CHAPTER II

GENERAL BACKGROUND

Starch is a substance commonly used as a tablet distintegrant. Since 1937, Spengler and Schenker used 10% corn starch as tablet disintegrant to improve disintegration property of tablet. At first, the starch used as a tablet disintegrant was plain starch from natural sources such as corn starch and potato starch. It is generally accepted that starch is a natural high molecular weight polymeric carbohydrate composed of glucose units as shown in Figure 1 (Chalmers,1968). Starch is not a uniform material. Most starches contain two types of glucose polymers: a linear chain molecule of glucose termed amylose and a branched polymer of glucose termed amylopectin. These two fractions occur in different amount in starches from various botanical sources. Amylose is a linear polymer containing up to 6000 glucose units connected by 1,4 linkage as shown in Figure 2 (Chalmers,1968). Amylose is insoluble in cold water but absorbs a large amount of water and swells. Amylose forms complex with iodine giving a characteristic blue color which is used to establish the presence of amylose-containing starch. Amylopectin has a highly branched structure consisting of short linear chains with a degree of polymerization ranging from10 to 60 glucose units. They are connected to each other by alpha-1,6-linkage as demonstrated in Figure 3. Amylopectin rapidly forms a viscous colloidal solution at room temperature (Shangraw, et al.,1980). Amylopectin forms complex with iodine giving a red to purple color.

Amylose most likely accounts for the disintegrant properties of starch. On the other hand, amylopectin is a good binder but retards tablet disintegration and dissolution of active ingredient (Ingram and Lowenthal,1966; Schwartz and Zelinski,1978).

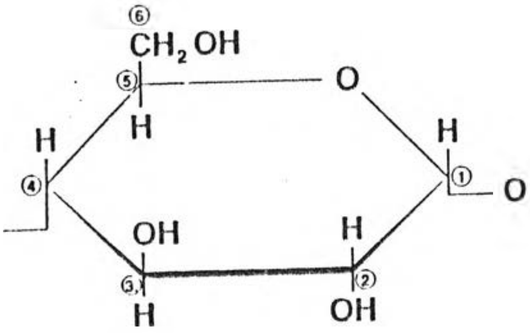

Figure 1 Glucose Unit.

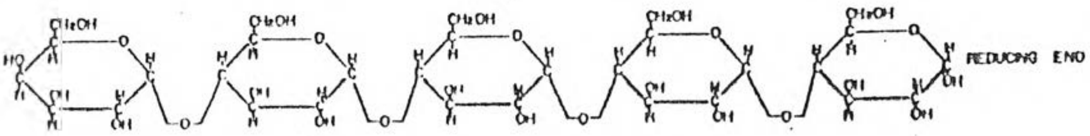

Figure 2 Starch Amylose.

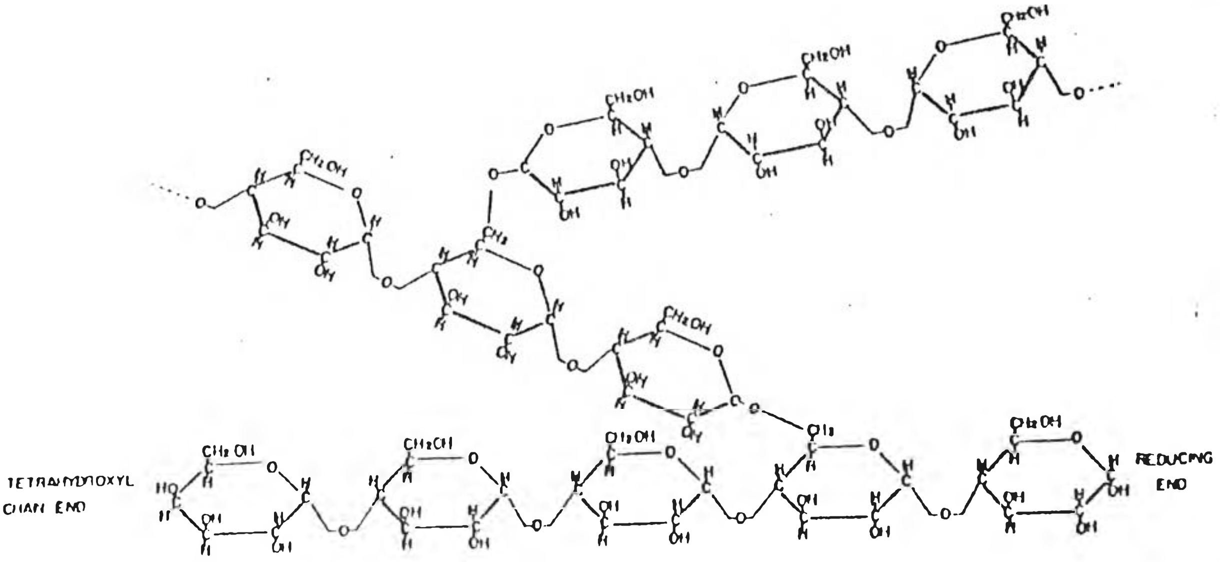

Figure 3 Starch Amylopectin.

In addition Lindenwald, et al. (1965) suggested that starch swelling was claimed to be dependent upon amylose and amylopectin content. The amylopectin expands and amylose gives osmotic pressure. Generally native starch are insoluble in water below their gelatinization temperature due to the hydrogen bonds, formed either directly via neighboring alcoholic OH-groups of individual starch molecules or indirectly via water bridges. The hydrogen bonding forces are weak, but there are so many hydrogen bonds in starch granule. Due to the presence of ionizable esterified phosphate groups in potato starch which assists swelling by the reason of mutual electric repulsion. Potato starch undergoes rapid swelling at low temperature. Therefore, potato starch is widely used as the tablet disintegrant. Until 1965 the first successful attempt to improve the disintegrant efficiency of native starch by chemical modification of potato starch was made. The product of the modification was carboxymethylated potato starch which exhibited a good disintegrating property.

In 1973 Khan and Rhodes have evaluated the disintegrating properties of sodium starch glycolate and a cation exchange resin in a variety of tablet systems. They concluded that even at low concentrations both disintegrants are extremely efficient disintegrants. Both disintegrants merit investigations from both the standpoint of efficiency and cost.

Three relatively new tablet disintegrants which included a water insoluble polymer derived from cellulose (CLD^{R}), a carboxymethyl substituted starch (Primojel^{R}) and a complex of aminoacetic acid and sodium carbonate (Sodium glycine carbonate) were compared with one another and against starch USP as to their abilities to effect the disintegration of compressed tablets. The experimental results clearly indicated that a cellulose polymer and a carboxymethyl starch performed well in the tests and deserved consideration as effective disintegrants (Bavitz, Bohidar and Restaino,1975).

In 1985 Rudnic, Rhodes and Bavitz have evaluated eight tablet disintegrants at low levels of concentrations in a direct compression systems. Eight common tablet disintegrants were Amberlite IRP^{R}-88, Corn Starch USP, CLD, Explotab^{R}, Ac-Di-Sol^{R}, Sta-Rx^{R}1550 Starch, Polyplasdone^{R} XL and Guar Gum. Low levels (0.25%-2.0%) of these disintegrants were effective to facilitate the tablet disintegration. The cellulose derivatives (Ac-Di-Sol^{R}) were the most effective and the next one was carboxymethyl starch (Explotab^{R}).

The effect of variation in the degree of cross-linkage and extent of substitution on the disintegrant properties of sodium starch glycolate in wet granulated system has been evaluated and also the rates of mixing shear were evaluated for their effect on the ability of the disintegrants to function after granulation. It was clear that the lower cross-linkage and carboxymethylation was favored over the higher levels of cross-linkage and substitution. The disintegration times, in general, tended to increase as the rate of shear or mixing speed increased. In addition, the disintegration times increased as the percentage of intragranular disintegrant increased. This might be due to the fact that some of the disintegrant acted as a binder within the granules (Rudnic,Kanig and Rhodes,1983).

Effect of variation of degree of substitution, crosslinking and purity on the disintegration efficiency of sodium starch glycolate has been investigated. A carboxymethylation of potato starch resulted in an increased solubility accompanied by increases in swelling capacity and viscosity when contacted with water. Crosslinking of substituted products resulted in decreases in solubility, swelling capacity and viscosity. The water uptake capacity of carboxymethylated starches was markedly increased at low levels of crosslinking and gradually decreased at higher crosslinking. Purification of the sodium starch glycolates enhanced their disintegration efficiency. Moreover, the results showed that minor changes in molecular structure did not effect the disintegration efficiency when the disintegrant was used in a concentration of 4% (Bolhius,et al.,1984).

The effect of molecular structure variation on the disintegration property of sodium starch glycolate has been investigated. The result indicated that relatively small changes in molecular structure, variation in the degree of cross-linkage and extent of carboxymethylation, could cause substantial modification of disintegrant properties (Rudnic, Kanig and Rhodes,1985).

Visavarungroj and Remon (1989) have evaluated the different types of crosslinked starches and pregelatinized-crosslinked starches as disintegrating agents in comparison to potato starch and a number of super disintegrants such as Ac-Di-Sol^R, Explotab^R and Polyplasdone^{R}XL. They found that the tablets formulated with pregelatinized starches, with or without crosslinking showed variable and long disintegration time of tablets, using pregelatinized-crosslinked starches, were influenced by the type of filler and lubricant. No variation in disintegration properties were observed for the different types of crosslinking agents used in the starch modification (Phosphate and Adipate).

In addition, Visavarongroj and Remon (1991) have evaluated hydroxypropyl and pregelatinized hydroxypropyl starch as disintegrant and binder in tablet formulations. The results showed that pregelatinized hydroxypropyl starch exhibited some good disintegrating properties and could be used as a binder in wet granulation.

The chemical modification of starch and other natural and synthetic materials has resulted in new disintegrants which exhibited higher efficiency than a plain starch. It breakthroughed a new generation of tablet disintegrant the so-called super disintegrant, which may be divided into the following categories:

1. Modified cellulose (an internally crosslinked sodium carboxymethyl cellulose). The crosslinking greatly reduces its water solubility while permitting the material to swell and to absorb many times its weight in water without losing individual fiber integrity.

Sodium carboxymethyl cellulose is prepared by the reaction of alkali cellulose with sodium monochloroacetate. After the substitution is complete, the excess sodium monochloroacetate hydrolyzes slowly to glycolic acid. The glycolic acid changes a few of the sodium carboxymethyl groups to free acid and catalyzes the formation of crosslinks. Two brands of commercial crosslinked sodium carboxymethyl cellulose are Ac-Di-Sol^R and CLD^R (Shangraw,et al., 1980).

2. Crosslinked polyvinylpyrrolidone is homopolymer of N-vinyl-2-pyrrolidone. It is insoluble in water but is highly hydrophilic. As water is absorbed the lattice structure of polymer expands and swells causing tablet disintegration. Two brands of commercial crosslinked polyvinyl pyrrolidone are Polyplasdone^R XL and Povidone^R XL.

3. Modified starch is sodium carboxymethyl starch of a low degree of substitution of potato starch. Addition of carboxymethyl group makes starch grains more hydrophilic but not completely water soluble. When it was exposed to water, the modified starch grains swell but maintain their integrity, causing tablet disintegration without releasing the soluble component inside each grain. Two brands of commercial sodium carboxymethyl potato starch are Explotab^R and Primojel^R.

In 1942, Hoppler reported that methanol fractionation of carboxymethyl potato starch, incorrectly called sodium starch glycolate, gives 85% yield of sodium amylopectin glycolate or ultraamylopectin, a product of remarkably high viscosity. Later, Moe (1950) described similar products from potato and mandioca starches.

The carboxymethyl ethers of starch and its fractions are anionic polyelectrolytes; as such, their salt-free aqueous solutions are highly viscous, but marked viscosity loss occur in the presence of added electrolytes.

The properties of starch can be altered by inducing crosslinking into the starch molecule. A wide variety of polyfunctional agents can be used and their degree of substitution can be varied to produce particular properties required. Crosslinking may take place between primary linkages or through weak temporary bonds. The properties of the starch may be changed after crosslinking such as: non-swelling starches could be prepared by treatment with formaldehyde (Chalmers,1968). Usually manufacturers of crosslinked starches do not determine the extent of crosslinking but prefer to examine the physical properties such as viscosity, swelling power, solubility pattern and resistance to the shear (Chalmers,1968).

The starch phosphate esters which are crosslinked have unusual properties which make them suitable for a number of industrial uses. They are more resistant to gelatinization and pastes made therefrom have increased stability as concerns breakdown by heating compared to untreated starch. In fact, depending upon the degree of crosslinking, starch ester may be prepared which are nongelatinizable in boiling water. As the crosslinking reaction progresses, viscosity reaches a peak and then declines to very low values; simultaneously shortness and opacity increase (Kerr,1954).

Although starch is widely used as tablet disintegrant and often the uses are perpetual today, but one of the limitation of starch used as tablet disintegrant is the lack of a clearly demonstrable theory explaining the starch mechanism.

The possible mechanisms of starch as tablet disintegrant can be summarized as the following :

1. Water uptake: Water uptake has been an important mechanism of tablet disintegrant. In order to validate the tablet disintegration, the first important step of sequence is water to be drawn up to the tablet matrix which called wicking. The ability of particles to drawn up water into porous network of a tablet was essential for effective disintegration (Khan and Rhodes,1975) and the rate of wicking or water uptake is responsible at least in part for disintegrant

action. Bolhius, et al. (1981) concluded that if wetting of the disintegrant particles was slow, disintegration of tablet was slow. They have not only implicated the extent of water uptake but have conclusively demonstrated the rate of water uptake is of critical importance for a number of the disintegrants.

Rudnic, Kanig and Rhodes (1985) have studied the effect of variation in degree of crosslinkage and extent of carboxymethylation on disintegration properties of sodium starch glycolate. It was found that an improved in water uptake of sodium starch glycolate, disintegrant efficiency also improved.

2. Swelling: The most widely accepted general mechanism of action for tablet disintegrant is swelling. It is foolproof that almost all disintegrants swell to some extent and swelling has been reported quite universally. The starch grains absorbed water and then swell with great force overcoming the adhesiveness of other ingredients in tablet and causing the tablet breakdown into primary particles. The extent of swelling of starch grains and the exact nature of the force created is still not completely understood (Shangraw,Mitrevej and Shah,1980).

3. Deformation: Hess (1978) has studied the evidence that disintegrant particles deform during tablet compression. The deformed disintegrants were shown to return to their normal shapes when exposed to the moisture. Fuhrer (1974) has reported that the extensive deformation of potato starch granules during compression not only returned to their original size but also improved the swelling.

4. Heat of wetting: Matsumaru (1956) observed that starch granules exhibited slightly exothermic properties when they were wet and he purposed that this was caused by localized stress resulting from capillary air expansion. The expanded air forced the tablet breakdown. List and Mauzzam (1979) reported that exothermic reactions upon wetting process did not encompass for all disintegrants.

5. Particle repulsion theory: The phenomenon concerning tablet disintegration are penetration of liquid into tablet and then destruction of the compressed structure. For a number of reports, the mechanical force which breaks the tablet containing starch as disintegrant is swelling. In reality the carboxymethyl starches, which swell much less in gastric medium, produce even shorter disintegration time in this medium. Hence, the destruction of the cohesion force between the constitutive elements of the tablet under the action of water may be ascribed to the creation of repulsive force when the tablet contact with water, or to a simple annihilation of hydrogen bonds or of the capillary cohesion forces (Hermann and Ringard,1981).

Although the mechanism of action of the starch is still undergoing study. The starches have been extensively studied as to their varying properties as tablet disintegrant.