Chapter Four

Discussion and Conclusions

1. The Optimum Condition of the Fluidized Bed Granulator

Before proceeding with preparation of the sugar-starch granules by fluidized bed granulator, the optimum conditions of the fluidized bed granulator were investigated with all types of binder as previously shown in Table 1. Initially, the investigation was concerned with the amount of binder in the formula and binder solution concentration. The amount of binder as least as possible which provided good granulation and tabletting characteristics would be employed in formulation. Binder solution concentration should provided the ease and smooth pattern of the spraying. It was suggested that low percent concentration of binder solution must be used in order to afford better quality of granules, i.e., larger bulk density, improvement of granule flow (23). It could be seen that the binder solution concentration of methyl cellulose and tapioca starch employed in the granulating process were lower than those of PVP and gelatin binders since higher concentration of binder solution of methylcellulose and tapioca starch binders were too viscous and difficult to spray. However, the binder solution concentration should not be too diluted as this

would cause the production time unnescessarily long. The adjustment of the other process parameters i.e., inlet air temperature, nozzle pressure and binder solution spraying rate employed in the granulating process certainly depended on the binder solution concentration and the amount of binder in the formula. However, low inlet air temperature, high binder solution spraying rate, and low nozzle pressure must be used to provide good granule qualities as described by Aulton and Banks (15).

2. Physical Properties of Powdered Sugar-Tapioca Starch-PVP Granules.

The sugar-starch granule size using PVP as a binder increased with increasing the amount of sugar in granule formulations. This may be explained that the granules of those formula were mainly composed of sugar crystals which possessed larger size than of starch grain.

As expected, the granules made by fluidized bed granulator obtained low bulk density. This was because the air was entrapped in the granules by the fluidizing air during the granulating process and no shearing force exerted on the powder during wet massing. This phenomenon made the granules become more porous and bulky. However, no relationship could be found among bulk density and the proportion of sugar and starch in the formula.

If the percent compressibility values were used to determine the flowing property of the granules, the granules of formula 9 would be classify into fair flow granule as having percent compressibility between 18-21 where the rests would be classify into poor flow granules as having percent compressibility between 23-35 (30). However, the weight variation of tablets prepared from all granulations were within the limit specified in USP standard. So this indicated that percent compressibility value may not be used generally to assess the flowing characteristic of the granules. Many factors can affect flowability of the granules such as particle size, shape, surface roughness, moisture content, and chemical nature as described by Udeala and Chukwu (30). It was seen that though the flow rate measurement of granules of formula 1 to 3 were unsuccessful, the weight variations of tablets were relatively low.

It is notable that the percent moisture content of the granules increased with increasing the amount of starch in the formula. This may be attributed to the intrinsic moisture content of tapioca starch (11.4 %) was higher than of powdered sugar (1.1 %) and tendency of starch to absorb moisture from binder solution during granulation process and difficult to eliminate during normal drying cycle.

The binding properties of the different formula were characterized by means of hardness of tablets compressed at different compressional forces. A general trend of increase in hardness with increasing compressional forces could be seen in all nine formula though the tablets were compressed under low increasing rate of compressional forces (1000-1600 lbs). Furthermore, compressional forces had no effect on tablet disintegration time in each granule formula. This may be due to the property of PVP which was used as the binder could be readily dissolved in disintegration medium. Therefore, the advantage of the use of PVP binder to prepare the tablet containing sugar and starch as the diluents is the variation in compressional force during tabletting will not cause substantial change in disintegration time.

When tabletting characteristics of granules were investigated on a single punch tabletting machine, great difference in percent coefficient of variation of tablet hardness and tablet disintegration time among nine formula was observed. The high variation values of tablet hardness occurred in the formula which contain high amount of starch.

Obvious difference in percent tablet friability among nine formula could be found after the friability

determination was prolonged to 15 minutes. The high values occurred in the formula which possesed high amount of sugar. This can be explained that sugar crystals are brittle and easy to break up by impact during friability test.

Base on the resultant granule and tablet properties, it could be convinced that formula 5 exhibited satisfactory granule and tablet quality. It provided the following properties ; good compressibility with low variation in tablet disintegration time at any compressional forces, low variation in tablet hardness, and lowest variation in tablet weight. These properties satisfy the basic requirement of direct compression tablet diluent. Although tablets from formula 4 exhibited the best compressibility but it gave high variation in tablet hardness and tablet disintegration time.

3. Physical Properties of Powdered Sugar-Tapioca Starch-Gelatin Granules.

Sugar-starch-gelatin granules which contained high proportion of starch possessed higher amount of fine granules than of the formula which contained high amount of sugar. High amount of the fine granules may be caused by the fracture of gelatin bonding among the particles in granules from the abrasion effect of the fluidizing air

during granulation process. This effect less occurred with the formula contained higher sugar content since sugar also has binding property which promoted stronger adhesion between particles. As expected, all of the granule fomulations presented low values of bulk density. The explanation are the same as described for sugar-starch-PVP granules. However, they were denser than the granules prepared using PVP as a binder.

According to the percent compressibility values, almost of the granule formula could be justified as poor flow granule. This is in contrast with the weight variation of tablet which are satisfactory.

It was seen that only the flow rate of granules from formula 9 could be measured. The flowability test of the granules was unsucessfal may be due to containing the high proportion of fine granules.

The moisture content of the granules prepared using gelatin as a binder proportionally decreased with decreasing the amount of starch. The reasons are the same as described for sugar-starch-PVP granules.

As expected, a general trend of increase in hardness with increase in compressional forces can be observed but lower trend of increasing in hardness than those of sugar-starch-PVP granules was found. This may

be caused by the nature of binding capacity of each binder. However, it can be concluded that compressional forces had little effect on tablet disintegration time. Their disintegration times were nearly the same at increased compressional forces. The use of gelatin as a binder in the formula may produce very hard tablet and retard disintegration time but in this experiment, tablets prepared using gelatin as a binder disintegrated within a short period (3-4 min) which was in contrast with the general description by Mendes and Roy (31).

Tablet characteristics of granules were investigated on a single punch tabletting machine. The formula 1, 2, and 3 which contained high amount of starch exhibited high variations in disintegration time since the starch may form more viscous and tacky mass and delay of disintegration could occurred. This effect could be observed during the test when 1-2 tablets took longer time to disintegrate by forming gelatinous particle adhering to the hole of the seive of the disintegration apparatus which led to high variation in disintegration time.

The tablets from the formula with high amount of sugar exhibited high values of percent friability. The reasons are the same as for sugar-starch-PVP granules.

In conclusion, it can be convinced that formula 5 exhibited better granule and tablet quality than of the

others. These can be explained that granules from formula 5 provided the best compressibility, lowest percent coefficient of variation of tablet hardness and tablet disintegration time, and accepted as good tablet weight uniformity. This means that formula 5 gave hard tablets with low disintegration time and weight variation.

4. Physical Properties of Powdered Sugar-Tapioca Starch-Methylcellulose Granules.

Inconsistent change in size distribution of each granule formula prepared by using methylcellulose as a binder was observed.

As expected, the granules made by fluidized bed granulator exhibited low bulk density because the air was entrapped in the granules by the fluidizing air during the granulating process. This phenomenon made the granules become more pourous and bulky. However, bulk density of the granules made from methylcellulose binder was higher than those of prepared from PVP and gelatin binders.

If the percent compressibility values were used to determine the flowing property of the granules, the granules of formula 9 was classified as good flow, granules of formula 4 and 5 were indicated fair flow whereas the rests were exhibited poor flow (30). However, the weight variations of tablets prepared from all nine

formulations were relatively low. The conclusion of percent compressibility are the same as descreibed for sugar-starch-PVP granules. It was seen that though the flow rate measurement of granules of formula 1, 2, 3, 6 and 8 were unsucessful, the weight variation of tablets prepared from granules were reasonably low.

From the results of percent moisture content of the granules, it increased with increasing the amount of starch in the formula. The explanation are previously discussed.

The binding properties of different formula were characterized by means of hardness of tablets compressed at different compressional forces. Tablet hardness increased with increasing compressional forces but the magnitude of increase in hardness was less than those of tablets prepared using PVP and gelatin binders. One reason was that low concentration (1.0%) of methylcellulose was employed in the formula .

From compressional forces-disintegration profile, it could be noted that the compacts prepared using methyl cellulose as a binder spent longer time to disintegrate than those of PVP and gelatin binders though they were softer. Compressional force had an effect on disintegration time. This may be due to the nature of the

binders. However, because of the water soluble property of sugar. the tablets contained high amount of sugar took shorter time than the tablets contained high amount of starch.

Tabletting characteristics of granules were investigated on a single punch tabletting machine. No relationship between variation of tablet hardness and variation in tablet disintegration time was found.

Tablets contained high amount of sugar exhibited higher values of percent friability than those contained high proportion of starch. This explanation may be base on the brittle property of sugar crystals.

In summary, it can be concluded that formula 9 exhibited better granule and tablet quality than of the others. This can be explained that the tablets from formula 9 provided the best compressibility and the hardness of the tablets had little effect on tablet disintegration time, and also exhibited lowest variation of weight and hardness.

5. Physical Properties of Powderd Sugar-Tapioca Starch-Tapioca Starch Granules.

It can be observed from the data that the granules prepared using starch as a binder exhibited larger size than the granules prepared using other binder

materials. This may be due to more viscosity of the binder solution resulted in larger spraying droplet size hence the larger granule size. Large size of the granules were found in the formula contained high amount of sugar. This can be explained in the same reason as previously described.

The low bulk density of the granules prepared using starch as a binder were also observed. The explanation of the cause are the same as described for sugar-starch-PVP granules.

As a result of percent compressibility, formula 1 to 5 and formula 6 to 9 were indicated as poor flow and fair flow, respectively (30). However the weight variation of tablets prepared from all granule formulations were within the limit specified in USP standerd.

The moisture content of the granules prepared using starch as a binder proportionally increased with increasing the amount of starch. The reasons are the same as described for sugar-starch-PVP granules.

The hardness of the tablets prepared using sugar-starch-starch granules increase with increasing compressional forces but the lower trend of increase in tablet hardness than those of sugar-starch-PVP and sugar-

starch-gelatin granules were found. One reason is that the amount of starch as a binder was used in low concentration.

Obvious difference in tablet disintegration time betweenin nine formula prepared using sugar-starch-starch granules at different compressional forces may be due to poor distribution of starch binder solution during granulation process. Poor distribution of the binder solution might be the result from wide range of droplet size of such viscous binder solution.

Tabletting characteristics of granules were investigated on a single punch tabletting machine. The disintegration time of tablets prepared from sugar-starch-starch granules decreased when the proportion of sugar in the granules increased. This is the consequence of the soluble property of sugar. However, the formula contained high amount of sugar exhibited high percent friability. This can be explained in the same manner as previously described.

It was concluded that, formula 8 gave better granule and tablet quality than of the others. This can be explained that tablets took least time to disintegrate, having low variation in tablet hardness and tablet disintegration. Although the compressional force had less

effect on the disintegration time of tablets prepared from formula 9 but the variation of tablet weight was so high. In addition, the particle size distribution of formula 8 were appeared to be better than of formula 9. The high amount of large granule size of formula 9 may cause segregation during mixing process with drug substances of smaller size.

The selected formula for all types of granule exhibited better hardness profiles of compacts than those of five direct compressional diluents except the compacts of sugar-starch-methylcellulose and sugar-starch-starch granules which showed lower hardness profiles of compacts than those of Emdex^{R} but better than of the others (Figure 19).. The compressional forces had little effect to the disintegration of compacts prepared using sugar-starch-PVP and sugar-starch-gelatin granules, in addition, the compacts disintegrated within a short time (3-4 minutes) despite no addition of disintegrant. This results was interesting if a diluent is autocompressible and compressional forces had a little effect to its disintegration.

6. **Aging Study**

The content uniformity of diazepam and chlorpheniramine maleate tablets prepared using sugar-starch-PVP, sugar-starch-gelatin, and sugar-starch-

methylcellulose granules were within the USP requirement while tablets prepared from sugar-starch-starch granules did not meet the compendial limit. This may be due to the greater difference in size between the granules and drug particles in comparing with the other types of granules which led to segregration of drug and diluents during mixing process.

In direct compression process special attention should be paid to the physical stability of the tablets. Sugar are known to be hygroscopic when stored under humid condition (32). If it is used in sufficient quantities the tablet will harden with time, which would interfere with the dissolution of drug from the tablet (33). The physical properties especially, dissolution behavior of aging tablets containing drug substances prepared from the sugar-starch granules were, thus, investigated to develop a comprehensive data of the three months storage.

Significant decrease of diazepam and chlorpheniramine maleate tablet hardness prepared using all type of granules were observed at the storage condition of 75 % R.H. in the period of 3 months. The dramatic decrease of tablet hardness among all type of granules were raked as follows ; sugar-starch-PVP > sugar-starch gelatin > sugar-starch-methylcellulose ~ sugar-starch-starch (as shown in Figures 21-28). Tablets

prepared using sugar-starch-PVP showed rapid decrease in tablet hardness because PVP tended to pick up moisture and the moisture uptake made the tablet became softer. The tablets prepared using gelatin as a binder or high sugar content in this experiment were not harden with time at the room condition storage. This finding is in contrast with the general description for gelatin and sugar (33). In addition, the moisture uptake of the tablets caused increasing tablet weight and tablet thickness in the same order as previously discussed for tablet hardness. The change in these physical properties were clearly observed during only the first month of storage, this may be due to reaching the saturation point of moisture obsorption of tablets. Their physical properties did not significantly change at the normal storage or low humid conditions. Finally, it can be concluded that the change in tablet weight, tablet hardness, and tablet thickness were depending upon the nature of the binders. However, in practice, the tablets are rarely exposed to high humid condition upto 75 % R.H. for a long time.

The change in tablet hardness during storage did not correspond with the change in disintegration time. Tablets were soften with aging but increasing in disintegration time were observed in tablets prepared using sugar-starch-PVP and sugar-starch-starch granules

stored at 75 % R.H.(Tables 32 and 35). Tablets prepared from sugar-starch-methylcellulose and sugar starch-starch granules spent longer time to disintegrate than those of PVP and gelatin binders, this is because methylcellulose and tapioca starch retarded tablet disintegration by forming viscous layer around the granules. However, it can be concluded that no dramatic change in tablet disintegration time were noted in all formulations during this period of storage.

The increase in tablet friability during 3 months of storage was obviously occurred only at the storage condition of 75 % R.H. which related to the decreasing in tablet hardness. However, tablet friability from all of the formulations were relatively low within very satisfactory limit.

The dissolution of freshly prepared diazepam and chlorpheniramine maleate tablets using sugar-starch-PVP and sugar-starch-gelatin granules were within the USP requirement and the time of 100 % drug release remained unchanged after storage for 3 months under various conditions. This may be due to their short disintegration times and water soluble property of the binders. The slight difference in chlorpheniramine maleate release rate among each month interval was observed in the same storage condition. The difference in dissolution profiles

of these tablets might be the result of high variation in content of chlorpheniramine maleate. The dissolution of diazepam and chlorpheniramine maleate tablets prepared using sugar-starch-methylcellulose and sugar-starch-starch granules did not meet the USP requirement. This is due to, when contacted with dissolution medium, methyl cellulose and starch may form viscous layer around granules which led to retardation of drug release from tablet. However, their dissolution may further increase by the addition of the disintegrant in the formula.

Diazepam and chlorpheniramine maleate tablets prepared from all storage granule formulations taken at the end of the first, second, and third month could be manufactured to required physical properties i.e., hardness, disintegration time, weight variation, thickness and friability in comparing with those made from freshly prepared granules.

The dissolution of diazepam and chlorpheniramine maleate tablets prepared from sugar-starch-PVP and sugar-starch-gelatin granules met the USP requirement both at initial and after storage with the same time of 100 % drug release. The explanation are the same as described previously for tablet storage. In addition, the dissolution profiles of tablets prepared from storage granules are the same pattern as of tablets under storage.

This may be concluded that tablets prepared from storage granules at room condition for 3 months still provided dissolution profiles at the same rate as freshly prepared granules. So in practice, the granules can be prepared in large quantity and storage for later use.

In contrast, the dissolution of diazepam and chlorpheniramine maleate tablets prepared from sugar-starch-methylcellulose and sugar-starch-starch granules did not meet the USP requirement. The reason of this failure are the same as previously discussed.

Conclusions

It has been seen that good fluidization of powdered sugar and tapioca starch had been achieved during processing without any difficulties. Satisfactory granulations of sugar-starch mixtures with four binders (PVP, gelatin, methylcellulose, and tapioca starch) could be conducted. Properties of granules depended on the proportion of sugar and starch in the granules as well as the type of binder materials employed.

The granules produced were ready to be used to prepare the tablet products of microdose drug substances by direct compression. Among four binders employed, PVP and gelatin provided good granule and tablet properties while the granules prepared using methylcellulose and

tapioca starch as binders gave satisfactory granule and tabletting characteristics but poor disintegration time and dissolution rate of drugs were observed.

However, the tablets prepared from sugar-starch-PVP granules tended to be soften when exposed to high relative humidity during storage. In this study gelatin should be the best of four binder materials used to prepared the sugar-starch granules. The tablet products made from sugar-starch-gelatin granules could retain required properties and exhibited lower moisture absorption during aging.

The pharmaceutical manufacturers may apply the fluidized bed granulator which already exists in their plants to produce the sugar-starch granules in this manner for later use in making tablets by direct compression process. The utilization of sugar and starch may reduce the cost of product. However, the process development is required and granulation process should be carefully controlled to prevent variation between production batches.

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