



# The crystallinity of cellulose controls the physical distribution of sorbed water and the capacity to present water for chemical degradation of a solid drug



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## ABSTRACT

The purpose of the research was to investigate the effect of moisture content of cellulose on the degradation of a drug in binary mixtures with cellulose. Physical mixtures of acetylsalicylic acid and two forms of cellulose, either microcrystalline cellulose or low crystalline cellulose, in the proportion 1:1 were stored at 50 °C at a series of relative humidities (0–90%) for up to 175 days.

The degradation rate constant of the drug increased with increased cellulose moisture content in a bi-regional fashion, with a low and a high degradation rate region. The shift from region 1 to 2 occurred at higher moisture content for the low crystalline cellulose. The relationships between rate constant and the temperature of maximum endothermic value overlapped for the two celluloses. It is proposed that the amount of water available for degradation of a solid drug is controlled by the water presenting capacity of cellulose which is dependent of the mechanism of sorption of water in cellulose. The water sorption of water can for cellulose satisfactorily be described by a two-site residence model with cellulose crystallinity as the structural correlate to the distribution between the two residence sites.

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## 1. Introduction

Knowledge of how water content of a solid affects the processing properties of a powder as well as the attributes of the formed product and its stability (shelf-life) is of great significance in the development of solid pharmaceutical products (Ceschel et al., 2003; Newman et al., 2008). More on, it is argued (Narang et al., 2012) that better understanding of physico-chemical interactions in solid dosage forms is needed under the quality by design paradigm of product development. Cellulose, especially in the form referred to as microcrystalline cellulose (MCC), is one of the most commonly used excipients in solid dosage forms (Kachrimanis et al., 2006) due to suitable technical properties, such as compactability (Michaut et al., 2010) and pelletizing ability (Mascia and Wilson, 2007). Since cellulose is hygroscopic the issue of how water associated with the cellulose affects the properties of the solid system of which cellulose is a part is of obvious relevance in the development and manufacture of medicines. An important aspect in this context is the deleterious effect that cellulose may have on the chemical stability of a solid active substance mixed

with cellulose. This issue has been the subject of investigation in a series of papers from our laboratory, in which a test model system consisting of a powder mixture of acetylsalicylic acid (ASA) and cellulose has been used. Ahlneck and Alderborn (1988) studied the degradation rate of ASA in powder mixtures with microcrystalline and microfibrillar cellulose and reported that although microfibrillar cellulose sorbed moisture to a higher degree than microcrystalline cellulose, the degradation rate of the ASA was somewhat lower in these mixtures. Later, Mihrianyan et al. (2006) and Heidarian et al. (2006) studied the degradation of ASA in powder mixtures with celluloses of different crystallinity and showed that the degradation rate tended to increase with increased crystallinity of the cellulose. Heidarian et al. (2006) also proposed that water molecules are more firmly attached to amorphous regions as compared to crystalline regions in cellulose due to a larger number of hydrogen bonds that binds each water molecule to the cellulose. This view may however not be consistent with later reports (Kocherbitov et al., 2008; Lepore et al., 2012) on the state of water sorbed to cellulose. Finally, it is also recently reported that the modification of the surface of cellulose may affect the stability of solid ASA (Carlsson et al., 2014).

Thus, it seems that for a water-mediated drug degradation process in the solid state, the water associated with cellulose can be described as being in different states in terms of its availability

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to take part in the degradation reaction and that the availability is related to the cellulose crystallinity. There is however a need to further clarify our understanding of the interplay between moisture content and crystallinity of cellulose in this context. In addition, since the reports published so far (Mihiranyan et al., 2006; Heidarian et al., 2006) have been studying the degradation of ASA under short periods of storage, i.e., up to 50 days, there is a need to follow drug degradation during longer storage times in order to assess the degradation kinetics in the binary system and thus explore the practical potential of the finding. In this study, the effect of a series of moisture content of cellulose on the degradation of model drug during storage up to 175 days in binary powder mixture with cellulose of two different crystallinities is investigated.

## 2. Materials and methods

### 2.1. Materials

Acetylsalicylic acid (ASA), labeled particle size of 450  $\mu\text{m}$ , and salicylic acid (SA) (Sigma–Aldrich Chemie GmbH, Germany,  $\geq 99\%$ ), and microcrystalline cellulose (MCC) (Avicel PH 102, FMC, Ireland, labeled particle size of 50  $\mu\text{m}$ ), were used as supplied. A second quality of cellulose, denoted low crystalline cellulose (LCC), was prepared by swelling MCC in 70% (w/w)  $\text{ZnCl}_2$  solution, using the same procedure as reported earlier (Mihiranyan et al., 2004). 50 g MCC was suspended in 1 kg 70% (w/w)  $\text{ZnCl}_2$  (Merck KGaA, Germany) solution and stored for 1 h. Additional water was then added to a final volume of 2 L and the cellulose was separated by filtration and washed with 95% ethanol. The filtrate was repeatedly washed with

de-ionized water until the conductivity of the wash water was below 14  $\mu\text{S}/\text{cm}$ . The cellulose was finally dried at 45  $^\circ\text{C}$  for 2 days.

A series of substances, i.e.,  $\text{P}_2\text{O}_5$ ,  $\text{LiCl}$ ,  $\text{CH}_3\text{COOK}$ ,  $\text{MgCl}_2$ ,  $\text{K}_2\text{CO}_3$ ,  $\text{NaBr}$ ,  $\text{NaCl}$ ,  $\text{HCl}$ , (Sigma–Aldrich Chemie GmbH, Germany,  $\geq 99\%$ ), was used to control the relative humidity (about 0–90% RH) of the storage atmosphere. Ethanol (95% analytical grade, Solveco, Sweden) was used in the chemical analysis.

### 2.2. Methods

#### 2.2.1. Moisture control of powders

A desiccator with  $\text{P}_2\text{O}_5$  in powder form was used to create an almost moisture free atmosphere (denoted 0(0)% RH). Saturated solutions of  $\text{LiCl}$ ,  $\text{CH}_3\text{COOK}$ ,  $\text{MgCl}_2$ ,  $\text{K}_2\text{CO}_3$ ,  $\text{NaBr}$ ,  $\text{NaCl}$  and 1 M  $\text{HCl}$  were used for moisture control in desiccators giving RHs of about 11(11), 23(14), 33(29), 43(40), 59 (63), 75(75) and 90(90)%. The two RH values reported for each salt used are firstly, RHs at room temperature reported in the literature (Greenspan, 1977; Mosharraf and Nyström, 2003) and, secondly (within parentheses) estimated RHs at 50  $^\circ\text{C}$ .

#### 2.2.2. Moisture content of celluloses

Portions (about 3 g) of MCC powder and LCC powder were dispensed into open glass jars and the glass jars were placed in desiccators containing  $\text{P}_2\text{O}_5$  in powder form. The desiccators were placed in a heat cabinet (Memmert UP 500, Germany) at a temperature of 50  $^\circ\text{C}$  and the cellulose samples were dried for one week. The dry weights of the samples were then recorded ( $w_0$ ) using an analytical balance. The cellulose samples were then transferred to a series of desiccators containing the salt solutions and stored for one week at 50  $^\circ\text{C}$ . The weight of the samples was

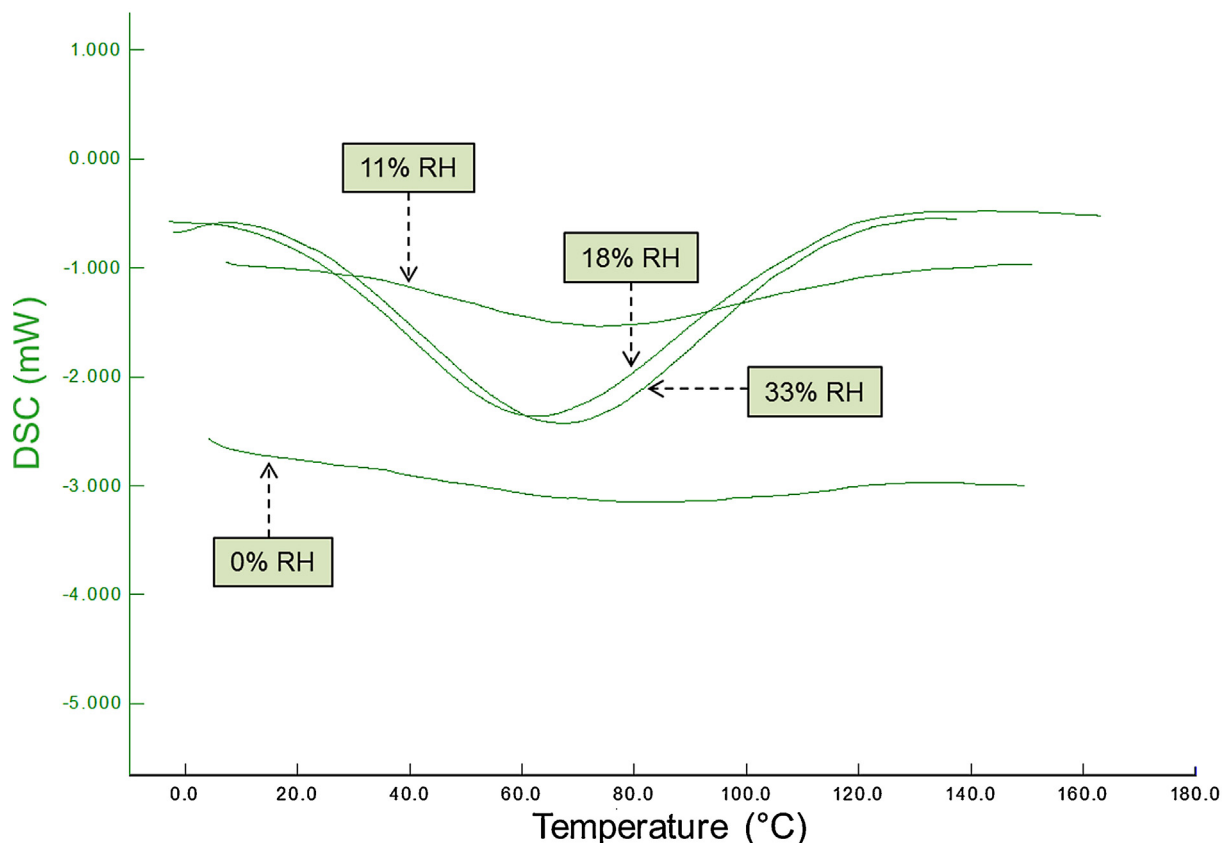


Fig. 1. Representative examples of DSC thermograms for MCC conditioned at relative humidities of 0, 11, 18 and 33%.

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