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Examining chemical structure at the interface between a polymer binder and a pharmaceutical crystal with neutron reflectometry

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ABSTRACT

The mechanical properties of many composites are determined in part by the chemical structure and bonding at the interface between constituents in the microstructure. The study of these interfaces in molecular crystal – polymer composites is difficult using traditional techniques such as electron microscopy or X-ray scattering because of weak or detrimental interactions between the probe and materials. Here, the interface between acetaminophen and a poly(ester urethane) copolymer is analyzed using ellipsometry, infrared spectroscopy, and neutron reflectometry. These materials were chosen for their relevance to pharmaceutical tablets and plastic-bonded explosives. The acetaminophen was shown to dissolve into the polymer coating and creates an interphase region between the two materials; this mixing is almost certainly produced by typical formulation conditions, and likely affects mechanical response of the composite. Additionally, reflectometry shows that plasticizing the polymer alters this interphase region. These techniques can be applied to similar composites to reveal the relation between formulation conditions, constituent interface microstructure characteristics, and bulk mechanical response.

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1. Introduction

The mechanical behavior of compacted granules is of importance for both pharmaceutical compacts and plastic-bonded explosives (PBX). Many pharmaceutical powders used in medicine display poor compaction behavior and consequently are coated with a binder to improve tablet-formation properties [1–4]. The powders are coated in a process called granulation, which can be performed with liquid (wet) or solid (dry) binding material. Dry granulation involves mixing the solid binder with the powder and pressing or rolling into a compacted solid. In wet granulation, a liquid binder is mixed with the powder by spraying, dissolving, or physical mixing. Typical binders are natural or synthetic organics such as acacia, starch, gum, gelatin, and various polymers [5–8]. The resulting granule typically is powder coated with a binder layer of some thickness. Initial powder size and shape, agglomerate size and shape, surface area, moisture content, and various processing parameters all affect the resulting tablet mechanical and chemical properties [9,10]. Tablet durability and mechanical failure is a serious problem with many pharmaceutical drugs, and determining the processing-structure-properties relationship for these powders is an active area of research [11].

Plastic-bonded explosives (PBX) are analogous to compacted pharmaceutical tablets as composites. A typical PBX consists of an explosive molecular organic crystal coated with a polymer binder [12]. Material formulation is similar to wet granulation for pharmaceuticals – the micron-sized explosive crystals are suspended in water and subsequently mixed with a polymer in a solvent. The polymer coats the particle by preferential wetting, displacing the water. For example, the Los Alamos National Laboratory material designated PBX 9501 is formulated by mixing cyclotetramethylene–tetranitramine (HMX) powder with a nitroplasticized statistical copolymer in methyl ethyl ketone (MEK) [13]. The agglomerates, referred to as “molding prills”, can then be pressed into billets suitable for machining. The plasticized binder provides mechanical stability and decreased sensitivity while retaining the detonative properties of HMX [14].

The mechanical properties of PBX and pharmaceutical compacts are defined similarly and display similar failure pathways. Cracking and debonding of the crystals from the binder results in anisotropy within the composite. Such brittle failure, sometimes termed “capping” in pharmaceutical tablet compaction, can cause

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processing and stability problems in these materials. In explosives, such cracks can have serious implications for safety and sensitivity, or the ease of accidental burning or detonation of the explosive [13–16]. Detonative properties in intentional use might also be affected; the effect of such cracks is poorly understood in this regime [17]. Observations of microstructures in these composites that have undergone mechanical failure reveal crack paths that primarily follow the interface between crystals and the binder matrix [13]. Therefore, characterization of the interface between the binder and the crystal is of interest. The properties of the interface depend on surface chemistry and structure [18–20]. Surface energies have been measured for several binders and active ingredients [21], but interfacial structure and chemistry and the effects of the formulation process in this interface have not been studied in detail. Current mechanical and failure models often assume that the interface is sharp, with no intermixing, and that the chemical composition of the polymer at the interface is the same as in the bulk [22,23]. This may be the case for certain formulations but has not been demonstrated previously, and that assumption is of particular importance for composites in which the crystals could be soluble in the polymer solution.

Mechanical properties and failure of both classes of materials have important consequences in terms of product development, durability, and safety. Here, the interfacial properties of a model system are studied systematically with a variety of complementary techniques. The chosen model is acetaminophen crystals coated with PBX 9501 binder. Acetaminophen (paracetamol) is chosen due to its poor compaction properties even in the presence of a binder [1] and is a suitable simulant for HMX. Acetaminophen is similar in crystal structure to HMX, being stable in the monoclinic space group $P2_1/c$ while HMX is referenced to $P2_1/n$, and both materials exhibit polymorphism [24]. Additionally, both crystals are known to be soluble in polar solvents, such as MEK [25], which may lead to diffusion of the crystals into the binder during formulation.

The PBX 9501 binder is a 1:1 mixture of Estane 5703 and a nitroplasticizer. Estane is a commercially available poly(ester urethane) with structure shown in Fig. 1. Estane segregates into hard and soft domains, causing mechanical heterogeneity throughout the polymer [19,26,27]. In the figure, the hard domains are repeated "*m*" units, while the soft domains are repeated "*n*" units. For Estane 5703, *m* and *n* represent typically 20 and 80 percent of the polymer by volume, respectively [19].

We present an ellipsometry, transmission infrared spectroscopy and neutron reflectometry investigation of the chemistry and structure of the acetaminophen – Estane interface with and without the addition of a nitroplasticizer. Ellipsometry was used to determine the optical properties of the samples and film thicknesses. Because acetaminophen is soluble in the MEK–polymer mixture and could wash off during the coating process, infrared spectroscopy was used to verify the presence of acetaminophen in the coated samples. Neutron reflectometry (NR) has been used to study the interfaces and inter-mixing of polymeric systems

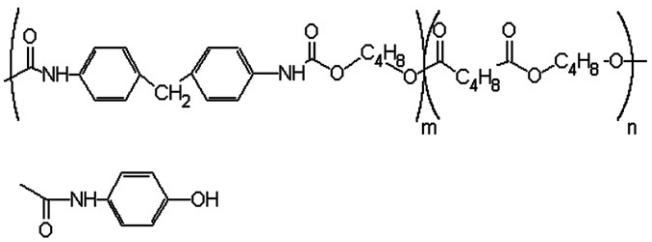

Fig. 1. The chemical structures of Estane (top) and acetaminophen. For Estane 5703, *m* and *n* represent typically 20 and 80 percent of the polymer by volume, respectively [17].

[28–30]. Incident neutrons are scattered from polymer nuclei, and therefore their scattering intensity is a function of the nuclear constituents. Since neutrons are weakly scattered by nuclei, they can probe buried interfaces [31]. Neutron reflectometry has been used previously by Smith et al. to investigate the migration of the nitroplasticizer within Estane 5703 [32]. Smith et al. examined samples of PBX 9501 binder spin-coated onto silicon wafers and found that the nitroplasticizer tended to concentrate at the Si-polymer and polymer–air interfaces. However, the effect of such phase segregation has not previously been experimentally determined at crystal/binder interfaces.

2. Experimental methods

2.1. Sample preparation

One of the historical difficulties in studying compressed agglomerates is the complex microstructure of the composite created in the formulation and pressing process. In order to focus only on the interfacial structure, composite interfaces were simulated with layers of thin films prepared with actual formulation materials. Two materials were used as film substrates, depending on the experiment technique employed. Silicon wafers (Silicon Sense, Inc., Neshua, NH) were used as the substrate for ellipsometry and neutron reflectometry. The Si wafers were cleaned with an acetone wash and atmospheric plasma etching prior to film deposition. For infrared spectroscopy IR-grade potassium bromide (KBr) powder (Acros, Morris Plains, NJ) was pressed into disks and used as an alternative substrate.

Acetaminophen powder (Acros, Morris Plains, NJ) was dissolved in ethanol (Pharmco-AAPER, Brookfield, CT) to form a 7.5 wt% solution. Acetaminophen films were formed by dip-coating the substrates in the solution at 50 mm/min in a humidity-stabilized environment (~25%). Estane 5703 (B. F. Goodrich, Jacksonville, FL) pellets were dissolved in MEK (Fisher Chemical, Pittsburgh, PA) along with the nitroplasticizer to make PBX 9501 binder. The nitroplasticizer (NP) is a eutectic mixture of bis-2,2-dinitropropyl-acetal (BDNPA) and bis-2,2-dinitropropyl-formal (BDNPF), often referred to as BDNPA/F. The plasticizer was manufactured in-house. Estane pellets were also dissolved in MEK without the plasticizer for comparison. The PBX 9501 solution was 1.5% Estane and 1.5% plasticizer by weight, while the Estane comparison solution was 3.0 wt%. Polymer films were dip-coated in a similar manner to the acetaminophen films. All films were allowed to dry at room temperature for at least 48 h prior to any measurements. Several acetaminophen films were then coated with polymer solutions for the representative composite interface samples. Polarized light optical micrographs of a layered acetaminophen–Estane film on Si are presented in Fig. 2. The figure shows a top–down view of the surfaces of the two films, with the polymer partially coating the acetaminophen film on the right in Fig. 2(a) and uncoated acetaminophen visible on the left. Fig. 2(a) highlights the boundary or interface of the two films, and shows the dissolution of the acetaminophen structure forming a gradient of composition at the interface. In Fig. 2(b) the rough polycrystalline surface of the uncoated acetaminophen film is shown in more detail.

2.2. Ellipsometry

Ellipsometry was performed with a variable angle spectroscopic ellipsometer (VASE) (J.A. Woolam Co., Inc, Lincoln, NE). The software was calibrated using a Si wafer with 137 Å of surface oxide. Each sample was scanned in the wavelength range of 3000–10,000 Å, recording data every 100 Å. The samples were aligned at 70° and measured at 65, 70, and 75°. Optical constants