

## CHAPTER II

### LITERATURE REVIEW

#### Filler/Binder

A tablet formulation contains a number of excipients in addition to the active ingredients. The major types of excipients used are fillers or diluents, binder, disintegrants and lubricants, which are present in nearly all tablet formulations.

#### Fillers

Fillers or diluents are used to increase the bulk of the tablets so as to enable a formulation to become suitable for compression. In addition to leading bulk to the formulation, fillers are selected to improve the binding properties of the formulation. It is essential that fillers be inert and stable. Although diluents are normally thought of as inert ingredients, they can significantly affect the biopharmaceutical, chemical, and physical properties of the final tablets (Bandelin , 1989 ).

Usually tablets are designed, so that the smallest tablet size which can be conveniently compressed is formed. Thus, where small dosage level drugs are involved, a high level of diluent of filler is necessary. If, however, the dosage level is large, little or no diluent will be required, and the other excipients may need to be kept to a minimum to avoid producing a tablet that is larger than is acceptable. In such large situations, nevertheless, excipient materials must often be added to produce a

granulation mixture, which may be compressed into acceptable tablets (Banker and Peck, 1980).

Tablet fillers or diluents comprise a various groups of substances. Table 1 shows the list of the more commonly used fillers in wet granulation.

**Table 1** Tablet Fillers

<b>Insoluble fillers</b>	<b>Soluble fillers</b>
Calcium sulfate, dihydrate	Lactose
Calcium phosphate, dibasic	Sucrose
Calcium phosphate, tribasic	Dextrose
Calcium carbonate	Mannitol
Starches	Sorbitol
Modified starches	
Microcrystalline cellulose	

Starch is naturally occurring filler, which is bleached white and can be obtained in varying degree of whiteness. The material most frequently used is corn starch. It is a multiple-purpose product which can also be used as a disintegrating agent and as a binder in the form of starch paste. It has the disadvantage to having compressibility too poor to make tablets of sufficient hardness. It also tends to expand after compression. Therefore, it is not used to great extent as a filler in compressed tablets (Sheth et. al., 1980).

## **Binder**

Binders are substances, which are included into solid dosage formulations as technical additives to improve the compactibility and flowability of powders or granules. This is achieved during the granulation and compaction stages of tablet manufacturing processes.

Binders are sometimes referred to as granulating agents which are solvents used in the process of wet granulation to aid in nucleation and coalescence of particulate into granules. These added components are intended to function in the particulate binding giving the granule strength, and during compaction by aiding in deformation and providing sites where bonding can occur under pressure.

Binders are either sugars or polymeric materials. The later fall into two classes (Bandelin, 1989 ):

- a). Natural polymer i.e. starches, gums, acacia, tragacanth and gelatin
- b). Synthetic polymer i.e. polyvinylpyrrolidone, methylcellulose, ethylcellulose and hydroxypropylcellulose.

Binder of both types may be added to the powder mix and the mixture wetted with water, alcohol-water mixtures, or a solvent, or the binder may be put into solution in the water or solvent and added to the powder.

Starch is a multipurpose excipient used in tablet formulation which can be formulated as a filler, a binder or as a binder. Native starch, however has its limitations in application. As a binder in a conventional wet granulation process, it must be converted into a paste. It does not show good compressibility nor flowability. Therefore, some accepted modified starches with improved properties have been evaluated as tablet excipients, i.e. thermal modified and chemical modified starches (Visavarungroj and Remon, 1990, 1991).

**Table 2** Starch Byproducts used as binders in tablet manufacture ( Symecko and Rhodes, 1995)

Binder	Regulatory acceptance	Usual Concentration (%w/w)
Liquid glucose	NF XVI	5-10
Dextrin	NF XXI BP 1980	1-10
Pregelatinized starch	NF XVI BP 1980	5-10

Symecko and Rhodes (1997) indicated that the pregelatinized starch has the ability to form gels in a cold aqueous environment, a characteristic which promotes its usefulness as a binder in the process of wet granulation. By choosing to include a pregelatinized starch, a formulator may decrease production time by eliminating the heating of native starch prior to granulation.

Pregelatinized starches commonly function in solid dosage formulations as binders and fillers. Due to their adhesive properties pregelatinized starches are commonly included in wet-granulated systems as binders. Their function is to aid in

interparticulate bond formation during granulation and compaction. The end product formed, tablets, exhibit the benefit of superior mechanical performance.

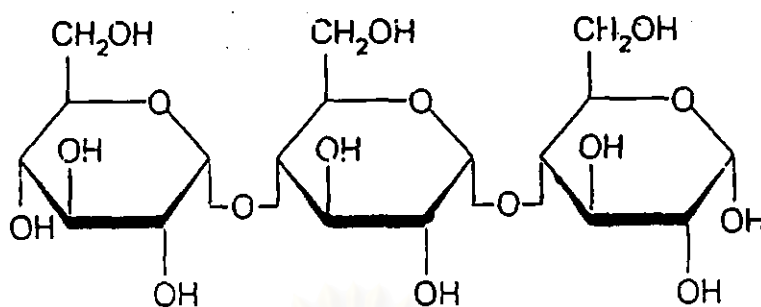
### **Starch Technology**

Starch is a polymeric carbohydrate composed of anhydroglucose units. It is extracted in granular form from plant tissues. Starch granules are deposited in the seeds of cereal grains (maize, wheat, sorghum, rice, glutinous rice), tubers (potato), roots (tapioca, sweet potato, arrowroot) and the pith of the sago palm, as a reserve food supply for period of dormancy, germination and growth. The microscope reveals that starch is composed with tiny, white granules, ranging in size from about 1 to 100 microns (micrometer) in diameter. Sized shapes of the granules are related to the botanical source of the starch. After cellulose, starch is the next most abundant compound synthesized by plant cells (Chaeley, 1982; Newman et al., 1996; Oates, 1998).

### **Starch Structure**

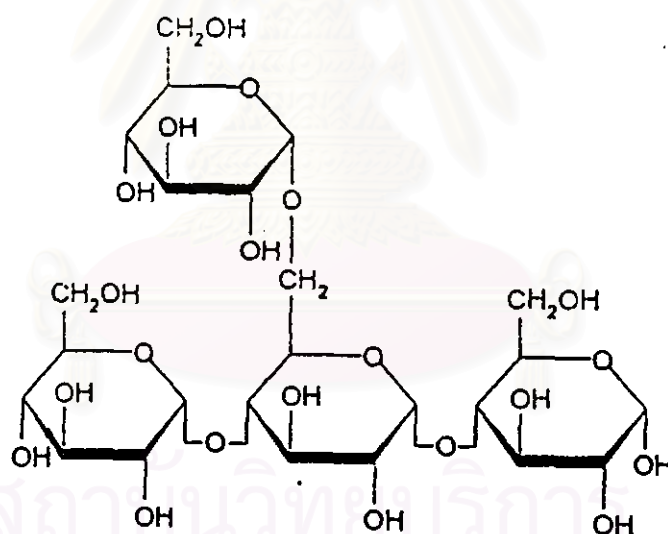
Starch is composed of glucose but not a uniform material. Most starches contain two types of glucose polymers (Chalmer, 1968):

- Linear chain molecule termed amylose. Each hexagonal group represents a dextrose unit.



**Figure 1** Linear chain structure of the amylose molecule.

– branched polymer of glucose termed amylopectin



**Figure 2** Branched chain structure of the amylopectin molecule.

The two fractions occur in differing amounts in starches from various botanical sources. Amylose comprises 15-30 % of the common starches.

Starch is a carbohydrate, composed of carbon, hydrogen and oxygen atoms in the ratio 6 : 10 : 5 (C: H: O)<sub>n</sub> glucose, consisting of anhydroglucose units. Glucose units are linked to one another with glucoside bond. Most starches are a mixture of amylose and amylopectin, each having a wide range of molecular sizes. Starches of different origin have different amylose to amylopectin ratios.

### **Amylose**

Amylose is essentially a linear polymer containing up to 6000 glucose units connected by 1,4 linkage-typical sizes range from 500-5000 units. The extent of branching varies from 9-20 per molecule and 4 to >100 units long. Maize, wheat and sorghum starches have a high amylose content (about 28%). Tuber and root starches contain only about 20% amylose. The waxy starches contain no amylose fraction. Amylomaize starch may contain up to 80% amylose.

### **Amylopectin**

Amylopectin has a highly branched structure, consisting of short linear chains with a DP ranging from 10 to 60 glucose units. They are connected to each other by alpha-1,6-linkage. The glucose units with an alpha-1,6-linkage are the branching points of the amylopectin. A unit of amylopectin cluster can thus be regarded as composed of an amorphous portion containing most of the tightly spaced branches (amorphous lamella) and a thin crystalline region.

## **Starch Properties**

The amount and distribution of water within starch granules is almost importance to the physical and chemical properties.

Native starches are insoluble in water below their gelatinization temperature. They can be chemically modified in suspension in water and recovered in purified form by filtration, washing with water and drying

### **Gelatinization and Swelling**

(Leach, 1965)

Heating starch granules causes the crystallites in the granule to disappear with loss of birefringence and x-ray diffraction, the temperature at which this occurs will depend on the extent of hydration.

Gelatinization of starch may be broadly defined as the reversible loss of the crystallites in the granules, so that all molecules in the granule are accessible to water and will swell irreversibly. The sequence of events have been summarized:

- a) Swelling begins in the least organized, amorphous, intercrystallite regions of the granule.
- b) As this phase swells, it exerts a tension on the neighboring crystallites and tends to distort them.
- c) Further heating leads to uncoiling or dissociation of double helical regions and break-up of crystallite structure. The liberated side chains of



amylopectin become hydrated and swell latterly, thereby exerting increased stress on the remaining crystallites so that their melting is facilitated.

Smaller, linear amylose molecules diffuse out of the swollen granule.

- d) Further heating and hydration weaken the granule and a sol results

### **Modified Starches**

Modified starches were developed to overcome and expand the usefulness for a myriad of industrial applications. These modifications are commonly called conversions and involve treatment of granule starch by chemical and/or physical means to cause rupturing of some or all of the starch molecules, thus weakening the granules, decreasing their capacity to swell on pasting or cooking in water, and decreasing the size of molecules. As a result, the viscosity of the product from the starch on heating in water is reduced, thus permitting the converted starch to be dispersed at higher concentration than unmodified starch (Wurzburg, 1987).

Amylose and amylopectin can be modified by chemical reaction, by enzyme-catalyzed reactions, and genetically, i.e., through kernel selection, plant breeding, mutant production and genetic engineering.

Starch granules can be modified by physical means although all chemical modifications of starch take place in the granular form.

**Principal reasons for starch modification. (Bemiller, 1997)**

- To modify cooking characteristics.

- To decrease retrogradation.
- To decrease gelling tendencies of pastes.
- To increase freeze-thaw stability of pastes.
- To decrease paste and/or gel syneresis.
- To improve paste and/or gel clarity and sheen.
- To improve and/or gel texture.
- To improve film formation.
- To improve adhesion.
- To add hydrophobic groups (for emulsion stabilization)

### **Practiced starch modification**

#### **I. Chemical modification**

##### **□ Derivatization**

- Monostarch substitution (etherification and esterification; includes polymer grafting).
- Crosslinking (via starch esterification)

- Acid-thinning/ hydrolytic depolymerization (both acid- and enzyme-catalyzed)
- Dextrinization (depolymerization and transglycosylation).
- Oxidation (bleaching and depolymerization).
- Hydrolysis (to maltodextrin, glucose syrups, glucose, etc.)

#### **II. Physical modification**

- Gelatinization (to produce pregelatinized starch).

□ Preparation of cold-water-swelling starch.



### III. Genetic

□ Waxy maize starch

□ High-amylose maize starch.

### Acid conversions or acid-modified starch

(BeMiller, 1965; Shildneck and Smith, 1967; Trubiano and Kasica, 1985)

The use of acid on granular starch probably originated in 1874. It was reported that cold aqueous hydrochloric acid will, over a period of many weeks, dissolve a good portion of the granule contents, leaving a fragmented granular residue composed of short (about 25 DP) linear molecules. In 1886 there was a research about acid modified starch by treating potato starch for several days with mineral acids to produce a highly converted acid-modified starch which is commonly called Lintner starch. It is of no real commercial significance, but still produced in small volume and sold by laboratory supply houses for use as an indicator in iodimetric titrations and in enzymatic analyses (Rohwer and Klem, 1984).

The acid-modified starches produce commercially date back to 1897 to 1901. The conditions used were elevated temperature in the range of 50-60°C (below the gelatinization temperature of starch), dilute acid (0.5 to 30% mineral acid), and short reaction times (0.5 to 14 hours).

Acid-modified starches are normally made by taking a concentrated starch slurry (about 36 to 40% solids) heated to a temperature below the gelatinization temperature of the starch (usually about 40 to 60 °C), adding mineral acid, and agitating for a period ranging from an hour or so up to several hours. When the desired viscosity or degree of conversion is reached, the acid is neutralized and the starch granules are recovered by filtering or centrifuging, washing and drying. The type of mineral acid, i.e. hydrochloric acid, sulfuric acid, etc.; the concentration of the acid; temperature; concentration of starch; and a reaction time will vary depending upon the manufacture and the desired properties.

During the process of acid modification, the acid hydrolyzes the glucosidic linkages shortening the chain length. Given comparable accessibility as in dispersed starch, the  $\alpha$ -D-(1-4) linkages are more prone to hydrolyze than the  $\alpha$ -D-(1-6) linkages. However, this does not appear to carry through in the acid modification of starch in the granule form where the linear portions containing a predominance of  $\alpha$ -D-(1-4) linkages are involved in the formation of crystallites held together by hydrogen bonding, thus decreasing the availability of these segments to acid. The amorphous regions containing branching point with  $\alpha$ -D-(1-6) linkages are more accessible to acid penetration and hydrolysis.

The acid was preferentially attacking the amorphous rather than the crystalline regions. It was also noted that there was a slight increase in the amount of linear material in the granule during the initial stages of acid hydrolysis. Their findings support the research, suggesting that the initial stages of acid conversion, the

amylopectin undergoes preferential hydrolyses followed by a slower attack on both fractions in the more crystalline areas (Karr, Shiromani and Bavitz, 1990).

## **Characteristics and properties of acid modified starch**

### **Intrinsic Viscosity**

As might be anticipated from the effect of acid modification on molecular weight, the intrinsic viscosity of acid-converted starch decrease as the fluidity increase

### **Solubility**

As the fluidity increase during acid conversion, the amount of the starch solubilized in hot water increases; and at high fluidities. The starch at the converting temperatures create handling problems and yield losses when it is recovered from the slurry by filtration or centrifugation and drying. For this reason, the extent of the starch is recovered in granule form is limited, and becomes necessary to resort to other conversion techniques to obtain lower viscosities.

### **Granule behavior**

While the granules of acid-modified starch resemble those of unmodified starch when examined microscopically at room temperature, they behave quite differently when heated in water. They do not swell to many times their original size like unmodified starches, but develop radial fissure and fragment as they are heated. The extent to which this occurs increases as the fluidity of the starch rises. It has also been

noted that the gelatinization temperature for the granule is about 7°C higher than that of unmodified corn starch.

### **Behavior of Cooked Starch-Hot and Cold**

Since acid-modified starches are much lower in viscosity than unmodified starch, they may be cooked at much higher concentrations.

The rheological properties of the hot pastes of acid-modified corn starches are also quite different than those of unmodified corn starch. In the latter, the swollen granules have a prominent role in imparting thixotropic characteristics, whereas in acid-modified starches the granules have been damaged to the point where they disintegrate or fragment rather than swell. As a result, the hot pastes of acid-converted starches are relatively clear fluids; however, on cooling, acid fluidities made from starches will retrograde, losing their clarity and forming opaque rigid gels. Acid-converted waxy corn starches have properties quite different from acid-converted starches, since waxy corn starch is essentially all amylopectin, their fluidities give clear fluid hot paste, but, unlike their corn counterparts, they do not retrograde readily and remain much clearer and do not form gels on cooling.

The conclusions explain some of the observed properties of acid-modified starch. When starch in water slurry is treated with acid below the gelatinization temperature, the product can be expected to have the same granular appearance, similar birefringence, and essentially the same insolubility in cold water as the parent starch. Using the same comparison, an acid treated starch can be expected to exhibit

the lower hot-pasted viscosity, higher ratio of cold to hot paste viscosity, higher alkali number, higher critical absorption of sodium hydroxide, lower intrinsic viscosity, lower iodine affinity, higher osmotic pressure, increase solubility in water at temperature just below the gelatinization temperature, higher gelatinized temperature, less granular swelling during gelatinization., higher content of pentasol-precipitate fraction in the lower modification level but not at high levels of modification, and slower rate of solution in cold anhydrous dimethyl sulfoxide.

### **Industrial Production**

The commercial manufacture of acid-modified starches is usually done by treating approximately 40% starch in a slurry of dilute hydrochloric or sulfuric acid at 25°C-55°C for the length of time required to obtain the thinned starch that is sought. Corn and waxy maize starch are the principal commercial parent starches. Small amounts of tapioca, wheat, and potato starch are also manufactured.

The conditions for treatment are varied, depending upon the ratio of cold- to hot-paste viscosity and gel characteristics that sought. If two samples of the same starch are treated with different amounts of acid to the same fluidity, the starch treated with the higher concentration of acid will exhibit the greater gel strength.

### **Process Control**

To modify a starch consistently, it is necessary to use the same starch concentration, the same acid, the same acid concentration, the same temperature conditions. However, even with careful control, the reaction time to produce the same modified starch varies. Viscosity is the primary control to obtain the desired starch

undergoes reaction. The reaction is stopped by neutralizing approximately pH 6 with soda ash (sodium carbonate) or a dilute caustic (sodium hydroxide) solution. The starch may then be filtered and dried.

#### **Acid Modification Combined with Other Starch Modifications.**

Acid modification may be used as premodification step in some cases or a postmodification step in others. In both cases, the acid treatment is used to make available the modified starch with a range of fluidities. In other reactions the medium is acidic owing to the reagent or conditions used, and the starch is simultaneously acid-thinned while undergoing other reactions.

It has been shown in unpublished work that high-fluidity starch ethers that appear to be the same can be manufactured either by acid modifying the parent corn starch before etherification or after the parent starch has been etherified. Acid-modified starches can be used as the parent starch for the production of cationic and cross-linked starch.

#### **Pregelatinized starch**

(Powell, 1967; Bowen and Vadino, 1984; Jeffcoat et al., 1998; Shah et al., 1998)

Starch NF and pregelatinized starch NF are common excipients in solid dosage forms and may be incorporated both as binders and as disintegrants. The binding efficiency of these materials has been studied extensively. It was found that, in general, formulations containing pregelatinized starch exhibited better processing



characteristics and produced superior tablet properties (Karr, Shiromani and Bavitz, 1990).

According to NF XVIII, pregelatinized starch is starch that has been chemically and/or mechanically processed to rupture all or part of the granules in the presence of water and subsequently dried. Some types of pregelatinized starch may be modified to render them compressible and flowable in character.

Pregelatinized starch may be used as a filler, binder and disintegrant. Its binding properties are slight greater than starch when it is used in place of starch as starch paste. Pregelatinized starch may also be used as the binder by adding in dry form to the powder mix and activating with water to granule. Several pregelatinized starches available are intended to be added in the dry form when they are called for tablet binder. Normally concentration used of pregelatinized starch, when added to the powder, is 5-10%.

Sufficient starch was required to form solid bridges on drying but adequate wetting occurred to give satisfactory damp granules.

Pregelatinized starches commonly function in solid dosage formulations as binders and fillers. Due to their adhesive properties pregelatinized straches are commomly included in wet-granulated systems as binders. Their function is to aid in interparticulate bond formation during granulation and compaction. The end product formed, tablets, exhibit the benefit of superior mechanical performance i.e., increased tablet hardness and tensile strength, and a decrease friability.

The current NF monograph for pregelatinized starches is completed as to the purity of the compound but is incomplete as to its functionality. This is exemplified by the inclusion of both partially and fully pregelatinized starches under one monograph.

Partially pregelatinized starch as an excipient for solid dosage forms is still widely used. To exemplify commercially available products, PCA (Asahi Chemicals) is a physically denatured corn starch, an excipients of natural origin, and is used in tablet production as an additive such s a binder, disintegrant, or absorbant. Starch 1500 (Nippon Colorcon) is also an excipient meeting the requirement under partially pregelatinized starch in Japanese Pharmaceutical Excipients. Since pregelatinized starch acts not only as a binder but also as disintegrant, it is incidentally called an all purpose excipient. However, it is known that this substance frequently causes variation in tablets properties depending on the method and conditions of granulation. National1551, Lycatab PGS and Pregefio M are fully pregelatinized corn starches while Era-Gel is a fully pregelatinized starch.

Pregelatinized starch was introduced as cold water swelling starch. Also, commercially important uses of pregelatinized starches at that time were described as dextrin (adhesives), paper making, bakery products, oil well drilling muds, and foundry core binders. The great increase in easily food "instant" foods and beverages in great variety has materially expanded the market for pregelatinized starches.

Pregelatinized starches are also applied for pharmaceutical use such as in compressed tablet by wet granulation. Pregelatinized starches is used as a binder,

filler, and disintegrant in tablet formulation. Because of its properties which soluble in cold water; it also can be used in place of starch paste without heating.

### **Production Methods**

The pregelatinization processing will be directed to those products that are gelatinized at higher temperature (more than gelatinization temperature) with excess water present and then dried.

Powell (1967 ) described various methods producing pregelatinization starch such as:

1. By drum dryer or "hot-roll" which is the most commonly used equipment for production of pregelatinized starches.
2. By Spray dryers, which have been used commercially, but they are generally uneconomical because the high viscosity of starch paste requires drying at low starch solids.
3. By foam mat drying process that is worthy of consideration since it converts the paste to thin films which are friable when dry.
4. By Puffing, which has long been known as another means for preparing pregelatinized starches. A recent improvement in the technique of puffing that show promise of practicality is continuous cooking-extrusion puffing. Advantages claimed are high throughput, lower steam and power costs, and lower mechanical

maintenance expense as compare to drum dryers. However, the mechanical shear factor in this machine can be quite high.

5. By fluidized bed, operated either continuously or discontinuously, in which the starch product is both cooked and dried.

### **Drum dryer**

(Rittenhouse, 1998)

The process is simple and straight forward in theory, but becomes unpredictable and elusive to control in actual practice. Minor drifts in operating conditions seem to produce magnified changes in the finished product. Operating and maintenance costs are generally considered high in relation to output of finished product. Illustrations of some of the possible arrangements of the basic unit are depicted in **Figure 3** It is impossible to select any one of these as the optimum arrangement for the production of pregelatinized starches. The arrangement depends on the nature of feed steam and the desired end product.

The double drum dryer, with feed into the center valley, is the most versatile and commonly used unit. It can handle a greater variety of feed materials and can be operated to give less mechanical shear to the paste than do applicator roll arrangements. It has the disadvantage of low rpm. which limits output per roll, and some inherent mechanical problems demand constant attention.

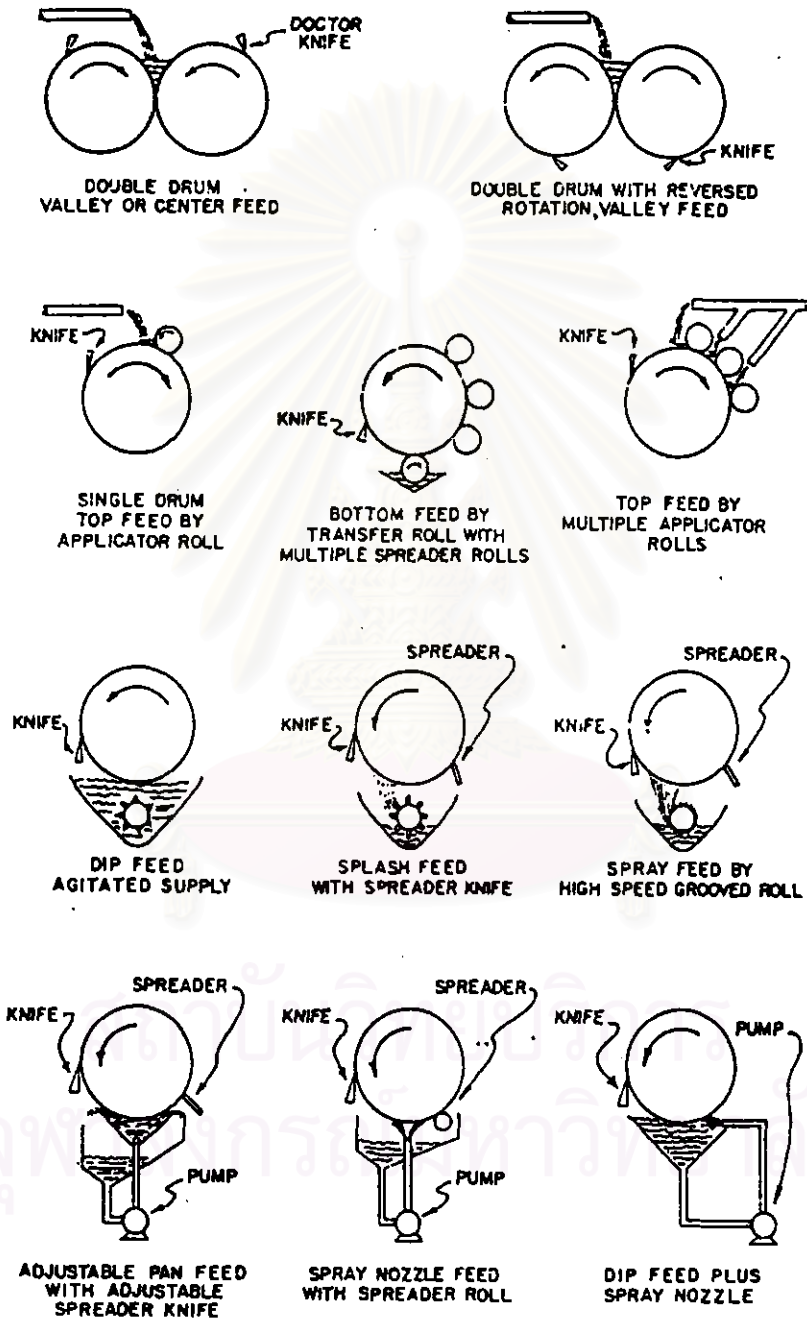


Figure 3 Drum dryer arrangements (Powell, 1967)

**The condition considered about drum dryer:**

(Powell, 1967 ; Shinn and Levingston, 1988; Shinn and Andrew, 1989)

The feed to the drum dryer may be a moist starch cake from a filter or centrifuge, a slurry of raw starch, or a thoroughly cooked starch paste from a jet cooker or scraped wall heat exchanger. Solids content may be as high as 44% in raw slurry or 42% in the cooked paste.

The supply starch can be chemical modified, enzyme converted, or dextrinized ahead of the drum drying process in accordance with the intended end use.

The depth of the starch paste pool in the valley is another variable that must be controlled to obtain a uniform product.

The cooking pastes, such as enzyme-converted starches, dextrans, and shear sensitive waxy maizes, are perhaps best handled on the double drum with valley feed.

Control of the gap at the nip of the two rolls is one of the more critical factors in drum dryer operation. Too thin a wet film results in the lost production and a low bulk density in the dried product. If the film is too thick, or too thick in spots, wet material clogs the knife. If the large rolls are ground and aligned cold, they tend to bulge or warp under high steam pressure and heat from differential heating or cooling at the ends so that clearance is no longer uniform along the length of the nip.

In large drums, the wall must be thick to contain the high-pressure steam safely so they may flex under their own weight. Various designs for internal bracing and

plate construction have been proposed to attain mechanically stable rolls. Equipment has been designed to grind the rolls in place under full steam load, but it is difficult to measure the gap with the both rolls hot and spinning. One method is to drop a soft metal such as electrical fuse wire between the rolls and then measure the degree of flattening with a caliper. Or, it may be possible simply to estimate or measure dry film thickness along the length of the knife. However the variation of  $\pm 0.003$  inch in gap width is enough to give less than optimum performance.

Conditioning of the roll surface is another problem that requires attention. Too high a polish, or a non-corrosive metal plating on the surface, may make it difficult to pick up the proper thickness of wet starch. It may also cause the partially dried film to fall from the roll ahead of the knife. Too tight a bond between the dried film and the roll makes it impossible for the doctor knife to remove the film properly. Hence, release agents are frequently applied to the roll surface or mixed with the applied starch slurry.

Sharp, well-adjusted doctor knives add to the mechanical maintenance expense of drum dryers. Knife adjustment that will provide proper product removal without excessive water presents problems similar to those of roll gap adjustment. Knives may be mechanically oscillated, adjusted hydraulically, or alternately raised and lowered to permit several layers of dried product to build up before the thickened sheet is removed. Multiple doctor knives with intricate adjusting devices have also been tried.

Mechanical or air-steam pick-up system, or some combination of these may be used to remove product from the roll. Milling and sorting of the product by screens or

air classifiers normally are necessary since particle size and particle size distribution are major factors in the over-all performance of the products.

**In pharmaceutical uses:**

Since pregelatinized starch acts not only as a filler but also as a binder and a disintegrant, it is incidentally called all-purpose excipient. However, it is known that this substance frequently causes variations in tablet properties, depending on method and tablet conditions of granulation.

There were many studies about pregelatinized starch in pharmaceutical used.

Margid and Clifton (1969) described that any modified starch, dextrin or pregelatinized starch which is at least partially soluble can be employing in preparing the composition of the formulation of compressed tablets of ascorbic acid caused of their convenience of expression as binders are commercially available from a variety of sources and under various trade names.

Herman, Remon and Vilder (1989) used three native starches varying their amylose/amylopectin content for pregelatinization by extrusion, drum drying and a controlled preegelatinization by spray-drying technique in order to produce cold water-swellable starches. They found that the partial pregelatinized starch could only be produced by the controlled pregelatinization technique.

In the same year, Visavarungrij, Herman and Remon (1989) studied different types of crosslinked waxy-corn starches and pregelatinized-crosslinked waxy-corn



starches used as binding agent in a conventional wet granulation process. The pregelatinized starch used in the paste form gave coarser granules with a greater average size in comparison to other starch modifications. Nevertheless, starches that were only pregelatinized or pregelatinized and crosslinked yielded granules having similar friability by using either a dry starch or starch paste. The pregelatinized starch and pregelatinized-crosslinked starches showed potential use as binding agent in the wet granulation process.

Karr, Shiromani and Bavitz (1990) described that the pregelatinized starch allowed faster release of a poorly water-soluble drug than did those containing starch N.F.

The pregelatinized starches were evaluated as disintegrating agents in comparison to potato starch and a number of super-disintegrants such as Ac-Di-Sol, Exprotab and Polyplasdone XL. It was found that tablets formulated with pregelatinized starches, with or without crosslinking showed variable and long disintegration times in comparison to the superintegrants. The disintegration time of tablets, using pregelatinized-crosslinked starches, was influence by the type of filler and the lubricant (Visvarungroj and Remon, 1990a).

Visavarungroj and Remon (1990b) furthered their study in the same year and found that the modified starches produced higher quality granules in comparison to those prepared with the native corn or waxy corn starches. There was no difference in binding properties between pregelatinized waxy-corn starch and pregelatinized phosphate-crosslinked starch.

The same authors also reported in 1991 that the use of pure hydroxypropyl starch showed no advantage as binder or disintegrant over the actually available tablet ingredients. Pregelatinized hydroxypropyl starch showed some good disintegrating properties and could be used as a binder in wet granulation.

There was a study by Sheskey and Dasbach (1995) about the effectiveness of polymers used as dry binders during the manufacture of an immediate-released tablet formulation using dry-granulation process. It was found that binder level did not affect drug release from tablet containing pregelatinized corn starch.

It was reported by Makino, Yamanaka and Kitamori (1995) who used pregelatinized starches as binders, fluidized-bed granulation and agitation were attempted to investigate the behavior of starch and to examine its relationship with the resultant of tablet properties. They found that in fluidized-bed granulation, the soluble starch content did not change noticeably during granulation, thus exerting no influence on tablet properties.

Two years after that, Symecko and Rhodes (1997) studied the influence of four commercial pregelatinized starches, National 1551, Lycatab PGS, Pregeflo M and Starch 1500 as binder, on the dissolution of acetaminophen. The study was shown that National 1551, Lycatab PGS and starch 1500 were not affected by compaction force in term of dissolution performance. Difference was observed between the fully pregelatinized systems of National 1551 and Lycatab PGS, in comparison to the partially pregelatinized systems, Starch 1500. The Pregeflo M starch produced a system with delayed drug dissolution and was influence by compaction force.

## **Starch Analytical**

### **Differential scanning calorimetry (DSC) method**

(Lund, 1983 ; Gomaz and Aguilera, 1984)

The term "Differential scanning calorimetry" was initially a source of some confusion in thermal analysis. The purpose is to record the difference between an enthalpy change, which occurs in a sample and that in some inert reference material when both are heated.

Most of the DSC units currently in use have sample pans, which generally hold 10 to 20  $\mu\text{l}$  of sample. For optimum peak sharpness and resolution, the contact surface between pan and sample should be maximized, which is usually accomplished by having the sample as thin discs, or films, or fine granules. Frequently, in applications in foods, the sample will be dispersed or soluble in water, which obviates any problem with contact surface. For homogeneous material, sampling can present a problem because of the small quantity required.

In these cases homogenizing the sample may be required, with care being exercised not to heat the sample during homogenizing (causing some irreversible transitions which are being looked for in DSC)

The samples are encapsulated in aluminum pans with lids that are crimped into position. For sample containing water, the pans must be hermetically sealed to prevent evaporation of water (with its large enthalpy of vaporization). Generally the pans and crimping devices currently in use will withstand internal pressure to 2 to 3 atm. For

higher pressures, there are high pressure DSC cells available from instrument manufacturers, and flint glass ampoules can be used which withstand internal pressure up to 30 atm. The most commonly used calibrant is indium ( $\Delta H_{\text{fusion}} = 6.80 \text{ cal/g}$ ; mp 156.4 °C).

Determination of enthalpy for the process under study requires measurement of the area of the endo/exotherm. Several attempts have been made to compare methods for determination of gelatinization characteristics i.e. Temperature and heat of gelatinization. Starches are different in their gelatinization characteristics.

#### **X-ray**

(Zaslow, 1965; Lund, 1983b; Newman et al., 1996)

X-ray diffraction studies have shown that starch exists in three crystal forms designated A, B, and C. These forms are dependent on the botanical source of the starch. Pattern A is observed for cereal grain starches, where as pattern B is characteristic of tuber, fruit, and stem starches. Pattern C is intermediate between the A and B patterns and has been attributed to mixtures of A and B type crystallites. The A type pattern is commonly observed for corn starch.

Powder x-ray diffraction patterns of representative unmodified and pregelatinized corn starches are given in Figure 4 The unmodified corn starch was found to have some crystalline character as evidenced by the broad peaks present. The pattern is indicative of a semicrystalline material and is similar to the A type pattern, but a definite determination of the form is difficult based on the quality of the pattern. The pregelatinized Starch 1551 material exhibits a broad amorphous halo in the

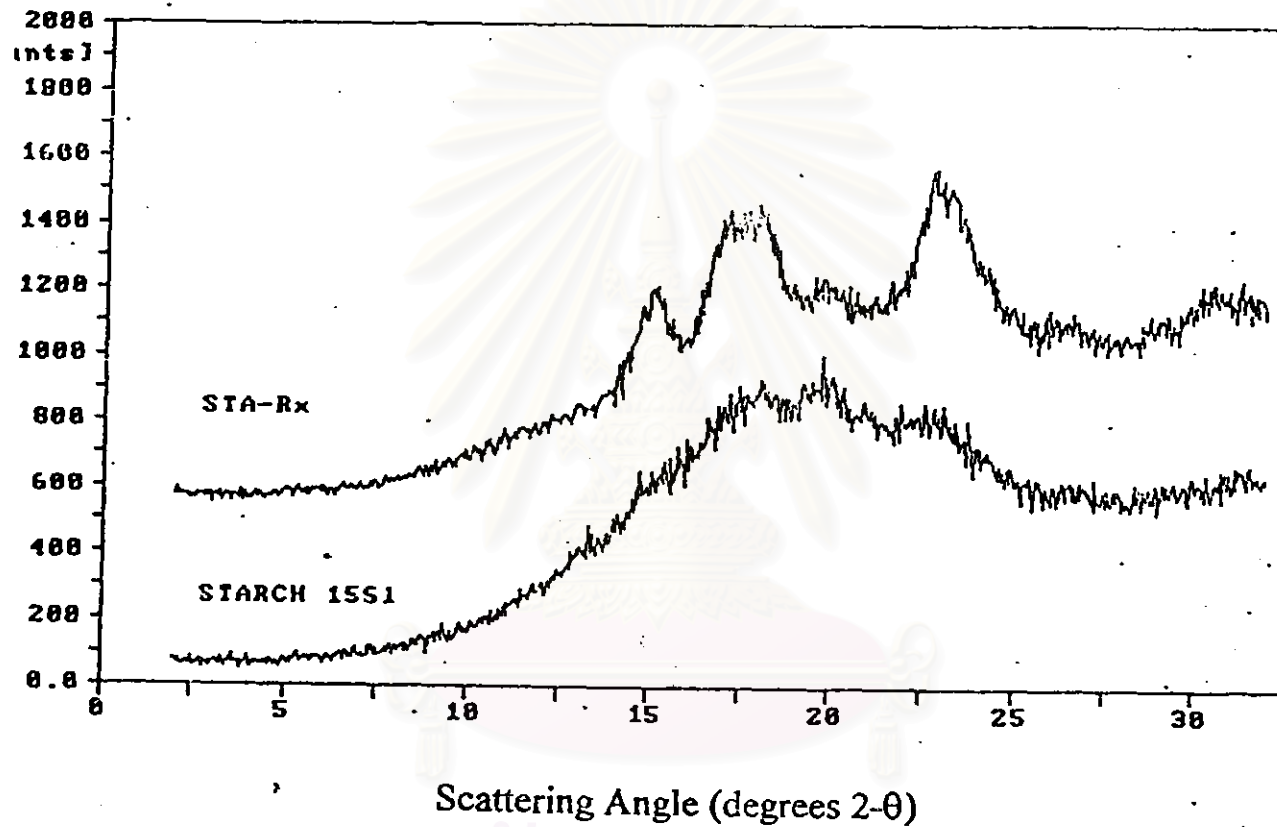


Figure 4 X-ray powder diffraction patterns of unmodified (upper trace) and pregelatinized (lower trace) corn starch. (Newman et al., 1996)

powder pattern indicating that the majority of the sample is amorphous material. This type of pattern was expected since the processing of pregelatinized starch destroyed the crystalline portion of the granule.

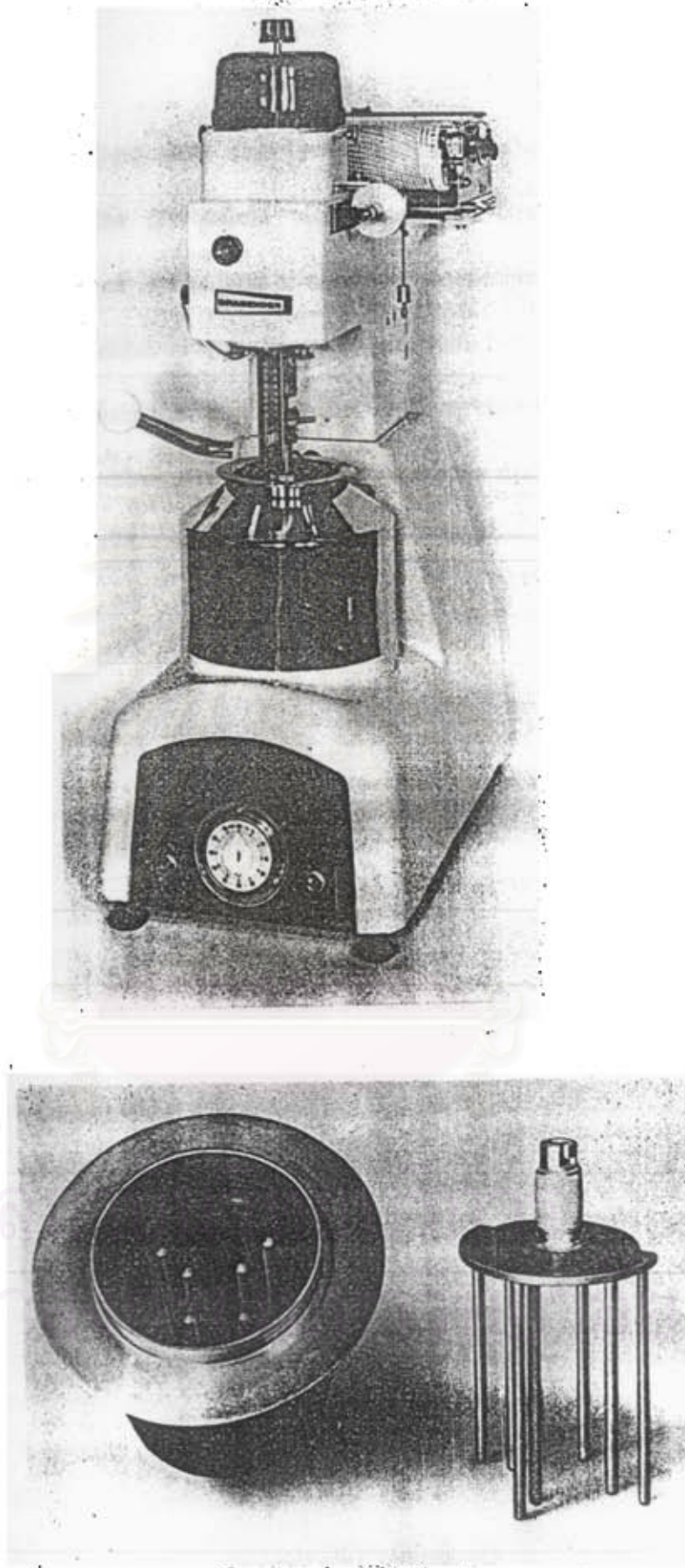
### **Brabender Viscoamylograph**

(Myers and Knauss, 1965; Radley, 1976; Willigen, 1976 )

The brookfield viscometer is often used to check the resulting paste viscosities at various temperatures. A preferred procedure is to pour the paste into recording viscometer , such as the Brabender or Corn Industries' viscometer, and to record the viscosity as the paste is heated to near 100°C

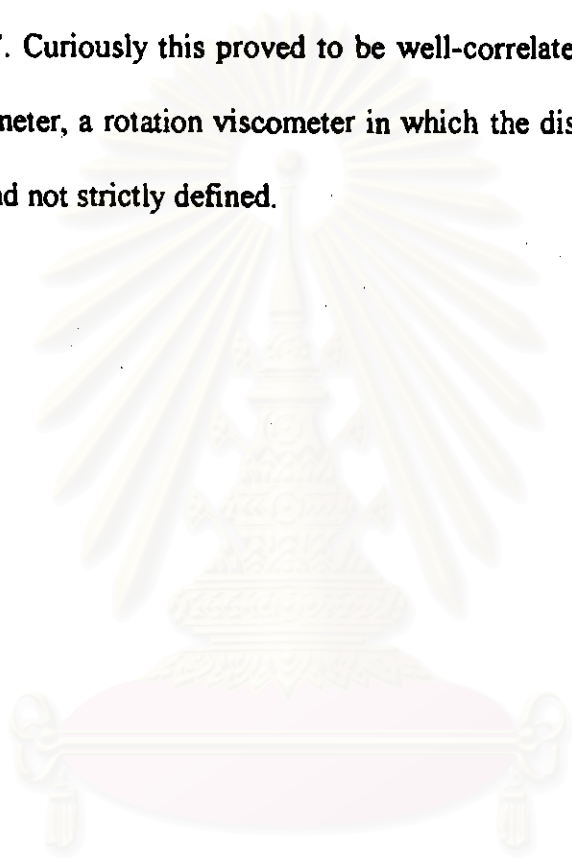
Method of following gelatinization; For starch the only instrument now available is the Brabender Viscograph. It works on the following principle, **Figure. 5**, a mixture of starch and water is put into a beaker provided with a set of vertical pins. It is coupled to a synchronous drive, which turns it around a vertical axis, and a stirrer is put in also consisting of a set of vertical pins. The mixture is heated by a set of heating spirals cylindrically arranged around the beaker. The rate of heating and cooling is controlled by a contact thermometer with continuously changing adjustment.

By this means the temperature is raised at the pace of 1.5 °C/min until a temperature of 92 °C or 95 °C is reached. From this point on the paste is kept at a constant temperature (usually for 15 minutes) after which a cooling spiral (with a tap also controlled by the thermometer) provides a constantly declining temperature until 30 °C is reached. The torque of the stirring rod is registered by a dynamometer, so that a curve is obtained in which consistency is plotted against time



**Figure 5** The Brabender amylograph with measuring bowl and sensor

A review compares the Brabender viscograph with five other instruments, viz, the Brabender Plastograph, the Brookfield viscometer, the Drageviscosimeter system Epprecht, the Rotavisko of Haake and a capillary viscometer. Woldendorp tries to correlate the results of another group of instruments with his subjective judgement of 'long' and 'short'. Curiously this proved to be well-correlated with the results of the Brookfield viscometer, a rotation viscometer in which the distance of the cylinders is relatively high, and not strictly defined.



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