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Confinement of Amorphous Lactose in Pores Formed Upon Co-Spray Drying With Nanoparticles

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ABSTRACT

This study aims at investigating factors influencing humidity-induced recrystallization of amorphous lactose, produced by co-spray drying with particles of cellulose nanocrystals or sodium montmorillonite. In particular, the focus is on how the nanoparticle shape and surface properties influence the nanometer to micrometer length scale nanofiller arrangement in the nanocomposites and how the arrangements influence the mechanisms involved in the inhibition of the amorphous to crystalline transition. The nanocomposites were produced by co-spray drying. Solid-state transformations were analyzed at 60%-94% relative humidity using X-ray powder diffraction, microcalorimetry, and light microscopy. The recrystallization rate constant for the lactose/cellulose nanocrystals and lactose/sodium montmorillonite nanocomposites was lowered at nanofiller contents higher than 60% and was stable for months at 80% nanofiller. The most likely explanation to these results is spontaneous formations of mesoporous particle networks that the lactose is confined upon co-spray drying at high filler content. Compartmentalization and rigidification of the amorphous lactose proved to be less important mechanisms involved in the stabilization of lactose in the nanocomposites.

Introduction

The growing interest for amorphous systems in the pharmaceutical science is often motivated by its potential to increase dissolution rate of poorly soluble drugs, which is a serious problem indeed in the development of drug delivery systems for new drug molecules.[1] Generally speaking, modifications of the solid state of pharmaceutical materials may strongly influence properties of importance for their functionality. For instance, the tablet binding properties of α-lactose can be improved by introducing amorphous regions in particles by spray drying[2] and the amorphous forms of sugars are utilized to preserve protein structure in freeze- and spray-dried formulations.[3]

The main disadvantage of disordered systems is their thermodynamic instability. The strategies used to stabilize amorphous materials are based on reduction of nucleation and crystal growth rate to a sufficient degree to achieve acceptable storage stability for the amorphous formulation. Two main strategies can be identified aiming at achieving this. One is based on a reduction in molecular mobility of amorphous substances by processing the drug with a polymer to form an amorphous mixture,[4-6] often denoted amorphous solid dispersions, which thereby may slow down both nucleation and crystal growth rate. In the other strategy, the drug substance is loaded in a disordered state into pores of a mesoporous material. In the latter case, the substance becomes confined into domains with smaller dimensions than the nucleus size of the specific substance, which will strongly reduce the nucleation tendency of an amorphous material.[7] The latter has been demonstrated in several reports, such as mesoporous calcium carbonate,[8] mesoporous magnesium aluminosilicate (Neusilin US2),[9-11] chemically modified porous crystalline cellulose,[12] mesoporous magnesium carbonate,[13] and mesoporous silicate.[14-17]

An alternative method to achieve stabilization of amorphous systems is to disperse inert solid particles into the amorphous phase.[18-22] The mechanism for stabilization achieved by solid

Abbreviations used: $A_f(t)$, integral between the heat flow signal and the baseline from a time below the peak to the time t; A_{peak}, total integral of the heat flow signal and the baseline; A200, fumed silica, Aerosil® 200 Pharma; ΔC_p^{Tg}, weight normalized (per gram lactose) change in heat capacity at T_g; CNC, cellulose nanocrystals; cryo-TEM, cryogenic-transmission electron microscopy; DSC, differential scanning calorimetry; DVS, dynamic vapor sorption; $f_{cryst}(t)$, fraction crystallized; k, recrystallization rate constant; MC, microcalorimetry; Na-MMT, sodium montmorillonite; RH, relative humidity; SEM, standard error of mean; t, time; T_g, glass transition temperature; ΔT_g, glass transition temperature width; t_0, induction time to recrystallization; τ^β, stretched relaxation time; XRD, X-ray diffraction.

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particle inclusion is not fully established, but Hellrup et al.[19] have suggested that compartmentalization, rigidification (reduced molecular mobility), and/or intraparticle nanoscale confinement can explain the lowered recrystallization rate constant in spray-dried powders of lactose/fumed silica (A200) nanocomposites.

"Amorphous solid dispersion" is a term often used to denote a system consisting of an amorphous drug whose solid state has been stabilized by incorporation of a stabilizing component, most often a polymer. The term is however not unambiguous, because when discussed in scientific literature these systems often are assumed being solid solutions, that is, the components are assumed being completely mixed on a molecular level. There is however an increasing awareness that phase separations actually do occur in these systems,[23-25] but the impact of phase separations on the stabilizing effect of polymers is poorly understood. Amorphous phase stabilized by inert solid nanoparticles possess similarities with both amorphous solid dispersions, especially phase separated, and mesoporous materials. To mention a few, the surface of the stabilizer[4,8-10,19,26] and domain size[17,19,27,28] are key features in all these systems. Therefore, we believe that there are lessons to be learnt from these systems in how nanocomposites are stabilized, but also that pharmaceutical nanocomposites can be seen as a model for phase separated amorphous solid dispersions.

Lactose is one of the most commonly used excipients in pharmaceutical drug delivery, food technology, and flavoring.[2] It is easily transformed into the amorphous state and is relatively stable at dry conditions, but is rapidly recrystallized at exposure to humidity.[19,29] In this study, lactose was co-spray dried with cellulose nanocrystals (CNC) and sodium montmorillonite (Na-MMT) in the range from 0 to 100 wt% lactose. CNCs, which in the literature are also referred to as cellulose whiskers, are rod-shaped nanoparticles that are produced by acid hydrolysis of the amorphous regions of cellulose raw material, leaving the acid-resistant crystals as a product.[30,31] MMT, the main constituent of bentonite, consists of clay mineral particles made up of turbostratically stacked MMT sheets, about 1-nm thick.[32,33,34] Its layered structure and extremely high surface area enable intercalation of other substances.[34,35]

This study aims at further investigating humidity-induced recrystallization of amorphous lactose co-spray dried with nanofillers. In particular, the focus is on how nanofillers with other shapes and characteristics than A200 will influence the nanometer to micrometer length scale nanofiller arrangement in the nanocomposites and how this arrangement influences the mechanisms involved in the inhibition of the amorphous to crystalline transition.

Materials and Methods

Materials

Alpha-lactose monohydrate (Fluka Analytical; Sigma-Aldrich, Buchs, Germany) was used to prepare 15% (wt/wt) solutions using deionized water. Na-MMT, Cloisite® Na^+ (Na-MMT), a kind gift from BYK Additives & Instruments (Wesel, Germany), and CNCs produced from wood pulp (University of Maine Process Development Center, Orono, ME) were used as nanofillers. The nitrogen absorption of fumed silica, Aerosil® 200 Pharma (A200), a kind gift from Evonik (Essen, Germany), was measured as a reference.

Sample Preparation

Na-MMT (5% wt/wt) was dispersed by sonication in an ultrasonic water bath (Branson 5210, Soest, The Netherlands) for 1 h and then stirred for 18 h in room temperature followed by 4 h in a water bath at 80°C. CNC (5% wt/wt) was dispersed by sonication in water with a VC 750 ultrasound processor equipped with a 13-mm standard probe with threaded end and replaceable tip (Sonics & Materials, Inc., Newtown, CT). The suspension was sonicated for 20 min with 100% amplitude, stirring it in a glass beaker which was cooled in ice water. The suspension was then centrifuged at 615 × *g* for 30 min to remove metal filings from the ultrasound probe. The centrifugations were done in an F0685 rotor in a Beckman Avanti 30 compact centrifuge (Palo Alto, CA). The suspensions were mixed with water and lactose solution (15% wt/wt) that had equilibrated with regard to spontaneous mutarotation, in proportions leading to a combined fraction dry material (nanofillers + lactose) of 6.5% wt/wt and 0%-100% wt/wt Na-MMT or CNC, respectively, in lactose.

The prepared suspensions were co-spray dried with a Mini Spray Dryer B-290 (Büchi, Flawil, Switzerland). A nozzle tip of 0.7 mm and nozzle screw cap of diameter 1.5 mm were used. The spray dryer was operated in an open mode, whereby the inlet drying gas was passed through a filter and a dehumidifier (B-296). A high-performance cyclone was used. During the spray drying, volume flow, nozzle cleaning, inlet temperature, spray air flow, and feed rate were set at 38 m^3/h, level 2, 150°C, 473 L/h, and 4 mL/min, respectively.

Nanofiller Imaging

The cryogenic-Transmission Electron Microscopy (cryo-TEM) specimens of Na-MMT were prepared according to the method described by Bodvik et al.[36] A grid with the mounted sample was rapidly plunged into liquid ethane held at a temperature just above its freezing point (−182°C) and then transferred to the Zeiss Libra 120 TEM (Oberkochen, Germany) using a Gatan CT3500 (Pleasanton, CA) cryo-transfer apparatus.

Nitrogen Gas Adsorption

The sorption properties of the neat spray-dried CNC, Na-MMT, and A200 as reference were analyzed from nitrogen gas sorption isotherms, recorded at 77 K using an ASAP 2020 instrument (Micromeritics, Norcross, GA).

Powder X-Ray Diffraction

The initial crystallinity of the samples was determined with X-ray diffraction (XRD). The XRD was measured using a Bruker D8 Advance coupled 2θ-θ diffractometer with a position sensitive detector, LynxEye (Bruker AXS, Inc., Madison, WI). The samples were irradiated with X-rays generated by a CuKα tube operated at 40 kV and 40 mA with a wavelength of 1.5406 Å. A motorized primary divergence slit with 0.5° opening was used. A step size of 0.02° with an integration time of 2.0 s was used.

Recrystallization Studies

The moisture-induced isothermal (25°C) recrystallization was investigated using a microcalorimeter (MC, 2277 Thermal Activity Monitor; Thermometric AB, Järfälla, Sweden) according to the method described earlier.[37] Between 14 and 16 mg samples were weighted into a 3 mL glass ampoule. A micro test tube containing a saturated salt solution (NaBr 60% relative humidity [RH], NaCl 75% RH, and KNO_3 94% RH) was added to the vial which was sealed. The vial was lowered in the MC and allowed to equilibrate for 30 min before thermal monitoring commenced. Monitoring was stopped once the thermal event had occurred and the signal returned to zero. The samples were analyzed in triplicates.