coating is defined as the total number of moles of material in the coating (polymer, crosslinker and plasticizer). The mole fraction polymer is defined by using the mole weight of one single monomer unit, or if a copolymer is used, the average mole weight of the monomer units.

Then the total molar volume, needed to calculate the water concentration in the polymer, is calculated by summation of the molar volume of water and the molar volume of the polymer.

The activity coefficients are calculated with the knowledge that at equilibrium the activity outside the film is equal to the activity inside the film. Since $\gamma = a/x_w$, we can calculate the activity coefficient at equilibrium sorption values and find a relation between the activity coefficient and the mole fraction water in the film. To estimate the values of the activity coefficient at mole fractions in-between the measured values we fit the data with a polynomial equation.

The result of the calculation of the Fick and Maxwell-Stefan diffusion coefficients is given in figure 5.13.

In the activity range 0.1 to 0.7 the three diffusion coefficients all show the same behaviour. The diffusion coefficient is more or less constant till a
water activity of 0.4 and decreases from a water activity of 0.4 on. From an outside water activity of 0.7 on the diffusion coefficients increase, and at a water activity of 0.9 (when the glass transition temperature has fallen below room temperature) the Fick diffusion coefficients decrease again but the Maxwell-Stefan coefficients continue to increase. Since the expected trend is an increase in the diffusion coefficients at these high water contents the Fick diffusion coefficients are not reliable at high water concentrations. This was expected because the level of swelling of the polymer cannot be neglected at higher water contents and thus the assumption of no swelling is not valid anymore.

The initial decrease in the diffusion coefficient (below a water activity of 0.4) is somewhat surprising because most findings in the literature describe an increasing diffusion coefficient with increasing water concentration. However, one must keep in mind that the material under investigation is not a pure component but a mixture of several components and thus the interaction with water is more complicated than most situations described in the literature with pure polymers.

![Figure 5.13](image_url)

**Figure 5.13** Diffusion coefficients calculated by Fick's law and Maxwell-Stefan as function of the outside water activity. Error bars denote standard deviation in the calculated diffusion coefficients from three independent sorption experiments.

In figure 5.14 the Maxwell-Stefan diffusion coefficient is given as function of the mole fraction water in the polymer. Because of experimental limitations no estimate of the diffusion coefficient can be given at water
activities higher than 0.97. A relation developed by Mackie and Meares [8]. (equation 5.14) gives an estimate in this region. The equation is based on a lattice model with geometric obstruction. In this equation $D_0$ is the self-diffusion coefficient of the solute (water) and $\Phi$ the polymer volume fraction.

$$D(\Phi) := D_0 \left(\frac{1 - \Phi}{1 + \Phi}\right)^2$$  \hspace{1cm} (5.14)

The equation fits the results of Muller-Platte [9] and Petit [10] reasonably well (diffusion of water in swollen Polyvinylalcohol membranes), experimental data as well data obtained by molecular dynamics simulation. As can be seen from figure 5.14 the Mackie and Meares equation only gives a result similar to our experimental results at very high water concentrations, which was expected because the equation was developed for this region.

Figure 5.14 Maxwell-Stefan diffusion coefficient for a crosslinked Eudragit L30D55 film as function of the mole fraction water in the film, compared to a theoretical prediction developed by Mackie-Meares [8].

**Prediction of the lag-time**

Since we now have the relation between mole fraction water and diffusion coefficient (figure 5.14) and all the other necessary data we can give an estimate of the lag-time using equations 5.10 and 5.11. A typical calculated one-sided pure water uptake profile is given in figure 5.15. It is seen that a
sharp front of high water concentration is moving through the film until the end of the film is reached and the concentration profile levels out to equilibrium. The concentration profile resembles to what in the literature is called “relaxation controlled transport” [11]. For glassy polymers, the rate of relaxation is slow and rate limiting. Thus diffusion of water takes place at two rates, at a slow rate in the dry (glassy) polymer and at a fast rate in the swollen (rubbery) polymer. Therefore a sharp front develops between the dry and the swollen polymer that travels through the polymer at a constant speed. The classical designation for this type of diffusion is non-Fickian Case II diffusion. However, in an ideal Case II diffusion the penetrant is always in equilibrium with the polymer in the swollen part of the film. It is seen in figure 5.15 that the model does not predict an ideal Case II diffusion. Instead the model predicts a penetration rate which is comparable to the diffusion rate in the glassy part of the film. This type of diffusion is called anomalous diffusion; the relaxation of the polymer chains together with the diffusion in the swollen part of the polymer determine the overall uptake rate of penetrant [12].

Figure 5.15 Calculated water concentration profile of a crosslinked Eudragit L30D55 film immersed in pure water. At $t=0$ the water activity outside the membrane at $x=0$ is increased to one. The relative film thickness denotes the distance into the film divided by the total film thickness at that point in time.

The actual moment of release is difficult to predict because we do not know the interaction between the dissolved contents of the core (sodium chloride) and the coating. However we can plot the increase in water
concentration at the last grid point in the film, i.e. the place in the film that is in contact with the core, against the release curves of the actual formulations. This is done in figure 5.16. After a certain time with a slow increase in water concentration there is a fast increase in the concentration at the last grid point in the film. This time period coincides with the lag-time of the different coating levels. Thus it is save to say that the model gives an excellent prediction of the lag-time at a certain coating thickness.

Concluding it can be said that creating a semi-IPN in an Eudragit L30D55 coating gives good pulse-release properties. Both the coating thickness and the duration of UV exposure time can be used to control the lag-time. The mathematical model predicts a anomalous diffusion; the relaxation of the polymer chains together with the diffusion in the swollen part of the polymer determine the overall uptake rate of water.

![Figure 5.16](image)

**Figure 5.16** Experimental release curves compared to the calculated relative concentration profiles at the boundary between coating and core at different coating levels. A 100 % water concentration denotes the equilibrium concentration of water in the film (exp. = experimental, calc. = calculated, conc. = concentration).
UV induced crosslinking of polyvinylalcohol and hydroxypropylmethylcellulose with sodium-benzoate.

Introduction
Sodium benzoate is used primarily as an anti-microbial preservative in cosmetics, foods and pharmaceuticals. It decomposes under UV light with an average wavelength of 254 nm and is then able to induce a crosslinking reaction in for example polyvinylalcohol (PVA) or hydroxypropylmethylcellulose (HPMC) [13, 14]. The mechanism of this crosslinking process is not completely elucidated.

The crosslinking decreases the water-solubility of the PVA and HPMC and therefore the UV crosslinking of these water-soluble polymers could be a method to induce a lag-time before the coating dissolves. In this part we describe the experiments to determine the suitability of crosslinked HPMC and PVA as delayed release coatings.

Experimental
The experimental procedure is as follows: low viscosity grades of HPMC (HPMC 5, Sigma-Aldrich, USA) or PVA (Airvol PVA1 103, Air Products, The Netherlands) are dissolved in demineralised water. After the polymers were totally dissolved 3-w/w% of sodium-benzoate (Sigma-Aldrich, Milwaukee, USA), based on the dry polymer weight, is dissolved in the solution. Pellets consisting of 37.5-w/w% MCC and 65.5-w/w% sodium chloride in the size range of 0.60-0.71 mm (PVA experiments) and 0.85-1.2 mm (HPMC experiments) are coated with this solution in a fluid bed. The coated pellets were dried in an oven at 60 °C for 12 hours and cured under an UV lamp in the same way as the pellets coated with Eudragit L30D55.

Release experiments
In figure 5.17 the result is given for the PVA coated pellets. As can be seen the curing process does not increase the lag-time. However, although the lag-time was not increased, the curing process did succeed because under the microscope it was clearly seen that a hydrogel layer is formed around the UV-cured pellets, which was not seen around the uncured pellets. Also free films produced from UV crosslinked PVA showed a swelling behaviour instead of dissolving in water.

Also in figure 5.17 the result is given for an experiment with a HPMC coating. Also here the UV-crosslinking does not increase the lag-time. However additional experiments with free films showed that, as with the PVA films, the solubility of crosslinked HPMC films is decreased considerably when compared with films without crosslinking.
Figure 5.17 Results release experiments on pellets in the size range 0.6-0.7 mm coated with HPMC and PVA-I coatings, influence UV-curing on release properties.

The most probable reason for the short lag-times of the UV cured HPMC and PVA-I coatings is the fact that the UV cured coating swells very rapidly in water which causes a drastic decrease in the mechanical properties of the coating. Therefore only a low internal pressure in the coated pellet induced by transport of water through the film is enough to rupture the coating.

This is confirmed by experiments with free films. Free films of UV crosslinked HPMC were placed in-between a compartment with pure water and one with a certain osmotic pressure. In these experiments 50 \( \mu \)m thick films (both PVA-I and HPMC) can only withstand the osmotic pressure of a 0.005 M sodium chloride solution for a few seconds.

Concluding it can be said that the water solubility of low viscosity PVA-I and HPMC films can be decreased by UV curing but these coatings take up water very rapidly and thus swell very rapidly. This rapid swelling increases the water permeability and decreases the mechanical properties in such an extent that a delayed release cannot be obtained with these coatings.

5.3 Hot melt coating of a solution of a water-soluble and a water-insoluble compound

In the previous paragraphs we decreased the solubility of the coatings by crosslinking the polymer physically or chemically. In the next part we
adopt a different strategy, we coat particles with a water-insoluble film-former while adding a water-soluble compound to the coating to control the release properties. We do this by melting the water-insoluble film-former and dissolving the water-soluble compound in this melt. The molten solution is then applied on spherical particles by fluid bed coating.

5.3.1 Hot melt coating of myristic acid and sodium-stearate

Experimental

Myristic acid (MA, C\textsubscript{14}H\textsubscript{28}O\textsubscript{2}) is a water-insoluble fatty acid with a melting point of 50 °C. Sodium stearate (NaS, C\textsubscript{18}H\textsubscript{35}NaO\textsubscript{2}) is a water-soluble surfactant that dissolves in molten myristic acid at approximately 75 °C. The maximum solubility of sodium stearate is 2 parts sodium stearate in 3 parts myristic acid when the temperature of the melt is 70 to 80 °C. Higher percentages of sodium stearate can only be dissolved at higher temperatures.

The procedure for coating pellets in a fluid bed from a melt is as follows: the myristic acid is molten and the sodium stearate is added to the melt and dissolved by vigorous stirring. The molten solution is sprayed onto the pellets by transporting the melt trough heated tubes into a heated pneumatic nozzle (figure 5.18) by means of a single rotor screw pump (Monopomp type EDD, Daurex GmbH, Germany). The atomizing air is also heated to prevent premature solidification of the melt in the nozzle.

The fluidization air is heated just below (5 to 10 °C) the melting temperature of the coating melt solution. We found that if the temperature fluidization air was far below (> 10 °C) the melting temperature of the coating material the produced coating was very porous. Another effect at lower temperatures was that a considerable amount of coating material was spray cooled and deposited on the walls of the fluid bed. If the temperature of the fluidization air was well above (> 10 °C) the melting temperature of the coating severe agglomeration of the pellets would occur.

![Figure 5.18 Schematic representation experimental set-up hot melt coating experiments.](image-url)
Release experiments

In figure 5.19 the release curves for two coating experiments are given for coating solutions with 2:1 and 3:2 mass ratios of myristic acid and sodium stearate. The cores consisted of 37.5-w/w% MCC and 65.5-w/w% sodium chloride in the size range of 0.6-0.85 mm. The formulation gives a lag-time at reasonable coating levels but the release after the lag-time is rather slow i.e. there is not a perfect pulse release. Increasing the level of the water-soluble sodium stearate in the coating decreases the lag-time.

The release mechanism of this formulation was investigated under the microscope and with release experiments conducted with single pellets. The result of measuring the release of single pellets from the formulation denoted with the open triangles in figure 5.19 (15-w/w% or 32 to 38 micron 2:1 MA:NaS coating) is given in figure 5.20. Some light microscope images of the same formulation immersed in water are given figure 5.21.

From the release of single pellets it is seen that the individual pellets give a pulse release but with a large deviation in the lag-time. The images in figure 5.21 show that the release is triggered by the mechanical failure of the coating. Thus the release mechanism is controlled by the mechanical failure of the coating, most probably caused by the increase of volume of the core.

Figure 5.19 Results release experiments on pellets (0.6-0.71 and 0.71-0.85 mm in diameter) with coatings consisting of 2:1 and 3:2 mass ratios myristic acid (MA): sodium stearate (NaS).
To investigate the water uptake properties of this coating gravimetric water sorption experiments were carried out; the results are given in figure 5.22 and figure 5.23. From these figures it can be seen that the coating only takes up a very small amount of water. From the experiments it was also seen that a free film of the material remains almost intact when immersed in water. When a film is dried after it is brought in equilibrium with pure water over prolonged periods of time only 0.8 w/w% of the coating is dissolved.
Figure 5.22  Water sorption curves for 2:1 a myristic acid : sodium stearate film, pure myristic acid and pure sodium stearate.

Figure 5.23  Pure water uptake vs. time for a 2:1 myristic acid:sodium stearate coating.

Since the coating does not take up much water and does not dissolve or partly dissolve when it is immersed in water the diffusion of water through the material should be very slow and thus the lag-time in the release should be very long. However the lag-time of the formulation is only a few minutes
which can be explained with SEM photo’s of the surface of a formulation with a 2:1 sodium stearate:myristic acid coating. These SEM photos showed that most of the coated granules show little holes or cracks in the coating (figure 5.24). Through these holes water can be taken up much faster than through the coating and thus the lag-time is decreased considerably. This could also explain the large deviation in the lag-time of the individual pellets since the distribution and size of the irregularities in the coating will be random and thus cause a random distribution of the lag-time.

Concluding we can say that although a large part of the coating is water-soluble the release mechanism is not controlled by the dissolution of this water-soluble compound. The release mechanism of this formulation is most probably controlled by the amount of irregularities in the coating. This makes this formulation only moderately successful in inducing a pulse release of its contents. Furthermore, since that this random distribution of irregularities is very difficult to predict there was no mathematical model developed to predict the release time.

5.3.2 Hot melt coating of polyethylene glycol and stearylalcohol.

Experimental & Release experiments

The experiments were set up in the same way as the MA/NaS experiments, the soluble compound in this case being polyethyleneglycol (PEG) and the insoluble compound stearylalcohol (1-octadecanol, chemical formula C_{18}H_{38}O, abbreviated as SA).

In preliminary experiments large cores (10 mm in diameter experimental procedure see chapter 4) were coated. In figure 5.25 the release profiles are given for large cores coated with different mixtures of PEG and stearylalcohol. The lag-time induced by these coatings increase with increasing percentage of stearylalcohol in the coating.

In figure 5.26 the result is given for small pellets (consisting of 37.5-w/w% MCC and 65.5-w/w% sodium chloride in the size range of 0.71 to 0.85 mm) coated with different levels of 1:1 SA:PEG. Compared to the large pellets experiments in figure 5.25 the smaller pellets are far less efficient in terms of the coating thickness and the resulting lag-time.
Figure 5.25  Release experiments for large cores (diameter app. 10 mm) coated with a mixture of PEG6000 and stearylalcohol. The PEG:SA ratio is based on the mass of the coating.

Figure 5.26  Release curves for pellets (composition: 37.5-w/w% MCC 65.5-w/w% NaCl, diameter: 0.7-0.85 mm) coated with 1:1 SA:PEG6000. Influence coating level.
The reason for this is depicted in figure 5.27 with SEM photos of the surface of the coated small pellets. It is seen that the coating is very irregular and contains many holes, while the larger pellets (not shown here) have very smooth surfaces. Therefore water can be transported very fast through the coating of the small pellets to the core. This is confirmed by single pellet release experiments (figure not shown) which show that a large percentage of the pellets do not have a lag-time. The relatively high viscosity of the molten PEG6000 (1000 cSt at 60 °C) makes it difficult to atomize the melt with a pneumatic nozzle. Therefore the droplet size of the atomized melt will be large compared to the size of the core resulting in an irregular surface. An attempt was made to solve this problem by using a low molecular weight PEG (PEG1000) with a melt viscosity of 100 cSt at 60 °C.

The coating quality was somewhat improved by incorporating PEG1000 as shown in figure 5.28. However the PEG1000 formulations failed to give a lag-time (figure not shown). This is probably due to the fact that PEG1000 is more readily soluble in water than PEG6000 [15] combined with the fact that the coatings on the pellets are still not flawless.
5.4 Conclusions Chapter 5

The formulations discussed in this chapter were all partly watersoluble or formed a hydrogel when immersed in water. From the hydrogel forming formulations (physically crosslinked calcium alginate and chemically crosslinked PVA, HPMC and Eudragit L30D55) only the Eudragit L30D55 coating gave the desired release characteristics.

When we investigated the release mechanisms of these coatings it was found that the calcium alginate coating swells very fast when immersed in water. This is due to the fact that this material has a high affinity for water even at low water activities. The crosslinked low molecular weight PVA and HPMC coatings also swell fast and have poor mechanical properties when immersed in water. These three crosslinked materials are not suitable to achieve the desired release properties.

The Eudragit coating swells slower and only at higher water activities and is thus more successful in inducing a lag-time. Creating a semi-IPN of the polymer and a poly-functional molecule decreases the water solubility of the Eudragit coating. The crosslink reaction is induced by UV-light. Both the coating thickness and the duration of the UV crosslinking time can be used to adjust the lag-time. When the Maxwell-Stefan diffusion coefficients are calculated for the crosslinked Eudragit coating an increase in the diffusion coefficients is found at higher water contents. The mathematical model predicts that the diffusion of water is rate-limited by the relaxation of the polymer chains and by the diffusion of water in the swollen part. The model gives a good estimation of the lag-time.

The formulations with a coating consisting of a water-soluble component and a water-insoluble component (sodium stearate/myristic acid and PEG/stearylalcohol) are able to induce a lag-time before release. However a perfect pulse-release is not obtained mainly because it is difficult to achieve a defect free coating with the hot melt coating technique. The release mechanism of these formulations is controlled by the mechanical failure of the coating. This mechanism is strongly influenced by defects in the coating and therefore the deviation in the lag-time in individual pellets is large resulting in a rather poor pulse release behaviour.
5.5 References

Semi-soluble coatings