CHAPTER IV

DISCUSSION AND CONCLUSION

In this investigation , durian rind extracts, D_1 and D_2 were evaluated for their binding property comparing with other commonly used binders at 1 , 2 and 4 % dry concentration in wet granulation process. The physical properties data of granules and compressed tablets prepared with D_1 , D_2 and various binders were evaluated and judged their chance to employ as a binding agent.

THE PHYSICAL PROPERTIES OF GRANULES

The photomicrographs in Figures 8-33 revealed the size and shape of powders and granules for both drugs in this study. Paracetamol powder possessed many small acicular particles together with large cylinder particles whearas pyridoxine hydrochloride was composed of thick rods and irregular-shape particles. Both clearly showed wide range of particle size distribution. The appearances of granules prepared with 1,2 and 4 % of various binders from scanning electron microscope showed similar results. Thus, the granules at 2 % were chosen to represent overall results. The typical granules prepared with 2 % concentration of various binders appeared to be similar and possessed quite round shape. Their appearances were almost changed from the original powder. This characteristics therfore influence on flowability of the studied granules. The surface of paracetamol granules consisted of intact, non - fracture particles bound together by a sponge - like network of solid binder. An original insoluble particles of paracetamol on the granules surface still 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

(8). They elucidated that during the solvent evaporation process, the dissolved solids were pricipitated. They were deposited to be crystalline bridges as the binders were solidified to an interconnecting film network. The binder network continued throughout the granule structure forming a sponge - like matrix and entrapped particles inside.

In contrast,the original pyridoxine hydrochloride particles were not clearly seen on granule surface owing to good dissolution of drugs in binder solution during granulation process. Thus, few particles were remained on the surface.

An increase in the binder concentration significantly yielded larger granules (Tables 8, 10 and Figures 43, 53). which are in agreement to the previous reports (11 - 13). These behaviors may be attributed to the corresponding increase in binder adhesiveness (13). For paracetamol granules, the size of granules prepared with D_2 and PVP k30 are larger than other granules. In the case of corn starch, the inverse results was found. Blank granule, however, showed the smallest size owing to lack of adhesiness property of pure water. Difference in granule size between solution incorporation method and dry incorporation method was not clearly seen except for D_2 (Table 9). According to pyridoxine hydrochloride granules, the greatest in granule size was also given by D_2. As a result, binder adhesiveness property of D_2 is probably higher than other binders. It was recognized that blank granule gave the smallest granule size except for granule produced with corn starch, Starch 1500$^{(R)}$ and gelatin at 1 % concentration. This may concerns with the surface tension of granulating solution which slightly lower than pure water. Thus, the powder may be better wetted by granulating solution than by pure water. In addition, the solid - liquid adhesion was increased as compared with solid - solid adhesion resulting in decrease of granule size (9). However at

higher binder concentration, binder adhesiveness increased and play more important role on granule size of drug.

In this study, bulk density and tapped density of the granules were less than 1 g/ml (Tables 8-11) and slightly diminished as binder concentration increased. Harwood and Pilpel (14) elucidated that the smaller granules were able to form a closer , more intimate packing with less interparticular space than the larger granules. Furthermore, the absence of fine particles to fill into interparticular space at higher binder concentration may be the reason one.

Generally, compressibility values of granules tended to increase with increasing binder concentation (Tables 8, 10 and Figures 54-55). For all cases, they were between 7.94 - 22.74 % which approximately in the range of free - flowing (15).

Granule flowability was found to be decreased as increasing amount of binder used (Tables 8, 10 and Figures 56-57). 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. Moreover, the lack of suitable fine particles to reduce frictional force on rough surface of larger granules also hinder flowabitity. Nevertheless, there are many factors could be affected and must be considered when evaluating granule flowability such as shape, size distribution, density, porosity and surface characteristic. (56,57). Because each factor may counteract the effect of another. Among the paracetamol granule, Starch 1500$^{(R)}$ gave the quickest flow rate whereas PVPk30, which produced the largest granule, had the poorest rate. D_2 possessed slightly better flowability than D_1. The granules prepared with dry incorporation method imparted inferior flowability to solution incorporation method (Table 9). This can be attributed to the granule size and

amount of fine particle as previously mention above. For pyridoxine hydrochloride granules, D_1 gave the best flowability (Table 11). Both D_1 and D_2 produced granules which imparted faster flow rate than corn starch.

However, blank granules of both paracetamol and pyridoxine hydrochloride showed the fastest flow rate as comparing with any granules in this study. The reason may be according to the results as previously mentioned

The angle of repose for all cases never greater than 40 ° (Tables 8-11). This indicated all granules have obtained good flowability. Furthermore, it is interesting that grunule flow rate illustrated conversely relationship with angle of repose and percent comperssibility as binder concentration increased.

The friability value of granules was inversely proportional to the binder concentration (Tables 8, 10 and Figures 58-59). The results are corresponding to many researchers (13, 16-17). It is possible to determine the relative granule strenth, 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 Methocel E15LV(R) and PVPK30 exhibited hard granules with low friability values whereas corn starch, Starch 1500(R) and D_1 gave quite high values. For both incorporation methods (Tables 9, 11), the different results of friability were observed. In the case of pyridoxine hydrochloride granules,the hardnest and weakest granules were produced with PVPK30 and Starch 1500(R) (except at 4 %), respectively. The results are similar to paracetamol granules.

However, the softest granule with high friability value was represented by blank granule. This can emphasized that binding agent importantly influences on granule stength .

Consideration with the percent fine of granules,it tended to decrease as binder concentration increased (Tables 8, 10 and Figures 60-61). The adhesiveness promoted the aggomeration of the powder, Thus, amount of fine particles may be reduced. In the case of paracetamol granules, PVPK30 gave the least amount of percent fine owing to its good binding properties. Surprisingly, Methocel E15LV(R) which produced hard granules, possessed quite high amount of fine particles. It may be explained that extensive attrition occurred with those hard granules during dry screening. Therefore, many of fine particles were noticed. All paracetamol granules except for blank showed amount of fine particles approximately less than 15 %. Unusual relationship between binder concentration and percent fine of pyridoxine hydrochloride granules were observed. Only percent fine of granules produced by PVPk30, corn starch and Starch 1500(R) were reduced as concentration increased but other granules show the inverse results. The reason may be due to the extensive attrition to the screen of stronger granule at higher binder concentration employed. On the other hand, blank granules obviously gave the highest amount of fine particles (except for granules produced by gelatin and Methocel E15LV(R) at 4 %) owing to weak strength of granule produced by pure water. In this study, the moisture content of all granule prepared with various binders were between 1.1 - 2.4%.

THE PHYSICAL PROPERTIES OF TABLETS

All tablets prepared with various binders in this study showed good weight variation owing to the free - flowing of granules. As a result, uniformity of tablet thickness was observed with standard deviation of less than 0.06.

The tablet hardness is mainly influenced with the amount of the binder utilized. (Tables 12, 14 and Figures 62-63). It clearly increased proportional to the binder concentration. This may be attributed to the stronger bond formation and increasing in crystalline bridge between the particles.

For paracetamol tablets, at all binder concentration used, Methocel E15LV$^{(R)}$ gave the hardest tablets whearas corn starch gave the weakest. The results are corresponding to the knowledge that cellulose groups usually form hard tablet but starch forms soft and brittle tablet (3). The comparative hardness values were found from the tablet prepared with D_1 and D_2. It appeared that solution incorporation method tend to produced stronger tablet than dry incorporation method (Table 13). Generally in solution incorporation method, binder was absolutely dissolved and hydrate before used in order to meet the optimal efficacy. However in dry incorporatiuon method, the binder was diluted or pre - drymixed with other ingredients. Thus, the total binder probably may be not dissolved and hydrated by the water.

The tendency of capping occurred as compressing paracetamol blank tablets. More recent research has attributed capping in paracetamol to a low degree of plastic deformation and bonding during compressional proccess (58-59). Carless et al (60) showed that capping of paracetamol tablet could be eliminated by using appropriate binders. The authors explained that employing the binders resulted in both an increase in residual die wall pressure and a decrease in elastic recovery. Therefore the lack of binder in blank tablets may cause capping due to the reason mention above. Cosideration with pyridoxine hydrochloride tablets (Table 14), Methocel E15LV$^{(R)}$ also imparted the strongest tablets whereas blank tablets were the weakest. Above 1 % binder concentration, obviouly higher in hardness value was found for D_1 than D_2. The same results

were noticed as comparing tablet hardness prepared by solution incorporation method and dry incorporation method (Table 15).

As regarding to the results of friability (Tables 12, 14 and Figures 64-65), it is noticed that friability decreased with increasing binder concentration. The increase in binder concentration caused tablet hardness to increased and may be the explanation of less friability. In the case of paracetamol tablets, PVPK30 possessed the least friability value. Capping was seen for the tablet prepared with corn starch and Starch 1500(R) at 1 % level. This could be remarked that the amount of binder used may not sufficient to impart binding properties for the tablet to withstand the abrasive test. At 1 % level, only PVPK30 showed friability value in acceptable limit (< 1 %). In the case of 2 %, PVPk30, Methocel E15LV(R) D_1 and D_2 , gave friability value of less than 1 %. Furthermore, at above 2 % concentration none of tablet friability was excess acceptable limit. For D_1 and D_2 , the friability values were comparable and within the limit as binder concentration greater than 1 %. In addition, the friability values of tablet prepared by solution incorporation methed was significantly less than dry incorporation method (Table 13). This may be due to the same reason as previously mentioned. When pyridoxine hydrochloride was used, the friability values of all tablet were in acceptable range (<1 %) (Table 15). The less friable tablets were given by PVPk30 and gelatin. As was expected, the friability values of tablets prepared by solution incorporation method were lower than dry incorporation method.

The tensile strength of tablet is an important measurment for characterizing the interaction between solid particles. Hiestand et al (51) explained that the higher the true areas of particles contacted, the stronger the interaction occurred. Figures 66-67 illustrated that tensile strength was increased as binder

concentration increased. The reason may be explained in the same manner of tablet hardness. Consideration with paracetamol tablets, PVPk30 and MethocelE15LV(R) gave high tensile strength values whearas corn starch represented low value. In the case of pyridoxine hydrochloride the high tensile strength was also found in Methocel E15LV(R). According to tablet prepared from both drugs, the different in tensile strength between D_1 and D_2 was not distinguished. In addition, tablet produced by solution incorporation method possessed superior tensile strength to dry incorporation method (Tables 13, 15).

In this study, relationship between porosity of tablets and binder concentration are not clearly seen (Tables 12, 14 and Figures 68-69). They slightly inconsistency changed with altering binder concentration. The porosity values of paracetamol tablets and pyridoxine tablets were ranging between 3.77-6.16 % and 3.90-6.62 %, respectively (Tables 12-15). It was interesting that PVPk30 produced the tablet with more porous than other binders. Lamination was occurred on the paracetamol tablets prepared with 1 % corn starch and Starch 1500(R) at high compressional pressure to obtain approximately zero porosity. This behavior could be attributed to the weaker bond formation of such binders.

The influence of binder concentration on tablet disintegration and dissolution were proposed in many reports (29-31, 46-49). It was found that they were increased with increasing of binder concentration (Tables 12, 14 and Figures 70-71). The presence of binders 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. They, therefore, affected the penetration of water in tablet which is necessary for the process of disintegration and dissolution (33). This effect are magnified as concentration of binding agent

increased. Furthermore, the increase in tablet hardness also hinder the water penetration. However, in this study, slow disintegration and dissolution did not mean poor tablet properties. In contrast, the retardation in both properties may indicated good binding property and can be used to elucidate binder efficacy. For paracetamol tablet, neither of tablets disintegrated within the USP. limit. It mainly due to the absence of disintegrant in the formulation and poor water solubility of paracetamol. At the same binder concentration employed, PVPK30, Methocel E15LV$^{(R)}$ and gelatin showed faster tablet dissolution than other binders. This may be owing to their good water solubility and adsorbing ability. Therefore, they enhanced tablet dissolution greater than corn starch and Starch 1500$^{(R)}$ which are less water soluble. Although D_1 and D_2 can dissolve and hydrate in the presence of water but they probably from viscous barrier against the penetration of water. As a result, in both cases slow dissolution were noticeable. Consideration with pyridoxine hydrochloride, all tablets show good disintegration and dissolution because of water solubity of active drug. Pyridoxine hydrochloride tablet produced with gelatin, PVPk30, Methocel E15LV$^{(R)}$, D_1 and D_2 gave faster dissolution rate than corn starch and Starch 1500$^{(R)}$. This may be attributed to the reason metioned above and the effect of viscous barrier from D_1 and D_2 could be overcomed by good water solubility of drug. In general, tablets produced by dry incorporation method possessed rapid disintegration and dissolution more than solution incorporation method (Tables 13, 15). Explanation for incorporation technique on binder efficacy is probably the same as mentioned before.

All the tablets in this study possessed good content uniformity within the range of USP (85-115%). The uniformity of weight variation may be the explanation.

According to tables 12-15, binder index was increased as binder concentration increased. In the case of paracetamol at all level of binder concentration utilized the binder index generally decreased as follow, PVPK30 > Methocel E15LV(R) > D_1 > D_2 > Starch 1500(R) > corn starch. For pyridoxine hydrochloride: PVPK30 > gelatin > Methocel E15LV(R) > D_2 > Starch 1500(R) > D_1. It is noticed that binder index of paracetamol tablets significantly appeared to be less than pyridoxine hydrochloride tablets owing to their poor dissolution.

CONCLUSION

It recognized that durian rind extracts: D_1 and D_2 possessed binding properties superior to corn starch and Starch 500(R) but inferior to PVPK30, Methocel E15LV(R) and gelatin for paracetamol and pyridoxine hydrochloride tablets, restectively. The significant physical properties of granules and tablets e.g. granule size and size distribution, granule friability, flowability, hardness, friability, disintegration, dissolution and binder index were used to assess their binding properties.

The results emphasized that both D_1 and D_2 showed accomplished binding properties as comparing with other binders in this study. For paracetamol tablets, D_1 and D_2 gave more satisfy tablet strength, friability value and binder index than corn starch and Starch 1500(R).

In addition, D_1 and D_2 also revealed good results for pyridoxine hydrochloride tablets. The binder index of D_2 was obviously higher than corn starch and Starch 1500(R) but lower than PVPk30, Methocel E15LV(R) and gelatin. Furthermore, D_1 gave more stronger tablet than PVPK30 and gelatin at concentration greater than 1 %. Generally, it was noticed that D_1 and D_2 produced

tablets with comparable properties. In the case of paracetamol, it was found that solution incorporation method tend to produced more satisfactory results than dry incorporation method. However, both methods gave equal results for pyridoxine hydrochloride tablets.

Ultimately, both durian rind extracts can be employed as binding agents in wet granulation process for tablet preparation containing either slightly water soluble or water soluble active drug, The effective concentrations were greater than 1% for paracetamol and at all concentration studied for pyridoxine hydrochloride, respectively.