CHAPTER IV

DISCUSSION AND CONCLUSION

In this study , binding property of Ispaghula husk (seed husk of *Plantago ovata*) was evaluated as the binding agent in wet granulation process comparing with binders from natural origin; corn starch, Starch 1500®, gelatin and synthetic binders ; HPC type L and PVP K30 which are commonly used in manufacture .

The Physical Properties of Granules Produced by Various Binders and Concentrations

The photomicrographs illustrated in Figure 9-31 revealed the size , shape and surface of powders and granules for paracetamol and nicotinamide. For paracetamol powder, it possessed many small acicular particles blend with large cylinder particles while nicotinamide was composed of thick rods. Both were clearly seen wide range of particle size distribution . The appearances of granules prepared with 1, 2 and 4 % of various binders by dry incorporation method from scanning electron microscope showed similar results . Additionally, the appearance of granules prepared at all concentration by solution incorporation method were also the same behavior. Thus, the granules at 2 % w/w concentration were selected to represent overall photomicrographs. The typical granules chosen appeared to be similar and possessed quite round shape therefore, it could affected on flowability of the studied granules . The surface of paracetamol granules consisted of intact , non-fracture particles bound together with a sponge-like network structure of solid binder . An original insoluble particles of paracetamol on the granule surface still be presented due to the limited solubility of drug in binding solution employed. The sponge-like network that bound these particles together was described by Newitt and Conway-Jones (Marshall 1985). They elucidated that during the solvent evaporation process, the dissolved solids were precipitated . They were deposited to be crystalline bridges as the binder were solidified to an interconnecting film network . The binder network continued throughout the granule structure forming a sponge - like matrix and entrapped particles inside especially seen in Ispaghula husk . The same results also were noticed in nicotinamide granules.

Normally , an increase in the binder concentration significantly yielded larger granules (Table 7,8 and Figure 32, 33, 34,35). These results are in agreement to the previous reports (Stanley-wood and Shubair, 1988; Marks and Sciarra, 1968; Jarosz and Parrott, 1983). These behaviors may be attributed to the corresponding increase in binder adhesiveness (Stanley-wood and Shubair, 1988) . For paracetamol granules prepared by solution incorporation method, the size of granules prepared with corn starch and Starch 1500® are smaller than other granules . In the case of Ispaghula husk employed by dry incorporation method, the inverse results was found. This may be elucidated that Ispaghula husk has great water absorbing and swelling properties (Sharma and Koul,1986; Willium ,1989), hence, most water used as granulating vehicle was absorbed for swelling of Ispaghula husk instead of utilizing in granulating process. From this result, granule size tended to decrease as increasing amount of binder used. Blank granules, however, showed the smallest size owing to the lack of adhesiveness property of pure water. In this study, the mean size of granules prepared by solution incorporation method were larger than dry incorporation . According to nicotinamide granules, the greatest in granule size was given by PVP K30. The same result was noticed as comparing the mean size of granules prepared by solution incorporation and dry incorporation method. This may be owing to the difference between solution and dry incorporation method which is described following .

Bulk density and tapped density of all granules were less than 1 g /ml (Table 7,8) and trended to slightly diminish as binder concentration increased . Harwood and Pipel (1968) illuminated that the smaller granules were able to form a closer and more intimate packing with less interparticular space than the larger granules . Moreover, the absence of fine particles to fill into the space at higher binder concentration may be the other reason .

Generally, compressibility values of granules tended to increase with increasing binder concentration, as the results presented in paracetamol granules (Table 7). In contrast, the results of nicotinamide granules showed that compressibility of granules decreased as increasing binder concentration . It may be explained that the difference between bulk and tapped density slightly diminished as amount of binder employed increased owing to the proper presence of fine particles .

Flowability of granule inclined to be decreased as increasing amount of binder employed (Table 7, 8 and Figure 40, 43). This can be explained that at higher binder concentration , the large granules form bridge or arch at an orifice area of funnel and obstruct the flow . Furthermore, the lack of appropriate fine particles to reduce frictional force on surface of larger

granules also impede flowability . Nevertheless, there are many factors that could be affected and must be considered when evaluating granule flowability such as shape , size distribution , density , porosity and surface characteristic (Gold et al., 1968; Sumner et al., 1966). Since each factor may counteract the effect of another, they can affect flowability of granule. From the result concerned with flow rate of paracetamol granules, Ispaghula husk gave the fastest flow rate where as PVP K30 — which produced large granule — had the poorest rate. The granules prepared by dry incorporation method imparted inferior flowability to solution incorporation method (Table 7) . This can be attributed to the previously reason above . For nicotinamide granules, Ispaghula husk gave the best flowability (Table 8). However, blank granules of both paracetamol and nicotinamide showed fast flow rate as comparing with the other granules in this study . This reason may be according to the results as previously mentioned .

The angle of repose for all cases was never greater than 40° (Table 7-8). These indicated all granules have obtained good flowability (Fonner et al., 1981; Sumner et al., 1966). Besides, it is interesting that angle of repose and percent compressibility tended to illustrate conversely relationship with granule flow rate as binder concentration increased .

Consideration with the percent fine of granules presented in Table 7,8 and Figure 44-47, it tended to decrease as binder concentration increased (except for Ispaghula husk). The adhesiveness promoted the agglomeration of the powder. Thus, amount of fine particles can be reduced. In the case of paracetamol, all granules (except for one prepared with Ispaghula husk by dry incorporation method at 4% w/w level) showed percent fine less than 18.33 % and PVP K 30 gave the least percent fine due to its good binding properties . Astoundingly, although friability of granule prepared with Ispaghula husk by dry incorporation method was nearly as hard as granule prepared with Starch 1500®, it possessed high amount of fine particles . This result may be explained owing to good water absorbing and swollen ability of Ispaghula husk. Thereby, water employed was mostly absorbed by Ispaghula husk instead of utilizing in granulating process and then many of fine particles were noticed . For nicotinamide granules, the results were similar to paracetamol granules . Ordinarily, blank granules obviously gave the highest amount of fine particles owing to weak strength of granule produced by pure water.

The friability value of granule was inversely proportional to the binder concentration (Table 7, 8 and Figure 48-51). The results are corresponding to many researchers (Stanley-Wood and Shubair, 1979 ; Marks and Sciarra, 1968 ; Jarosz and Parrott, 1983). It is possible to determine the relative granule strength, subjecting them to the friability test . The more amount of binder used , the stronger bond formation of particles was occurred with resulting in robust granules. As usual, soft granules are more friable than hard granules . The results of paracetamol granules showed that HPC type L, PVP K30 and gelatin slightly offered harder granules as comparing with Ispaghula husk, corn starch and Starch 1500®. In the case of nicotinamide granules, HPC type L, PVP K30, Ispaghula husk and gelatin produced hard granules with low percent friability whereas corn starch and Starch 1500® gave quite high values. For paracetamol granules and nicotinamide granules produced by both incorporation methods (Table 7,8), the different results of friability were observed. It also revealed that granules prepared by solution incorporation was more sturdy than granules obtained by the other way. Nevertheless, the softest granule with high friability value was present by blank granule. This can emphasized that binding agent substantially influences on granule strength .

In this study, moisture content of all granules prepared with various binders and concentrations were between 1.08 - 2.82 %.

The Physical Properties of Tablets Produced by Various Binders and Concentrations

All tablets produced in this study showed good weight variation due to the free flowing of granules . Thus, consistence of tablet hardness was observed with standard deviation of less than 0.05.

The tablet hardness is chiefly influenced with the amount of binder employed (Table 9,10, 14 - 25 and Figure 52,53). Hardness clearly increased proportional to the binder concentration . This result may be attributed to the stronger bond formation and increasing in crystalline bridge between the particles .

For paracetamol tablets, in solution incorporation method at higher concentration used , HPC type L gave the hardest whereas Starch 1500® gave the weakest . The results are corresponding to the knowledge that cellulose groups usually form hard tablet but starch forms soft and brittle tablet (Mendes and Roy, 1978) . At lower concentration , Ispaghula husk gave the hardest and Starch 1500® also showed the weakest. From

comparative hardness values presented in Table 9, it appeared that solution incorporation method tend to produced stronger tablet than dry incorporation method. Usually in solution incorporation method, binder was absolutely dissolved and hydrate before used in order to meet the optimal efficacy. However in dry incorporation method, the binder was pre-blended with other ingredients. Hence, the total binder probably may be not dissolved and hydrated by water.

In the case of capping, it occurred in compressing paracetamol blank tablets and it may be illustrated to a low degree of plastic deformation and bonding during compression process (Obiorah and Shotton, 1976; Doelker and Shotton, 1977). Carless et al. (1974) showed that capping of paracetamol tablet could be eradicated by using appropriate binders. They explained that employing the binder resulted in both an increase in residual die wall pressure and a decrease in elastic recovery. Because of this reason may cause capping in paracetamol blank tablets. In addition of nicotinamide tablets (Table 10), at 1% w/w level and above, HPC type L also imparted the strongest tablets whereas blank tablets were the weakest. The same outstanding results were noticed as comparing tablet hardness prepared by solution incorporation method and dry incorporation method.

The tensile strength of tablet is an important measurement for characterizing the interaction between solid particles. Hiestand and Peot (1974) illustrated that the higher the true areas of particles contacted, the stronger the interaction occurred. Figure 54 ,55 showed that tensile strength of tablets was increased as binder concentration increased. The reason may be explained in the same manner of tablet hardness. Consideration with paracetamol tablets, HPC type L and PVP K30 gave the high tensile strength values whereas Starch 1500® provided low value. In the case of nicotinamide the high tensile strength was also found in tablets prepared by HPC type L and PVP K30. According to tablets prepared from both drugs, tablets produced by solution incorporation method possessed superior tensile strength to dry incorporation method (Table 9,10).

The influence of binder concentration on friability of tablets are presented in Table 9,10 and Figure 56,57. It is noticed that friability decreased with increasing binder concentration. The increase in binder concentration brought about tablet hardness to increase and may be the explanation of less friability. In the case of paracetamol tablets, HPC type L possessed the least friability. Capping was observed for the tablet prepared with Starch 1500® and corn starch at 0.5 and 1% level. This could be remarked that the amount of binder utilized may not be sufficient to impart binding properties for the tablet to resist the abrasive

test . In solution incorporation method at 0.5 % w/w level, friability of all formulations did not pass the acceptable limit (< 1%). At 1% w/w level, only HPC type L and Ispaghula husk showed friability value under 1% . Moreover, at 2 % w/w level only tablets prepared with corn starch and Starch 1500® exceeded acceptable limit. In dry incorporation method , just tablets prepared with PVP K30 at 2%, 4% and Ispaghula husk at 4% possessed friability value in acceptable limit . In addition , the friability values of tablet prepared by solution incorporation method was obviously less than dry incorporation method (Table 9). This result may be due to the same reason as previously mentioned . Consideration with nicotinamide tablets produced by solution incorporation method , the friability values of all tablets were in acceptable range except for tablets prepared with corn starch at 0.5% w/w, 1% w/w and Starch 1500® at 0.5% w/w level (Table 10). In the case of dry incorporation method, only tablets prepared by Starch 1500® gave excess 1%. The less friable tablets were given by HPC type L, Ispaghula husk and PVP K30. As was expected, the friability values of tablets prepared by solution incorporation method were lower than dry incorporation method .

According to the result in this study, relationship between porosity of tablets and binder concentration are not clearly seen (Table 9,10 and Figure 58,59). Their consistency slightly changed with altering binder concentration . The porosity values of paracetamol tablets and nicotinamide tablets were ranging between 3.16- 5.27% and 3.91 - 6.53% , respectively . It was interesting that PVP K30 produced the tablet with more porous than other binders. Lamination was occurred on the paracetamol tablets prepared with corn starch and Starch 1500® at 0.5 and 1% concentration at high compressional pressure to obtain approximately zero porosity . This conduct could be ascribed to the weaker bond formation of such binders .

The effect of binder concentration on disintegration and dissolution of tablets were reported by many workers. It was found that disintegration and dissolution time were increased with increasing of binder concentration (Table 9,10 and Figure 60,61,81,82). The roles of binder in tablet formulation would be expected to reduce size, number and alter the shapes of capillary space between the particles which are contributing to the transport of water . Water transportation affected the penetration of water in tablet which is necessary for the process of disintegration and dissolution (Esezobo et al.,1989). This effect are enlarged as concentration of binding agent increased . Besides, the increase in hardness of tablet also hinders the water penetration . However, in this study slow disintegration and dissolution did not mean poor tablet properties. On

the other hand, the retardation in both properties may indicated good binding efficacy. For paracetamol tablets, none disintegrated within the limit of USP. It presumably due to the absence of disintegrant in the formulation and poor water solubility of paracetamol. At the same binder concentration employed, HPC type L, PVP K30 and gelatin showed faster tablet dissolution than other binders . This may be owing to their good solubility and absorbing ability. Consequently, they could expedite tablet dissolution faster than corn starch, Starch 1500® and Ispaghula husk which are less water soluble . Although Ispaghula husk can dissolve and hydrate in the presence of water but it probably from viscous or gelating barrier against the penetration of water and retard the release of drug from hydrophilic matrix (Singla and Singh , 1990) . As a result , in both cases slow tablet dissolution was noticed . Consideration with nicotinamide, all tablets showed good disintegration and dissolution because of good water solubility of active drug. Nicotinamide tablets prepared with gelatin, HPC type L and PVP K30 also gave faster dissolution rate than corn starch, Starch 1500® and Ispaghula husk. This may be attributed to the reason mentioned above and the effect of viscous barrier from Ispaghula husk could be subjugated by good water solubility of drug. Generally, tablets produced by dry incorporation method possessed quick disintegration and dissolution more than solution incorporation method (Table 9,10). Explanation for incorporation technique on binder efficacy is probably the same as mentioned before.

Since all tablets in this study showed the uniformity of weight variation , they occupied the percent label amount of drug within the range of USP XXIII (90-110%) .

According to Table 9,10 , binder index was increased as binder concentration increased . In the case of paracetamol tablets produced by solution incorporation method at all levels of binder concentration utilized the binder index generally decreased as follow, PVP K30 > HPC type L > gelatin > Ispaghula husk > corn starch > Starch 1500®. Additionally, in dry incorporation method at the same concentration , the ranks of binder index decreased as follow , PVP K30 > Ispaghula husk > Starch 1500®. For nicotinamide tablets, it also found that the greatest and least binder index were PVP K30 and corn starch , respectively. As a result of both drugs, paracetamol and nicotinamide, it was prominently illustrated that binder index obtained from solution incorporation method manifested superior than dry incorporation method. Since Ispaghula husk can form vicous and gelating barrier which retarded disintegration and dissolution of tablet, swelling property of binder should be embraced in binder index (including tensile strength, porosity, median dissolution time and percent friability of tablet) .

CONCLUSION

According to the overall result obtained from this study, it recognized that Ispaghula husk (seed husk of *Plantago ovata*) possessed binding properties superior to corn starch and Starch 1500® but inferior to PVP K30, HPC type L and gelatin for paracetamol and nicotinamide tablets. The physical properties of granules and tablets eg. granule size and size distribution , percent fine , flowability , granule friability , hardness , tablet friability, disintegration , dissolution and binder index were used effectively to assess their binding properties .

The results in this study illuminated that Ispaghula husk showed more accomplished binding properties as comparing with other binders. For paracetamol tablets, Ispaghula husk yielded more satisfied tablet strength, friability, value and binder index than corn starch and Starch 1500®. Furthermore, Ispaghula husk gave harder tablet than PVP K30 and HPC type L at low concentration level. Binder efficacy of Ispaghula husk employed by solution incorporation method was greater than utilized by dry incorporation method. From the result of percent fine obtained from paracetamol, it suggested limitation of utilization of Ispaghula husk that it was properly used at concentration 2% w/w or below .

In the case of nicotinamide tablets, Ispaghula husk also showed good results . The binder index of Ispaghula husk was outstandingly higher than corn starch and Starch 1500® but lower than PVP K30 , HPC type L and gelatin . It was noticed that Ispaghula husk and gelatin produced tablets with comparable hardness at all concentration levels .

Eventually , Ispaghula husk can be employed as effectively binding agents at low concentration level in wet granulation process for tablets preparation containing either hydrophobic or hydrophilic drug .