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Short communication

Spheronization of micronized theophylline anhydrate and monohydrate using a mechanical powder processor

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ABSTRACT

We investigated the spheronization of micronized drug powder using a mechanical powder processor that can produce spherical particles with a drug content of 100%. Theophylline anhydrate and monohydrate were micronized through a jet-mill process and then subjected to mechanical treatment. The anhydrate was very slightly agglomerated and was not converted into spherical particles, whereas the monohydrate was remarkably agglomerated and yielded spheres at the end of processing. These results indicate that the spheronization of theophylline monohydrate powder is more likely to occur than that of theophylline anhydrate powder, despite these materials exhibiting similar powder cohesiveness (which is believed to determine the success of mechanical spheronization). Consequently, theophylline monohydrate may be spheronized by driving factors other than the native cohesiveness of the material. Crystalline analysis and water determination data showed that part of the monohydrate powder was dehydrated during processing and transformed into anhydrate, indicating the release of free water during mechanical treatment. Furthermore, the presence of solid bridge between primary particles of the spheronized theophylline monohydrate suggests that the liquid bridge is generated during the processing and results in the spheronization. Therefore, the spheronization of theophylline monohydrate is due to the agglomeration through the water released by the dehydration.

1. Introduction

Spherical particles with symmetric morphology exhibit good flowability and thus are ideally suited for unit processes in pharmaceutical manufacture such as sieving, blending, capsule filling and tableting. In addition, spheres are favorable for the fabrication of coated particles with controlled release, as a low specific surface area and rounded edges facilitate uniform coating using a minimum amount of coating agent, thereby enhancing the reproducibility of product characteristics. Thus, drug particles with round shape are among the most useful materials for the pharmaceutical industry. Since pharmaceutical drug crystals usually exhibit nonspherical morphology, spherical drug particles are generally produced using pelletization techniques including extrusion/spheronization [1]. To avoid the enlargement of final products and the increase of the drug dose, the drug content of spherical particles should be as high as possible. However, using a large amount of inactive ingredients (such as fillers and binders) is required for the pelletization of drug powder, thereby making it difficult to enhance the drug content of resulting particles. Therefore, direct spheronization of drug crystals would be an ideal process that can maximize drug content.

Spherical crystallization (including spherical agglomeration [2,3] and emulsion solvent diffusion [4]) is known as a spheronization technique that can produce spherical particles consisting solely of the drug by controlling the crystallization process based on drug-solvent and solvent-solvent interactions. Continuous crystallization approaches have also been investigated [5]. Solventless process has recently attracted attention as the energy required for solvent evaporation is reduced, there is no need for a drying step, and elimination of the solvents minimizes environmental impacts. However, to our knowledge, there are no reports describing methods for the solventless spheronization of drug crystals. In the inorganic industry, particle shape modification using a mechanical powder processor has previously reported, such as the mechanical treatment of metal [6], cement [7] and graphite [8,9] to generate spherical particles. A mechanical powder processor (known as a mechanofusion or hybridization machine) is a high intensity mixer that subjects sample powder to powerful impact, shear and compressive forces. The mechanical stress promotes the deagglomeration of adhesive powder, thereby allowing the uniform mixing of nanoparticles and the formation of an ordered mixture. This processor is usually used as a dry particle coater in the inorganic materials, cosmetics and pharmaceutical fields [10], while its application to particle shape modification of organic compounds such as pharmaceutical materials is expected. Hence, we focused on particle shape

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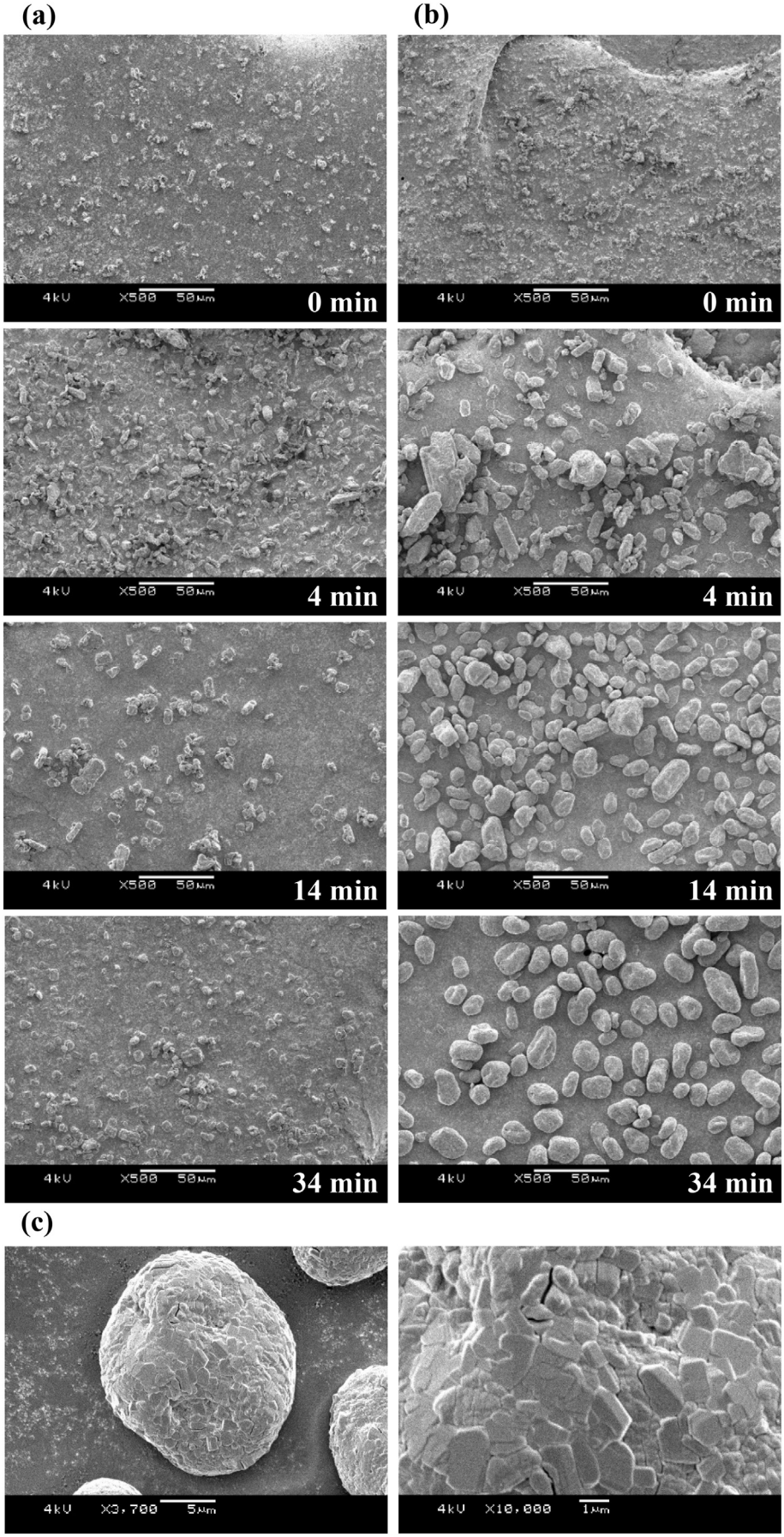

Fig. 1. Scanning electron micrographs of (a) TPL-AH and (b) TPL-MH products at the start of processing (0 min; intact material), and at 4 min (immediately after the preliminary run), 14 min, and 34 min (after the main run). (c) Light and right panels are magnified images of a particle and 10,000 times of TPL-MH product at 34 min, respectively.