CHAPTER 1

INTRODUCTION

RATIONALE

The compressed tablet has become the most common dosage form owing to such properties as good production, economy, precision of dosage, physical and chemical stability and convenience of administration. However, absorption of a drug into the bloodstream from an intact tablet dosage form follows fairly well defined sequence of events, disintegration, deaggregration, dissolution and absorption as shown in Figure 1.

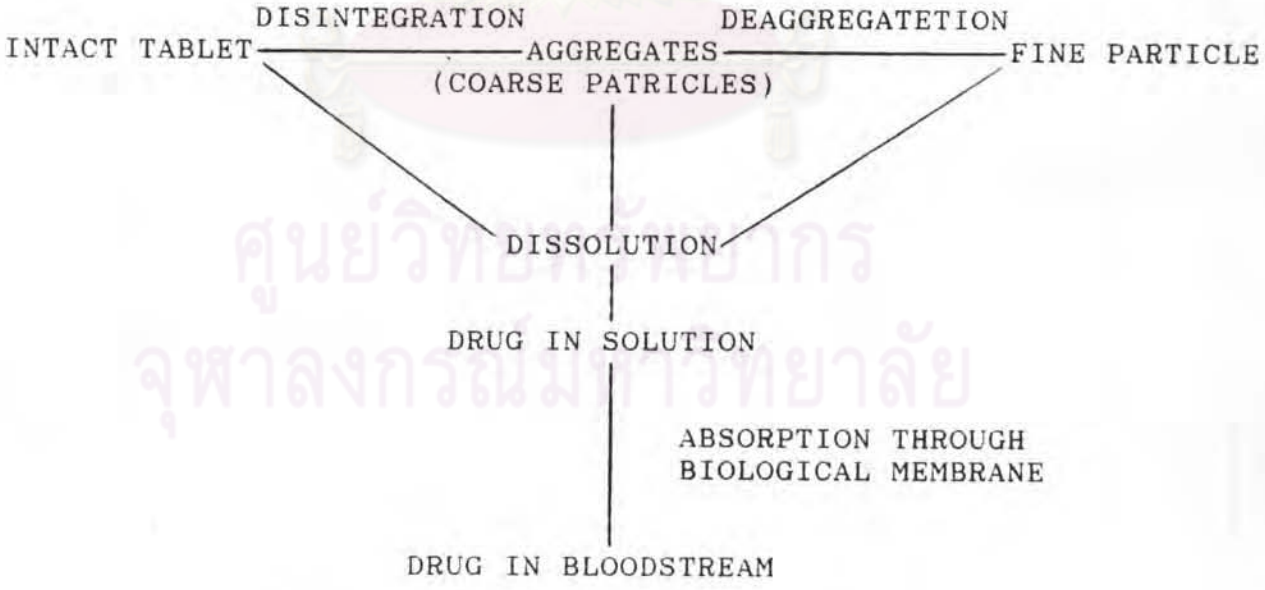

Figure 1. The absroption of a drug into the bloodstream from an intact tablet dosage form.

Tablet formation is a complex matter both regarding the mechanisms involved and the desired properties of the final tablet. The tablet must possess good mechanical properties in order to withstand treatment during production and distribution. The tablet should release the drug in a reproduction and predictable manner; ie. have good uniformity, suitable disintegration, dissolution properties, physical and chemical stability during storage.

Most drugs used in acute therapy must be available for action in a very short period of time following oral administration, for such agents, the disintegrated and dissolved drug must be presented to the absorption site as rapidly as possible. During the course of this evaluationary process, incoporation of efficient disintegrant prior to granulation provided pharmaceutical formulations with the means of quantitatively and qualitatively controlling the disintegration of solid dosage form.

Not only the biopharmaceutical properties but also the technical performance may be of importance in the medical use of tablets. Sufficient mechanical strength and resistance to abrasion are obviously necessary to deliver intact tablets and thus a complete dosage to the patient. Obvious physical defects in the tablets may raise doubts about the overall medical quality of the preparation and thus reduce patient compliance. It is thus essential to obtain optimal

compressional force to cohere all of these properties.

LITERATURE REVIEWS

A. GENERAL

Many compound have been proposed as tablet disintegrants, six basic categories of these disintegrant properties have been discribed. (1,2,3,4,5,6)

STARCH

Starch is a polymeric carbohydrate obtained from the root seed and fruits of various plants, including corn and potato. It occurs as a fine white powder consisting of polygonal, rounded, or spheroidal grains. It is insoluble in cold water and in alcohol but gelatinized in hot water to release insoluble amylopectin and soluble amylose. Corn starch and potato starch probably have best disintegrating properties and thus are the most widely used. When wetted, corn starch granules may swell by 10-25% of the original value. Lowenthal (9) showed that the conditions best suit for rapid tablet disintegration are a sufficient number of starch agglomerates, low compressive pressure and presence of water. It is used in concentration range of 5-10%.

Sodium starch glycolate (sodium carboxymethyl starch) is prepared by introducing sodium carboxymethyl

groups at the "6" position of the glucose unit in starch molecule. It is a white flowable powder. On contact with water, the hydrophilic sodium carboxymethyl groups in the molecule cause rapid hydration and swelling of the polymeric network. This results occurs in the tablets and causes tablets to disintegrate. It is normally used in a concentration range of 4-8% by weight of the tablet.

CLAY

Clay is colloidal magnesium and aluminium sililcate such as bentonite and Veegum HV. It has been used as a disintegrant at a level of about 10%. Bentonite is a very fine odorless cream to grayish powder, insoluble in water but highly hygroscopic. Bentonite swells approximately 12 times in volume when wetted. Veegum is odorless white soft, flaky powder. It is insoluble in water and alcohol. Veegum swells when wetted and forms a gellike colloidal dispersion.

CELLULOSE (7)

Cellulose is a polysaccharide with α,B-glucose linkage that is derived from fibrous plants. Pure cellulose is white and is insoluble in water. It is generally used in a concentration of about 10%. It helps the disintegration of tablets by means of its rapid water absorption property.

Microcrystalline cellulose (Avicel) is a purified partially depolymerized alphacellulose. It is a white crystalline, tasteless odorless fibrous powder and insoluble in water and alcohol. It does not act as a disintegrating agent except at high concentration. It promotes tablet disintegration by facile penetration of disintegrating liquid into pores and reducing the physical bonds forces between particles.

ALGINATES

Alginates are hydrophillic colloidal substance extracted from certain species of seaweeds. Alginic acid is an odorless tasteless white to yellowish white fibrous powder that is insoluble in water. It has a capable of absorbing 200-300 times its own weight of water. It is usually added in concentration ranging from 5-12%.

POLYVINYL POLYPYRROLIDONE (PVPP, Cross-povidone)

Polyvinyl polypyrrolidone is a cross linked homopolymers of N-Vinyl-2 pyrrolidone (PVP). It is an off-white, free flowing powder that is insoluble in water and has a moisture content of 5.0%. Upon absorption of water, the lattice structure of the polymer expands and the particles swell, causing the tablet to disintegrate. It also possesses some binding properties and produces tablets with low friability. It is generally used in a concentration of 2-5%.

MISCELLANEOUS

Miscellaneous disintegrants include gums, surfactants, natural sponge, resins, effervescent mixture and hydrous aluminium silicates.

Several articles have been proposed an overview of current understanding comprehensive in the mechanism of disintegrants or the function of disintegrants in compressed tablet system. Those mechanism can be referenced by the physical and chemical properties of the different disintegrants.

MECHANISM OF ACTION OF DISINTEGRANTS (8,9,10,11)

WATER UPTAKE

Water uptake has been implicated as an important mechanism of action for tablet disintegrants. Khan and Rhodes (12) concluded that the ability of particle to draw up water into the porous network of a tablet was essential for efficient disintegration. Similar work by Mitrevej and Hollenceck (13) supported this claim.

Kernblum and Stoopak (14) observed that cross linked polyvinylpyrrolidone swell very little, although it takes water up into its network quite rapidly.

Some workers observed that as the molecular structure of sodium starch glycolate was altered to improve

water uptake, disintegrant efficiency also improved. They illustrated that the rate and extent of water uptake by sodium starch glycolate were inversely proportional to the extent of cross linkage and the degree of carboxymethyl substitution of the starch compound.

Disintegrants that uptake about 20% water and are insoluble in water are said to be good disintegrants; ie. alginic acid, methylcellulose. Those that uptake about 40% water and are soluble in water increase disintegration times; ie. polyvinyl polymer. Those that uptake very poor are poor disintegrants.

SWELLING

Swelling is the most widely accepted mechanism of action for tablet disintegrant. Nagomi, et al. (15) developed a reliable test to measure swelling and water uptake simultaneously with the aid of two graduated columns connected by rubber tube. Gissinger and Stamp (16) and Rudnic, et al. (17) also used this apparatus and found a passive correlation between the rate of sweling and disintegration action. This apparatus was also adapted by List and Muazzam (18) to test both the rate and the force of swelling. They concluded that disintegrants capable of producing a significant force of swelling generally were most effective disintegrants.

Rudnic, et al. (17) also found that the bulk swelling of disintegrants was dependent upon a number of variations such as water transport through a gel layer and rate of hydration.

By using photomicrographic technique, Mitrevej and Hollenbeck (13) studied hydration of disintegrants by prolonged exposuring at high humidities. They concluded that the super disintegrant functioned effectively because of their remarked ability to swelling and absorb water.

Gissinger and Stamm (16) concluded that cross linked carboxymethyl cellulose was a superior disintegrant because of its ability to swell and uptake water.

Also Bolhuis and co-worker (19) found that rapidly swelling particles such as sodium starch glycolate and croscarmellose sodium type A were capable of overcoming the negative effects of hydrophobic tablet component that normally would block the passage of aqueous fluids through the porous network within tablet matrix.

But it is also important to understand that, as particles swelling; if the compacted powder matrix yields elastically to the swelling, little or no face will be expanded on the system and disintegration will not take place. If matrix is rigid and does not accommodate swelling, deaggregation by disintegrant will occur.

The swelling of some disintegrant particles is dependent upon pH. Shangraw and co-workers (11) reported that the sedimentation volume of anionic cross linked starch; such as Explotab and Primojel and cellulose; such as Ac-Di-Sol are significantly altered in acidic media while Polyplasdone XL remained unchanged.

DEFORMATION

The existence of plastic deformation under the stress of tableting has been reported for many years. Hess (20) with the aid of photomicrographs reported that disintegrant particles deform during the compression. The deformed particles were shown to release to their normal shapes when exposed to moisture.

In some cases the swelling capacity was improved when the granules were extensively deformed during compression such as potato starch granules. It was postulated that compression decresed grain stability, resulting in an energy-rich material being formed so that no more energy was necessary for swelling. Supposedly ordinary starch requires heat to swell whereas deformed starch does not.

Starch in starch tablets holdings together by cohesion, although 5-10% melting at contact points, were suggested. The greater the pressure, the greater is the

plastic deformation and the greater is adhesion. By the way adhesion is lost spontaneously and contact points are dissolved when water is added.

PARTICLE REPULSION THEORY

Ringard and Harmann (10) proposed a particle/particle repusion theory based upon the observation that particle that do not seem to swell may still disintegrate tablets by using microcrystalline cellulose (Avicle) as an example of a non-swelling excipient. They explained that the destruction of the cohesion forces between the constitutive elements of the tablet under the action of water may be ascribed to the creation of a repulsion force when the elements of the tablet enter into contact with water, or to a simple anihilated of hydrogen bonds of the capillary cohesion force.

Fox, et al. (21) claimed that disintegration was due to entrance of water into the tablet by means of capillaries and subsequent breaking of hydrogen bonds between adjacent bond of micorcrystalline celulose.

Reir and Shangraw (22) postulated that microcrystalline cellulose in tablets were a special form of cellulose fiber in which the individual crystallites were held together largely by hydrogen bonding and disintegration occuring when these bonds were broken by water. They also

found that as the polarity of disintegrating fluid decreased, disintegration times increased.

Safiulin (23) calimed that particles of kaolin acquired a negative charge in the presence of moisture, repeling each other, which caused disintegration of the tablets.

HEAT OF HYDRATION

The starch granules exhibited slightly exothermic properties when wetted because of localized stress resulting from capillary air expansion which might be at the origin of the mechanical destruction of the tablet.

In addition, for this mechanism to operate moisture appears to be necessary. It was found that there was no effect of hydrate heat on the disintegration of tablets with cross linked gum arabic or cation exchange resin or calcium carboxymethylcellulose (24). However, this hypothesis can explain only a few type of disintegrants.

It now seems obvious that no single mechanism of action applicable to all disintegrants. In some instance, a combination of mechanisms may be operated.

B. FACTORS AFFECTING DISINTEGRATION TIME (9)

There are many factors affecting disintegration

time such as:

1. Effect of fillers and active ingradients.

The filler will affect tablet disintegration time, sometimes depending on its solubility (25). The solubility of the drugs may also have an effect. The formation of hydrates after compression will increase disintegration time. Knoechel, et al. (6) stated that the nature of the formula of drug affects disintegration more than pressure used.

Tablets containing lactose and disintegrants disintegrated faster than those containing aspirin. Some investigators purposed that for tablet containing lactose and starch, the lactose interfered disintegration.

Fox, et al. (21) disclosed that added microcrystalline cellulose reduced the disintegration time of aluminium hydroxide gel and spray dried lactose.

Khan, et al. (27) reported that tablets with water insoluble drugs disintegrated quickly with starch, while those with water soluble drugs did not disintegrate as well due to the diminished absorption capacity of starch.

Lerk, et al. (28) studied the effect of microcrystalline cellulose on liquid penetration and disintegration of dibasic calcium phosphate and spray

crystallized maltose dextose tablets. They found that spray crystallized maltose dextose showed high penetration rates than dibasic calcium phosphate. They explained that this because of the dissolution of the freely soluble dextose during the penetration process, resulting in wider pores and increased in pore volume.

Kamp, et al. (29) found that the volumetric water uptake for dicalcium phosphate dihydrate corresponded with the calculated pore volume. In spite of the fast and complete penetration, the tablets did not disintegrate because the excipient was practically insoluble in water. Tablets compressed from more soluble excipient, α-lactose monohydrate took more water than their calculated pore volume. This effect was caused by dissolution of the excipients at the pore walls, resulting in a fast tablet disintegration.

2. Effect of lubricants

Most lubricants were reported to increase in disintegration times because of initially repeled disintegrating liquid. Disintegration time increases with increase lubricants concentration. The deleterious effect of magnesium stearate as hydrophobic tablet lubricant was found to be reduced when strong swelling disintegrant was incorporated in the granulation (30).

Kwan, et al. (31) found that lubricants affected disintegration time of starch-lactose tablets. It was suggested that the lubricant effect may due to increasing the hydrophobicity of the material.

Lerk and co-workers (28) showed that liquid penetration into tablets compressed from microcrystalline cellulose was much more than tablets compressed from microcrystalline cellulose plus 0.5% magnesium stearate and this result was the same as tablet compressed from spray crystallized maltose dextose.

3. Effect of Binder

The tablet binder may be too efficient, delaying disintegration. It may produce a gel like barrier around the tablet. Holstius, et al. (32) found that rate of disintegration for sulfathiazole, sodium bicarbonate and aspirin tablets were probably due to the interaction effect of binder.

Mendes, et al. (33) observed that disintegration time of aminophylline tablet increased with binder concentration while sulfathiazole certain binder prevented tablet disintegration. It was found that disintegration time increased with increasing Gum and Sugar-Invert Mixture.

Wan and Chong (34) reported that increasing

concentration of polyvinylpyrrolidone, as binder in phenacetin tablets, decreased the rate of water penetration.

Kwan, et al. (31) found that binder had significant effect of disintegration time. Starch paste gave lower disintegration time compared with gum. Gum types binder may form a gel barrier around the tablet to inhibit disintegration.

4. Effect of manufacture procedures and equipment

The effect of compressional force and tablet hardness on tablet disintegration times have been investigated under various conditions. The following is a summary of the reported results.

4.1 Disintegration time increase with an increase of pressure.

Lerk, et al. (28) reported that disintegration time of dicalcium phosphate dihydrate and spray crystallized maltose dextose tablets increased with an increase of compressional force.

Kamp and co-workers (29) reported that tablets made from dicalcium phosphate dihydrate, α-lactose monohydrate and calcium sulphate dihydrate compressed at 10 KN showed high penetration rates and water uptake than those compressed at 20 KN.

Miller, et al. (35) also found that disintegration time increased with increasing compressional force in all cases of acetaminophen tablets prepared by using low substituted hydroxypropyl cellulose, cross linked polyvinylpyrrolidone and sodium carboxymethyl cellulose as disintegrants.

Vadas, et al. (36) studied the effect of compressional force on tablet containing cellulose as disintegrator and found that Dimensionless Disintegration Value of tablets containing low substituted hydroxy propyl cellulose and microcrystalline cellulose increased when compressional force increased.

Khan and Rooke (37) observed that disintegration time generally increased with compressional force when using sodium carboxymethylcellulose, calcium carboxymethylcellulose and casein fomaladehyde as disintegrants in lactose system.

4.2 Logarithmic of disintegration time increased with an increase in pressure.

Higuchi, et al. (38) studied the effect of compressional force on the disintegration time of sulfathiazole tablets and indicated that there appears to be a good exponential relationship between disintegration time and compressional force.

Further investigation made by Higuchi and co-workers (39) showed that the logarithm of the disintegration time of Aspirin, lactose lactose-asparin and Griseofulvin varies directly with compressional force.

4.3 Disintegration time increased with an increase in tablet hardness.

Sakr and Kassem (40) showed that disintegration and hardness of compressed coated tablets were increased as the compression pressure and weight of coating increased.

Kalidindi and Shangraw (41) observed that lactose tablets containing either soy polysaccharide or cross-linked carboxymethyl cellulose exhibited a continuing increased in disintegration times as hardness was increased which was typical of tablets with a soluble filler in which disintegration was dependent primarily of filler dissolution.

4.4 Disintegration time decreased with increased compressional force.

Hill (42) found that the tablet disintegration time could become faster when compressional force was increased. It was purposed that starch grains could exert a force on the surrounding particles more effectively.

Khan and Rhodes (27) found that when using starch and cation-exchange resin as disintegrants in dicalcium phosphate dihydrate system, disintegration time dramatically decreased with pressure but after further increased pressure no effect on disintegration time was observed.

Ingram and Lowenthal (43) found that the relationship between compressional force and disnitegration time varied with the ingradients. They showed that disintegration time for the aspirin, sodium chloride and sucrose increased with increasing compressional forces whereas disintegration time for the calcium carbonate and the calamine tablets decreased with increasing compressional force.

Patel and Hoppoen (44) studied the mechanism by which starch may cause disintegration time of aspirin tablet. They found that disintegration decreased with increasing compressional force. It was ascribed that as long as the starch grain were in continuous contact with each other their affinity for water would draw it into the tablet without regarding pore size.

4.5 Disintegration time was not affected by pressure.

Vadas and co-workers (36) stated that

tablets containing crosscarmellose sodium type A and spray dried lactose showed complete insensitive of disintegration behaviour to compressional force.

Khan and Rhodes (45) found that the disintegration time of tablets containing sodium starch glycolate, sodium carboxymethylcellulose, calcium sodium alginate as disintegrants was largely unaffected by the increase in compressional force. They explained that after penetration of water, the disintegrant particle absorbed water and began to swell and also to dissolve. All these factors cause of reduced penetration due to reduction in pore size.

Besides compressional force other factors also influcence disintegration such as: speed of compression, granulation process and moisture content and dryness of disintegrants.

The method of addition of disintegrant , disintegrant concentration and the particular disintegrant also appear to affect disintegration time.

It was found that the sulfisoxazole tablets compressed by eccentric tablet press grater disintegration time than when compressed by rotary press and starch-lactose tablets compressed with the flat-face punch had slightly longer brake up times than the biconvex punch.

THEORITICAL CONCEPT

Compressional force with accompanying changes in disintegration of the compressed tablets has received little attention although it has been the cause of some results and problems within the industry. Previously, it has been shown on the out line above that there are different effects of compressional force on tablet disintegration.

The effect of disintegrant type upon the relationship between compressional force have been studied. Khan, et al. (37) found that the inherent properties of a disintegrant in a tablet formulation could exert a very significant effect upon compressional force. Another study by Khan and Rhodes (27) showed that there was relative effectiveness between disintegrants and diluents, both soluble and insoluble. They also showed the effect of disintegration concentration upon disintegration time, in terms of their properties and mechanism by which the disintegrants act.

There is thus a manifest need of simple effective methods for determining the parameters that control the disintegration of compressed tablets. These methods are:

1. MOISTURE SORPTION

The interaction of water and solid play an

importance role in many pharmaceutical processes. Equillibrium moisture adsorption and desorption have used to evaluate the interaction of disintegrants with moisture both quantitative and qualitative manners such as; volume, moisture sorption and hardness.

The rates and amounts of moisture sorption change upon variations properties of disintegrants. Khan, et al. (12) observed that cation-exchange resins exhibited the highest moisture sorption followed by sodium starch glycolate, sodium carboxymethylcellulose and starch. They also demonstrated that the disintegrants with the highest moisture sorption were generally the most effective in most tablet systems.

Kornblam and Stoopak (14) comparing between cross-linked polyvinylpyrrolidone, alginic acid and starch; cross-linked polyvinylpyrrolidone showed singificantly greater moisture sorption than either of the others.

Moisture sorption of microcrystalline cellulose is very rapid and follows first-order kinetics. The amount of microcrystalline cellulose influences the rate of sorption. It might be assumed that the rate of water diffusion in microcrystalline cellulose was rate limiting (46,47). The rate of moisture sorption was also directly propotional to the relative density of the compressed microcrystalline cellulose (48).

The rate of mositure sorption was retarded upon addition of magnesium stearate (47). This could be assumed that the hydrophobic lubricant retards the moisture sorption by surface coation causing to repel penetrating moisture.

Some disintegrants swell when exposed to high humidity. Mitrevej and Hollenbeck (13) showed that cellulose derivatives did not show any sign of swelling when exposed at 80% relative humidity while sodium starch glycolate swelled at 60% relative humidity.

Khan and Rhode (27) observed that tablets containing 10%(w/w) cation-exchange resin showed the highest decrease in apparent density followed by tablets containing sodium starch glycoate, sodium carboxymethyl cellulose and starch respectively. Latter, the same authors (12) concluded that there was some rank order correlation between solubility and swelling characteristic of direct compression excipients when exposed to 100% relative humidity.

Udela and Chukwu (49) found that between direct compression vehicles tablets made from microcrystalline cellulose (Avicel PH101) showed highly moisture sorption and increasing in volume after exposed at high humidity than α-lactose monohydrate(Fast Flo lactose) and dicalcium phosphate dihydrate and modified polysaccharide (Musol).

There are numerous reports showed the effect of

moisture sorption on hardness of tablet containing disintegrants (50,51,52,53,54). Horhota, et al. (50) showed that direct compression tablets containing sodium starch glycolate, alginate and povidone as disintegrants reduced in hardness after storage under high humidity. A similar results was found by Sangekar (51).

Chowhan (52) studied the effect of low-and high humidity aging on hardness of dibasic calcium phosphate tablets and found that hardness increased on aging in low humidity while hardness decreased under high humidity. The rate of hardness decrease followed very well with the rate of moisture sorption increase . The reduction in the hardness of tablets can be explained by the absorption of moisture by the disintegrants, thus causing swelling and bond disruption. Chawhan (54) also explained that the increasing in hardness was due to general hardening through the bulk of the tablets.

2. WATER UPTAKE

There is, however, no doubt that water uptake must be the first step in any process of disintegration. The penetration of liquid into a porous structure depends on the balance between capillary and opposing vicous forces. If the total cross sectional area of the pore does not vary with their length, there is a linear relationship between the square of volumetric uptake (V) and the time (t) as:

$$V^2 = \frac{2m\gamma \cos\theta \cdot t}{k \eta}$$

where

m = the hydraulic pore radius

γ = the surface tension of penetration liquid

θ = the contact angle between liquid and solid in the pores

η = the liquid vicosity

k = the constant dependent on pore shape

This equation derived by Washburn (34,55,56) indicates that water penetration in pharmaceutical tablets is determined by the controlling factors like porosity, pore size and contact angle with the pore wall. It cannot be applied for liquid penetration into tablets, when the tablet structure changes during the penetration process.

Lerk, et al. (28) found that magnesium stearate caused large depression of the penetrate rate. This was due to the hydrophobicity of magnesium stearate rendering the coated particle water-repellant. This result as was expected from the work of Wan and Choong (34).

The excipients used in the formulation some aid penetration, some any impede the process. The influence of surfactant on liquid penetration was investigated by Cheong and Heng (57). They found that Polysorbate and sodium lauryl

sulfate enhanced water uptake due to increase hydrophilicity in tablets of microcrystalline cellulose.

It has been reported that microcrystalline cellulose promoted aqueous uptake in tablets though it was hardly swell when wetted (28,58). Microcrystalline cellulose demonstrates extremely fast aqueous penetration even at low tablet porosity. The liquid volume uptake is much larger than the calcualte pore volume. Lerk, et al. (28) conceived that the disruption of hydrogen bonds of cellulose particels on wetting contribution to an increase uptake.

Fukuoka, et al. (58) also found that the penetration into tablets of microcrystalline cellulose could not be described by Washburn's equation . Because during the penetration process crack was generated in the tablets as a results of swelling or weakening of binding forces between particels, then the viscosity resistance to liquid flow at these enlarged capillaries be markly decrease and could be ignore.

An increasing penetration is found for tablets compressed from highly soluble excipients, because of widening the pore by dissolution of the pore wall. Penetration, however, can slow down again, when dissolution increases the viscosity of the penetration liquid (28,29).

Wan and Choong (34) studied water penetration

behaviours of phenacetin tablets formulated with starch, PVP and magnesium stearate. The absorption of water by starch was the primary mechanism involved in penetration of water into tablets. Increasing PVP concentration resulted a strong binding of granules in the tablets, consequently this prevented further swelling of the starch which in turn prevented further uptake water by starch.

An extremely strong effect on volumetric water uptake and penetration rate can be seen when disintegration is presented in the tablet formulation (15,16,29). Gissinger and Stamm (16) showed that disintegrant powders such as sodium starch glycolate and hydroxypropylcellulose could uptake more than ten times their own weight of water. They also showed that the rate of water uptake from tablet made from dicalcium phosphate dihydrate and different disintegrants depended to the type of the disintegrants.

Yuasa and Kanaya (59) found that the penetration rate increased with increased hydroxypropyl starch concentration. The main cause of this phenomenon may be the increase in the mean pore diameter and decrease in contact angle with increasing hydroxypropyl starch concentration.

Compressional force was found to have strong affected on the penetration rate, as compressional force increase due to decrease penetration rate (28,34,60). This effect was mainly due to decrease porosity when increasing

compressional force.

3. DISINTEGRATION TIME

Disintegration time is a certain physical parameter to evaluate the disintegration of compressed tablets. Most articles dealing with compressing tablets reported that increased compressional force resulted in tablets with longer disintegration times (38,39,41,61). This cause-effect can be seen logically, the higher the compressional force the less the porosity with the particles more strongly bonded together as reflected by increasing in hardness and disintegration time.

Comparatively, few investigators reported the opposite effect of faster tablets disintegration times with increase compressional force(18,45,61,62). It was purposed that if wicking was the primary mode of action, disintegration time should increase with increasing compressional force; but if grain swelling was the mechanism of action, decreasing tablet porosity by increasing compressional force resulted in faster disintegration time. Because disintegrants can exert a force on the surrounding particles more effectively (30,56).

However, it must be concerned that the soluble excipients perhaps counteract the effect of water penetration into tablet by increase viscosity of penetration

liquid(54,62).

The concentration of disintegrant used also showed the effect on disintegration time (18,33,62,63). Most investigators showed that an increase in concentration of disintegrants caused a decrease disintegraion time. But some disintegrants, microcrystalline cellulose (15) and sodium starch glycolate (27), show optimal concentration.

4. FORCE OF DISINTEGRANT

Measurment of swelling force of disintegrant was made by List and Muazzam (18,65). The method was carried out by meausring pressure exerted to the flexible bar which connected to a strain gauge. They showed that disintegrants with insignificant swelling, eg. starch, cross-linked polyvinylpolypyrrolidone, could be the best disintegrants because of their high swelling force. They also showed that swelling force increased with increasing compressional force.

Colombo, et al. (64) used a disintegrating force as a formulation parameter. They concluded that the disintegration force development rate could be employed as a new parameter since, when correlated with the disintegration time.

The results obtained from Gould, et al. (66) also indicated that tablet disintegration time did not correlate with maximal swelling force but correlated with fluid

penetration kinetic function involving a lag time and a time for 50% tablet swelling.

Carmella, et al. (68) observed that tablets made of water insoluble and hydrophilic materials such as dicalcium phosphate dihydrate, a correlation exited between disintegrantion times and disintegration force development. This indicated that the role in the disintegration process was played by disintegrant themselves. On the other hand, poor correlation exited in tablets compressed by water soluble and hydrophilic materials. This indicated that dissolution of diluents played important role than disintegrants.

PURPOSE OF THE STUDY

The purpose of this study is to investigate if any relationship exists between compressional force and disintegration time. This study intend to use simple effective methods such as: moisture sorption, water uptake and disintegration times with the aim of assessing this relationship. This study also shows the relative effectiveness of disintegrants, both in a soluble and insoluble systems.

α-lactose monohydrate (Tablettose) as a soluble material and dicalcium phosphate dihydrate (Emcompress) as a practically insoluble, hydrophilic material were used as

diluents. Four disintegrants with differents mechanism of action; sodium starch glycolate (Explotab) with high swelling volume, cross-linked polyvinylpyrrolidone (Kollidon CL) with high water uptake and moderate swelling volume, microcrystalline cellulose (Avicel PH101) with heat of hydration and particle/particle repulsion force and starch with limitted swelling and high water uptake were used as disintegrant in tablet formula.

The tablets were directly compressed by using instrumented single punch tablet machine at four different forces, starting at 1200 pounds and increasing in approximately 600 pounds increments.