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Research Paper

Changes in the solid state of anhydrous and hydrated forms of sodium naproxen under different grinding and environmental conditions: Evidence of the formation of new hydrated forms

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ABSTRACT

The aim of the present work was to investigate the solid state change of the anhydrous and hydrate solid forms of sodium naproxen under different grinding and environmental conditions. Grinding was carried out manually in a mortar under the following conditions: at room temperature under air atmosphere (Method A), in the presence of liquid nitrogen under air atmosphere (Method B), at room temperature under nitrogen atmosphere (Method C), and in the presence of liquid nitrogen under nitrogen atmosphere (Method D). Among the hydrates, the following forms were used: a dihydrate form (DSN) obtained by exposing the anhydrous form at 55% RH; a dihydrate form (CSN) obtained by crystallizing sodium naproxen from water; the tetrahydrate form (TSN) obtained by exposing the anhydrous form at 75% RH. The metastable monohydrate form (MSN), previously described in the literature, was not used because of its high physical instability.

The chemical stability during grinding was firstly assessed and proven by HPLC. Modification of the particle size and shape, and changes in the solid state under different grinding methods were evaluated by scanning electron microscopy, and X-ray powder diffractometry and thermogravimetry, respectively. The study demonstrated the strong influence of starting form, grinding and environmental conditions on particle size, shape and solid state of recovered sodium naproxen forms. In particular, it was demonstrated that in the absence of liquid nitrogen (Methods A and C), either at air or at nitrogen atmosphere, the monohydrate form (MSN) was obtained from any hydrates, meaning that these grinding conditions favored the dehydration of superior hydrates. The grinding process carried out in the presence of liquid nitrogen (Method B) led to further hydration of the starting materials: new hydrate forms were identified as one pentahydrate form and one hexahydrate form. The hydration was caused by the condensation of the atmospheric water on sodium naproxen particles by liquid nitrogen and by the grinding forces that created a close contact between water and drug. The simultaneous disruption of the crystals, occurring during grinding, and their close contact with water molecules promoted the conversion in higher hydrates. Under the Method D, it was possible to highlight a certain tendency to hydration probably due to a rearrangement of water already present into the hydrates, but results were substantially different from Method B. Thus, summarizing, the different SN forms behave differently under different grinding and environmental conditions.

1. Introduction

Sodium naproxen (SN), a non-steroidal anti-inflammatory drug (NSAID), is used in the treatment of rheumatoid and arthritic diseases. It exists as anhydrous form (anhydrous sodium naproxen, ASN) [1,2], which is the commercial one. Crystallizing ASN from water yields a dihydrate form (crystallized sodium naproxen – CSN) [1,3–5], while the desiccation of the CSN for 2 days at 0% relative humidity (RH) gives an unstable monohydrate form of SN [1,4,5] (MSN). Exposure of ASN to different relative humidities gives rise to two hydrate forms: a dihydrate form of sodium naproxen was formed by exposing the powder to a RH higher than 55% [3–5], while the tetrahydrate one was formed at RH > 76% [6,7]. The hydration degree of SN strongly influences its

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physicochemical and technological properties [8–11], with enormous repercussions on the solid dosage form characteristics and shelf life. This is why it is necessary to carefully investigate possible solid state transitions that may occur intentionally or unintentionally during technological processes. Among the most frequently used technological processes, grinding is applied in the industrial pharmacy to mainly improve drug dissolution rate and the homogeneous dispersion of a drug into a mix, for example for direct compression. Classically, industrial grinding is carried out by using different types of millers characterized by different properties and characteristics. They operate as closed apparatus to respect the GMP requirements, and generally powders are exposed to controlled atmosphere (20 °C and 40–60% RH) or to inert gas for materials sensitive to oxidation.

More recently, grinding has been associated with the use of cryogenic liquids in order to improve the fragility of solid material and increase their propensity to particle comminution. Actually, cryogenic properties of liquids such as liquid nitrogen are quite attractive to break the materials because the substances usually become brittle under such cold condition [12].

Ultra cryo-milling was efficiently applied to phenytoin, ibuprofen and salbutamol sulfate. Each drug was suspended in liquid nitrogen together with small spherical zirconia balls in a special ultra-cryo-milling apparatus [13], leading to an efficacious particle size reduction.

It must be noted that ultra cryo-milling may favor the transition from the crystalline state of a drug to its completely amorphous state: the conversion of glibenclamide from the crystalline to a completely amorphous state after 3 h grinding under ultra cryo-milling conditions was described [14].

In a previous work, a very simple grinding technique, the laboratory scale ultra cryo-milling, consisting of grinding powders under nitrogen liquid, was described. In particular, grinding glibenclamide under liquid nitrogen for 40 min permitted the recovery of nanocrystals with a consequent important improvement in particle dissolution [15]. Also indomethacin underwent the same laboratory scale ultra cryo-milling and nanocrystals were obtained. A significant improvement in particle dissolution was demonstrated [16]. In both cases, a tendency to the reduction of solid crystallinity degree was observed.

In the present study, the authors aimed at elucidating the effect of sodium naproxen starting form, different grinding and environmental conditions on the particle size, shape and solid state of the following sodium naproxen forms:

a. the commercial anhydrous sodium naproxen (ASN);
b. the dihydrate sodium naproxen (DSN), obtained by exposing the ASN at 55% RH [3];
c. the dihydrate sodium naproxen (CSN), obtained by crystallizing sodium naproxen from water [1,3];
d. the tetrahydrate form (TSN), obtained by exposing the ASN at 75% RH [6].

Four different grinding conditions were then used:

Method A: Grinding at room temperature under air atmosphere,
Method B: Grinding in the presence of liquid nitrogen under air atmosphere,
Method C: Grinding at room temperature under nitrogen atmosphere,
Method D: Grinding in the presence of liquid nitrogen under nitrogen atmosphere.

2. Materials and methods

2.1. Materials

Anhydrous sodium naproxen (ASN) BP was kindly supplied by ACRAF (Ancona, Italy). From ASN, the following three different hydrate forms of sodium naproxen were prepared and used:

a. one dihydrate form (CSN) was recovered by crystallizing ASN from water [1,3];
b. a second dihydrate form (DSN) was obtained by exposing the ASN at a RH of 55 ± 2% [3];
c. the tetrahydrate form (TSN) was obtained by exposing the ASN at a RH of 75 ± 2% [6].

Before use, all the hydrates were analyzed by X-ray Powder Diffractometry (XRPD) to study their crystalline form by comparing their powder patterns with those of known forms. The analysis confirmed the compliance of all the powders with the crystalline forms previously characterized.

Liquid nitrogen and gaseous nitrogen were supplied by Air Liquide (Milan, Italy).

2.2. Grinding procedure

The ultra cryo-milling technique consisted in immersing 1 g of SN powders in liquid nitrogen and grinding it manually in a mortar of 500 mL volume with a pestle for different time intervals (15, 30, 45, and 60 min), refilling nitrogen when evaporated (Methods B and D). The same grinding procedure was applied to all the powders at room temperature. Grinding was carried out either under air atmosphere (60.0 ± 1.0% RH) or under nitrogen atmosphere, realized by saturating the closed mortar with gaseous nitrogen (5.0 ± 1.0% RH).

Summarizing, four different grinding conditions were used:

Method A: Grinding at room temperature under air atmosphere (60.0 ± 1.0% RH),
Method B: Grinding in the presence of liquid nitrogen under air atmosphere (60.0 ± 1.0% RH),
Method C: Grinding at room temperature under nitrogen atmosphere (5.0 ± 1.0% RH),
Method D: Grinding in the presence of liquid nitrogen under nitrogen atmosphere (5.0 ± 1.0% RH).

All the grinding procedures were repeated three times to assess the repeatability of results. No batch to batch variability was observed and results were always highly reproducible.

2.3. Physico-chemical characterization

The chemical stability of NS was determined by a HPLC 1100 (Agilent Technologies, Santa Clara, CA, USA) equipped with a detector VWD 1200 (Agilent Technologies). The separation was performed on a reversed-phase column (Purospher C18 4.6 9 125 mm i.d., 5 lm, Merck, Milan, Italy) using a mobile phase consisting of methanol:sodium acetate buffer in ratio of 60:40, v/v pH 3.6 adjusted with glacial acetic acid. Before use, the mobile phase was mixed, degassed on an ultrasonic bath and then filtered by a Millipore vacuum filter system equipped with a 0.45 μm filter. The detection wavelength was 266 nm. Samples (2 μL) were injected manually at the concentration of 3.0 mg/mL in methanol. The flow rate was 1 mL/min. The retention time for the peak of sodium naproxen was 7.50 min.