GENERAL BACKGROUND

1 INTRODUCTION

Starch is one of the most abundant naturally occurring materials derived from agricultural source. Starches are applied extensively as components and/or processing aids in various industries such as foods, textiles, adhesives, papers as well as pharmaceuticals.

In pharmaceutical system, starch is, at first, used directly in native form without modification as an important adjuvant in the formulations and products of solid dosage forms, e.g., diluent, binder, disintegrant. As a consequence that the characteristics of starch can be altered by chemical, physical and/or enzymatic means to improve its intrinsic properties or to impart a new one, so attempts have been made to modify starches by various processes in order to make their properties more appropriate and effective for pharmaceutical uses such as to be employed as directly compressible vehicle in direct compression process, highly effective disintegrant, bioadhesive materials and retarding agent in sustained release

products. (Chalmers ,1968 ; Herman et al.,1989)

Existing commercially available modified starches for pharmaceuticals are imported products with relatively high price and produced from such starches that are commonly available in western countries. For example, Explotab[R] and Primojel[R], modified potato starch employed as tablet disintegrant are sold at 370-385 bahts per kg. or Starch 1500[R] , a partially gelatinized corn starch recommended to be used as directly compressible vehicle is sold at 150 baht per kg. Recently Eratab[R], a modified rice starch produced locally was introduced to be employed as directly compressible vehicle with cheaper cost (50 bahts per kg.).

Thailand is an agricultural country, producing tremendous amount of starches annually. As located in the tropical zone, the various varieties of starches are cultivated commonly. Starch powders from different native sources may not have identical properties with respect to their uses as additives in pharmaceutical dosage forms. So it is essential to direct the research area toward pharmaceutical technology of starches by extensive investigation on development and modification of various starches available locally for

pharmaceutical purposes. This report is a part of the work in pharmaceutical technology of starch by investigating various sources of native starches having potential to be developed as more effective pharmaceutical additive in direct compression process of tablet dosage form.

2 OBJECTIVES

The objectives of this research project are, therefore, concerned with

(a) the investigation of various varieties of starch available locally that are most appropriate to be modified as directly compressible vehicle for tabletting.

(b) the methods of modification which include the use of spray drying technique , crosslinking reaction and deproteinization of the most appropiate starch prior to spray drying.

(c) development of the conditions of spray drying process which provide the satisfactory starch aggregates for direct tabletting.

3 AN OVERVIEW : STARCH

Structure & Properties

Starch is the reserve carbohydrate in various parts of land plant. It is synthesized from glucose which is formed in the photosynthesis from carbon dioxide and water (Figure 1).

Because the growth conditions and genetic types are different in each plant, the starch from each source will vary in appearances, composition and properties.

Chemical Composition

Starch is a kind of carbohydrate with carbon, hydrogen and oxygen in the ratio of 6 : 10 : 5 $(C_6H_{10}O_5)_n$. It is a condensation polymer of glucoses, which are present in the form of anhydroglucose unit (AGU) (Figure 2).

The glycosidic linkage is stable under alkaline conditions, but acid hydrolysis leads to depolymerization , yielding glucose if carried to completion. The hydroxyl group can react to form ethers and esters and can be oxidised to aldehyde, ketone and carboxyl group. This is one of the most important properties of starch that it can be modified into nearly unlimited new derivatives with different physical and chemical properties.

$$6H_2O + 6CO_2 \xrightarrow[\text{chlorophyll}]{\text{light}} C_6H_{12}O_6 + 6O_2$$

water + carbon dioxide $\longrightarrow$ glucose + oxygen

$$n\ C_6H_{12}O_6 \xrightarrow{\text{enzymes}} (C_6H_{10}O_5)_n + nH_2O$$

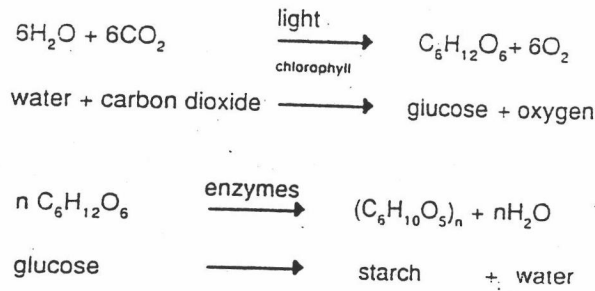glucose $\longrightarrow$ starch + water

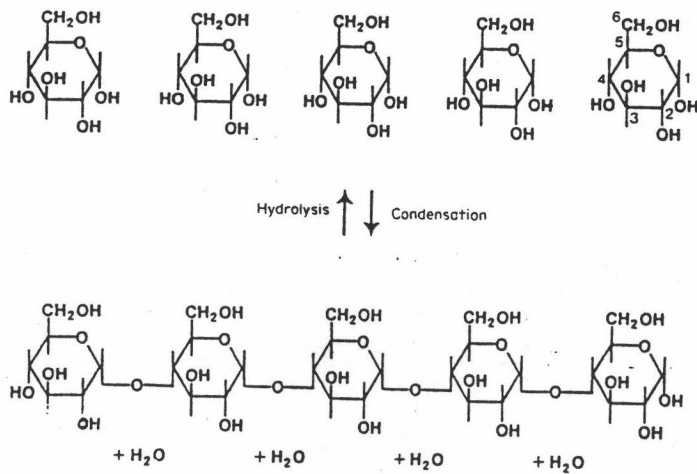Figure 1   Synthesis of starch from glucose in plant which is previously formed in the photosynthesis process.

Figure 2   Condensation of glucoses to starch which, upon hydrolysis, converts back into glucoses.

Depending upon the variety, starch contains small amount of proteins, lipids and inorganic materials, such as phosphorus or phosphate groups(Table 1-3).

Molecular Structure

Most starches contain two types of polymers, amylose and amylopectin in various ratios, depending on varieties.

Amylose (A Fraction)

This is a linear polymer consisting of glucose units connected by α-1,4 linkages (Figure 3).

The degree of polymerization of amylose ranges from 200 to 6000 according to plant sources.

Amylose forms complexes with iodine to give a blue color. The color is related to chain length. Shorter chains give purple, red, brown or yellow complexes. Amylose consists of a large number of hydroxyl groups which give hydrophilic properties leading to an affinity for water. Nevertheless, the numerous hydroxyl groups can form hydrogen bonds making bridges between adjacent molecules causing lower water solubility. Dilute starch solution will precipitate upon standing at room temperature.

Table 1   Starch Granule Properties (Rutenberg,1980)

Starch	Type	Size (diameter,) μm	Shape (light microscope)	Gelatinization temperature, °C	Amylose content, %
Corn	Cereal	5–26(15)	Round, polygonal	62–72	22–28
Waxy corn (waxy maize)	Cereal	5–26(15)	Round, polygonal	63–72	<1
Tapioca (Thailand)	Root	5–25(20)	Truncated, round, oval	62–73	17–22
Potato	Root	15–100(33)	Oval, spherical	59–68	23
Sorghum	Cereal	6–30(15)	Round, polygonal	68–78	23–28
Wheat	Cereal	2–35	Round, lenticular	58–64	17–27
Rice	Cereal	3–8(5)	Polygonal, angular	68–78	16–17
Sago	Pith	15–65	Oval, truncated	—	26
Amylomaize (high-amylose corn)	Cereal	3–24(12)	Round, elongated, deformed	63–92	50–80

Table 2   Average   Chemical   Composition   of   Starch Granules (Swinkles,n.p.)

Starch 65 % RH[1]	Moisture at on d.s.[2] and 20 °C	Lipids % on d.s.[2]	Proteins % % on d.s.[2] N[3] x 6,25	Phosphorus %	Amount of taste and odour substances (relative)
Potato	19	0.1	0.1	0:08	low
Maize	13	0.8	0.35	0.02	high
Wheat	13	0.9	0.4	0.06	high
Tapioca	13	0.1	0.1	0.01	very low
Waxy Maize	13	0.2	0.25	0.01	medium

1. RH   = Relative Humidity of the atmosphere
2. d.s.   = Dry substance
3. N   = Nitrogen content

Table 3   Chemical Composition of Various Starches.
               (Mukprasert,1992)

Chemical Components of Various Flours

Variety	Protein %	Fat %	Carbohydrate %	Fiber %	Ash %	M.C. %
Rice	6.64	0.65	81.93	0.39	0.51	9.88
Glutinous Rice	7.33	1.37	81.02	0.41	0.12	9.57
Mung Bean	5.20	0.36	82.05	0.31	0.26	11.82

Table 4   Enthalpy of Gelatinization ($-\Delta H_G$) for Native
               Granular Starches (Zobel,1984)

X-ray type A		X-ray type B		X-ray type C	
Starch	$-\Delta H_G$ (Cal./g.)	Starch	$-\Delta H_G$ (Cal./g.)	Starch	$-\Delta H_G$ (Cal./g.)
Corn	4.1-4.9	High amylose corn	6.7	Arrowroot	4.6
Wheat	2.9	Potato	4.5	Tapioca	4.0
Rice	3.4-3.9	ae wx	3.9		
Dasheen	4.3				
Waxy maize	4.8				
Compacted corn	2.2				
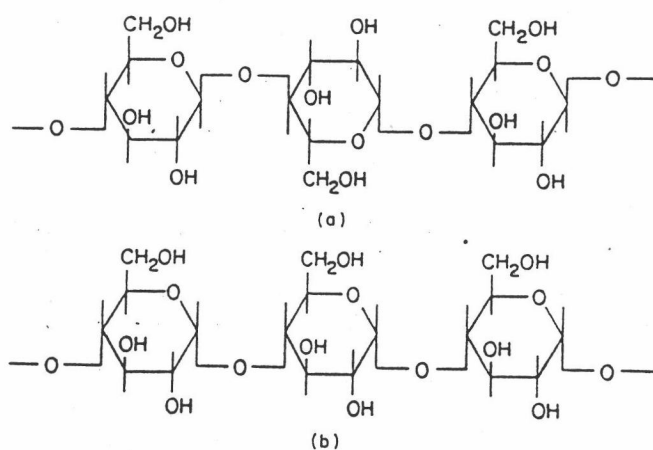
Figure 3   The beta-glucosidic linkage of Cellulose (a)
            and the alpha glucosidic linkage of Amylose
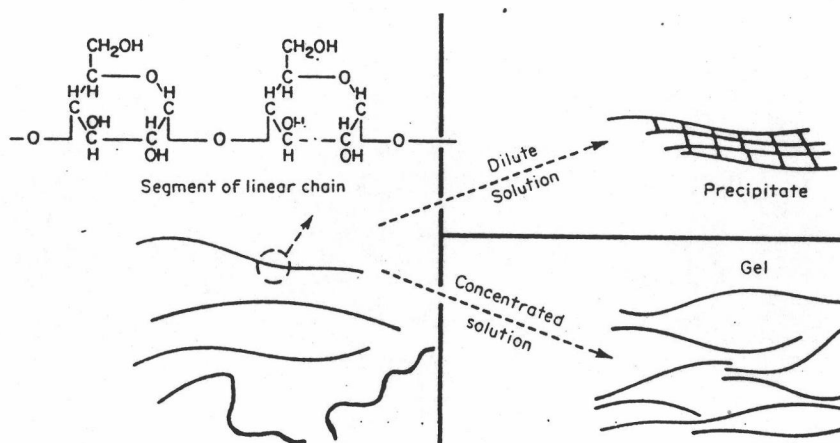   (b).

Figure 4   Mechanism of starch retrogradation (Amylose)

Concentrated starch dispersion will form gel containing of three dimensional networks (Figure 4). This process is called retrogradation or set back.

Amylopectin (B Fraction)

Amylopectin has a highly branched structure, consisting of short linear amylose chain which a degree of polymerization ranging from 10 to 60 connected to each other by α-1,6 linkages (Figure 5).

From .enzymatic analysis, the average chain length of the outer chain before reaching a branch point is about 12 AGU, while those of inner chain is about 8 AGU.

The structure of amylopectin was proposed to be a cluster which a large number of branches run paralell to each other (Figure 6).

Amylopectin is highly branched, therefore its dispersion does not form gel under normal condition. However, when refrigerated, the dispersion can become cloudy and gel owing to association of the outer chains of amylopectin molecules.

Amylopectin does not give blue color with iodine, but a reddish-purple because of the outer chain are not as long as amylose molecules.
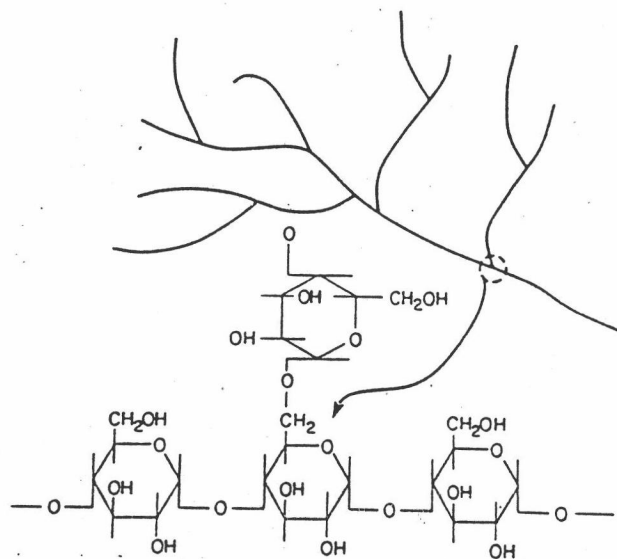
Figure 5   Branched   structure   of   Amylopectin   and
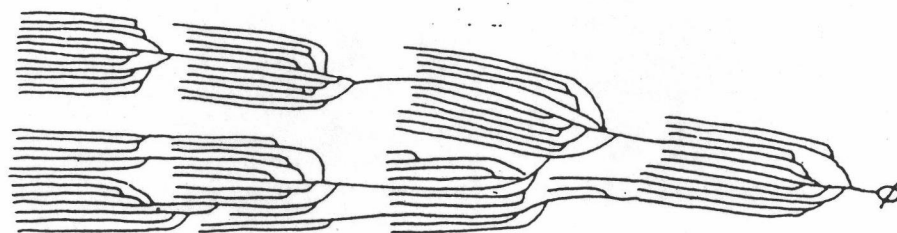chemical configuration at the branch point.

Figure 6   Amylopectin   structure   according   to   the
cluster hypothesis of D. French.

The Starch Granule

Viewed under polarized light, the starch granules usually show a cross, centered through the hilum (Figure 7). This suggests a radial organization of some sort. Moreover, the X-ray diffraction patterns show that there are areas of crystallinity in the starch granule. The starch molecules are arranged in the granule in a radial fashion toward the hilum (Figure 8).

When the segments of starch molecules run paralell one another, hydrogen bondings pull the chains together to form crystalline regions which are called micelles (Figure 9).

The crystallinity of the granules is essentially due to amylopectin. When the segments run paralell one another, the granules develop crystalline micelles. When not paralell or in a random fashion, they form amorphous areas. The area of crystallinity in various starches are about 25 - 50% of the total volume of the granules.

The recent evidence from X-ray diffraction suggests that the configuration of starch is a helix (Figure 10).

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(a)

(b)
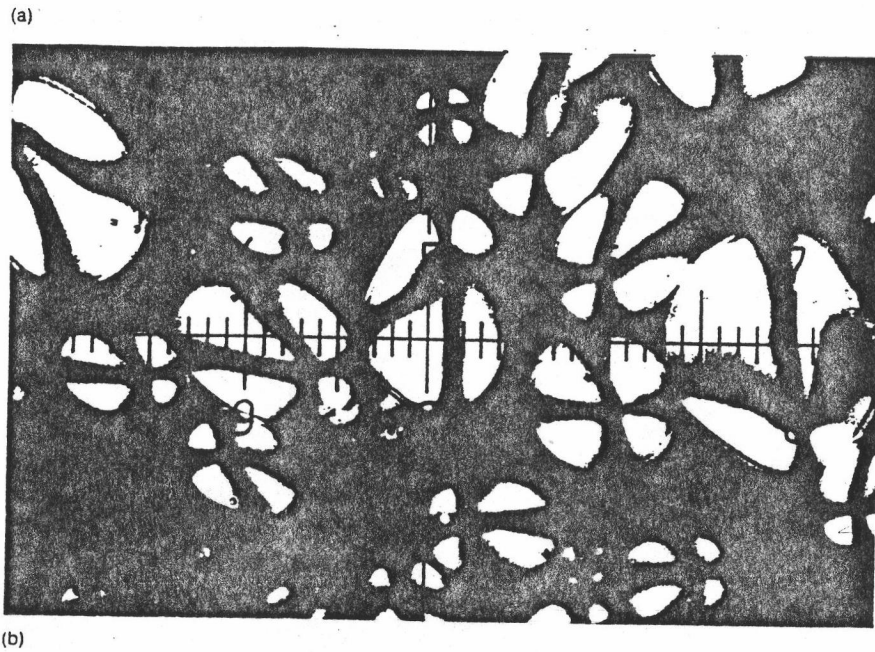
Figure 7   Potato Starch, Polarized Light.
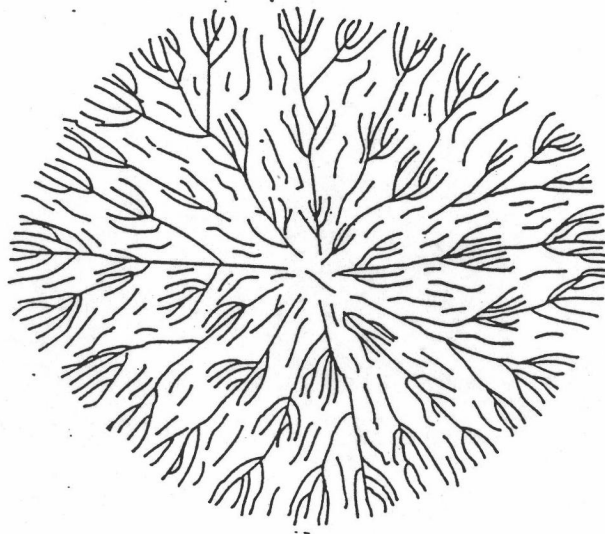

Figure 8   Schematic model of the structure of a   starch
                  granule.

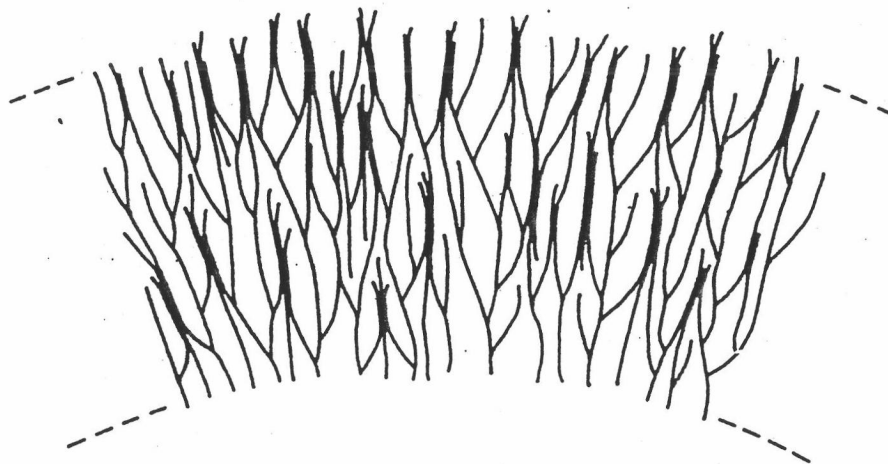Figure 9   Structure of molecules in a layer of a starch
             granule. Thickened areas represent micelles
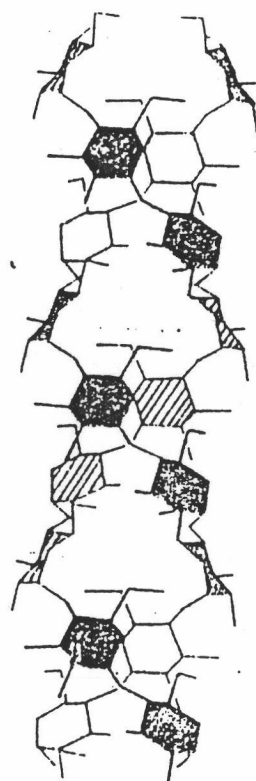   produced by association of chains.

Figure 10   Computer drawing of starch double helix.

Granule Swelling & Thermal Gelatinization

Starches are insoluble in water at room temperature. This is due to extensive hydrogen bonding in the starch molecules in spite of the polar character of a vast amount hydroxyl groups. When starch granules are heated in water to higher temperature, the polarization cross will start to fade at a certain temperature and the granules start to swell irreversibly. These phenomena are called gelatinization and perhaps, it is the most important property of starch. The temperature at gelatinization takes place is called gelatinization temperature or pasting temperature (Figure 11).

The heat applied causes disruption of weak hydrogen bonding in the amorphous regions and hydration takes place . This makes initial swelling of the granule and the fading of polarization cross due to disruption of radial organization of the starch molecules. Then various regions begin to be disrupted and hydrated, causing the micelles to expand to a greatly swollen reticulated network held together by persistent micelles, the swollen granules start to rupture, and yield dissolved molecules and colloidal swollen granule fragments. Further cooking does not

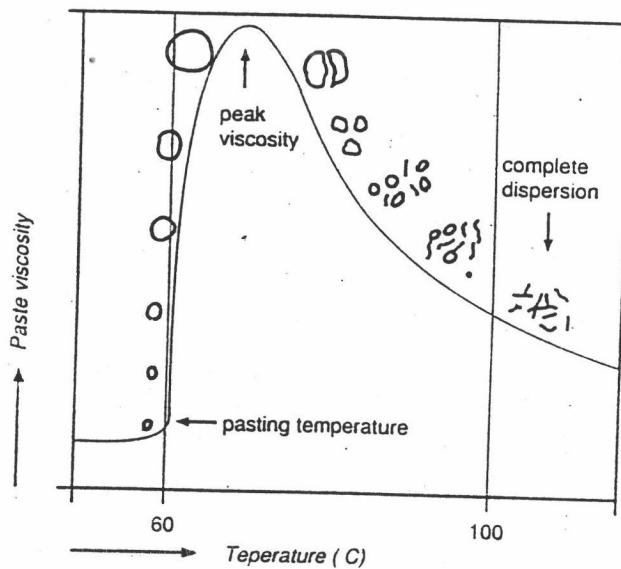Figure 11   Swelling, disruption and dispersion of a
             starch granule during gelatinization.

Figure 12   Micellar organization within swollen starch
   granules.

dissolve the swollen fragments which can be dissolved only by autoclaving in dilute solution. As the heating stops and the gel begins to cool down, the viscosity will rise again, sometimes more than the peak viscosity. This results from retrogradation which the dissolved molecules and swollen micelles rearrange to form new hydrogen bonding. This can be seen as the hardening and skinning of the cooled paste (Fig. 12).

All phenomena described above must be measured with specific apparatus called Brabender viscoamylograph (Fig. 13)

This is a special viscometer designed to record continuously viscosity of heated starch dispersion in thermostatic chamber with adjustable speed agitator. Moreover, it has microprocessor controlled heating unit with adjustable heating rate which can hold the sample at the desired temperature as long as required.

Chemical Gelatinization

Certain chemicals can gelatinize starch granules at room temperature without heating. These include aqueous solution of alkali, certain salts and organic compound. The cationic salts are calcium,
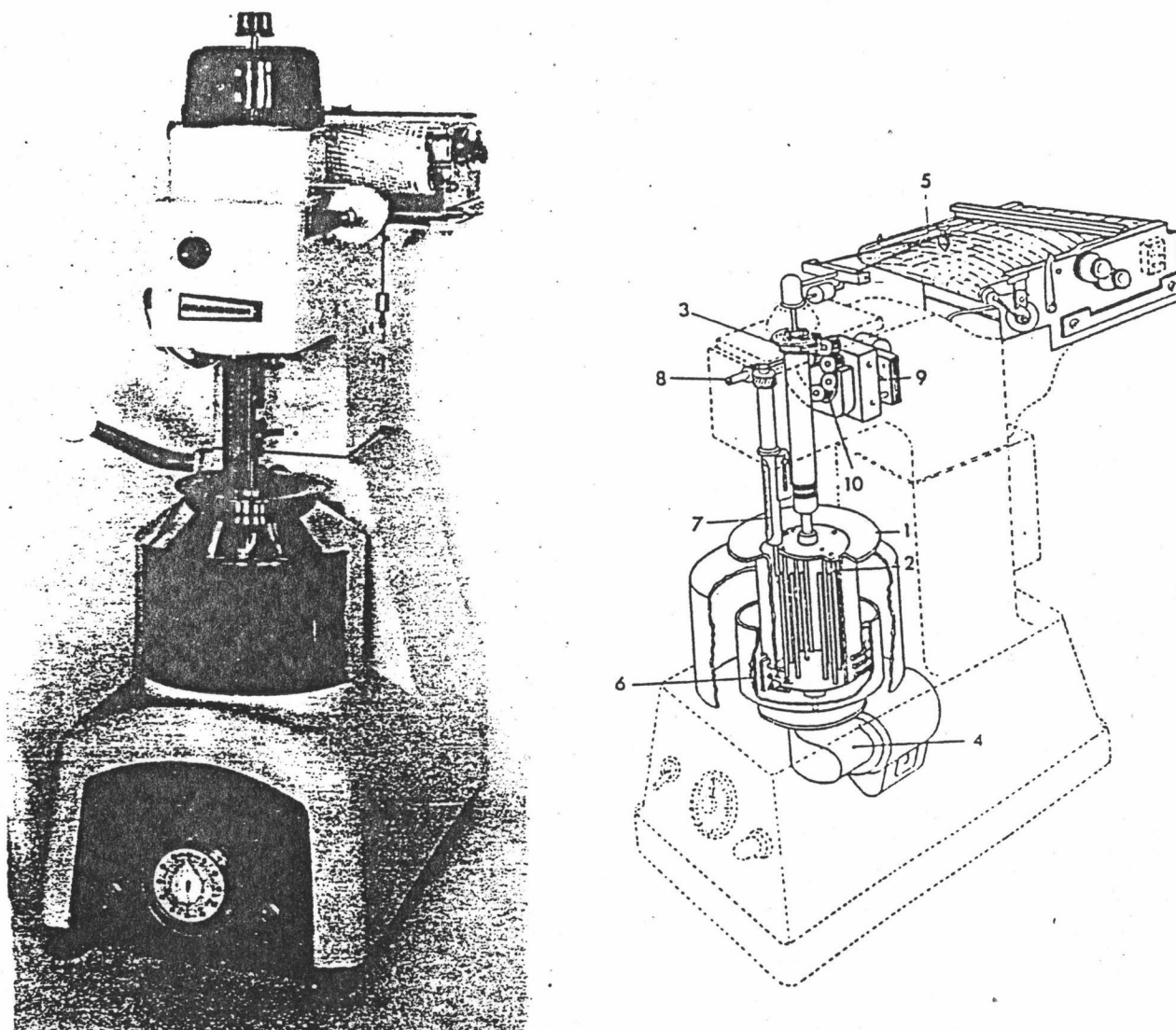
Courtesy of C. W. Brabender Instruments

PICTURE AND SCHEMATIC OF THE AMYLOGRAPH
1—Rotating bowl. 2—Suspended feeler. 3—Balance system. 4—Support. 5—Motor-driven chart paper. 6—Heating elements. 7—Contact thermometer. 8—Temperature adjustment. 9—Synchronous motor. 10—Gear unit.

Figure 13   Brabender viscoamylograph.

barium, potassium, sodium, lithium, benzyltriammonium, tetramethylammonium, etc. The anions are hydroxide, salicylate, thiocyanate, iodide, bromide, etc. These salts are adsorbed by the starch granules and will gelatinize them when exceeding the critical concentrations which are specific for each kind of salt and starch, for example, rice starch can adsorb up to 0.23 to 0.24 milliequivalent of sodium hydroxide per gram.

Degree of Gelatinization

The term gelatinization generally is used to describe the swelling and hydration of starch granules at certain temperature range. The process can also be described as the melting of starch crystallites which can be subjected to thermal analysis. The instruments that automatically take samples through programmed temperature cycles and record heat flow as thermal events occur such as differential thermal analyser (DTA) and differential scanning calorimeter (DSC) can be used to investigate such starch properties. DTA can be used to determine starch gelatinization quantitatively as an enthalpy $(-\triangle H_G)$ of gelatinization.
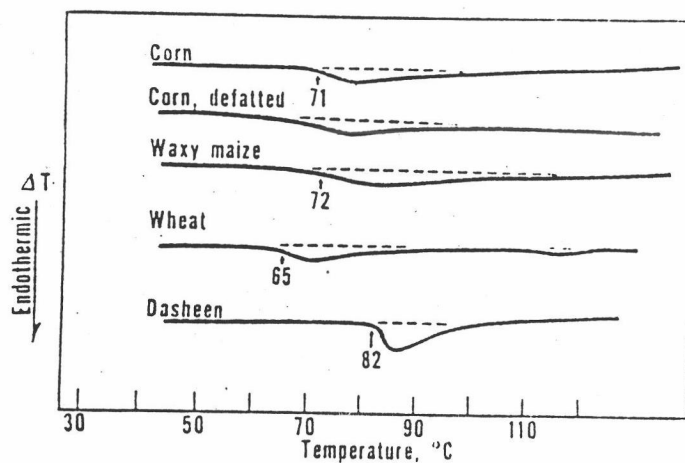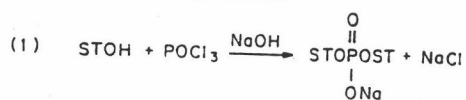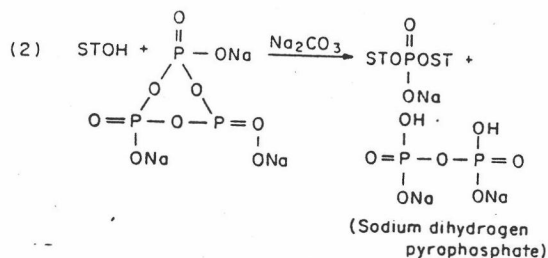
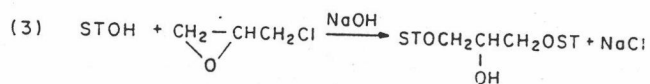Figure 14   Gelatinization   endotherms   of   granular
            starches.
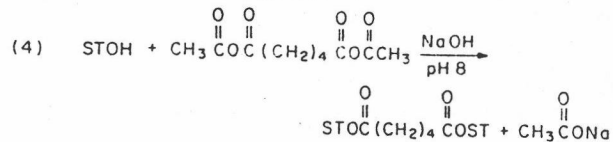
Figure 15   Crosslinking reaction of starch.

In other words, degree of gelatinization can be determined as the change of enthalpy during heating of the samples using DTA or DSC (Zobel, 1984, Herman et al, 1989).

Figure 14 shows typical gelatinization patterns for several cereal starches at a 1:1 starch-water ratio.
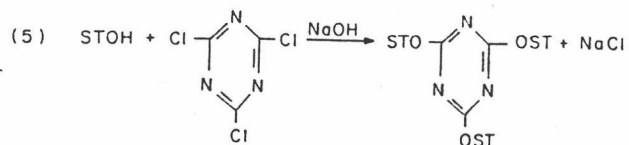
Table 4 shows enthalpy of gelatinization ($-\triangle H_G$) for native granular starches.

Modifications of Starch

Very often, the properties of native starches are not suitable for a particular application or process. Modifications of native starch must be carried out to provide the properties needed for specific uses. The modifications can produce nearly every property required by physical and chemical methods.

Table 5 summarizes various types of modification of starches (Rutenberg, 1980).

For brevity, it will be explained in detail only the modifications that concern with this experiment.

Pregelatinized (Cold-water Swelling) Starch

This is a starch product that is swellable (soluble, dispersible) in cold water without cooking.

Table 5   Modification of Starch (Rutenberg, 1980)

Type	Objectives	Treatment
1. Hybrid	Stability of sols (amylopectin) High gel strength (amylose) High film strength (amylose)	Plant breeding
2. Amylose Amylopectin	Same as 1.	Fractionation
3. Acid fluidity	Lower viscosity High gel tendency	Acid hydrolysis
4. Oxidized	Lower viscosity with improved sol stability	Oxidation (hypochlorite)
5. Dextrins	Lower viscosity Range of sol stability Range of solubility in cold water	Heat treatment, dry (may be in presence of acid)
6. Inhibited	Modify cooking characteristics	Crosslinking
7. Stabilized	Improve sol stability (resistance to gelling) Lower gelatinization temperature	Esterification Etherification
8. Functional groups	Change colloidal, hydrophobic, hydrophilic, cationic, anionic character	Esterification Etherification
9. Changed physical character	Improve moisture absorption, molding flow characteristics, cold-water-dispersibility	Redrying to low moisture additives (oil, MgO) drum-drying

Table 6   Chemical Composition of Broken Rice (Hogan, 1967)

Constituent	Range (%)	Average (%)
Ash	0.36–0.61	0.48
Protein (%N × 6.25)	6.0–10.0	8.0
Lipids	0.26–0.95	0.54
Starch	87.2–93.5	90.2 α

α Moisture-free basis.

In fact, the starch is precooked by the manufacturer for the user. The pregelatinized starch has the following properties :

1. cold water solubility

2. slightly lower viscosity (than the starch cooked in the ordinary way)

3. less tendency to gel

The starch can be pregelatinized fully or partially by drum drying, extrusion, jet cooking (by steam under pressure), and spray drying.

Pregelatinized starch used as directly diluent (as well as binder, disintegrant) is Starch 1500^R manufactured by Colorcon, USA (Bolhuis & Lerk, 1973, American Pharmaceutical Association, 1986).

Crosslinked (Crossbonded, Inhibited) Starch

The crosslinking reaction can change the gelatinization and swelling properties of starch granules considerably. If carried to the extreme, it can even inhibit gelatinization completely, hence the name inhibited starch. The crosslinking reaction makes bridges between adjacent molecules by replacing hydrogen bonds with covalent bonds which are much stronger. This causes the toughening of the granules

to resist hydration and swelling during cooking.

The crosslinking reaction can be done with several crosslinking agents. The reagents must have, at least, two functional groups which can react to two or more hydroxyl groups of starch molecules. The list includes phosphorus oxychloride, sodium trimeta phosphate, epichlorohydrin, adipic-acetic anhydride, cyanuric chloride, etc. (Figure 15).

The crosslinking agent used in this experiment is sodium trimetaphosphate. It is selected based on its low price, safety, and water solubility. It has been approved for use in food starches in USA and Germany (Federal Register, 1964 , Graefe, 1964) since 1964. The method of crosslinking starch in this experiment is based on the US. Patent No. 2,938,901 (Kerr & Cleveland, 1960). The principle of this method is as follows.

A slurry of ungelatinized starch in water containing the requisite amount of sodium trimeta phosphate and having a suitable pH is heated with agitation at an appropriate temperature which is low enough to maintain the starch in the unswollen states. After the reaction proceeds to the desired degree, the crosslinked starch is filtered, neutralized,

washed with water to remove the unreacted salt and the by-product formed and the product dried.

Degree of Crosslinking

Degree of crosslinking is measured by the amount of anhydroglucose units substituted by the crosslinking agent which is proportional to the reaction time. Therefore, this experiment varied degree of crosslinking by changing the reaction time. However, it is difficult to determine directly the degree of crosslinking because the amount of crosslinking agent introduced are very low compared to the weight of starch and the total number of AGU in the granules. Accordingly, the degree of crosslinking must be determined indirectly by the measurement of physical properties of the crosslinked starch such as swelling power, viscosity during the production (Rutenberg & Solarek, 1984).

Swelling power is calculated as the weight of sedimented swollen granules per gram of dry starch at the pasting temperature.

Viscosity is usually determined by Brabender viscoamylograph which records viscosity change continuously from room temperature to the pasting

temperature and after cooled down.

Figure 16 shows the effects of various degrees of crosslinking on the viscosity of corn starch.

After preliminary investigation on modification of various varieties of starch, it was found that rice starch provided the most promising outcomes to be modified as direct compression vehicle and it is the main starch material employed in this study. As information, rice starch and its properties is delineated.

Rice Starch

Rice starch consists of very small polygonal granules with diameters ranging from 3 to 8 microns. This is the smallest granule size of the common starches. The rice grain is made up of the hull, (husk), the seed coat (pericarp), the embryo (germ) and the starchy endosperm (Figure 17). The seed coat consists of six layers of different types of cells, the last being the aleurone layer, which is rich in proteins, lipids, and B complex vitamins. Protein and mineral salts are present in the aleurone cells and also in the outer starch-containing cells (Schoch 1967).

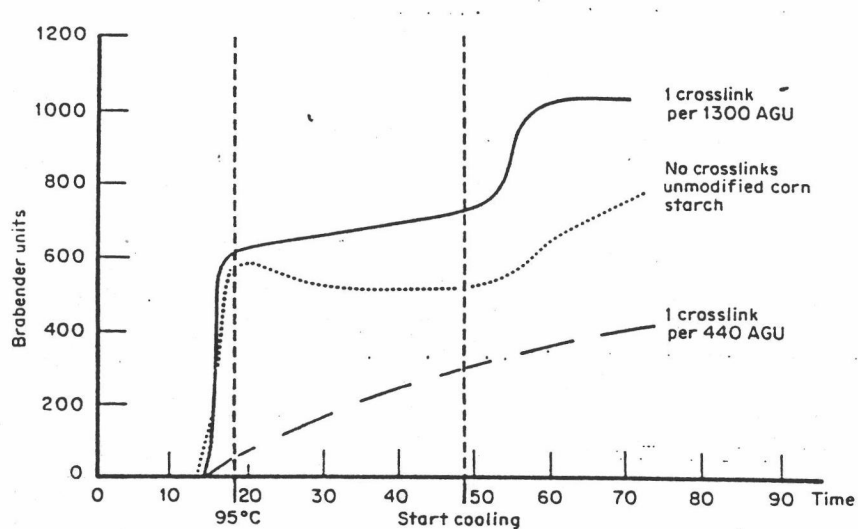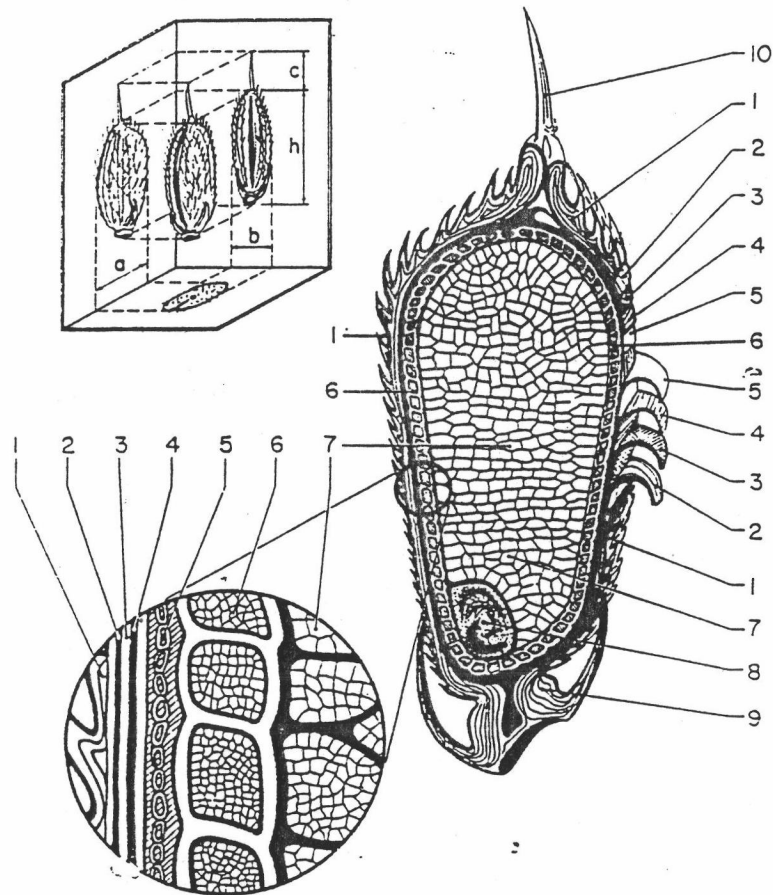Rice flour, a by-product from rice milling, is

Figure 16   The   effect   of   crosslinking   on   the gelatinization and viscosity of corn starch.

.—Structure of the rice grain (?): 1, hull (glume and palea); 2, epicarp; 3, mesocarp; 4, gross layer; 5, testa; 6, aleurone layer; 7, starchy endosperm; 8, embryo; 9, non-flowering glumes; 10, apex or beard; a, breadth; b, thickness; h, length; c, length of the beard.

Figure 17   Structure of the rice grain (Schoch, 1967)

ground broken milled rice. Chemical composition of rice flour (broken rice) is shown in the Table 6.

Rice granules are bound by protein in close association with the starch. The glutelin or alkali-soluble fraction forms the major component in the composition of rice protein.

In the manufacturing process of rice starch, it is necessary to separate this protein fraction from the starch. There are several processes to do this, but all of them employ the properties of alkali solubility of the protein.

Every separation method uses sodium hydroxide solution to dissolve the protein which is then separated from the starch by sedimentation or centrifugation (Hogan, 1967).

Rice Starch Aggregates and Spray-drying

Rice starch granules have the smallest average sizes of the common starches as well as irregular polygonal shapes. Therefore the flowability of rice starch is not sufficient for use in tablet compression. Rice starch granulations must be prepared in order to improve the flowability by enlarging the particle sizes. The granulations have the better

flowability and compressibility that are sufficient for tabletting. (Bos et al., 1987)

However, the granulation method is not the best way to produce a direct compressible diluent for various reasons. Normally, the granulation sizes are much larger than the particle size of drugs to be mixed which can cause segregation or demixing. If the granulation sizes are reduced, their flow-ability are reduced too which can make a flow problem.

Spray-drying method can solve the above problem completely. Its advantages over the other methods are as follows. It can increase the rice starch particle sizes by transforming the granules into aggregates. The aggregates produced are more spherical and uniform which give excellent flowability. Moreover, the aggregates' sizes can be adjusted to be close to the drugs, particle size, so segregation will not be likely to occur. Finally, the degree of gelatinization can be varied to obtain the highest compress ibility and disintegration by adjusting the atomizing variables.

Figure 18 shows the diagram of spray-dryer used in this experiment.

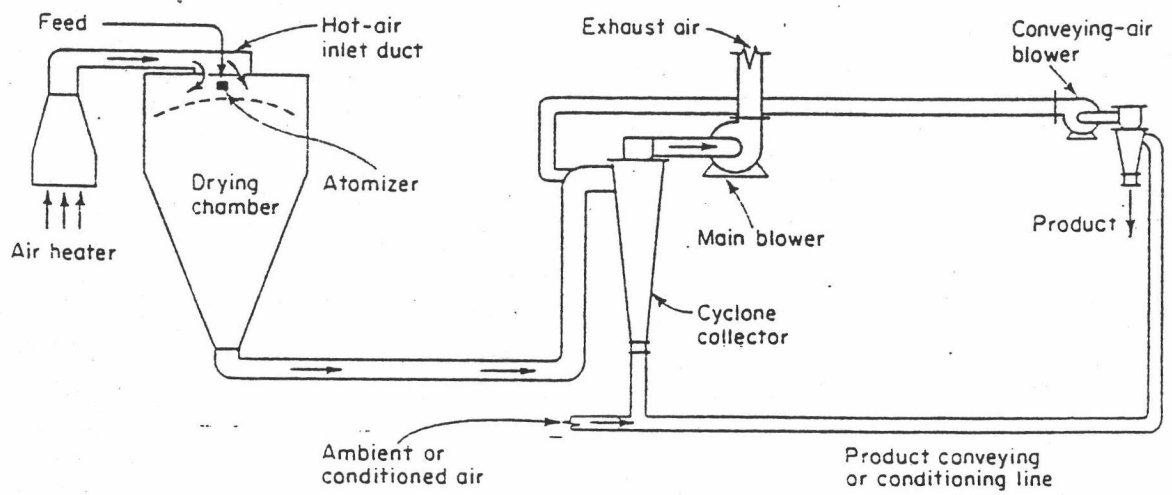The spray-dryer used was co-current centrifugal

Figure 18   Diagram of Spray Dryer.

disk type which was suitable for starch slurry.

The average drop size is calculated from the relation of Friedman, Glukert, and Marshall (Perry & Chilton, 1973).

$$D_{vs} = 0.4\, r\, (\Gamma/\rho N r^2)^{0.6}\, (\mu/\Gamma)^{0.2}\, (\alpha \rho L_w/\Gamma^2)^{0.1}$$

D_{vs} = Average Drop Diameter, ft.

r = Disk Radius, ft.

Γ = Spray Mass Velocity, lb./(min.)(ft. of L_w)

ρ = Liquid Density, lb./cu.ft.

N = Disk Speed, r.p.m.

μ = Liquid Viscosity, lb./(min.)^2

α = Surface Tension, lb./min.^{2}

L_w = Wetted Disk Periphery, ft.

This equation shows the correlation of all atomizing variables. In order to increase the particle size of a spray-dried product from a certain spray dryer , solid content , viscosity, density, feed rate must be increased, while disk speed decreased. The solid content, viscosity, density are related to concentration of starch dispersion. Disk speed is related to atomizing pressure.

Moreover, the rate of heat transfer must be considered to obtain a completely dry product. The rate of heat transfer is related to inlet temperature.