Micronization of Active Pharmaceutical Ingredient Using the Rapid Expansion of Supercritical Solution Method

Pai-Ching Lin [(1)], Yan-Ping Chen[(1)], Muoi Tang[(2)], Sheau-Ling Ho[(2)]

Department of Chemical Engineering
(1) National Taiwan University, (2) Chinese Culture University
Taipei, Taiwan, Republic of China

ABSTRACT

The re-crystallization and micronization results of active pharmaceutical ingredient (API) using the rapid expansion of supercritical solution (RESS) method is presented in this study. After the RESS process, the dissolution rate of the active pharmaceutical ingredient (API) can be improved. This study used an anti-arrhythmic API lidocaine as an example, and demonstrated that the original API particles were successfully micronized with more uniform particle size distribution. The dissolution rates of the original and RESS treated API were examined in a simulated gastro-intestinal fluid. Significant enhancement in dissolution profile was observed for the RESS-treated API. The dissolution behavior has shown novelty by investigating the difference and similarity factors.

INTRODUCTION

Supercritical fluid was taken as an advanced and green fluid and it has been extensively applied for extraction, materials processing and particle formation. This technology has also been used for the micronization of pharmaceutical particles. After the re-crystallization and micronization process, the dissolution rate of the active pharmaceutical ingredient (API) can be enhanced. The new products can improve the route of taking medicines and decrease possible side effects. We have presented the experimental results using the supercritical fluid processes [1-3]. The rapid expansion of supercritical solution (RESS) method is a solvent-free supercritical fluid technology. It is an environmentally friendly process for API with high enough solubility in supercritical CO_2. In this study, we present our experimental results of

lidocaine using the RESS process.

EXPERIMENTAL

The API of lidocaine ($C_{14}H_{22}N_2O$) was 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 [4]. The original solid API of lidocaine was firstly extracted by supercritical CO_2. The supercritical solution was then depressurized to the atmospheric condition through an orifice with diameter of 25 μm. The micronized lidocaine particles were formed in a short time period. The morphologies of particles were examined using the scanning electron microscope (SEM, JOEL JSM-5600). The mean particle size and its distribution were determined using image analysis software ImageJ. The crystal structures of particles were detected using the X-ray diffractometer (XRD, PANalytical X'pert) where data were collected between $2\theta = 5^{o}$ to 40^{o} with a scanning rate of 3^{o}/min. Thermal behavior of the particles was studied using differential scanning calorimetry (DSC, DuPont TA 2010) with a heating rate of 3 K/min.

RESULTS AND DISCUSSION

The SEM images of the original and RESS treated lidocaine were compared as shown in Fig. 1. The original lidocaine has the block shape with large mean particle size about 134±58 μm. The optimal RESS operation conditions for this API were found at the extraction pressure of 200 bar, extraction temperature at 318 K, pre-expansion temperature at 343 K, post-expansion temperature at 273 K, and spraying distance at 2.5 cm. After the RESS treatment, the lidocaine API showed elliptical morphology with more uniform and much smaller mean particle size about 5±2 μm. The comparison of particle size distributions before and after the RESS treatment is shown in Fig. 2. The XRD and DSC experimental results showed that lidocaine retained the similar crystal structure after the RESS process. The dissolution rate test was carried out according to the United States Pharmacopeia in a phosphate buffer solution with pH value of 6.8. The results are presented in Fig. 3 for the original and RESS-treated lidocaine. We applied the Weibull model [5] to fit the experimental dissolution rate data. From the best-fitted dissolution rate constant, it was observed that the dissolution rate was enhanced by 2 times after the RESS treatment. The similarity and difference factors had been evaluated from the dissolution rate data [5, 6]. We have determined these factors for

lidocaine after the RESS process. It was observed that the dissolution behavior for the RESS-treated lidocaine was different to the original API.

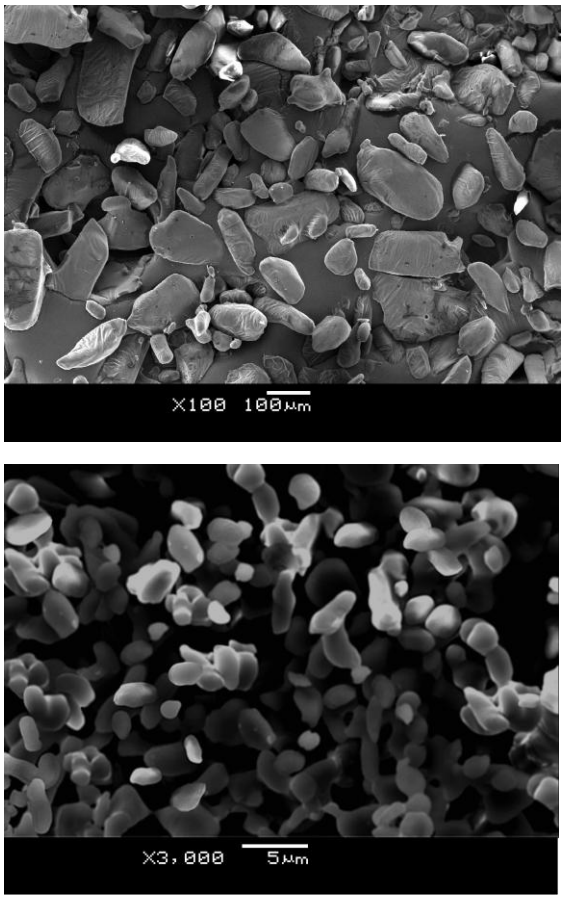

Fig. 1 The SEM images of lidocaine (top): original, (bottom): RESS treated

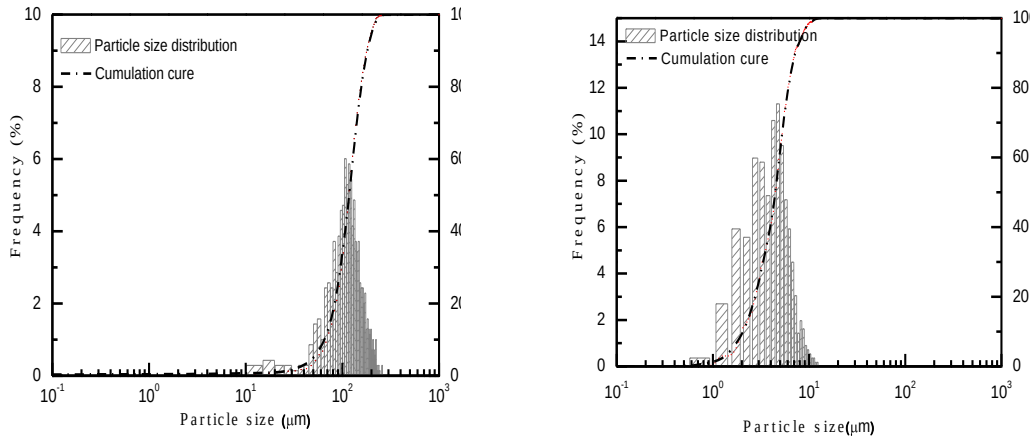

Fig. 2 Comparison of the particle size distribution for lidocaine, (left): original, (right) RESS-treated

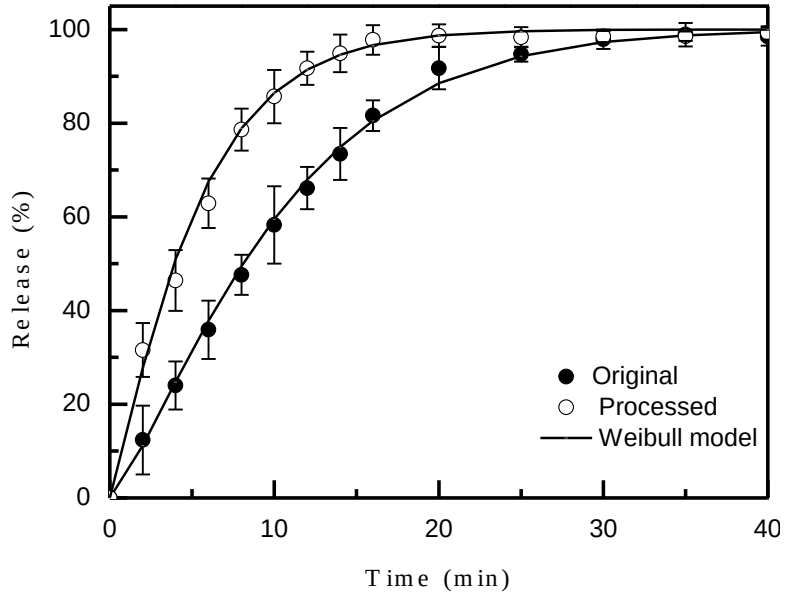

Fig. 3 Dissolution rate profiles for the original and RESS-treated lidocaine

CONCLUSION

Re-crystallization and micronization of the API of lidocaine had been investigated using the RESS process. The mean particle size was significantly reduced from 134 to 5 μm. The RESS- treated lidocaine also showed much narrower particle size distribution. The dissolution rate of the micronized lidocaine was enhanced by 2 times with different dissolution behavior.

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