Chapter IV

Discussion and Conclusions

Preparation of Modified Rice Starch

Modified rice starch was produced by deproteinization and crosslinking reaction as mentioned above and sprayed into the spray drying apparatus, using proper condition to have rice starch aggregates. The deproteinization was found to improve the hardness of modified rice starch when compressed into tablets. Siriyos Timaroon (1994) indicated that the protein which co-existed with starch molecules, bound with the hydroxyl groups of starch molecules in some way. This hindered the reaction of functional groups of sodium trimetaphosphate with the hydroxyl groups of starch. When the protein was eliminated, sodium trimetaphosphate could bind with the hydroxyl groups more effectively.

The explanation of crosslinking reaction was that crosslinking gave more strength to the starch granules by replacing hydrogen bonds in starch molecules with covalent bonds which were much stronger.

For spray drying process, modification of condition such as concentration of dispersion, inlet air temperature, atomizing air pressure and feed rate could alter the properties of modified rice starch. Spray drying could be used to significantly enhance the compactibility and flow of rice starch. It can be concluded that the more concentration of dispersion or atomizing air pressure was used, the higher tablet hardness

was obtained. The outlet air temperature from the spray dryer was a critical process control parameter. This temperature, which was a function of the mass flow rate and humidity of the process air and the rate at which water was evaporated during the process, could have a profound effect on the property of modified rice starch.

Detection of Phosphate and Crosslinking Reaction in Modified Rice Starch

The degree of crosslinking in modified rice starch was measured directly by determining phosphate content in the specimen. Table 6 shows the phosphate content in modified rice starch. It can be calculated in term of the degree of crosslinking. The reaction of crosslinking was confirmed by differential scanning calorimetry, X-ray diffraction and the determination of viscosity. A minimum amount of crosslinking which reinforces the associative hydrogen bonds holding together can change considerably the gelatinization properties of the starch granules. Gelatinization characteristics of these starches could be investigated by differential scanning calorimetry and viscoamylograph.

Supporting evidence for the crosslinking reaction of rice starch was obtained from thermal analysis. The DSC properties of native rice starch, deproteinized rice starch, crosslinked rice starch and modified rice starch are presented in Figure 6.

By deproteinization of native rice starch with sodium hydroxide, the enthalpy of gelatinization (ΔH) increased from 2.840 cal/g to 3.034 cal/g. That was because there was more portion of starch granules in

deproteinized rice starch than that of starch granules in native rice starch which could be gelatinized by heat. The deproteinization could reduce the protein content of starch from 8.75 % to 1.87 %.

For crosslinked rice starch, The enthalpies of gelatinization decreased from 3.034 cal/g to 2.747 cal/g. Yook, Pek and Park (1993) reported that more highly crosslinked starches had less enthalpies of gelatinization. Since there was less portion of starch granules which could be gelatinized by heat and it led to a decrease in energy required for starch gelatinization.

By further spray drying of crosslinked rice starch, gelatinization temperature decreased slightly to 64.6 ^{0}C and the enthalpy of gelatinization decreased from 2.747 cal/g to 2.653 cal/g. Ford (1989) reported that the enthalpy of gelatinization will decrease if gelatinization has previously occured. When crosslinked rice starch was sprayed into the spray drying chamber at 130 ^{0}C, it would be gelatinized partially.

The X-ray powder diffractograms of sodium trimetaphosphate, native rice starch, deproteinized rice starch, the physical mixture of sodium trimetaphosphate and deproteinized rice starch, crosslinked rice starch and modified rice starch are presented in Figure 7. From X-ray diffraction pattern, it was observed that sodium trimetaphosphate exhibited crystalline characteristic and deproteinized rice starch exhibited crystalline and amorphous characteristics.

The peak pattern of the physical mixture resulted from the combined peak patterns of sodium trimetaphosphate and deproteinized rice starch. For crosslinked rice starch, the diffraction pattern is varied

from the others. This indicated that the orientation in crosslinked rice starch is different from sodium trimetaphosphate and the physical mixture. In the case of modified rice starch, the peak pattern is similar to crosslinked rice starch. Given this, it can be concluded that the spray drying process did not change the crystallinity of crosslinked rice starch.

The viscoamylograph is presented in Figure 8. When rice starch was deproteinized, the viscosity of heated deproteinized rice starch increased from 960 to 980 B.U. This resulted showed that protein had the interferring effects on viscosity of rice starch. Owing to protein had many different functional groups such as carboxyl, amino, sulfhydryl etc., these group could interact with hydroxyl group of starch in various ways forming hydrogen bond, electrostatic, Van der Waal's forces, ionic bond etc. These forces made water molecules solvate starch molecules more difficult; therefore, the starch granules could not swell to their full capacity resulting in lessened viscosity. After crosslinked for 6 hrs, viscosities decreased to 20 B.U. Rutenberg (1980) indicated that crosslinking the molecular chains lead to a more rigid macromolecular network inside the granule. The reinforcing effects of chemical covalent bonding, which is not as susceptible to rupture during heating as are the hydrogen bond, cause the granules to resist the swelling, and hence the decreasing of viscosity.

Evaluation of Physical Properties of Modified Rice Starch Compared with Commercial Diluents

Modified rice starch was scaled up in the large batch size and was investigated according to USP XXIII. The results showed that the

modified rice starch passed all of the tests as presented in Table 8. Then, the physical properties of modified rice starch powders and its tabletting characteristics were compared with those of the other commercial diluents: Era-Tab^R, Starch 1500^R, Avicel PH 102^R and Emcompress^R.

The term % compressibility calculated from tapped and bulk density refers to the packing characteristics of the materials and it has been suggested that the lower the value, the better the flow. In this study, the order of increasing flowability was Avicel PH 102^R < Starch 1500^R < modified rice starch < Era-Tab^R < Emcompress^R. Flow rate of these diluents demonstrated similar results as in % compressiblity.

Angle of repose indicated flowability of powders. The highest value demonstrated the poor flow property. The order of decreasing angle of repose was Avicel PH 102^R > Emcompress^R > Starch 1500^R > modified rice starch > Era-Tab^R . It can be seen that modified rice starch possessed good flowability while Era-Tab^R showed slightly better flowability.

Mitrevej, Varavinit, and Sinchaipanid (1990) reported that the shape of Era-Tab^R is spherical. It would flow better than any diluents in this study. The bulk density of Emcompress^R, however, was higher than that of Era-Tab^R. The flow of Emcompress^R by weight was therefore better than that of Era-Tab^R. For modified rice starch, It was the aggregates of rice starch granules. The flowability would be improved by spray drying. Starch 1500^R exhibited fair flowability because the shapes of Starch 1500^R were irregular. Avicel PH 102^R exhibited lower flowability, caused by its fine particle size as compared to the other

diluents. The particles of Avicel PH 102^{R} could cause the interchain locking of the long fiber and hence the flow properties were fair.

Tabletting Characteristics of Modified Rice Starch Compared with Commercial Diluents

Figure 23 shows the compression force-hardness profiles for unlubricated tablets prepared from modified rice starch and various diluents. It can be seen that the compression force-hardness profiles of modified rice starch was much steeper as compared to the other starches diluent. In summary, modified rice starch owned the highest compressibility as compared to starch-based filler. This was explained by crosslinking of rice starch, it provided more strength to the starch granules by replacing hydrogen bonds in starch molecules with covalent bonds which were much stronger. (Siriyos Timaroon, 1994).

Avicel PH 102^{R} possessed the highest pressure-hardness profiles. Reier and Shangraw (1966) suggested that the extremely large surface area were formed between particles, followed by hydrogen bonding.

Compression force-friability profiles were correlated with hardness value, the stronger tablet hardness, the less friability value. Starch 1500^{R} possessed higher friability because it had lower compressibility. Avicel PH 102^{R} showed low friability due to its high compressibility.

Compression force-disintegration time profiles are illustrated in Figure 25. Modified rice starch, Era-Tab^{R} and Avicel PH 102^{R} explicited short disintegration time even at high hardness. Since modified rice starch and Era-Tab^{R} mainly comprised the agglomeration of starch grains, the

tablet probably fell apart easily when being immersed in the water. The disintegration time of modified rice starch tablets were slightly longer than that of Era-Tab^R because its hardness value was higher at the same compression force. The disintegration time of modified rice starch and Era-Tab^R seemed to be independent on the compression force except of Era-Tab^R at 2,000 pounds compression force.

For Avicel PH 102^R, the mechanism of disintegration was explained to the uptake of water into the tablet by means of capillary pores, which subsequently disrupts interparticulate the hydrogen bonding beween adjacent microcrystals (Fox *et al.*, 1963). In the case of Starch 1500^R, the tablets would become gel when wetted. The gelatinous layer impeded the penetration of water into the the tablet, thus prolong the disintegration (Manudhane *et al.*, 1969).

Comparative Dilution Potential Ability of Modified Rice Starch and Commercial Diluents

Sheth, Bendelin and Shangraw (1989) indicated that an ideal direct compression should have a high capacity, which is defined as the amount of active ingredients which the diluent can successfully carry in the direct compression technique.

Ascorbic acid was known to place a high demand on the filler-binder system. It was a poorly compactible, so that it was used as model excipient for this study. The increase in ascorbic acid content in the mixture decreased the tablet hardness of any diluent tested.

Comparison between modified rice starch and Era-Tab^{R}, modified rice starch seemed to have better dilution potential ability than Era-Tab^{R}. The dilution potential of Emcompress^{R} was the worst since it can't be compressed at 30 % of ascorbic acid.

Avicel PH 102^{R} was far superior to any diluents in this study because of its high compressibility.

Effect of Lubricant on Tabletting Characteristics

In general a solid lubricant decreases the mechanical strength and increases the disintegration of a tablet, because it acts as a physical barrier between the particles that undergo deformation and interferes with bonding during compression.

Hardness

The strength of a tablet depends on the area of contact between the particles. The addition of a lubricant reduces the amount of clean reactive surface produced by shear at the sliding contact areas between particles(York, 1984; Jarosz and Parrot, 1984).

The tablet of materials such as starch and microcrystalline cellulose, which are plastically deformed, will be weakened mechanically to a greater extent by a lubricant than a material which is fragmented, i.e., dicalcium phosphate dihydrate.

The effect of magnesium stearate on the tablet hardness at different compression forces are presented in Table 17-21 and Figure 35-

43. The hardness decreased with increased magnesium stearate concentration, except that of Emcompress^{R}. Khan and Rhodes (1975) reported that dicalcium phosphate dihydrate is consolidated by brittle fracture. The strength of compacts of brittle material, which fragment during compression, are little affected by the addition of a lubricant because new, clean surface produced by fragmentation are available for bonding.

For rice starch based fillers such as modified rice starch and Era-Tab^{R}, the reduction of the hardness of those were distinct. Sufficient binding capacity for modified rice starch is left after lubrication. The hardness of these tablets were acceptable, except that of Era-Tab^{R} compressed at 500 pounds with 1.0 % magnesium stearate.

Avicel PH 102^{R} was also affected by the concentration of lubricant but the decrease in the hardness was not apparent. On the contrary, the hardness of Starch 1500^{R} tablets was markedly decreased. The hardness of the tablets compressed at 500 pounds with any content of magnesium stearate was unacceptable.

Disintegration time

The disintegration time of tablets in relation to magnesium stearate at different concentrations are shown in Table 17-21 and Figure 44-51. In general, the disintegration time increased with increased lubricant concentration. Bolhuis, Smallenbroek and Lerk (1981) indicated that magnesium stearate can have a strong negative effect on binding properties of tablet excipients. The phenomenon is caused by the formation of lubricant film interferring with particle binding. The

lubricant film is a result of adhesion to the substrate of magnesium stearate molecules, which are sheared off mechanically from the magnesium stearate crystal during mixing. The formation of such a hydrophobic film can dramatically decrease the wettability of a powder mix.

For modified rice starch and Era-Tab^{R}, those tablets disintegrated rapidly within 5 min at all compression forces and any lubricant concentration. The disintegration time of tablets seemed to be independent on magnesium stearate concentration. In the case of Starch 1500^{R} tablets, they explicited long disintegration time even at low content of magnesium stearate or low compression force. Starch 1500^{R} and Avicel PH 102^{R} were also affected by the concentration of lubricant.

Application in Manufacturing of Tablet Products

For the evaluation of modified rice starch as a direct compression diluent in tablets. Isoniazid and hydrochlorothiazide were represented as model drugs. Isoniazid is a very soluble drug and hydrochlorothiazide is a practically insoluble drug. Each formula did not contain disintegrants in order to study only the effect of diluents.

Tablet thickness of modified rice starch was higher than that of Era-Tab^{R} as the bulk density was lower. The cause of this was due to the lower compressibility of Era-Tab^{R} . It must use higher compression force to produce tablets which possessed the same hardness as modified rice starch, causing lower thickness value.

Avicel PH 102^{R} tablets and Starch 1500^{R} tablets had the highest and lowest thickness. Avicel PH 102^{R} and Starch 1500^{R} had the highest and lowest compressibility, respectively. Different compression forces were employed to make the tablets of different diluents to have the hardness of the products within the limit of 4.5$\pm$0.5 kps.

The disintegration time of isoniazid tablets containing modified rice starch or Era-Tab^{R} were within 3 min. The reason was attributed to modified rice starch and Era-Tab^{R} mainly comprised the agglomeration of starch grains, the tablet probably fell apart easily when being immersed in the water. The longest disintegration time of Starch 1500^{R} tablets containing isoniazid could be due to it become gel impeding the penetration of water into the the tablet when wetted.

In the case of isoniazid tablets containing Avicel PH 102^{R}, they showed short disintegration time because Avicel PH 102^{R} owned the highest compressibility. It used lower compression force to produce tablets which possessed the same hardness as the other diluents. The mechanism of disintegration time of Avicel PH 102^{R} was due to the breaking hydrogenn bonds by water.

With respect to dissolution of isoniazid tablets, Era-Tab^{R} had very rapid dissolution rate. Modified rice starch possessed high dissolution rate and was not markedly different from Avicel PH 102^{R}. An explanation for difference was resulted from the term of the rapid disintegration time of Era-Tab^{R} Dissolution rate of Starch 1500^{R} tablets containing isoniazid was the slowest. For Avicel PH 102^{R} , they disintegrated rapidly but they disintegrated into cellulose agglomerates.

The amounts of isoniazid dissolved within 45 min were more than 80 % (Q). The time when 80 % of drug released ($T_{80\%}$) was complied with the USP XXIII requirement in 45 min.

When hydrochlorothiazide was incorporated into these same diluents, the tabletting properties of them such as thickness, hardness and disintegration time, depicted similar results as in isoniazid tablets and could be explained by the same reason, except that of Starch 1500^R tablets. Disintegration time of hydrochlorothiazide tablets containing Starch 1500^R was lower than that of isoniazid tablets containing Starch 1500^R. This indicated that the incorporation of insoluble drug substance in formulation using Starch 1500^R would exert more effect on disintegration time than that of soluble drug substance.

Dissolution profiles of hydrochlorothiazide tablets containing modified rice starch, Era-Tab^R, Starch 1500^R and Avicel PH 102^R were different from isoniazid tablets. Dissolution rate of each diluent was slower and $T_{60\%}$ of each diluent was longer than $T_{80\%}$ of isoniazid tablets. The reason was due to hydrochlorothiazide is practically insoluble in water. The amounts of hydrochlorothiazide dissolved within 60 min were more than 60 % (Q). The time when 60 % of drug released ($T_{60\%}$) met the specification of the USP XXIII monograph.

Conclusions

Modified rice starch in this study was produced by chemical and physical modification. It has been evaluated and compared to four

commercial directly compressible diluents. The conclusions of the studies were as follows.

1. The results of flow studies of modified rice starch, Era-Tab^{R} and Emcompress^{R} exhibited excellent flow properties as evidenced by a rapid flow rate. Starch 1500^{R} and Avicel PH 102^{R} exhibited flow problems.

2. Tabletting properties indicated satisfaction for modified rice starch. It showed higher binding properties than Era-Tab^{R}, Starch 1500^{R} and Emcompress^{R} but lower than Avicel PH 102^{R}. Its disintegration time was short and the friability was low.

3. Dilution potential was determined by using non-compressible diluent (ascorbic acid). Avicel PH 102^{R} had the highest dilution potential. Modified rice starch could produced with higher hardness value than Era-Tab^{R}, Starch 1500^{R} and Emcompress^{R} at all compression forces.

4. Negative effect of lubricant can have on strength and disintegration time of tablet. Magnesium stearate distinctly reduced the hardness of plastic material such as modified rice starch, Era-Tab^{R}, Starch 1500^{R} and Avicel PH 102^{R}, where as brittle materials, e.g. Emcompress^{R} were not suspectible to the lubricant. Magnesium stearate prolonged the disintegration time of each diluent.

5. The properties of tablets containing isoniazid and modified rice starch possessed fast disintegration time and drug released comparable with Era-Tab^{R}. Dissolution of hydrochlorothiazide from modified rice starch complied with the USP XXIII requirement.