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Wet milling induced physical and chemical instabilities of naproxen nano-crystalline suspensions

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ABSTRACT

Wet-milling is the most common approach to formulate nano-crystalline suspensions. The effect of high intensity wet-milling on the physical and chemical stability of a poorly soluble drug was investigated. Naproxen (1%, w/v) was suspended in two different stabilizers (*i.e.* HPMC E15 and Tween 80) and stabilizer concentrations (0.2% or 0.6%, w/v) in distilled water. Wet-milling was performed at two different speeds (*i.e.* 3400 rpm and 2000 rpm) for four continuous hours. The milled samples were analyzed for physical and chemical instabilities. Wet-milling of naproxen-HPMC E15 at high milling intensity caused both physical and chemical instabilities as observed by particle size measurement and chemical analysis, respectively. The naproxen-Tween 80 formulations were stable regardless of milling intensity. Naproxen-HPMC E15 wet-milled samples, showed an IR peak shift suggesting strong bond formation or molecular interaction (*i.e.* amorphous phase). In addition, naproxen has a strong interaction with HPMC E15 as determined by MTDSC (*i.e.* melting point depression). The generation of amorphous phase at the naproxen-HPMC E15 crystal surface may be responsible for both aggregation and degradation during wet milling. Decarboxylated naproxen was identified as a degradation product. Milling intensity and/or selection of stabilizer/s are crucial for the stability of nano-crystalline suspensions.

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1. Introduction

Active pharmaceutical ingredients (APIs) can exist in different solid-state forms: crystalline polymorphs, defected crystals and amorphous. These solid-state forms have different energetics that in turns lead to different physical and chemical properties (Cui, 2007; Hancock and Zografi, 1997; Huttenrauch et al., 1985; Bernstein, 2002). Crystalline polymorphs have different packing arrangements of the same molecules and amorphous solids have long-range three-dimensional packing disorders (Bernstein, 2002; Crowley and Zografi, 2002). Conversion from one solid-state to another (*i.e.* polymorph or amorphous transformation) requires passing through a thermodynamic energy barrier and involves a discontinuous change in free energy (Crowley and Zografi, 2002). In addition, crystalline polymorphs have different energy states and the energy of the system increases or decreases depending on the solid-state transformation. Introduction of crystal defects and/or amorphous formation results in an increase in Gibbs' free energy as well as an increase in free volume and thus results in thermodynamic instability.

The number of poorly soluble drug candidates coming out of drug discovery has increased tremendously over the past 20 years or so (Amidon et al., 1995; Kipp, 2004; Lipinski et al., 2001; Lipinski, 2000; Lipinski, 2002). One of the approaches to increase solubility and thus oral bioavailability is to produce nano-crystalline suspensions. Milling (wet and dry) is the most common unit operation utilized to reduce particle size in pharmaceutical manufacturing. Milling induces defects and/or solid-state transformation, which in turn may affect material properties such as solubility and thus may alter bioavailability. There have been many literature reports on solid-state transformation during dry milling (Feng et al., 2008; Otte and Carvajal, 2011; Chamarthy and Pinal, 2008; Wildfong et al., 2006) and also a few reports related to wet milling (Sharma et al., 2009). Wet media milling is widely utilized to form nano-crystalline suspensions to improve the dissolution rate of BCS (biopharmaceutical classification system) class II/IV compounds. High intensity mills and relatively long milling processing times (sometimes up to 24 h) are

Abbreviations: API, active pharmaceutical ingredient; FTIR, Fourier transform infra-red spectroscopy; BCS, biopharmaceutics classification system; HPLC, high performance liquid chromatography; LC–MS, liquid chromatography–mass spectrometer; MTDSC, modulated temperature differential scanning calorimeter.

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generally required (Yang et al., 2008) to produce nano-crystalline suspensions. During this process, mechanical energy is applied (*i.e.* collisions such as drug–drug, drug–chamber and drug–milling beads), which in turn generates strain on the crystal lattice and thus results in particle size reduction. The applied mechanical stress or strain can cause crystal defects and/or formation of amorphous phase. Amorphous regions or crystal defects are undesirable due to their high reactivity, which can lead to further chemical and/or physical instability such as nano-crystal aggregation, drug degradation, unstable formulations and polymorph conversion (Buckton and Darcy, 1999). Solid-state transformation during the wet milling process may depend on the formulation (excipient/stabilizer, pH, buffering species *etc.*) and/or processing (processing time, temperature, milling intensity *etc.*) conditions. Appropriate stabilizer selection for wet milling is crucial for nano-crystalline suspension stability and performance. Not many studies are available which focuses on the effect of different stabilizer on the wet milling of poorly soluble drugs.

In this case study, physical and chemical instabilities of naproxen (a poorly soluble drug) are investigated following low and high wet milling intensity in the presence of HPMC-E15 (polymeric stabilizer) or Tween-80 (small molecular surfactant) (Table 1). Naproxen is categorized as a non-steroidal anti-inflammatory drug (NSAIDs). HPMC-E15 and Tween 80 are non-ionic stabilizers widely utilized for nano-crystalline suspension formulations. The influence of wet milling (*i.e.* Netzsch media mill) intensities in the presence of two different excipients and concentrations were evaluated.

2. Materials

Crystalline naproxen was purchased from Fagron (St. Paul, Minnesota). HPMC E15 was purchased from Dow chemical company (Midland, MI). Tween 80 and LC–MS grade solvents (ACROS chemicals) were purchased from Fisher Scientific (Pittsburgh, PA). Hermetic pans and lids were purchased from TA instruments.

3. Methods

3.1. Wet media milling

Briefly, naproxen (1%, w/v) was suspended in the required amount of stabilizer solution in distilled water (either 0.2%, w/v or 0.6%, w/v) using a magnetic stirrer. The prepared macro-suspension was milled using a Netzsch® media mill (NETZSCH, Blandon, PA) at different processing conditions *i.e.* milling intensity. The chamber and milling media have a coating of zirconium oxide to provide high-energy efficient milling and low contamination from the metal parts during the attrition process. The macro-suspensions were milled either with HPMC E15 or Tween 80 at two different drug-to-stabilizer ratios *i.e.* 1:0.2 and 1:0.6. The concentration of the drug was kept constant at 10 mg/ml in macro-suspensions and milled for 4 h either at low (*i.e.* 2000 rpm) or high (*i.e.* 3400 rpm) milling intensity. The milled samples were collected every 15 min and analyzed for change in particle size and chemical degradation.

3.2. Dry milling

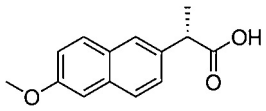
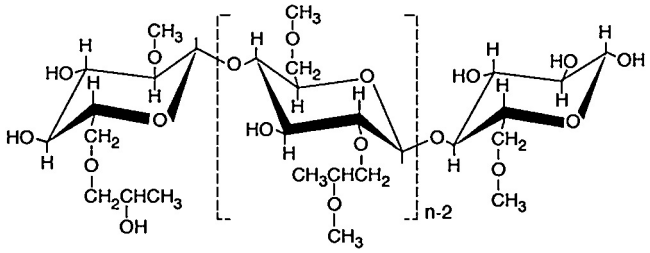
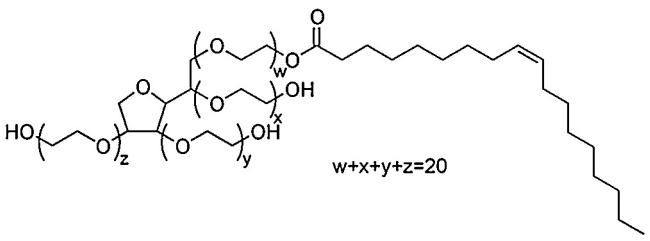
3.2.1. Ball-milling

A Retsch MM330 ball mill (RETSCH, Haan, Germany) was utilized. Briefly, 3 g of sample (*i.e.* mixtures of naproxen-HPMC E15 at 1:0.6 ratio) was filled into the milling chamber. The sample was milled for 2 h (30 milling min and 10 min wait time) at a frequency of 20/s. The milled samples were analyzed for chemical degradation, powder X-ray diffraction and FTIR.

3.2.2. Cryo-milling

A Freezer mill (SPEX SamplePrep, Metuchen, NJ) 6750 was utilized. Approximately 3 g of sample (*i.e.* naproxen-HPMC E15 at 1:0.6 ratio) was filled into the milling chamber. Liquid nitrogen was used as a cryogenic liquid. The milling chamber and the instrument were pre-chilled with the liquid nitrogen before milling processing. The sample was processed for 2 h (2 min

Table 1
Chemical structure of the drug and stabilizers.

Drug and Stabilizer	Structure
Naproxen	
HPMC E15 (Methocel E15 premium LV)	
Tween 80 (Polysorbate 80)	

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