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Short Communication

Recrystallization of phenacetin and sulfathiazole using the sonocrystallization process

Chie-Shaan Su*, Pei-Yu Wu, Wun-De Jheng

Department of Chemical Engineering and Biotechnology, National Taipei University of Technology, Taipei 10608, Taiwan

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ABSTRACT

In this study, a cooling sonocrystallization process is used to recrystallize two active pharmaceutical ingredients (APIs), phenacetin and sulfathiazole, to modify the solid-state property and enhance the dissolution behavior. Recrystallization results using different organic solvents are presented and discussed. For both APIs, the crystal habit and mean particle size are modified significantly after the cooling sonocrystallization process. Recrystallized API particles show more regular habit and its mean particle size can be reduced to about 10 μm. In addition, for sulfathiazole, polymorph modification is also observed when different organic solvent is used. Furthermore, by dissolution studies, recrystallized APIs show enhanced dissolution behavior compared with the original samples. These results demonstrate that the sonocrystallization process is an efficient tool in pharmaceutical industry for solid state property control and dissolution rate enhancement.

1. Introduction

Crystallization process is a crucial step in manufacture of active pharmaceutical ingredient (API) for solid state property control and modification [1–3]. With appropriate solid state property, solid API can be efficiently processed with excipient in downstream formulation procedure to obtain final dosage form. In general, cooling or antisolvent crystallization method is most commonly used. However, these conventional routes still have disadvantages such as batch-to-batch variation and limitation of supersaturation design. In addition, the mean particle size of API powders produced from conventional crystallization process is difficult to control within few microns. In this case, additional mechanical milling is frequently required for further particle size reduction but the additional milling also brings problems such as surface property destruction and wide size distribution. For efficiently controlling the solid state property of API and overcoming the disadvantages in conventional route, novel crystallization processes such as supercritical fluid crystallization, sonocrystallization and nonphotochemical laser-induced nucleation technology have been designed and developed [4–6]. Sonocrystallization or ultrasonic crystallization, which is a process by incorporating power ultrasound in crystallization process, has been found to be a novel technique for controlling the different stages of crystallization and providing uniform mixing to reduce crystal agglomeration.

In literature, sonocrystallization has been successfully applied for processing of various specialty chemicals. For example, Park and Yeo recrystallized carbamazepine using antisolvent crystallization and discussed the effect of the presence of power ultrasound [7]. Ambrus et al. studied the effect of power ultrasound in recrystallization of gemfibrozil [8]. Park and Yeo applied power ultrasound in antisolvent crystallization for recrystallizing a non-steroidal anti-inflammatory drug, phenylbutazone [9]. Hatkar and Gogate evaluated the process intensification of salicylic acid crystallization using ultrasonic irradiations [10]. Li et al. investigated the effect of power ultrasound on the reactive crystallization of cloxacillin benzathine [11]. Kim et al. designed a spray sonocrystallization process using a flow-through ultrasonic horn for the crystallization of pharmaceutical agents [12]. Khan et al. produced the curcumin powders by the melt sonocrystallization and studied its therapeutic potential [13]. Bučar et al. used sonocrystallization process to yield monoclinic paracetamol with significantly improved compaction behavior [14]. In addition, the role and mechanism of power ultrasound in sonocrystallization process are also widely studied and discussed. For example, Kuppa and Moholkar addressed the matter of mechanistic features of power ultrasound including microstreaming, microturbulence, acoustic waves and microjet [15]. Reddy et al. discussed the effect of cavitation bubble dynamics in details on particle growth, particle morphology and size distribution in synthesis of zinc ferrite particles [16].

In this study, a cooling sonocrystallization process is adopted to recrystallize two APIs, phenacetin and sulfathiazole. Phenacetin is a non-steroidal anti-inflammatory drug, which is used as a pain-relieving and fever-reducing drug. On the other hand, sulfathiazole is a sulfa drug and used as an antimicrobial agent. In our previous

* Corresponding author. Tel.: +886 2 2771 2171.
E-mail address: cssu@ntut.edu.tw (C.-S. Su).

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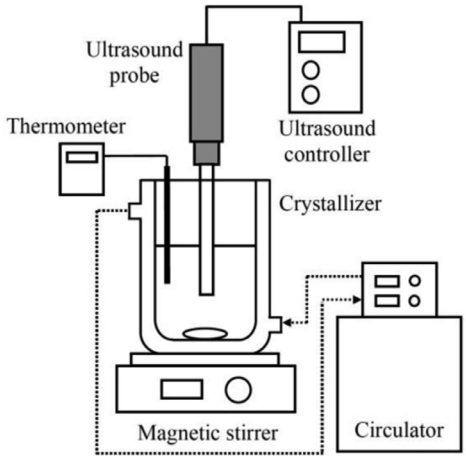

Fig. 1. Experimental setup of the sonocrystallization process.

Table 1
Results of sonocrystallization of phenacetin and sulfathiazole.

Exp. no.	Solvent	Conc. (mg/mL)	Crystal form	Mean size (μm)	Span
Phenacetin					
Ori.	—	—	I	52.7	1.5
1	MEK	64	I	15.0	1.6
2	THF	76	I	19.3	1.7
3	EA	25	I	14.4	1.4
4	Ethanol	76	I	23.6	1.7
5	Methanol	99	I	27.3	1.6
Sulfathiazole					
Ori.	—	—	III + trace IV	28.2	1.4
6	Methanol	28	III	10.1	1.4
7	Ethanol	10	II + trace V	12.9	2.0
8	ACN	16	III + trace IV	17.9	1.5
9	THF	12	III + trace I and IV	9.9	1.4

study [17], phenacetin has been successfully recrystallized by the sonocrystallization process using acetone as the solvent. In this study, recrystallization of phenacetin and sulfathiazole using different organic solvents is investigated and discussed. The solid-state properties of recrystallized crystals from different organic solvent are examined and compared. In addition, dissolution rate studies for

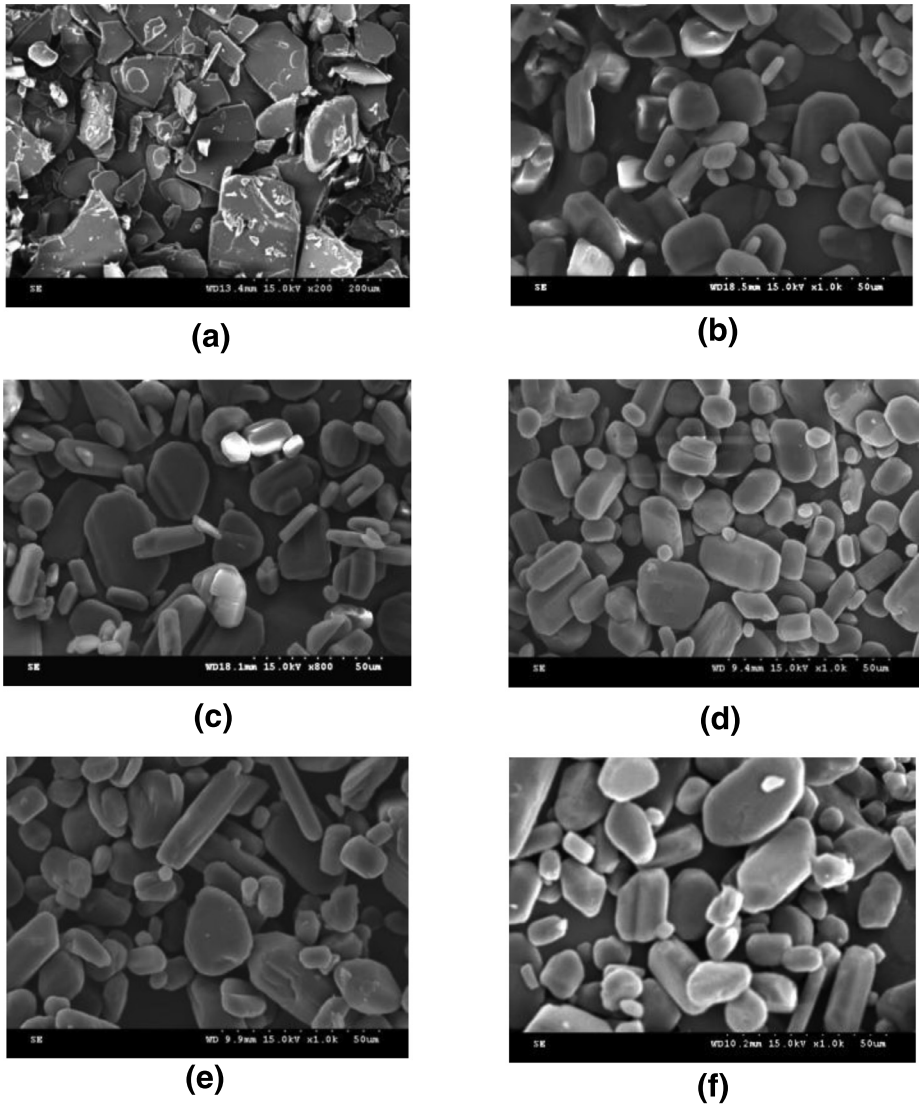

Fig. 2. SEM images of phenacetin before and after the sonocrystallization process (a) original sample (b) powders from Exp. 1 (c) powders from Exp. 2 (d) powders from Exp. 3 (e) powders from Exp. 4 (f) powders from Exp. 5.