Chapter IV

Discussion and conclusion

The physical properties of chitin and chitosan from two different sources were determined to differentiate their relative efficiency as tablet disintegrants. These physical properties were studied upon pure disintegrants as powder or tablet and in tablet formulations, and they were evaluated in comparison to the properties of various commercial disintegrants such as corn starch, microcrystalline cellulose, sodium starch glycolate and croscarmellose sodium.

The photomicrographs of disintegrants by scanning electron microscope provided a better understanding of both particle size and shape. The particle size of sodium starch glycolate were larger than that of corn starch, at the same magnification. The shape of corn starch was polygonal while sodium starch glycolate appeared in an ovoidal-like shape. And corn starch particles had a smooth surface, whereas particles of sodium starch glycolate had not. Microcrystalline cellulose and croscarmellose sodium were similar in their size and shape. Their shape were fibrous-like. In the case of chitin (J), chitin (U), chitosan (J) and chitosan (U), their shape were similar. They performed a flake-like and irregular shape. However, their photomicrographs showed different size at the same magnification.

Chitin (J) exhibited the largest while others were similarly smaller.

Sieve analysis studies showed that the particle size and size distribution of these disintegrants were much different from each other. But the particle size data from both studied methods were confirmed to each other except for corn starch. Due to screening on mechanical sieve machine, corn starch particles were aggregated and seemed to be larger than when determining by scanning electron microscope. Chitin and chitosan from different sources were different in particle size.

The swelling capacity of various disintegrants in deionized water and diluted hydrochloric acid were observed. It was indicated all samples were swollen in both medium. The swelling capacity was much different in each sample. Corn starch was slightly swollen in both medium. Swelling of starch grains was claimed to be dependent upon the ratio of the amylose and amylopectin and their molecular structure. Amylose was insoluble in water but absorbed a large amount of water and swelled. It might restrict the swelling of the starch grains (30,90). Change in pH had no significant difference in the swelling of corn starch. As well as corn starch, microcrystalline cellulose was slightly swollen in deionized water and diluted hydrochloric acid, and change in pH had no significant difference in the swelling capacity. On the other hand, the swelling capacity in deionized water and in diluted hydrochloric acid differed in both sodium starch glycolate and croscarmellose sodium. Sodium starch glycolate showed the highest swelling capacity in deionized water among other disintegrants, whereas its swelling capacity was significanty decreased in alcidic medium. It might be due to the interaction between sodium moieties containing in its structure and hydrochloric acid resulted in sodium chloride. The results were in agreement to the study of sodium starch glycolate which the reduction of swelling capacity at lower pH occured (70). This phenomenon could also be seen in croscarmellose sodium. And it was noticed that croscarmellose sodium partially dissolved in deionized water. It could be indicated that the swelling capacity of sodium starch glycolate and croscarmellose sodium was dependent upon pH. Thus it could be concluded that for materials possessing an ionizable acid group, the swelling was more pronounced in deionized water than in diluted hydrochloric accid (86).

Chitin (J), chitin (U), chitosan (J) and chitosan (U) could swell in water. Since the absence of the hydrogen bonding between the sheets of sugar ring of β-chitin explained the ease that chitin could be swollen in water to produce hydration (52). The swelling capacity in diluted hydrochloric acid differed from in deionized water. Chitosan dissolved in diluted hydrochloric acid solution, and only chemically treated or acid hydrolyzed chitin, formed viscous solution. Whereas chitin swelled but was insoluble in diluted hydrochloric acid (59).

The comparison of water uptake of various disintegrants indicated sodium starch glycolate was the highest water uptake followed by chitin and its derivative. In the case of sodium starch glycolate, Rudnic and coworkers (91) observed that the rate and extent of water uptake was inversely proportional to the degree of carboxymethyl substitution of the starch compound. They observed that as the molecular structure of sodium starch glycolate was altered to improve water uptake, disintegrant efficiency also improved. For chitin and chitosan, a marked difference in water uptake was found. There were several possible explanations for the differences in water uptake properties between chitin and chitosan. These included differences in the crystallinity of the product (92,93). And since protein residues remained with the chitin even after the most drastic alkali treatment, differences in the protein content of the material, especially between chitin or chitosan might also affect water uptake properties (94). It was noticed that the large size of particles showed substantially greater rate and extent of water uptake than did the small particles.

There was no important difference in the rate and extent of water uptake by corn starch and microcrystalline cellulose. Water could penetrate into starch tablet either as a result of pore capillarity or by sorption. The latter was often accompanied by swelling. In microcrystalline cellulose tablet, an entrance of water was by the means of capillary pores, thus helping to break of the hydrogen bonding between adjacent bundles of cellulose microcrystals (95). In the case of croscarmellose sodium, it could absorb water into tablet. The total amount of penetrated water was due to the swelling ability of its particles. The rate of water penetration was clearly slower into croscarmellose sodium tablet than into microcrystalline tablet. This was attributed to the gelling surrounded the particle surfaces due to the partial dissolution of this material in water (34,41).

The moisture sorption by various disintegrants as a function of time was observed. Sodium starch glycolate exhibited the highest moisture sorption followed by croscarmellose sodium, and microcrystalline cellulose exhibited the slowest moisture sorption. The moisture sorption affected the changing of physical properties of tablets.

Tablet weight increased as disintegrant concentration increased but disintegrant types and concentration levels did not have any effect on weight variation and coefficient of variation of tablets. For all formulations, coefficients of variation were not much different.

The tablet hardness did not affected by disintegrant type. For some disintegrant such as microcrystalline cellulose, the hardness of tablets was increased with increasing its concentration because microcrystalline cellulose particles had large cohesive force and inner frictional coefficient, thus microcrystalline cellulose may be more adhesive than other disintegrants (84,96). Increasing in disintegrant concentration of chitin and chitosan in the tablet found that tablet hardness was slightly decreased possibly due to the reduction of inter-particulate forces between particles of tablet. The hardness of chitin tablets was greater than that of chitosan tablets at the same concentration and compression levels. These results might be attributable to the greater structural rigidity of chitin due to its acetylamino groups, and further the degree of polymerization of chitin might decrease during the deacetylation of chitin with strong alkali to prepare chitosan from chitin (53). Chitin and chitosan from different sources had a little effect on tablet hardness. The tablet hardness was dependent upon the compressional force. As compressional forces increased, tablets normally become more dense and consequently less porous, with particle-to-particle bonds becoming stronger. This phenomenon was reflected in an increase in tablet hardness (97).

The results of friability for all formulations confirmed those of hardness. The concentration of disintegrants increased, the friability values increased possibly due to the reduction of interparticulate forces between particles of tablet. However, the friability value of croscarmellose sodium tablet remained almost constant, althought its concentration increased. The compressional force was affected on tablet friability as well as tablet hardness. The friability was decreased with increasing the compressional force. The reason was the same as in tablet hardness that was the stronger of particle-to-particle bonds in tablet.

Disintegration time of tablet was affected by disintegrant concentration. In general the concentration of the disintegrant increased, the disintegration time decreased, such as microcrystalline cellulose, chitin (J), chitin (U), chitosan (J) and chitosan (U) tablets. However, disintegration prolonged with the increase in concentration in croscarmellose sodium tablets. The reason was the same as in water uptake that it might attribute to the gelling of the particle surfaces due to the partial dissolution of this material in water. Disintegration time was dependent upon the compressional force. Since the compressional force increased as well as tablet hardness increased, the disintegration time was prolonged. This phenomenon could be explained by a progressive decrease in tablet porosity (97). An increase in the disintegration time with a high compressive force could be attributed to the reduction of the speed penetration of liquid into the tablet (79). These results were found in all formulations except formulations containing 5% sodium starch glycolate and 2% croscarmellose sodium. In these formulations, an increase in compressional force did not change the disintegration time. It was interesting to see that the well known supposition "harder tablets take longer to disintegrate" was not applicable to both formulations. This might attribute to the high ability of water uptake and high swelling ability of sodium starch glycolate particles. And in croscarmellose sodium tablets, it was possibly due to the slight solubility of this material in water. Moreover, disintegration type could affect the disintegration time. For all disintegrants in this study, sodium starch glycolate and croscarmellose sodium appeared to be sufficient to disaggregate tablets in very short time among others. Both disintegrants were so called super-disintegrants.

The results obtained in disintegration tests completely support observations obtained in tests of water uptake to pure disintegrant tablets. Thus, water uptake seemed to be the step that limit the rate of disintegration for the tablet. Sodium starch glycolate, croscarmellose sodium, chitin (J), chitin (U), chitosan (J), and chitosan (U), all of which particles had swelled, seemed to be relatively more potent in tablets. However, the swelling capacity did not directly related to the disintegration efficiency. Chitin and chitosan at concentration below 3 percent prolonged the disintegration time. At concentration above 3 percent, the disintegration time was faster, and tablets containing 7 percent of these disintegrants were disintegrated within one minute.

Microcrystalline cellulose slightly swelled in water and did not draw water into the tablets very actively thus, had prolonged disintegration time. This agreed with the study of Khan and Rhodes (20) that microcrystalline cellulose was a relatively ineffective disintegrant in insoluble tablets. Since microcrystalline cellulose was an only slightly swelling material. Its disintegration action was related to an increased entrance of water by the means of capillaries and the breakage of hydrogen bonds holding cellulose together (95), not a swelling mechanism. There appeared to be no particular correlation existing between water uptake and disintegration time for corn starch. Swelling of starch grains was not the main mechanism to cause tablet disintegration. From the results, it could be concluded that a higher water uptake did not lead to a shorter disintegration time.

Many theories relating to the mechanism of action of tablet disintegration had been proposed, but none had fully explained the disintegrant properties of all the agents. However, no single mechanism of disintegrant action was applicable to all disintegrants. In some instances, a combination of mechanisms might be operative. The mechanisms of each disintegrant were summarized in Table 35. In this study, it was found that the possible

Table 35 Mechanism of disintegrant action

Disintegrants	Mechanism of action
Corn starch	- Swelling (34)
	- Porosity and capillary action (34)
	- Deformation (37)
	- Particle-particle repulsion (79)
Sodium starch glycolate	- Water uptake
	- Swelling
Microcrystalline cellulose	- Porosity and capillary action (41)
Croscarmellose sodium	- Water uptake
	- Swelling
Chitin	- Water uptake
	- Swelling
Chitosan	- Water uptake
	- Swelling

mechanisms of disintegration of chitin and chitosan related to their water uptake and swelling ability. However, other theories might additionally relate to their disintegrant action, too.

Corresponding to the results of dissolution of drug, sodium starch glycolate tablets appeared to be the most efficiency. These tablets showed a slight initial decrease in dissolution efficiency with increasing the compressional force. Statistical analysis at the p = 0.05 level of formulations containing different disintegrants at different concentrations compressed at forces of 600 and 900 pounds was shown in Table 36. There was no significant difference in drug dissolution between tablets containing 5% sodium starch glycolate, 2% and 5% croscarmellose sodium, 7% chitosan (J) and chitosan (U) at the same compressional force (p = 0.05). $T_{80\%}$ of all formulations were shown in Table 37. $T_{80\%}$ of tablets containing 5% sodium starch glycolate was shortest followed by 2% and 5% croscarmellose sodium and 7% chitosan (J) and chitosan (U), respectively. The dissolution efficiency of tablets containing croscarmellose sodium remained unchange over the compressional force, and the concentration of it had a little effect on dissolution efficiency. The tablets containing chitin and chitosan were slightly affected on dissolution efficiency with increasing the compressional force as well as croscarmellose sodium, but they were tremendously large affected with increasing the disintegrant concentration. The corre-

Table 36 Statistical analysis at the $p = 0.05$ level of formulations containing different disintegrants at different concentrations compressed at forces of 600 and 900 pounds before exposure to accelerated condition

Compressional forces (pound)	Formulations	Formulations			
		5% Corn starch	5% Sodium starch glycolate	2% Croscarmellose sodium	5% Croscarmellose sodium
600	5% Chitin(J)	NS	S	S	S
	5% Chitin(U)	NS	S	S	S
	5% Chitosan(J)	NS	S	S	S
	5% Chitosan(U)	NS	S	S	S
	7% Chitin(J)	S	NS	S	S
	7% Chitin(U)	NS	S	S	S
	7% Chitosan(J)	S	NS	NS	NS
	7% Chitosan(U)	S	NS	NS	NS
900	5% Chitin(J)	NS	S	S	S
	5% Chitin(U)	NS	S	S	S
	5% Chitosan(J)	NS	S	S	S
	5% Chitosan(U)	NS	S	S	S
	7% Chitin(J)	S	S	S	S
	7% Chitin(U)	NS	S	S	S
	7% Chitosan(J)	S	NS	NS	NS
	7% Chitosan(U)	S	NS	NS	NS

S = significant

NS = not significant

Table 37 $T_{80\%}$ of the formulations containing different disintegrants compressed at forces of 600 and 900 pounds before and after exposure to accelerated condition

Formulations	$T_{80\%}$ (minutes)			
	Before exposure		After exposure	
	600 lbs.	900 lbs.	600 lbs.	900 lbs.
5% Corn starch	15.01	18.81	> 30	> 30
5% Sodium starch glycolate	9.53	10.68	10.56	10.90
5% Microcrystalline cellulose	> 30	> 30	> 30	> 30
10% Microcrystalline cellulose	> 30	> 30	> 30	> 30
2% Croscarmellose sodium	10.78	11.25	17.25	17.43
5% Croscarmellose sodium	11.25	12.50	17.84	18.40
1.5% Chitin (J)	> 30	> 30	> 30	> 30
3% Chitin (J)	> 30	> 30	> 30	> 30
5% Chitin (J)	19.68	20.62	23.71	23.09
7% Chitin (J)	14.25	16.06	19.06	21.25
1.5% Chitin (U)	> 30	> 30	> 30	> 30
3% Chitin (U)	> 30	> 30	> 30	> 30
5% Chitin (U)	19.31	22.12	23.71	25.25
7% Chitin (U)	17.78	18.81	17.93	20.56
1.5% Chitosan (J)	> 30	> 30	> 30	> 30
3% Chitosan (J)	> 30	> 30	> 30	> 30
5% Chitosan (J)	19.34	19.93	20.78	22.15
7% Chitosan (J)	11.71	12.84	13.15	14.00
1.5% Chitosan (U)	> 30	> 30	> 30	> 30
3% Chitosan (U)	> 30	> 30	> 30	> 30
5% Chitosan (U)	19.65	19.96	22.96	24.37
7% Chitosan (U)	14.96	14.93	15.37	15.31

lation of disintegration time and dissolution efficiency in this study could not be established because some formulations showed different disintegration times but almost equal in dissolution efficiency.

The effect of storage at 75% relative humidity at 45°C could change the physical properties of all tablet formulations. The slight increase in tablet weight after five days exposure could have been due to a moisture gained into tablets. Tablet containing sodium starch glycolate had a greater change in tablet weight because of its high moisture sorption. Whereas microcrystalline cellulose exhibited the lowest moisture sorption, thus the weight of this tablet was less increased than other formulations. An increased in moisture sorption was observed as the increase in amount of microcrystalline cellulose in the tablets. The compressional force was not affected the change in tablet weight. The hardness of tablets was increased for all formulations. This could have been partially due to the dissolution of some of the soluble excipients at high humidity and then recrystallization by the partial loss of that water under storage condition which might improve interparticulate bonding in tablet (98). The tablet hardness increased as well as the friability decreased. Important parameters which could be affected by the exposure related to the hardness increment in compressed tablets were the disintegration time and drug dissolution. The results suggested that the disintegration time of tablet increased after storage under accelerated condition. The disintegration time of tablets containing sodium starch glycolate and croscarmellose sodium showed a less change than other formulations. The increase in disintegration time of tablets was due to the reduced disintegration action of the disintegrants by moisture which resulted in a loss of absorption and swelling ability. This could be substantiated by the decrease in disintegration time of dried tablets which contained dried disintegrants. Moreover, aging would affect the drug dissolution. All formulations exhibited poorer dissolution. In sodium starch glycolate and croscarmellose sodium formulations, the dissolution in 30 minutes did not change after aging ($p = 0.05$). This indicated that aging did not decrease the effectiveness of the super-disintegrants in promoting in vitro dissolution. This could be supported by the study of Gordon and Chowhan (99). Comparison of drug dissolution among tablet formulations containing 5% sodium starch glycolate, 2% and 5% croscarmellose sodium, 7% chitosan (J), and 7% chitosan (U) after exposure to high humidity and temperature at the $p = 0.05$ level was shown in Table 38. It was showed no significant difference in formulation between 7% chitosan (J) and 7% chitosan (U), 7% chitosan (J) and 5% sodium starch glycolate and 7% chitosan (U) and 5% sodium starch glycolate at both compressional forces ($p = 0.05$). There was significant difference in formulations between 7% chitosan (J) and 2% and 5% croscarmellose sodium, and 7% chitosan (U) and 2% and 5% croscarmellose sodium at both

Table 38 Statistical analysis at the p = 0.05 level of formulations containing different disintegrants at different concentrations compressed at forces of 600 and 900 pounds after exposure to accelerated condition

Compressional forces (pound)	Formulations	Formulations			
		5% Corn starch	5% Sodium starch glycolate	2% Croscarmellose sodium	5% Croscarmellose sodium
600	5% Chitin(J)	S	S	S	S
	5% Chitin(U)	S	S	S	S
	5% Chitosan(J)	S	S	S	S
	5% Chitosan(U)	S	S	S	S
	7% Chitin(J)	S	S	NS	NS
	7% Chitin(U)	S	S	NS	NS
	7% Chitosan(J)	S	NS	S	S
	7% Chitosan(U)	S	NS	S	S
900	5% Chitin(J)	S	S	S	S
	5% Chitin(U)	S	S	S	S
	5% Chitosan(J)	S	S	S	S
	5% Chitosan(U)	S	S	S	S
	7% Chitin(J)	S	S	NS	NS
	7% Chitin(U)	S	S	NS	NS
	7% Chitosan(J)	S	NS	S	S
	7% Chitosan(U)	S	NS	S	S

S = significant

NS = not significant

compressional force (p = 0.05). $T_{80\%}$ of tablets containing 5% sodium starch glycolate was the shortest followed by 7% chitosan (J), 7% chitosan (U), 2% and 5% croscarmellose sodium, respectively. However, aging greatly affected disintegration and dissolution at high compressional force than at low compressional force. Percent labeled amount of the tablets was not altered by aging.

Conclusion

The preceding results clearly revealed that pharmaceutical tablets, containing chitin and chitosan as disintegrants made by wet granulation method, possessed highly beneficial disintegration properties. Chitin and chitosan performed better than corn starch as a tablet disintegrant at the same concentration. And they exhibited superior to microcrystalline cellulose, too. However, they were inferior to those super-disintegrants such sodium starch glycolate and croscarmellose sodium. Very highly advantageous results were obtained when chitin and chitosan were presented in the tablet in an amount sufficient to provide about 7 percent by weight, that they were comparative to the super-disintegrants in the efficiency of both disintegration and dissolution. Beneficial results could be obtained, however, when the amount of chitin and chitosan was presented as low as about 5 percent by weight. No advantage was envisioned if the amount of chitin and chitosan less than 1.5 percent by weight.

The criteria to elucidate the disintegrant's efficiencies such as swelling capacity, water uptake, disintegration time and dissolution properties showed margional difference between chitin and chitosan. The rate of water penetration into chitin and chitosan was quite similar. This rate was higher than corn starch and microcrystalline cellulose but it was slower than sodium starch glycolate. Total amount of water uptake of chitin and chitosan were markedly greater after sodium starch glycolate. The difference on the disintegrating properties of chitin and chitosan from different sources were observed. That might due to the variation in manufacturing proces. The possible mechanisms of disintegration in the case of chitin and chitosan were the ability to accelerate water penetration into the tablets and swelling ability of their particles.

In conclusion both chitin and chitosan seemed to be effective disintegrants for tablets containing slightly soluble drug made by wet granulation method. They should be used at the concentration of more than 5 percent. The mechanism of disintegration of these two materials was found to relate to their water uptake and swelling ability.