Chapter One

General Background

1. Introduction

Powdered sugar and tapioca starch are abundant agriculture products of the country. But both materials have gained no wide spread popularity in the field of tablet production among the local pharmaceutical manufacturers. This may be due to it is always recognized that tablets containing high proportion of powdered sugar may exhibit tendency to undergo moisture uptake and harden with time. As well as the extensive use of starch as the additive in tablet, the tapioca starch is seldom selected in comparing with the other types of starches, e.g., corn starch.

One reason is probably the consequence concerning the lack of useful information on the experimental data supporting the utilization of these two materials together in tablet products. So an attempt has been made here in order to encourage the use of powdered sugar and tapioca starch in combinations in the manufacture of tablets. This combination is considered appropiate since tapioca starch may play the role as a sorbent agent to reduce hygroscopic property of powdered sugar. Successful application of powdered sugar-tapioca starch mixtures in making tablet of drug substances by wet granulation process have been demonstrated but extensive studies are still required to generate more useful information (1). So in this investigation another alternative application of the powdered sugar-tapioca starch mixtures is proposed by preparing such mixtures in the form of granules which are ready to be employed in manufacturing tablet products especially of microdose drug substances by direct compression process.

The development of the excipients suitable for compression may be mainly classified into physical modification and physico-chemical modification processes. Spray-dried lactose and Nutab^{R} (compressible sugar) are the examples of direct compressible diluents produced by physical modifications. Spray-dried lactose is produced by spray drying process. While Nutab^{R} is prepared using dry granulation process by roll compaction of sugar with small amount of starch and magnesium stearate as processing adjuncts. Pregelatinized starch and microcrystalline cellulose are the direct compressible diluents which are produced by simultaneous modification of both physical and chemical nature of materials. However, in each case the changes have resulted in materials that more closely resemble minigranulations than individualized crystal particles in order to endow them with properties of fluidity and compressibility.

In fact conventional wet granulation is as well a process that designed to achieve modification of the physical nature of the materials into the granule forms. To simplify the process of modification, the ordinary wet granulation process is employed in this study to produce powdered sugar-tapioca starch granules using fluidized bed granulator equipment. Fluidized bed granulation technique provides several attractive considerations to be chosen as the process of modification :

- the process of granulation can be accomplished in one unit, with no material handling between steps.
- automatic fluidized bed granulation is available including powder loading into and discharge finished granules from the granulator.
- automatic operation will reduce the variation between production batches or between the operators
- an equipment is not so sophisticated technology and it is able to be assembled locally

2. **An Overview of Fluidized Bed Granulation**

The process known as fluidized bed granulation has been extensively used for wet granulation since early 1960's. Fluidized bed granulation of pharmaceutical was first introduced by Wurster in 1959 (2). Subsequently, in

1964 Scott et al (3) and Rankell et al (4) introduced the theory, design, and operating equipment that may be applied to the continuous production of tablet granulation by fluidized bed process.

Fluidized bed technology was first used in the pharmaceutical industry for the rapid and intensive drying of powdery and granular materials (5). The next technological step was the application of the fluidized bed to spray granulation.

The greatest merit of this method is that it meets the requirement of GMP very well, since mixing, wetting and drying are combined in a single process, reduction of cross-contamination and escape of toxic material. Pollution of air by solvents can also be prevented by using a specially constructed fluidized bed operating in a closed system. Some of the advantages of fluidized bed granulation technology for the preparation of solid dosage forms are (6)

- It is a single vessel process where powders can be blended, agglomerated and dried in one operation. Efficiency is excellent with yields of 97 to 100 % with typically less than 1 % fines and 3 % overs.
- Granulation characteristics, mean particle size and particle size distribution are controllable.

- Uniform distribution of high dilution ratio of drug particles and diluents can be achieved as a batch to batch reproducibility.
- The granulate material exhibits high flow characteristics, is virtually fine free and normally allow for the use of less lubricant, high press speed of tabletting machine, and reduced compression forces.
- Tablets exhibit excellent disintegration and dissolution properties while retaining good hardness and friability. Frequently, expensive disintegrants can be removed from formulation when the transition from conventional granulating techniques to fluidized bed granulation is used.

For the economic advantages of using fluidized beds, can be summarised as (5, 7)

- reduced operating time
- reduced direct labour requirements
- reduced stream and power requirements
- reduced space requirements
- reduced equipment requirements
- reduced clean up requirements
- imporved yield
- minimum handling of material between processing steps.

For the disadvantage of fluidized bed granulator is the enhanced risk of explosion due to the large amount of oxygen conveyed by the fluidized air. The explosion might involve dusts, solvents or hybrid mixture of dusts and solvents being ignited by a spark induced by electrostatic charging. However, many different methods of preventing explosions in fluidized bed granulators are found with success. Inertisation relies on the avoidance of oxygen by using inert gas. Such a process can only be made economic by recirculation of the inert gas in a closed system (8).

Fluidized Bed Granulator

Figure 1 illustrates a schematic cross section of a typical fluidized bed granulator. The fluidized bed granulator is composed of three product contact sections, although different types are commercially available, all standard equipments are similar to that shown in Figure 1. First, the conically shaped product container has a perforated bottom for incoming air flow and holds the product to be processed. Second, extending vertically above the product container is the cylindrical expansion chamber where a nozzle is centred to spray the binder solution downward upon the fluidized bed of material. Third, extending upward from the expansion chamber is the outlet air filter housing. Fluidized bed equipment is

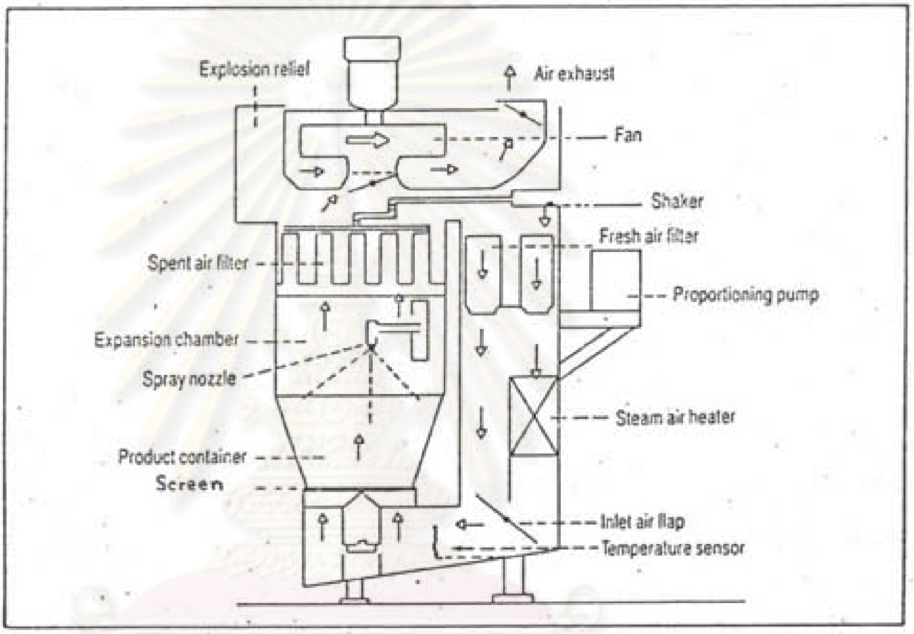

Figure 1 Schematic Cross Section of a Typical Fluidized Bed Granulator

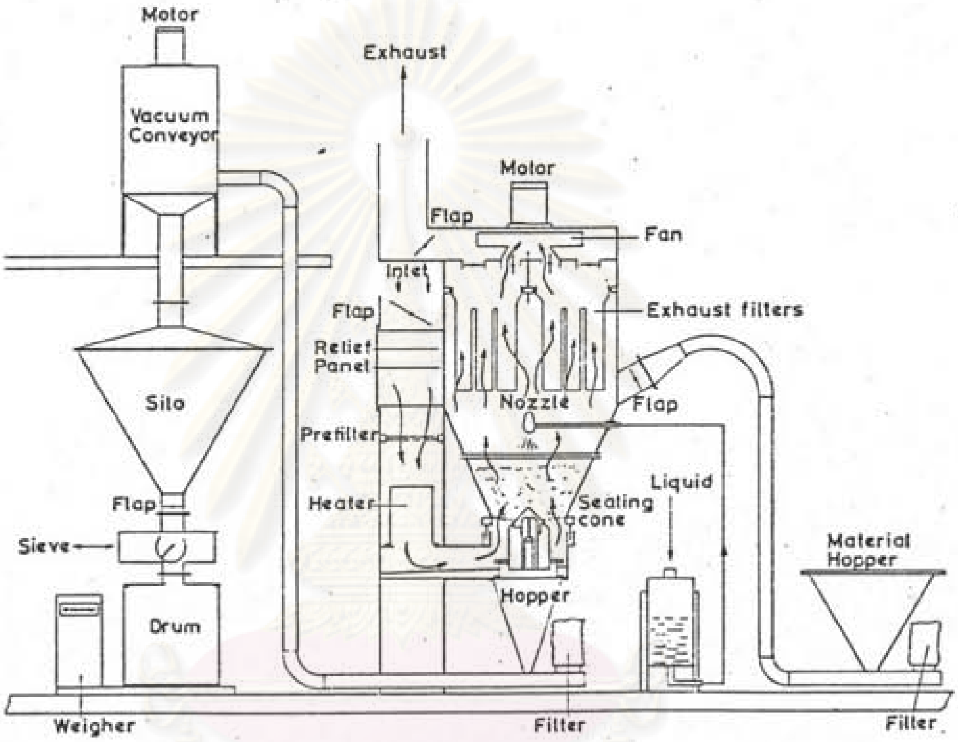

Figure 2 Schematic Cross Section of an Automatic Fluidized Bed Granulator

usually provided with a shaking type bag filter which retains powder material in process. During the process, the fluidization stops and the filter bag is mechanically shaken so that the fine material returns to the bed for agglomeration. Figure 2 shows a schematic view of the automatic fluid bed spray granulator system with its integrated material-loading and handling system.

A typical fluidized bed granulation process involves three major phases (9) :

1. preblending the powder
2. granulating by means of a suitable liquid binder
3. drying to a suitable moisture content.

The typical formulation granulated by this process may contain the active ingredient and a number of excipients that are preblended for several minutes in the granulating container by the fluidized air which generated by a suction fan mounted in the top portion of the unit which is directly driven by an electric motor (see Figure 1). The air used for fluidization is heated to the desired temperature by heater, after first being drawn through prefilters to remove any impurities. After this phase the binding agent, more often in aqueous solution than an organic solution, is sprayed at suitable rate onto the fluidized powder mass through a nozzle arm assembly situated at a predetermined height in the expansion chamber to initiate the agglomeration process. The drying phase also had occurred during the granulation phase as well as in the drying phase (10).

Granules Formation Mechanisms

In a manner similar to granule growth in a rotating drum, the granule growth process in fluidized bed granulation may be devided into three stages ; nucleation, transition, and ball growth (5).

At the start of the "nucleation" region, nuclei of two or more primary particles are formed and are held together by liquid bridges whcih are primarily pendular (see Figure 3). The size of these nuclei will depend on the size of the atomised drops. After addition of binder solution in a certain quantity, most of the primary particles are agglomerated and the nucleation region passes into a "transition" region reflected in a fall in growth rate. In this region liquid bridges change gradually from the pendular into the funicular state and finally into the capillary state due to the continuous addition of liquid and to consolidation of agglomerates caused by mechanical stress and hydrostatic tension in the liquid bridges.

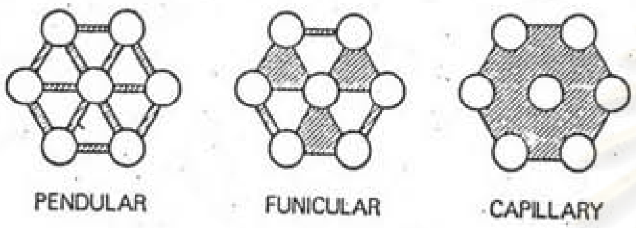

Figure 3 Granule Formation Mechanism as Described by Story (Reference 5)

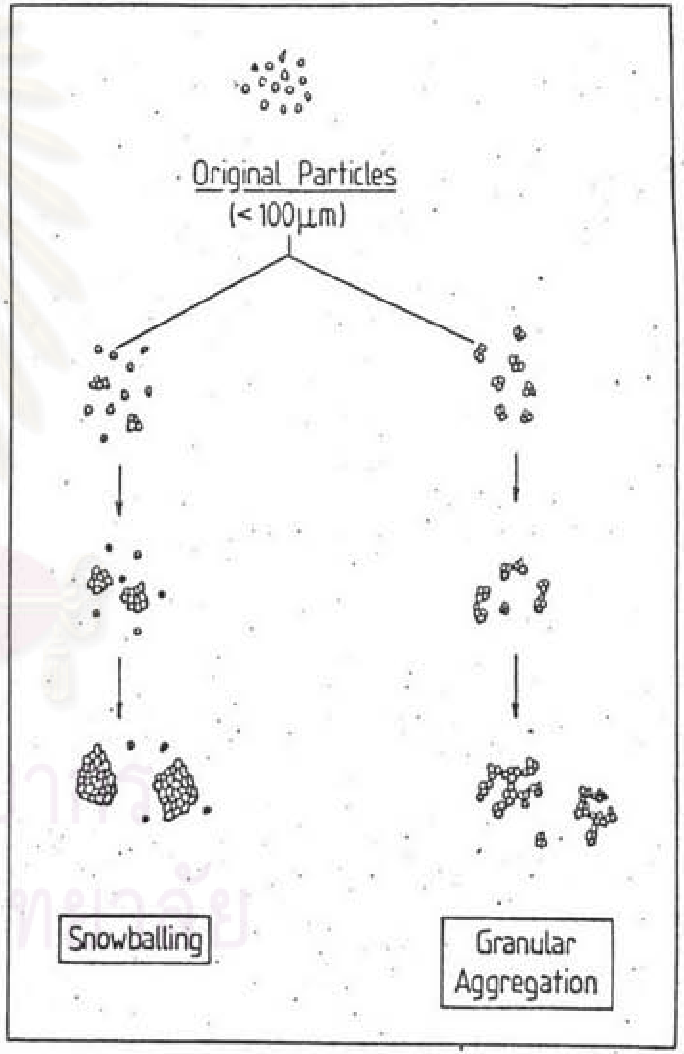

Figure 4 Granule Formation Mechanism as Described by Alkan and Yuksel (Reference 11)

As most of the liquid bridges change into the capillary state due to further addition of liquid, a considerable growth will occur through coalescence of granules. At this stage the transition region proceeds into the "ball" growth region exhibited by a sudden and uncontrolled growth.

Cohesion forces between granules are augmented with increasing water content, which necessitates an increased air velocity in order to keep the granules fluidized. The fluidizing air will tend to separate the granules and thus counteract agglomeration.

But Alkan and Yuksel (11) had described the granule formation in a fluidized bed granulator into two mechanisms, snowballing and granular aggregation. These are shown schematically in Figure 4. The first mechanism involves the initial formation of primary granules by the aggregation of a few individual particles (nuclei). The second mechanism involves the formation of large granules by the direct agglomeration of the primary granules with each others. They explained that the rate of growth of granules with this second mechanism should be higher than that occurring with snowballing.

Factors Affecting Fluidized Bed Granulation

There are many parameters affecting the properties of the final granules prepared in a fluidized bed. This can classified the possible variables during fluidized bed granulation into three groups (11)

1. apparatus parameters
2. process parameters
3. product parameters

1. Apparatus Parameters

Apparatus variables are related to the construction of the fluidized bed granulator equipment. Aulton and Banks (12) concluded that there are 3-4 numbers of the apparatus parameter that may affected the granule properties, i.e., air distribution plate, shape of product container and positive or negative pressure operation within the granulation chamber. But these parameters seem to make little effect on granule properties as optimisation of designs of the fluidized bed granulator equipment has already been considered by the manufacturer.

2. Process Parameters

Most of the published work on fluidized bed granulation has been carried out to investigate the effect of process parameters (13). Practically, process variables need to be controlled very carefully within fine limits. This means that when each of these has been adequately investigated for one product, there is often a need to start anew with the next formulation.

2.1 Effect of Moisture during Processing

In general, fluidized bed granulation is controlled by the moisture content of the bed. If the moisture content is too high, the bed becoming overwetted and defluidized rapidly, and if the moisture content is too low, no agglomeration will occur (13). Controlling of fluidized air by relative humidity measurement is needed during granulating process (14).

At any given time, the moisture content of the granule depends on wetting and evaporation, which are primary controlled by liquid flow rate and inlet air temperature (5). Aulton & Banks (15) concluded that the properties which produced a good granules were those which tended to increase the wetness of the granulation and delay its drying, i.e.

- a more dilute solution of granulating fluid
- a larger spray rate
- a lower inlet air temperature

2.2 Bed Load

The amount of powder in a given production batch must be suitably adjusted. With too little powder in the bed, the process is inefficient and thus uneconomical. Wetting of the wall of the container by the spray can also occur (12). Too much powder leads to ineffective fluidization and over wetting of the surface layers. This can result in the production of large lumps which then fall to the bottom of the bed.

2.3 Fluidizing Air Flow Rate

Aulton and Banks (15) indicated that fluidizing air flow rate did have a significant effect on granule quality, a higher air velocity producing small granules. This was attributed to two factors ; firstly an increase in evaporation rate at a higher air velocities reduced the wetness of the particles during aggregration and, secondly greater attrition of the granules in the more turbulent air condition causing fragmentation of large size granules.

The volume of fluidizing air can be affected by several factors (16). For instance, as the outlet air filter or the product container screen becomes occluded by binder, or by fine powder, resistance to air flow increases. The volume of air can drop enough to cause the bed moisture to increase, thereby increasing the bulk density of the finished granules. However, the volume of fluidized air which affects the process of agglomeration generally cannot be maintained at one level throughout the granulation process. Because the density of the fluidizing mass is constantly changing as a result of the wetting process and granule growth. So it must be continuously adjusted to maintain a constant level of fluidization.

2.4 Fluidized Air Temperature

The inlet air temperature has been shown to exert a highly important influence upon granule quality because it is critical for granule formations (12, 17). If the temperature is too low (below 40°C), excessive wetting of particles will promote side wall caking and excessive lump formation and will hinder and eventually stop particle fluidization. Conversely, if the temperature is too high(above 100° C), the air will spray-dried the binder solution resulting in no agglomeration (9). In a laboratory-size fluidized bed granulator (15 kg or less) ; inlet air temperature of 40-60°C for granulating and of 80-95°C for drying are recommended. In production scale (300 kg or larger), an inlet air temperature in the range of 80-95° C can be used in both phases.

Since granule size and moisture content are increased during liquid addition, the fluidizing air has to be increased simultaneously in order to keep the bed expansion constant. When using fluidized air of low temperature, climatic conditions can play a significant role in the fluidized bed process (16). In geographic location where the specific humidity varies during the year, its effect on the relative humidity of the heated fluidized air becomes pronounced. Of the several possible approaches to solving this problem, the simplest is dehumidification to a predetermined maximum dew point.

A number of investigation (12, 15, 17-18) have been tried to understand the effect of the inlet air temperature. The conclusions for these factors are :

1. increasing the temperature yields
    - smaller granules
    - friable granules
2. decreasing the temperature yields
    - increased granule size
    - reduced granule friability
    - increased bulkiness of the granules
    - increased flow rate of the granules

2.5 Binder Solution Spraying Rate

The adjustment of the spraying rate of binder solution should depend on the amount of moisture in the fluidized air, the evaporation rate of the solvent, and must be balanced with the temperature of the fluidized air (3, 19). If the fluid addition is too fast the bed is overwetted, if too slow there is insufficient wetting of the powder and granulation is not achieved.

Several authors (15, 17-18, 20-21) found that an incrased liquid flow rate, results in a larger granule size, reduced friability and increasing granule flow rate. A linear correlation has been found between flow rate and granule size with the slope of the line dependent upon the type of binder (3).

2.6 Nozzle Height

The relationship of the height of the nozzle to the height of the powder bed in the granulating container affects granule size and friability resulting from over and under wetting (9,.13). If, for example, the nozzle is too close to the fluidized mass, it interferes with the fluidized pattern, caking and lump formation of the powders occurred because of overwetting, and the nozzle is more likely to clog. If the nozzle is located at a higher than optimum level, however, the atomized binder drops are spray-dried before they can wet the fluidized particles, resulting in under wetting and reduced agglomeration, and can also of wetting the wall of the apparatus, exists.

However, in practice, nozzle height variables within a rather wide range have slight effect on granule properties. Within that range it is sufficient to maintain a combination of nozzle height and spray angle of the nozzle that brings about a proper wetting of the bed surface without wetting the wall of the apparatus.

2.7 Drop Size of the Binder Liquid

Drop size of the atomized binder solution is one of the most important process variables in fluidized bed granulator (13). Several authors have reported that increased atomized air flow rate or air pressure result in a smaller granule size. Davies and Gloor (20) showed that increasing the air pressure results in a finer spray because of the substantial reduction in droplet size. The finer spray results in a reduced average granule size, increase granule friability and reduced bulk density. This effect is comparable to decreasing the rate of binder solution while keeping atomizing air pressure constant. Schaefer and Worts (22) observed an increase in mean droplet size with decreasing air to liquid mass ratios, liquid flow rate and with increasing viscosity of the binder and spraying angle. They also derived an empirical equations that can be used to estimate the mean droplet size produced by a pneumatic nozzle. A linear correlation was found between the droplet size calculated from the equation and granule size as shown in Figure 5.

Nozzle type can also affect the granule properties. A pneumatic (compressed air) nozzle is more suitable for granulation in a fluidized bed than a pressure (airless) nozzle (12).

3.Product Parameters

Of the possible variables introduced by the product itself, the effect of the type and concentration of the binder have received the greatest attention. Only a limited effort has been directed towards a study of the effect of physico-chemical properties of the powdered starting materials on the fluidized granulation process.

3.1 Type of Binder

The type of binder is essential on fluidized bed granulation (13). Evaporating during the process results in agglomerates being partly held together by solid bridge or binder, but if the binder is too weak, the agglomerates are broken down and re-agglomeration occurs by further liquid addition followed by break-down.

A wide range of binders have been used and granule growth is found to be affected by the type of binders (20). The granule properties which could affect by the type of binder are average granule size, granule friability, granule porosity and flowability. Figure 6 illustrates the effect of type of binders and concentration, on the granule size prepared by fluidized bed granulation process.

3.2 Quantity of the Binder

An increase in the binder concentration in the formula increase binder adhesion resulting in less

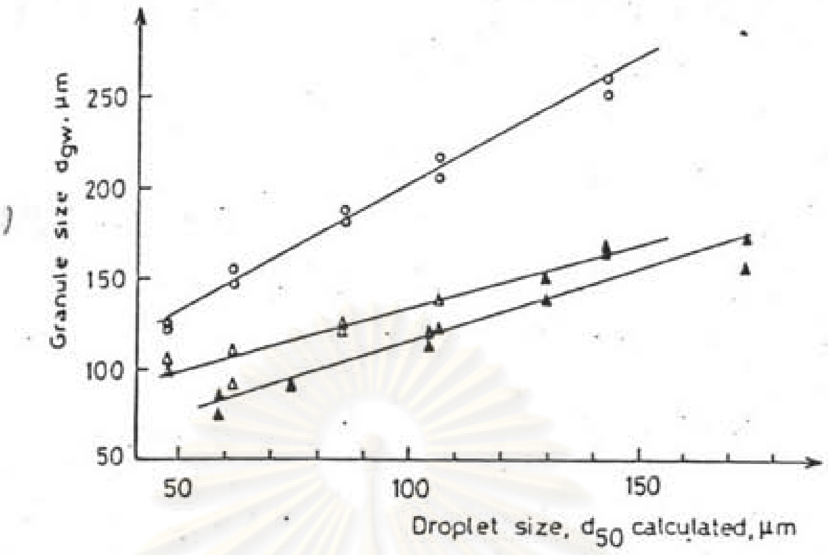

Figure 5 A Linear Correlation between Droplet Size and Granule Size
Key : ○ Gelatin △ Kollidon 25
▲ Methylcellulose

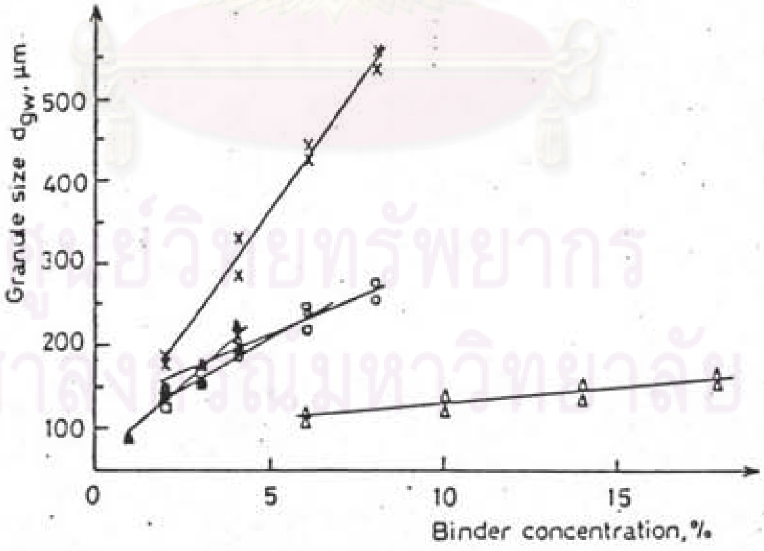

Figure 6 Effect of Types of Binder and Concentration on the Granule Size
Key : ○ Gelatin △ Kollidon 25
× Kollidon 90 □ Sodium CMC
▲ Methylcellulose

friable granules of a larger average size (20). Alkan and Yuksel (11) found that the amount of binder in the formula can affect the properties of the final granules, i.e., mean size, size distribution and friability. It has been shown that there was an optimum amount of binder at which the formation of the primary granule would occur by snowballing mechanism (as described in section of granule growth mechanism). In this fashion the granule have the smallest size distribution and friability. An excess of binder is unadvisable, since it can change these desired properties and also increased production time and cost.

3.3 Solvent Employed to Prepare Binder Solution

Most of the work published on fluidized bed granulation has involved water as the solvent for reason of economy and in order to avoid pollution and risk of explosion, and if the physical and chemical properties of the material and binder permit it (13). The volatility of the solvent will affect the liquid saturation of the agglomerates especially when a granulation method of high evaporation rate is used. Accordingly, a small granule size was obtained in a fluidized bed granulator when using an organic solvent instead of water (13). Small granule size formation and growth were assumed to be affected by the lower surface tensions of organic solvents.

3.4 Concentration of Binder Solution

Several authors had examined the effects of binder concentration on the size of the granule produced in a fluidized bed granulator (11, 20-21) and found a rise in granule size growth with increasing binder solution concentration. The concentration of granulating solution is also of interest since the quantity of solvent used in preparing a binder solution can also be influenced by other factors such as solution viscosity. The influence of the quantity of solvent on the physical properties of the final granulation has been assessed by Davies and Gloor (23). Results indicated that with an increase in dilution (quantity of solvent) there was slight reduction in final mean size, produced a less friable granule with a larger bulk density and improved flow properties. This explained that it was attributed to increased penetration and wetting of the fluidized solids by more dilute solution. These findings were in accordance with those reported by Aulton and Banks (15) and Gore et al (9). However, in contrast, the experiment reported by Johnson et al (19) found that granule properties were not affected significantly by changing the granulating solution concentration.

3.5 Temperature of the Granulating Solution

The influence of granulating solution

temperature has limited attention. Temperature will have an effect on granulating solution viscosity. A linearly increasing relationship between mean granule size and solution viscosity was found. However, works done by Aulton and Banks (15) on 128 different combinations of process conditions, no statistically significant effect on granulating solution temperature on granule quality was observed.

3.6 Starting Material Parameters

Fluidized bed granulation is much more material sensitive than most other methods of wet granulation. In most blade mixers the applied shear can be increased to overcome problems with materials which are difficult to wet, but no shearing force is exerted on powder during granulation process by fluidized bed technique. Physical properties of different starting materials may lead to variation in following processing conditions (12).

3.6.1 Fluidisation

Optimum fluidization of some pharmaceutical powders can be serious limitation to granulation by this technique. This is rarely a problem with fluidized bed drying since the granules used for tabletting are of a size and shape suitable for fluidisation.

Efficient fluidisation is difficult, and in some cases impossible, for very cohesive fine powders, micronised powders, neeedle-shaped or plate-shape particles, and materials which can become easily electrostatically charged.

3.6.2 Powder Hydrophobicity

The wetting stage of granulation is much easier with hydrophilic materials. Fluidized bed granulation works well for individual formulae where this is the case and for many low-dose drugs where the base is mainly lactose with some starch. If the starting material is poorly wettable, granule formation and growth are difficult to achieve, which results in a smaller granule size.

Problem with the granulation of hydrophobic material have been overcome in practice by slightly over wetting the bed with binder solution. This can be achieved by beginning the spray before fluidisation of the powder (23).

During processing, wettability properties of powder may be improved by using suitable solvent (13) or by adding surfactant to the binder solution. Aulton et al (25) found that the addition of (0.75 %) sodium laurly sulfate (SLS) to the powder bed resulted in a linear increase in mean particle size of the granules in comparing with the absence of SLS. Flow rate of the granules through the orifice also increased from 6.2 to 8.4 g/sec when incorporated the surfactant in powder bed. An increase of granule size was also observed when SLS was added to the granulating solution, however, only a slightly better improvement per total SLS added was noted in this latter case. In addition, the presence of SLS increased the rate of dissolution because of increasing wettability of the powder.

Scale-up Factors

The successful scale-up of fluidized bed granulation process to pilot or production sized equipment depends greatly on the existence of an effective laboratory development program.

Before scaling-up, it is necessary to have a detailed knowledge of the influence of all major variables so that the increased size of the apparatus and the increased weight of the product are the only unknown factors.

Scale-up is also complicated by the fact that the moisture content is result of a balance between liquid addition and evaporation. The ratio of the depth of the bed to the diameter of the air distributor plate is typically larger in production scale equipment (13), resulting in a machine that accommodates a large batch of material without a proportional increase in volume of air to achieve an adequate fluidization pattern (16). The increase in volume of fluidizing air, therefore, is not proportional to batch size. Consequently, the spraying rate must be based on the increase in air volume of drying air instead of the increase in batch size. An increase in liquid flow rate proportional to the batch size might result in overwetting, since the air volume and consequently the drying capacity of the fluidizing air are relatively lower by scaling-up. Rowley (25) stated that spray rate could not always be directly scaled up with batch size. In some case, the optimum spray rate of a binder solution plateaus at the 300-kg level and increase only slightly at the 500-kg level.

If necessary, the drying capacity of the air can be increased by increasing the inlet air temperature. When scale-up from laboratory to pilot scale, the relative increase in an flow rate was found to be only slightly lower than the relative increase in batch size. Most workers examined scale-up of fluidized bed granulation process by the "trial and error" method.

Gore et al (9) had carried out the experiments involved in converting the process from laboratory scale to production scale. The relationships among the various processing parameters throughout several scale-up stages were presented. They found that when the batch size increased, the binder addition rate, total process time and wetting were not substantially increased.

Fluidized Bed Granulation in Practice

During the last decade high shear mixers have gained an increasing interest in the pharmaceutical industry at the expense of fluidized bed granulation equipment. Conventional wet massing is a simple, whereas fluidized bed granulation is much more delicate, and lengthy and expensive development work.

Many of the problems can be ascribed to the lack of shear forces in a fluidized bed : densification of voluminous materials and fluidization of cohesive materials might therefore be difficult to achieve in a fluidized bed granulator but granules from fluidized bed granulators more porous than from high shear mixer, this might be advantage in better dissolution.

Gore et al (9) conducted an experimental to compare three granulation process :

- conventional wet granulation (Sigma Blade Horizontal Mixer)
- high-intensity wet granulation (Fielder)
- fluidized bed granulation (Glatt WSG-15 granulator)

The Differences bulk densities were most pronounced between the high-shear (0.71 g/ml) and fluidized bed granulator (0.39 g/ml). SEM (scanning electronphotomicrograph) showed that granules processed in the fluidized bed had a higher intergranular porosity which exhibiting greater compressibility, low friability, shorter disintegration time.

By conclusion of fluidized bed granulation ; yield granulations with excellent flow characteristics and a narrow size distribution of almost spherical particles with high porosity and a wide range of compressibility. High production output reduced overall production costs.

Although the potential advantage of using fluidized bed granulator techique are very encouraging, it was a difficult task when the pharmaceutical industry attempted to transfer its granulation from conventional approaches to the fluidized bed granulator. Existing formulation could not be easily transfered without lengthy and expensive redevelopment work. The new process development are always researched when the fluidized bed granulation is selected to be employed with new formulation. Not all powder system are able to be granulating with fluidized bed technique because of unsuitable powder density or adhesion of the powder to the wall of the fluidized chamber as a result of electrostatic charges.

3. Objectives of the Study

On the basis of rationale mentioned earlier, the aims of this research are, therefore, concerned with :

(a) the process development of fluidized bed granulation technique in producing powdered sugar-tapioca starch granules using various liquid granulating agents.

(b) the evaluation of physical properties of granules and tablet matrices prepared from the granules which are composed of different proportions of powdered sugar and tapioca starch.

(c) the application of the finished powdered sugar-tapioca starch granules to prepare the microdose drug tablets by direct compression process.

(d) the investigation of the effect of aging on the physical stabitity of microdose drug tablets prepared from powdered sugar-tapioca starch granules.