

## CHAPTER I

### GENERAL BACKGROUND

#### INTRODUCTION

Tablets have been in widespread use since the latter part of the nineteenth century. They are now still remain the most popular of all medicinal preparations intended for oral usage. The reasons for the popularity of tablets include relative ease and economy of manufacture, acceptable dosage accuracy, good physical and chemical stability, ease of handling and administration, and good palatability. (Jones, 1983)

In order to compress medicinal substances, with or without diluents, to be made into solid dosage forms by using available equipment, it is necessary that the materials, either in crystalline or powdered form, possess a number of physical characteristics. These characteristics include the ability to flow freely, compressibility and lubrication. Since most materials have none or only some of these properties, methods of tablet formulation and preparation have been developed to impart these desirable characteristics to the material which is to be compressed into tablets.

These are three general methods of tablet preparation: wet granulation, dry granulation, and direct compression (Gunsel and Kanig,

1986). The most widely used and most general method of tablet preparation is the wet granulation method. The pharmaceutical industry benefits from wet granulation by improvement of one or more of the properties of powder flow and handling, bulk density, dust formation, appearance, solubility and resistance to segregation.

The appearance, elegance and ease of compression of tablets are directly related to the granulation from which the tablets are compressed. The qualities of the granulation produced, in turn, are dependent on the materials used, processing techniques and equipment for the quality of the granulation produced. Of these variables, none is more critical than the binder used to form the granulation, for it is largely the binder that is fundamental to the granulation particle size uniformity, adequate hardness, ease of compression, and general quality of the tablet.

Starch is a multipurpose excipient used in tablet formulation which can be formulated as a filler, a binder, a disintegrant or as a lubricant depending on its type, concentration, modification and methods of incorporation. However, native starch has its limitations in application (Banker, Peck and Baley, 1980). As a tablet binder in conventional wet granulation process, it must be heated to be starch paste before use because the starch granule can not develop viscosity in cold water. Therefore, modified starches have been developed to overcome this shortcoming, and thus expand the usefulness of starch for a myriad of industrial applications, i.e. thermal modified and chemically crosslinked starches (Visavarungroj and Remon, 1990 ; Visavarungroj,

Remon and Herman, 1990). Carboxymethyl starch is one of the modified starches which provides cold-water solubility and viscosity. Because of these properties of this chemically modified starch, it is interesting to study the use of carboxymethyl starch as a binder in tablet formulations (Chalmers, 1968b ; Filbert, 1952 ; Hofreiter, 1987 ; Radley, 1968 ; Robert, 1967 ; Rutenberg, 1980 ; Wurzburg, 1987). Furthermore, each type of starches has difference binding property because they vary in size and shape of starch granules, amylose and amylopectin content, molecular size of amylose and degree of swelling of starch granules etc. All of these factors effect the properties of starch paste, for example, Whistler (Wurzburg, 1987) demonstrated that after slight acid hydrolysis, potato amylose was degraded sufficiently to enable the molecules to associate more readily so the sols on cooling rapidly lost their clarity and formed rigid and opaque gels.

So, in the present study, a number of native starches were chemically modified by carboxymethyl substituted reaction to produce cold water soluble starches with optimum property to be used as tablet binders in both dry form and paste form.

The modified starch products which could disperse in cold water to form viscous gel when directly contact with water would be advantageous without the step of preparing starch paste by heating.

## THE PURPOSES OF THIS STUDY

The aims of this study are:

1. To study the properties of modified rice starch (MRS), modified glutinous rice starch (MGS), modified corn starch (MCS), modified tapioca starch (MTS) and modified potato starch (MPS) preparing by various carboxymethylation methods.
2. To study the binding properties of the carboxymethyl starches when use as granulating agents in manufacture of tablet products.
3. To investigate the effect of degree of substitution and the amount of the modified starches on the properties of granules and tablets.
4. To compare the binding property among modified starches prepared from various types of carboxymethylation substitution.
5. To compare the binding property of the modified starch with commonly used binding agent : PVP K30 and other modified starch products: Era-Pac<sup>R</sup> and Era-Gel<sup>R</sup>.

## LITERATURE REVIEW

Binder are solid materials used in the manufacture of solid dosage forms because of their adhesive and cohesive properties (Kristensen, 1988). The role of binders is to assist size enlargement by adding cohesiveness to powders, thereby providing granules and tablets with necessary bonding strength.

Rumpf divided agglomerate bonding mechanism into five major groups. More than one mechanism may be apply during a given size-enlargement operation (Kristensen and Schaefer, 1987 ; Perry and Chilton, 1973).

### 1. Solid bridges

There are five mechanisms are reported to be responsible for the formation of solid bridges (Fonner, Anderson and Banker, 1981).

- A. Crystallization of dissolved binders
- B. Hardening binders
- C. Particle melting or localized fusion welding
- D. Particle deformation followed by sintering
- E. Chemical reaction

Of these fives mechanisms, the pharmaceutical industry primarily utilizes method A and B for wet granulation and methods C and D for roller compaction.

Crystallization of dissolved and/or suspended binders can be formed by changing pressure and/or temperatures. The strength of a crystalline bridge depends not only on binder and binder concentration but also drying conditions. The tensile strength of the granule increases with the increasing of the binder and binder concentration (Banker and Anderson, 1986 ; Baykara and Acarturk, 1989). The drying conditions such as drying rate and drying temperature effect crystallization rate and distribution of binding agent which influence the granule structures. At high crystallization rates finer crystal structures and a high strength are obtained. And, as the granulating medium begins to evaporate at the surface of the granule, the liquid flows to the surface by means of capillary forces. The binder crystallizes and forms a crust which may hinder further drying of the porous granule.

Hardening binders and chemical reactions depend on the material involved, their ability to harden and their chemical reactivity. Chemical reactions are often activated by moisture.

Particle melting are formed which solidify quickly at the contact points between particles which partially melted when no additional heat is introduced. This mechanism is often responsible for agglomeration and coating tendencies of thermoplastic materials.

## 2. Mobile liquid bridges or mobile liquid bondings

Mobile liquid bridges produce cohesion through interfacial forces and capillary suction. Newitt and Conway-Jones (Kristensen

and Schaefer, 1987 ; Marchall, 1986) described three states of mobile liquid.

- A. The pendular state
- B. The funicular state
- C. The capillary state

The three states are distinguished by the relative amounts of liquid phase as expressed by the liquid saturations,  $S$ .  $S$  is the ratio of pore volume occupied by liquid to the total volume of pores available in the agglomerate.  $S$  may be expressed as the percentage ratio.

The pendular state, small amounts of liquid are held as discrete lens-shaped rings at the points of contact of the particles. The degree to which contact is established between any two adjacent particles is a function of the size, shape, and surface roughness of the particles. As the liquid content increases ( $S \geq 25\%$ ) the ring coalesces, and there is a continuous network of liquid interspread with air ; this is the funicular state. When all the pore spaces in the agglomerate are completely filled ( $S > 80\%$ ), the capillary state has been reached.

The liquid saturation depends on the amount of liquid and the intragranular porosity according to the equation :

$$S = \frac{H(1-\epsilon) p}{\epsilon}$$

H is the ratio of the mass of liquid to the mass of solid particles. For an agglomerate of particles that are insoluble in the liquid, H is the humidity on dry basis.  $\epsilon$  is the intragranular porosity and  $\rho$  is the particle density. The equation presupposes that the liquid density is unity.

### 3. Immobile liquid bridges

Immobile liquid bridges formed from highly viscous materials such as asphalt or pitch fail by tearing apart the weakest bond. Then adhesion and/or cohesion forces are fully exploited and binding ability is much larger.

### 4. Intermolecular and electrostatic forces

Intermolecular and electrostatic forces bond very fine particles without the presence of material bridges. Such bonding is responsible for the tendency of particles less than about one micron in diameter to form agglomerate spontaneously under agitation. With large particles, however, these short-range forces are insufficient to counterbalance the weight of the particle, and adhesion does not occur.

### 5. Mechanical interlocking or interlocking bonds

Mechanical interlocking of particles may occur during the agitation or compression of fibrous, lamellar and/or bulking particles, but it is probably only a minor contributor to agglomerate strength in



most cases. The strength of the bonds depends directly on the particle strength and type of the interlock.

Binders are divided into three classes as the following (Gunsel and Kanig, 1986 ; Kristensen, 1988 ; Sheth, Bandelin and Shangraw, 1980) :

- a) Sugar : sucrose, dextrose, glucose
- b) Natural polymers
  - Starch : corn starch, potato starch, tapioca starch, pregelatinized starch, starch 1500
  - Gum : acacia, tragacanth, gelatin
- c) Synthetic polymers
  - Cellulose derivatives : ethylcellulose, methylcellulose, carboxymethylcellulose, hydroxypropylcellulose
  - Others : Polyvinylpyrrolidone (PVP), Polyethylene glycol

The binder is added either dry or in liquid form during wet granulation to form granules (Banker and Anderson, 1986 ; Sheth et al., 1980).

By solution incorporation method, the binder is dissolved or slurried in the water or solvent as a paste or solution form and added to the powder mix.

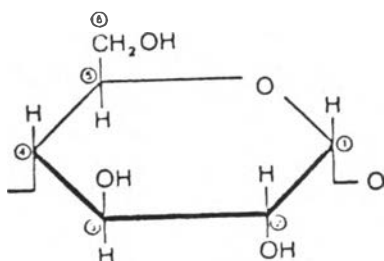
But dry incorporation method, the binder is added in dry form and blended with drug(s) and diluent(s). Then the mixture is granulated with water, alcohol-water mixtures or a solvent.

## STARCH

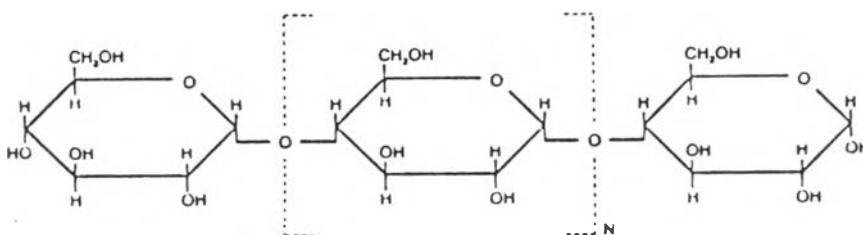
Starch, the starting polymer source for all starch derivatives, has always been an item in the diet of men and their ancestors. It is the most available natural polymeric raw material. Most plants in the plant kingdom contain starch. It is generally deposited in the form of minute, discrete particles or granules or cells which are distinctive to the plant in which they are formed, varying in size, shape and relative proportions of amylose and amylopectin. These granules are mainly deposited in the seeds, tubers or roots of botanic plants. Based on its widely distribution in nature, starch is generally used as components and/or processing aids in the manufacture of products such as adhesives, textiles, paper, food, pharmaceuticals, and building materials.(Rutenberg, 1980 ; Wurzburg, 1987)

Various types of processes are used in the manufacture of starch, depending upon the plant source. In general, they involve extracting starch granules from the other constituents such as the fiber, germ, protein and extraneous materials, then purifying, washing, dewatering usually by filtration and drying.

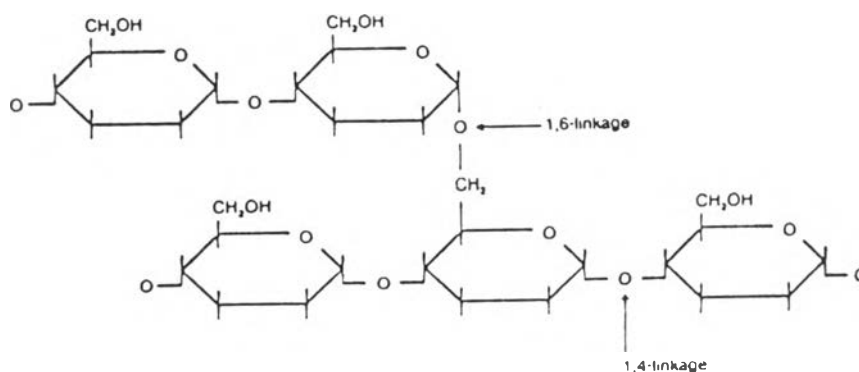
Structurally, starch is a polymeric carbohydrate consisting of repeating units of anhydroglucose (Figure 1), linked together by alpha-D- (1→4) glucosidic bonds. The anhydroglucose unit is in the “alpha - D- glucopyranose” form. Furthermore, starch is a heterogeneous material containing two chemically distinct components, amylose and



**Figure 1** Anhydroglucose unit; carbon atoms are labeled from 1 to 6. The glucosidic bond appears as C-O-C.



**Figure 2** Linear-chain structure of the amylose molecule.



**Figure 3** Branched chain structure of the amylopectin molecule.

amylopectin. (Chalmers, 1968a ; Williams, 1968 ; Rutenberg, 1980 ; Wurzburg, 1987)

Amylose, a linear polymer, consists of a chain of anhydroglucose units connected to each other by alpha-D-(1→4) glucosidic bonds (Figure 2). The amylose chain has a single reducing end group and a single nonreducing end group.

Amylopectin is a branched polymer containing anhydroglucose units linked together as in amylose through alpha-D- (1→4) glucosidic bonds, periodic branches at the carbon-6-position (Figure 3 ).

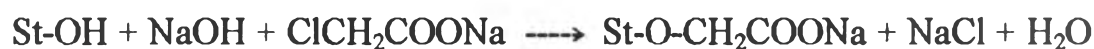
The principal reaction sites in starch are : 1) the glucosidic linkages between glucose units ; 2) the primary hydroxyl group on carbon atom 6 ; and 3) the secondary hydroxyl groups on carbon atoms 2 and 3. The glucosidic linkage is an acetal, stable under alkaline conditions and hydrolyzable under acid conditions. Thus, acid hydrolysis leads to depolymerization of the starch, which if carried to completion results in the release of glucose (also known as dextrose). The hydroxyl groups can react to form ethers and esters and can be oxidized to aldehyde, ketone and carboxyl groups.

Although native starch has been widely used for many years, modified starch now has limitless applications. Modification of native starch can be grouped into three main classes. There are plant breeding, physical modifications and chemical modifications. The later can be subdivided into four groups : crosslinking, degradation, derivertization

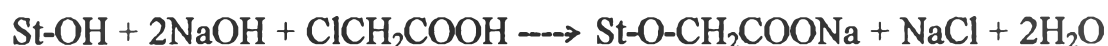
and graft and block polymerization (Figure 4). (Chalmers, 1968b ; Rogols, 1986)

### **Sodium Carboxymethyl starch**

Carboxymethyl starch is a starch ether derivative, usually obtained as the sodium salt. It is prepared by the reaction of starch with chloroacetic acid or sodium chloroacetate in the presence of aqueous sodium hydroxide according to the equation.



or



Low degree of substitution (D.S.) carboxymethyl starch, up to about 0.1, is not cold water soluble. Hence, they may be obtained by conducting the reaction in an aqueous alkaline slurry containing added salts such as sodium sulfate. Higher D.S. product, up to 1.0 has been obtained in a water-miscible solvent. The solvents which are widely used are isopropanol, methanol and ethanol. (Roberts, 1967 ; Hofreiter, 1987)

### **Mechanism of reaction**

The reaction mechanism of carboxymethylation is a bimolecular displacement (Substitution nucleophilic bimolecular ; S<sub>N</sub>2). This means the formation of an intermediate complex. Therefore, the etherification



they be used in pharmaceutical application (as tablet binders and disintegrants) and in detergent (as antiredeposition) (Rutenberg,1980 ; Hofreiter, 1987). Furthermore, carboxymethyl amylose has been used as the anion of a polymeric salt in which the cation is a basic drug such as an alkaloid, anesthetic, or antibiotic, with the resulting polysalts showing increased ability to enter the lymphatic system and clinically, carboxymethyl starch has been used for its laxative effect. (Chalmers, 1968b)

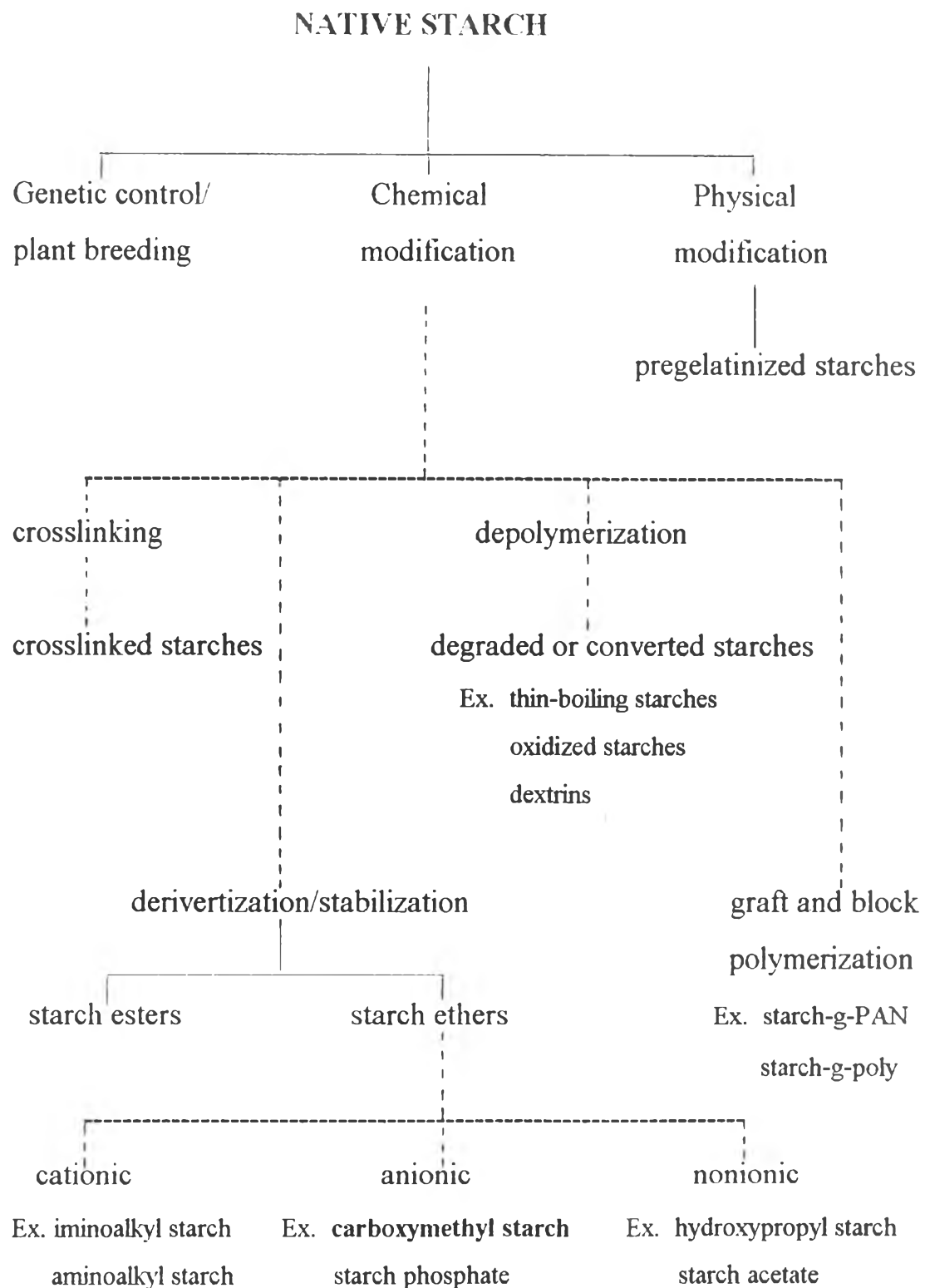


Figure 4 Modifications of starch.