Recrystallization and Micronization of Phenylbutazone and Nabumetone Using the Rapid Expansion of Supercritical Solution (RESS) Method

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Abstract

This study presented the re-crystallization and micronization results of active pharmaceutical ingredients (APIs) using the rapid expansion of supercritical solution (RESS) method. It is shown that phenylbutazone was micronized after the RESS treatment with a different polymorph. Nabumetone was also successfully micronized after the RESS process. The orifice nozzle yielded smaller and more uniform particle size of nabumetone than that from the capillary nozzle.

Introduction

Supercritical fluid technology has been extensively applied for various fields such as materials processing and biotechnology. This technology has also been used for the production micronized pharmaceutical particles. After the micronization process, the dissolution rate of the active pharmaceutical ingredient (API) can be improved. New polymorphs can also be obtained. These results provide the advantages of high efficiency, low dosage requirement and avoiding possible side effects. We have presented the supercritical anti-solvent (SAS) experimental results in recent literature [1, 2]. Another approach, the rapid expansion of supercritical solution (RESS) method, does not require the use of solvent. It is recognized as an environmentally friendly process for API which has higher solubility in supercritical CO_2. In this study, we present our experimental results of phenylbutazone and nabumetone using the RESS process.

Experimental

Phenylbutazone ($C_{19}H_{20}N_2O_2$) and nabumetone ($C_{15}H_{10}O_2$) were purchased from

Sigma-Aldrich with the purity greater than 99 %. Carbon dioxide with the purity better than 99.8 % (San Fu, Taiwan) was used as the anti-solvent. The schematic diagram of apparatus and procedures in this study is present in our previous study [3]. Applying the RESS process, solid phenylbutazone or nabumetone was firstly extracted by supercritical CO_2. The supercritical solution was then depressurized to the atmospheric condition through a nozzle. The micronized phenylbutazone or nabumetone particles were formed in a short time period. The morphologies of particles were examined using the scanning electron microscope (SEM, JOEL JSM-5600). Particle size distributions of the particles were determined using image analysis software ImageJ. The crystal structures of particles were detected using the X-ray diffractometer (XRD, Philips X'pert diffractometer) where data were collected between $2\theta = 5\ ^{o}$ to $40\ ^{o}$ with a scanning rate of $5\ ^{o}$/min. Thermal behavior of the particles was studied using differential scanning calorimetry (DSC, DuPont TA 2010) with a heating rate of 5 K/min.

Results and discussion

Fig. 1 shows the comparison between the SEM images of the original and RESS treated phenylbutazone. The original phenylbutazone has the long bar shape with unfavorable flowability. The RESS-treated phenylbutazone showed irregular morphology with much smaller mean particle size. Fig. 2 shows the XRD patterns for phenylbutazone before and after the RESS treatment. Compared with the literature data [4], it is observed that phenylbutazone changed from the original δ form to β form after the RESS process. This result has also been presented by Moribe et al. [5]. It is also demonstrated in Fig. 2 that the XRD intensities of phenylbutazone decreased after the RESS process. This result can be beneficial to the increase in dissolution rate.

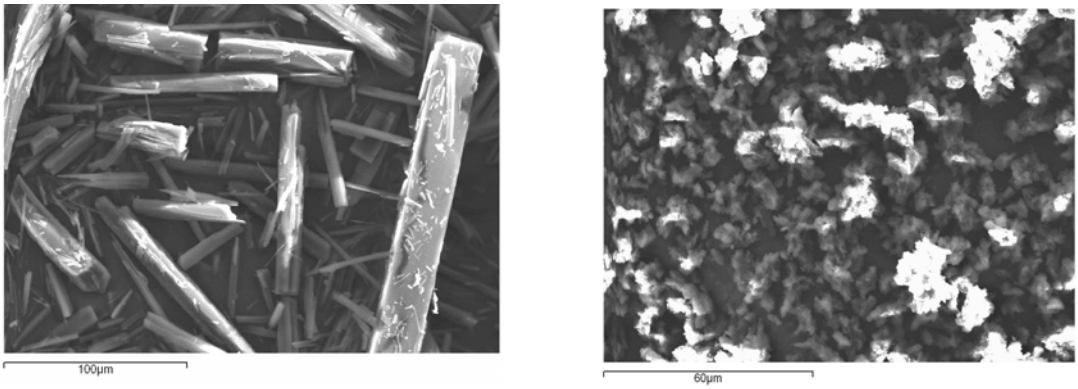

Fig. 1 The SEM images of phenylbutazone (left):original, (right): RESS treated

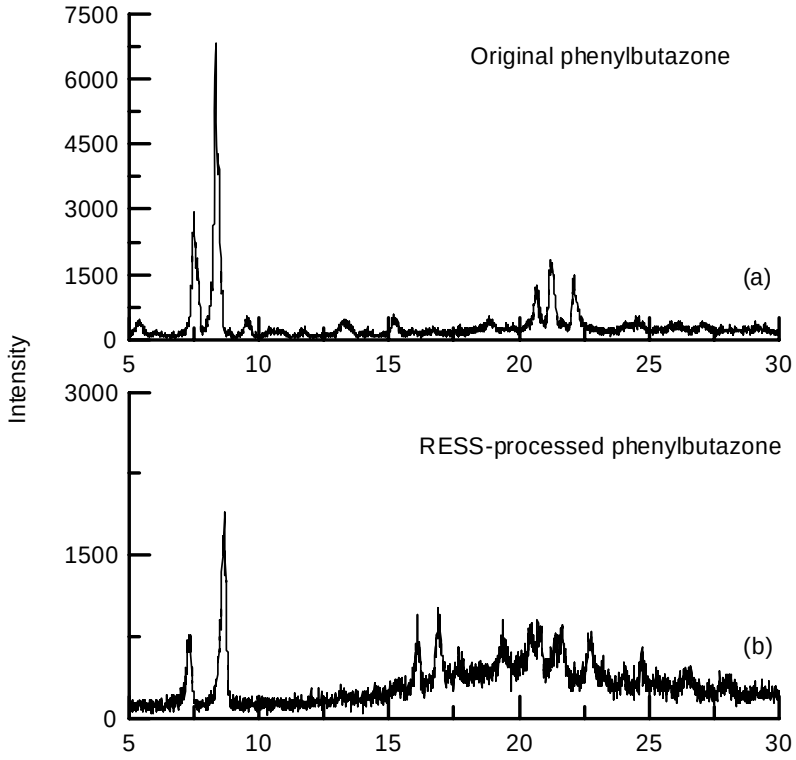

Fig. 2 The XRD patters for the original and RESS treated phenylbutazone

The re-crystallization and micronization of nabumetone has been presented in our previous study [3]. The mean particle size was reduced from the original 32.6 μm to 3.3 μm using a capillary nozzle. This study investigated the micronization effect due to different nozzles in the RESS process. Fig. 3 shows the SEM images of the micronized nabumetone using either the capillary or orifice nozzle. It is observed that the mean particle size of nabumetone was 3 μm resulting from a capillary nozzle. The mean particle size of nabumetone was further reduced to 1.7 μm by using an orifice type nozzle. The orifice nozzle also yielded more uniform particle size distribution.

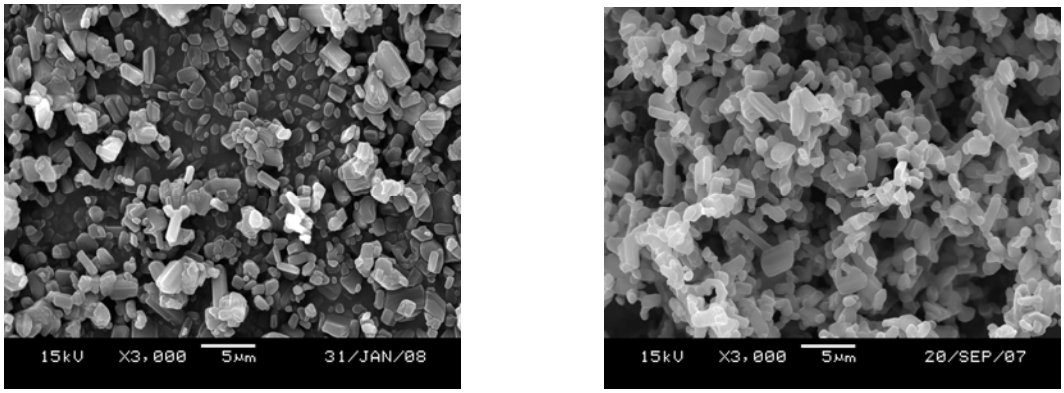

Fig. 3 SEM images of RESS treated nabumetone (left): capillary nozzle, (right): orifice nozzle

Conclusion

The RESS process has been applied for the micronization of two APIs of phenylbutazone and nabumetone. Significant size reduction has been observed for both APIs. Phenylbutazone showed a different polymorph after the RESS treatment that was consistant with literature report. The orifice type nozzle yielded smaller and more uniform nabumetone micronized particles.

References

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