Chapter I

General Background

Introduction

Starches are used as components and/or processing aids in the manufacture of products such as adhesives , textiles , paper , food , building materials , and pharmaceuticals. The use of this natural polymeric material is based on its thickening , gelling , adhesive , and film-forming properties , as well as its low cost , chemically inert , controlled quality and availability (Rutenberg , 1980).

In pharmaceutical applications , starch is well-established as pharmaceutical ingredient , particularly in solid dosage forms. The traditional applications include use as diluent or filler , binder , tablet disintegrant or as lubricant in tablet formulation depending on its type , concentration , modification and incorporated methods. In addition , starch has many other more active applications such as a base material for microspheres and microcapsules , and as a bioadhesive and drug carrier. However , native starch has some limitations in application (Banker et al.,1980 ; Remon and Voorspoels , 1996). As a binder in tablet formulation , starch must be heated to be starch paste before use in wet granulation process because the starch granule can not develop viscosity in cold water. In many cases , the properties of the native starch preclude their use in particular applications or processes.

Modification of native starches and starch derivatives are carried out to overcome the previous problems and provide products with the properties needed for specific uses. The modifications are designed to change some properties of native starch such as gelatinization characteristics, solid-viscosity relationships, gelling tendency of starch dispersions, hydrophilic character, moisture content and water-holding power. Starch can be modified by physical,

chemical or physico-chemical treatments. Crosslinked and pregelatinized-crosslinked starches were evaluated for potential use as binding agent (Visavarungroj, Herman and Remon, 1990 ; Visavarungroj and Remon , 1991) and disintegrating agent (Visavarungroj and Remon , 1990). Recently, different types of starch were chemically modified to obtain a superdisintegrant (Thavisak Teruya, 1995), binder in tablet formulation by solution and dry incorporation methods (Tasana Pituksuteepong, 1995), and suspending agent (Ornanong Suwannapakul, 1996).

Carboxymethyl starch is a chemically modified starch which is very hydrophilic, provides cold-water solubility and when in contact with water, it forms a high viscosity apparent jelly. Owing to this developed viscosity, carboxymethyl starch can be used not only as a disintegrating agent but also as a binding agent. (Filbert, 1952 ; Guyot-Hermann and Guyot, 1983; Hofreiter, 1986; Roberts, 1967; Wade and Weller, 1994). In the recent study, Tasana Pituksuteepong (1995) investigated the tablet binding properties of various types of modified starches. The result showed that modified glutinous rice starch at 0.35 degree of substitution was the best binder in manufacture of tablet by wet granulation method. It imparted the hardest tablets with short disintegration time and could be added in tablet formulation by dry incorporation method. Thus , this study is another expansion of the research works on the pharmaceutical application of sodium carboxymethyl starch by using it as the aid in preparation of pellets by extrusion and spheronization technique.

Pellets are spheres of varying diameters depending on the application. As a drug delivery system, pellets offer not only therapeutic advantages such as less irritation of GI tract and a lowered risk of side effects but also technological advantages, for example, lowest surface area to volume ratio, flows freely, less friable dosage form, narrow particle size distribution, uniform packing and ease of coating due to the ideal shape. (Ghebre-Sellassie and Knoch, 1995 ;O'Connor and Schwartz, 1989 ;Reynolds, 1970 ; Rowe, 1985 ; Vervaet, Baert and Remon, 1995). There are many processing methods available

to prepare pellets; however, the most popular method is by extrusion-spheronization technique.

Recently, the use of powdered cellulose for the production of pellets by extrusion/spheronization was studied (Linder and Kleinebudde, 1994). Furthermore, modified native starch base binder for pelletizing mineral material was patented. The result revealed that modified starch, used in this study, exhibited strong binding characteristics which are desirable in good binders (Dingeman and Skagerberg, 1991)

Therefore, in this study, glutinous rice starch was chemically modified by substitution reaction with carboxymethyl group to produce 3 degrees of substitution of modified starch. These modified starches were evaluated as an excipient in the production of pellet by extrusion-spheronization process.

A typical composition of pellet might contain the following ingredients : drug or other fillers, extrusion aid, binder and fluid (water or solvent). An extrusion aid is an essential component of the pellets : microcrystalline cellulose is commonly used. It controls the movement of water through the wet powder mass during extrusion and modified the rheological properties of the other ingredients in the mixture, conferring a degree of plasticity which allows it to be readily extruded (Fielden and Newton, 1992). In this study, however, modified glutinous rice starch was assessed as an extrusion aid in pellet preparation. The resulting pellet may present the good characteristics such as increasing in hardness when compared with blank pellet. In addition, the effect on the pellet properties of varying the added water content and other processing variables was also assessed.

Objectives of This Study

1. To modify the glutinous rice starch by carboxymethylation reaction and evaluate some characteristics of the obtained modified starches.

2. To investigate the extrusion aid properties of sodium carboxymethyl starches in the manufacture of pellets by extrusion and spheronization process.

3. To study the effect of degrees of substitution and the amount of modified glutinous rice starches on the various physical properties of pellets.

4. To determine the influence of some process and formulation parameters on the characteristics of products made by extrusion/spheronization process : amount of starting materials and water used , spheronizer speed , and spheronization or residence time.

5. To evaluate and compare some physical properties of pellets preparing from different formulations and process conditions.

หอสมุดกลาง สถาบันวิทยบริการ
จุฬาลงกรณ์มหาวิทยาลัย

Literature Review

Starch is widely distributed as the reserve carbohydrate deposited in the seeds , tubers or roots , leaves and stems of most land plants. It is generally occurring in the from of small granules or cells. The starch is described by its plant source as corn starch , rice or glutinous rice starch , potato starch , tapioca starch , etc. Since the conditions of growth are different in each plant , the starch from each plant source will vary somewhat in appearance , composition and properties.

Chemically , starch is a heterogeneous material consisting of anhydroglucose units (in the α-D-glucopyranose form) linked together through α-D-(1→4) glusidic bonds. Most starch consist of a mixture of two polysaccharide types : amylose , an essential linear structure , and amylopectin , a highly branched polymer. The ratio of these fractions in a particular starch varies depending on the source and is a major factor in determining the properties of that starch (Chalmers , 1968a ; Coutts and Smail , 1996 ; Remon and Voorspoels , 1996 ; Rutenberg , 1980 ; Wurzberg , 1986).

The linear polysaccharide , amylose , compose of about 200-2000 anhydroglucose units link through α-D-(1→4) glusidic bonds with a small amount of branching (Figure 1). In contrast , amylopectin is a large branched polymer consisting of short linear amylose chains which is connected to each other by α-1,6-linkages (Figure 2). Each branch contains about 20 to 30 units.

Properties of starch pastes such as clarity , viscosity , film-forming ability , gel-forming ability , gel texture , tendency to retrograde , and ability to withstand acid , shear and temperature extremes are determined by the amylose : amylopectin ratio (BeMiller , 1993).

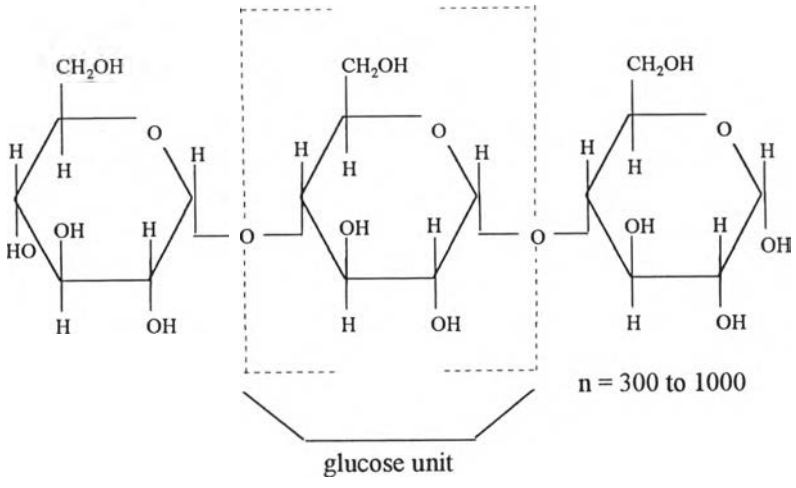

Figure 1 Linear structure of amylose molecule.

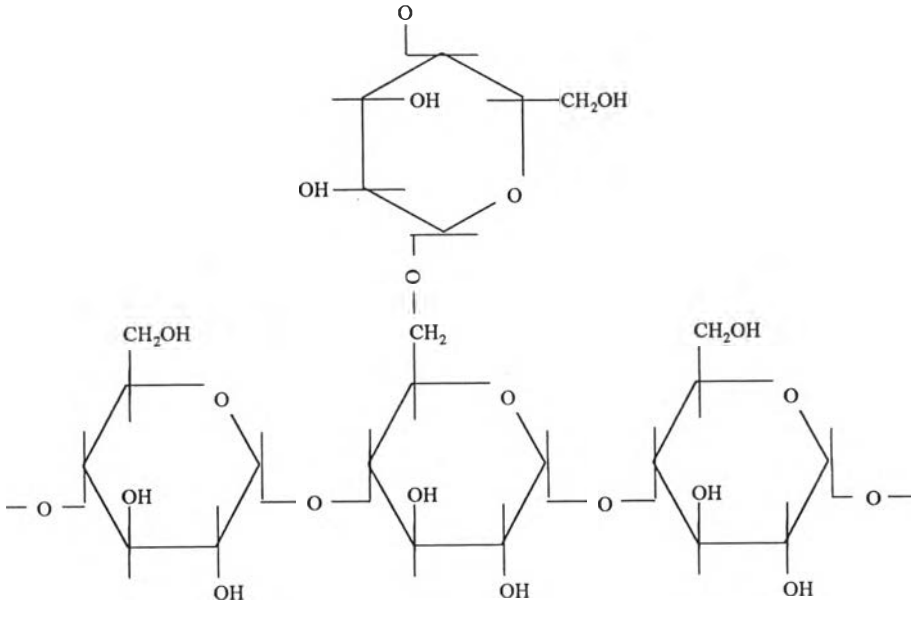

Figure 2 Branched structure of amylopectin molecule.

Modified Starches and Derivatives

The physical properties of native unmodified starches and of the colloidal sols produced from these starches on heating limit the usefulness of starch in many application. Depending upon the application , these imperfections may include the lack of free-flowing properties or water repellency of the starch granules ; insolubility or failure of the granules to swell and develop viscosity in cold water ; excess or uncontrolled viscosity after cooking ; etc.

Modified starch were developed to overcome one or more of these imperfections and thus expand the usefulness of starch for a myriad of industrial applications. Any product in which the chemical and/or physical properties of native starch have been altered might be considered to be modified. The term " starch derivatives " includes the modifications which change chemical structure of some of the D-glucopyranosyl units in the molecule. From a chemical modification standpoint the significant structural features of the starch are the glucoside oxygen linkages between anhydroglucose units , the primary hydroxyl group on carbon atom 6 , and the secondary hydroxyl groups on carbon 2 and 3 on almost every anhydroglucose unit in the starch molecule. The glusidic linkage is an acetal , stable under alkaline conditions and hydrolyzable under acid conditions. Thus , acid hydrolysis leads to depolymerization of starch , which if carried to completion results in the release of glucose. The hydroxyl groups can react to form ethers and esters and can be oxidized to aldehyde , ketone and carboxyl groups. The range of modifications cover the molecular scission , molecular rearrangement , oxidation , or introduction of substituent chemical groups into starch molecules.

Modified products include converted starches such as acid fluidities, pyroconversions , cross-linked starches , and all derivatives in which substituent groups have been introduced onto the starch molecules. Pregelatinized starches , redried starches , extruded starches and blend or mixes are products in which the properties of the starch have been physically modified (Rutenberg , 1980 ;

Rutenberg and Solarek , 1984 ;Whistler and Daniel , 1984 ; William , 1968 ; Wurzberg , 1986).

Modification or derivatization of starch is conducted to change the gelatinization and cooking characteristics of granular starch , to decrease the retrodegradation and gelling tendencies , to increase the water-holding capacity of starch dispersions at low temperature thereby minimizing syneresis , to enhance hydrophilic character , to impart hydrophobic properties , and/or introduce ionic substituents. Modification of starch properties is an important factor in the continued and increased use of starch to provide thickening , gelling , adhesive , and film-forming functionality (Rutenberg and Solarek , 1984).

The modified starches can be divided into 3 main groups which are:

I. Chemical reaction
   A. Crosslinking : Esterification , Hemiacetal and acetal formation
   B. Stabilization or Derivatization : Etherification , Esterification , Oxidation
   C. Graft and Block polymerization
   D. Depolymerization : Acid-catalyzed , Enzyme catalyzed , Oxidation followed by alkaline pH
   E. Transglycosylation plus depolymerization (dextrinization)
II. Physical transformations
   A. Pregelatinization
   B. Preparation of cold water-swelling starch
III. Genetic control / Plant breeding (BeMiller , 1993 ; Rutenberg , 1980)

Sodium O-carboxymethyl starch

Carboxymethyl starch , highly water-soluble starch ether derivative and usually obtained as the sodium salt , is prepared by reacting starch with chloroacetic acid or sodium chloroacetate in the presence of aqueous alkaline solution (sodium hydroxide). The preparation , properties and uses of this derivative have been reviewed (Chen , 1977 ; Hsieh , Chen and Yang , 1978 ;

Radley , 1968 ; Taylor , 1979 ; Wang , 1950) and patented (Filbert , 1952). The reaction of substitution with carboxymethyl group may be presented as the following equation.

$$ST\text{-}OH \xrightarrow[Na^{+}OH^{-}\ (pH > 11.8)]{ClCH_2COONa} ST\text{-}O\text{-}CH_2COONa + NaCl + H_2O$$

The reaction of monochloroacetate with starch molecule is undoubtedly bimolecular displacement (S_N2). It means the first formation of an intermediate complex , an alkaline starch , called starchate nucleophile. The substitution is said to be preferential at the secondary hydroxyl groups (Hofreiter ,1986; Radley ,1968 ; Roberts 1965). A major improvement in carboxymethylation technique involves conducting the reaction in a water-miscible solvent containing minor amounts of water. Furthermore , the high solubility of the derivatives precludes the preparation of product above DS 0.1 in aqueous systems with retention of granule form. Therefore , the lower alkyl alcohols , usually isopropanol , and acetone in varying proportions with water have served as reaction media. The higher DS products , up to 1.0 , have been obtained in nonaqueous media.

The carboxymethyl starch are anionic polyelectrolytes. When in contact with water, it form an apparent jelly which in fact the accumulation of grains swelled with water and huddled together. However, marked viscosity losses occur in the presence of added electrolytes. The viscosity of cold pastes is dependent upon the extent of degradation of the starch and on the carboxyl content.

Proposed or actual usages of carboxymethyl starch were component of absorbents , adhesives, medical poultices , paper and textile sizing , solid-suspending agents , thickening agents , film-forming , and numerous other uses resulting from the ability to form viscous aqueous solution and gel. Various studies reviewed the pharmaceutical uses of this starch ether derivatives such as

disintegrating agent in wet granulation or direct compression (Bolhuis , Kamp and Lerk , 1986 ; Guyot-Hermann , 1983 ;Soonthorn Worakul et al., 1980 ; Thavisak Teruya , 1995) , binding agent (Tasana Pituksuteepong , 1995) , suspending agent (Mishra , Jain and Agrawal , 1990 ; Ornanong Suwanapakul , 1996) , starch microcapsules (Remon and Voorspoels , 1996) , etc.

Pellets

Pellets are spheres of varying diameter depending on the application and the wish of the producer. Historically , the pellet has been used by a number of industries to describe a variety of agglomerates produced from diverse raw materials , utilizing different pieces of manufacturing equipment. These agglomerates include fertilizers , animal feeds , iron ores , polymer and pharmaceutical dosage forms , and hence do not only differ in composition but also encompass different sizes and shapes. This article reviews the pharmaceutical aspect of pellets.

Pellets are commonly filled into hard gelatin capsules and can also be compressed to tablets (Conine and Hadley , 1970 ; Jalal , Malinowski and Smith , 1972 ; Malinowski and Smith , 1974). The commercially available pellet formulations are mainly coated with a polymer film in order to obtain a controlled release effect. The use of different coating materials allows targeted drug delivery , for example , in the small intestine or in the colon. Pellets , manufactured in the pharmaceutical industry , are sized between 500 and 1500 μm.

In the manufacturing process , pellets provide a high degree of flexibility during the design and development of oral dosage forms. They can be divided into desired dose strengths without formulation or process changes , and can also be blended to deliver incompatible active ingredients simultaneously or particles with different release profiles at the same or different sites within GI tract. In addition , pellets have various therapeutic advantages such as less irritation of GI tract , maximize drug absorption , lowered risk of side effects.

Furthermore, they have technological benefits , for example , better flow properties , less friable dosage form , narrow size distribution , uniform packing and ease of coating (Ghebre-Sellassie and Knoch , 1995 ; Reynold , 1970 ; Vervaet , Baert and Remon , 1995).

A variety of techniques are available for production of pellets : layering (solution , suspension and powder layering) , extrusion-spheronization , balling , spray congealing and drying , and emerging technologies such as cryopelletization and melt spheronization. These pelletization processes are described briefly (Ghebre-Sellasie and Knoch , 1995). The most recent method for the production of pharmaceutical pellets is by means of the fluid-bed rotogranulator or by the centrifugal granulator performing the whole cycle in one closed system (Goodhart , 1989 ; Robinson and Hollenbeck , 1991).

Extrusion - Spheronization Technique

Extrusion and spheronization technique is the most commonly used and an appropriate method for producing pellets with desired qualities. This process was developed in the early 1960s , and since then has been extensively researched and discussed. Extrusion-spheronization process is a multistep procedure , as present in Figure 3 , and can be described as follow (O'Connor and Schwartz , 1989 ; Vervaet , Baert and Remon , 1995).

1. Dry mixing and granulation operation

The overall process begins with a dry mixing or blending operation of the drug and excipients in suitable mixers to prepare a uniform , heterogeneous mixture. Then , granulation step that is similar to a conventional wet granulation is performed. The endpoint of granulation is determined by the behavior of wetted or plastic mass that can be operated during extrusion operation. Typically , the blending and granulation steps are performed in the

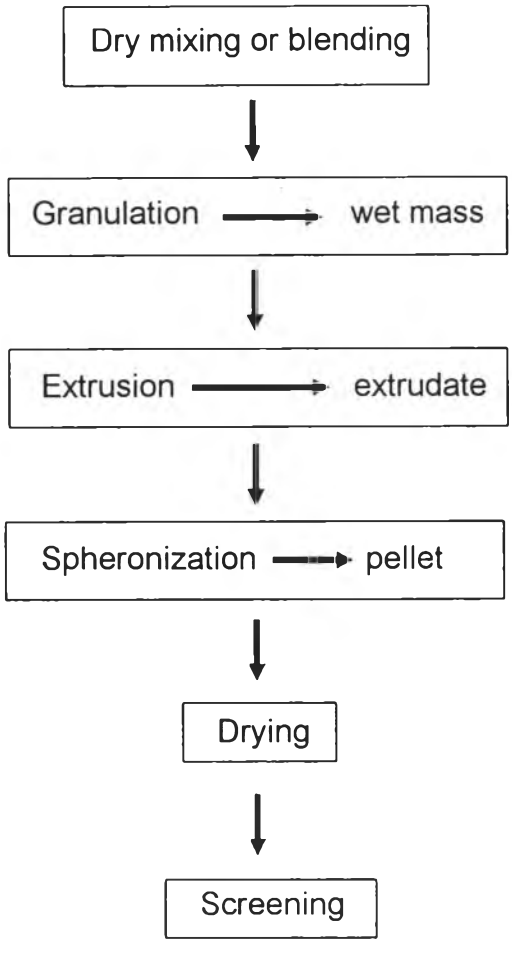

Figure 3 Flow chart of a typical extrusion-spheronization process

same equipment , i.e., a planetary mixer is commonly used. A special feature of the granulation step is the homogeneous distribution of the liquid phase throughout the granulated mass. During this step the evaporation of the fluid phase should be restricted to a minimum.

2. Extrusion operation

In the extrusion step , the wet mass is passed through the extruder to form rods , similar to short strands of spaghetti. This extruded strands are called extrudate. The extrudate length may vary , depending on the physical characteristics of material to be extruded , the method of extrusion , and how the particles are manipulated after extrusion. Different types of extruders can be

grouped into four classes , i.e., screw , sieve and basket , roll and ram extruders (Hick and Freese , 1989 ; Vervaet , et al.,1995).

A. Screw extruder

This type of extruder is the only strictly continuous devices as a result of extrudate can exit in a smooth continuous flow. As the name implies , screw extruder utilizes one or two (twin-screw) screw to develop pressure forcing the mass through opening. Two fundamentally different mechanisms for screw extrusion are possibles ; axial discharge type , in which the screen is placed perpendicularly with the axis of the screw and the material exit at the end of the barrel in the same direction as it is transported ; and radial type where the die is placed around the screw and the pathway for extrudate flow is perpendicular to the axis. Figure 4 show the schematic of screw extruder.

B. Sieve- and Basket- type extruders

In the sieve and basket extruders , the plastic mass is fed by gravity into the chamber and pressed through the screen by rotating or oscillating device. Basket-type extruder is similar to sieve extruder except that a vertical , cylindrical wall of the chamber make up the extrusion screen (Figure 5). So , the extrudate exit vertically from the screen of a sieve extruder , while , in the case of basket-type extruder , the extruder is formed in horizontal plane , perpendicular to the way that the mass is fed.

C. Roll extruder

In this type , the mass is fed and pressed between roller and perforated plate. Two different types can be described : the first type equipped with two contrarotating rollers which one or both are perforated and the extrudate is collected inside the extrusion rollers (Figure 6A and B). The second type of roll

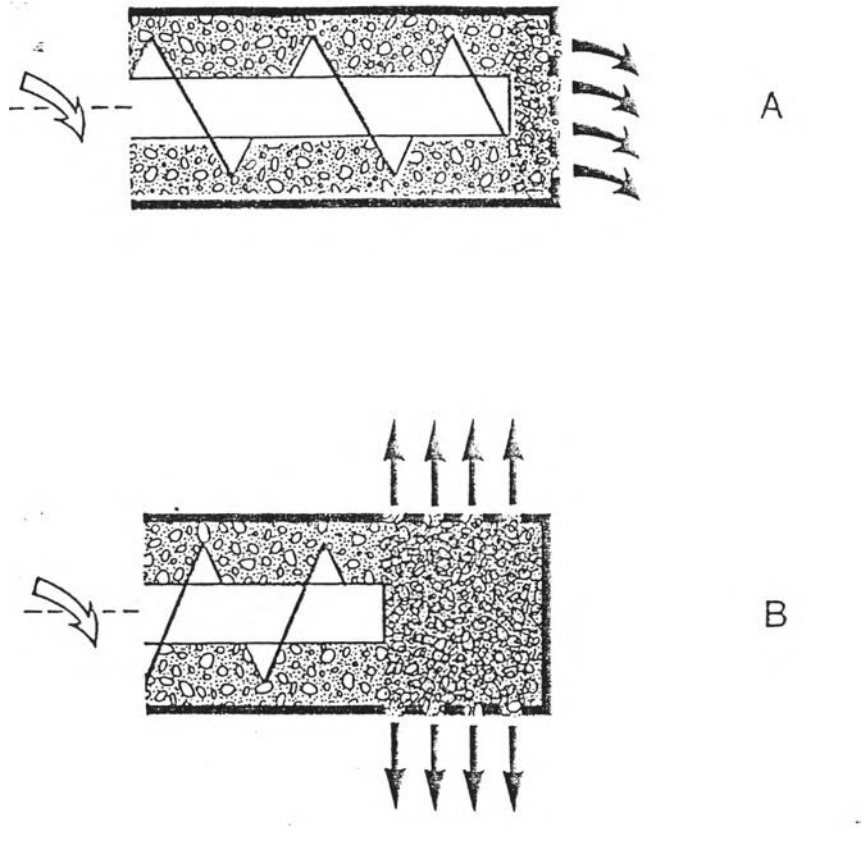

Figure 4 Schematic representation of screw extruder.

A : Axial type. B : Radial type

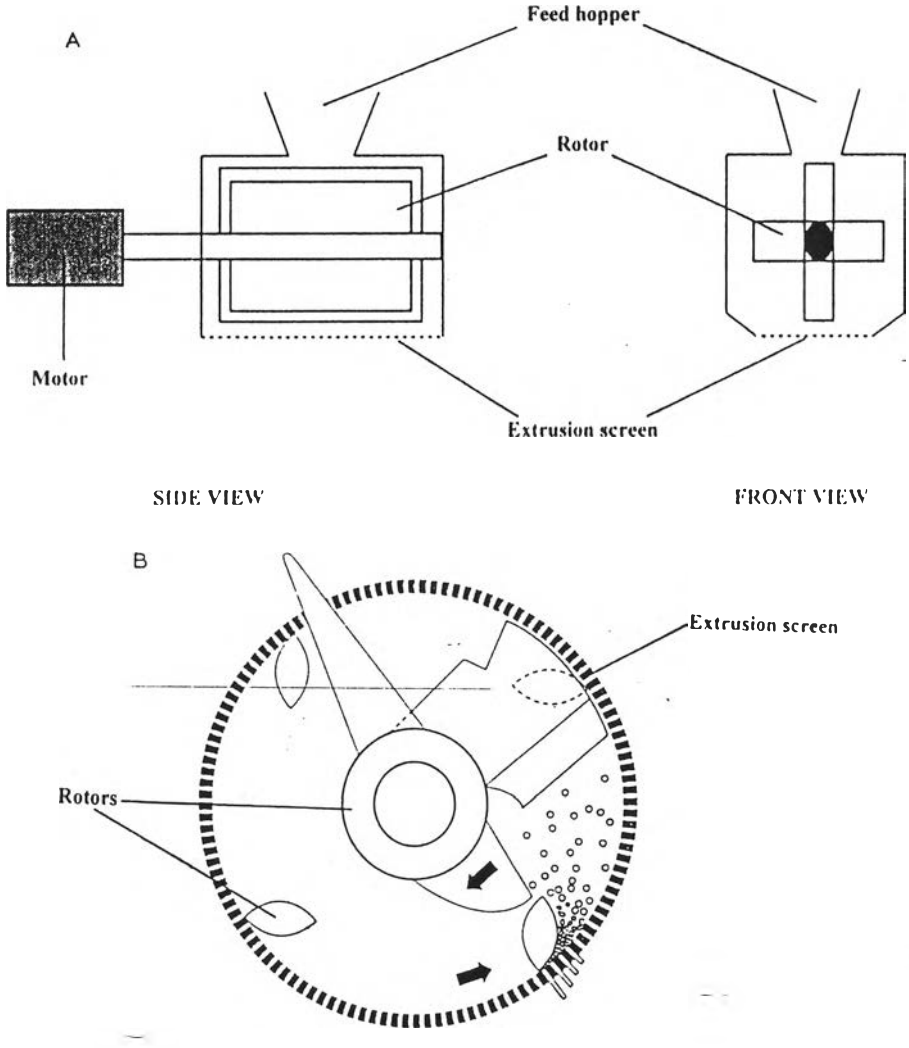

Figure 5 Schematic of a sieve extruder (A) and basket extruder (B)

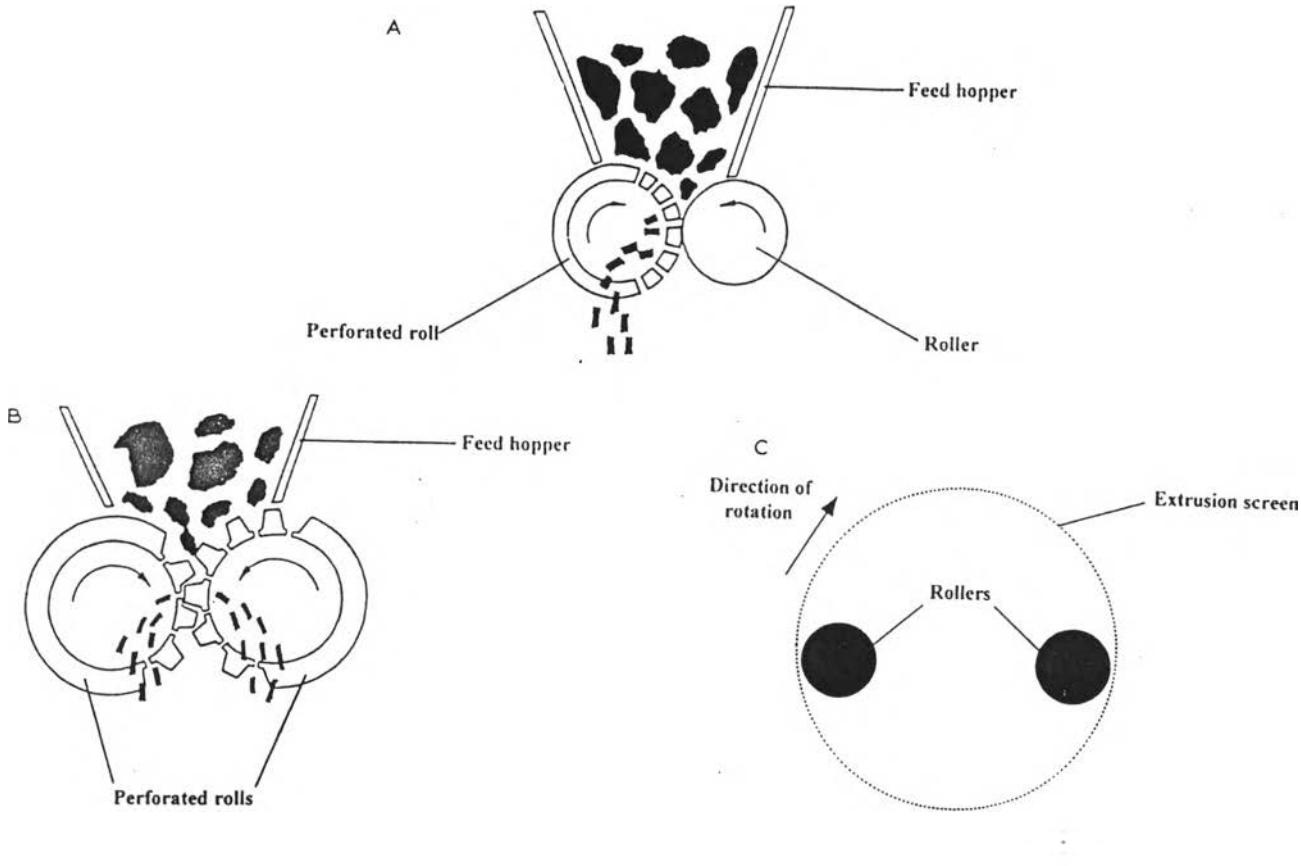

Figure 6 Schematic of roll extruders. (A) with one perforated roll , (B) with two perforated rolls , (C) with the extrusion screen rotating around rollers.

extruder has a perforated cylinder rotates around one or more rollers installed inside that cylindrical chamber and discharging the material outward (Figure 6C).

D. Ram extruder

Ram extruder , probably the oldest type of extruders , compose of a piston inside a cylinder or channel which compress the wet mass and force it through the screen situated at the end of the barrel (Figure 7).

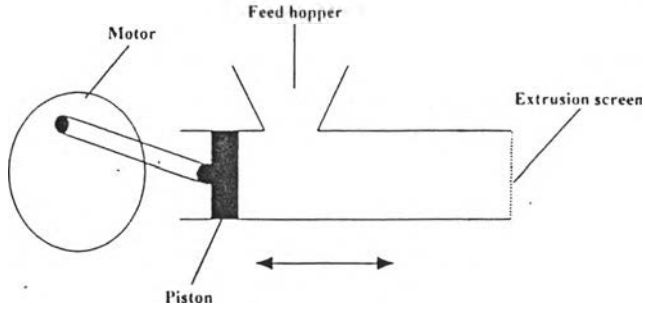

Figure 7 Schematic of ram extruder

The extrusion operation is the major contributing factor in the final pellet size. The diameter of extruder-screen openings directly controls the diameter of the extrudate , which is related to the mean pellet size. However , the mean pellet diameter has also been found to be dependent on the formulation. During extrusion step , the product temperature increases very little, probably because of a shorter compression zone and shorter depth of die opening. The heat generation can result in premature drying of the extrudate which can lead to a poor-quality of pellet. This aspect of the extrusion operation can be monitored by measuring the power consumption during extrusion , which is based on the extrusion force necessary to process the granulation (O'Connor and Schwartz ,

1989 ; Kleinebudde , Solvberg and Linder , 1994). The absence of heat build up may allow the processing of thermolabile drug substances.

3. Spheronization operation

In this phase , the extrudates are transported into a spheronizer , where the extrudates contact with the rotating friction plate and are broken up into short cylindrical rods. Then this rods are pushed toward and up the stationary wall of the processing chamber by centrifugal force. Finally , due to gravity , the particles fall back to the friction plate and the cycle is repeated until the desired sphericity is achieved. Thus , the extrudate is spheronized by interparticle collisions and particle-to-wall frictional forces. The spheronizing time is usually 2-10 min. , depending on the formulation characteristics.

A spheronizer , know as Marumerizer , consists of static hollow cylinder and rotating friction plate located inside. The friction plate has a grooved surface to increase the frictional forces. The geometry of grooves has two types , cross-hatch geometry and radial geometry (Figure 8). The friction plate is responsible for providing the energy necessary to produce pellets and for controlling the extent of pellet growth.

The requirements for spheronization of cylindrical extrudate are as follows : (Fielden and Newton , 1992 ; Ghebre-Sellasie and Knoch , 1995)

1. The extrudate must possess sufficient mechanical strength when wet , but it must be brittle enough to be broken down in spheronizer.
2. The extrudate must be sufficient plastic to enable the cylindrical rods to be rolled into spheres by the action of friction plate.
3. The extrudate must be non-adhesive to itself in order that each spherical particle remain discrete throughout the process.

In all cases it is possible to obtain uniform dense pellet with a narrow size distribution and provide cylindrical and smooth extrudate. If defects

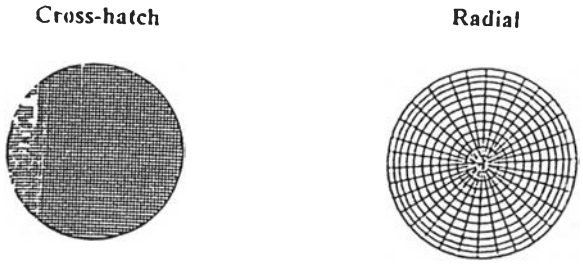

Figure 8 Geometry of the spheronization plate

such as shark skinning - the presence of regular , sharp , circumferential ridges with deep cracks penetrating the core of the extrudate - exist , the process becomes difficult to control , since initial breakage occurs randomly and poorly shaped pellet with wide size distribution are produced (Fielden and Newton , 1992 ; Rowe , 1985).

4. Drying and screening operation

The resulting pellet can be dried by conventional method such as air drying , oven drying and fluidized-bed drying prior to further processing. Fluidized-bed drying usually yields a product with a greater bulk density (Conine and Hadley , 1970). Recently , the use of microwave oven drying compared with oven drying was reported (Bataille et al., 1993).

A screening or sizing step might be necessary to separate the various fractions if the particle size distribution is wider than intended.

Pellet Formulation

The formulation is one of the most important parameters in the production of pellet. The result from many studies demonstrated that the quality of pellet was depended on the starting material (O'Connor, Holinej and Schwartz , 1984 ; Pinto , Buckton and Newton , 1992). The granulated mass should be

plastic and sufficiently cohesive and self-lubricating during the extrusion step. The degree of liquid saturation of the granulation is one of the most critical factors in the formulation , and must be just high enough to bring about the optimum surface plasticity required for spheronization.

A typical formulation or extrusion mixture may contain the following ingredients :

Drug and/or diluents	50-90 %
e.g. lactose , dicalcium phosphate	
Extrusion aid	5-50 %
e.g. microcrystalline cellulose	
Binder (if necessary)	qs.
e.g. polyvinyl pyrrolidone (PVP)	
cellulose derivatives (Sodium CMC)	
Other excipients (if necessary)	qs.
e.g. lubricant , pH modifier	
Fluid	qs.
e.g. water or solvent	

Extrusion offers the advantage of incorporating a relative high proportion of drug , up to 90 % , however , depending on the physico-chemical properties of the drug. Microcrystalline cellulose is one of the most important and widely investigated excipients as extrusion aid in extrusion-spheronization process (Fielden and Newton, 1992; Ghrbre-Sellasie and Knoch, 1995; O'Connor and Schwartz , 1989). It modifies the rheological properties of the other ingredients in the mixture and imparts plasticity to the pellets. In addition , it provides highly absorbent and moisture-retaining characteristics. Variation in type of microcrystalline cellulose significantly change the rheological properties of the mixture and therefore the extrusion characteristics (Hileman et al., 1993 ; Sonaglio et al., 1995). Binder and other excipients may or may not be necessary , based on the properties of other ingredients. Binder can increase plasticity and reduces extrudate friability.

หอสมุดกลาง สถาบันวิทยบริการ
จุฬาลงกรณ์มหาวิทยาลัย

Factors influencing pellet characteristics

There are various process and formulation parameters that influence on the qualities of pellet. These parameters can be described as follows.

1. Formulations

1.1 The moisture content in granulated mass

The moisture content play a critical role in the extrusion-spheronization process. Many researches presented the effect of moisture content on the characteristics of final pellet (Baert and Remon , 1993 ; Fielden , Newton and Rowe , 1993 ; Hasznos , Langer and Gyarmathy , 1992 ; Hellen et al., 1993a; Malinowski and Smith , 1975 ; Otsuka , Gao and Matsuda , 1994 ; Pinto , Buckton and Newton , 1992). If the moisture or water content is more than the possible range , an overwetted mass and agglomeration of individual pellet during spheronization may occur. Furthermore , mean diameter , size distribution, sphericity , hardness and drug release rate may be increased. The increasing of hardness due to the decreasing of porosity and friability of pellet.

1.2 The physical properties of starting material

As mentioned previously , the different types of microcrystalline cellulose , or other starting materials , can change the characteristics of pellets. Hileman et al. (1993) reported that Avicel RC-591 produced more dense pellets than did Avicel RC-581. Herman et al. (1988) demonstrated that using different types of microcrystalline cellulose (Avicel PH 101 and Avicel RC-581 ; microcrystalline cellulose blended with carboxymethyl cellulose) provided the pellets with different release rate in various types of dissolution fluids. Application of low substituted hydroxypropylcellulose (L-HPC) in the production of pellets was investigated by Kleinebudde (1993). The results showed that porosity increased

with increasing hydroxypropyl content of L-HPC , consequently , faster dissolution was obtained.

In addition to the consideration of different types of starting material , the use of similar materials but different in particle size has a profound influence on the size and roundness of the spheres (Fielden , Newton and Rowe , 1992a ; Wan , Heng and Liew , 1993). Furthermore , the different trade name of the same material affect the qualities of final pellets.

2. Extrusion process

2.1 The type of extruder

Several researches have investigated the effect of extruder type on the pellet characteristics (Baert et al., 1992b ; Fielden , Newton and Rowe , 1992 b). Fielden and coworkers compared some behaviors of wet mass using the different types of extruder, ram and cylinder or roll extruder. The results showed that the pellets obtained from the two types of extruder differed in particle size distribution and sphericity. The uncontrolled agglomeration occurred when ram extruder was used and this behavior depended on the particle size of starting material. This occurrence was due to differences in shear rate or shear stress between these two types of extruder. Furthermore , the different in particle size distribution was owing to distinction in the length-to-radius ratio (L/R ratio) of the extrusion screen when the different types of extruder was used.

2.2 The extrusion speed

Harrison et al. (1985) reported that an increase in extrusion speed (high throughput rate) affected the extrudate quality including surface impairments , for example , roughness and shark-skinning. These defects produced pellets with wide particle size distribution because the extrudate will break up unevenly during the initial stages of spheronization process. This

finding agree with Pinto et al. (1992) whose noted that extrusion speed has a significant influence on the size of pellets. On the other hand , the other researches found that the extruder speed has no significant effect on size and size distribution of pellets (Hasznos , Langer and Gyarmathy , 1992 ; Hileman et al., 1993).

2.3 The extrusion screen size

The extrusion screen size is characterized by the thickness of the screen and the diameter of the dies. The diameter of the dies determines the size of the pellets. Fielden and Newton (1992) noted that shark-skinning is caused at very short die lengths (L/R; length to radius ratio = 2) . Further increase in the L/R ratio (L/R > 8) improves the quality of the extrudate and results in a smooth surface. Hileman et al. (1993) reported that pellet size was determined by the extrusion screen size and increasing screen size (0.8 to 1.2 mm.) improved the shape score of pellet. Many authors also observed the influence of screen size on the quality of pellet (Harrison, Newton and Rowe, 1985; Malinowski and Smith, 1975; Newton , Chapman and Rowe, 1995; Pinto, Buckton and Newton, 1993).

3. Spheronization process

3.1 The spheronization speed

Several authors indicated the effect of spheronization speed (speed of friction plate) on the characteristics of pellets (Baert et al., 1993 ; Bataille et al., 1993 ; Hasznos et al., 1992 ; Hellen et al., 1993a ; Hellen and Yliruusi , 1993 ; Newton et al., 1995 ; Wan et al., 1993 ; Woodruff and Nuessle , 1972). An increasing in spheronization speed resulted in a size reduction of pellets with narrow size distribution. Rounder pellets could be produced using faster speed of friction plate and those rounder pellets have better flow properties than dumbbell or rod shaped pellets. Bataille et al. (1993) observed that any increase in the spheronization speed provokes a decrease in porousness and gives a greater

hardness and smoother surface condition. The friability , bulk and tapped densities and flow rate of pellets were also influenced a change in spheronization speed.

3.2 The spheronization time

The spheronization time or residence time appear to have a significant influence on the quality of the spheres. A longer spheronization time yielded the pellets with rounder (Baert et al., 1993 ; Hellen et al., 1993a ; Hellen and Yliruusi , 1993) , increasing bulk and tapped densities (Hellen et al., 1993a ; Malinowski and Smith , 1975) , small particle size and decreasing the amount of fines (Wan et al., 1993) , narrower particle size distribution (Bianchini et al., 1992). In contrast , some authors found no influence of residence time on the hardness and friability when formulations containing only Avicel PH 101 were spheronized for different residence time. Some researches found that pellet size distribution may or may not be influenced by a change in spheronization time.

3.3 The spheronizer load

The influence of spheronizer load was studied by Hasznos et al. (1992) and Newton et al. (1995). The small loads such as 50 and 100 g. produced granules of great length and diameter , low density and low spherical form. The higher load eventually produced more round granules. According to Hasznos et al. (1992) , the mean diameter of pellets increased with increasing spheronizer load. Barran and coworkers (1993) noted that the hardness increased and roundness decreased with increasing load.

4. The drying method

The importance of drying method on the quality of pellets was determined by several authors (Bataille et al., 1993 ; Dyer et al., 1994). The results showed that fluidized-bed technique produced pellets with slower drug

release , smoother surface , lower mechanical strength but higher elasticity when compared with tray-drying. Bataille et al. (1993) reported that pellets dried in microwave oven , compared with ordinary oven , had rougher surface , more porousness and lesser hardness.

In studying either of the previous described parameters that influencing the quality of pellet , the other parameters should be simultaneously considered or be controlled in the constant values. The effects of these parameters is also depended upon the formulation characteristics.

Method used to evaluate the characteristics of pellet

The method used to evaluate the quality of pellet was briefly described by Vervaet , Baert and Remon (1995). Some of these methods are also noted in this article.

1. Particle size and size distribution

The size of pellet can be expressed using variety of parameters such as mean diameter , geometric mean diameter , and mean particle width and length. Simple sieve analysis is the most commonly used in particle size analysis. The weight of pellets in a certain size range is plotted against the size range , so-called frequency distribution curve. Then , the cumulative percentage over- or undersize is plotted versus particle size. If pellet size distribution is log-normal type , a linear relationship is obtained when the logarithm of particle size is plotted against the cumulative percent frequency on a probability scale (Martin et al., 1993). Two parameters used from this plot is slope of the line ; geometric standard deviation (σ_g) , and the point which is the logarithm of particle size equivalent to 50 % on the probability scale (50 % size or geometric mean diameter or d_g). The geometric standard deviation can be calculated from the following equation.

$$\sigma_g = \frac{50\ \%\ \text{size}}{16\ \%\ \text{undersize (or 84 \% oversize)}}$$

The more advanced method used to determine the size of pellet is computer-aided image analysis (Hellen et el., 1993b ; Wan et al., 1993 ; Fielden et al., 1992a).

2. Friability

The tendency of pellets to flake off during handling resulting in the formation of dust is assessed by rotating the pellets in a friabilator for a fixed period of time. The glass or metallic beads is used to increase the mechanical strength on the pellets. Turbular mixer can be used instead of the friabilator. Utilization of the following equation , the percent friability is obtained.

$$\%\ \text{Friability} = \frac{(\text{Initial weight of pellets} - \text{Weight retained})}{\text{Initial weight of pellets}} \times 100$$

3. Hardness or strength

The hardness of pellet is performed by measuring the force required to break a pellet of well known size. Baert and Remon (1993) used the tensile tester for the determination of pellet hardness. The strength of pellet increases with increasing diameter and can be correlated with the friability.

4. Density

The bulk and tapped densities of pellets are determined to gain an idea of the homogeneity of the particle size distribution (Robinson and Hollenbeck , 1991 ; Woodruff and Nuessle , 1972). The true and apparent densities evaluate the porosity of the pellets and can be determined by the displacement of helium or mercury using densitometer or porosimeter. The principle of this method is forcing either helium or mercury into pellets void

spaces under pressure (Bataille et al., 1993 ; Linder and Kleinebudde , 1994 ; Millili and Schwartz , 1990). The porosity can be calculated as :

$$\varepsilon = (1 - \rho_t / \rho_a) \times 100 \quad (\%)$$

in which ρ_a is the apparent density and ρ_t is the true density of the particles. The true density can also be measured by a pycnometer.

5. Morphology by scanning electron microscopy

Scanning electron microscopy (SEM) pictures are taken to observe the microstructure of the pellet surface and/or internal structure of cross-sectioned pellet.

6. Sphericity

Several methods exist to determine the sphericity or roundness of pellet (Eriksson et al.,1997). These methods can be briefly described as follows :

6.1 Visual inspection of the pellets and classification into a group (Hellen and Yliruusi , 1993 ; Hellen et al., 1993a).

6.2 One plane critical stability (OPCS) that is the measurement of the angle to which the plane must be raised before the particle will roll (Chapman et al., 1988 ; Fielden et al., 1992a ; Newton et al., 1995) using a microscope and computer-linked digitizing unit. The method is particularly applicable to differentiate the various shapes formed during the production of pellets. The angle is high , greater than 35° , for elongated shapes such as rods or dumbbells , and is reduced to less than 15° for the spheres obtained at the end of spheronization. However , The OPCS differentiates small change in roundness and a special computer system with a licensed routine are needed. In addition , each pellet has to be measured individually (Podczeck and Newton , 1994).

6.3 The ratio of the largest and the smallest diameter of a pellet , and shape or form factor , calculated by means of the projected area of the pellet and its perimeter , are measured with computer-aided image analysis (Baert et al., 1992 ; Baert et al., 1993 ; Hellen and Yliruusi , 1993 ; Kleinebudde , 1993 ; Linder and Kleinebudde , 1994 ; Podczeck and Newton , 1994 ; Wan et al., 1993). These parameters can be expressed as the following equations.

$$\text{Aspect ratio} = \frac{\text{Longest diameter or length}}{\text{Smallest diameter or width}}$$

$$\text{Form factor} = \frac{4\pi[\text{Area}]}{[\text{Perimeter}]^2}$$

For optimal round particles , aspect ratio close to one is obtained. The measured values for form factor exhibit the same dependencies as the value for aspect ratio. However , the form factor does not distinguish between round and less round pellets. The form factor is an important factor in the case of irregularly shaped particles.

7. Dissolution testing

The drug release profile from pellets is an other main characteristic. The dissolution systems used in dissolution testing are depended on the properties of drug. Several authors correlated parameters such as hardness , composition , drug loading , etc. with the release profiles of drug but it is difficult to take general conclusions since the work has been different dissolution systems.