CHAPTER I

INTRODUCTION

Pharmaceutical manufacturing process plays an important role for new drug formulation development. One of the most significant processes in the pharmaceutical manufacturing procedure is drying operation. Drying can generally be achieved by employing either elevated temperature or reduced pressure. However, thermal drying is commonly used more than vacuum drying in industrial scale due to ease of operation. Regarding thermal drying, the solid phase conversion of materials may occur during dehydration (Byrn et al., 1999).

Proteins and peptides are well known for their thermal-labile property. Therefore, chemical properties of proteins often changed upon drying. Thermal dehydration of proteins eventually lead to stability problems and a failure in dosage form development (Abdul-Fattah, Kalonia and Pikal, 2007). Physical properties will also markedly be affected during dehydration such as cracks on the outer surface of particles can take place after thermal drying for some materials (Sakata, Shiraishi and Otsuka, 2004). Molecular adduct is an example which showed the solid state transformation during thermal dehydration. Ansolvate, a solvate without solvent molecules in the crystal structure, will be generated after the solvate is subjected to high temperature. The solvent molecule in the solvate is impeded as a result of the input energy from high temperature. Consequently, packing integrity of dehydrated materials will be altered and lead to structural weakness and finally structural collapse (Byrn et al., 1999). For example, drying of beclomethasone dipropionate monohydrate (BDM), antiasthmatic drug, resulted in the particle size reduction up to several folds after drying (Amolwan Chinapak, 2000). In addition, several groups of pharmaceutical solvates showed the same behavior as BDM where the particle sizes were reduced by desolvation. The removed solvent molecule from a solvate is a key factor to determine the extent of particle size reduction. This phenomenon has a complex behavior because the dehydration and size reduction occurred synchronously. The main mechanism behind the drying process of BDM that led to particle size reduction after dehydration must be thoroughly examines. The dehydration energy and the energy required to reduce the particle size of BDM are of great concern. Furthermore, different in stoichiometry of solvate/hydrate might

determine the possibility of the particle size reduction by dehydration. Thus, it is important to study the relationship between molecular structures of solvate/hydrate and the possibility for particle size reduction after thermal dehydration. In this study, norfloxacin (NF) is selected as model compound due to the versatility of stoichiometric hydrates. It is necessary to determine the interconversion pathways amidst NF hydrates prior to evaluate the possibility of the particle size reduction by thermal dehydration of the different stoichiometric NF hydrates.

Objectives of This Study

1. To determine the mechanism of particle size reduction of BDM during thermal dehydration including the relationship between the energy used for size reduction and dehydration.
2. To determine the interconversion of various NF hydrates used as model molecule
3. To evaluate the particle size reduction potential of NF hydrates by thermal dehydration
4. To evaluate the relationship between the stoichiometry of NF hydrates and the extent of particle size reduction by thermal dehydration