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Hydration and swelling of amorphous cross-linked starch microspheres

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ABSTRACT

Hydration of cross-linked starch microspheres, commercially available as a medical device, was investigated using a multi-method approach. We found that the uptake of water is accompanied by substantial swelling and changes of the polymer structure. Sorption calorimetry provided information about thermodynamics of water sorption, revealed presence of isothermal glass transition and absence of hydration-induced crystallization, observed in non-cross linked starch material. The changes in the surface and bulk properties of microspheres at different water–starch concentrations were investigated using synchrotron radiation X-ray scattering and analyzed using concept of fractals. The obtained information, combined with the results of differential scanning calorimetry, was used to construct a phase diagram of the studied material. Finally, hydration induced evolution of polymer structure revealed by the X-ray scattering was linked to the changes observed during swelling with optical microscopy.

1. Introduction

Starch is a biopolymer that is highly abundant in nature where it serves as energy storage in plants. It is synthesized as densely packed granules and consists of the two polysaccharides amylose and amylopectin. Because of the great availability and low price, starch has found a wide range of applications in almost all branches of industry, e.g., in the food, paper, packaging and pharmaceutical industry. Different physical and/or chemical modifications are often employed to tune the properties of starch for practical uses. An example of a modern material obtained by modification of starch is starch microspheres that are used for oral, nasal and intramuscular drug delivery, i.e. for transporting active compounds into the body to achieve a desired therapeutic effect in the target place. Examples of such formulations can be found in the literature and may contain proteins or large molecular weight organic compounds (Edman, Björk, & Rydén, 1992; Elfstrand, Eliasson, Jönsson, Reslow, & Wahlgren, 2006; Illum, Jørgensen, Bisgaard, Krogsgaard, & Rossing, 1987; Illum, Farraj, Davis, Johansen, & O'Hagan, 1990; Pereswetoff-Morath, 1998; Rodrigues & Emeje, 2012). Degradable starch microspheres are also in use as a medical device for acceleration of wound healing by promoting hemostasis. The microporous starch particles are applied directly on the wound site where they take up fluid from the blood and create a gel which stops the bleeding (Björses et al., 2011; Malmsjö et al., 2011; Tan & Tope, 2004).

The hydration properties of native starch granules as well as modified starches have been widely investigated since they are very important for most applications (Carlstedt, Wojtasz, Fyhr, & Kocherbitov, 2014; Carlstedt, Wojtasz, Fyhr, & Kocherbitov, 2015; Svensson & Eliasson, 1995). In native starch granules only a minor part of the polymer is mobile, most of the chains are densely packed and thus isolated from bulk water (Larsen, Blennow, & Engelsen, 2008) while the chains of the amorphous starch microspheres are more accessible for water so their structure resemble hydrogels: hydrophilic three-dimensional networks, held together by chemical or physical bonds. Some examples of starch-based biodegradable hydrogels may be found in the literature (Elvira, Mano, San Román, & Reis, 2002).

An important phenomenon related to hydration is the glass transition in the amorphous parts of starch. Glass transitions of starch can be detected by, e.g., DSC (Thiewes & Steeneken, 1997). They can be caused by increase of temperature and/or addition of plasticizers, i.e. small molecules such as water or glycerol, which shift the glass transition to lower temperatures (Lourdin, Coignard, Bizot, & Colonna, 1997). Interestingly, parts of the same chain can be in

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a crystalline whereas another part in a disordered state in semi-crystalline polymers (Thiewes & Steeneken, 1997).

Another important aspect of hydration is the swelling of the material. In the drug delivery systems release from the microspheres is conducted in the sustained swelling-controlled manner (Fang et al., 2008). When used for stopping bleeding, it is of particular importance that the starch microspheres are highly absorbing so that they can prevent the blood flow.

In the present work hydration of cross-linked degradable starch microspheres was investigated with a multi-method approach. Methods such as sorption calorimetry, small angle X-ray scattering, gravimetrical swelling, rheology and differential scanning calorimetry were applied to characterize interactions of the amorphous starch and water. The aim of this study is to investigate hydration of the material including its high absorption capacity and swelling properties. In addition, we use X-ray methods to study structural rearrangements that accompany the hydration of the studied material. The obtained data are collected in a temperature vs. composition phase diagram of the starch microspheres – water system.

2. Materials and methods

2.1. Materials

2.1.1. Starch microspheres

The starch materials were provided by Magle AB (Kristianstad, Sweden). Spray-dried acid hydrolyzed potato starch (maltodextrin) was produced by Lantmännen Reppe AB (Växjö, Sweden). The degradable starch microspheres (DSM) are manufactured by Magle AB (Kristianstad, Sweden) by emulsion crosslinking (polymerization) of acid hydrolysed potato starch with epichlorohydrin. Prior to measurements the starch material was dried at room temperature in vacuum with 3 Å molecular sieves overnight. The samples were subsequently prepared by equilibration with saturated salt solutions vapor or by adding liquid water.

2.1.2. Salt solutions

Seven different saturated salt solutions were used for setting up relative humidity: LiCl, $MgCl_2$, $Mg(NO_3)_2$, NaCl, KCl, KNO_3 and K_2SO_4 with corresponding relative humidity values (RH%) 11.30, 32.80, 52.90, 75.30, 84.30, 93.28 and 97.30 (Greenspan, 1976). Prior to use, the saturated salt solutions were equilibrated for a few weeks at room temperature.

2.2. Scanning electron microscopy

The morphology of dry starch microspheres was examined with a scanning electron microscope (Zeiss EVO LS10 SEM). The experiments were performed at 25 °C in vacuum at an acceleration potential of 2 kV. The material was dried in vacuum prior to examination to ensure minimal moisture content, and then deposited on a graphite covered standard sample holder.

The obtained micrographs were analyzed with respect to morphology and size of the microspheres. The size was established as the mean value of the diameters measured horizontally and vertically for each particle as a distance in pixels. The value was then converted from pixels to μm using the size of the scale bar.

2.3. Sorption calorimetry

Hydration of starch at 25 °C was investigated with sorption calorimetry. During the experiment, the water activity a_w and the hydration enthalpy H_w^{mix} are measured simultaneously as a function of water content (Wadsö & Markova, 2002). As all physical and chemical processes are accompanied by release or absorption of heat, sorption calorimetry provides information about the processes occurring within the sample.

The measurements are performed in a two-chamber calorimeter cell inserted in a double-twin microcalorimeter (Wadsö & Wadsö, 1996). The thermal powers from the two chambers are recorded and the thermal power of evaporated water recorded in the vaporization chamber is used to calculate the water activity using an earlier proposed equation (Kocherbitov, 2004)

The partial molar enthalpy of mixing of water is calculated from the relation below:

$$H_w^{mix} = H_w^{vap} + H_w^{vap}\frac{P^{sorp}}{P^{vap}} \quad (1)$$

where P^{sorp} and P^{vap} are the thermal powers recorded in the sorption and vaporization chambers, and H_w^{vap} is the molar enthalpy of vaporization of pure water (44.0 kJ/mol at 25 °C).

2.4. Optical microscopy

An optical microscope (Nikon OptiPhot) was employed to investigate morphological changes and swelling of starch microspheres caused by addition of liquid water. Dry microspheres were placed directly on glass slides and their behavior upon hydration was captured in form of a movie. The recorded movies were subsequently analyzed in terms of changes in size of the microspheres by comparison of the sizes in pixels before and after swelling.

2.5. Gravimetric swelling study

To analyze the swelling limit and water absorption capacity five samples of 1–5 wt% of starch microspheres in water were prepared. After equilibration the suspensions were separated by centrifugation (10,000 rpm). The mass of water absorbed by the microspheres $m_{w,a}$ was established based of the masses of the water used to prepare the suspension and the mass of the supernatant:

$$m_{w,a} = m_w - m_{sup} \quad (2)$$

where m_w – mass of water used to prepare suspension, m_{sup} – mass of the supernatant.

The degree of swelling expressed as the ratio of the absorbed mass to the mass of dried microspheres was calculated based on the swelling study:

$$Q_m = \frac{m_{w,a}}{m_s} = \frac{m_p - m_s}{m_s} \quad (3)$$

where Q_m – degree of swelling, m_p – mass of particles, m_s – mass of starch used to prepare suspension.

2.6. Rheology

Viscosities of suspensions of microspheres with concentrations ranging from 0.5 to 2 wt% were determined with a capillary viscometer calibrated with miliQ water. A measurement is performed by first pumping up the suspension into a glass capillary. Then the time required for the liquid to flow, due to gravity, between two points marked on the capillary was measured. The viscosity was calculated based on the Hagen–Poiseuille equation which relates the pressure drop in the fluid flowing through the tube to the viscosity of the fluid (Hagen, 1839; Poiseuille, 1841)

$$\Delta P = \frac{8\eta L \Delta V}{\Pi r^4 \Delta t} \quad (4)$$

where η – viscosity, ΔP – the pressure drop, ΔV – volume of the fluid, Δt – time required for the liquid to flow between marked points, L – length of the capillary, r – radius of the capillary.