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Monitoring the recrystallisation of amorphous xylitol using Raman spectroscopy and wide-angle X-ray scattering

Emmi Palomäki[a,*], Patrik Ahvenainen[b], Henrik Ehlers[a], Kirsi Svedström[b], Simo Huotari[b], Jouko Yliruusi[a]

[a] Faculty of Pharmacy, P.O. Box 56, FI-00014 University of Helsinki, Finland
[b] Department of Physics, P.O. Box 64, FI-00014 University of Helsinki, Finland

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ABSTRACT

In this paper we present a fast model system for monitoring the recrystallization of quench-cooled amorphous xylitol using Raman spectroscopy and wide-angle X-ray scattering. The use of these two methods enables comparison between surface and bulk crystallization. Non-ordered mesoporous silica micro-particles were added to the system in order to alter the rate of crystallization of the amorphous xylitol. Raman measurements showed that adding silica to the system increased the rate of surface crystallization, while X-ray measurements showed that the rate of bulk crystallization decreased. Using this model system it is possible to measure fast changes, which occur in minutes or within a few hours. Raman-spectroscopy and wide-angle X-ray scattering were found to be complementary techniques when assessing surface and bulk crystallization of amorphous xylitol.

1. Introduction

Today, poor aqueous solubility is a common problem when developing new drug products. There are several approaches to deal with solubility issues, such as formation of salts or prodrugs, reducing the particle size or rendering the drug into a disordered state (Hancock and Zografi, 1997; Yu, 2001). Amorphous substances have a solubility superior to their crystalline counterparts due to their higher levels of molecular disorder, free energy and molecular mobility. The beneficial properties of amorphous drug substances are counterweighted by their inherent physical instability and tendency to undergo solid-state changes to reach the most stable crystal form.

Recrystallization from the amorphous state can take anything from hours to years. Considerable effort and resources have been invested in trying to achieve amorphous formulations with high enough stability to ensure sufficient physical stability of the active pharmaceutical ingredient throughout the shelf life of the final product. Still, a complete understanding of the crystallization of amorphous solids has not been achieved (Laitinen et al., 2013; Bhugra and Pikal, 2008). Typical stability studies of pharmaceuticals take several months to complete, and in order to facilitate the development of drug products to the market there is a need to be able to rapidly screen the physical stability challenges of amorphous drugs.

It has been shown that the surface crystallization is more rapid than bulk crystallization in amorphous glasses aged below their glass transition temperature (Zhu et al., 2010, 2008; Wu et al., 2007; Wu and Yu, 2006; Yu, 2016). The reason for this can not only be found in the higher molecular mobility of surface molecules compared to bulk molecules, but also in the more pronounced structural relaxation of the surface as compared to the bulk (Hasegawa et al., 2009). When the temperature exceeds the glass transition temperature, the viscosity of the sample decreases, and surface diffusion of molecules is disturbed by viscous flow of the material (Yu, 2016). This interrupts surface crystal growth, and as bulk diffusion is simultaneously promoted the difference between

* Corresponding author at: Division of Pharmaceutical Chemistry and Technology, Faculty of Pharmacy, University of Helsinki, P.O. Box 56 (Viikinkaari 5E), FIN-00014 University of Helsinki, Finland.
E-mail address: emmi.palomaki@helsinki.fi (E. Palomäki).

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the rate of surface and bulk crystallization is expected to become smaller.

Raman spectroscopy is a method commonly used to identify amorphous systems and quantify the amount of crystalline content (Chieng et al., 2011; Strachan et al., 2007). The method provides chemical information of the investigated molecules, and in addition Raman spectroscopy also provides information on inter-molecular interactions, which enables quantifying different solid states of substances. Crystalline content in amorphous samples has been detected down to 1% using Raman spectroscopy (Strachan et al., 2007). Raman spectroscopy is non-invasive, non-destructive, rapid and requires no sample preparation (Chieng et al., 2011), which makes it ideal for real-time monitoring of solid-state changes in pharmaceutical systems.

Powder X-ray diffraction is the most frequently used technique in solid-state analysis, and it is often combined with a spectroscopic method for complementary information (Chieng et al., 2011). Wide-angle X-ray scattering has been used to study the crystal structure of pharmaceutically active substances, excipients and drug products (Dong and Boyd, 2011) and is capable of detecting crystalline content in amorphous systems in amounts comparable to Raman spectroscopy (Paudel et al., 2015). It does not provide chemical information on the sample, but readily provides information on the structure of the studied material, and is able to distinguish molecularly ordered and disordered material (Chieng et al., 2011). In analysis of amorphous systems, WAXS is an indirect method, since it detects lack of order rather than disorder.

In the present study, the crystallization rate of amorphous xylitol was studied. Xylitol is a crystalline pentitole with only one reported stable polymorphic form (Carson et al., 1943; Diogo et al., 2007). Curiously enough, xylitol is an example of a substance with a polymorphic form going extinct, since the stable orthorhombic form has completely superseded over the metastable monoclinic form (Dunitz and Bernstein, 1995). Xylitol has a relatively low glass transition temperature of −24 °C (Talja and Roos, 2001), and it recrystallizes readily in room temperature. To alter the rate of crystallization, non-ordered mesoporous silica (Syloid 244FP) was added to the system in the present study. According to the manufacturer, Syloid 244FP has large surface area of 350 m^2/g, pore size of 15–20 nm and pore volume of 1.6 ml/g. It has previously been shown to increase the solubility of drug substances by allowing them to maintain an amorphous state by confinement in pores and molecular level interaction between the carrier particles and drug substance (Kinnari et al., 2011; Limnell et al., 2011).

The aim of the present study was to investigate whether xylitol can be used as a model substance to study rapid solid-state changes. Furthermore, the study set out to see whether Raman spectroscopy and wide-angle X-ray scattering could be used in studying the recrystallization of amorphous xylitol. The crystallinity and crystallization rate results from Raman measurements were compared with the wide-angle X-ray scattering results.

2. Materials and methods

2.1. Sample preparation

In the present study crystalline xylitol (University Pharmacy, Helsinki, Finland) was used as a model substance. Non-ordered mesoporous silica (Syloid 244FP, Grace GmbH & Co., KG, Germany) was used to modify the crystallization rate of amorphous xylitol. The substances were kept in a zero-humidity desiccator for a minimum of two weeks prior to the experiments. Amorphous xylitol was prepared by melting the crystalline powder on a hot plate set at 180 °C, which is well above the melting point of xylitol (92–96 °C) but clearly below its boiling point (215–217 °C). The melt was quench-cooled in liquid nitrogen and roughly ground while submerged in liquid nitrogen. In samples comprised of xylitol and 10% (m/m) of silica, Syloid 244FP was added to the melt and thoroughly mixed prior to quench cooling and grinding as described above. The amount of sample was 1.35 g in both cases. The liquid nitrogen-sample suspension was transferred into a sample holder and the liquid nitrogen was left to evaporate, and, upon complete evaporation, the solid samples were enclosed between two sheets of 6 μm thick Mylar film in order to insulate them from ambient humidity (Fig. 1). To avoid exposure to atmospheric moisture and oxygen, all the steps of the sample preparation following melting and mixing were performed in a dry nitrogen atmosphere. The final samples had a thickness of 2 mm and a diameter of 15 mm. The lag-time between complete evaporation of the liquid nitrogen and initiation of Raman and wide-angle X-ray scattering measurements was no more than 4 min in all experiments. The sample holder was designed to accommodate both Raman and X-ray measurements. The ibuprofen (Boots Pharmaceuticals, UK) and ϒ-indomethacin (Orion

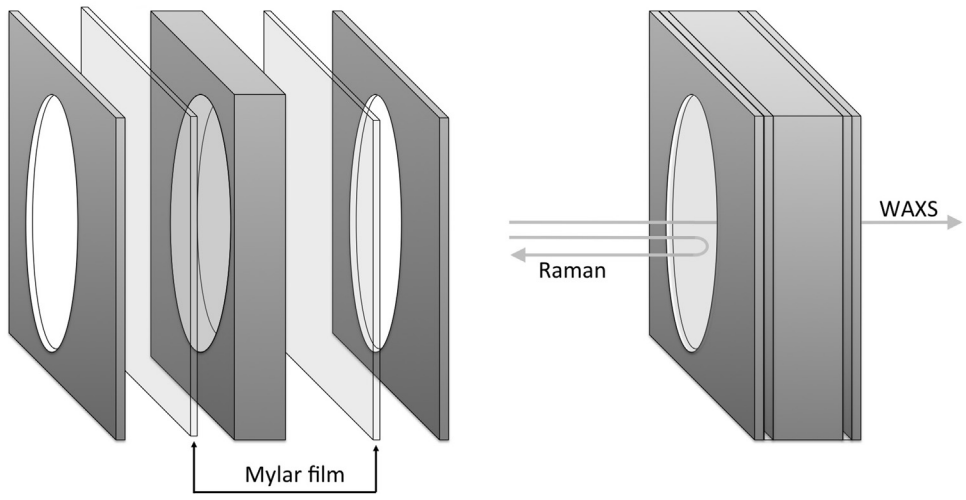

Fig. 1. Sample holder. The 2 mm thick sample (ø 15 mm) is enclosed between two sheets of 6 μm thick Mylar film. Raman-spectroscopy is performed using backscattering geometry and wide angle X-ray scattering is measured with perpendicular transmission geometry.