CHAPTER 1

INTRODUCTION

A. LITERATURE REVIEWS

Tablet granulations can be made by various methods. They are wet granulation and dry granulation methods. The easiest method is direct compression. All ingredients are mixed and readily to be compressed. However , some drugs cannot be directly compressed because they lack of properties in the flow rate for precise volumetric feeding, the compressibility to form the compact, and the lubricacy to eject the tablet. To improve the drug , the drug powder is granulated into granule.

For dry granulation method , powder drug and diluents are mixed together in a mortar or in a mixer without the use of heat and solvent. The basic procedure is to form a compact of the material by compression and then to mill the compact to obtain a granulation. The more commond method is slugging, where the powder is precompressed on a heavy-duty tablet press, and the resulting tablet slugs are milled to yield the granulation. The other method is to precompress the powder with pressure rolls using a machine such as the chilsonator or the hutt compactor (1).

For wet granulation method, powder drug and diluents are mixed together in a mortar or in a mixer. Then the binder is added in solution form or in powder form and solvent is later added. When the ingredients are thoroughly mixed ,the wet mass is passed through a sieve. This method is called manual method.For a larger scale of powder, granulators can be used. They are oscillating granulator and rotary granulator (2).

The oscillating granulator is composed of an oscillating bar contacting a moven-wire screen. A hopper above the oscillator and screen provides a receptacle for this feedstock,which is forced through the screen by the oscillating motion or the bar ,size reduction is primarily by shear ,with some attrition. Collection of the product may be directly onto trays in the case of wet granulations ,or into drums via a sleeve ,from a specially fitted collector funnel that minimizes dust during this processing of a dry granulation. The oscillator speed is constant , whereas the screens , which are readily interchangeable range in size from 4 to 20 mesh. There are three types of oscillating granulators:-

1) Stokes granulator
2) Manesty rotogran mark III
3) Frewitt granulator machine.

The rotary granulator is composed of the same as the oscillating granulator except the tubes are one-way rotated. There are also three types of rotary

granulators:-

1) Apex rotary wet granulator

2) Chung Yong rotary wet granulator

3) Stokes tornado mill.

The granulation which prepared by oscillating granulator is called oscillating granulator method. The granulation prepared by rotary granulator is called rotary granulator method. The granule should then be dried in a hot air oven for a specific temperature and time consuming. After the granule is passed through the granulator of the same sieve again , the lubricant and glidant are added. The final step, the granule is compressed into tablet.

Other wet granulation method in preparing granule is to use a fluid bed spray dryer. The powder drug and diluent are put into the chamber , then the binder solution is sprayed to the powder mixture which is suspended in the air. This step , granule is formed. Then the granule is dried ,and glidant and lubricant are added. The mixture is compressed into tablet. In fluid bed spray drying method, Davies and Cloor (3) found that the tendency to increase granule size are to

a. increase in the formula weight of binder

b. increase in the amount of solution used to granulate

c. increase in the addition rate of granulating solution

d. increase in the air inlet temperature during the granulation cycle

e. decrease in the air pressure to the nozzle, and

f. decrease in the nozzle height above the distribution grid.

The advantages and disadvantages of the three wet granulation methods (4) are

1) Manual method:

1. fewer equipment are used and a small batch of granule is produced

2. it is conveniently produced

3. solvents as granulating fluid are hazardous

4. granule of irregular shape is produced

2) Oscillating method

1. more equipment are used and a larger batch of granule is produced

2. more time and cost are consumed

3. solvents as granulating fluid are hazardous

4. granule of irregular shape is produced

3) Fluid bed spray drying method

1. variables are able to be controlled

2. granule is uniformly produced

3. it can be used to granulate particles varying greatly in size

4. the process does not restrict either the

kind of binder material used or the solvents employed.

Evaluation of The Granule

1. Bulk Volume

The bulk volume determination is a measure of the bulk of mass by getting the same weight of the mass which prepared by different method or different formula and slowly pouring to the specific known volume container usually used a volumetric cylinder and then measuring the bulk of the mass. The unit is in cm^3.

The bulk volume is used in calculation of the bulk density. The equation for determining the bulk density ,Pb is

$$Pb = \frac{M}{Vb} \qquad (\text{eq } 1)$$

where M is the mass of the particles and Vb is the total volume of packing. To find the bulk volume which is the reciprocal of the bulk density (5) , Chalmers and Elworthy (6,7) found that granules produced by slugging showed much lower granule porosity values than those produced by wet granulation. And they also found that increasing the wet mixing time increased granule density for granulations produced by the wet granulation technique.

Davies and Gloor (8,9) had studied the effect of various formulation and processing variables in lactose granulations produced in a fluid bed dryer. For processing variables , their results may be summerized that the

granule density would increase which meant that the bulk volume would decrease as the addition rate of water , the inlet air temperature and the nozzle height above the grid were increased. For formulation variables, these authors found that as the formula weight of binder was increased, the granule density tended to increase, the latter effect was observed for the binders povidone, hydroxypropyl cellulose, gelatin and acacia.

Fonner, et.al (10) determined the granule density of lactose granulations produced from several different types of granulation equipment. In general, they found that granules produced from an oscillating granulator were the most dense and those produced from a fitz mill and liquid-solid V-shaped blender were the least dense.

2. % Fine of Granule

The % fine of granule is the amount of small size of fine particle in the granule which will effect the flow rate of granule. Danish and Parrott (11) found that the small particle in the granule in the appropriate amount would help the flow of granule. If the present of fine of granule was too much or too little it would cause poor flow rate.

3. Size Distribution

Various chemical and physical properties of drug substances are affected by their particle size distribution and shape. The effect is not only on the

physical properties of solid drugs but also, in some instances, on their biopharmaceutical behavior. The poorly soluble drugs showing a dissolution rate-limiting step in the absorption process will be more readily bioavailable when administered in a finely subdivided state rather than as a coarse material.

Size plays a role in the homogeneity of the final tablet. Fine materials can be expected to be distributed more uniformly. Size and shape, influenced the flow and the mixing efficiency of powders and granules. Size can also be a factor in stability. Fine materials are relatively more opened to be attacked from atmospheric oxygen , humidity, and interacting excipients than are coarse materials. For example, the bioavailability of griseofulvin and phenacetin is directly related to the particle size distribution of these drugs (12). It is important to decide the size of the granule distribution, fine and coarse granule and a desired size range.

Mark and Sciarra (13) noted that as the granule size became smaller, the weight variation of the tablets was found to decrease but the weight of granules required to fill the die increased. Arambulo and Deardorff (14) found that as the granule size was reduced, the average tablet weight increased, presumably due to the decrease in void space. Arambulo, et al (15) noted the effect of granule size upon the weight variation of compressed tablets that as the granule size decreased, the

weight variation drcreased, passing through a minimum at 400-800 um and then the weight variation increased. They also noted that larger granules were found to yield greater weight variation. This effect was presumed to be caused by variation in the proportion of voids, which they attributed in part to the varying amount of breakage of granules and the resultant removal of the powder by the movement of the feed shoe of the single-press tablet machine.

Forlano and Chavkin (16) reported a definite relationship of the amount granule, size, disintegration time, and degree of capping, using a sodium bicarbonate granulation. Tablets compressed with granules in the 8-40 mesh range exhibited a rise in disintegration time and a decrease in capping. Tablets compressed using granule of 60 mesh or smaller exhibited a decreased disintegration time and an increase in capping. Riddfo et al (17) showed that the bioavailability of benaxoprofen was increased by reducing particle size.

Das and Jarowski (18) noted that granules of the same materials produced by different granulating method yielded different average particle size and size distribution, when compressed into tablets at the same compaction pressure.

4. Flow Rate

The flow rate of granule is the weight of granule flow through a narrow orifice per unit of time. There are many forces that can act between solids particles. Pilpel (19) identified five types:

(1) frictional forces

(2) surface-tension forces

(3) mechanical forces caused by interlocking or particles of irregular shape

(4) electrostatic forces, and

(5) cohesive or van der waals forces

All of these forces can affect the flow properties of solids. With fine powder (< 150 um), the magnitude of frictional and van der waals forces usually predominates (19). Surface-tension forces resulting from absorbed films of gases are generally quite small and not significant in comparison to other forces active between particles. Although electrostatic forces of a magnitude greater than van der waals forces are theoretically possible. The usual presence of even minute quantities of water are sufficient to minimize the effect of electrostatic forces for larger particles (> 15 um), such as granules produced by a wet granulation technique. Frictional forces normally predominate over van der waals forces. Thus, when evaluating interparticle forces of granules, agglomerates, or other large particles, cohesive or van der waals forces are often assumed to be

insignificant or equal to zero.

Fonner and coworker (10) found that the flow ability of granules was affected by method of preparation. The granule produced from granulator was flow better than the granule produced by manual method. Marks and Sciarra (13) also found that the flowability of granules to be affected by the size of the granules. They observed greater flow rate of the granules through an orifice as the size was decreased. Jordan and Rhodes (20) found that when increasing in flow rate of granule, the tablet weight which it produced would be increased.

Marks and Sciarra (13) and Harwood and Pilpel (21) also found that hopper flow rate was inversibly proportinal to averge granule size. Pipel (19) concluded that many glidants would improve this flowability , or bulk solids and that several mechanisms of action may be involved. Glidants may act by one or more of the following mechanisms, reduction of interparticulate friction, change in surface rugosity, separation of coarse particles, reduction of liguid or solid bridging and minimization of static sharge. Many glidants are lubricants and often possess a coefficiency of friction less than that of the bulk solid to which they are added.

Gold, et. al. (22) pointed out the flow may be affected by many fundamental properties of powders such as: moisture content, particle size, shape, density, distribution, surface charge, etc. And also, they found

that in binary mixtures the addition of increasing proportion of binder particles to 10/20 mesh granules increased the flow rate to a maximum followed by a decrease flow rate of granules. The flow rates were also found to vary considerably, depending upon the particular granulating agent used.

Jordan and Rhodes (20) found that increasing magnesium stearate would increase flow rate.

Danish and Parrott (11) reported that the addition of fine particles to a monosized particulate solid increased the flow rate to a maxinum value, then as a greater concentration of fines was added, the flow rate was decreased.

Henry, et. al. (12) found that the pelletization increased flow rate and provided a narrow particle-size distribution and much less fines.

5. Repose Angle

The more common ways of determining angle of repose are illustrated in Figure 1. In the fixed-funnel and free-standing cone method, a funnel is secured with its a given height of 12 inches above a graph paper which is placed on a flat horizontal surface. Powder or granulation is carefully poured through the funnel until the apex of the conical pile just touch the tip of the funnel; thus,

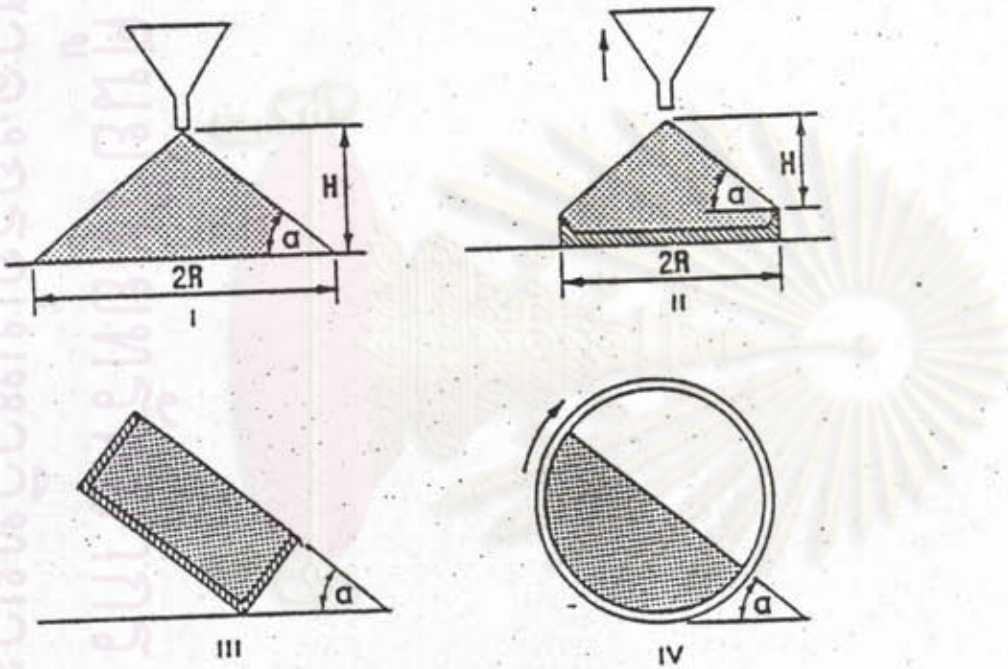


Figure 1 Four principal methods of measuring the angle of repose. I, Fixed-funnel and free-standing cone, II, Fixed-bed cone; III, Tilting box; IV ,Revolving cylingder.

$$\text{TAN } \alpha = H/R$$

or

$$\alpha = \frac{\text{arctan } H}{R}$$

where α is the angle of repose, H is the height of the granule and R is the radial of the base.

In the fixed-bed cone method, the diameter or the base is fixed by using a circular dish with sharp edges. Powder is poured into the center of the dish from a funnel that can be raised vertically until a maximum cone height H is obtained. The angle of repose is calculated as before. In the tilting box method, a rectangular box is filled with powder and tipped until the contents begin to slide. In the revolving cylinder method, a cylinder with one end transparent is made to revolve horizontally when half filled with powder. The minimum angle that the plane of powder makes with the horizontal on rotation is taken as the angle of repose.

The angle of repose is best suited for particles larger than 150 mm (24). In this size range, cohesive effect will be minimal and the coefficient of friction will be largely dependent upon the normal component of the weight of the test specimen. Values for the angle of repose less than 30 generally indicate a free flowing

material, and the angle larger than 40 suggest a poorly flowing material (25). The value of the angle of repose for a given material is depending upon particulate surface properties which will also affect flow ability. However, Gold et al (22,23) concluded that there is no correlation between actual flow properties and the repose angle.

Evaluation of tablets

1. **Weight Variation**

The tablet is designed to contain a specific amount of drug in a specific amount of tablet formula. To check that a tablet contains the proper amount of drug, the weight of the tablet being made is routinely measured. The test is run by weighing 20 tablets individually, calculating the average weight, and comparing the individual tablet weight to the average. The tablets meet the USP weight variation if no more than two tablets are outside the percentage limit and no tablet differs by more than twice the percentage limit. The weight variation tolerances for uncoated tablets differ depending an average tablet weight.

The weight variation test is a satisfactory method of determining content uniformity of tablets if (1) the tablet is all-drug or essentially (90 to 95%) all-active ingredient, or (2) the uniformity or drug distribution of the granulation or powder from which the tablets are made is perfect. For tablets which are usually 90% or

more active ingredient, the 15% weight variation should come very close to defining true potency and content uniformity.

The causes of weight variation can be separated into granulation problems and mechanical problems. The actual weight of the tablet is determined by the geometry of the die and the position of the lower punch in the die. The weight can be varied by a poorly flowing granulation, which causes a spasmodic filling of the dies. The improper mixing of the glidant into the granulation can influence the weight variation by not allowing for uniform flow. If the granular size is too great for the die size, the dies will not be uniformly filled, causing weight variation. Granulations that have a wide particle size distribution can have a localized uniformity of density in the granulation. With the geometry being fixed, nonuniform densities will cause varying amount of granulation to fill the dies, causing variations in the resulting tablets' weights. Awide particle size distribution can also be produced when a granulation has not been thoroughly mixed or when the granulation has been stored in an area where vibration were presented to cause particle segregration which produced a wide particle size distribution.

Marks and Sciarra (13) observed that the size distribution of the granule in the wide range would cause the high weight variation of the tablet. Ridgway and

Williams (26) found for uniform size granulation that as the particle shape became more angular, the weight variation increased.

Mechanical problems can cause weight variation with a good granulation. A set of lower punches of nonuniform length will cause weight variations as will lower punches that are dirty enough to restrict, the movement to their lower point during die fill. A cupped lower punch that filled in with a sticking granulation will cause weight variation for a given granulation.

2. Hardness

Tablet requires a certain amount of strength, or hardness, to withstand mechanical shocks of handling in its manufacture, packaging, and shipping. In addition, tablets should be able to withstand reasonable abuse when in the hands of the consumer. Adequate tablet hardness and resistance to powdering and friability are necessary requisites for consumer acceptance. Hardness may influence tablet disintegration and drug dissolution release rate. It is important to carefully monitor tablet hardness for drug disolution release rate. It is important to carefully monitor tablet hardness for drug products that posses real or potential bioavailability problem or are sensitive to altered dissolution-release profiles as a function of the compressive force employed.

Historically, the strength of a tablet was determined by breaking a tablet between the second and third fingers with the thumb acting as a fulcrum. If there was a "sharp" snap, the tablet was deemed to have acceptable strength (27). Probably minimal for uncoated tablets, although some chewable tablets may be somewhat softer.

Kassem et al (28) observed that as the size of granule decreased when compression with the same force, hardness would increase. It was thought to be due to an increased area of contact because of a decrease in void space.

Serveral testers do not produce the same results. For essentially the same tablet studies found that operator variation, lack of calibration, spring fatique, and manufacturer variation contribute a great deal to the lack of uniformity (29).

Recently, the tablet hardness has been defined as the force required to break a tablet in a diametrial compression test. The test, a tablet is placed between two anvils, pressure is applied to the angles, and the crushing strength that just causes the tablet to break is recorded. Hardness is sometimes termed tablet crushing strength. The devices operating to test tablet hardness are the monsanto tester (30), the strong-cobb tester (31), the pfizer tester (32), the erweka tester (33), and the heberlein tester (34).

Tablets generally are harder several hours after compression than they are immediately after compression. Lubricants can affect tablet hardness when used in too high a concentration or mixed for too long a period. The lubricants will coat the granulation particles and interfere with tablet bonding (28). Large tablets require a greater force to cause fracture and are therefore "harder" than small tablets and for a given granulation, flat-faced tooling will produce a harder tablet than will a deep-cup tool. A hardness of about 5 kgs as probably minimal for uncoated tablets.

The variation in tablet thickness may produce variation in tablet hardness. As additional pressure is applied to make a tablet, the hardness value increases.

Factors that may alter tablet hardness in the course of production run are substantial alterations in machine speed, a dirty or worn camtrack, and change in the particle size distribution of the granulation during the course of the run, which alters the weights of the fill in the dies. Dies having a light fill will produce a softer tablet than dies that receive a heavy fill.

Fonner, Banker, and Swarbrick (10) found that the hardness index increased as the density of the granule increased. Chowhan (35) noted that the moisture related effect on tablet hardness was not limited to the moisture content of the granulations at the time of compression. The moisture gain followed by the moisture loss on storage

may also induce an increase in tablet hardness.

3. Disintegration Time

For most tablets the first important step in the sequence is the breakdown of the tablet into smaller particles or granules. This process is known as disintegration. The time that it takes a tablet to disintegrate is measured. It is called disintegration time. Disintegration is still used as a guide to the formulator in the preparation of an optimum tablet formula and as an in-process control test to be sure lot-to-lot uniformity (18). The United States Pharmacopeia was long had a device to test disintrgration, which was called U.S.P. Disintegration Apparatus.

The time to cause the tablet to be disintegrated depend on these factors:

(1) Size of the granule . The granule which is small size will increase disintegration time (28).

(2) The amount of binder. Increase in binder will cause the tablet to increase disintegration time (28).

(3) Compression force. Compression force has affected the disintegration time of tablet. It will cause tablet to increase and decrease disintegration time (36).

(4) The kind of binder. 10 % of acacia has ability to bind more than 10% starch and 10% starch has ability to bind more than 10% PVP (28).

(5) The method. Compression of tablet derived by dry method increases disintegration time than tablet

derived by wet method (37).

(6) The fresh compression of tablet. It will give in fast disintegration time than the tablet which keeps too long (38).

4. Friability

Friability is related to a tablet's ability to withstand both shock and abrasion without crumbling during the handling or manufacturing, packing, shipment, and consumer use. Tablets that tend to powder, chip, and fragment when handled lack elegance, consumer acceptance, can create excessively dirty processes in such areas of manufacturing as coating and packing, and can add to a tablet's weight variation or content uniformity problem. The roche friabilator (39) by utilising a plastic chamber which revolves at 25 rpm.,dropping the tablets a distance of 6 inches. with each revolution. Normally, a preweighed tablet sample is placed in the friabilator, which is then operated for 100 revolutions. The tablets are then dusted and reweighed. Conventional compressed tablets that lose less than 0.5 to 1.0% in weight are generally considered acceptable.

Marks and Sciarra (13) concluded that degree of granule friability was found to decrease as the size of the granule increased. As the size of the granule becomes smaller, there is a greater loss of weight due to the friability of the granule.

5. Content Uniformity

The tablet weight can not be used as a potency indicator, except where the active ingredient is 90 to 95% of the total tablet weight. In tablets with smaller dosages, a good weight variation does not ensure good content uniformity.

In the test, 30 tablets are randomly selected for the sample and at least 10 of them are assayed individually. Nine of the 10 tablets must not contain less than 85% or more than 115% of the labeled drug content. The tenth tablet may not contain less than 75% or more than 125% of label. If these conditions are not met, the remaining tablets of the 30 must be assayed individually, and none may fall outside that 85 to 115% range.

It is advisable to determine the drug content uniformity of the granulation before compression, especially with new production runs of a product with which there is little experience or in tableting systems where uniformity problems are known to exist.

The problem of nonuniform distribution is illutrated in Figure 2. The irregularly shaped drug particles are dispersed in irregularly shaped diluent particles of various sizes, and it is not difficult to comprehend why a perfect physical mixture never occurred geometrically. The squares drawn in the figure illustrate various possible random samples that might be drawn from

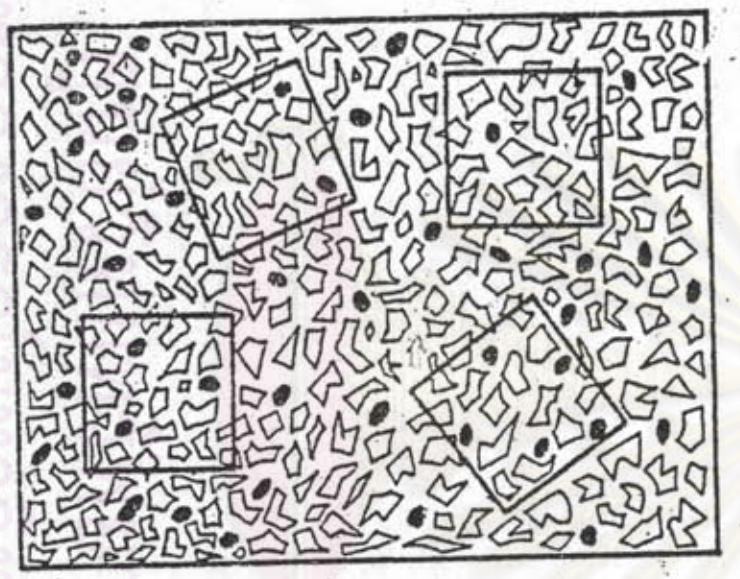


Figure 2 A powder mixture; angular open particles represent excipient; dark circles represent drug. The squares represent identical-size powder samples, which contain as few as one to as many as five drug particles. Solid dosage fows represent similar powder or granule "samples" The presence of large number of drug particles per dose is critical to low-dose variation between tablets.

the mixture and represent the amount of mixture required for one tablet. The squares contain as many as five particles and as few as one drug particle.

In the case of wet granulations, segregation is most likely to occur if the drug is very soluble in the granulating fluid and if a static during method is used. As the granulation fluid (drug solvent) evaporates, the drug tends to be carried to the surface of the drying granulation. This migration destroys the homogenous mix obtained prior to the drying step and reduces the changes of good content uniformity in the tablets, because the uniformity is now dependent on the mixing in the lubrication step (40).

Das and Jarowski (41) found that the tablets prepared by the microgranulating method were found to have the best content uniformity than those prepared by the slugging method. The tablet manufactured by wet granulation and direct compression method showed the poorest content uniformity.

6. Dissolution

Since a drug must normally be in solution before absorption can take place, orally administered tablets must have their drugs dissolved in the contents of the gastrointestinal tract before the absorption of drug can occur. Often, the rate of drug absorption is determined by the rate of drug dissolution from the

For drugs that are highly absorbed in the gastrointestinal tract (i.e. acidic drugs), which have a large dose and a low solubility, rapid dissolution may be especially important. The design on the tablet and the dissolution profile for such drugs may determine the total amount of drug absorbed as well as its rate of absorption. The most direct assessment of the drug's release would be in vivo bioavailability test. However, there are several reasons that restrict the use of in vivo studies, length of time required, highly skilled personnel required especally for human studies, low precision of the measurements, inadequate discrimination between products, and a correlation with the disease state might have to be made with human subjects or with animals.

The objectives of an in vitro dissolution test should be to show that

(1) the release of the drug from the tablets is as close to 100% as possible.

(2) the rate of the release is uniform batch to batch and is the same as the release rate from those batches proven to be bioavailable and clinically effective.

Method for increasing dissolution rates.

1) Reduction in particle size (17,42)

2) Reduction in hydrophobicity (eg. coating and granulation with a hydrophobic material or surfactants

(36,37,43).

3) Increase in solublity and dissolution rates (e.g salt formation,pH effect, polymorphism, complexation, solid dispersion (7).

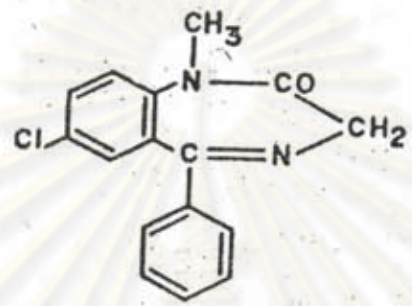
Das and Jarowski (41) noted that both dexamethasone and sulfadiazine microgranulates and their tablets had the faster dissolution rates than dexamethasone that prepared by direct compression.

Chalmers and Elworthy (44) noted that an increased concentration of PVP in the binder solution decreased the rate of tablet dissolution. It did not significantly alter the tablet dissolution, when the amount of PVP was constant. Finholt (37) showed that dissolution rate of phenacetin powder increased with increasing particle size and decreasing surface area in direct contradiction to the effect seen for benaaxoprofen. Levy (45) showed that in some cases a reduction in particle size may decrease efficacy.

Khan (46) found that although tablets freshly made from the solid dispersion to tablets made by traditional methods, they become harder on ageing and tended to have decreased dissolution rates. Marlow and Shangrow (47) showed that directly compressed spray dried lactose containing sodium salicylate was shown to have superior dissolution properties compared to sodium salicylate tablets prepared by moist granulation using crystalline lactoce as the diluent and ethylcellulose plus acacia

mucilage as the granulating agents.

Diazepam: (7-chloro-1-methyl-5-phenyl-1,3 dihydro-2H-1,4 benzodiazepine-2-one)



DIAZEPAM

Diazepam is yellow-white crystalline powder. Its melting point is between 130-133 C. It is poorly soluble in water, but soluble in ethanol, methanol, chloroform, ether, acetone and propylene glycol; the pKa is 3.3 (48).

In this investigation diazepam is chosen to be the model drug becuase diazepam is a potent drug, for evalution of finished tablet the variation of content uniformity due to the process in making tablet could be more easily observed than the non-potent drug. Moreover, the method for analysis of diazepam is not too complicate.

B. THE PURPOSES OF THIS INVESTIGATION

1. To study the wet granulation of diazepam prepared by different methods, manual, oscillating granulation and fluid bed spray drying methods.

2. To compare the physical properties of granules prepared by those methods; bulk volume, repose angle, flow rate, percent fine, mean size and size distribution.

3. To compare the physical properties of tablets prepared by different wet granulations, weight variation, hardness, friability, disintegration time, content uniformity and dissolution.

4. To study the effect of seive size on the physical properties of both diazepam granules and tablets.

5. To study the effect of concentration of binder on the physical properties of diazepam granules prepared by fluid bed spray drying method.