CHAPTER 4

DISCUSSION AND CONCLUSION

Tablet disintegrating properties of durian rind extract by alcohol and acid-alcohol extraction, D_1 and D_2, were studied in comparison with various commercial disintegrants. Certain physical parameters of pure disintegrants and tablets were determined in attempt to predict their relative efficiency as tablet disintegrants.

The visualization of disintegrants through scanning electron microscope may provide a better understanding of both inherent properties and the mechanisms which they function.

D_1 and D_2,which are carbohydrate compose of polysaccharide, are fiber in appearance by D_2's particles are larger than D_1 (Figures 6-7). D_2's particles are more sticky and hardly to sieve as compared with D_1 particles. Ac-di-sol$^{(R)}$ and Nymcel$^{(R)}$ are similar in their fiber-shape and both are only different in substitution groups of the same cross-linked sodium carboxymethylcellulose structure (Figures 12-13). Kollidon CL$^{(R)}$ which are cross-linked polyvinylpyrrolidone showed their irregular shape in account of the trends of small particles to fuse into large porous agglomerates (Figures 11). Corn starch and Explotab$^{(R)}$ both appeared in an ovoidal-shape with smooth surface. However, Explotab$^{(R)}$ showed their sizes larger than corn starch because of addition of the carboxymethyl groups (Figure 9).Starch1500 $^{(R)}$,on the other hand,composed of individual starch grain along with aggregates of starch grains bonded to hydrolysed starch as given in Figure 10. From the results of

particle size and specific surface area analysis of various disintegrants, D_1 and D_2 were the two larger in their particle size and smaller in their specific surface area than the other disintegrants in this study. Both properties, however, might have little effect on disintegrants efficiency. For example, superdisintegrants such as Ac-di-Sol(R) and Nymcel(R) were known to be much more effective than corn starch in spite of the less specific surface area they possessed.

Percent compressibility of various disintegrants were calculated from bulk and tapped density indicate low compressibility of all disintegrants but this property would not much affected to the tablets prepared because it was used at rather low concentration. As the same as percent compressibility, although D_1 and D_2 exhibited superior flow rate than other disintegrants, the difference in effect of this property is quite small.

Significant differences of swelling index of Ac-di-Sol(R), Explotab(R) and Nymcel(R) in water and in Ø.1N hydrochloric acid indicated their swelling property is pH dependency. It may be due to the interaction between sodium moieties containing in their structures and hydrochloric acid resulted in sodium chloride.The results are in agreement to the study of sodium starch glycolate which the reduction of swelling capacity at lower pH occurred (20). D_1 which showed no significant differences in both solvents possessed the highest swelling index in Ø.1N hydrochloric acid. In the case of D_2, some particles dissolved immediately and the swelling index could not be determined.The directly relationship between hydration capacity and swelling index of various disintegrants as given in Figure 22

suggested that one parameter could be substituted by the other in order to estimate the efficiency of disintegrants.

Disintegrants did not have effect on weight variation of tablets and also had no interfere in flow rate of granules probably because of the low concentration employed. However, thickness increased as increasing concentration of disintegrant in dibasic calcium phosphate dihydrate system. It may be due to high porosity produced by low compressibility of disintegrants. For α-lactose monohydrate system, which possessed higher porosity than dibasic calcium phosphate dihydrate, the effect of disintegrant on thickness values was not found. Corresponding to hardness values of both diluents, in all cases except for Ac-di-Sol(R) and Nymcel(R) hardness decreased on increasing concentration of disintegrant. This indicated that high porosity may reduce interparticulate force between particles of tablet. In the case of Ac-di-Sol(R) and Nymcel(R) the above effect was not clearly seen. This effect was minimized in most formulations compressed at 1,500 kg because the influence of high compressional force involved.

As was expected ,Ac-di-Sol(R). Explotab(R) and Nymcel(R) gave nearly instant disintegration of less than 100 seconds at all concentrations and compressional forces in dibasic calcium phosphate dihydrate tablets. These corresponding to high hydration capacity and swelling index they possessed. In addition , the results of water penetration also showed the higher rate and volumetric of water uptake than other disintegrants. These may indicated swelling and water uptake were their mechanisms of action. Compressional force exerted influence on water penetration of these three disintegrants. Tablets compressed with low compressional force had higher rate

of water uptake and had less lag time than those compressed at higher force denoted large pore sizes they possessed. At higher concentration of disintegrants , the volumetric of water uptake at high compressional forces were sometimes larger than the lower ones. In these cases the continuous contact of disintegrants' particle may be involved when compressed at high forces.However,the disintegration times were directly related to compressional force indicated pore sizes were more important factor.

In dibasic calcium phosphate system, it is interesting to note that Ac-di-Sol(R), Explotab(R) and Nymcle(R) reached their equilibrium water uptake quicker than the other studied materials especially Ac-di-Sol(R) tended to be the quickest one. This high rate of saturation and good swelling power entailed very short disintegration time for tablets containing Ac-di-Sol(R) and contributed to it efficacy (3).

The maximal volume uptake of Explotab(R) and Nymcle(R) were higher than Ac-di-Sol(R) denoted the larger volume of water they uptake and the high swelling power they possessed.

The different behavior of these three disintegrants in α-lactose monohydrate system were observed. As concentration of disintegrants increased from 0.5 to 5% , the influence of the more contact of disintegrants' particles at high compressional force upon water penetration were increased, whereas the influence of pore size tended to reduce. Thus the highest water uptake could be clearly observed from tablets compressed with compressional force of 1,500 kg at 5% concentration of disintegrants. For Explotab(R) at concentration of 0.5%, water penetration of tablets compressed

with low compressional force were higher than those compressed with high compressional force indicated pore sizes were more important. In contrast , Ac-di-Sol(R) and Nymcel(R) which are fibers in shape,the contact of particles were enhanced , so this result were not observed.

For Ac-di-Sol(R) ,Explotab(R) ,and Nymcel(R) , disintegration of tablets were slightly effect by compressional forces and concentration. In the case of Nymcel(R) at 5% concentration, resist penetration of water was found as compared with the lower levels.This may be due to gelatinization effect when excessive amounts of Nymcel(R) were added. This effect, however,may corresponding to the prolong on disintegrantion time and may retard the dissolution of the active drug.

Corresponding to the result of comparative between disintegrants,water penetration rate of Kollidon CL(R) was next to Ac-di-Sol(R),Explotab(R) and Nymcel(R) at compressional force 1000 and 1500 kg so as to disintegration time was slightly longer.In this case, water penetration tended to play an important role on disintegration property of Kollidon CL(R) which swelling may be the secondary mechanism owing to it small swelling power.

In the case of α-lactose monohydrate system,both increasing compressional force or concentration of Kollidon CL(R) caused increasing on water penetration.In all cases, disintegration time of tablets were slightly different and could not be related to water uptake. The results of short disintegration time of water soluble system would depend upon the combine effect between dissolution of water soluble diluent and and water uptake of disintegrant as the same as in Ac-di-Sol(R), Explotab(R) and Nymcle(R) system.

Water uptake tended to play an important role on disintegration of dibasic calcium phosphate dihydrate tablet containing corn starch.At 0.5 and 1% concentrations,which showed no water uptake ,tablets were disintegrated after 30 minutes.For concentrations of $\geq$ 2% ,the more water uptake occurred and disintegration time of tablets were reduced significantly.The important of water uptake in corn starch system was confirmed by the increasing compressional force form 500 to 1000 kg tended to improve water uptake and disintegration time due to the continuous contact between starch grains.On the other hand, at high compressional force of 1500 kg, the pore sizes were too small so water uptake tended to decreased but disintegration time were not prolonged.This may be due to other mechanism such as swelling of corn starch took part in disintegration process by exerted sufficient pressure in small(but optimum)pores sizes to cause tablet disintegration.The previous reason is in agreement with data reported by Lowenthal(27) on the effect of compressional force upon disintegration of corn starch.

Increasing compressional force exerted influence on water penetration of α-lactose monohydrate and corn starch tablets by reducing pore size resulted in prolonged disintegration time.However,at high concentration as 5%, the continuous contact of disintegrant's particle would become more influence,thus leading to the opposite result as previously described.

However,the rate and volumetric of water penetration of corn starch was so small resulted in the least effective to improve water penetration as compared with other disintegrants.

Starch 1500(R) showed slightly superior in hydration capacity and water uptake to corn starch . Decreasing on compressional force or increasing concentration of starch 1500(R) enhanced water uptake and improved disintegration time of dibasic calcium phosphate dihydrate and -lactose monohydrate tablets. At 5% concentration of Starch 1500(R) in -lactose monohydrate system,the continuous contact between disintegrant within the pore may occurred leading to maximize water uptake at higher compressional force.

Durian rind extract D_1 and D_2 which exhibit higher rate of water penetration and swelling index than corn starch and Starch 1500(R) in dibasic calcium phosphate dihydrate tablets tend to have superior efficiency to improve disintegration time. Increase in compressional force exerted influence on pore size and will lead to reduce in water penetration and prolong disintegration time. In contrast, with increasing concentration of D_1 or D_2 results in higher water uptake and caused disintegration time to reduce. From these results indicate that water uptake was an important factor for disintegration of dibasic calcium phosphate dihydrate tablets containing D_1 or D_2 in addition to the swelling property which was considered to be the high ones.D_2 tended to has slightly lower water uptake and hydration capacity than D_1 and the disintegration time of tablet containing D_1 tended to be improved slightly more than D_2.

Compressional forces exerted influence on disintegration time of α- lactose monohydrate tablets as the same manner as in dibasic calcium phosphate dihydrate tablets. It may be seen

that, increasing on concentration of D_1 or D_2 were not much increased much water uptake. In addition, at 5% concentration of D_1 or D_2 the reduction in water uptake was observed as compared with at lower concentration. It may be due to dissolution of some disintegrant particles and soluble diluent thus caused viscosity of liquid in the pore to increase and resulted in prolong disintegration time. In the case of 5% concentration of D_2, in spite of decreasing in water penetration due to increasing compressional force, disintegration time of tablets were still improved. This behavior may be owing to at high compressional forces the swelling force may played an important role and had more influence on disintegration than water penetration.

From the results of this evaluation the distinguish for lag time of water penetration in to tablets were found. Lag time occurred according to the surface phenomena such as surface tension of water and contant angle between liquid and solid. In α-lactose mohohydrate system, lag time of water uptake at various condition were less than in dibasic calcium phosphate dihydrate system. The possible explanation was the dissolution of surface diluent led to widening pore in tablet surface. Although the initial rates of α-lactose monohydrate system seemed to be higher than those in dibasic calcium phosphate dihydrate but the increasing rates were slowly due to the viscous solvent produced by dissolution of diluent and disintegrant. In addition, disintegration time of α-lactose monohydrate tablets were not much different among various disintegrants utilized as found in dibasic calcium phosphate dihydrate system. However, the difference would be greater when tablets were compressed at high force. This meant at high compressional force, water uptake started to play an important role along with dissolution. The study indicated dibasic calcium phosphate dihydrate diluent was

prefer to α-lactose monohydrate in evaluate comparative efficiency among disintegrants because it is insoluble in water and has practically no intrinsic disintegrant property, thus the result of disintegration would occur by true effect of disintegrant.

Various properties of hydrochlorothiazide and pyridoxine hydrochloride tablets such as weight variation, thickness, hardness, friability and percent labelled amount were well within acceptable limit of USP XXI. Corn starch and Explotab(R), which represent standard and superdisintegrant, respectively, were chosen to compare efficiency with D_1 and D_2 due to the most commonly used disitegrants. This present study intended to use concentration of disintegrant as low as possible. According to D_1 and D_2 at 0.5% concentration seemed to be ineffective, thus 1 and 2% concentrations were chosen. As was expected, disintegration time of hydrochlorothiazide tablets were improved significantly except for formula containing corn starch which was considered ineffective at low concentration. Corresponding to the results of dissolution of drug, Explotab(R) appeared to be the most efficiency disintegrant followed by D_1 and D_2 which were nearly the same, and corn starch. D_1 or D_2 at 2% concentration could be considered as effective in such water insoluble system.

The different behaviors were found in pyridoxine hydrochloride tablets which active ingredient are freely soluble in water. A 1% concentration of D_1 or D_2, dissolution of drug might cause benefit by widening pore wall thus enhanced water penetration in to tablet and resulted in shorter disintegration time compared with hydrochlorothiazide. At both 1 and 2% concentrations dissolution of drugs containing D_1, D_2 and Explotab(R) were nearly the same according to dissolution

property of drug. In this case, disintegrant needed only to produced hydrophilicity of tablet and both concentrations employed were considered effective in such water soluble system.On the contrary, corn starch that possessed low water uptake and swelling still showed no improvement in disintegration and dissolution.

CONCLUSION

The disintegrating properties of durian rind extract by alcohol (D_1) and acid-alcohol extraction (D_2) exhibited superior to corn starch and Starch 1500$^{(R)}$ at the same concentration in both water soluble and insoluble base directly compressed tablets. However, they were inferior than those superdisintegrants such as Ac-di-Sol$^{(R)}$, Explotab$^{(R)}$, Kollidon CL$^{(R)}$ and Nymcel$^{(R)}$.

The important criteria to elucidate efficacy of disintegrants such as hydration capacity, swelling index, water penetration, disintegration property and release of drugs, these results showed satisfaction for both D_1 and D_2 as compared with other disintegrants in this study. Evaluation of the resulting tablets showed that even at very low disintegrants' concentration significant reduction in disintegration time took place except for corn starch and Starch 1500$^{(R)}$ which required rather high concentration. D_1 also showed slightly superior on physical properties (i.e. hydration capacity and water penetration) than D_2, however the efficiency to improve disintegration time of tablets were approximately the same. The results obtained from disintegration studies indicated that the water penetration for dibasic calcium phosphate dihydrate system, appeared to be the rate limitting step for disintegration process. It is apparent that compressional force had significant effect upon water

penetration by either reducing pore size or producing continuous contact between disintegrants particles during the disintegration.

In the case of α-lactose monohydrate system, since the dissolution took place by erosion at the surface, the requirement of disintegrant only to assist in drawing water inside the compact. In this case, the combining roles between water penetration and dissolution are somewhat important for tablet disintegration. For water soluble diluent, this suggested that the limited-swelling disintegrants should work as well as, and or even better than the strongly swelling materials.This was confirmed by disintegration and dissolution of pyridoxine hydrochloride, a water soluble drug, in dibasic calcium phosphate dihydrate system, which D_1 and D_2 exhibited efficiency nearly the same as Explotab$^{(R)}$.

On the other hand, in water insoluble base formulations, the disintegrant was capable of developing its maximum swelling force, besides drawing water inside the compact. Therefore, not only highly hydrophilic, but also strongly swelling disintegrants are to be preferred as confirmed by the results from disintegration and dissolution of hydrochlorothiazide tablets.

In conclusion, both durian rind extracts seem to be possible disintegrants for directly compressed tablets and can be used at low concentration. Both have an essential disintegrating properties such as swelling of primary particles which were similar to Ac-di-Sol$^{(R)}$, Explotab$^{(R)}$ and Nymcel$^{(R)}$ and enhancing water penetration which were slightly less than those of three superdisintegrants. The efficiency of both fractions, however, are better than corn starch and Starch 1500$^{(R)}$.