# CHAPTER V

# CONCLUSIONS

This research was conducted to examine the effect of particle size on particle size reduction by desolvation process of beclomethasone dipropionate monohydrate, which has been used as a model drug in this study. Solid state chemical characterizations of beclomethasone dipropionate that were measured in this study include kinetics of desolvation, solid phase identification, and particle size analysis.

The preparation of three different sizes of hydrated beclomethasone dipropionate was carried out by varying rate of water addition in solution of drug in absolute ethanol at 7, 23, 60, 120, and 300 ml/hr during crystallization process. When the rates of adding water were 7 and 23 ml/hr, transparent, well-formed crystals were produced. On the other hand, with higher addition rates applied, produced thin white needle like form and bulky product, which were not the desired characteristics. It is the result of rapid nucleation that overgrows the crystal growth. Thus, crystals with the rate of water addition of 7 ml/hr referred to as "intact crystal" were used for future studies.

To produce the smaller sizes, the intact crystals were subjected to grinding in glass mortar and pestle, passing through the analytical sieves of apertures of 150, 75, and 38 μm, respectively. Ground crystals ranging between 38-75 and 75-150 μm were collected. As a result, three different sizes of hydrated beclomethasone dipropionate were obtained, i.e., large (intact particles), medium (particles of 75-150μm), and small (particles of 38-75μm). Their median sizes, as determined by laser light scattering, are 429.89, 150.8 and 63.88μm, respectively. Morphology of the samples as obtained by SEM is columnar in habit while the ground samples are

more irregular in shape. In other word, irregularity is pronounced when the crystals are smaller. Meanwhile, light microscope shows the anhydrous barrier (shown by non-transparency) on the surface of the ground sample. This barrier was due to the surface dehydration of beclomethasone dipropionate by the grinding process.

DSC and TGA thermograms of all three samples show that the hydrated form has weight loss of approximately 3.3%, which is very close to the amount of water in the theoretical yield of beclomethasone dipropionate monohydrate (3.34%). The anhydrous barrier on the surface caused by grinding process protected water removal and increased the endothermic dehydration temperature of ground samples when observed by DSC. The x-ray powder diffraction patterns of all three samples are similar to the standard beclomethasone dipropionate monohydrate diffractogram.

The desolvation kinetics of beclomethasone dipropionate monohydrate was evaluated. The objective of this investigation was to examine their possible mechanism and desolvation activation energies (solvent stability) of all three sample sizes over a range of temperatures as a % fraction versus time.

To investigate the kinetics of desolvation, % fraction dehydrated was plotted against time. This could be done by applying the kinetic equations based on the reaction of solid state decomposition. The mechanism of desolvation of the large particles (intact) was best expressed by the model of Avrami-Erofeev equation (n=1/3) while medium crystals behaved in accordance with the Avrami-Erofeev equation (n=1) assuming that the volumes within the solid at a given time are activated where n being the proportion of numbers of nuclei generated.

The small particle, however, has two mechanisms working at two ranges of temperatures, below 85.5 °C and higher than 85.5 °C (101.5 and 90.5°C). At lower temperatures, the particle's dehydration behavior follows Avrami-Erofeev equation

(n=1). At high temperature, the particle had a higher rate of dehydration, which was assumed to be due to amorphous phase generated on the surface and promoted rapid water removal. This high temperature should not be applied due to the higher energetic state induced and therefore, resulted in a decrease in physical and chemical stability. Nevertheless, if these high temperatures were to be applied in both large and medium particles, the same phenomenon may occur as well (Nachiengtung, 1997).

The x-ray powder diffraction patterns of all three samples shows that temperature used in the desolvation process promoted a solid phase transformation to the anhydrous form. This anhydrous beclomethasone dipropionate was collected on the surface of the particle resulting in a shield that slow-down water removal.

Using Arrhenius equation, activation energies obtained from all correlated equations were 178.45 237.42 and 239.44 KJ/mol for large, medium and small crystals (temperatures below 85.5°C), respectively.

The activation energies for dehydration increase with particles that went through grinding process. Grinding may produce a shield of dehydrated layer on the surface of the crystal, which hindered water removal of the crystal (surface barrier effect), resulting in higher Ea needed and higher melting temperatures as shown by DSC thermograms compared to intact one. The activation energy of large crystals, however, was found to be lower than that of the medium and small crystals. It was assumed to be due to the higher water vapor pressure generated within larger crystals during the heating process and there was no initial barrier effect from grinding, which resulted in rapid dehydration.

After desolvation process, the results clearly show that the desolvation of hydrate beclomethasone dipropionate plays an important role in reducing the particle

size. The lattices were rearranged to the anhydrous form when there was sufficient heat energy to induce a collapse of the structure.

In regards to ground samples, the original size of the particle plays no role in the resulting size reduction because there was no significant differences among the sizes of particle resulting from dehydration. The extent of size reduction was assumed to be limited to the size of the unit cell of the anhydrous crystal. Further study using single crystal x-ray powder diffraction should be conducted to reveal the internal structure of beclomethasone dipropionate monohydrate and to provide more insight into the nature of the solid. The effect of temperatures on particle size reduction was not observed at temperature higher than 70°C. This might be due to the fact that temperatures used were above the required barrier (energy) to reduce the size of particles. Should the temperatures used to dehydrate these samples were lower; the influence of temperature on the particle size reduction may be observed as was seen for the intact crystals when low temperatures were used for dehydration.

It was clearly observed that the size reduction of intact crystal depended on the temperature, i.e., particle size reduction is affected by increasing temperature. At lower temperature (56 °C), the structure was not collapsed but appeared as opaque crystals. Hence, the rate of dehydration affected the particle size reduction. Further investigation by heating the particles for another 72 hours showed that particles collapsed to a certain size (approximately 40 μm). Thus, one criterion for particle size reduction by desolvation is the accumulated energy within each of the crystal to induce an anhydrous structure. It is therefore interesting to investigate the energy used in size reduction separating from energy required for the desolvation process.

Although, the particle size reduction by desolvation was not aimed to produce particles in the size range intended for inhaler (2-5 μm), this method demonstrated the

particle size reduction by desolvation technique could be applied efficiently. Prediction of other drugs likely to undergo the same phenomenon is possible. The knowledge of kinetics of desolvation was shown to be independent on the size of particle, but dependent on the temperatures used and surface irregularities induced from other processes, such as grinding.

Finally, from this experiment it was found that the major limitation to this technique is the uncontrollable final particle size, which is assumed to be governed by the nature of the crystals, temperatures used and position of solvent molecules.