CHAPTER I

GENERAL BACKGROUND

INTRODUCTION

Direct compression is a technology which was developed in the 1960's. Due to the intensive research in tabletting machinery and the development of new potent excipients over the three decades, direct compression has been an interesting alternative for the pharmaceutical manufacturer. Apart from the economic point of view and the simplicity of the process, direct compression offers many advantages compared with techniques such as pre-compression or wet granulation in term of an improved process reliability and product stability (Khan and Rhodes, 1973). For example, thermolabile substances and active ingredients liable to hydrolysis can be tabletted without difficulty.

The poor flowability of the powder mixes and the limited dilution potential of the available filler/binder form the main problems with direct compression. Furthermore segregation of the drug can occur, debasing the content uniformity of low drug content dosage forms. The physicochemical properties of individual ingredients such as particle size, fluidity, and moisture are mostly to be more critical in tablets prepared by direct compression than in those prepared from granulations. Despite these difficulties, by choosing the correct equipment and proper consideration, the majority of the drugs can be tabletted via direct compression.

The advent of direct compression was made possible by the commercial availability of directly compressible tablet diluents which possess both fluidity and compressibility. The first such diluent was spray dried lactose, which initiated the direct compression revolution. Afterthat, other direct compression diluents were commercially introduced , including Avicel PH 102^{R}, Starch 1500^{R} and Emcompress^{R}. The price and the availability of used ingredients in pharmaceutical manufacturing should be considered. Unfortunately, many of directly compressible diluents are too costly. The use of native excipients is preferred (Sheth, Bandelin and Shangraw, 1989).

Thailand is an agricultural country, producing a tremendous amount of starches annually. The research area toward pharmaceutical technology of starches should be enhanced. Manudhane *et al.* (1969) indicated that flow properties of starch are insufficient for use as directly compressible filler-binders. However, special starch product such as pregelatinized starch could improve flow and binding properties as compared with the native starch. It is available in directly compressible quality. Pregelatinized starch is partially hydrolyzed corn starch and marketed as Starch 1500^{R}. Although it was claimed to have many advantages over starch USP with respect to fluidity and compressibility , the flow properties were poor as compared with other filler-binders for direct compression.

Recently, Siriyos Timaroon (1994) reported that rice starch aggregates which were deproteinized and crosslinked for 6 hrs before being spray-dried exhibited excellent flow and the best tabletting

properties when compared with other commercial modified starch products.

This present study is the further expansion of above mentioned research work by investigation on the application of modified rice starch in manufacturing of tablet products.

Objectives of this study

1. To study the physical properties of modified rice starch compared with other commercial diluents.

2. To study the tabletting characteristics of modified rice starch compared with other commercial diluents.

3. To study the dilution potential ability of modified rice starch with low compressible drug in comparison with other commercial diluents.

4. To study the effect of lubricant on physical properties of modified rice starch compared with other commercial diluents.

5. To study the use of modified rice starch as directly compressible diluent to produce the tablets of two model drug compared with other commercial diluents and evaluate their physical properties.

LITERATURE REVIEW

Rice Starch

Starch is a polymeric carbohydrate consisting of anhydroglucose units linked together primarily through ∝-D-(1 → 4) glucosidic bonds. It has been established that starch is a heterogeneous material consisting at the extremes of two major types of polymer -- amylose and amylopectin.

Amylose

Amylose is essentially a linear polymer in which the anhydroglucose units are predominantly linked through ∝-D-(1 → 4) glucosidic bonds. It is illustrated in Figure 1. The anhydroglucose unit contains one primary and two secondary hydroxyls as well as an aldehydic reducing group in the form of an inner hemiacetal. This is called the reducing ends of the molecule. The opposite end, or nonreducing end, contains an anhydroglucose unit containing one primary hydroxyl and three secondary hydroxyls. The other anhydroglucose units contain one primary and two secondary hydroxyls.

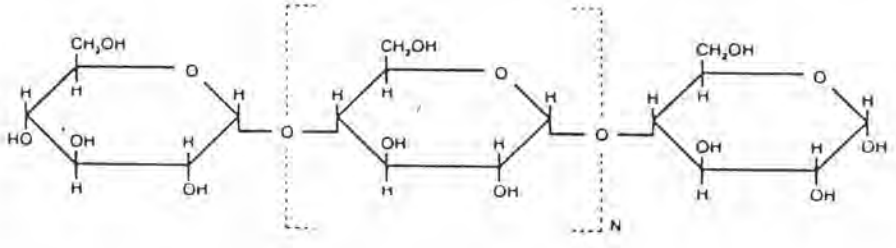


Figure 1 Linear-chain structure of amylose molecules

The abundance of hydroxyls imparts hydrophilic properties to the polymer, giving it an affinity for moisture and dispersibility in water. However, because of their linearity, mobility, and hydroxyl groups, amylose polymers have a tendency to orient themselves in a parallel fashion and approach each other closely enough to permit hydrogen bonding between hydroxyls on adjacent polymers. As a result, the affinity of the polymer for water is reduced and the sol becomes opaque.

Amylose molecules also have an affinity for iodine. The complex of amylose with iodine produces a deep blue color which is used to identify amylose-containing starches.

Amylopectin

Amylopectin is a branched polymer containing, in addition to anhydroglucose units linked together as in amylose through ∝-D-(1 → 4) glucosidic bonds, periodic branches at the carbon-6 position. These branches are linked to the 6 carbon by ∝-D-(1 → 6) glucosidic bonds. Each branch contains about 20 to 30 anhydroglucose units. A schematic diagram of the amylopectin molecule is shown in Figure 2.

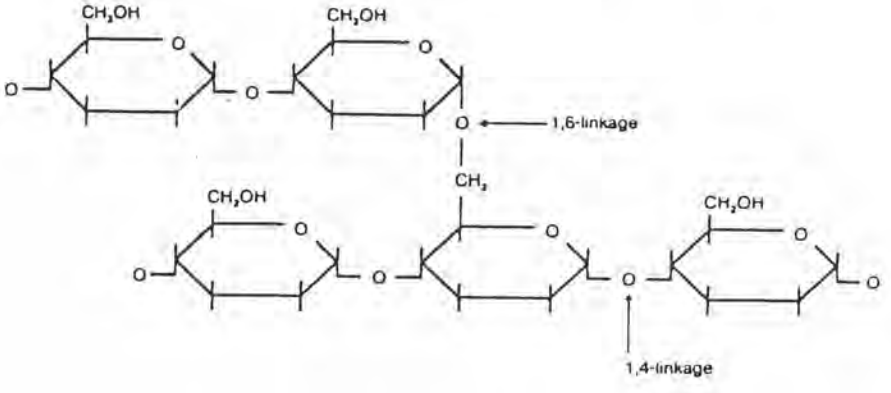


Figure 2 Structure of amylopectin branching points

The large size and branched nature of amylopectin reduce the mobility of the polymers and interfere with any tendency for them to become oriented closely enough to permit significant levels of hydrogen bonding. As a result, aqueous sols of amylopectin are characterized by clarity and stability as measured by resistance to gelling on aging. Amylopectin sols do not form as strong and flexible films as the linear amylose. They do not form an iodine complex with its associated deep blue coloration (Rutenberg, 1980; Wurzburg, 1986).

For rice starch, Hogan (1967) reported that the rice grain is made up of the hull (husk), the seed coat (pericarp), the embryo (germ), and the starchy endosperm. The seed coat consists of six layers of differentiated types of cell, the last being the aleurone layer, which is rich in proteins, lipids, and B-complex vitamins. Proteins and mineral salts are present in the aleurone cells and also in the outer starch-containing cells. Rice starch granules are bound into a rigid structure by proteins in close association with the starch in the manufacturing process. A summary of the composition of rice endosperm is given in Table 1. The glutelin or alkali-soluble fraction forms the major component in the composition of rice protein.

Table 1 Chemical composition of broken rice

Constituent	Range (%)	Average (%)
Ash	0.36-0.61	0.48
Protein (%N X6.25)	6.0-10.0	8.0
Lipids	0.26-0.95	0.61
Starch	87.2-93.5	90.35

Crosslinked Starch

Starch contains an abundance of hydroxyl groups. Each anhydroglucose unit contains two secondary hydroxyls and a large majority contain primary hydroxyls. These hydroxyls potentially are able to react with any chemical capable of reacting with alcoholic hydroxyls. This would include a wide range of compounds such as acid anhydrides, organic chloro compounds, aldehydes, epoxy, ethylenic compounds, etc.

The concept of cross-linking solutions or dispersion of starch or dextrin molecules through interaction with bi- or polyfunctional reagents in order to thicken or to reduce the solubility or insolubilize their solutions or films is widely practiced in numerous industrial applications. Basically, crosslinking reinforces the hydrogen bonds in the granule with chemical bonds which act as bridges between molecules. As a result, when the cross-linked starch is heated in water, the hydrogen bonds may be weakened or destroyed; however, the granule will be kept intact to varying degrees by the chemical bridges. Since the cross-linking involves treatment of the starch in its granular state, the amount of chemical cross-links introduced into the starch is usually very small relative to the weight of the starch and the total number of anhydroglucose units present in the granule. Most of the cross-linked starches will contain about 1 cross-link for every 100 to 30,000 anhydroglucose units.

The reaction conditions used in making cross-linked starches vary widely depending upon the specific bi- or polyfunctional reagent used for the cross-linking. In general, most of the reactions are run on aqueous suspensions of starch at temperatures ranging from room temperature up

to about 50 ^{0}C. Often an alkali such as sodium hydroxide is used to promote reaction. The reactions are normally run under neutral to fairly alkaline conditions, but below the level which will peptize or swell the starch. In some cases, however, such as situations where aldehydes are used, the reactions are run under acidic conditions. If the cross-linking reaction is run in an aqueous suspension of starch, when the desired level of cross-linking is reached, the starch suspension is neutralized and the starch is filtered and washed to remove salts, any unreacted reagent, and other impurities produced by side reactions of the cross-linking reagent with water.

Cross-linking is a key technique for modifying the properties of starch and all types of modified starches:

1. It offers a means for reinforcing the granule to the point where the intact granule can be used as such under conditions which would swell granules of noncrosslinked starch. This opens up usages as surgical dusting powders, carriers, absorbents, and ion exchange resins.

2. It toughens the granule so that on swelling, the integrity of the swollen granule is maintained, thus providing

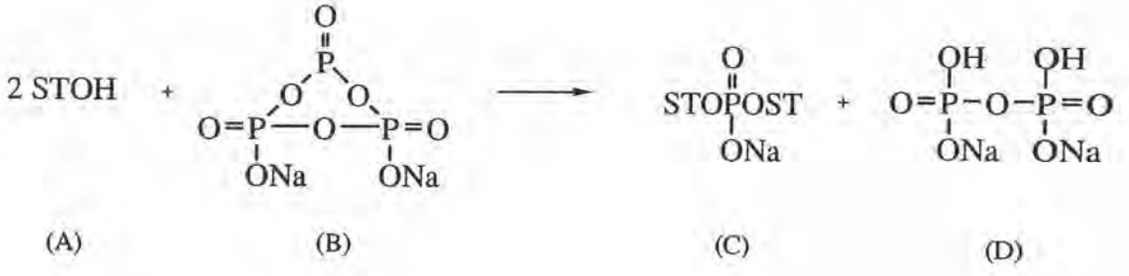
   - High-viscosity thickeners
   - Short salve-like paste texture
   - Resistance to viscosity breakdown in acidic media
   - Resistance to mechanical shear
   - Resistance to viscosity breakdown at high temperature

3. It permits controlled released of amylose from the swollen granule, providing improved film properties. (Hullinger,1967; Rutenberg, 1980; Wurzburg, 1986).

Starch Phosphate Diesters

Starch phosphate diesters contain an ester bridge or bridges connecting adjacent starch molecules. Commercially they represent a class of starch derivative wherein the starch granule is inhibited from swelling and rupture. Such cross-linked starches have greatly enhanced stability to heat, to agitation, and to acidity.

Sodium trimetaphosphate is primarily used to produce cross-linked starches. The reaction is believed to occur in the manner shown in Figure 3. Although the product is referred to as a distarch phosphate ester, it is probable that small amounts of the mono- and trisubstituted esters occur. Phosphorus oxychloride may also give mono-, di-, and triesters.



Figre 3 Crosslinking reactions on starch

A = Starch B = Sodium trimetaphosphate

C = Sodium distarch phosphate D = Sodium dihydrogen pyrophosphate

Esterification of starch with trimetaphosphate salts in aqueous medium. Alkaline materials, such as sodium hydroxide, calcium hydroxide, and sodium carbonate, catalyze the esterification. A starch phosphate with a maximum hot-paste viscosity in normal cooking, that is, 15 minutes at 95^0 - 100^0 C, may be prepared by heating a starch slurry at 50^0 C with 2 % sodium trimetaphosphate, based on starch, for 1 hour at pH 10-11.

Starch phosphates can use in pharmaceuticals. For example, corn starch reacted with disodium hydrogen phosphate and urea (3.9 g and 7.8 g/g starch, respectively) at 160 to 180 ^{0}C for 2 hr at 9.0 pH was useful for hydrophobic powder bases in dry hair shampoos or fillers for pharmaceutical. Starch phosphates stabilized prostaglandins to heat, and defatted starch phosphates were used to prepare acceptable, radiolabeled, diagnostic agents by combination with ^{99m}Tc radionuclide. Plasticized starch phosphate films were useful in treating skin wounds. Rapid healing, less infection, more rapid tissue growth, and less interference with the natural healing process were claimed (Robert, 1967; Solarek, 1986).

Modified Starch as Pharmaceutical Excipients

Binding Agent

Pregelatinized starch can be used as a diluent, disintegrant and binder. Its binding properties are slightly 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 granulate. Several pregelatinized starches available are intended to be added in the dry form when are called for tablet binder. Normally concentration used of pregelatinized starch, when added dry to the powder, is 5-10 %.

Visavarungroj, Herman and Remon (1990) studied modified waxy corn starch as binder and they found that starches which were only cross-linked showed no advantage in binding properties over native or waxy corn starch unless they were pregelatinized. The use of pregelatinized and pregelatinized-crosslinked starches as a binding agent gave higher-quality lactose granules than with corn starch or waxy-corn starch. These pregelatinized starches could be used in a dry form and gave granules with properties similar to those in the case of the paste form.

Disintegrating Agent

Starch is the most common disintegrating agent in use today. It was once as a disintegrating agent depended on its swelling when wetted. However, it has been shown that starch does not swell when exposed to water at the temperature found in gastric fluids. It has been suggested that the disintegrating action of starch is not due to swelling but rather arises from capillary action. The activity of starch as a disintegrant has been defined as being involved in formation of intermolecular hydrogen bonding during compression and release in the presence of excess moisture. Despite a long and proven record as a disintegrant, starch possesses disadvantages when used in direct compression formulation. The relatively high levels required and the lack of compressiblity often

weaken the tablet structure. Therefore, the development of new disintegrants that are effective at lower levels is of great importance in formulations for direct compression (Curlin,1955; Ingram and Lowenthal, 1966).

Soontorn Vorakul (1980) reported that carboxymethyl starch can be used as disintegrating agent in sulfadimidine tablets and the amount of carboxymethyl starch required in the tablets were less than that of native starch. The optimum quantity of carboxymethyl starch in the granules was 5.0 %. For method of addition, intragranular method was better than extragranular method.

Visavarungroj and Remon (1990) investigated modified waxy - corn starch as a disintegrating agent. The crosslinked-only waxy-corn starches showed the same disintegrating properties as potato starch. They revealed the lowest granule swelling power and a poor rate and amount of water uptake. The pregelatinized-crosslinked waxy-corn starches showed better disintegrating properties than the crosslinked only starches. The tablets containing pregelatinized starch revealed considerble variation and longer disintegration time than those formulated with pregelatinized-crosslinked starches.

Direct Compression Filler

Parrott (1989) presented that Soludex 15, a new corn-based maltodextrin made from commercial spray-dried materials obtained by the hydrolysis of starch, exhibited excellent flow and compressibilty, and model tablets using Soludex 15 as the direct compression diluent met

specification and provided a rapid dissolution of the active ingredient. Maltodextrins are carbohydrate products obtained from the reaction of starch with acid/or enzymes in the presence of water. They are used as excipients in direct tablet compression since they exhibit free flow properties and compressibility characteristics comparable to those of other excipients (Papadimitriou, Efentakis and Choulis, 1992).

Recently, a new direct compression diluent, a spray dried rice starch was produced and marketed under the trade name Erá-Tab^{R} and Primotab^{R}ET (Bos *et al.*, 1992).

Pregelatinized starches containing a low amount of amylose (25 % and lower) revealed promising properties as directly compressible tabletting excipients for sustained released purposes. Because of their cold water swellability, non-toxicity and low cost. The formation of an obstructive gel layer is required to ensure a sustained drug release (Herman and Remon, 1989). However, Visavarungroj, Remon and Herman (1990) indicated that crosslinked modified waxy-corn starches, either pregelatinized or not, in comparison to purely pregelatinized waxy-corn starch are not suitable to use as hydrophilic matrix in sustained release formulation.

Spray Drying Technique

Spray drying is a process that enjoys widespread acceptance in the chemical, the food, and the biochemical and pharmaceutical industries. Many familiar products such as powdered milk, detergents and some pharmaceutical material are manufactured in this manner. Its

main uses in the pharmaceutical industries include drying of heat-sensitive materials, improving solubility of poorly water soluble substances, preparing granulations for tabletting, coating drugs with suitable polymers to produce controlled release products and producing tablet excipients

The Design and Operation of Spray Dryers

In the spray drying method, fine powders or granular products are recovered from solutions or dispersion in a continuous one-step operation. A flow diagram of the spray drying process is presented in Figure 4. The spray drying process includes of four stages

1) Atomizing of the feed into a spray
2) Spray-air contact
3) Drying of the spray
4) Separation of the dried product from the drying gas

The basic principles involved concern the atomization of the feed liquid into a spray of very small droplets. These droplets have a very large surface area and evaporation is completed rapidly. There are a variety of atomization systems available, which may be classified according to the nozzle design as rotary atomization , pressure atomization or two-fluid (pneumatic) atomization. In rotary atomization the feed fluid is introduced into the drying chamber by means of a spinning disc or wheel which creates a spray of droplets. Pressure atomization , as the name suggests, occurs when the feed is fed into the nozzle under the pressure which causes the fluid to be dispersed into droplets as it leaves the nozzle.

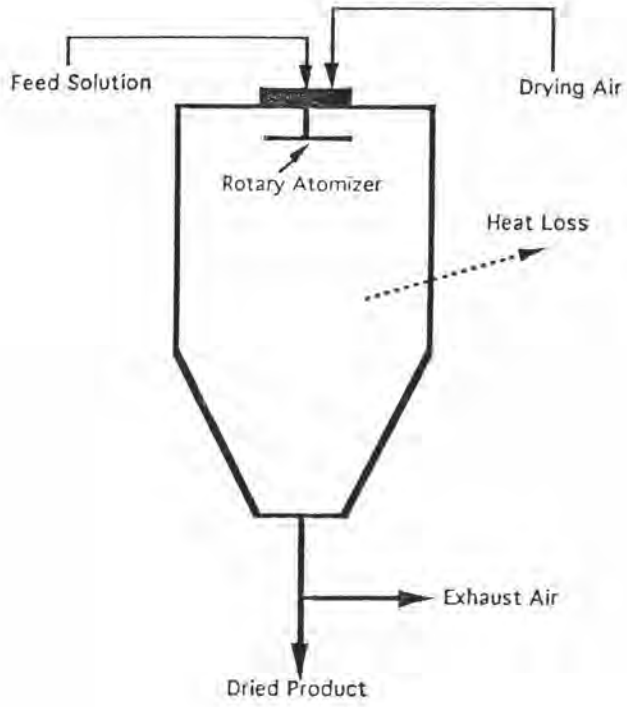


Figure 4 Schematic of the spray drying process

Finally, in two-fluid nozzles, the feed fluid and atomizing air are passed separately to the nozzle where they mix and the air causes the feed to break up into a spray. Two-fluid nozzles are generally confined to laboratory scale spray dryers.

The spray dryers has been designed to operate in a co-current, counter-current or mixed flow manner. In co-current dryers, the atomized feed and drying air enter together at the top of the drying chamber. The droplets and air then pass down the dryer in a co-current manner. The evaporating rate of liquid is rapid and the evaporation time is short. The dry product is in contact with only the coolest air at the end of the drying cycle so co-current dryers are preferable for the drying of heat sensitive materials. In counter-current drying, the spray and drying air enter the

chamber at the opposite ends. The feed is sprayed into a cooled gas stream and the evaporation of the liquid is slow. Counter-current dryers subject the driest powders to the hottest gas stream so this method is suitable only for the heat resistant products. Mixed flow dryers incorporate both co-current and counter-current flow designs. This method is used for spray dryers with a smaller chamber design and suitable only for the heat resistant products (Broadhead, Rouan and Rhodes, 1992).

The Properties of Spray Dried Products

The physical properties of spray dried products are subjected to considerable variations depending on the design of atomization, the direction of flow of the inlet gas, the solids content of the feed, the feed rate and the drying air temperature. Spray dried powders are usually approximately spherical with a narrow size distribution and hollow. The hollow nature imparts a low bulk density to the powders, but despite this, their spherical shape means that they are usually free-flowing. By modifying the spray drying process, it is possible to alter and control the following properties of spray dried powders; appearance, particle size and size distribution, bulk density, porosity, moisture content, flowability, stability, dispersability, friability and retention of activity, aroma and flavor. An increase in the energy available for atomization (i.e. rotary atomizer speed, nozzle pressure, or air-liquid flow ratio in a pneumatic atomizer) will reduce particle size. Particle size is usually increased as the feed concentration or viscosity increases. The surface tension has a minimal effect on particle size, although an increase in particle size with an increase in feed surface tension and density as well as with

concentration and viscosity. If the feed rate is increased, particle size will again increase. The effect of temperature on particle size appears to be highly dependent on the material being dried. It was observed that for crystalline materials, such as sodium sulfate, temperature had very little effect whereas for coffee extract the mean particle diameter was significantly reduced by increasing the inlet air temperature. In contrast, Newton (1966) reported a study where the particle size of some materials was shown to increase as the drying air temperature increased. High drying air temperture also seem to be associated with lower bulk densities. As a general rule, smaller particles will usually be more dense, and so the bulk density of a powder with a small particle size will be higher. Bulk density will also increase with a narrower particle size distribution. As it would be expected, increased dryer outlet temperatures result in a lower final product moisture content.

In practice, the inlet air to the spray dryer is heated to a particular temperature and the spray (feed) rate of the solution is adjusted to maintain a fixed outlet (exhaust) temperature, humidity or product moisture content. The exhaust temperature (humidity) must be high (low) enough to insure proper drying of the product. Since these conditions can influence the physical properties of the product it is important that they are properly controlled. A thermodynamic analysis greatly enhances the ability to predict, control and understand the process, particularly during scale-up.

As an example, consider the case of drug. Drug is formulated as an instant release tablet of relatively high strength. This substance is non-hygroscopic, freely soluble in water, incompatible with many common

pharmaceutical excipients and exhibits poor flow and compactibility. Drug tablets produced using high shear wet granulation methods are relatively large. This problem is resolved by using a spray dry granulation process. Spray drying allows preparation of drug tablets that contain a minimum quantity of excipient. Drug's poor flow properties are clearly derived from its morphology. The spray dried powder, on the other hand, exhibits excellent flow due to the spherical nature of its particles. The feed solution provides intimate contact between drug and binder which leads to significantly enhanced compactibility. After lubrication, the spay dried powder can be directly compressed into tablets. These tablets, which contain drug in excess of 96 % W/W, exhibit excellent weight variation, hardness, friability, and dissolution. Furthermore, since the inlet stream is a solution, the formulation and process are protected from variations in the physical properties of the drug substance, such as particle size and shape, which normally occur during development. These considerations, plus the fact that the process is independent of batch size, significantly simplify scale-up and validation.

The Application of Spray Drying in Excipients Production

Spray drying is a useful method for the processing of pharmaceutical since it offers a means for obtaining powders with predetermined properties, such as particles size and shape. In addition a number of formulation processes can be accomplished in one step in a spray dryer.

Spray dried lactose is by far the most commonly encountered spray dried pharmaceutical excipient, and has been available for many

years. It is prepared simply by spray drying a lactose concentrate, as opposed to centrifuging and drying the concentrate, which had been the traditional method for lactose preparation. The main advantage of spray dried lactose compared to conventionally prepared lactose is that it is directly compressible.

Gunsel and Lachman (1963) evaluated and compared a number of formulations containing traditionally prepared and spray dried lactose. Superior physical properties, such as reduced friability were observed, in most of the formulations containing spray dried lactose as opposed to conventionally processed lactose. However, spray dried lactose was more susceptible to discoloration on aging than conventionally processed lactose.

Vromans *et al.* (1987) shed light on the mechanism by which spray drying improves the compressibility of lactose. Commercially available spray dried lactose was reported to consist of about 15 % amorphous lactose and 85 % crystalline lactose. Lactose of this type could be produced by spray drying a dispersion of crystalline lactose in a saturated solution of lactose . The amount of lactose dissolved at the time of spray drying determines the proportion of amorphous lactose present. Lactose with varying amorphous contents was prepared by suspending crystalline lactose of a known particle size in a saturated aqueous lactose solution maintained at different temperatures. In conclusion, the amorphous lactose acts essentially as a binder for the crystalline lactose, by coating the individual crystals. A significant increase in tablet strength was observed with a decrease in the particle size of the crystalline

component; this factor seemed to be more significant than the proportion of amorphous lactose present in the product.

Dicalcium phosphate was also spray dried from a suspension in a saturated lactose solution resulting in a surface coating of amorphous lactose around the dicalcium phosphate crystals. The tablets produced from this product also had a significantly increased crushing strength when compared to those produced from physical mixtures of the two excipients. This evidence also seemed to indicate that amorphous lactose can act as a binder for crystalline material.

Microcrystalline cellulose is derived from purified wood α-cellulose. The hinges of amorphous cellulose which link the naturally occuring microcrystals are preferentially removed by a severe acid hydrolysis, yielding a cellulose with a so-called "level-off degree of polymerization" of about 200 to 300. The microcrystals (with diameters ranging from 1 to 10 μm) are freed from their fibrous, packed structure by mechanical shearing of a water slurry and obtained as a powder by spray-drying (Doelker, 1993).

Recently, a new direct compression diluent, a spray dried rice starch was produced in Thailand and marketed under a trade name Era-Tab^{R} . It was spherical and made up entirely of agglomerates of rice starch grains.

Effect of Lubricants on Some Properties of Tablets

The tablet lubricant is one of the most essential excipient components in tablet formulation. Lubricants are materials which, when

positioned between rubbing surfaces, reduce the friction at their interface. They are added generally in powder form to most tablet formulations, primarily to reduce frictional forces at the interface between powder (or granule) and tablet surfaces with die wall during tablet formulation and ejection (true lubricant). Additional advantageous properties of lubricants have been recognized , such as prevention of sticking of tablets to punches in tablet machines (anti-adherent) and reduction of wear of tablet tooling , improvement of the flow and filling properties from hoppers and delivery devices into the die cavities (glidant). Most powder lubricants exhibit varying degrees of these properties. An ideal lubricant should reduce friction effectively in small quantities with no adverse effects upon the formulation. It should be inert and cosmetically acceptable with respect to other dosage form ingredients. From a pharmaceutical viewpoint this usually means white and odourless but water-solubility may also be an essential requirement.

The ideal lubricant should be unaffected by changes in process variables, consistent from batch to batch, readily available and cheap. As yet there is no ideal lubricant material for pharmaceutical powders. No material has yet been identified which is efficient in all categories although the metallic soaps, and in particular magnesium stearate, are the lubricants most widely used by the pharmaceutical industry. These materials are reported to exhibit excellent lubricant properties, good anti-adherent characteristics and poor glidant behaviour (York, 1984).

A given lubricant may posses one or more of these activities to varying degrees and formulators often combine such agents in an attempt to optimize these processing charateristics. However, careful selection

procedures should be applied when choosing lubricants and defining their concentration in process and product specifications not only to achieve efficient compaction and ejection during tablet manufacture, but also in consideration of the well documented deleterious effects lubricants can have on tablet crushing, disintegration, drug dissolution rate, compatibility with active drugs as well as problems associated with batch variation of lubricant powders. These effect were reported for several products, but seems that the degree of the effect depends on the kind of lubricant and the physical structure of the excipient (Bossert and Stamm, 1980).

Decreases in tablet crushing strength have been attributed to weaker bonds resulting after compression between lubricant-lubricant molecules rather than stronger host-host bonds. The significance of increases in dissolution time is due to lubricant films. These effect are also known to increase with prolonged mixing or with high mixing intensity. It was found that the effect of lubricant admixing on tablet crushing strength was strongly dependent on type, size and rotation of mixer used (Mitrevej and Augsburger, 1980, 1982).

When operated at the same rotation speed, the decrease in crushing strength was much faster for the large industrial mixers than for the small laboratory mixers. These differences were explained by differences in shear forces during the mixing process and the efficiency of the mixing procedure (Bolhuis, Jong and Lerk, 1987).

It appears that the effect of lubricant on mechanical strength depends on the bonding mechanism. The strength of a tablet depends on

the intimate contact between the particles and the adhesive strength over this area. The strongest bonds are formed between clean surfaces; therefore, the addition of a lubricant interferes the bonding by acting as a physical barrier between particles for a material which undergoes plastic and/or elastic deformation. For materials, which are brittle and fragment, new clean surfaces are formed during compression, and the lubricant does not interfere the bonding as it does for a plastic material so that a stronger tablet is formed (Jarosz and Parrott, 1984).

Salpekar and Augsburger (1974) found that the compressibility of spray dried lactose , directly compressible sucrose and terra alba granulation was affected less by lubricants than microcrystalline cellulose and pregelatinized starch. The authors suggested this to be due to differences in bonding mechanisms of the substances.

The decrease in tablet strength is caused by lubricants via a less intensive lattice disturbance as an effect of the decreased interparticulate friction. De Boer *et al.* (1978) found that the effect of degree of mixing on the bonding properties of blends of magnesium stearate and tablet excipients depended upon the compression behavior and bonding mechanism of the excipient studied.

Directly Compressible Starch in Pharmaceutical Dosage Form

Modified Rice Starch

Modified rice starch was produced by physical modification of rice starch and composed almost entirely of aggregates of rice grains in the form of spheres. It is a dry, white, odorless, tasteless, insoluble and neutral powder. Modified rice starch exhibits excellent flowability and compressibility, It can be used as an excipient in tablets prepared by direct compression. It marketed as Era-Tab^{R} and Primotab^{R}ET.

Five directly compressible fillers, i.e., modified rice starch, microcrystalline cellulose, lactose, pregelatinized starch and dicalcium phosphate dihydrate were studied for their flowabilities and tabletting properties. Both flow rate and percent compressibility values indicated that modified rice starch exhibited excellent flow characteristic while microcrystalline cellulose and pregelatinized starch had flow problem. Although a strong decrease in crushing strength can be seen for modified rice starch after prolonged mixing with the lubricant, the effect is much less than found for other starch-based filler-binders. After intensive mixing with a lubricant, the tablet hardness is sufficient.

The hardness of tablets made from brittle materials, lactose and dicalcium phosphate dihydrate, was not affected by increasing concentration of lubricant. Disintegration of soluble material, lactose, was prolonged with the increase in magnesium stearate level. The addition of colloidal silica increases the crushing strength for all the tablets examined. This effect is caused by a reduction of the negative

effect of magnesium stearate on the binding properties. When colloidal silica is mixed with a tabletting mixture prior to mixing with a hydrophobic lubricant, the lubricant film formation is reduced. Dicalcium phosphate dihydrate tablets did not disintegration with in 45 minutes. Dilution potential or carrying capacity was determined by using ascorbic acid. Microcrystalline cellulose had the highest capacity and pregelatinized starch had the lowest. Modified rice starch, lactose, and dicalcium phosphate dihydrate possessed comparable carrying capacities (Mitrevej, Varavinit and Sinchaipanid, 1990).

Tablets containing oxazepam as a model drug were prepared with modified rice starch as unique filler-binder or with a blend of equal parts of modified rice starch and a commonly used filler-binder. The tablet properties show that modified rice starch is a useful product for the preparation of tablets by direct compression. It can be used as a unique filler-binder, or in combination with other excipients such as ∝-lactose monohydrate or anhydrous lactose. Combinations with microcrystalline cellulose should be avoided because of the poor flowability of the blends and the slow disintegration of the tablets (Bos *et al.*, 1992).

Pregelatinized Starch

Pregelatinized Starch is a partially hydrolyzed corn starch which is relatively free-flowing (compared to starch USP), and which will compress into a compact and still maintain its disintegrant properties. A commercially available form is marketed as Starch 1500^{R}. It occurs as a moderately coarse to fine, white to off-white colored powder. Moreover, it is odorless and has a slight characteristic taste. Starch 1500^{R} consists of

intact starch grains and ruptured starch grains which have been partially hydrolyzed and subsequently aggromerated. It has an extremely high moisture content (12 to 13 %), but there is little indication that this moisture is readily available to accelerate the decomposition of moisture-sensitive drugs (American Pharmaceutical Association Staff, 1986).

Even though pregelatinized starch will readily compact by itself, it does not form hard compacts. Its dilution potential is low, and it is not generally used as the filler and binder in direct compression, but as direct compression filler and disintegrant. The only major advantage of Starch 1500^{R} is that it retains the disintegrant properties of starch without decreasing the fluidity and compressibility of the total formulation, as is the case with plain starch. Because Starch 1500^{R}, like all starch, deforms elastically when a compression force is applied, it imparts little strength to compacts. As new clean surfaces are formed during compaction, lubricant, particularly the alkaline stearate lubricants, tend to dramatically soften tablets containing high concentration of Starch 1500^{R}, and they should be avoided whenever possible in formulating tablets (Sheth, Bandelin and Shangraw, 1989).

To investigate the tabletting properties of Starch 1500^{R}, the addition of a lubricant becomes necessary when even small proportions of adherent drugs were introduced. Magnesium stearate noticeably softens compressible starch tablets and should not be used in concentrations greater than 0.5 %. Besides, it is generally recommended that a glidant such as 0.25 % pyrogenic silica be employed to maximize fluidity.

Lubricant such as stearic acid or hydrogenated vegetable oil are preferred in such formulations (Bolhuis and Lerk, 1973).

Differential Scanning Calorimetry of Starch

Differential scanning calorimetry (DSC) is one of the thermal methods of analysis. Measurement of differential power necessary to keep a sample and reference substance isothermal as temperature is changed linearly is the basis of differential scanning calorimetry. These data can be used to study heats of reaction, kinetics, phase transitions, thermal stabilities, sample composition and purity, critical points and phase diagram (Jespersen, 1978)

Care should be exercised in using thermal analysis in the determination of the gelatinization process of starches, not because of limitation of the technique but because of the inhomogeneity of starches due to their natural origin.

The process of gelatinization (heating starch with water) includes the following stages:

1) the granules hydrate and swell
2) loss of birefrigence
3) increase in clarity of the mixture
4) rapid increase in consistency
5) dissolution and diffusion of linear molecules out of the ruptured starch granules
6) retrogression of the mixture to a paste-like mass of gel

The phenomenon is linked to amylose concentration, the length of its molecular chains and their state of dispersion. In wheat starch the behaviour can be represented by a small amount of swelling at 60-70 ^{0}C involving disruption of weakly bound or readily accessible amorphous sites and followed at higher temperatures (80-90 ^{0}C) by disruption of more highly bound or less accessible sites and eventual fragmentation of the starch granules.

Yook, Pek and Park (1993) reported that chemically modified rice starches were prepared by treating with propylene oxide. Gelatinization and retrogradation characteristics of these modified rices were investigated by using DSC. Hydroxypropylation of rice with propylene oxide caused an extreme decrease in gelatinization temperature from 62 ^{0} C to 50 ^{0}C. The enthalpies of gelatinization also decreased with increasing propylene oxide treatment. The lowering of gelatinization temperature was due mainly to the presence of the substituted groups which weaken or strain the internal bond structure holding the granules together.

DSC may be used to determine the amount of gelatinization in starch suspensions. Since the endotherm area corresponds to the amount of gelatinization, it follows that this will decrease if gelatinization has previously occurred. Thus by exposing a suspension to heat and analysing at different time intervals it is possible to determine the ungelatinized starch (Botha, Lötter and Preez, 1987; Ford and Timmins, 1989).

X-Ray Diffraction

The diffraction of X-rays is of great analytical significance, as it is applied to the study of the crystalline material producing the diffraction. No two chemical substances would form crystals, in which the spacing of planes is identical in all analogous directions. Thus every crystalline substance would scatter the X-ray in its own unique diffraction pattern, giving a fingerprint of its atomic and molecular structure. X-ray diffraction has been found to be a convenient method for identification of any compound that can be obtained essentially pure in crystalline form.

X-ray diffraction is currently of prime importance in elucidating the structure of such complex material products as steroids, vitamins and antibiotics. Its application is based upon the fact that an X-ray diffraction pattern is unique for each crystalline substance. Thus, if an exact match can be found between the pattern of an unknown and authentic sample, chemical identity can be assumed. In addition, when the guest compound is a substance, a comparison has to be made between the diffractogram of the compound and the mechanical mixture of the guest reactants. Comparison of the diffractograms is possible because compound preparation processes may change the crystallinity of the pure substances and this may also lead to different diffraction pattern. The diffraction patterns of compound are apparently different from each constituent and lead to a new solid phase with different diffractogram (Ewing, 1985; Khandpur, 1989; Skoog, 1984).

Brabender Viscoamylograph

The best method for following the viscosity changes during cooking of a starch paste is with the Brabender viscoamylograph. This apparatus measures the viscosity of starch-water dispersions that are stirred and heated at a uniform rate, held at any desired temperature for a specific time, and then cooled at uniform rate. A suspension of starch in water is transferred to the sample cup of the Brabender viscoamylograph. The instrument is started, and the temperature of the sample is increased at a rate of 1.5 ^{0}C/min. Heating is continued until the sample reaches 90 or 95 ^{0}C, and the sample is maintained at this temperature for 20, 30, or 60 min while stirring and recording the viscosity continuously. The paste is then cooled to 50 or 25 ^{0}C at a rate of 1.5 ^{0}C/min and held for 1 hr, for example, at this temperature while stirring.

With the help in Figure 5, the processes underlying such a diagram and the information that can be gained from the individual parts will be illustrated (Sietz and Zöller 1992). At the beginning of the measurement, the viscosity is still very low because the starch grains have practically not yet swelled at all in the cold water (a). When the temperature rises, the starch grains start to absorb water and begin to swell (b). Due to their enlarged volume, they collide more frequently within the crowd, rub each other, and the viscosity which is a measure for internal friction increase (c). Besides, more and more particles are dissolved from the starch grain, so that the liquid becomes more and more viscous and the starch grains tend to stick within the liquid. Consequently, the viscosity rises further (d). Up to now, only the processes causing the viscosity to the rise were described. Parallel to these processes, however, there are others

provoking a decrease in viscosity. Chemical bonds are destroyed due to the rising temperature. Swelled starch grains and the surrounding gel are broken by the mechanical action of the stirrir (e). Consequently, the balance tends from rising viscosity to decreasing viscosity again. The viscosity curves shows a maximum, the gelatinization maximum, together with the corresponding gelatinization temperature (i.e. the temperature in the gelatinization maximum). This gelatinization maximum may already be reached during the heating phase, or during the subsequent period of constantly high temperature (f). During the last stage of measurement (cooling), the dissolved and loosened molecules rearrange into more regular forms (retrogradation), and the viscosity increases again (g).

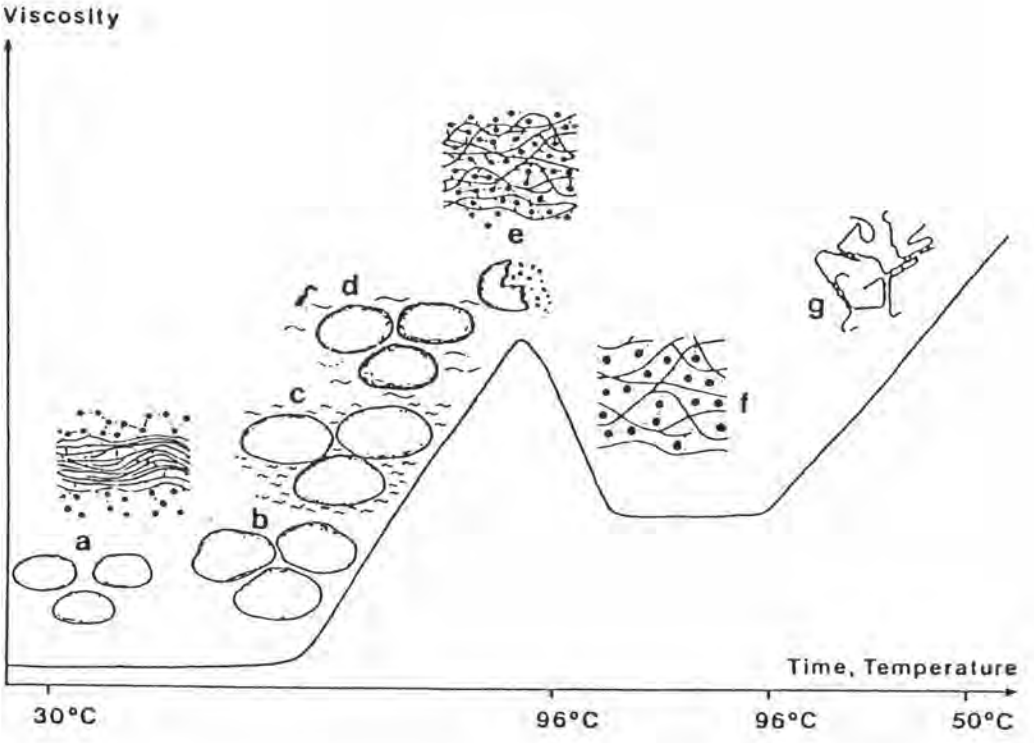


Figure 5 Brabender viscosity diagram

The crosslinking reaction is carried out commercially by adding the required amount of crosslinking agent to the aqueous starch suspension at the required temperature and pH. The reaction conditions are chosen to yield an ungelatinized granular starch. In most cases, the treatment level is in the range of 0.005 to 0.1 % crosslinking reagent, to give a relatively low degree of crosslinking (one crosslink per 200 to 1,000 AGU). Increasing levels of crosslinking result in changes in the hot peak viscosity and the degree of breakdown in viscosity after the peak with continued heating and stirring. With corn starch, mild crosslinking has little effect on the initial rate of gelatinization but does cause an increase in the maximum viscosity during the 30-min holding period at 95 ^{0}C, eliminating the viscosity breakdown seen with the native starch. As the level of crosslinking is increased, the reinforcing effects of the chemical covalent bonding, which is not as susceptible to rupture during cooking as are the hydrogen bonds, cause the granules to resist the swelling, and hence the viscosity tends to decrease proportionately. If the level of crosslinking is carried far enough, the granules will not gelatinized at all, even when heated at superatmospheric pressure, as in autoclave sterilization. Crosslinking leads to a more rigid macromolecular network inside the granule (Rutenberg, 1980).