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Polymorph stabilization in processed acetaminophen powders

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ABSTRACT

A novel approach has been developed to stabilize the metastable form II of acetaminophen (APAP) prepared from the melt of micronized and nano-silica coated APAP I. It is suggested that stabilization of form II APAP occurs by pinning via van der Waals-type interactions on low energy defects created by micronization and impinging particles during dry coating in form I APAP, heating to the melt phase, and cooling. The defects are likely to persist into the near-molten isotropic phase due to a permanent memory effect similar to that previously observed in silica-liquid crystal composites and re-crystallize together with form II APAP. Raman spectroscopy, scanning electron microscopy (SEM), powder X-ray diffraction (PXRD), and conventional as well as intrinsic dissolution have been used to characterize the stabilized APAP II obtained. Raman measurements up to 18 months and PXRD data for micronized form II APAP show no indication of APAP I formation. Aged samples of dry-coated APAP II however display Raman features indicative of APAP I within 5 months. PXRD and SEM techniques also detected small fractions of APAP I in dry-coated APAP II. Both micronized APAP II and dry-coated APAP II give rise to a time-dependent background scattering superimposed on the Raman spectra which increases in integrated intensity with time, saturates at 180 and 90 days, respectively, and then decreases in intensity with further aging. The time-dependent scattering background occurs in the stabilized form II APAP samples only after cooling from the melt and is more intense in micronized APAP II compared to dry-coated APAP II. It is assigned to disorder associated with slowly diffusing defects created by micronization and dry coating with impinging nano-silica particles in form I APAP. Intrinsic dissolution profiles for the stabilized APAP II samples showed measureable increases, particularly for micronized APAP II.

1. Introduction

Acetaminophen (APAP) is a widely used analgesic drug which provides an excellent example of an organic polymorphic system since it is known to exist in three forms with different crystalline structures in addition to its structurally disordered amorphous phase. Form I APAP is monoclinic, form II is orthorhombic, and form III is too unstable for its structure to be determined by X-ray methods. The commercial form I is the most stable at room temperature, but it has poor binding and densification properties [1]. Both form I and II can be grown out of the molten state of APAP crystals; however the unstable form III can only be grown from the molten state at specific conditions, for example, between two flat surfaces [2] or by use of a nanoporous host [3]. From the commercial point of view, it is desirable to stabilize the metastable form II because of its enhanced compression behavior and higher intrinsic dissolution rate [4,5] compared to form I. The compression properties of the form I and II polymorphs relate to different molecular packing in the two forms. The molecules form puckered layers in the form I polymorph and flat sheets or layers in form II, as evident from Fig. 1(a) and (b), respectively. Van der Waals intermolecular bonding occurs between the sheets and stronger intermolecular hydrogen bonding exists among the molecules in the sheets. As shown in Fig. 2(b), two types of hydrogen bonding, NH···O and OH···O, which differ significantly in their corresponding bond lengths — 2.91 Å and 2.65 Å in form I and 2.97 Å and 2.72 Å in form II, are observed in APAP crystals [6]. The shorter (stronger) intra-layer hydrogen bonding in form I results in its higher melting point and greater thermodynamic stability relative to the form II [7,8]. Another interesting feature is the higher plastic deformability of form II relative to the form I, which is consistent with its flat layered architecture in contrast to the puckered architecture of the molecules in the form I.

The relative orientation of layers of acetaminophen molecules in each structural type relates to compaction properties and behavior of each phase under pressure. The more planar orientation of the sheets in form II is responsible for its well-developed slip planes and higher plastic deformability [9]. Form I does not deform plastically since the relative orientation of the molecular sheets are in a puckered arrangement. As a result, form I crystallites break by brittle fracture and require

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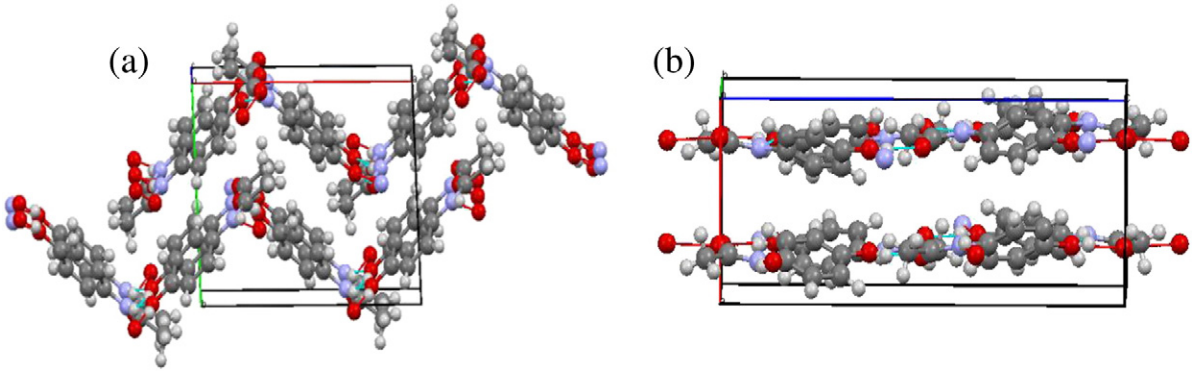

Fig. 1. Crystal unit cells of acetaminophen in: (a) form I, and (b) form II.

binding agents during manufacture to ensure that the tablets remain intact after compression [9].

APAP can form unstable polymorphic crystal structures compared to the drug griseofulvin which has one stable form and no known polymorphs except for its amorphous form. It is of importance to understand how process design can potentially benefit from understanding polymorphic transitions of a crystal. A large body of work has been devoted to APAP's structural behavior during pharmaceutical processing [1,4,5,10,11] since its polymorphism can influence its mechanical properties and dissolution rate. In particular, the more elastic but metastable form II APAP can be compressed directly but it transforms to the stable form I, typically within days. Several techniques have been employed to stabilize form II APAP by compression using stabilization agents, such a gelatin, polyvinylpyrollidone (PVP) or starch [12]. For example, Di Martino et al. prepared the pure orthorhombic form II of APAP for direct compression with stability up to 11 months [11].

Here, two novel approaches to enhance the stability of form II APAP are discussed. In the first method, metastable form II APAP is produced from the melt using micronized form I APAP as the starting material. In the second method, as-received coarse form I APAP is first dry-coated with nano-silica and then form II APAP is generated from it via the molten phase. For the reference samples, form II APAP was also generated using as-received coarse form I APAP that was not dry-coated, (see schematic in Experimental section). In the first method increased surface area in the starting powder is obtained by micronization, and in the second method new interfaces are produced between nano-silica and APAP particles. Form II crystallites nucleated from the melt of these processed form I APAP powders showed enhanced structural stability. Since form II APAP has improved tabletting properties the newly developed stabilization process would have important pharmaceutical implications. Raman spectroscopy and analysis by scanning electron microscopy (SEM), powder X-ray diffraction (PXRD), and conventional and intrinsic dissolution were conducted to characterize the stabilized form II APAP. The PXRD experiments also confirmed Raman data showing that no structural change to the form II occurs when the form I is initially micronized or dry-coated with nano-silica. Raman spectroscopy moreover showed a time-dependent defect-induced scattering background in stabilized APAP II similar to the time-independent scattering observed in cryomilled griseofulvin [13]. The results are discussed here together with a qualitative explanation for the stabilization process.

2. Experimental

Table 1 lists the volume average particle size D_{10}, D_{50} and D_{90} distributions and the commercial sources of the starting raw materials used. The coarse APAP I, for example, has a broad size distribution with a weighted average of about 50% of particles smaller than 29.5 μm (cohesive) and 10% greater than 228.9 μm (non-cohesive). The micronized APAP I contains on a weighted average basis about 90% cohesive particles. In this work, only

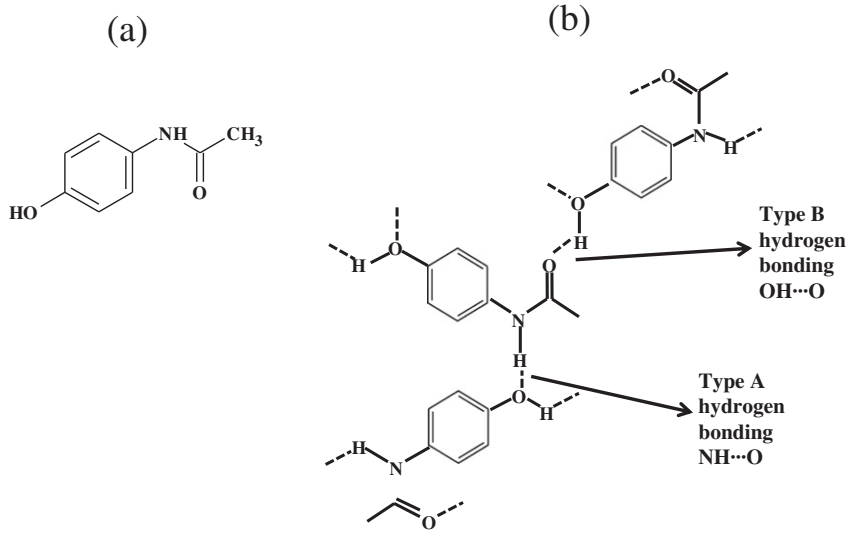

Fig. 2. (a) Molecular structure of acetaminophen, and (b) type A and type B hydrogen bonding between acetaminophen molecules in form I and form II [6].