CHAPTER 1

INTRODUCTION

RATIONALE

One of the most important problems for formulators has always been to provide quick and complete disintegration of tablets in an aqueous medium so as to assure release and absorption of the active drug in the gastrointestinal tract after oral administration (1). Although the complete disintegration of a tablet does not necessarily mean complete dissolution, however a tablet that fails to disintegrate completely will not be able to permit the full availability of the active portion at the absorption site. Efforts have been done to satisfy the requirement of rapidly reversing the compression process and of achieving a homogeneous distribution of the active ingredient in an aqueous medium by adding tablet disintegrant.

Established materials typically used as disintegrating agents include various starches, alginic acid and guar gum. Some more later developments include modified starches, and cellulose derivatives. All these materials mentioned previously offer advantages and limitations, suggesting a continuing need to search for and evaluation of new, more efficient tablet disintegrators such as cross-linked carboxymethylcellulose (2-5), cross-linked polyvinylpyrrolidone (1,4,6-7) and recently developed disintegrants : nonfibrous attapulgite (8), xylan (9) and Key-Jo clay (10).

Durian, one of the most favorite Thai fruits, is popular eaten in Thailand and in neighbouring countries. In every year

there are a lot of Durian rind which have been thrown out as garbage. Recently, Pongsamart et al (11) extract durian rind from alcohol and acid alcohol as described in Figures 1 and 2, respectively. The results of extraction, which composed of carbohydrate, after recrystallized gave a slightly offwhite powders. Preliminary data dealing with toxicity in rats found no effect after oral administration 0.5 g/kg/day continually for 2 months. When its contact with water both powders obtained from durian rind extract show instantly much swelling many times its weight which is similar to the property of most of the disintegrants that have been studied by many investigators (2,6,9-10,12-20).

LITERATURE REVIEW

A. GENERAL

The following categories are commonly used tablet disintegrants described in a number of published studies (21-25).

1. Starches and it derivatives

Starches is the least expensive and the most commonly used disintegrating agent . They are obtained from various sources such as wheat, corn, rice and potato. Corn starch is the most widely used. The typical amount used as tablet disintegrator is in a range of 5-20% w/w. However, starches at a high levels used possesses some disadvantages in direct compression since it's lack of flowability and compressibility. Its often weakens the tablet structure sufficiently to preclude in use.

Sodium Starch Glycolate (Sodium Carboxymethylstarch) is the sodium salt of a relatively low substituted carboxymethylether of potato starch. It possesses inherent

compressibility in the concentrations range as low as 2-4%. Sodium starch glycolate is now widely used in tablets prepared by both wet granulation and direct compression.

Pregelatinized Starch is prepared by subjecting ordinary corn starch to physical compression or shear in high moisture conditions; that preparation causes both an increase in temperature and a partial gelatinization of some of the starch moieties. It does not offer any advantage over corn starch as a disintegrant. It is generally used in a concentration range of 5-10%.

2. Celluloses and it derivatives

Microcrystalline Cellulose is a purified, partially depolymerized alphacellulose prepared by treatment of pulp with mineral acids. It does not act as disintegrating agent except at high concentration (5-20%). It can be used in combination with other disintegrants to improve tablet disintegration.

Crosscarmellose Sodium is a modified cellulose gum which are different in degree of substitution. The cross-linking greatly reduces water solubility while still permitting the material to swell and absorb many times its weight in water without losing individual fiber integrity. It may be used as a tablet disintegrant in a concentration range of 1-2% for tablets made by direct compression and approximately 3% for those made by wet granulation.

Carmellose Calcium is obtained by carboxymethylation of cellulose which is followed by formation of the calcium salt. It absorbs water and swells considerably without changing to a

viscous gel. It is normally used in a concentration about 5% by weight of granulation.

3. Pyrrolidones

Crosspovidone is a cross-linked homopolymer of N-vinyl-2-pyrrolidone. Because of its high molecular weight and cross-linked structure,it is insoluble in water but is still very hydrophilic. It has been found to be a good disintegrant at the levels of Ø.5-5% for tablets of poorly water-soluble drugs prepared by wet granulation and direct compression.

4. clays

Veegum is an inorganic complex of colloidal magnesium and aluminium silicate, it's used in a concentration range of 2-1Ø%. Because of it gel-forming property, the excessive amounts used may retard disintegration rate by forming a slimy gel on the tablet surface. Commonly used modern tablet disintegrants are summarized in Table 1(21).

Table 1

Commonly Used Modern Disintegrants.

Category	Chemical Name	Trade Name	Supplier
Starches	Corn starch	*	*
	Sodium starch glycolate	Explotab(R)	Edward Mendell Co. Carmel, New York
		Primojel(R)	Generichem Corp. Little Falls, New Jersey
	Pregelatinized starch	Starch 1500(R)	Colorcon, Inc. West Point, Pennsylvania
Cellulose	Microcrystalline cellulose	Avicel(R)	FMC Corp. Philadelphia
	Carboxymethyl-cellulose (CMC)	*	*
	Crosscarmellose, Type A	Ac-di-Sol(R)	FMC Corp. Philadelphia
	Calcium CMC	ECG(R)	Laporte, Inc. Hackensack, New Jersey
Pyrrolidones	Crosspovidone	Polyplasdone XL(R)	GAF Corp. New York
		Kollidon CE 5050(R)	ASF Corp., Parsippany, New Jersey
Clays	Magnesium aluminium silicate	Veegum(R)	R.T. Vanderbilt Co. Norwalk, Connecticut

* This material is available from several sources under a variety of trade names.

B. MECHANISMS OF ACTION

Although many investigators have attemped to elucidate mechanisms of action of various tablet disintegrants. None have been succeeded in advancing an explanation of disintegration behaviour that approaches a universal understanding applicable to most modern disintegrants. The current thinking of mechanisms of action for disintegrating agents are presented as follows :

WATER UPTAKE

A process called water uptake is the process of particles to draw up water into the porous network of a tablet (21). It has been implicated as an important mechanism and must be an initial step in any disintegration process (26). It has been stated that substances that can absorb about 20% water and are insoluble in water are good disintegrants such as methylcellulose. In the case of carboxyvinyl polymer and sodium carboxymethylcellulose, which are soluble in water, the increase in disintegration time was observed. For substances such as ethyl cellulose that can absorb water poorly are poor disintegrants (27).

Not only the extent but also the rate of water uptake is an important factor for a number of tablet disintegrants (21). Bolhuis et al (22) found that if wetting of disintegrant particle was slowed, disintegration of the tablets also slowed.

Kanig and Rudnic (21) reviewed that the main mechanism of action for cross-linked polyvinylpyrrolidone is wicking, since, it swells very little but takes water up into its network quite rapidly. According to the work done by List and Muazzam, these authors found that Emcompress(R) tablets containing

Polyplasdone XL(R) disintegrated just as in water but not in acetone or glycerol. So, with approximately the same capillary uptake of those three liguids into the network, the tablet disintegrates only in water in which polyvinylpyrrolidone can swell (even if very little) indicate swelling is a secondary mechanism.

For sodium starch glycolate, the rate and extent of water uptake is inversely proportional to the extent of cross-linking and the degree of carboxymethyl substitution of the starch compound (28).

In the case of starch as a disintegrant, Ingram and Lowenthal (13) argued that starch swells enough to break the tablet apart, after they have tested both damage and undamage starch grains and found no correlations between starch grain damage and disintegration or between starch grain swelling and compressional force (29). These authors suggested that other purposal based on capillaries effect, starch wettability and liquid penetration into tablets. Other supporting made by Nasipuri and Omotosho (30), they showed that disintegration of surfactant-treated starch was shorter than that of plain starch.

Pore size and porosity are the two parameters associated with capillary network. Porosity varies in the reverse order of compressional force (up to about 5,000 lb) and logarithm of disintegration time is directly proportional to the applied pressure (31). For methylcellulose, water uptake is directly related to the amount used in the formulations (32). It exhibits extremely fast aqueous penetration into compacts even at low porosities caused by breaking of the hydrogen bonds and widening of the pore during penetration. However, the above can be

suppressed by fast dissolving of highly soluble excipients in the formulation (33).

SWELLING

The most widely accepted general mechanism of action for table disintegrants is swelling. Primary this may be due to almost all disintegrants swell to some extent, and swelling has been reported quite universally in the literature (21).

List and Muazzam (15) concluded from their studies of several disintegrants that swelling pressure within the tablet is a primary factor responsible for disintegration. They found correlation of swelling pressure to the percentage of disintegrant employed and also dependence of disintegration time on the swelling pressure. Swelling pressure (34), however, cannot be determined by volume dilation.Good disintegrants are excipients that have high swelling pressure but a limited degree of gel formation in the presence of water, because the barrier that forms prevent water from penetrating into the tablets, which in turn prevents further swelling. In all cases, the investigators found that cross- linked natural or synthetic product with limited swelling and gel formation such as Ac-di-Sol$^{(R)}$ and Polyplasdone XL$^{(R)}$ were superior to the different natural starches, Nymcel types, and microcrystalline cellulose.

The bigger particles of disintegrant gave higher values of swelling force will shorter disintegration time than the smaller particles of the same chemical constitution (16). The reason is the bigger particles can fill the empty space better and there by have a greater swelling pressure.

The swelling of a tablet not only includes swelling volume but also the rate of swelling. Most disintegrants increase their volume in a short period of time (19); for example sodium starch glycolate increases 39-110% of volume within only 5 minutes, Polyplasdone XL(R) reaches 112% of volume within 9 min, etc.

It is important to understand that, as particles swell, there must be no accommodation by the tablet matrix of that swelling, so disintegration occur. The swelling of some disintegrant particles is depend upon pH (21). The sedimentation volumes of anionic cross-linked starches such as Explotab(R) and Primojel(R) and celluloses such as Ac-di-Sol(R) and CLD-2(R) are significantly altered in acidic media while Polyplasdone XL(R) and Starch 1500(R) remained unchanged.

Swelling capacity of disintegrants plays a dominant role in the disintegration process when a hydrophobic lubricant is coperated in tablet formulation (35). This capacity is of minor importance when no hydrophobic excipients are presented. When the tablets contain a disintegrant such as starch or methylcellulose that is slightly swelling but hydrophilic, water penetration is the controlling step in the disintegration process and disintegration is strongly affected by the presence of a hydrophobic lubricant.

In contrast, strongly-swelling disintegrants are much less affected by a hydrophobic lubricant. Strongly swelling disintegrants are the primary target for water absorption as opposed to slightly swelling disintegrants, in which a well-established network of pores is essential.

The results of the investigation indicate that the swelling is the governing factor regarding the kinetics of the disintegration process because it is linked both to water penetration and force development (17). The role of the swelling materials is to make pore walls hydrophilic, providing enough swelling force to produce interparticle bond disruption.

Mitrevej and Hollenbeck (35) concluded that the superdisintegrants function efficiently because of their remarkable ability to swell and absorb water.

There are such complex mechanism of disintegrant action that some disintegrants for example, cross-linked carboxymethyl-cellulose swells much quickly and has high water uptake (3).

Water Uptake is the controlling step in the disintegration process of insoluble, slightly swellable but hydrophilic materials such as Avicel$^{(R)}$, etc (34). Very soluble materials such as pregelatinized starch retard liquid flowing into the pores by enhancing liquid viscosity and gel formation. These will delay liquid penetration and will also prolong disintegration time. For water soluble tablets, the previously mentioned problem is not a significant effect and less swellable materials can be utilized. The reason may be due to if strongly swellable disintegrant is used, after dissolving of soluble ingredients, there is more space for the strongly swellable disintegrant to swell and partially refill the formed voids without breaking the tablet.

HEAT OF WETTING

The heat generated by wetting of the ingredients that occurs when the tablet is immersed in a fluid has been suggested as a possible machanism of action for tablet disintegration (27).

Kanig and Rudnic (21) reviewed that starch granules exhibited a slight exothermic properties when wetted and the heat may cause the air in capillary expand pushing the tablet apart. For aluminium silicate tablets increasing of compressional force result in decreasing of heat of adsorption and increasing of disintegration time (37).

However, the exothermic reactions upon wetting were not universal for all disintegrants and that when significant heat of wetting is generated,there is not always corresponding to a decrease in disintegration time. So this explanation is limited to only a few types of disintegrants and cannot be utilized to describe the action of most modern disintegrating agents(21).

PARTICLE REPULSION

Another attempts to explain the swelling of tablets made with "nonswellable" starch. Guyout-Hermann (38) have proposed a particle / particle repulsion theory based upon the observation that particles that do not seem to swell may still disintegrate tablets.From their study,the tablets made with highly reticulate starch that does not swell, show in contact with water a swelling which is just as important as the swelling of the tablets made with native starch. Possible explanation of the above event is the constituent elements just loss the cohesive force and separate one and another under the action of water.

There are two possible causes for the destruction of the cohesive force between the constitutive elements of a tablet and may be described as follows(39) : a) creation of a repulsive force when the elements of a tablet enter into contact with water; b) a simple annihilation of the hydrogen bonding or the

capillary cohesive force. However, Kanic and Rudnic (21) argued that this theory is not supported by an adequate data, and the explanation and applications of the hypothesis is doubtful.

DEFORMATION

The deformed particles occurs during tablet compression were shown to return to their normal shapes when exposed to moisture (3). Kanig and Rudnic (21) reviewed the deformation of potato starch granules and stated that not only did those granules return to their original size, but in some cases the swelling capacity was also improved when the granules were extensively deformed during compression. Vadas et al. (36) discovered that two cellulose derivatives (Ac-di-Sol$^{(R)}$ and CLD$^{(R)}$) tended to increase disintegration efficiency with increasing compressional force. This may be indicate the deformation during compression as one of the mechanism of tablet disintegrant. Obviously, the role of deformation and rebound under actual production conditions needs to be studies extensively before the full effect of this phenomenon can be understood.

DISINTEGRATING FORCE

It has been mentioned previously that both water penetration associated with related action and swelling are usually found in most disintegrant system. Some scientists tried to simplify a compact disintegration charateristics in the term of "disintegrating force". A disintegrating force must develop inside the tablet, capable of weakening and breaking interparticle bonds to obtain a rapid disintegration (39).

Colombo et al (40) divided the mechanism of tablets disintegrants on the basic of their capability to promote disintegrating force development. They are :

a) The disintegration force exerted by the air entrapped in pore structures due to a hydrodynamic process or to the heat of wetting (hydrodynamic force).

b) The disintegration force from swelling of the disintegrating agent (swelling force).

c) The disintegration force from the repulsion among particles caused by contact between solid and liquid. (repulsion force)

They also stressed their concept that force is not a mechanism by itself but the outcome of a series of events beginning with water penetration and leading to the activation of one of the mechanisms cited. Colombo et. al (40) found that only water can activate the force and they also determined such parameters as the maximum force developed and the time of half maximum force development to describe these disintegration characteristics.

Caramella et.al (41) studied the relationship between water penetration and disintegration force development. They found that, in tablets made of water insoluble and/or hydrophobic materials, a correlation exists between disintegration time and disintegrating force development kinetics indicated that the prevailing role in the disintegration process is played by an active mechanisms. Therefore, highly hydrophilic and strongly swelling disintegrants are preferred for its capable of developing its maximum swelling force, besides drawing water inside the compact.

On the other hand, the lack of such a correlation in tablet made of hydrophilic, water-soluble materials indicated that passive mechanisms (such as dissolution or hydrogen bond annihilation) are also involved in the disintegration process and

may prevail over active mechanisms. Therefore, the disintegrant when needed, assists in drawing water inside the compact, but is not always able to develop its maximum swelling force. For this reason the efficiency of strongly swelling disintegrants should be limited used in this situation and slightly swelling may be or even better than strongly swelling materials.

C. METHODS FOR STUDYING DISINTEGRATING PROPERTIES

Because of the number of tablet disintegrants available is continually increase, the suitable methods of testing a new product for evaluation are required.

Over the past years, general researchers have introduced a number of test methods. Some of these methods are :

1. Hydration Capacity is a measure of water binding ability and also swelling capacity which are the two important properties of tablet disintegrants. Kornblum and Stoopak (6) described a method of determining the hydration capacity of cross-linked polyvinylpyrrolidone in comparison with starch and alginic acid. With this method, the amount of water taken on by one gram disintegrant after shaking, centrifuging and decanting is determined. The advantage of this method is that it can be carried out quickly and easily, whilst being very reproducible.

2. Swelling of Particles

2.1 Microscopic method is the direct observation of the increase in disintegrant particle dimensions due to water absorption. Microscopic method has been widely used by many researchers in the past as follows :

2.1.1 By Modrzejewski and Wochna (42)

A grain of the examined substance was placed on a microscopic slide covered with a cover-glass and a small drop of water was cautiously added by means of a pipette

which caused swelling of the grain. The surface of the swollen grain's contour was photomicrographically determined on the screen of the microscope, the increase in volume being calculate from it. The volume of the sphere was calculated from Eq. (1)

$$V = 4/3 \cdot \pi \cdot r^3 \qquad (1)$$

The radius of the sphere was calculated from the surface of the cross-section measured as given in Eq (2)

$$r = \sqrt{S/4\pi} \qquad (2)$$

2.1.2 By Beukelaer, Ooteghem and Ludwig (43)

The diameters of the 'dry' and swollen particles were measured on a suspension in paraffin oil and in simulated gastric fluid, respectively. Microphotograph of the suspensions were brought on the digitizer "pas of a Kontron MOP-AMO 2" apparatus, diameter of particles were calculated and compared.

2.1.3 By Mitrevej and Hollenbeck (35)

A dry sample was scaled in the stage chamber on the microscope and after maintaining the sample for 24 hours at 0% RH, a photomicrograph was taken. The sample was then exposed to 100%RH for another 24 hours and a photomicrograph was taken again and swelling ratio was calculated from Eq. (3)

$$\text{Swelling Ratio} = \frac{\text{Particle dimension at 100\% RH}}{\text{Dry particle dimension at 0\% RH}} \qquad (3)$$

2.1.4 By Caramella et.al. (20)

Samples of monodispersed materials were prepared in various solvents and photomicrographs of a suitable

number of microscopic fields, depending on the magnification employed, were taken. The projected dimensions of the particles were averaged on a suitable number of individual measurements. The volume increase of particles changing from an inert to a swelling medium was expressed as the ratio between the mean particle volume in the swelling medium and the particle volume-diameter in the inert medium (swelling index).

2.2 Coulter Counter Method is proved to be applicable to many kind of materials and media. The method is rapid, satisfactorily accurate and reproducible and seems to be useful especially for materials which swell to a limited extent, which can be hardly evaluated by optical microscopy (20).

An accurately weighed quantity of powder was dispersed in a 200-400 ml electrolyte solution. Then, the particle size distribution of the suspended particles was determined. The volume of the sample analyzed was metered by the manometric method or by weighing the amount of sample passed through the orifice. Total particulated volume (V_{tot}) was calculated as follows :

$$V_{tot} = \pi/6.K. \sum_{i=1}^{i=16} .\Delta n_i \bar{v}_i .S/s \qquad (4)$$

Where K is the volume calibration constant determined for each electrolyte and aperture using standard materials; n_i is the total particles count in channel i corrected for background; v_i is the mean volume of channel i; s and S are the volume of the sample analyzed and the total electrolytes volume, respectively.

Then the percent volume increase in swelling media (Vs) was calculated as given in Eq (5);

$$\% \text{ volume increase} = \left(\frac{V_{tot}}{V_{true}} - 1 \right) \times 100 \qquad (5)$$

Where V_{true} was calculated from true density of the sample.

3 . Water Uptake of tablet : The disintegration of uncoated tablets is controlled largely by penetration of body fluids from the gastrointestinal tract into the compressed matrix. The penetration rate of a liquid into a porous structure depends on the balance between capillary and opposing viscous forces. If the total cross-sectional area of the pores does not vary with their length, there is a linear relationship between the square of volumetric uptake (V) and the time (t) as given by the Washburn's equation below (26).

$$V^2 = \frac{2mr \cos\theta}{K_\theta \cdot \eta} \cdot t \qquad (6)$$

Where m is the hydraulic pore radius; r is the surface tension of the penetrating liquid; Ø is the contact angle between liquid and solid within the pores;n is the liquid viscosity;and K is the proportional constant depending on pore shape.

This equation indicated that water penetration in the tablets matrix is determined by the controlling factors like porosity, pore size and size distribution, and contact angle with the pore wall. However, this equation cannot be applied when the tablet structure changes during the penetration process.

4. Disintegration time is one of the important physical parameter for evaluating disintegration of tablet. Because of it depending on a number of many factors such as fillers, active ingredients, lubricants, binder, manufacturing procedures, equipments and compression pressure. Disintegration time can be used and combine with other parameters for comparing disintegrant efficacy.

5. Dissolution of tablets is currently the most commonly used means of assessing the equivalence of dosage forms. Because only a disintegration test was never meant to serve as an indicator to assure that the drug content might be absorbed by the body (37). Dissolution testing is intended to provide a step toward, the evaluation of the bioavaibility of the drug substance. The dissolution test can be used to demonstrated that a given tablet formulation is the same, with respect to dissolution, as that in the batch of tablets shown initially to be clinically effective. It also provides an in vitro control procedure to eliminate variation among production batches.

PURPOSE OF THE STUDY

The objective of this research is to study tablet disintegrating properties of a new disintegrating agent, durian rind extract, and to compare with other well recognised effectiveness and typically used tablet disintegrating agents such as corn starch, pregelatinized starch (Starch 1500®), sodium starch glycolate (Explotab®) , cross-linked carboxymethylcellulose(Ac-di-Sol®, Nymcel®) and cross-linked polyvinylpyrrolidone (Kollidon CL®).

The study intend to use simple effective methods such as hydration capacity, swelling of particles, water uptake, disintegration time and other physical properties of tablet for studying properties and efficiency of the disintegrants.

Dibasic calcium phosphate dihydrate(Emcompress®) and α-lactose monohydrate (Tablettose®) were chosen as a practically water insoluble and soluble direct compression vehicle, respectively. The tablets were directly compressed by using instrumented single punch tablet machine at 3 different forces : 500, 1000 and 1,500 kg, and the effect of compressional force upon efficiency of disintegrants were also studied.

Hydrochlorothiazide and Pyridoxine Hydrochloride which are represent water insoluble and soluble active ingredients were prepared in dibasic calcium phosphate dihydrate directly compressed tablets to study the efficiency of durian rind extracts as tablet disintegrant in such systems.