CHAPTER IV
DISCUSSION

4.1 Determination and Optimization of Formulation Properties

4.1.1 Powder Properties

- Angle of Repose

As the result of angle of repose, it can be seen that almost formulations were ranged between 30-40 (Table 3.2 and Figure 3.2). However, the angle of repose of the few formulations were more than 40°. The selected area was choosing only the area that had angle of repose less than 40°. Although the excellent flow is required for the direct compression formulation but in this study, no formulation had the excellent and good flow; angle of repose < 25 and 25-30, respectively (the relationship between repose of angle and flow can be seen in Table 1.2, page 32). In this study, the selected angle of repose was in range 30-40°, that the powder mixture had the passable flow. The area that had angle of repose more than 40° was excluded because this area had very poor flow ability that inappropriate for direct compression.

The model of angle of repose was in Table 3.14 with R-square equal to 0.669. The contour plot of angle of repose was shown in Figure 3.7. From the contour plot, it was found that the vertex which the mixture had only one excipient as corn starch (the proportion of corn starch equal one) had the highest angle of repose as more than 44°. While the less angle of repose was shown in the opposite area of the vertex which the proportion of chitin equal to one and the area in the middle of dibasic calcium phosphate (DCP) side. It implied that, in each point within triangle indicated the various proportion of each excipient that affects the angle of repose of mixture. The angle of repose of mixture that had more than one excipient was reflected to sum of the properties of each excipient, which contained in it.

Many factors of each excipient influence the angle of repose such as shape, size, porosity, cohesion, surface area, and bulk. The effect of varying concentrations of corn starch on the flow rate and angle of repose of aspirin has been reported (Gold et

al., 1966). Increasing in concentration of corn starch (at high concentration) will increase in angle of repose and decrease the flow rate.

In case of size, the particle size and size distribution of each mixture have considerable impact on the flow properties of powder mixture. Large dry particles (DCP) have tendency to flow better than the small dry particles (corn starch and chitin) because they have greater mass. Small particles may create mixing problems because surface area are very great, and may give rise to strong electrostatic forces as a result of processing and/or inter-particle friction from movement. These forces may prevent the desired distribution of these smaller particles throughout a mixture because of fine particle agglomeration (Lentz and Schwartz, 1989).

The angle of repose is not only a relative measure of friction between powder particles but also is a measure for the most part of the cohesiveness of fine particles. However, certain generalizations can be made regarding to the angle of repose (Lantz and Schwartz, 1989).

- Angle of repose > 60 for cohesive particles
- Angle of repose < 25 for non-cohesive particles
- High angle of repose usually means poor powder flow and particles are usually less than 70 to 100 μm
- Low angle of repose usually mean good powder flow and the particles are usually greater than 250 μm

- Percent Compressibility

The percent compressibility is also important for evaluate the flow of material as same as angle of repose. The term compressibility is defined as the ability of a powder to decrease in volume under pressure (Leuenberger, 1982). So that, the less flow material will be more compressibility, while conversely the less compressibility indicates good flow.

This study limited the range for percent compressibility at less than 21 because the scope of this range was classified as excellent, good, and fair to passable flow (the

relationship of compressibility and flow can be seen in Table 1.3 page 33). For percent compressibility more than 21, the poor flow was occurred, that might be the problem for direct compression.

From the contour plot of percent compressibility (Figure 3.8), it was found that the percent compressibility was lowest at the vertex which the proportion of DCP equal one. However, the other vertices that the proportion of chitin or corn starch equal one also had low percent compressibility. It could be possibly explained that because in the area near the vertex of triangle which had content of one excipient more than the others, had the uniform size and shape, thus it lead to had more flowability (less percent compressibility) than the area near the middle of triangle, which combined more than one excipient. In addition, the other factors that affect the percent compressibility are deformability, surface area, cohesion and moisture content.

4.1.2 The Studies of Tablet Properties

- **Hardness**

In pharmaceutical industry, the hardness of tablet about 4 kilograms is considered to be the minimum permitted for a satisfactory tablet (Ansel, 1985). Also in this study, the limited range of hardness were more than 40 N. The hardness of tablet that less than 40 N were not included in further study.

In formulations F1, F2 and F3, each formulation containing 100 % of chitin, dibasic calcium phosphate and corn starch in mixture, respectively when compare the tablet hardness of formulation containing only one excipient at 1.0 ton compressional pressure, it was found that the tablet hardness of F1>.F2 >.F3. This result indicates that the tablet containing chitin 24.5 % (proportion of chitin equal one) was the highest hardness and tablet containing corn starch at the same concentration was the lowest hardness. Similarly, at 1.5 ton compressional pressure, F11 also had the maximum hardness. More over, the formulation containing high concentration of chitin such as F8 and F18 (consists of 16.33 % chitin) also had high hardness. These results indicated that concentration of chitin affect the tablet hardness. When compare the same

formulation at different compressional pressure, it reflects that increasing compressional pressure will increase the hardness of tablet. Because when increase the pressure, all pore space including both interparticulate and intraparticulate voids will decrease and each particle will be closer with more interparticulate attraction (Paronen and Ilkka, 1995; Nystrom, 1988). The interparticulate attraction will increase when increase more pressure. This result affects tablet hardness as seen in Figure 3.4.

The contour plots of hardness at 1.0 ton and 1.5 tons compressional pressure were showed in Figure 3.9 and 3.14, respectively. At 1.0 ton, the selected range was found in two areas. It was found that, these areas had the high proportion of chitin or DCP and low of corn starch. On the other hand, the higher concentration of corn starch made the lower hardness of tablet.

The compaction of powders can be devided to two stages (Paronen and Juslin, 1983): firstly, the filling by particle movement of voids of the same or larger size than the particles, secondly, the filling of the smaller voids by plastic deformation or fragmentation of particles. The die filling and rearrangement processes are dependent on the particle size, the size distribution and shape of the particles. The densification of corn starch particle is less in process of die filling and more in rearrangement. Thus, if the contact time of applied pressure not so long it can be assumed that, the rearrangement process may be incomplete then the tablet may causing extensive bond rupture and reducing the tablet strength.

- **Percent Friability**

Also the hardness of tablet, percent friability of tablet is the term that widely used to indicate mechanical strength (Marshall and Rudnic, 1990). The friability of tablet had the reverse relation with hardness. When the hardness increased, the friability decreased (Upadrashta et al., 1992). In Figure 3.4, the F3 had the lowest hardness but its friability was highest (Figure 3.5). In addition, the friability of tablet at 1.5 ton compressional pressure was lower than 1.0 ton compressional pressure in all formulations because the hardness of 1.5 tons compressional pressure were higher than 1.0 ton pressure.

Friability is a measure of the tablet's ability to withstand both shock and abrasion without crumbling during the handling of manufacturing, packaging, shipping and consumer use. According to BP. 1998, this study limited the percent friability of tablet at less than 1 % then the percent friability more than one was excluded.

- Disintegration Time

In this study, F2 and F12 were the two formulations that had long disintegration time (more than 3600 seconds). While the other formulations had disintegration time less than 30 seconds. When the study time to be over (at 1 hour), the tablet of F2 and F12 could not have the complete disintegration, while the disintegration apparatus was automatic stopped so 3600 seconds was used as the disintegration time of both formulations. However, it can be seen that the both formulations had much longer disintegration time than the other formulations. When using SAS® program to evaluate the response model of disintegration time from the data in Table 3.3 page 61, the incorrect model was occurred with R-square 0.483. This is the problem that could not use the real value of disintegration time to evaluate the response model. To solve this problem, the data treatment was used by transform the real data to logarithmic data (Judd and McClelland, 1989) and used these data (as seen in Table B3 in appendix B) to evaluate the model. The limited range of log DI was less than 2.5, this range was selected only area that had disintegration time less than 316.23 seconds (5.27 minutes).

The varying disintegration time of formulation F2 (F12) and the others were related to the presence or absence of disintegrant. In this study both formulations had single excipient; dibasic calcium phosphate at 24.5 % (the proportion of DCP equal one) and no other substance that may act as disintegrant. Tablets produced with dibaic calcium phosphate do not disintegrate readily and a disintegrant is necessary (Koparker at al., 1990; Rubinstaine and Bodey, 1976; Fischer, 1992).

Other formulations, that had some chitin or/and corn starch as excipients can rapidly disintegrate because these substances act as disintegrants and affect to shorter disintegration time. Starch is one of disintegrants that its mode of action is probably

more of inducing water uptake in the tablet than by the swelling action (Marshall and Rudnic, 1990). However, other two theories indicated the mechanisms of starch were proposed (Hill, 1976): one is that the starch grains form channels or pores that act to draw water into the tablet by capillary or wicking. Disintegration or erosion occurs when the water dissolves the soluble components in the tablet. The other theory is that the starch grains swell upon contact with water and cause the tablet to disintegrate by physically rupturing the particle to particle bonds.

Chitin is also had disintegrant property, the possible mechanism of chitin related to its moisture sorption and water uptake. Crytallinity, degree of acetylation, chain length and particle size of chitin affected the disintegration time (Ritthidej et al., 1994).

The contour plot of disintegration time seem similar in both compressional pressures. The effect of compressional pressure was not observed clearly in disintegration time because almost formulations had the disintegration less than 30 seconds, the similar value of disintegration time and contour plot were found in both compressional pressures.

- **Dissolution**

The calibration curve (Figure A1 in appendix A) was constructed by plotting the absorbance versus the concentration of aspirin in acetate buffer pH 4.5. The calibration plot showed a linear relationship. The equation of the calibration curve and correlation coefficient (r^2) are as following;

$$Y = 3.626X - 0.0073 \qquad R^2 = 0.9966$$

Where Y = UV-absorbance

X = concentration of aspirin in acetate buffer

The content of aspirin in aspirin powder was found at 94.53 %, this value was used to adjust the correct percent dissolution in this experiment.

In formulation F2 and F12 (Figure 3.6), the percent drug release at 45 minutes was low at 10 % approximately. The dissolution was related with the disintegration time of tablet (Table 3.3) that the prolong disintegrate of tablet affected to decrease the drug release from tablet as seen in Table 3.3 and Figure 3.6. This result possibly due to the fact that the tablet of formulations F2 and F12 could not disintegrate then the dissolution medium could not penetrate into tablet so that the dissolution of aspirin occurs only from the surface of the tablet.

The limited of percent drug release of aspirin tablet was according to BP 1998, selected area which had percent drug release more than 70 % at 45 minutes so that another area, which less than 70 % drug release was excluded.

The response model of percent drug release at 45 minutes of 1.0 ton and 1.5 tons compressional pressure were showed in Table 3.5 as correlation of determination equal to 0.792 and 0.835, respectively. In this study, the Weibull equation was used to illustrate the dissolution data with Td and b parameter. The dissolution of aspirin was also affected by proportion of excipient. The high percent drug release (> 70 %) at 45 minutes was found in formulations F1, F4, F6, F8 and F10 and also found in 1.5 tons pressure. This result was observed more clearly in the contour plot of percent drug release in Figures 3.12 and 3.17. At the area with high concentration of chitin (as the top vertex), it produced the tablet with high percent drug release. In the area, which lower concentration of chitin and higher concentration of DCP, the tablet had lower percent drug release. This can be confirmed by the release profile of formulation F2, when the proportion of DCP equal one (the tablet containing only one excipient), the dissolution of aspirin was retarded. Because the tablet containing only DCP can not disintegrated but it was dissolved by acid (dissolution medium) and slowly release aspirin. This indicated with the high Td at more than 1440 minutes (24 hours). It can be observed that the Td parameter was related with percent drug release at 45 minutes. The formulation which had high Td will had low percent drug release at 45 minutes. On the other hand, the lower Td was occurred from the formulation which had higher percent drug release. The b parameter indicated the rate of drug dissolution, all

formulations of both compressional pressure had the same drug release characteristic (as b < 1) (Table 3.4) that mean the release rate of aspirin of all formulation was decreased with the time increase.

In fact, the dissolution will be increased until the maximum percent release and constant in the final of release process but in this study when the drug dissolved reach to the maximum point, the release profile was turn down that may be incorrect. This problem may reflect that the excipient may absorb aspirin resulting to decrease of the dissolved drug. So that, if all points of dissolution profile were used to calculate the Weibull parameter, the incorrect data was occurred lead to obtain the nonlinear in the plot of log [- ln (1-m)] versus log t. To solve this problem, the turn down of terminal release points were excluded from the analysis.

4.3 Scale Up the Direct Compression Tablet

- Angle of Repose

In formulation X1, the significant difference was found in the experiment and the predicted data, while no significant difference was found between the experiment and the prediction of X2. The difference of experimental value from predicted value may be occurred from the following reasons;

1. From Table 3.14, it can be seen that the R-square of response surface model of angle of repose as 0.699, the low R-square indicated the decrease of reliability of the model that may predict the response.
2. In the determination process, the peak of the cone of powder can be distorted by the impact of powder from above that may be yield an error value of angle of repose (Amidon et al., 1999).

- Percent Compressibility

As well as angle of repose, the incorrect proportion of powder mixture may affect the percent compressibility of mixture. Another factor was the error from reading volume scale of graduate cylinder because after finished tap the surface of powder mixture in

cylinder was not in horizontal plane that resulting in difficult to approximate the correct volume.

- Hardness

From the result of hardness, it was found that the experiment hardness of X1 and X2 were higher than the predicted value because Hanseaten Single Stroke do not have the accurate scale of compressional pressure, then it is difficult to control the pressure. However, the hardness of tablet of X1 and X2 were higher than the limited range (40 N) and commercial tablet.

The hardness of tablet is a function of many factors all working together. Hardness is a function of applied compressional force and therefore a function of those factors that cause the force to vary. Factors that may alter tablet hardness in the course of a production run are substantial such as: alterations in machine speed, alteration of proportion of powder mixture, the irregular mix of powder mixture and irregular weight fill into the die. This latter change affect the die fills and resulting in hardness variation.

- Percent Friability

The friability of tablet related with the hardness. When increase the hardness, the friability was decreased. In this study, because the hardness of tablet produced by using Hanseaten Single Stroke was not controlled so the friability of tablet was different from the predicted value. However, the friability of X1 and X2 were similar to the commercial tablet.

- Disintegration Time

When the commercial tablets contacted with water, they disintegrated into the small granules but in formulation X1 and X2, the tablet was rapidly disintegrated to the fine particles and had shorter disintegration time than the commercial tablets. This reason is possible due to the fact that disintegration time can be affected by tablet formulation and method of manufacture (Gordon et al., 1989). However, the increase of

compression pressure that used to compress generally resulting in an increase in disintegration time. Although the limitation of instrument that caused to could not control the desire pressure but the hardness reflected the pressure. The higher hardness of tablet indicated the increasing in disintegration time from the predicted value that can be seen from formulations X1 and X2. When increasing compressional force, tablet porosity decrease and water penetration in to the tablet would slow down. The other investigators indicated that porosity, hydrophilicity (solubility if the tablet constituents are water soluble), swelling ability of particles, and interparticle force are important factors for tablet disintegration (Bi et al., 1996). When porosity decreases, more solid bridges are formed, which would make the strong interparticle force (Bi et al., 1999).

- **Dissolution**

The content of aspirin in formulations X1, X2, and the commercial tablets were found at 100.58, 95.48, and 96.94 %, respectively. These values were used to adjust the correct percent dissolution in this experiment.

Also other properties, dissolution of tablet was affected from tablet composition, tablet hardness, and disintegration times. In formulations X1 and X2, the proportion of excipient was difference. Because the higher proportion of dibasic calcium phosphate had more influence on poor disintegration and resulting in low dissolution, in X2, the proportion of chitin was lower than X1, while dibasic calcium phosphate was higher and corn starch was also higher than X1, its dissolution still lower than formulation X1.

In the comparison of Weibull parameter, the Td of X1 were significant difference ($p < 0.05$) from X2 and commercial, but this parameter of X2 and commercial was no significant difference ($p > 0.05$) as seen in Table 3.16. The b parameters of the optimized formulations (X1 and X2) were less than one, it indicate that the dissolution rates of both formulations were decreased during the time. While the b parameter of commercial tablet was more than one, it can be concluded that, aspirin dissolution had maximum release rate after some time and decreased in the latter time. The difference release characteristic of the optimized and commercial tablet may causing from the

process of manufacturing and/or composition of formulation. When the optimized tablet contacted with dissolution medium, it rapidly disintegrated into individual particles and aspirin rapidly dissolved resulting to fast release rate in the first time and decreased in the latter time because most of drug dissolved already. In other side, when the commercial tablet contacted with dissolution medium, it was disintegrated into granule after that the granule should be disintegrate to the fine particle so that the maximum rate of aspirin dissolution was occurred during the second step.

However, the experimental percent dissolution of both optimized formulations were less than the predicted values because the effect of uncontrolled compressional pressure influence the other properties lead to decrease dissolution.

According to BP 1998, the dissolution of each tablet should not less than 70 % but in this study, the formulation X2 had percent drug release of one tablet less than 70 % (63.2 % as seen in Table C5 in appendix C). When repeat again with six determinations, the two tablets of less than 70 % dissolution were occurred. But the mean percent dissolution was still more than 70 %. The cause of this result may occur from the irregular of mixing. The result of irregular of mixing may occurred from the cube mixer, it should be have enough free space to allow free of movement of the powder when the mixer was operated. The other cause was the segregation of powder might occur from the differences in particle size in feed shoe. The small particles such as corn starch, chitin could move faster into the lower plane while the larger particles such as dibasic calcium phosphate was still in the upper plane that resulting to irregular content in each tablet. Some tablet may have aspirin content lower than the labeled, but the tablet weight was still in the normal range. When these tablets were used to determine the dissolution, the percent drug release may lower than 70 % because these tablet had lower content of aspirin.

- Weight Variation

The X1, X2 and commercial tablets had weight variation not more than specification in USP 24 which stated that weight of individually 20 tablets not more than 5 % difference from average weight of tablet.

Weight variation of tablet in direct compression are indirect relation to the rate and uniformity of flow. Angle of repose are frequently used to gauge the possible performance of a powder on compressing or filling equipment partly because there is a correlation between angle of repose and flow rate (Carstensen, 1980).

The shape of particle affected the flow properties of material because the round shape particles will have the best flow. A roundish shape gives a minimum number of interparticle contacts. Particles which exhibit random or irregular shapes have many points of contact as edges, corners and ragged asperities. A mass of non-flow materrial will in variably consist of elongated or angular, or irregular-shaped, and also may have a light bulk density, this adding to its characteristic of non-flow nature. Roundish and squarish particles tend to be more flowable. A circular, columnar, platey, dendritic, fibrous, irregular and angular units tend to be less flowable (Carr, 1970).

- **Thickness**

In this study, the tablet weight was ranged from commercial > X1 >X2 then the tablet thickness were the same range of the weight. In fact, the increasing of content in each formulation (can be observed from the increasing of tablet weight) would be increase the space between the upper and lower punch when the powders were compressed that lead to increase the thickness. However, the different in compressional pressure of X1 and X2 or the unknown compressional pressure of the commercial tablet were also affecting the thickness.