

## CHAPTER IV

## DISCUSSION AND CONCLUSION

DISCUSSION

The disintegration of compressed tablets depends a great extent upon the compressional force. The dependency, however, remains obscure and is often described as complex. However, the disintegrant type was proposed to have effect upon this relationship.

This investigation intended to combine simple effective methods such as, moisture sorption, water uptake and disintegration time with the aim of assessing the role played by different disintegration mechanisms and tablets base material on compressional forces.

Moisture sorption to the tablets increased with increasing relative humidity for almost all formulations except formulas containing low concentration of cross linked polyvinylpyrrolidone, corn starch and microcrystalline cellulose. This data definitely indicated that it was judicious to select effective concentration of disintegrant incorporation into a direct compression formula.

Higher humidity exposure gave higher moisture sorption while moisture sorption did not change significantly

with compressional forces. This meant that moisture sorption was affected by humidity rather than compressional force.

Tablets containing high concentration of disintegrant absorbed more moisture than those containing low concentration comparing among tablets using the same disintegrant. Direct relationship was found between the sorption and the amount of disintegrant in tablets with correlation coefficient  $> 0.9$  at 98% relative humidity exposure. This correlation follows Langmuir's adsorption theory in which indicated that the amount of moisture sorption is directly proportional to the vapor pressure of the gas and the amount of adsorbent (72). X coefficient or slope of correlation between moisture sorption and amount of disintegrant of tablet was not change significantly when compressed with different forces. This can be concluded that moisture sorption was depended on the amount of disintegrant rather than compressional force.

Tablets containing sodium starch glycolate showed highest moisture sorption followed by cross linked polyvinylpyrrolidone, microcrystalline cellulose and corn starch respectively. It was also shown that tablets made from  $\alpha$ -lactose monohydrate absorbed higher moisture than tablets made from dicalcium phosphate dihydrate.

Maximum moisture sorption was found in almost all formulations at 98 % relative humidity within 48 hours except

for tablets containing any concentrations of sodium starch glycolate, dicalcium phosphate dihydrate tablets containing 50% microcrystalline cellulose and  $\alpha$ -lactose monohydrate tablets containing 40%, 50% microcrystalline cellulose, 12% corn starch, 7% cross linked polyvinylpyrrolidone that those tablets continuously picked up moisture beyond 48 hours. The moisture sorption of tablet having maximum sorption also followed a first order process. No significant difference between the slope of kinetics plot was found. This indicated that compressional force did not affect the sorption kinetic.

From the results of density change, the apparent density of the tablets decreased for all formulations at 98% relative humidity exposure. This indicated that all tablets expanded when moisture was absorbed.

At initial stage, 6 hours exposed at 98% relative humidity, all formulation, except dicalcium phosphate dihydrate tablets containing 3% starch, showed a markedly decrease in apparent density. In consequence, the decreasing in apparent density was also found with increasing concentration of disintegrants. This meant that tablet containing lower concentration than effective concentration did not sensitive to moisture.

Sodium starch glycolate exhibited the highest decrease in density followed by cross linked polyvinylpyrrolidone, microcrystalline cellulose and corn

starch. It was notable that higher moisture sorption disintegrants did not always show higher decreasing in density. This may be due to the differently operated mechanisms of different types of disintegrants themselves. Similar to moisture sorption, compressional forces had no effect on density decreasing.

The hardness of the tablets decreased on aging under high humidity and the magnitude of the decrease was related to the amount of moisture sorption by the tablets. Nevertheless, hardness was not significantly changed on aging under low humidity. This indicated that no relationship between moisture loss and hardness but hardness decreased as gaining moisture sorption.

From the results above it can be suggested that there was no relationship between the change of physical properties of the tablets such as; moisture sorption, density change and hardness of the tablets on aging under various humidities and compressional force existed. The result was expected in view of the same composition in the formula that all formulations in the series showed the highest change at the highest concentration of disintegrants.

As expected, porosity decreased as increasing compressional force and decreasing concentration of disintegrants except formulations containing microcrystalline cellulose. However, porosity did not exert any influence on

moisture sorption and density change. This indicated that neither compressional force nor porosity exerted effect on moisture sorption and density change.

Compressional force exerted influence on water penetration of dicalcium phosphate dihydrate - sodium starch glycolate tablets. Tablets compressed with low compressional force had tendency to uptake more water. Therefore, water uptake by the tablets depended on pore size. Moreover, tablets did not uptake water immediately but exhibited a lag time at the early stage of the penetration. This initial obstacle was due to the surface condition of the tablets which may be presumed as a surface tension or contact angle by which compressional force and properties of ingredients may affected the surface condition.

Gelatinization of sodium starch glycolate caused increasing viscosity of the penetration liquid during the process, resulting retarded the penetration. This effect was markedly notable when incorporated higher amount of sodium starch glycolate and compressed at higher force.

Corresponding to the penetration results, disintegration times of dicalcium phosphate dihydrate containing sodium starch glycolate as disintegrant increased with increasing compressional force. Dicalcium phosphate tablets containing 6% sodium starch glycolate showed the fastest disintegration time, although the tablets did not

uptake the highest amount of water. This can be explained that when incorporated sodium starch glycolate higher than effective concentration gel formation occurred. Consequently, disintegration depended on dissolution of the tablets resulting in prolonged disintegration time.

Conversely, the tablet made from lactose and sodium starch glycolate exhibited slightly increase in water penetration when compressional force was increased and the penetration curve did not show the initial obstacle as in dicalcium phosphate system. This indicated that surface condition had no effect on penetration. Water uptake was also increased when amount of disintegrant was increased. Thus, the water uptake depended on amount of disintegrant and compressional force. A rapid penetration was observed even with the highest force. This pointed out that continuous contact of sodium starch glycolate particles when compressed at high force produced high affinity to draw water into the tablet without regard to pore size.

Water continuously penetrated into  $\alpha$ -lactose monohydrate - sodium starch glycolate as a function of time. This may attribute to the dissolution of lactose during the penetration process resulting in wider pore. Dissolution, however, increased viscosity of penetration liquid resulting to impede the penetration.

High compressional force seemed to improve both

disintegration and water uptake of  $\alpha$ -lactose monohydrate - sodium starch glycolate tablets. This meant that the penetration characteristic played an important role in the disintegration behavior of these tablets. For the tablets of the concentration more than 10% of this disintegrant, disintegration time increased as increased compressional force. This can presume that tablets containing high concentration of sodium starch glycolate tended to form adhesive gel when contact water and enhanced resistance to water penetration thus disintegration time relied on the dissolution.

Compressional force enhanced penetration in all formulations containing corn starch. The intensity of this effect increased with compressional force. This effect must be ascribed to the continuous contact of starch grains at high compressional force, thus increased water penetration rate.

The initial hindrance in the penetration of dicalcium phosphate tablets containing 3% corn starch indicated the surface condition which retarded the penetration, similar to dicalcium phosphate - sodium starch glycolate tablets. This effect was recessed when concentration of corn starch was increased. According to this effect, dicalcium phosphate dihydrate tablets containing 3% starch showed prolonged disintegration time than tablets of



other concentrations.

Dimensionless disintegration value of dicalcium phosphate dihydrate tablets containing 3% corn starch increased with increasing compressional force while the others were found to decrease. This indicated that the tablets of 3% corn starch did not show profound effect on break-up because they exhibited the initial hindrance during penetration process. Therefore, mechanism of disruption the tablets by corn starch was fully realized at concentration higher than 3%.

In the early stage of penetration, the rate of water uptake into compacted  $\alpha$ -lactose monohydrate tablet was not so fast as in dicalcium phosphate tablets, especially at high concentration of corn starch. Since the filler dissolved, the penetration was obstructed by resistance due to the increase of the viscous of penetration liquid. However, the overall rate of penetration increased with increasing compressional force. The dimensionless disintegration value also confirmed this result, that is disintegration time decreased as increased compressional force.

In the case of  $\alpha$ -lactose monohydrate - cross linked polyvinylpyrrolidone tablets, there was a tendency for tablets to pick up more water, with higher compressional force. This may due to higher affinity to draw water after closer contact between cross linked polyvinylpyrrolidone



particles occurring with higher compressional force.

Short lag time in the penetration profile was found for dicalcium phosphate tablets containing 1% cross linked polyvinylpyrrolidone. The tablets of 1% cross linked polyvinylpyrrolidone showed increasing in disintegration time when compressional force was increased. This could be attributed to the incorporation concentration of disintegrant lower than effective concentration, hence disintegration of tablets was due to deaggragate of dicalcium phosphate. At higher concentration, compressional force aided water penetration, therefore, disintegration times decreased with increased compressional force.

Prolonged disintegration time of dicalcium phosphate dihydrate containing 7% cross linked polyvinypyrrolidone was found even in those compressed with 1200 pounds. This was due to the formation of adhesive gel of the disintegrant when hydrated. Then disintegration was the result from tablet dissolution.

From the results of dimensionless disintegration value and the disintegration time,  $\alpha$ -lactose monohydrate-cross linked polyvinylpyrrolidone tablets were sensitive to compresssional force. As expected, disintegration times were prolonged with forces similar to the result from the water uptake. Increasing concentration of this disintegrant tended to increase the disintegration time, although higher

concentration expedited water uptake. Gelatinization was observed on disintegration test. This manner led to tablet dissolution than tablet disintegration.

Lag time was notable in dicalcium phosphate dihydrate system containing low concentration of all disintegrants. This effect may due to property of dicalcium phosphate affecting on surface condition of the tablet. It would restrict the initial of wetting resulting in prolonged disintegration time.

Another hypothesis which supported the decreasing in disintegration time as increasing in compressional force is force of swelling. List and Muazzan (56, 57) concluded that synthetic polymers showed high swelling pressure which was responsible for the disintegration of the tablets. Limitedly swelling substances, which tend to be mucilageous and gel forming, retarded the entrance of water into tablets. They also found that Kollidon CL showed high swelling pressure when concentration and hardness was increased.

Addition of microcrystalline cellulose to dicalcium phosphate tablets aided water uptake while compressional force retarded. The increasing in penetration rate was caused by the breaking of the hydrogen bonds between the microcrystalline cellulose particles. Consequently, pore volume increased resulting in rapid penetration. This

behavior explained the rapid disintegration in the tablets containing 20% - 40% microcrystalline cellulose. The relatively long disintegration times for tablets containing high amount of microcrystalline cellulose may attribute to structure of microcrystalline cellulose which lined themselves up into layer, thus decreased the bond distance between particles and further increased the interparticle force. This effect was characterized by markedly increasing in hardness of tablets containing 50% microcrystalline cellulose.

Increasing in disintegration time with increasing in compressional force for dicalcium tablets containing microcrystalline cellulose may ascribe to the impeded penetration according to a notable decrease in porosity, led to prolonged disintegration times.

The effect of compressional force on the penetration of  $\alpha$ -lactose monohydrate - microcrystalline cellulose tablets may also be attributed to the pore volume. Thus, high compressional force showed less water uptake. In the early stage of penetration, water uptake was impeded by the dissolving of the lactose, resulting in an increase in liquid viscosity. However, the high water penetration into lactose tablets containing 40%, 50% microcrystalline cellulose was found when high compressional force was used. This effect may ascribe to the masking of lactose by microcrystalline

cellulose then reducing the dissolution velocity.

Nevertheless, disintegration time was increased with increasing compressional force for all concentration of microcrystalline cellulose. Thus, the masking of lactose by microcrystalline cellulose seemed to exert less influence on disintegration than binding force produced by microcrystalline cellulose at high compressional force.

From the results of this evaluation, it is apparent that in the dicalcium phosphate dihydrate base, there appears to be a minimum effective concentration for tablet containing disintegrants, at which the tablets show a reduction in the disintegration times, and neither lower nor higher than that concentration they show prolong disintegration times at all compressional force. These results confirmed the finding of Khan and Rhodes (27) who using sodium starch glycolate, cation exchange resin and corn starch as disintegrants, also found that dicalcium phosphate tablets did not disintegrate at a particular concentration. This indicated that the prevail role in the disintegration process of dicalcium phosphate is played by disintegrants.

On the other hand, the disintegration time of  $\alpha$ -lactose monohydrate base seemed to be different. It was suggested that the soluble filler and disintegrant which possess adhesive or binding properties then retarded disintegration as the concentration increases. Consequently,

the disintegration depend primary on filler dissolution.

It therefore appears that disintegration of tablets contain disintegrant lower or higher than effective concentration depend on deaggregation or dissolution of the tablets themselves.

Compressional force also showed important role in disintegration behavior. High compressional force produced tablet with low porosity resulting in low water uptake, consequently, prolonged disintegration time. High compressional force, however, increased interparticular contact of disintegrant particles resulting high water uptake then decreased disintegration time.

#### CONCLUSION

It is apparent that disintegrant type have a significant effect upon compressional force. Also, it is interesting to see that the well known supposition, "high compressional force take longer to disintegration", is not applicable to all systems. In fact, some disintegrants show that the converse may be true.

Various discussions can be given to the tablet disintegration phenomena based on the penetration of water into the porous structure of the tablet. The application of Washburn's equation to water penetration into tablet containing disintegrant can provide a qualitative profile of

the disintegration process. Such a relationship would indicate among the factors involved in the capillary penetration process of a liquid i.e. surface tension, contact angle, pores radius and liquid viscosity. Consequently the mechanism by which the disintegration occurs depends on those factors grouped in the following manner:

- (a) Initial obstacle to water penetration linked to surface tension or contact angle.
- (b) Wider pore size by dissolution or breaking hydrogen bonds of the filler.
- (c) Resistance to fluid penetration arising inside tablet due to dissolution of soluble diluent.

On the other hand, moisture sorption of the tablet compressed with various forces exhibited no effect on disintegration. This suggest that the disintegration process is not completely rate - limited by moisture sorption property.

These disintegrants with different mechanism of action; sodium starch glycolate (Explotab) a dispersion with a high swelling and water uptake, cross linked polyvinylpyrrolidone (Kollidon CL) an insoluble with moderate swelling and wicking and corn starch a insoluble with limited swelling and high water uptake, showed a decrease in disintegration times with increasing compressional force except for Emcompress-Explotab tablets of which exhibited

initial obstacle of penetrate liquid. For microcrystalline cellulose (Avicel PH101), an insoluble with non-swelling and breaking hydrogen bond, showed prolong disintegration times when compressed with high pressure.

Since the dissolution of the soluble system take place by erosion at the surface, therefore the tablet prepared from lactose would be expected to show different behavior from that prepared from dicalcium phosphate tablets. For dicalcium phosphate tablets system, the tablet showed an optimum concentration range of the disintegrant to give a minimum disintegration times.

Such conclusion have been drawn from a simple model formulation. It is conceivable that the addition of an active ingredients or other excipients as are capable of these factors, would claim the relationship between water uptake and disintegration.

ศูนย์วิทยทรัพยากร  
จุฬาลงกรณ์มหาวิทยาลัย