# CHAPTER V
# CONCLUSION

In this study, it was found that drug-solution-dropping tablet could be prepared by using blank tablet with good physical property of both DC and WG blank tablet of 1000, 1400 and 1800 kg CF. It is expected that many of the another drug substances which posses undesired properties in term of formulation especially with respect to e.g. water solubility and oral bioavailability. Therefore, this novel preparation, which enable especially therapeutically and/or prophylactically active substances to be delivered to the body in a relatively easy manner and at the same time enables the desired therapeutic and/or prophylactic response, is highly needed (Gole *et al*, 1996). Dicalcium phosphate dihydrate and lactose monohydrate were used as water insoluble and water soluble fillers of DC and WG blank tablet respectively. The time for disintegration of WG blank tablet was longer than DC blank tablet and very longer when compression force was increased. However the disintegration time of each tablet met the required time specification which not more than 15 minutes. CPM and DZP were used as soluble and poorly soluble drug respectively. The drug solution was prepared by dissolving drug with non-aqueous solvents, i.e., the mixture of alcohol and dichloromethane or only dichloromethane, and then dropped on DC and WG blank tablet surface respectively by using microsyringe 50 µl size. The drug solution could penetrate only superficial but not deeper especially by the case of smooth surface of WG blank tablet of 1800 kg CF because of less porosity such that 11 % v/v. A loadable tablet should be 30% v/v or more (Gole *et al*, 1996). Moreover it was found that 2, 4 or 6 times of blank solvent flushing after drug solution dropping could not only increase but in the opposite way this intervention decrease the dissolution rate of DSDT prepared from both blank tablet of 1000 kg CF.

The DSDT were characterized by SEM, XRPD and DSC method. The SEM method revealed the difference between the surface of DC and WG blank tablet including of the change of tablet surface after dropping of drug solution. It was found that WG blank tablet was smoother than DC blank tablet and roughness appeared when compacted at lower CF which corresponded to their porosity. The surface of DSDT prepared from DC blank tablet was not different from their blank tablet of all tested CF. In contrast, the surface of DSDT prepared from WG blank tablet, looked like laminar layer which more clearly discovered in DZP than in CPM-solution-dropping tablet especially of 1800 kg CF. By SEM method it could not point out both CPM and DZP particles from the surface, either superficial area or deeper area of DSDT from the other excipients of both blank tablet. It might be of very small size occurred after solvent evaporation and of extremely small amount of drug.

For XRPD method, the intensity of X-ray diffraction peak of the powder scratched from the surface of CPM-solution-dropping tablets prepared from DC and WG blank tablets seems to be of the same pattern as powder from the DC and WG blank tablets of all CF. It was clearer when using single-crystal X-ray diffraction method to characterize the scratched powder from the tablet surface especially region of dropping drug solution. Although their patterns looked similar to the patterns from blank tablets of all tested CF but it was different between DZP-solution-dropping tablets prepared from DC blank tablet of 1400 kg CF and DC blank tablet of the same CF. It was found more peaks, i.e. 17.6 and 27.1 degree of angle 2Θ. It suggested that the crystal habit of DZP might be different from that of DZP-solution-dropping tablet prepared from DC blank tablet of 1000 and 1800 kg CF. In addition it was found the major peaks at angle 2Θ of about 20.0 degree in the patterns of CPM-solution dropping tablet prepared from WG blank tablet of all tested CF which also were appear in sample of CPM and also of powder of WG blank tablet. For the patterns of DZP-solution-dropping tablet prepared from WG blank tablet, they looked similar to that of CPM-solution-dropping tablet except of tablet at 1800 kg CF. It was found the different peak at angle 2Θ of about 24.6 degree. It might be that the crystalline of DZP was appearing more on the tablet surface which is the result of the drug solution did not penetrate deeply via pore as in 1000 and 1400 kg CF tablet.

For DSC method, the thermal peak of CPM and DZP in CPM and DZP-solution-dropping tablets prepared from DC blank tablets of 1000 kg CF could not be found clearly and also of CPM-solution-dropping tablet from WG blank tablet. It might be the change of drug crystal or too small amount of drug in the scratched powder near the surfaces of DSDT. It was found the endothermic peak of Pharmatose® and small peak of DZP in DZP-solution-dropping tablet prepared from WG blank tablet of 1000 kg CF. It might be due to the reduction of DZP crystalline and the presence of some DZP particle in amorphous form.

It could be concluded that, both XRD and DSC were not the methods to be used to characterize the drug in the DSDT because of too small amount of drug.

The amount of active ingredient and the content uniformity of DSDT prepared from both DC and WG blank tablets met the requirements. Then this novel tablet preparation could apply to prepare tablet with the same amount of drug.

To verify the possibility of using the novel tablet preparation in end effect, dissolution study was a powerful tool for characterization of this novel tablet preparation. One of main goals of *in vitro* dissolution testing is to provide reasonable prediction and correlation with the product's *in vivo* bioavailability. Anyway, the dissolution profile may be introduced to show the advantage, i.e., dissolution profile of CPM-solution-dropping tablet in comparison with tablet prepared by conventional methods, CPM DC and CPM WG, especially when using DC blank tablet of 1000 kg CF and WG blank tablet of 1800 kg CF.

For the DZP-solution-dropping tablet prepared from DC blank tablet of 1000 and 1800 kg CF it showed their dissolution rates were faster than of DZP DC tablets at the beginning phase of the profiles about 3-5 minutes. Of 1400 kg CF tablet, its release rate was slower than that of DZP DC tablet. This phenomenon corresponded to its XRPD pattern. All of any kinds of tablet prepared released more than 85% of 5 mg of diazepam within 30 minutes. It was found no difference in the profile of DZP-solution-dropping tablet prepared from WG blank tablet and DZP WG tablet of 1000 kg CF but however it released slower than DZP WG tablet of 1400 and 1800 kg CF. On the other hand, DZP was released more than 85% of 5 mg from DZP-solution-dropping tablets prepared from WG tablets of 1000 and 1400 kg CF within only 5 minutes and of 1800 kg CF within 10 minutes.

The dissolution rate was affected by the applied force for CPM- and DZP-solution-dropping tablet prepared from DC and WG blank tablet respectively, which their dissolution rates were slowed as the compression force was increased. For CPM- solution-dropping tablet prepared from WG blank tablet, the tablet of 1800 kg CF showed the release of CPM in the leading. DZP-solution-dropping tablet prepared from DC blank tablet, diazepam was released from tablet of 1400 kg CF in comparison with another slowest. More to the point, the dissolution rate of CPM-solution-dropping tablet prepared from DC blank tablet was faster than that of tablet prepared from WG blank tablet at all tested CF especially at 1000 kg CF. In the contrast, release rate of DZP-solution-dropping tablet prepared from WG blank tablet was faster than the rate of tablet prepared from DC blank tablet when the compression force was increased.

For the stability study, amount of active ingredient in DSDT prepared from DC blank tablet of 1000 kg CF after 3 months storage was significantly still met the requirement and not so much different from the 0 month during three months storage. The amount of drug released of DSDT of all tested CF were not less than 80% of the labeled amount of CPM and 85% of the labeled amount of DZP within 30 minutes throughout 3 months except the CPM-solution-dropping tablet prepared from WG blank tablet of 1800 kg CF. Besides it was found that the dissolution rates of both DC and WG conventionally prepared tablet were decreased when compared to DSDT during 3 months storage especially CPM DC blank tablet of 1000 and 1400 kg CF. The exception was the dissolution rate of DZP-solution-dropping tablet prepared from DC blank tablet of 1400 kg was decreased more than of DZP DC tablet of the same CF.

In conclusion it was suggested that DSDT could be a new suitable process for the preparation of tablet dosage form not only for water soluble but for poorly water soluble drug or other therapeutic substances especially for the low dose drugs. It was appropriate method for some drug which their physical properties such as crystallinity was altered or changed under mixing; compression force or uniformity including its poor compressibility was exactly needed. To solve this problem this preparation was started by using DC and WG blank tablet and then introduced an active ingredient in liquid form into the blank tablet. The results revealed that it should be prepared from

blank tablet with insoluble excipient for soluble drug and with soluble excipient for poorly soluble drug especially for the blank tablets of 1000 kg CF. It corresponded to the porosity of the blank or loaded tablet with porous delivery matrix.

DSDT purpose the advantage over conventional tablet. The advantages are as followings: 1) there are no requirements on the compressibility of the active ingredients 2) the exact concentration of drug solution dropping on the blank tablet, resulting in a more uniform dispersion of fine particles; and 3) the bioavailability of the drug substance could be improved when it is dispersed at the molecular level in drug solution.

The suggestions in this study are the followings.

1. Additional study about the penetration of solution after dropping on the DC and WG blank tablets of all tested CF should be investigated. The reason was that some peaks in XRD pattern of the powder from the surface of DZP-solution dropping tablet prepared from DC blank tablet at 1400 Kg CF and prepared from WG blank tablet at 1800 kg CF which were different from their blank tablet. The method of adding the coloring solution onto the blank tablet might be not enough to examine how depth the penetration of drug solution would be. The depth and the pattern of the penetration would be investigated by cutting the tablet in half. Another method may be used NIR chemical image as shown in appendix D. Its application is to visualize chemical composition, characterize particle size distribution of components in both blank tablet and DSDT and might be able to detect polymorphs on the tablets.

2. It was found the layer of CPM cover the surface of CPM-solution-dropping tablet and small crystals of diazepam on the dropped side of the surface of DZP-solution-dropping tablet at higher CF. The cause might be rapid evaporation of dichloromethane and the drug could not be penetrate into the tablet but adsorbed onto the tablet and might be recrystallized to be other polymorphs. Therefore the solvent using to dissolve drug should be chosen the slower evaporation than dichloromethane i.e. the mixture of absolute alcohol and dichloromethane in 1:2 or 2:1 by volume.

3. The magnification of SEM to characterize DSDT should be increased until the drug particle was clearly seen in order to obviously compare with intact single particle of CPM and DZP. The maximum magnification of the SEM used in this study is 250,000X which produces three dimensional images.

4. Both DC and WG blank tablets should be prepared by using the same type of fillers because the property of the different filler may affect drug solubility and adsorption on the tablet. For example, Dicalcium phosphate dihydrate, unmilled and milled grade, may be used in DC and WG blank tablet, respectively. Lactose anhydrous and spray-dried lactose could be used in DC tablet as filler while lactose monohydrate could be used in WG tablet.

5. The dissolution profiles comparison for characterization of DSDT should be additional analyzed by kinetic models in which the amount of drug dissolved ($Q$) is a function of the test time, $t$ or $Q = f(t)$. The $Q(t)$ function is used to identify the kinetic models such as zero order, first order, Hixson–Crowell, Weibull, Higuchi, Baker–Lonsdale, Korsmeyer–Peppas and Hopfenberg models. Other parameters, such as dissolution time ($t_{x\%}$), assay time ($t_{x\ min}$), dissolution efficacy (ED), difference factor ($f_1$), similarity factor ($f_2$) and Rescigno index ($\xi_1$ and $\xi_2$) can also be used to characterize drug dissolution profiles; especially the first order model, the dissolution rate could be compared by using t-test.