J. of Supercritical Fluids 108 (2016) 96–103

Contents lists available at ScienceDirect

The Journal of Supercritical Fluids

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

Modification of indomethacin crystals using supercritical and aqueous antisolvent crystallizations

Dae-Chul Kim, Sang-Do Yeo*

Department of Chemical Engineering, Kyungpook National University, Daegu 702-701, Republic of Korea

ARTICLE INFO

Article history:
Received 13 July 2015
Received in revised form 30 October 2015
Accepted 31 October 2015
Available online 10 November 2015

Keywords:
Antisolvent
Aspect ratio
Crystallization
Habit-modifying agent
Indomethacin

ABSTRACT

Indomethacin, a non-steroidal anti-inflammatory medicine, was crystallized from an organic solution using supercritical and aqueous antisolvents. Carbon dioxide and water were used as antisolvents for the crystallization of indomethacin in acetone. When the drug solution and antisolvent were brought into contact, solid crystals precipitated. Sebacic acid and urea were employed as habit-modifying agents in the supercritical and aqueous antisolvent experiments, respectively. As the drug concentration in acetone increased from 0.01 to 0.07 g/mL, the average particle size of indomethacin decreased from 26.0 to 7.0 μm (supercritical) and from 2.3 to 0.7 μm (aqueous). Increasing the temperature by 20 °C increased the particle size by 97 (supercritical) and 28% (aqueous). The aspect ratio of the indomethacin crystals decreased from 13 to 2 when habit-modifying agents were added to the system (up to 0.851 wt%). Crystals obtained from the supercritical antisolvent experiments were of the α + γ-form, while the crystals produced from the aqueous antisolvent experiments existed in the α-form. The use of habit-modifying agents did not influence the DSC or XRD profiles of the original indomethacin crystals.

1. Introduction

The modification of the crystal properties of a drug compound is an important challenge in the crystallization of pharmaceutical products [1]. Crystal properties such as particle size, crystal shape, crystalline structure and thermal properties are directly related to drug performance. Indeed, the external morphology and internal structure of the crystalline particles of a pharmaceutical compound control its bioavailability, solubility, dissolution rate, physical stability, filterability and flow behavior [2]. Therefore, researchers try to explore different methodologies to modify crystal properties by changing process conditions in various types of crystallization techniques such as cooling, evaporative and antisolvent crystallizations.

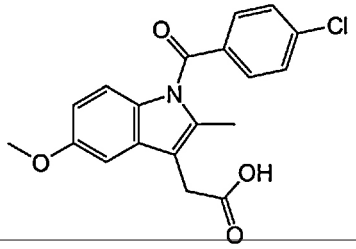
Antisolvent crystallization is a useful technology for the production of heat-sensitive pharmaceutical products because the heating and cooling steps that are involved in cooling and evaporative crystallizations are completely eliminated [3–5]. Antisolvent crystallizations feature a diversity of controllable operating parameters, which can influence the degree of supersaturation, nucleation mechanism and crystal growth, and hence alter the physical properties of resulting crystals. An advantage of antisolvent crystallization is fast supersaturation, which is achieved by the instantaneous mixing of the solution and antisolvent. This feature enables the production of smaller crystals compared to other crystallization techniques. On the other hand, fast supersaturation may cause the unbalanced growth of an individual crystal that can result in the rapid growth of a particular face of a single crystal. Therefore, crystals with an acicular habit are frequently obtained from antisolvent crystallization. An acicular crystal habit, however, is undesirable because it has poor powder flow properties, poor filtration characteristics, a tendency to cake and is often brittle [6].

Several strategies can be carried out to prohibit the formation of acicular crystals, including crystallization under a lower level of supersaturation, the use of different solvents, changing the process conditions, application of external disturbances such as ultrasonic waves, and addition of growth retardant or habit-modifying agents [7–10]. Among these methods, habit-modifying agents are frequently employed to improve crystal shape because they can be applied without causing unwanted crystallization, such as the formation of different polymorphs and new hydrates. One important role of the habit-modifying agent is to retard the abnormally rapid growth of a specific face and to maintain the growth of crystal faces at an equal rate. Indeed, the aim of utilizing habit-modifying agents is to change only the external shape of a crystalline particle without altering the internal structure or chemical properties of the original crystal. In order to achieve this purpose, a variety of habit-modifying agents such as metal ions, inorganic and organic acids, surfactants, and polymers with varying hydrophobicity have been

* Corresponding author.
E-mail address: syeo@knu.ac.kr (S.-D. Yeo).

http://dx.doi.org/10.1016/j.supflu.2015.10.026
0896-8446/

Table 1
Physico-chemical properties of indomethacin.

Properties	
Chemical formula	$C_{19}H_{16}ClNO_4$
Molecular weight	357.79 g/mol
Solubility	Soluble in acetone, ether and ethanol Practically insoluble in water
Melting point	161 °C (γ-form), 155 °C (α-form)
Usage	Non-steroidal anti-inflammatory drug
Chemical structure	

used depending on the nature of the target compound. In particular, the use of polymers to inhibit crystal growth is an important topic of research in the area of drug delivery design [11].

Crystal properties of pharmaceutical compounds can also be modified by varying the process conditions of crystallization. In antisolvent crystallization, temperature, drug concentration, mixing rate of the drug solution and antisolvent, and the type of organic solvent are the main variables that can be controlled in order to modify crystal properties. So far, many researchers have investigated the effect of these variables on the properties of the produced crystals [12]. However, few studies have been performed to examine the effect of antisolvents on crystallization. Different types of antisolvents can affect crystal properties such as particle size distribution, crystal habit, and crystallinity because the properties of the antisolvent may govern the mixing with the drug solution, which can manipulate the rate of nucleation and growth of the resulting crystals. Therefore, it is worthwhile to investigate how antisolvents in two different states (liquid and supercritical) can influence the crystal properties of a selected drug compound. One of the objectives of this study is to compare the effect of antisolvent on the properties of the resulting crystals. Micronization of the particle is not the purpose of this investigation.

In this study, a model drug compound, indomethacin, was crystallized from acetone solutions using carbon dioxide and water as supercritical and aqueous antisolvents, respectively. Indomethacin has been previously investigated by many researchers [13–16]. Here, indomethacin crystals were modified by changing experimental variables such as temperature, drug concentration and mixing rate of the solution and antisolvents. Sebacic acid and urea were added to the crystallization system as habit-modifying agents. Properties such as morphology, particle size, particle aspect ratio, thermal properties and crystallinity of the indomethacin crystals obtained from the two sets of antisolvent experiments were compared.

2. Experimental methods

2.1. Materials

Indomethacin (CAS 53-86-1, 99.0%) was purchased from Sigma–Aldrich Co. Acetone (Aldrich, 99.5%) was used as an organic solvent to dissolve indomethacin, and carbon dioxide and distilled water were used as the supercritical and aqueous antisolvents, respectively. Sebacic acid (CAS 111-20-6) and urea (CAS 57-13-6) were obtained from Sigma–Aldrich Co. All chemicals were used as received. Table 1 summarizes the properties of indomethacin.

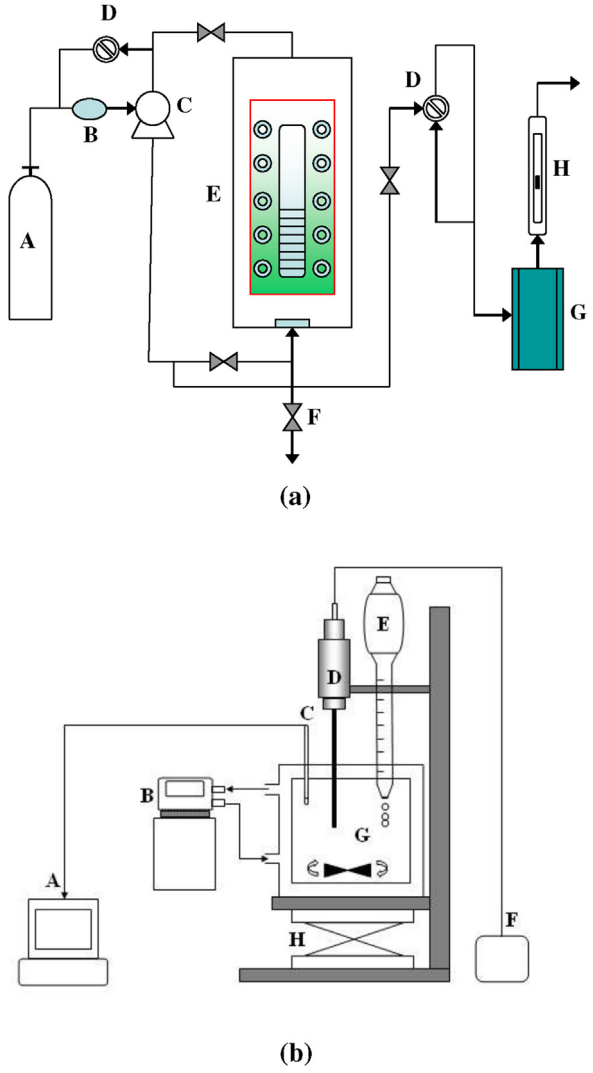


Fig. 1. (a) Apparatus for the supercritical antisolvent experiment: (A) carbon dioxide cylinder, (B) cooler, (C) high pressure pump, (D) back pressure regulator, (E) crystallizing chamber, (F) ventilation valve, (G) solvent trap, (H) rotameter. (b) Apparatus for aqueous antisolvent experiment: (A) particle size analyzer, (B) constant temperature bath, (C) sample collector, (D) sonication probe, (E) drug solution injector, (F) ultrasonic generator, (G) crystallizing vessel, (H) magnetic stirrer.

2.2. Apparatus and experimental procedure

Fig. 1 shows the experimental apparatus used in the supercritical (Fig. 1(a)) and aqueous (Fig. 1(b)) antisolvent experiments. First, indomethacin solutions in acetone were prepared in the concentration range of 0.01–0.07 g/mL. At these concentrations, indomethacin was completely dissolved in acetone. The prepared solutions were used in the both supercritical and aqueous antisolvent experiments. When necessary, habit-modifying agents were added to the indomethacin solutions prior to loading in the experimental apparatus. Sebacic acid and urea were used as habit-modifying agents in the supercritical and aqueous antisolvent experiments, respectively. The concentration range of sebacic acid and urea in the indomethacin solutions was 0.122–0.851 wt%.

The supercritical antisolvent experiment was carried out using the high-pressure antisolvent crystallization equipment as shown in Fig. 1(a). The equipment consisted of a carbon dioxide supply, crystallizing chamber (Jerguson Gauge, Model 19-T-40), and depressurizing section. The crystallizing chamber was placed in an air bath to maintain a constant temperature during the