RE-CRYSTALLIZATION AND MICRONIZATION OF A PHARMACEUTICAL COMPOUND OF ANTIPYRINE BY APPLYING THE SUPERCRITICAL FLUID TECHNOLOGY

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ABSTRACT

This study presents the experimental results for the micronization of an API of antipyrine using the rapid expansion of supercritical solution (RESS) process. The high pressure experimental system included three sections of carbon dioxide delivery, extraction of antipyrine, and the precipitator. Particle morphology and crystallinity were examined by SEM and XRD, respectively. Particle size and its distributions were determined using image analysis software Image-J. The optimal operating conditions of extraction, pre-expansion and post-expansion temperatures were determined. The mean particle size was reduced to one tenth of its original value after the optimal RESS process. The dissolution rate of the micronized antipyrine was enhanced by 20% in a simulated intestinal buffer solution.

INTRODUCTION

Many of the discovered drugs are poorly soluble in aqueous media that affect their absorptions in the gastrointestinal tract. The dissolution rate of compounds is a function of the surface area. In this respect, particle size reduction has become a vital strategy which can significantly contribute to the efficiency of using the active pharmaceutical ingredients (APIs). Besides many conventional particle micronization processes, the supercritical fluid technology has been widely recognized as an advanced approach with much simpler steps and the minimum use of organic solvent. For API with high enough solubility in supercritical carbon dioxide, the rapid expansion of supercritical solution (RESS) method is applicable.

Typical literatures have been cited for the employment of the RESS technology in micronizing the APIs [1-3].

The main purpose of this study is to investigate the micronization of antipyrine using carbon dioxide as the supercritical fluid in the RESS process. Antipyrine is an analgesic and antipyretic API. The physicochemical characteristics of the drug particles include particle size and morphology, thermal behavior, crystal habit and structure, crystallinity and polymorphic behavior were analyzed to explore the performance of RESS process under different experimental conditions. Finally, the dissolution profiles before and after RESS process were conducted to compare the effect of particle size reduction on dissolution rate.

EXPERIMENTAL

Carbon dioxide was purchased from Liu-Hsiang Gas Co. (Taipei, Taiwan) with a minimum purity of 99%. Antipyrine ($C_{11}H_{12}N_2O$) was purchased from Sigma-Aldrich Co. with a minimum purity of 99 %. All chemicals were used without further purification.

The experimental system was similar to that of our previous study [3] with three main parts for the feeding of supercritical CO_2, the extraction of solute, and the particle formation. The pressurized CO_2 flew through the pre-heating coil immersed in a water bath before it was charged into the pre-extraction and extraction cells. Each extraction cell had a volume of 75 cm^3 where antipyrine was packed layer by layer with glass beads. The extraction temperature was measured by a thermocouple and pressure was measured using a pressure transducer (Druck, PTX 610). After the extraction procedure, the solution was heated to the pre-expansion temperature using a heating tape. It was finally expanded to atmospheric pressure through a nozzle with diameter of 50 μm. The spraying distance is at 4 cm. The micronized antipyrine powder was collected in an expansion vessel at a post-expansion temperature.

The crystal properties were examined by scanning electron microscope (SEM, JEOL JSM-5600), X-ray diffractometer (XRD, MAC Science M03XHF) and differential scanning calorimetry (Jade, Perkin Elmer). Particle sizes and distributions were determined by counting at least 300 particles using a software image J.

The dissolution rates were studied on a calibrated dissolution tester (Shin Kwang Machinery, DT3) using the paddle method according to the criteria of USP [4]. The dissolved amount of antipyrine was determined using an UV/Vis spectrometer (Shimadzu, TCC-240A).

RESULTS AND DISCUSSION

Eleven experiments have been investigated in this study at various operation conditions.

The experimental results show that there exists an optimal extraction temperature, and a lower pre-expansion temperature favors the smaller particle formation. A typical example for the effects of operation conditions on the resulting mean particle size is illustrated in Figure 1. The optimal operation parameters are determined as the extraction temperature at 318 K, pre-expansion temperature at 383 K, and post-expansion temperature at 283 K. The original antipyrine had quite large particle size with rather broad particle size distribution. Its mean particle size and standard deviation were 35.12 μm and 34.40 μm, respectively. After the RESS treatment, the minimum mean particle size is reduced to 2.28 μm with standard deviation of 1.79 μm. Figure 2 shows the SEM images that the RESS-processed particles are reduced significantly compared to that of the untreated API. The morphology of antipyrine changes from the original irregular shape to the more uniform rectangular shape after the RESS process. The X-ray diffraction patterns for the original and RESS-processed antipyrine particles indicate identical structures. The RESS-processed API, however, has lower crystallinity intensities. The DSC measurement result also demonstrates that there is no polymorph change after the RESS process.

The dissolution rates have been tested for the original and RESS-processed antipyrine using simulated intestinal buffer solution at pH value of 6.8 [5]. We find that even though the particle size for antipyrine has been reduced significantly after the RESS process, the dissolution rate for the micronized antipyrine has only slightly enhanced by 20%. Particle size may not be the only factor that influences the dissolution rate of API that has also been discussed in previous literature [6].

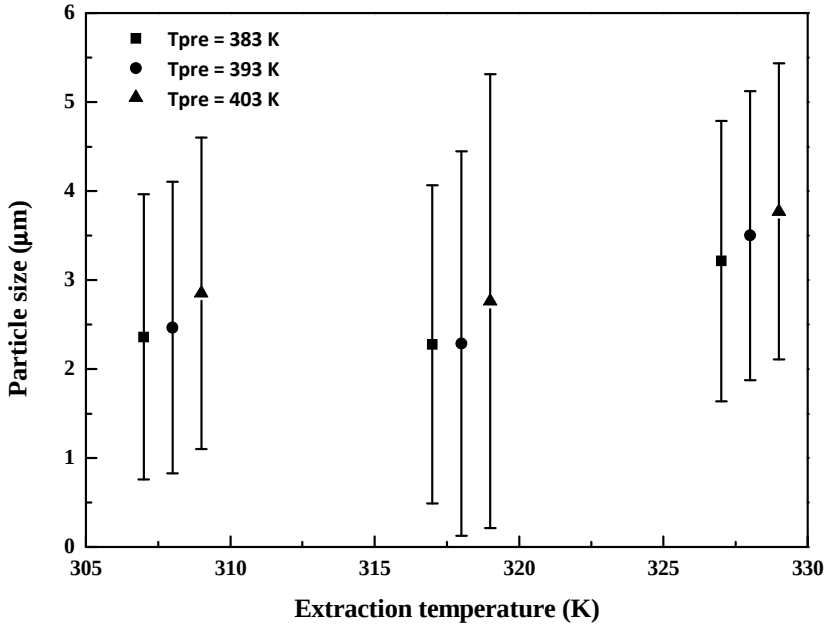

Fig. 1. Typical results for various RESS operation conditions on the mean particle size.

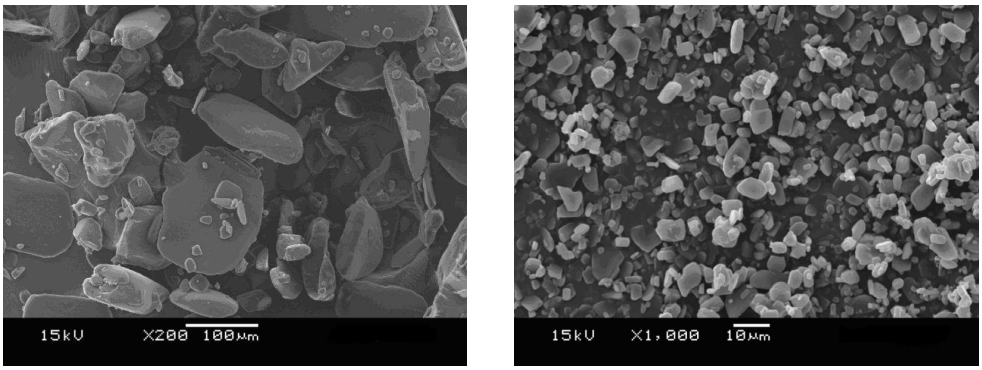

Fig. 2. The SEM images of the original (left) and RESS-processed (right) antipyrine.

REFERENCES

[1] Kayrak, D., Akman, U., and Hortaçsu, Ö., Journal of Supercritical Fluids, Vol 26. **2003**, p. 17-31.

[2] Chingunpitak, J., Puttipipatjhachorn, S., Tozuka, Y., Moribe, K. and Yamamoto, K., Drug Development and Industrial Pharmacy, Vol 34, **2008**, p. 609-617.

[3] Su, C. S., Tang, M. and Chen, Y. P., Journal of Supercritical Fluids, Vol 50, **2009**, p. 69-76.

[4] United States Pharmacopeia ; the National Formulary, 32nd ed. Rockville, MD, **2009**.

[5] Zakeri-Milani, P., Barzegar-Jalali, M., Azimi, M. and Valizadeh, H., European Journal of Pharmaceutics and Biopharmaceutics,Vol 73, **2009**, p. 102-106.

[6] Wang, J. and Flanagan, D. R., Journal of Pharmaceutical Sciences, Vol 91, **2002**, p. 534-542.