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Crystallization of acetaminophen on chitosan films blended with different acids ☆

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HIGHLIGHTS

- Acetaminophen crystal grew the fastest on citric chitosan film.
- Acetaminophen crystal grew the slowest on hydrochloric chitosan film.
- Kinetics results are consistent with results of crystal growth rate.
- From simulation, the crystal has highest stability on citric chitosan film.
- There is a strong correlation between enhanced crystallization and higher number of H-bond donor/acceptor doped on the films.

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ABSTRACT

Using polymeric surfaces is a novel way to control crystallization. However, the mechanism is still ambiguous. In the present study, chitosan (CS) films that were doped with different molecules were employed to investigate the impact of surface chemistry on the heterogeneous crystallization behavior of acetaminophen (APAP). Crystal growth rate and crystallization kinetic measurements of APAP on various substrates were performed. Fourier transform infrared spectroscopy was used to probe intermolecular interactions between APAP and CS films. The results were interpreted with the aid of molecular simulations. It was found that substrates with more hydrogen bonding groups that could interact with APAP promoted its crystallization.

1. Introduction

Due to the increasing demand for advanced functional materials, manufacturing products with controllable properties has become crucial for many fields such as semiconductors and pharmaceuticals. One technique to approach to control material properties is through the nucleation and growth of inorganic/organic crystals upon functionalized surfaces.

Via an epitaxy mechanism, previous studies have successfully demonstrated the use of crystalline heterosurfaces to control nucleation and polymorphism of various materials (Hooks et al., 2001; Mitchell et al., 2001; Koma, 1995; Mannsfeld and Fritz, 2005). The lattice match between a surface designed to resemble a particular crystal face and the nucleus reduces the energy barrier of crystallization and promotes nucleation and formation of polymorphs that may be not thermodynamically favored. In addition, the importance of surface morphology has been described in many studies. Ward et al. have shown significant evidence that nucleation on organic molecular single crystals may occur through ledge-directed epitaxy (LDE) (Carter and Ward, 1993). Ying et al. found polymer films with nanoscopic pores can lead to order-of-magnitude faster aspirin nucleation rates compared to films without pores (Diao et al., 2011).

In recent years, polymer-induced heteronucleation (PIHn) has been established as a general approach to control solid form selection and discovery (Price et al., 2005). Examples with small molecules (Grzesiak and Matzger, 2007; López-Mejías et al., 2009), supramolecular complexes (Grzesiak and Matzger, 2007), and proteins (Foroughi et al., 2011) have been demonstrated. Molecular

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functionality of the polymeric films is known to play an important role, but the mechanism is still ambiguous. Chadwick et al. (2012) utilized surfaces with different lattice constants and chemical functionalities to investigate whether epitaxy or surface chemistry is more significant in promoting nucleation of acetaminophen (APAP). Their results showed that nucleation was preferred on substrates whose surface functionality matched with that of APAP even when other substrates exhibited a better lattice match with specific APAP crystal face.

In this study, to better understand the importance of surface functionality on crystal growth, chitosan (CS) films doped with different molecules were formed. In an acidic environment, the free amino group on CS backbone is protonated and carries a strong positive charge, which makes CS soluble in the solution. The acid counter ions are attracted to a position close to the ionized amine groups (Ravi Kumar, 2000) This property of CS was utilized to dope molecules with different chemical structure on the films. CS was dissolved into citric, lactic, acetic, and hydrochloric acid, respectively, to prepare different substrates. Using this method, the interference from surface morphology and structure, which can be prominent when preparing with different polymers, can be minimized. APAP was employed as the crystallizing material and crystal growth rate and crystallization kinetics experiments on different substrates were conducted. Fourier transform infrared spectroscopy (FTIR) was used to investigate the interfacial interaction between the films and APAP. Finally, the results were interpreted with the aid with computational models. This research is expected to contribute to studies of "drugs-on-demand" where the individualized doses are formed on an edible substrate (Hsu Hy et al., 2013; Sandler et al., 2011), providing important information about the drug–substrates interaction.

2. Materials and methods

2.1. Materials

Acetaminophen (APAP) was purchased from Sigma-Aldrich (St. Louis, MO, USA). Chitosan (CS) with a degree of deacetylation of approximately 85% and molecular weight 250 kDa was purchased from Koyo Chemical Co. Ltd. (Tokyo, Japan). Citric acid, L-(+)-lactic acid, glacial acetic acid, and hydrochloric acid were purchased from Sigma-Aldrich (St. Louis, MO, USA). The molecular structures of materials used in this study are shown in Fig. 1.

2.2. Solution of chitosan film preparation

1.5 M hydrochloric, acetic, lactic, and citric acid solutions were prepared. Chitosan was dissolved in the 4 acidic solutions, respectively, with 2% (w/v) concentration.

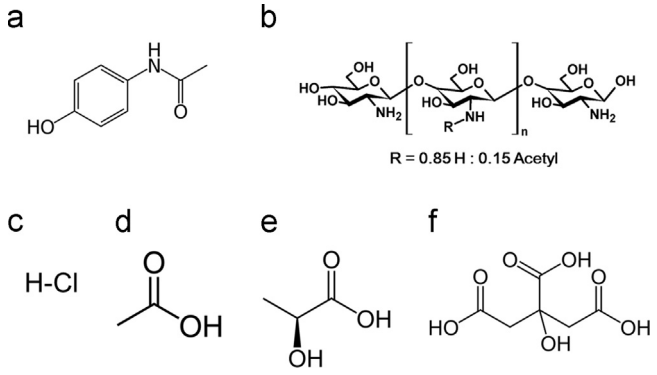

Fig. 1. Chemical structure of (a) acetaminophen, (b) chitosan, (c) hydrochloric acid, (d) acetic acid, (e) lactic acid, and (f) citric acid.

2.3. Growth rate measurements

The chitosan solutions prepared in Section 2.2 were spin-coated on cover slides using a KW-4A spin coater (Chemat Technology Inc., Northridge, CA) at a speed of 2000 rpm, and then dried in a desiccator.

The isothermal crystal growth rate of APAP at 40 °C on different substrates was determined using hot stage microscopy. 3–5 mg of APAP powder was placed between two cover slips, melted at 185 °C and subsequently quenched in liquid nitrogen. The samples were then examined using a polarizing microscope (Nikon Eclipse E600 POL microscope, Nikon Corp, Tokyo, Japan). The temperature of the sample was controlled by a hot stage (Linkam THMS 600, Surrey, UK). As shown in Fig. 2, crystals of APAP grew as spherulites. The pictures of the growing spherulite were taken at constant intervals using time lapse photography. When the radius of the spherulite was plotted against time, it resulted in a linear line, and the slope of which was the growth rate. All experiments were done with three replicas.

2.4. Time-resolved wide-angle X-ray scattering (WAXS)

The time-resolved WAXS experiments were conducted to study crystallization kinetics of APAP on different substrates. The data was collected at the Advanced Photon Source beam station 12-ID-B, Argonne National Laboratory. The WAXS system was equipped with a Pilatus300 detector. The energy of X-ray source was 13.9984 keV ($\lambda = 0.88$ Å), and the distance between the sample to the detector was 455.26 mm. The q (scattering vector) range was $0.9 - 2.12$ Å^{-1}. The WAXS range was calibrated using silver behenate (AgBeh), and the absolute intensity was calibrated using glassy carbon.

400 μl of chitosan solutions prepared in Section 2.2 were poured into small aluminum pans (Tzero DSC sample pans, TA Instruments, New Castle, DE) to prepare chitosan films. After the solution dried, 0.1 mL of molten APAP was deposited on the film using a syringe pump, and quenched in liquid nitrogen. Subsequently, the pan was mounted on a Linkam THMS600 stage to control the crystallization temperature at 40 °C, and the WAXS patterns were collected every 5 s.

The theoretical scattering pattern of the APAP polymorph I was calculated by the crystal structure analysis software, Mercury 3.3. The peaks measured in the WAXS patterns were assigned to reflections for specific crystal directions. Then, the surface chemistry presented on individual facets was determined by cleaving the theoretical crystal structure with the specific crystal direction.

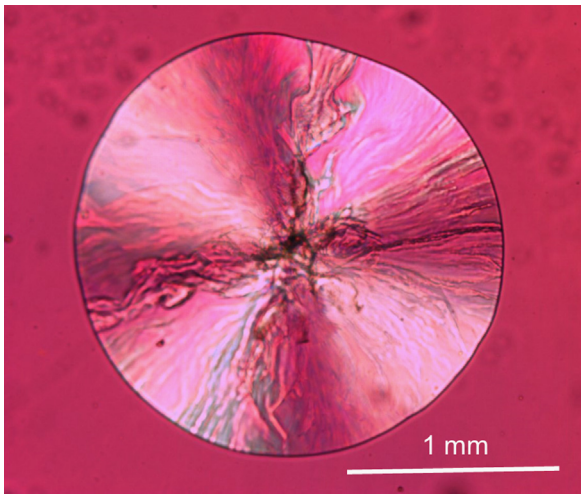

Fig. 2. Photomicrographs of APAP crystal taken at 40 °C.