CHAPTER 1

INTRODUCTION

1.1 Background and Hypothesis

Starch is one of main materials used in wide range of industrial applications including food and non-food industries (Dong-Fang et al., 2005). However, native starches have the limit in application due to its many undesirable characteristics. Nowadays, the industry is interested in searching for starches product with improved functional properties such as viscosity, solubility, and low retrogradation. Modifications of starch are important methods to improve the properties of native starch which leaded to value-added itself. Chemical modification of starch leads the reaction of the hydroxyl groups on starch structure. This method has been used to produce starch derivatives.

Carboxymethyl starch (CMS), one of starch derivatives, is obtained by reaction of starch and monochloroacetic acid under alkaline condition. CMS is soluble in water, non-toxic, and non-irritant. These noticeable points effect CMS is always interested and it covers a wide range of applications in industries such as food, pharmaceuticals, textile, paper, plastics as well as biomedical. From literature reviews, many starches have been used for synthesis of CMS such as arrowroot starch (Kooijman et al., 2003), mungbean starch (Kittipongpatana et al., 2006), rice starch (Kittipongpatana et al., 2007), and water yam starch (Lawal et al., 2008a). CMS was found to have potential utilizations in pharmaceuticals as controlled release matrix (Anutrakulchai, 2010; Onofre et al., 2009), film coating agent (Tehkhunmag, 2007) and (Kittipongpatana et al., 2006). Cross-linking starch is obtained by modifying starch with multifunctional reagents (cross-linking agents). This modified starch is normally formed on ester or ether linkages with hydroxyl groups in starch. Cross-linking starch shows increasing shear and high thermal stability properties from the cross-linked network. It is usually employed in combination with other types of modification (Whistler et al., 1984a). Epichlorohydrin (ECH), one of cross-linking

agents, is used in cross-linking of polysaccharides since 1999 by De Miguel et al (1999).

In recent year, the popularity and acceptance of fast disintegrating for drug delivery systems much increases. Many researchers have studied for a new, safe and sufficient disintegrating agent that can disintegrate the tablet rapidly (Kittipongpatana et al., 2010; Rawas-Qalaji et al., 2006; Riley et al., 2008). The disintegrating agent is found as a considerable required component in tablet dosage form, it is normally needed in general drug formulation especially in a drug which is not soluble. Disintegrant is added into a tablet to simplify the breakup of tablet components into smaller particles when it contacts with a liquid solution. A good disintegrant has to be effective to diminish cost and has no effect on quality of the tablet such as hardness, compressibility and friability. Many works were reported that polymer from natural and synthetic can be used as a tablet disintegrant and many types of polymers have been studied to utilize as a tablet disintegrant such as cellulose derivatives (Chang et al., 1998; Rowe et al., 2006), starch and modified starches (Adebayo et al., 2008; Bos et al., 1987; Gadalla et al., 1989; Jaiyeoba and Opakunle, 1978; Kittipongpatana et al., 2010; Nattapulwat et al., 2008; Yotwimonwat, 1999).

Starch is extensively used as a tablet disintegrant such as cassava starch (Jaiyeoba and Opakunle, 1978), maize starch (Gadalla et al., 1989) and rice starch (Bos et al., 1987) but it is required to use at high concentration about 10% for giving good properties in tablet disintegration. The important problems of employment much of starch in formulation are less hardness and high moisture content of tablet. Microcrystalline cellulose (MCC) is one of disintegrants which exhibits very good disintegrating properties. However, it is expensive and provides a rough surface and humid tablet at high concentration. Thus, it has to be combined with the other disintegrants to give the better properties of disintegration. Nowadays, demand for faster disintegrating formulation is increased. Rapid disintegrant (superdisintegrant) is efficient at low concentration and have greater disintegrating efficiency. Superdisintegrant can be obtained from modified starch such as cross-linked carboxymethyl potato starch (Rowe et al., 2006) and now it is one of the commercial superdisintegrants in the trade name of Explotab® or Primojel®.

Starch is plentifully produced from many sources such as rice, cassava, corn, yam and beans. Rice starch is one of major sources of cereal starch in Thailand. The modifications of rice starch including carboxymethylation, hydroxypropylation, cross-linking has been reported to investigate the starches potential for apply as an excipient for tablet preparation such as a binder and film former (Kittipongpatana et al., 2007; Tehkhunmag, 2007; Tehkhunmag et al., 2008) and a tablet disintegrant (Kittipongpatana et al., 2010). Recently, cross-linked carboxymethyl rice starches were prepared using sodium trimetaphosphate (STMP) as a cross-linking agent (Kittipongpatana et al., 2010). Onofre et al. (2009) presented sustained release properties of cross-linked carboxymethyl starches. Cross-linked carboxymethyl konjac glucomannan was utilized for adsorption of heavy metal ions from aqueous solution (Niu et al., 2007). In addition, preparation of cross-linked carboxymethyl corn starch was studied to develop for calcium ion absorption by Chen and Wang (Chen and Wang, 2006). Furthermore, Rowe (2006) found that cross-linked carboxymethyl potato starch could be used as a tablet superdisintegrant. Nevertheless, to the date, there is no research that reports preparation of cross-linked carboxymethyl rice starch (MRS) using epichorohydrin (ECH) as a cross-linking agent. The application of MRS as a disintegrant has not been also reported. Therefore, this work focuses on preparation of MRS with different organic solvents (methanol and 2-propanol) and different amounts of ECH. The physicochemical properties of MRS as a potential material for pharmaceutical industry were evaluated. The potential of MRS as a tablet disintegrant was also investigated.

1.2 Objectives

1. To prepare cross-linked carboxymethyl rice starches (MRSs) using two different types of organic solvents (methanol and 2-propanol) and various amounts of epichlorohydrin (ECH)

2. To investigate the physicochemical properties of the prepared modified rice starches

3. To study the potential and possible utilization of the MRS as tablet disintegrant

4. To study the suitable amount of MRS for use as a tablet disintegrant

1.3 Literature Review

Starch and its components

Starch is a composing of a large number of glucose units connected together by glycosidic bonds. Starch is commonly used worldwide commodity because of its low price. This polysaccharide is generated by all green plants as an energy source. It is the most considerable carbohydrate in the human and animal diet. Starch is a white, tasteless and odorless powder. It is insoluble in cold water or alcohol. It contains two different polymeric structures: the linear and helical amylose and the branched amylopectin. Depending on the plant, starch normally consists of 20 to 30% amylose and 70 to 80% amylopectin.

Amylose

The long chain structure of amylose is formed by the linkage of glucose unit with α-1, 4 glycosidic bonds. Single helical amylose has hydrogen-bonding O2 and O6 atoms on outside covering of the helix with only the ring oxygen indicating inwards. The chemical structure of amylose is shown in Figure 1.1. The number of repeated glucose subunits (n) is generally in range between 300 and 3000, but can be many thousands.

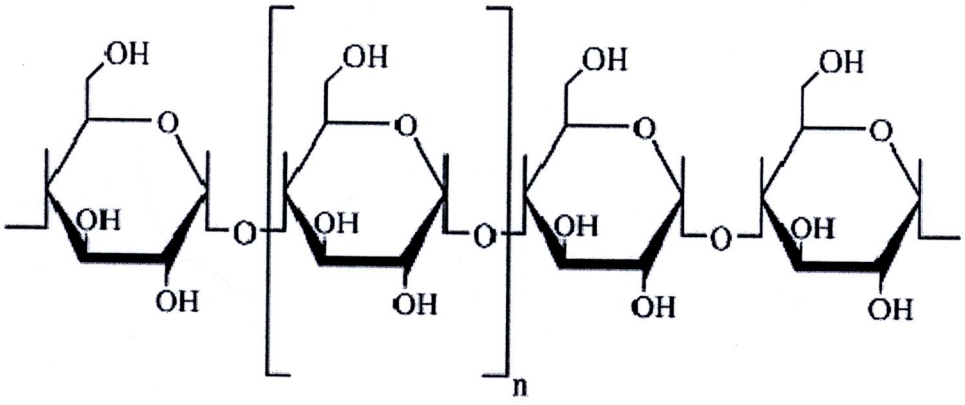

Figure 1.1 Chemical structure of amylose

Amylopectin

Amylopectin is a branch polymer of the long chains that are linked together with α-1, 4 glycosidic bond and the branching takes place with α-1, 6 linkages occurring every 24 to 30 glucose units (Figure 1.2). Amylopectin molecule is composing of many glucose residues (up to 2,000,000 units) in a compact structure with hydrodynamic. Starch contains about 70% amylopectin by weight but it varies depending on the source of starch, for example, 100% in waxy rice, waxy potato and waxy corn starch, and lower in long-grain rice and russet potato.

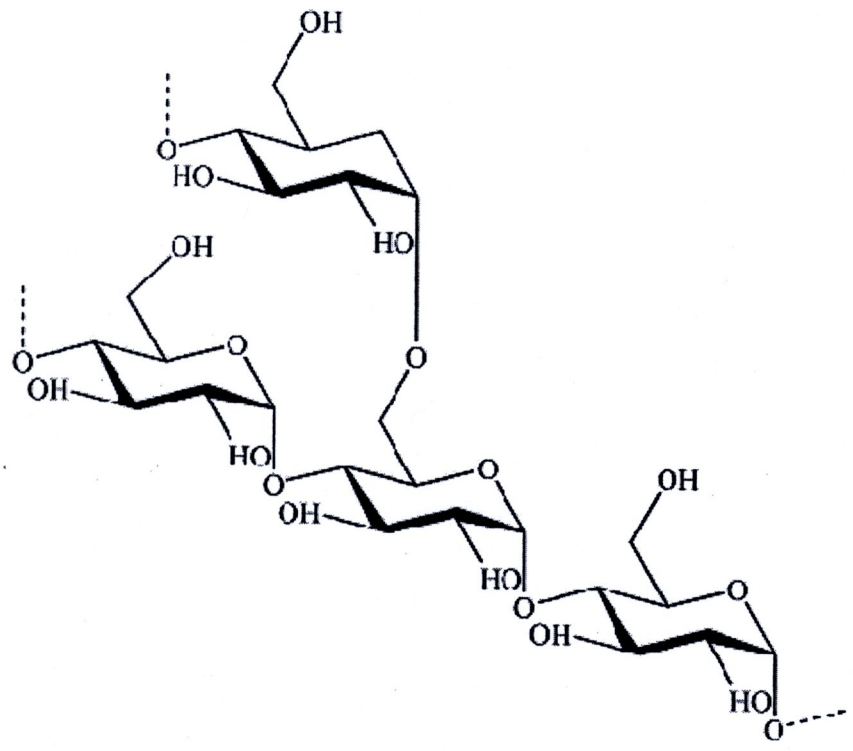

Figure 1.2 Chemical structure of amylopectin

According to the structural difference of amylose and amylopectin in starch granule, it results in deviation of their physicochemical properties which is shown in Table 1.1.

Table 1.1 The differences of physicochemical properties between amylose and amylopectin (Sriroth, 2007)

Amylose	Amylopectin
1. Consisting of long chain structure of glucose units with α-1, 4 glycosidic bond	1. Consisting of long chain structure of glucose units with α-1, 4 glycosidic bond and branch chain with α-1, 6 glycosidic bond
2. Contains 200-6000 glucose units	2. Each branch contains 20-25 glucose units
3. Less soluble in water	3. Soluble in water
4. Low viscosity in boil water	4. High viscosity and transparent in boil water
5. Dark blue color with iodine	5. Purple color with iodine
6. Retrograde	6. Stable to retrogradation

The different amylose content in starch from different starch source is the one considerable characteristic of starch. The table 1.2 shows the different amount of amylose from various types of plants.

Table 1.2 Amylose content of starch from various types of starch source

Types of starch	Amylose content (%)
Barley	23.6[a]
Oat	23
Rine	26
Wheat	23
Rice	14.7-29.1[b]
Corn	22.5[a]
Waxy maize	0
Amylomaize	55–75
Sago	28
Potato	16.9[a]
Sweet potato	20
Tapioca	18
Canna indica Linn.	22.7[a]
Mungbeen	30-45[c]

Modified from: Tester et al., 2004[a]; Kittipongpatana et al., 2006[b], 2007[c]; Sriroth, 2007)

Modification of starch

Starch can be modified in 3 ways of modification such as chemical, physical or biotechnological modification. The description is classified below.

Types of modification:

1. Chemical modification
   1.1. Derivertization
      - Substitution of starch with monofunctional reagent including esterification (e.g. acetate starch) or etherificstion (e.g. *carboxymethyl starch*).

- Substitution of starch with multifunctional reagent (e.g. epichlorohydrin, phosphorus oxychloride). The starch modified by this type of modification is called *cross-linked starch.*

1.2. Acid thinning

1.3. Dextrinization

1.4. Oxidation

1.5. Hydrolysis: Starch is hydrolyzed by enzyme or acid into small molecular sugar.

2. Physical modification

2.1. Gelatinization

2.2. Granular-Cold-Water-Soluble-Starch: This modified starch can soluble in cold water without gelatinization.

2.3. Resizing of starch by mechanical: The starch granules are broken, and then the size of starch is smaller.

2.4. Annealing: This process can run by heating starch granule at temperature lower than temperature of gelatinization.

2.5. Heat moisture treatment: This process can run by heating starch granule containing low moisture content with temperature over gelatinization.

3. Biotechnological modification

3.1 Waxy starch: Starch containing low or without amylose content.

3.2 High-amylose starch

Carboxymethyl starch

Carboxymethyl starch (CMS) is one of starch derivatives modified by etherification. It is a nontoxic, nonirritant material, and is soluble in water. These noticeable points effect CMS is always in interest and covers a wide range of applications in industries. CMS is obtained from reaction of starch and monochloroacetic acid (MCA) under alkaline condition. The first step of reaction is an alkalization where sodium hydroxide (NaOH) reacts with the hydroxyl groups of the starch molecule and transformed into alkoxide form (St-O-) (Lawal et al., 2008a; b):

$$St\text{–}OH + NaOH \longleftrightarrow St\text{–}ONa + H_2O \quad (1.1)$$

In the second step etherification take places:

$$St\text{–}ONa + Cl\text{-}CH_2\text{-}CO\text{-}ONa \longrightarrow St\text{–}O\text{-}CH_2\text{–}COONa + NaCl \quad (1.2)$$

Then, the CMS is occurred (chemical structure is shown in Figure 1.3. In addition, a side reaction happens which competes with the carboxymethylation process (Equation 1.2), that being the reaction between sodium hydroxide (NaOH) and sodium monochloroacitate (SMCA) to form sodium glycolate as a byproduct:

$$NaOH + ClCH_2COONa \longrightarrow HOCH_2COONa + NaCl \quad (1.3)$$

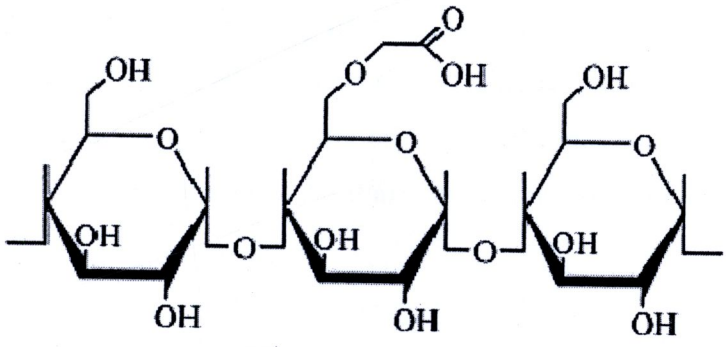

Figure 1.3 Chemical structure of carboxymethyl starch

Many researchers have been studied the effect of reaction parameter on the carboxymethylation of starch such as concentration of NaOH (Kamel and Jahangir, 2007; Lawal et al., 2008a; b; Sangseethong et al., 2005), amount of carboxymethylating agent (Lawal et al., 2008a; b; Sangseethong et al., 2005), types of organic solvent (Kamel and Jahangir, 2007; Kittipongpatana et al., 2006; Kooijman et al., 2003; Lawal et al., 2008a; b), temperature (Kooijman et al., 2003; Lawal et al., 2008a; b), and amylose content (Kittipongpatana et al., 2007).

The properties of CMS are generally accepted rather than native starch in many applications. Therefore, CMS is widely used in many fields of the food (e.g. as a stabilizing agent for ice-cream and soft drink, as a preservative for fresh meat, vegetable and fruit) and pharmaceutical (e.g. as a film-former for tablet coating (Tehkhunmag, 2007; Tehkhunmag et al., 2008), as a gelling agent (Kittipongpatana et al., 2006) and as a control release agent (Anutrakulchai, 2010; Onofre et al., 2009). CMS has also been applied in non-food industries, for example, used as a sizing and printing agent in the textile industry (Dong-Fang et al., 2005).

Cross-linked starch

Cross-linked starch is obtained by modifying starch with multifunctional reagents (cross-linking agents). Cross-linking occurs when a hydroxyl group (OH) on one chain bonds with a hydroxyl group on an adjoining chain. This toughens the starch molecule and aids it oppose heat and acids. Cross-linked starch shows increasing shear and high thermal stability properties from the cross-linked network. The cross-linking can be completed by heating, or by reacting with compounds such as glycerol or phosphates. Epichlorohydrin (ECH) (Figure 1.4) is one of cross-linking agents, and it is employed in cross-linking of polysaccharides since 1999 (De Miguel et al., 1999). This cross-linking can be done by reaction of starch and ECH under alkaline condition:

$$\text{St–OH} + \underset{\diagdown\,\text{O}\,\diagup}{\text{CH}_2\text{-CH-CH}_2\text{-Cl}} \xrightarrow{\text{NaOH}} \text{St–O–}\underset{\displaystyle\text{OH}}{\text{CH}_2\text{-CH}_2}\text{–O–St} + \text{NaCl} \qquad (1.4)$$

The cross-linked starch with ECH is called distarch glycerol (Figure 1.5).

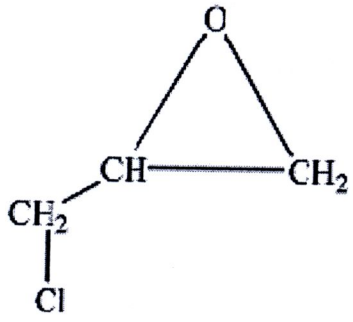

Figure 1.4 Chemical structure of epichlorohydrin

In literatures, many researchers have studied cross-linking of starch using ECH as a cross-kinking agent. Carmona-Garcia et al. (2009) reported the properties of cross-linked banana starch synthesized using various cross-link reagent types (sodium trimetaphosphate (STMP)/sodium tripolyphosphate (STPP), phosphorous oxychloride ($POCl_3$) and epichlorohydrin (ECH). Onofre et al. (2009) studied the effects of structure and modification on sustained release properties of starches. Starches were cross-linked with ECH and substituted with carboxymethyl or aminoethyl groups at different levels. They found that modified starches cross-linked with low level of ECH exhibited an overall better sustained release. Chen and Wang (2006) studied the adsorption properties of cross-linked carboxymethyl starch with ECH for calcium ion. Silva et al. (2006) presented the characterization of cross-linked cashew gum derivatives synthesized using ECH as a cross-linked reagent. The increasing of ECH/cashew gum ratio affected swellability of starch decreased.

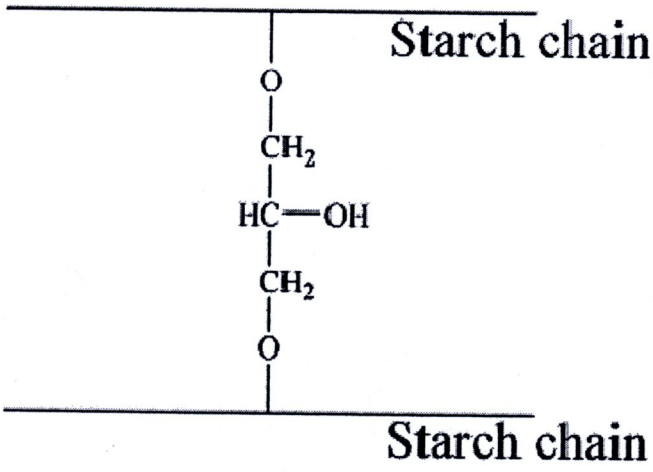

Figure 1.5 Chemical structure of distarch glycerol

Tablet disintegrant

A disintegrant is an excipient used in pharmaceutical preparation of tablets. The disintegrating agent is introduced into a tablet to support breaking up of the compressed mass while it is placed in a fluid environment. The disintegrant is a considerable excipient for tablet especially in drugs that requires rapid release of their substance. The disintegrant can be used in many methods for tablet preparation including direct compression, encapsulation, and wet granulation. In recent years, the newer agents that are more effective at lower concentration than the general disintegrants have been developed referred as superdisintegrants. An effective superdisintegrant exhibits an improving of compressibility, compatibility and has no effect on the strength of the formulations composing high-dose drugs. Some commonly superdisintegrants are shortly described below.

Sodium starch glycolate

Sodium starch glycolate (SSG) is a modified starch, the sodium salt of carboxymethyl ether of potato starch. It can be used as 2-8% to activate effectively. SSG has high swelling capacity owing to its ability to absorb the water more than 20 times of its weight rapidly. This is considered as high disintegration rate and efficiency.

Croscarmellose sodium

Croscarmellose sodium (CCS) is cross-linked sodium carboxymethyl cellulose; it is a white powder with high absorption capability. It has excellent swelling properties and gives a fast disintegration and drug dissolution at low concentration which the advised level is only 1-5%.

Cross-linked polyvinylpyrrolidone

Cross-linked polyvinylpyrrolidone is a completely water insoluble superdisintegrant. It provides the highest rate of swelling compared with the other superdisintegrants and it is effective at only 1-3%.

Cross-linked alginic acid

Cross-linked alginic acid is a water insoluble and a hydrophilic colloidal disintegrant that has high sorption capability.

Mechanism of tablet disintegrants

The tablet breaks into primitive particles by one or more of the mechanisms listed below.

Capillary action or wicking

Disintegration by capillary action is usually the first step. When the tablet was put into appropriate medium solution, the solution infiltrates into the tablet and replaces the air adsorbed on the particles. This can debilitate the intermolecular bond and breaks the tablet into fine particles (Guyot-Hermann and Ringard, 1981). The uptake of water by tablet depends on hydrophilicity of the drug or excipient in formula and on tableting conditions. For these types of disintegrants preservation of permeable structure and low interfacial tension towards aqueous fluid is essential. These will help in disintegration by creating a hydrophilic network around the drug particles.

Swelling

The most extensively accepted normal mechanism of action for tablet disintegration is possibly swelling. The tablets containing high porosity show poor

disintegration owing to deficiency of sufficient swelling force. In contrast, adequate swelling force is exerted in the tablet with low porosity. It is worthwhile to report that if the packing portion is very high, fluid is unable to infiltrate in the tablet. Then, the disintegration is further slows downward. The swelling capacity of various starches has been reviewed in many publish researches (Guyot-Hermann and Ringard, 1981).

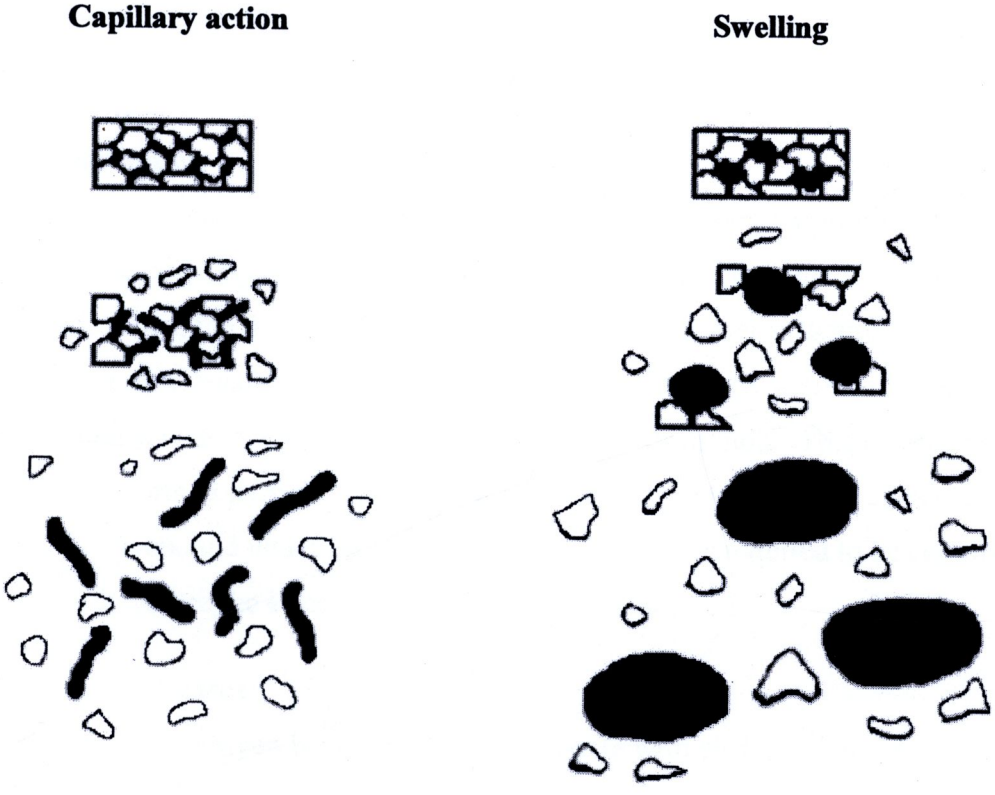

Figure 1.6 Disintegration of tablet by capillary action and swelling

(Redrawn with modification form http://www.pharmainfo.net/tablet-ruling-dosage-form-years/formulation-tablets)

Heat of wetting (air expansion)

This mechanism is performed from the localized stress owing to capillary air expansion when disintegrants that own exothermic properties get wetted. Nevertheless, this demonstration is limited for only a few types of disintegrants and it cannot use to explain the action of most current disintegrants.

Particle repulsive theory /disintegrating particle

This is another mechanism of disintegration that tries to describe the swelling of tablet made with non-swellable disintegrants. Guyot-Hermann and Ringard (1981) has recommended a particle repulsion principle based on the review that non-swelling particle also make disintegration of tablets. They also reported that the electric repulsive forces between particles are the mechanism of disintegration and water is necessary for it. Moreover, researchers presented that repulsion is secondary to wicking.

Deformation

The deforming of disintegrant particle from tablet compression was proved using aid of photomicrographs. During tablet compression, particles of disintegrant get deformed. Then, the deformed particles get into their general structure when they contact with aqueous media. The swelling capacity of starch was sometime enhanced when the granules were extensively deformed during compression. This enlargement in size of the deformed particles generates a break-up of the tablet. The character of deformation and rebound under actual reproduction conditions required to be certainly evaluated vastly before the effect of this result and be conceived.

Release of gases

Interaction between bicarbonate and carbonate with citric acid or tartaric acid affects carbon dioxide can release inside tablets on wetting. The tablet disintegrates owing to reproduction of pressure inside the tablet. The carbonated mixture is utilized when the fast disintegrating tablet or very rapidly dissolving tablets was required to formulate. However, these disintegrants are very sensitive to small changes in humidity level and temperature.

Enzymatic reaction

Enzymes which presents in the body can act as disintegrants. The enzymes annihilate the binding activity of binder and aids in disintegration.

Pharmaceutical application of starch as a tablet disintegrant

Native Starch

Starch was the first disintegrant vastly utilized in tablet manufacturing due to its readily available, non-toxicity, inert and inexpensive. The mechanism of action of starch is wicking and restoration of deformed starch particles when it contacts with aqueous solution. However, native starches have confident limitations. The concentration of starch employed is very importance parameter. If it is below the optimum concentration then there are inadequate channels for capillary action. In addition, if it is above optimum concentration then it will be hard to compress the tablet. Thus, it has been replaced by certain modified starches with specialized characteristics. Many endeavors have been carried out to study the efficiency of native starches for using as a tablet disintegrant, for example, cassava starch (Jaiyeoba and Opakunle, 1978), maize starch (Gadalla et al., 1989), rice starch (Bos et al., 1987), breadfruit starch and corn starch (Adebayo et al., 2008).

Modified Starches

Starch is modified by carboxymethylation followed by cross-linking to provide a high swelling characters and quicker disintegration. Recently, this modified starch is available in commercial. One of them is sodium starch glycolate in the trade name of Explotab® or Primojel®.

Mechanism of action of these modified starches is fast and extensive swelling with minimum gelling. Its optimum concentration for use is 2-5 %. At beyond this range of concentration, it is limited and then generates viscous and gelatinous mass which increase of disintegration time by obstruction the breakup of tablet. They are highly productive at low concentration owing to their greater swellability.

Nattapulwat et al. (2008) studied to compare the efficiency of native and carboxymethyl yam starch (*Dioscorea esculenta*) using hydrochlorothiazide (HCTZ) as a model drug. They found that carboxymethyl yam starch showed higher swelling power and more viscous gel compared with native one. Carboxymethyl yam starch could be used as a tablet disintegrant at low concentration. However, it had less

efficiency to be satisfying disintegrant compared with native yam starch because of its ability to form gel.

Kittipongpatana et al. (2010) studied preparation of cross-linked carboxymethyl rice starch (CL-CMRS) and its physicochemical and pharmaceutical properties. They reported that CL-CMRS which modified with low concentration of cross-linking agent had good tablet disintegrant properties because of this CL-CMRS is less soluble and less viscous but shown water uptake capability.