CHAPTER I

INTRODUCTION

Not many raw materials used in pharmaceutical industry exist in the optimal size range. Most materials must be comminuted at some stage during their production. For example, during the process of direct compression in tablet production, most materials must be milled to produce particles of uniform size, which are allowed to flow freely and produce tablets of uniform weight. Also, conventional milling is a dominant mechanical process that has been used to improve dissolution and bioavailability of poorly water-soluble drugs (Parrot, 1986).

As of today, a number of different techniques are used to reduce the size of pharmaceutical powders. The most common techniques are ball milling, hammer milling, cone milling and fluid energy milling (Lantz, 1999; Rubinstein and Gould, 1987; Parrot, 1974). The reduction of particle size of the drug can also be done by using solid dispersion technique, which is a mechanical process to enhance dissolution rate of solids (Mooter et al., 1998; Mura et al., 1996). Mackellar and co-workers, in 1994, found that the poloxamer adsorbed to the surface of hydrophilic face of ethylparaben crystals inhibited the crystal growth and led to a decrease in particle size. Microfluidizer is another equipment used to reduce the particle size of water-insoluble materials in suspension. The minimal contamination and ease of production scale-up are two major advantages for using microfluidizer in industrial scale during pharmaceutical manufacturing (Illig et al., 1996). Sencar-bozic and co-workers applied a supercritical fluid method during a high pressure material processing. This application led to the reduction of the particle size of water-soluble calcium antagonist, nifedipine, from 50 microns to 15 microns. However, it caused degradation of

nifedipine, which was probably due to high temperature (185°C) and pressure used (Sencar-bozic et al., 1997). It was demonstrated that the use of improper milling conditions can lead to undesirable changes in the milled materials, including polymorphic transformations, increased rate of degradation and the build up of static charge (Florence and Salole, 1976; Otsuka and Kaneniwa, 1990).

Being such the case, a method of particle size reduction by making use of the phase conversion from a solvate to the original drug compound was reported and it was demonstrated experimentally that this method could be applied easily and efficiently without problems accompanied with mechanical milling procedures. For examples, desolvation of NH_3 from sulfonamide solvate resulted in a smaller particle size of sulfonamide (Sekiguchi et al., 1974). The same result appeared when desolvation was applied to chloramphenicol pyridinate, a pyridine solvate (Himuro et al., 1971), and griseofulvin with dioxane solvate (Sekiguchi et al., 1976). However, dehydration of drugs has not yet been reported to be the technique for particle size reduction

A preliminary promising result in the reduction in particle size of hydrated beclomethasone dipropionate by dehydration process was demonstrated by Nachiengtung in 1997. By this method, the drug powder was exposed to low energy environment. It was cost efficient and there was no need to use any elaborated high technology instruments.

Even though the particle size reduction methods mentioned above seem promising, further investigations are necessary. Factors affecting the reduction of particle size, physicochemical properties of the particles, desolvation kinetics and solid state stability are needed to be evaluated. The aim of this study is to investigate the effect of particle size on desolvation process used in reducing the particle size of

hydrated beclomethasone dipropionate and to study the changes in physicochemical properties of the resulting particles through solid-state chemistry and also their solid state stability.

General objective:

To study the effects of desolvation on the physicochemical and solid state properties of hydrated beclomethasone dipropionate

Specific objectives:

1. To study factors affecting the solid state chemistry and physicochemical characteristics of hydrated beclomethasone dipropionate before and after desolvation.
2. To study the solid state stability of hydrated beclomethasone dipropionate

Limitation

This research demonstrates the basic science of particle size reduction by the process so called 'desolvation'. Results of this study can give insights to predicting the likelihood of other drugs undergoing the same phenomenon. The results at this stage are not yet intended for the large scale applications in the production and formulation of any drugs.