CHAPTER IV
DISCUSSION

4.1 Evaluation of blank tablet properties

4.1.1 Weight variation

Because of using blank tablets in the study, weight variation test in USP 30 <2091> were referred. The tests provide limits for the permissible variations in the weights of individual tablets in term of the allowance deviation from the average weight of a sample. From the result in Table 3.1, the weight of both DC and WG blank tablets conform to the criteria given in Table 3.2. It showed that weight of each blank tablet at all tested CF was uniform. The percentage of relative standard deviation of DC blank tablet was lower than WG blank tablet. The reason is the good flow property of DCP in the formulation of DC blank tablet and glidants are generally not necessary (Shangraw, 1989; Raymond et al., 2006). In the case of WG blank tablet, talcum was used as glidant in the formulation as shown in Table 2.2. Moreover the wet granulation as well as mechanical problems can contribute to tablet weight variation (Gordon et al., 1989). However, the weight variation of both DC and WG blank tablet comply the requirement of USP for uncoated tablet.

4.1.2 Hardness testing

A tablet requires a certain amount of strength or hardness to withstand the shocks of handling in its manufacture, packing, shipping and dispensing. Hardness is a function of the applied pressure. As additional pressure is applied to make a tablet, the hardness value increased (Gordon et al., 1989), as shown in Table 3.3. the hardness of both DC and WG blank tablet. The increased hardness of DC blank tablet was higher than WG blank tablet when CF increased. The reason was DCP dihydrate

as filler in DC blank tablet was more compressible than lactose and apparently deforms by brittle fracture when compressed, forming clean bonding surfaces (Shangraw, 1989). Greater force cause fracture and are therefore “harder” than lower force.

The optimum hardness for a given tablet formulation will depend to some degree on the intended use for the tablet. For tablets intended to directly packed and eventually swallowed by a consumer, disintegration and dissolution properties may be prime considerations for tablet hardness, so long as the tablets can withstand packaging (Gordon et al., 1989). Therefore DC and WG blank tablet of all CF tests with low and high hardness were included in further study. An appropriate balance between a minimally accepted tablet hardness to produce an adequate friability value and a maximally accepted tablet hardness to achieve adequate tablet dissolution may be required.

4.1.3 Tablet friability

Another measure of a tablet’s strength is its friability. Friability is related to an ability of tablet to withstand both shock and abrasion without crumbling during the handling of manufacturing, packing, shipment and consumer use. Conventional compressed tablets that having friability less than 0.5 to 1.0% in weight after operation by using friabilator are generally considered acceptance (Gordon et al., 1989). Table 3.4 showed percent friability of both blank tablets was decreased when CF increased. They were lower than 1.0% by weight except WG blank tablet of 1000 kg CF was over the acceptance value although its hardness was higher than DC blank tablet of the same CF. However the friability of WG blank tablet of 1000 kg CF was slightly more than 1.0 % by weight. All of them were included further in the study.

4.1.4 Tablet porosity

In general the tablet porosity will decrease when the CF increased because of the increasing of bonding of the particles in tablet by three theories such as mechanical theory, the intermolecular theory and the liquid-surface film theory (Parrot, 1989). Figure 3.5 showed percent porosity of DC and WG blank tablet corresponding to the previous mentioned which tablet porosity decreased when CF

increased. In addition, percent porosity of WG blank tablets at all tested CF was lower than DC blank tablets. The reason was the water soluble filler, Pharmatose®, in WG blank tablet attributes bonding to the presence of a thin liquid film. The local effect of the high pressure on the melting point and solubility of Pharmatose® is essential bonding (Parrot, 1989). In a granulation process, the particles are bound together and so segregation is less likely to happen. Moreover substances that deform plastically typically give tablets of lower porosity than those which fragment such as DCP dihydrate (Armstrong, 2007). Dropping drug solution into WG blank tablet may be less penetration than DC blank tablet.

4.1.5 Disintegration test

Figure 4.1 illustrates a scheme of the ways in which drugs formulated into a tablet become available to the systemic circulation. For most conventional tablets, the first important step in the sequence is the disintegration which as breakdown of the tablet into smaller particles or granules. (Gordon et al., 1989). Usually, as the applied pressure to prepare a tablet is increased, the disintegration time is longer (Parrot, 1989). The result was the mean of disintegration time of both blank tablets were higher when CF increasing. DC blank tablet disintegrated very faster than WG blank tablet about 20 times of all tested CF as shown in Figure 3.2. Although the same amount of Ac-Di-Sol® as super disintegrant added in both blank tablets but the water soluble filler, Pharmatose®, in WG blank tablet reduced the efficiency of water for wicking and swelling ability of the disintegrant. In addition, the porosity of WG blank tablet was less than DC blank tablet as shown in Figure 3.3. It affected the ability of water to penetrate into the tablet by capillary action. This study will proof that the disintegration of blank tablet also affect the dissolution of DSDT or not.

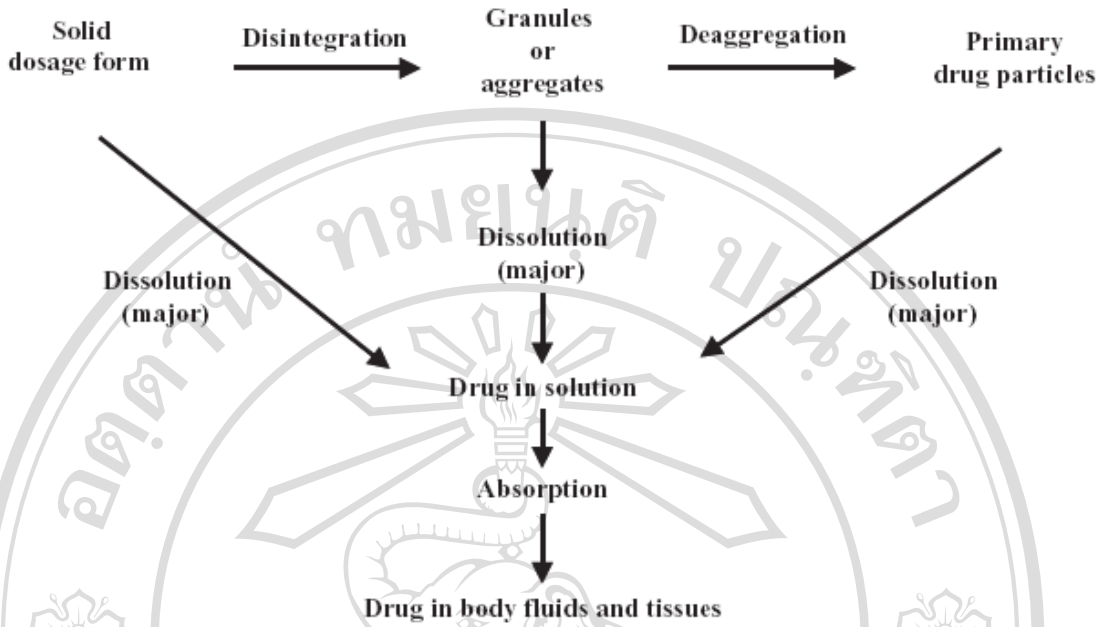

Figure 4.1 Disintegration and dissolution pathways of solid dosage forms for absorption of drug.

4.2 Study of the depth of solution after dropping on blank tablet

Figure 3.3 showed DC blank tablet with green color of 0.1% fast green FCF in alcohol distributed on dropping surface and a half depth of lateral side. It may be assumed that drug solution could distribute and penetrate into blank tablet in the same manner and direction as 0.1% fast green FCF in alcohol do.

4.3 Tablet characterization studies

4.3.1 Morphology studies by digital camera

Figure 3.4 indicated that drug solution might be dropped on blank tablets of all tested CF because of no physical change of tablet such as lamination or breakage after dropping solvent or solvent mixture without drug. Absolute alcohol and dichloromethane in ratio 1:3 could solubilize CPM and DZP better than absolute alcohol or another ratio of the alcohol and dichloromethane such as 1:1, 1:2 because the solubility of CPM or DZP in dichloromethane was more than in alcohol (White, 2000a, 2000b). Therefore the volume of drug-solution was used as less quantity as possible. Nevertheless the mixture of solvents could not be used to prepare DSDT

from WG blank tablet of all tested CF as shown in Figure 3.5. The reason was the low porosity of WG blank tablet as shown in Table 6.1. CPM solution could not be penetrate and the surface appearance of CPM-solution-dropping tablet was rough and non-homogeneous which differs from its blank tablet especially of 1800 kg CF. Therefore only dichloromethane was used instead of the solvent mixture for DSDT prepared from WG blank tablet of all tested CF.

Surface of DSDT prepared from DC blank tablets of all tested CF were smoother than their blank tablets as shown in Figure 3.6 – 3.8. The reason was the drug solution easily penetrated into the DC blank tablet with more porosity than WG blank tablet. Especially DSDT prepared from WG blank tablet of higher CF possessed rougher surface as shown in Figure 3.9 – 3.11. The drug solution could not penetrate into smooth surface of WG blank tablet of 1800 kg CF instantly and dichloromethane as a single solvent rapidly evaporated. Multilayer of CPM and DZP crystal could be seen on the tablet surface as shown in Figure 3.12 and Figure 3.13 respectively.

4.3.2 Morphology studies by scanning electron microscope

4.3.2.1 Morphology of tablet surface

The continuous surface was found in some area of DC blank tablet surface and lower porosity in tablet of higher CF as shown in Figure 3.14 (a), 3.15 (a) and 3.16 (a). The result corresponded to percent porosity of DC blank tablet in Figure 3.4. DCP dihydrate, major ingredient in DC blank tablet, had different shape and smaller size from intact DCP dihydrate especially under magnification 1000X as shown in Figure 3.20 (c). The reason was DCP dihydrate apparently fractures well under compression, forming clean bonding surface (Shangraw, 1989). The small amount of other excipients of tablet i.e., Ac-Di-Sol® and magnesium stearate as shown in Figure 3.21 and 3.23 respectively could not be found and characterized on surface of DC blank tablet especially tablet of higher CF. The higher porosity in DC blank tablet of 1000 and 1400 kg CF showed more advantage for penetration of drug solution into tablet than DC blank tablet of 1800 kg CF. It is not clear to point out which one is drug particle, CPM or DZP as shown in Figure 3.25 and 3.26 respectively, on the tablet surface of 1000 and 1400 kg CF DSDT as shown

in Figure 3.14 (b), (c) and 3.15 (b), (c). For tablet of 1800 kg CF, the solution spread on the surface and became the layer after the evaporation of solvent as shown in Figure 3.16 (b), (c). The size and shape of drug particles might be changed if they were found on the tablet surface.

The SEM morphology of the surface of WG blank tablet of 1000 kg CF was smoother than DC blank tablet of 1800 kg CF but less smooth than WG blank tablet of 1400 and 1800 kg CF as shown in Figure 3.18 (a) and 3.19 (a) respectively. It corresponded to percent porosity in Table 3.5. All of excipients in WG blank tablet such as Ac-Di-Sol®, Pharmatose®, magnesium stearate and talcum as shown in Figure 3.21 – 3.24 could not be identified on tablet surface because soft granule of Pharmatose® or anhydrous lactose, major amount in the tablet, closely adhered together better than DCP dihydrate particles done in DC blank tablet. CPM particles were apparently found on the surface of CPM-solution-dropping tablet prepared from WG blank tablet of all CF as shown in Figure 3.17 (b), 3.18 (b), 3.19 (b) because the porosity of WG blank tablet was insufficient for CPM solution penetration into the tablet and rapid evaporation of dichloromethane as single solvent. The size of CPM particles found was in the range of 10 micron while the CPM particles before preparing solution were about 50 micron. In the case of DZP-solution-dropping tablet prepared from WG blank tablet of all tested CF, DZP particles could not be found on tablet surface which looked smoother than WG blank tablet as shown in Figure 3.17 (c), 3.18 (c) and 3.19 (c). Since only dichloromethane was used as the single solvent for preparing of drug solution, unlike DC blank tablet which drug solution was prepared from the mixture of ethyl alcohol and dichloromethane. Then the drug solution will spread and evaporate rapidly, resulting in the multiple layer of dropped drug.

4.3.2.2 Morphology of powder scratched from superficial and deeper surface of drug-solution-dropping tablet

The objective of this study was inspection of ingredients especially the active ingredients, CPM and DZP, in DSDT at superficial and deeper area whether their appearance were changed or not. It was found that the particles shape and size changed under compaction forces of their plastic, viscoelastic and

brittle fracture properties as shown in Figure 3.27 - 3.29 and 3.30 – 3.31 for CPM-solution-dropping tablet prepared from DC and WG blank tablet of all tested CF, respectively. For superficial area of DZP-solution-dropping tablet prepared from DC and WG blank tablet of all tested CF, the ingredient morphology was shown in Figure 3.32 - 3.33 respectively. CPM and DZP could not be identified from another composition although they were not compressed only were dropped on the surface. The both active ingredients may be transformed to very small size particles after solvent evaporation and another reason an extremely small amount was used. Therefore this method could not be used to evaluate the characterization of CPM- and DZP-solution-dropping tablet.

4.3.3 XRPD of powder of the tablet compositions and the powder from DSDT

It is important to study the polymorphic changes of the tablet compositions on the surface of tablet especially CPM and DZP. XRPD diffraction is the most powerful method for detecting polymorphs because polymorphs have own different crystal structures (Ando and Radebaugh, 2005). In XRPD, the amorphous form shows a shallow peak or halo, as opposed to sharp and intense peaks for a crystalline drug compound (Omathanu, 2008). The XRPD patterns of scratched surface powder from DSDT prepared from DC blank tablet of all tested CF were shown in Figure 3.41 - 3.43 for CPM-solution-dropping tablet and Figure 3.47 – 3.49 for DZP-solution-dropping tablet revealing that the prominent peaks were similar to that of DCP dihydrate at angle 2Θ about 11.4, 20.7 and 29.1 degree as shown in Figure 3.36. The peak of CPM did not appear in the mentioned pattern when compared to the XRPD of CPM which showed distinct sharp peaks at 19.2 and 20.2 degree (Eckhart and McCorkle, 1978) or 19.1 and 20.0 degree as shown in Figure 3.34. The pattern from powder of DZP-solution-dropping tablet had not shown the peak of DZP when compared to XRPD of pure DZP whose very sharp peaks were 18.6 and 22.6 degree as shown in Figure 3.35. The reason was the very small amount of CPM and DZP including other compositions such as Ac-Di-Sol® and magnesium stearate combined.

The results of XRPD of scratched surface powder of DSDT prepared from WG blank tablet as shown in Figure 3.44 - 3.46 for CPM-solution-dropping tablet and

Figure 3.50 – 3.52 for DZP-solution-dropping tablet were the same as prepared from DC blank tablet of all tested CF. The prominent peak was similar to that of the main composition such as Pharmatose® at the diffraction angle 2Θ were of about 19.7 degree as shown in Figure 3.37. These obtained patterns could not support to inform the crystal forms of CPM and DZP in both DSDT prepared from DC and WG blank tablets.

Single crystal X-ray diffraction pattern of powder

The powder scratched from tablet surface may contain a very small amount of CPM or DZP which is not enough in studying their crystal properties after dropping drug solution on blank tablet. From Figure 3.3, it also showed that the tested color solution penetrated slightly through tablet. Therefore powder from the tablet surface especially in solution dropping area was studied again by X-ray monochromator (single crystal). Single-crystal X-ray provides the most complete information about the solid state because the exact relative locations of atoms in the molecular crystal could be determined (Ando and Radebaugh, 2005). The patterns of diffracted X-ray of the scratched powder from the surface of blank tablets revealed the same major peaks of DCP dihydrate for DC tablets and Pharmatose® for WG tablets as previous study of all tested CF but more clearly as shown in Figure 3.53 – 3.55 and 3.56 – 3.58 respectively. For the patterns of the scratched powder from the surface of CPM and DZP-solution-dropping tablets which possibly was found to have high quantity of CPM and DZP are shown in Figure 3.59 – 3.61 and 3.62 – 3.64 respectively as prepared from DC blank tablet. Their patterns looked similar to the patterns from blank tablets of all tested CF except for DZP-solution-dropping tablet prepared from DC blank tablet of 1400 kg CF. However it was found more peaks, i.e. 17.6 and 27.1 at angle 2Θ. It suggested that the crystal habit of DZP may be different from DZP of DZP-solution-dropping tablet prepared from DC blank tablet of 1000 and 1800 kg CF.

The distinct peak at angle 2Θ about 20.0 degree in the patterns of CPM-solution dropping tablet prepared from WG blank tablet of all tested were found in the same range of CPM as shown in Figure 3.34 and this phenomenon was also the similar patterns as in WG blank tablet. However the result patterns from DZP-

solution-dropping tablet prepared from WG blank tablet looked similar to CPM-solution-dropping tablet except at 1800 kg CF, which showed the different peak at angle 2Θ about 24.59 degree. It might be concluded that DZP crystallized more on the tablet surface and the drug did not penetrate deeply via pore as in 1000 and 1400 kg CF tablet.

It may contribute to enhancement of dissolution of the drug if the crystallinity of both drugs is reduced or behaved amorphous form in tablets (Shah et al, 2007). However it could not be convinced that the habits of CPM and DZP particles after solvent evaporation were amorphous or crystalline form. The reason may be drug content in sample having a very small amount.

4.3.4 Differential scanning calorimetry analysis

The thermal behaviors of the scratched powder near the surfaces of DSDT were revealed by the following details. The endothermic peak of CPM-solution-dropping tablet prepared from DC blank tablet of 1000 kg CF as shown in Figure 3.71 was in the range of CPM which corresponding to Eckhart et al, 1978 which were shown in Figure 3.72 and DCP dihydrate as shown in Figure 3.73 and. Interaction between CPM and DCP dihydrate may occur. Figure 3.75 showed the thermogram of Pharmatose® which similar as the study of its polymorphism had the peak at 150°C depending on the particle size of sample (Raymond et al, 2006). For the thermal peak of tablet from WG blank tablet of 1000 Kg CF shown in Figure 3.74 was not corresponding to Pharmatose®, the major ingredients in WG blank tablet as shown in Figure 3.75 and CPM peak could not be found clearly. It might be the transition of CPM to amorphous form or too small amount of CPM in the powder.

According to DSC thermogram of DZP-solution-dropping tablet prepared from DC blank tablet of 1000 kg CF revealed the endothermic peaks different from both DCP dihydrate and DZP as shown in Figure 3.76 and 3.77. The supportive reason might be the same as CPM-solution-dropping tablet prepared from DC blank tablet. It was found the distinct endothermic peak of Pharmatose® and small peak of DZP in DZP-solution-dropping tablet which prepared from WG blank tablet of 1000 kg CF as shown in Figure 3.78 when compared with onset and peak temperature in

DSC thermogram of Pharmatose® and DZP and as shown in Figure 3.75 and 3.77. It might be due to the transforming in some extent of DZP to amorphous form.

4.4 Determination of the active ingredient content

The content of CPM and DZP in DSDT prepared from DC blank tablet of 1000 kg CF were within the range of percent labeled amount as stated in Pharmacopoeia. It could point out that this method of dropping drug solution on blank tablet could be applied to prepare tablets as alternative method and the drug content complied with the accepted level.

4.5 Content uniformity testing

The test of content uniformity is required for both CPM and DZP tablet monograph. Uniformity of dosage units and uniformity of content are the requirements of USP 30 and BP 2007 respectively. Table 3.5 showed that CPM- and DZP-solution-dropping tablet prepared from DC blank tablet of 1000 kg CF met the requirement / criteria as in APPENDIX C and APPENDIX D for CPM tablet USP and DZP tablet BP respectively. The reason was DSDT preparing by dropping solution with exact quantity of drug solution by microsyringe on blank tablet. Then the content uniformity of the drug in each tablet will be reliable.

4.6 Dissolution studies

Bioavailability of tablet could be predicted by dissolution studies. *In vitro* dissolution might be relevant to the prediction of *in vivo* performance (Armstrong, 2007). Dissolution profiles of various tablet preparations were evaluated as following items.

4.6.1 Effect of time of solvent dropping

According to 0.1% fast green FCF in alcohol could not penetrate deeply into DC blank tablet as shown in Figure 3.3, promoting drug penetration was needed by dropping blank solvent after dropping drug-solution. The crystal habit of drug may be amorphous form when drug solution was penetrated through the small void of tablet. The amorphous form of drug usually is dissolved more rapidly than the corresponding crystalline form to increase its dissolution and bioavailability. The

dissolution profiles of CPM-solution-dropping tablet prepared from DC and WG blank tablet were shown in Figure 3.79 – 3.80 and DZP- solution-dropping tablet prepared from DC and WG blank tablet in Figure 3.81 – 3.82. It was revealed that 2, 4 or 6 times of blank solvent dropping after drug-solution dropping did not increase drug dissolution in profile when compared with no solvent dropping. In addition, more times of solvent dropping more resulted in negative effect of decrease of drug dissolution. It was possible that the polymorphic of drug transform to stable form during recrystallize after solvent evaporation, except for DZP-solution-dropping tablet prepared from WG blank tablet as shown in Figure 3.82. The result suggested that Pharmatose® or lactose monohydrate, the majority ingredient of WG blank tablet, is freely albeit slowly soluble in test medium and as such lactose is a suitable diluent for active ingredients of low water solubility such as DZP (Armstrong, 2007). The times of blank solvent dropping had affected only a minor influence on the amount of drug dissolution. Then it could be concluded that dropping the blank solvent after dropping of drug solution apparently did not promote the drug dissolution.

4.6.2 Dissolution profiles of CPM-solution-dropping tablet

The 90% dissolution of CPM from the CPM-solution-dropping tablet of 1000 kg CF was within 5 minutes and significantly faster than non solution dropping CPM DC tablet ($p<0.01$) as shown in Figure 3.83. It could be explained by the penetration of CPM solution through high porosity and very small crystal or amorphous form of CPM occurred during solvent evaporation and then promoted it to increase dissolution rate (Holm et al, 2006; Shanbhag et al, 2008). However, factors can affect drug dissolution rates of tablets, including the crystal size of the drug; tablet disintegration mechanisms and rates (Peck et al., 1989). Of 1400 and 1800 kg CF tablet, the dissolution rate comparing between the profile of the CPM DC tablet and the CPM-solution-dropping tablet was not significantly different ($p>0.01$) as shown in Figure 3.84 and 3.85 respectively. From this point, CPM solution could not penetrate easily into the tablet of higher CF, i.e., less porosity.

The dissolution rate of the CPM-solution-dropping tablets prepared from WG blank tablets and the CPM WG tablets were not significantly different ($p>0.01$). Except that of the tablet at 1000 kg CF which drug dissolution rate from

CPM-solution-dropping tablets were significantly slower than that of the CPM WG tablets, especially at 3 and 5 minutes ($p<0.01$) as illustrated in Figure 3.86. The CPM solution dropped might be unable to penetrate through the smooth surface of the tablet and then CPM crystallized on the surface after solvent evaporation. For tablet of 1800 kg CF at 1 minute test, the CPM dissolution of CPM-solution-dropping tablets were significantly faster than that of the CPM WG tablets ($p<0.01$) as shown in Figure 3.87. It pointed out that the dissolution rate of the CPM-solution-dropping tablets was not dependent on disintegration time as CPM WG tablet being when CF is increased. In comparison to the commercial CPM tablets, the dissolution rates of the CPM-solution-dropping-tablets at 1000 and 1400 kg CF at 1, 3 and 5 minutes were faster than the commercial CPM tablets ($p<0.01$) as shown in Figure 3.86 and 3.87 respectively. Drug dissolution of CPM-solution-dropping tablets of 1800 kg CF was faster than the commercial CPM tablets at all times of study which was in accordance with the explanation mentioned before. Dissolution rate of commercial CPM tablet was also shown having slower rate than CPM DC and CPM-solution-dropping tablet prepared from DC blank tablet of all tested CF. The reason was that the commercial tablet might be prepared by wet granulation using water soluble filler such as lactose monohydrate. α-lactose monohydrate is used in tableting by the wet granulation method in the sense that on wetting some goes into solution thereby coating the drug and offering an amount of protection and slow release (Bandelin, 1989). On the other hand CPM and Pharmatose® were both water soluble substance. But for Pharmatose®, the major part as water soluble filler in tablet, competed with CPM to get water for dissolving itself.

Anyway, the dissolution profiles met the requirement in monograph of USP that not less than 80% of 4 mg of CPM is dissolved within 30 minutes (USP 30). These results suggest that CPM-solution-dropping tablets especially prepared from DC blank tablet could be a suitable process for the novel preparation

4.6.3 Dissolution profiles of DZP-solution-dropping tablet

At 3 and 5 minutes of 1000 kg CF, of dissolution test DZP-solution-dropping tablet prepared from DC blank tablet, DZP was dissolved significantly faster than that of the DZP DC tablets ($p<0.01$) as shown in Figure 3.89 and 3.91. It could

be explained by a higher porosity and their irregular surface obtained at lower CF. DZP solution could possibly penetrate into the DC blank tablets and after drying, DZP will be small particle eventually being in amorphous form and then increased the dissolution rate (Holm et al, 2006; Shanbhag et al, 2008). Of 1400 kg CF tablet, the dissolution rate of DZP-solution-dropping tablet was significantly slower than dissolution rate of DZP DC tablet at all points ($p<0.01$) as shown in Figure 3.90. It showed different performance in 1800 kg CF tablet which their dissolution rates of DZP-solution-dropping tablet was not significantly different from DZP DC tablet ($p>0.01$). This corresponded to the XRPD of DZP-solution-dropping tablet prepared from DC tablet of 1400 kg CF. It was found more peaks which suggested that the crystal habit of DZP may be different from DZP-solution-dropping tablet prepared from DC blank tablet of 1000 and 1800 kg CF. The dissolution of DZP from commercial tablet studied was shown to be faster than both DZP DC and DZP-solution-dropping tablet prepared from DC blank tablet of all tested CF. It could be concluded that the commercial tablet which prepared by wet granulation, the lactose monohydrate as water soluble filler play an very important role. Lactose monohydrate is freely albeit slowly soluble in water and as such it is a suitable diluent for active ingredients of low water solubility such as DZP (Armstrong, 2007).

The dissolution rate after 3 minutes of DZP-solution-dropping tablet prepared from WG blank tablet of 1000 kg CF was not significantly different comparing to DZP WG tablet ($p>0.01$). However more than 85% of 5 mg of DZP was dissolved from both kinds of tablet of 1000 and 1400 kg CF within only 5 minutes as shown in Figure 3.92 and 3.93 respectively. This pattern supported the XRPD which showed the different peaks between intact DZP and DZP-solution-dropping tablet. Of 1800 kg CF, the dissolution rate of DZP-solution-dropping tablet was clearly lower than DZP WG tablet as shown in Figure 3.94. This could be due to the smoother surface which the DZP solution dropped might be unable completely to penetrate and then DZP crystallized on the surface during solvent evaporation. DZP dissolution of commercial tablet was shown to be not significantly different from DZP WG tablet of all tested CF. The reason was that the commercial tablet might be prepared by wet granulation using water soluble filler such as lactose monohydrate as DZP WG tablet.

These results suggest that DZP-solution-dropping tablets especially from WG blank tablet could be a suitable process for the novel preparation in term of the dissolution profiles which met the requirement in monograph of USP that not less than 85% of 5 mg of DZP is dissolved within 30 minutes (USP 30).

4.6.4 Effect of compression force on drug dissolution of DSDT

The effect of applied pressure on the dissolution of disintegrating tablet is difficult to predict (Parrot, 1989). If fragmentation of the granules occurs during compression, the dissolution is faster as the applied force increased, and the fragmentation increases the specific surface. If the bonding of the particles is the predominate phenomena in compression, the increase in applied pressure causes a decrease in dissolution (Lesson and Cartstensen, 1974). In case of CPM-solution-dropping tablet prepared from DC blank tablet it could not explain as above mentioned although the good binding property of DCP in blank tablet. Since CPM was not either mixed together with all diluents of blank tablet or compressed. It may supposed that the size of CPM crystal which occurred during solvent evaporation in tablet of 1000 kg CF was smaller than of 1400 and 1800 kg CF tablet (Peck et al., 1989). Another factor may be the disintegration time which increase when the compression forces increase (Parrot, 1989). The disintegration times were not different between 1400 and 1800 kg CF tablet which had no effect on the dissolution of 1400 and 1800 kg CF tablet. Anyway their drug dissolution were slower than of 1000 kg CF tablet as shown in Figure 3.95. The reason is longer disintegration time than of 1000 Kg CF tablet might be supportive for this phenomenon.

CPM-solution-dropping tablet prepared from WG blank tablet was different from that of DC blank tablet. The cause may come from Pharmatose®, the majority ingredient in WG blank tablet of 1800 kg CF was slowly soluble than CPM because of longer disintegrating time than 1000 and 1400 kg CF tablet. So the drug from CPM-solution-dropping tablet prepared from WG blank tablet of 1800 kg CF was dissolved faster than of 1000 and 1400 kg CF tablet as shown in Figure 3.96. It pointed out that the dissolution rate of the CPM-solution-dropping tablets prepared from WG blank tablet was not dependent on disintegration as prepared from DC blank tablet.

The dissolution profile of DZP-solution-dropping tablet prepared from DC blank tablet was not affected by CF whilst it affected on dissolution of DZP of tablet prepared from WG blank tablet which their dissolution rates decreased when CF increased as shown in Figure. 3.97 and 3.98. In general as the tablet void increases, the penetration of water into the tablet is accelerated due to faster dissolution of lactose region and partly collapse of the tablet (Fukunaka *et al*, 2006). When CF was lower such as DZP-solution-dropping tablet prepared from WG blank tablet of 1000 kg CF, porosity was increase and disintegration time lower and then resulting in faster dissolution of lactose and diazepam.

It showed that the dissolution rate of the DZP-solution-dropping tablets prepared from DC blank tablet was not dependent on disintegration as prepared from WG blank tablet when CF is increased. The drug dissolution rate of DZP-solution-dropping tablet prepared from DC blank tablet of 1400 kg CF was slowest because of diazepam crystal occurred during solvent evaporation as stated in XRPD pattern as shown in Figure 3.63.

4.6.5 Comparison of DSDT dissolution profiles of tablets prepared from DC and from WG blank tablet

Drug dissolution of CPM-solution-dropping tablets prepared from the DC blank tablets of all tested CF were shown having positive tendency of dissolution in comparison with WG blank tablet as in Figure 3.99 and 3.100 respectively. The slow dissolution of the drug in CPM-solution-dropping tablets prepared from the WG blank tablets might be caused by the very fast dissolution of lactose monohydrate from the disintegrating tablet (Drooge et al., 2004). Pharmatose® i.e., lactose monohydrate with hydrophilic property was the major part and affected the dissolution of CPM which was the minor part. The dissolved amount of drug of the tablet prepared from WG blank tablet of 1800 kg CF was not significantly different comparing to tablet prepared from DC blank tablet ($p>0.01$) as shown in Figure 3.100 (c). The drug dissolution of tablet prepared from DC blank tablet decreased because of lower porosity in DC blank tablet while prepared from WG blank tablet increased because of bonding of lactose particles.

DZP dissolution rate from DZP- solution-dropping tablet prepared from WG blank tablets using lactose as diluent was faster than that from DC blank tablets using Emcompress® (DCP) as DC filler at 1000 and 1400 kg CF as shown in Figure 3.100 (a) and (b) respectively. The reason was dissolution rates for diazepam-Emcompress® interactive mixtures were lower than those of pure diazepam. The rate of dissolution of diazepam in the lactose interactive mixture was markedly higher than that of pure diazepam (Always et al., 1996; Supabphol and Stewart, 1996). Moreover DCP is not recommended for use in high concentrations in combination with drugs of low water-solubility such as DZP. (Shangraw, 1989)

At 1800 kg CF, the dissolution rate exhibited no significant difference between the DZP- solution-dropping tablet prepared from WG and DC blank tablet. It might be of the same reason due to the extreme smoothness of tablet surfaces, lower porosity and a very long disintegration time of the tablet prepared from WG blank tablet. Therefore DZP dissolution from tablet prepared from WG blank tablet decreased while DZP dissolution increased as in the case of tablet prepared from DC blank tablet.

4.7 Stability Studies

4.7.1 Drug content

The amount of CPM and DZP in DSDT of 1000 kg CF still remained within the range of monograph requirement with only a little change in each month of 3 months storage as shown in Table 3.8. It pointed out that both drugs were compatible with the ingredients in DC and WG blank tablets (Raymond et al, 2006). Moreover both drugs did not mix together with both blank tablet ingredients by this preparation of dropping the drug solution on the tablet surface. It might be difficult to come out drug-excipient interactions which are often directly related to the moisture present in one or another of the components or to the humidity to which the formulation is exposed during processing or storage (Augsburger and Zellhofer, 2007).

4.7.2 Dissolution profiles

Although the tablet may be expected to retain the full label potency of the active ingredient provided the tablet is stored as directed. The dissolution rate also is

the one of tablet physical parameters recommended for testing. Drug dissolution profile of CPM-solution-dropping tablet prepared from DC blank tablet of 1000 kg CF including tablet of 1400 kg and 1800 kg CF after 3 month storage were shown in Figure 3.101. The results conformed to the content stability when compare to the sample at 0 day. It revealed that CPM-solution-dropping tablet prepared from DC blank tablet of 1000, 1400 and 1800 kg CF might be stable. Although tablet of 1000 kg CF only initial period showed rapid dissolution followed by a decrease of dissolution rate after 2 month storage. Moreover their dissolution rates were not corresponded with the storage time. In contrast to CPM DC tablet, after 3 months storage CPM was dissolved less amount when compared to CPM-solution-dropping tablet of all tested CF. Their dissolution rates were corresponded with the storage time except after 2 and 3 months storage as shown in Figure 3.102. It might explained that the drug-excipient interactions which are often directly related to the moisture present in one or another of the tablet components or to the humidity to which the formulation is exposed during processing or storage (Augsburger and Zellhofer, 2007). Of CPM-solution-dropping tablet prepared from WG blank tablet of 1800 kg CF, it was physically unstable and showed the tendency of slower dissolving of CPM in tablet of 1400 kg CF after 3 months storage as shown in Figure 3.103. It might be explained that there was the change of crystalline of CPM during storage.

Dissolution rate of DZP-solution-dropping tablet prepared from DC blank tablets and DZP DC tablet of all tested CF were decreased when CF increased after storage 3 months as shown in Figure 3.104 and 3.105 respectively. It pointed out the effect of the property of DCP, major ingredient, on dissolution behavior after storage. In contrast to DZP-solution-dropping tablet prepared from WG blank tablet of all tested CF the dissolution rate did not change too much when storage in 3 months as shown in Figure 3.106. They are quite stable than both DZP-solution-dropping tablet prepared from DC blank tablets and DZP DC tablet. This may be caused by water soluble property of Pharmatose® (lactose monohydrate) still was a suitable diluent for active ingredients of low water solubility.