Advanced Powder Technology xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Advanced Powder Technology

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

Original Research Paper

Effect of organic solvent vapors on the crystallization rate of amorphous indomethacin

Naoto Hirota [a], Yusuke Hattori [b,1], Makoto Otsuka [b,*]

[a] Faculty of Pharmacy, Musashino University, Nishi-Tokyo, Japan
[b] Research Institute of Pharmaceutical Sciences, Musashino University, Nishi-Tokyo, Japan

ARTICLE INFO

Article history:
Received 15 July 2015
Received in revised form 16 October 2015
Accepted 19 October 2015
Available online xxxx

Keywords:
Amorphous indomethacin
Polymorphism
Phase transformation
Solvent vapor
Crystallization rate

ABSTRACT

Many pharmaceutical bulk powders are known to have various solid states, such as polymorphic forms, solvates, and amorphous forms. The amorphous form is known to be recrystallized by absorbing various solvent vapors depending on the chemical properties. It is possible to perform a search for polymorphs of drugs by utilizing this property. In this study, the solvent properties of solvent vapor by using amorphous indomethacin (A-IMC) as a model drug were measured using X-ray diffraction (XRD) in terms of the effect on crystallization. A-IMC was exposed for 2 h at 30 °C in a sealed container with normal alcohols with different carbon number (ethanol, 1-propanol, 1-butanol, 1-pentanol, and 1-octanol), and changed to the stable crystalline form (γ-IMC) and the metastable form (α-IMC). Exposure to alcohol vapor with a long alkyl chain provided a high yield of the γ-form and a long induction period. It was considered that the rapid generation of crystal nuclei was performed by increasing the polarity of alcohol.

1. Introduction

Many pharmaceutical bulk powders are known to have various solid states, such as polymorphic forms, solvates, and amorphous forms [1]. The chemical and physical stability and dissolution rate of the crystalline form of pharmaceuticals are significantly affected by storage conditions depending on the temperature and humidity. A change in the polymorphic form of poorly water-soluble bulk drug powder during storage may lead to changes in the solubility and dissolution rate because the solid stability depends on the chemical potential of the solid state pharmaceutical. Therefore, the crystallization process of meta-stable bulk drug powder is important for the quality assurance of drugs depending on the bioavailability of the pharmaceutical formulation [2–5]. On the other hand, the amorphous state is also an effective solid state as a bulk powder of pharmaceuticals; it is a state lacking regularity with a wide range of orders and orientations of the molecule [6]. An amorphous solid has great influence on the physicochemical properties and stability, with high chemical potential and molecular mobility compared with the crystalline solid [7]. Since amorphous solid with high chemical potential is more easily soluble in water than the crystalline solid, poorly water-soluble pharmaceuticals have been subjected to many examinations to prepare the amorphous state, with the expectation of improving the dissolution rate in water. However, the amorphous state has the potential to change to a more stable state, namely the crystalline state, by adsorbing various solvent vapors during the storage of pharmaceuticals [8]. Therefore, control of the crystallization process for obtaining a high yield of polymorphic forms has been desired in order to obtain the stable states to the solubility and bioavailability of pharmaceuticals through transition to a crystalline state from an amorphous one [9].

Recently, a search for crystalline polymorphs of active pharmaceutical ingredients was performed by exposing amorphous solids to various types and compositions of organic solvent vapor [10]. However, quantitative and kinetic studies of solvent vapor-mediated crystallization have not yet been reported. Therefore, in order to create a quantitative method to evaluate the crystallization, the crystallization process was kinetically investigated by exposing the amorphous solid to various kinds of organic solvent vapors. For clarification of the crystallization mechanisms upon exposure to a solvent vapor, it may be useful to investigate the relationship between the solvent vapor properties and the crystallization kinetics. In this study, indomethacin (IMC) is used as a

* Corresponding author at: Research Institute of Pharmaceutical Sciences, Faculty of Pharmacy, Musashino University, 1-1-20 Shinmachi, Nishi-Tokyo 202-8585, Japan. Tel./fax: +81 424 68 8658.
E-mail address: motsuka@musashino-u.ac.jp (M. Otsuka).
[1] Equal first author.

http://dx.doi.org/10.1016/j.apt.2015.10.010
0921-8831/

model drug, which has two polymorphic forms of stable and metastable crystalline forms [11]. The amorphous IMC is obtained by a melt quenching method. The crystallization process of the amorphous solid is investigated by X-ray diffraction measurement upon exposure to various kinds of alcohol vapor with different numbers of carbon atoms under constant condition.

2. Material and methods

2.1. Materials

A bulk sample of indomethacin (γ-IMC) was purchased from Tokyo Chemical Industry (Tokyo, Japan). High-purity solvents (ethanol, 1-propanol, 1-butanol, 1-pentanol, and 1-octanol) were purchased from Wako Pure Chemical Industries (Osaka). Solvent vapor pressure of ethanol, 1-propanol, 1-butanol, 1-pentanol and 1-octanol at 20 °C were 5.95, 1.99, 0.58, 0.20, and 0.020 kPa, respectively [12].

2.2. Preparation of the samples

Metastable crystalline form (α-IMC): The bulk powder (5 g) of γ-IMC was dissolved in ethanol (100 mL) at 50 °C. After cooling down to room temperature, water was added to the solution until a precipitate was formed. The precipitate was collected by filtering out the solvent and dried at room temperature under a vacuum.

Amorphous indomethacin (A-IMC): The bulk powder (5 g) of γ-IMC was put into a stainless steel tube and melted at 160 °C for 30 min. Liquid nitrogen was poured into the tube to quench it. After the liquid nitrogen was evaporated, it was brought to room temperature to avoid moisture absorption under a vacuum. Then, the resulting solid was pulverized in an agate mortar.

2.3. Methods

2.3.1. Powder X-ray diffraction measurement (PXRD)

Powder X-ray diffraction patterns of solid samples were obtained using a RINT2100-Ultima III (Rigaku, Tokyo, Japan). The measurement conditions were as follows: target, Cu; filter, Ni; voltage, 40 kV; current, 40 mA; temperature, 30 °C; receiving slit, 0.3 mm scan range, 7.5–12.5° (2θ); step size, 0.02°; and heating rate, 1 °C/min. A-IMC powder at 5 mg was loaded on an aluminum sample holder in an XRD/DSC measurement chamber with a volume of 50 mL at 30 °C. The PXRD measurements were performed for a sample with exposure to bubbling air in a variety of alcohol-based solvents at 100 mL/min and 25 °C. The amorphous solid was exposed to a saturated organic solvent vapor of ethanol, 1-propanol, 1-butanol, 1-pentanol, or 1-octanol for 2 h at 30 °C. The XRD profiles of the A-IMC were measured at pre-determined intervals during storage passing through organic vapor. The resulting XRD profile was carried out the quantitative analysis by JADE 6 (Rigaku, Tokyo, Japan), and the peak area of each crystal forms were separated by performing fitting based on pseudo-Voigt function after removing the background [13]. Miller index of diffraction peaks of the α- and γ-forms were evaluated by DASH software [14] as shown in Fig. 1.

2.3.2. Differential scanning calorimetry (DSC)

Differential scanning calorimetry profiles of A-IMC were obtained using a DSC 8230 (Rigaku, Tokyo, Japan). A-IMC powder at 9 mg was crimped in aluminum pan. The profile conditions were heated from 25 to 170 °C at a rate of 2 °C/min.

2.3.3. Crystallization kinetics of A-IMC

The crystallization kinetics of amorphous solid was analyzed based on the solid-state reaction models [15,16]. Kaneniwa et al. [16] reported that changes to α-IMC and γ-IMC from A-IMC were analyzed using Eq. (1). They assumed a two-dimensional interface rate-determining model as follows:

$$2[1-(1-x)]^{1/2} = k(t-t_0) \tag{1}$$

where x is the fraction of the crystalline part at time t, k is the crystallization rate constant, and t_0 is the time of the induction period for crystallization. The α-IMC and γ-IMC crystalline contents (x_α and x_γ) in the samples were separated quantitatively from the characteristic peaks at $2\theta = 8.5°$ and 11.8° in the XRD profiles by a curve fitting software (JADE 6) based on the pseudo-Voigt function. The crystallization rate constant is determined from the slope of the plot obtained from Eq. (1), and the induction period for nucleation is determined from the x-intercept of the plot. Since the nucleus formation rate follows first-order kinetics, the nucleation rate constant, NR, is determined from the reciprocal of the induction period by the following equation [17]:

$$NR = \frac{\ln[N_c]}{t_0} \tag{2}$$

where N_c is a nucleus concentration required to start crystallization. Nuclear density required to initiate crystallization was calculated assuming obtained by a constant amount of the solvent.

3. Results and discussion

3.1. Crystal form determination by XRD and DSC measurements

The steady-state XRD profiles of the crystallized solids via exposure to various solvent vapors are shown in Fig. 1. When exposed to a solvent, it is known that the peak of the XRD is shifted to a higher angle 2θ of diffraction [18]. The solid exposed to ethanol vapor displayed characteristic diffraction peaks corresponding to the α-IMC. In contrast, that of 1-octanol showed peaks due to γ-IMC. Upon exposure to the lower molecular-weight solvent vapor, the XRD measurements denoted a tendency to increase α-IMC content, and the content of γ-IMC increased with exposure to the longer-chain alcohol vapor. But XRD cannot determine the amorphous state in detail. Accordingly it was performed to confirm the amorphous state by using DSC.

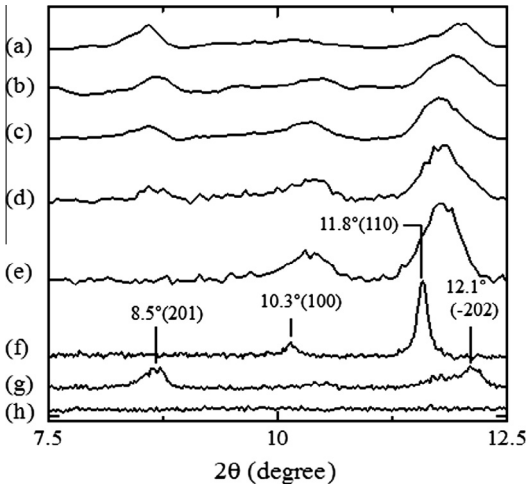

Fig. 1. XRD profiles of amorphous indomethacin after exposure to various kinds of organic solvent vapor for 2 h at 30 °C. (a) Ethanol; (b) 1-propanol; (c) 1-butanol; (d) 1-pentanol; (e) l-octanol; (f) stable γ-form; (g) metastable α-form; (h) amorphous.

Please cite this article in press as: N. Hirota et al., Effect of organic solvent vapors on the crystallization rate of amorphous indomethacin, Advanced Powder Technology (2015), http://dx.doi.org/10.1016/j.apt.2015.10.010