International Journal of Pharmaceutics 515 (2016) 416–421

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

The effect of structurally related impurities on crystallinity reduction of sulfamethazine by grinding

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ARTICLE INFO

Article history:
Received 9 May 2016
Received in revised form 20 September 2016
Accepted 24 September 2016
Available online 5 October 2016

Keywords:
Sulfamethazine
Crystallinity reduction
Grinding
Effect of impurity
Raman spectroscopy

ABSTRACT

In this study, the effect of structurally related impurities on crystallinity reduction of sulfamethazine by grinding was evaluated. The crystallinity of sulfamethazine was not decreased when it was ground alone. However, when structurally related impurities with sulfonamide derivatives were blended, the crystallinity of sulfamethazine was decreased by grinding. Other materials without a sulfonamide moiety showed no such effect. The Raman spectra of sulfamethazine demonstrated that there was a difference between its crystalline and amorphous states within its sulfonamide structure. It was suggested that the sulfonamide structure of the impurities was important in causing the inhibition of recrystallization of sulfamethazine during grinding.

1. Introduction

In the manufacture of pharmaceuticals, it is of great importance to assure the efficacy and stability of a pharmaceutical drug product during its storage period (Yonemochi et al., 1999). To achieve this, the physical properties of an active pharmaceutical ingredient (API) should be characterized precisely. Crystallinity is one of the important physical characteristics of an API, which is considered to affect the physicochemical properties such as chemical stability (Otsuka and Kaneniwa, 1990; Kitamura et al., 1989; Matsunaga et al., 1996; Adrjanowicz et al., 2011), hygroscopicity (Ohta et al., 2000), and solubility (Mah et al., 2015). Hence, it is important to control the crystallinity of an API for the development of a pharmaceutical drug product during its manufacturing procedure and storage period. However, we sometimes witness a “lot-to-lot variation” of the physicochemical properties of an API and drug product within the research and development field. One of the possible factors affecting this “lot-to-lot variation” is supposed to be the impurity profile of an API.

APIs usually contain some minor component referred to as an “impurity”. The amounts of impurities, such as heavy metals, moisture, residual organic solvents and organic substances, are rigorously evaluated in the manufacturing process of an API and the drug product. However, these impurity profiles can vary depending on the manufacturer or the process scheme. The synthetic procedure in the stage of research and development is usually immature, so we commonly experience handling various APIs with different impurity profiles. Especially, organic substances, such as process intermediates, by-products and degradation products, are structurally related to the API compound, but their physicochemical properties are thought to show quite a great diversity, which is dependent upon each impurity compound. It is possible for the content of organic impurities to be around as much as several percent of API. It may be possible that this affects the physical properties of the API. For instance, we often experience variations in the behavior of the crystallization process of an API depending on the material used. The reason for such variation is also considered to existence of active impurity compound to inhibit the crystallization and that the deference in their impurity profiles was suspected. As described, the behavior of crystallization and amorphization may be affected by the existence of structurally related impurities.

Currently, however, reports relating the effects of impurities on the behavior of crystallization or amorphization are quite rare. Needham et al. reported that estradiol crystallization affected the sustained release drug product for an implant delivery system (Needham et al., 1992). And they pointed to the possibility that the difference in the impurity profile could be the cause of the crystallization occurrence. Yu et al. determined the glass properties of D-mannitol, which has a highly crystallizing tendency, using

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http://dx.doi.org/10.1016/j.ijpharm.2016.09.069
0378-5173/

sorbitol as an impurity to retard the crystallization tendency in thermal analysis (Yu et al., 1998). Yet, the limited number of reports does not answer what the magnitude of the effects of impurities might be.

The purpose of our research is to clarify the effects of structurally related impurities on the amorphization and crystallization kinetics of a drug substance. In this study, sulfamethazine was used as the model drug substance. And commercially available, structurally related compounds were used as the virtual impurities of sulfamethazine by manual incorporation. Effects of these impurities on the crystallinity of sulfamethazine during grinding were studied.

2. Materials and methods

2.1. Materials

Sulfamethazine, which was used as the main compound in this study, was purchased from Sigma-Aldrich (US). Purity of the sulfamethazine was confirmed as being about 99.3% in HPLC area percent. The compounds used as the virtual impurities for sulfamethazine were as follows. Sulfamerazine (SMR) was purchased from Sigma-Aldrich. Sulfanilamide (SNA), sulfadiazine (SDA), sulfamonomethoxine (SMM) and sulfadimethoxine (SDM), 2-amino-4,6-dimethylpyrimidine (ADP) and 4,6-dimethylpyrimidine (DMP) were purchased from Tokyo Chemical Industries Ltd. (Japan). Their chemical structures are shown in Fig. 1. They were used without further purification. Polyvinylpirrolidone K30 (PVP) was purchased from BASF Japan Ltd. (Japan). Mannitol was from Merck KGaA (Germany). Microcrystalline cellulose, Ceolus PH101 (MCC) was obtained from Asahi Kasei Chemicals Co., Ltd. (Japan). The physicochemical properties of materials are shown in Table 1.

2.2. Grinding of sulfamethazine

About 100 mg of sulfamethazine alone or a physical mixture of sulfamethazine with other compounds and one zirconia ball (φ 5.0 mm) was placed in a 2-mL polypropylene tube. Grinding was performed using a mixer-mill, MM-400 (Retsch GmbH, Germany). Shaking was operated with 25 Hz as the frequency. The experiment was performed all at once in a laboratory in which the temperature was controlled by a usual air conditioner. Therefore, other variables for the grinding procedure affecting the grinding efficacy were considered as same for all samples. Small amounts of the ground samples were periodically taken out during grinding and used for powder X-ray diffraction analysis.

2.3. Powder X-ray diffraction

Powder X-ray diffraction patterns were corrected using an X-ray diffractometer, RINT TTR-III (Rigaku Corporation, Japan), equipped with Cu radiation of wavelength 1.54 Å. The instrument was operated at 50 kV with a currency of 300 mA. The relative crystallinity of ground samples was calculated from the ratio of the diffraction peak areas after removal of the background to the total areas of the diffraction patterns. Integral analysis version 6.0 (Rigaku Corporation) was used for the calculations.

2.4. Differential scanning calorimetry (DSC)

DSC was measured for before and after grinding for each sample using DSC Q2000 (TA Instrument Inc.) and about 4 mg of each sample was embedded in an aluminum pan without lid. DSC curve was obtained with a heating rate was 10 °C/min from 20 °C to 210 °C above its melting point.

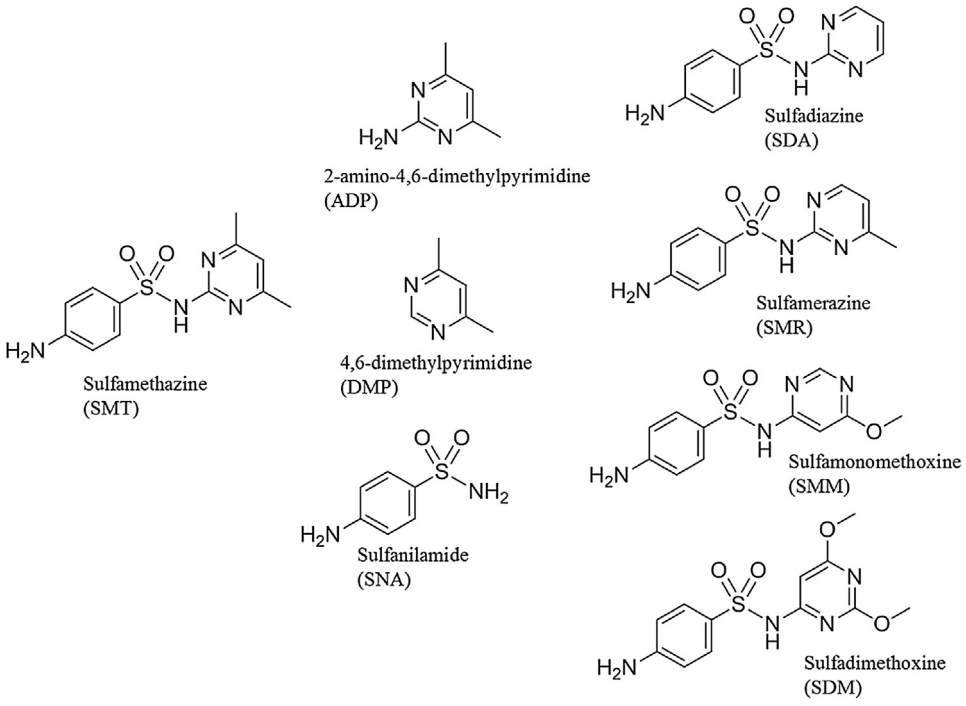

Fig. 1. Chemical structures of materials used in this study.