CHAPTER I

INTRODUCTION

The rate of absorption of drugs is often limited by the rate of dissolution of the drug substance, especially the slightly soluble drug. Therefore, the rate of dissolution of drugs is a major factor affecting the drug bioavailability (1, 2). Absorption in the gastrointestinal tract normally occur only after drugs are in solution and the drug administered must released and reach its site of action in an active state before it can exert a pharmacological response. Normally, drug dissolution improved when particle size was reduced, probably because an increased surface area was available for dissolution (3), especially for slightly soluble drug. Micronization has been employed to improve the dissolution rate of slightly soluble drug and can be explained by the equation of Noyes & Whitney:

$$dC/dt = (D/h) \cdot Sc \cdot (Cs-Ct)$$

where D is the diffusion coefficient, h is the thickness of the diffusion layer and Sc is the contact surface area between liquid and solid. Cs is the concentration in the diffusion layer (i.e.the solubility of the solid in the liquid). Ct is the concentration of dissolved solid in the bulk of the dissolution medium at time t.

For a given dose of drug, increasing the specific surface area by reducing the particle size will lead to a proportional increase in the dissolution rate. However formulations containing micronized drugs do not always exhibit an improved dissolution rate, even reduced rates have been reported (4,5). This is due to differences in how surface area is defined. In Noyes & Whitney equation the term Sc defines the surface area taking part in the dissolution process, i.e. the contact area between solid and liquid. This parameter is not necessarily equivalent to the values of surface area determined experimentally by various techniques and expressed as a measured of powder fineness.

If the powder exists in an agglomerated or aggregated form, values for surface area will depend on whether primary particles or agglomerates are characterized (6).

However, the resultant micronized drug particles are extremely cohesive and will form into drug agglomerates which is difficult to wet and this may result in slow dissolution rate (6, 7). This conformed to the experiment of McGinity et al.(7), as they compared the dissolution rate between micronized griseofulvin formulated as tablet containing Emdex as a diluent prepared by ordered mixing with micronized griseofulvin contained no diluent, resulting that the formulation containing Emdex as a diluent had a higher dissolution rate than the pure micronized

griseofulvin which had a makedly decreased in dissolution rate. Therefore, these micronized drug should be dispersed, either by physical or chemical method in order to give a higher dissolution rate. Solid dispersion (8) is introduced as a method for reducing drug particle size and thus increasing the dissolution rate. Solid dispersion is defined as the dispersion of one or more active ingredients in an inert carrier or matrix at solid state, this can be prepared by solvent or melting-solvent method. But there are some disadvantage, for example, for the melting method only low melting point drugs or drug carriers can be used, due to problems of thermal degradation or sublimation of drug or drug carriers and for the solvent method the solvent used must be suitable and safe. Besides this, the major problem is the occurances of recrystallization which causes the negligible change in solubility. Therefore this method may not be suitable to all drug items. Consideration of each drug and drug carrier must be concerned. Solid dispersion described above can also be simply prepared by traditional mechanical mixing by the theory of ordered mixing (9, 10, 11).

Ordered Mixing Concepts

Powder mixing has been the subject of numerous investigations over the past decade (12, 13). For simplicity, most of the systems examined have consisted of comparatively coarse, free-flowing particles and have led to the concept of randomization or "shuffing" of the particles as the mixing process. The randomization may

be brought about by a variety of mechanisms, including diffusion and convection, according to the variety of mixer employed. Randomization requires equally sized and weighted particles, with little or no surface effects, showing no cohesion or interparticle interaction, to achieve the best results. Undoubtedly, this is an important process in powder technology today and has served a useful purpose in enabling mixing theories to be quantified. However, it can not be applied to all practical mixing situations, especially for cohesive or interacting particulate systems and may, therefore, not be unique amongst explanation of powder mixing phenomena. In this situation, a concept of ordered mixing which was introduced by Hersey (10) may be useful in explaining powder mixing of cohesive or interactive fine particles.

Ordered mixing is described as the use of mechanical, adhesional or coating forces or methods to prepared ordered units in the mix, so that ordered unit will be the smallest possible ordered unit in the mix and will be nearly identical in composition to all other ordered units in the mix. To which it requires particle interaction, such as adsorption, chemisorption, surface tension, electrostatic or other form of adhesion. And the ordered mixture are expected to result from an adherence of fine particles of one constituent to considerably more coarse particles of a second constituent. In case of a coarse-fine particle mixture, the fine particle will tend to cohere together. As the mixture gently rotated

or tumbled the larger particles will break up these agglomerates of the fine particles, a situation which is analogous to a ball mill mechanism. Thus the fine particles will be free to adhere to the larger particles of the second constituent. The drug powder is, therefore, deagglomerated in the dry state. This may used to increase the dissolution rate of the drug powders (6, 7, 14) because a larger contact surface area is exposed to the dissolution medium.

Ampolsuk et al. (14) has reported that, by spreading digoxin or hydrocortisone over a lactose surface using frictional pressure, a trituration with a significantly enhanced dissolution rate was produced which was higher than that of other triturations prepared by simple blending or solvent deposition. Such a system was characterized as a specific example of the use of ordered mixing by Hersey.

Nystrom & Westberg (6) also reported the enhancement of the dissolution rate of griseofulvin by the used of ordered mixing, showing that highly soluble carrier materials gave an extremely fast dissolution of the drug.

McGinity et al. (7) reported that ordered mixes containing 0.25-1.00% griseofulvin with a carrier showed rapid drug dissolution.

Recently, direct compression of tablets becomes an interesting technique and has numerous advantages over the more traditional wet granulation method (15-19).

Since its process involves only one unit operation, that of mixing of drug and vehicle, prior to compression. The most obvious advantages of direct compression is economy. It is safe to say that there would be a relatively minor interest in the process of direct compression tabletting if economic saving were not possible. Saving can occur in a number of areas, including reduced processing time and thus reduced labor costs, fewer manufacturing steps and pieces of equipment, less space, and a low consumption of power.

The advantage which is of greatest significance in terms of tablet quality is that of processing without the need for moisture and heat, which is inherent in most wet granulation process, and the high compaction pressures involved in the slugging stage of producing tablets from dry granulations. The unnecessary exposure of any drug to moisture and heat can never be justified, it can not be beneficial and may certainly be detrimental. In direct compression the drug is in the extragranular position so when the tablet was disintegrated, the drug is rapidly released, thus enhanced a more increased in the dissolution rate than the wet granulation method, by which the drug is in the intragranular position and also contains binding agent to adhere drug powder and diluent into granules. This may retard in releasing the drug from the tablet.

By the concept of ordered mixing, therefore it is possible that a small concentration of fine drug, which can usually develop cohesive properties by increasing

fineness, can be mixed with coarse direct compression vehicle to obtain a high degree of homogeneity, and non-segregation ordered system (20). By careful selection of drug and direct compression carrier, direct compression could be a useful method of presenting small amounts of relatively insoluble drugs in a homogeneous form. The extragranular positon of the drug should also ensure high dissolution rates.

In ordered mixture, a large particle with small particles adhering is considered to be the smallest part and called "ordered unit" (9) as illustrated in Figure 1.

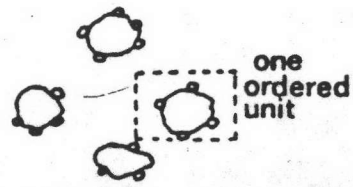

Figure 1. Ordered unit of the adhesional ordered mixture (9).

The single ordered unit is an important parameter in ordered mixing theory, since it control both homogeneity and degree of segregation in an ordered system. If each ordered unit of the system is identical, it may be considered to consist of a single material and the mixture will be very homogeneous.

The drug carriers, in ordered unit system, which participated in breaking drug agglomerate should possess an optimum particle size to be free flowing and break drug agglomerate.

Lai and Hersey (21) has reported that by using a computer simulation of ordered powder mixing to ascertain the properties of ordered mixtures, the results showed that for real ordered powder mixtures, the carrier particle size should be as large as possible and of narrow size range in order to prepare homogeneous dose forms.

A wide size range of carrier particles has been suggested to cause "ordered unit segregation" which subsequently leads to a less homogeneous ordered mixture (22).

A narrow size range of carrier particle has dual advantages of both increasing the homogeneity by avoiding "ordered unit segregation", while monosized carrier particles will produce a perfectly uniform mixture.

Thanomkiat et al. (23) reported that mixing of micronized prednisone (1%) with different size fractions of starch-lactose granules, the results showed clearly that the mixing of prednisone with more homogeneous vehicles resulted in satisfactory degree of homogeneity. However, it exhibited poor mixing with the wide particle size range carriers.

Johnson (24) found that better quality mixtures are produced using the finer grade crystalline lactose rather than spray dried lactose because crystalline lactose possessing a narrow distribution of sizes than spray dried lactose.

The drug weight ratio to carrier in ordered mixing

is very restricted, since it is necessary that a single layer of fine drug particles is produced on the surface of a carrier in the system (10).

If a lower percentage of fine particles had been used then the total number of adherence sites in the layer particles would not have been filled. Under these conditions it is propable that some large particles would have a large number of small particles associated with them than others. In such a case each unit may be different and the system could be considered to consist of many components.

If an excess of fine particles had been used, then the equilibrium situation will be attained by adherence at all available sites and the excess fines may attempt to mix with this material in a random manner. Thus, a binary mixture could theoretically exist, but its composition would be different from that considered by the ingredient concentrations present, resulting ultimately in a complete separation of the two ingredients, and this is called "constituent segregation" (22).

Staniforth et al. (25) studied about ordered unit segregation in ordered mixes containing different concentrations of fine particle sodium salicylate and starch-Avicel granules by mixing in a tumbling mixer. They found that ordered unit segregation occurred at all concentrations studied, but constituent segregation was only found at 5%, the highest concentration studied. Ordered unit segregation occured as a result of

disproportionate distribution of adherent particles allowing drug-rich finer carrier particles to move to a specific region of the powder bed.

The surface characteristic of the drug carrier should also be regarded, as the carrier possessing a smooth surface could not give the same degree of homogeneity to those carrier with macroporous or indented surface characteristic.

Shallam et al. (26) found that the indented surface of sucrose acted as a mechanical entrapment sites for drug particles which result in area containing highly localized drug content and this is possibly affected to the state of homogeneity of powder mixtures. This could be explained by Staniforth (27) when using two chemically similar excipients with comparable coarse particles size distribution as Emdex and Dipac to form homogeneous powder mixes with a fine particle model drug. When these two mixes were subjected to vibration condition, only one mix remained homogeneous the other mix was found to segregate. The physically stable mixture contained the excipient Emdex, a coarse macroporous crystal agglomerate of dextrose. The unstable mixture contained Dipac, a coarse relatively smooth surfaced crystal agglomerate of sucrose. The reason for formation of physically stable adhesive mixtures between macroporous coarse particles and fine adherent particles is due to three effects;

1. Formation of adhesive couples due to multiple interparticle contact (Figure 2). Particle adhered to smooth surfaces will have only a single adhesive contact.

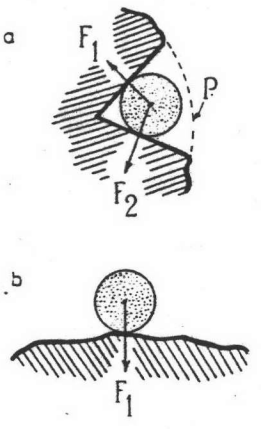

Figure 2. Diagram showing drug particle adhered (a) in a cleft on an excipient particle surface and (b) on an smooth excipient surface (the arrows represent adhesion forces, F, at point contacts and P is the equivalent spherical projected perimeter) (27).

2. Prevention of adhered particles being rolled from the carrier surface. Particles can be rolled off surfaces using lower applied forces than those required to pull particles off the same surface. Entrapment of particles in surface clefts ensures that the particle must always be pulled from one surface, no matter which direction the removal force is applied (Figure 2).

3. Protection of adhered particles from becoming detached by abrasion during further mixing or processing. Particles adhered in clefts effectively lie within the carrier particle projected perimeter and are not exposed in the same way as adhered to smooth surface carriers (Figure 2).

Ordered mixing time is another factor influencing the homogeneity of the ordered mixture. It can be defined as the period which elapses before uniform adhesion occurs, along with any rearrangement of ordered units to produce the required homogeneity. Ordered mixing times vary according to the powder system studied and the percentage of fine component.

Yip & Hersey (22), studying the mixing of fine salicylic acid with coarser sucrose powder, found that after 10 min. in a revolvo cube blender the powders were within the required homogeneity.

Bryan et al. (28) found that ordered mixing time for microfine salicylic acid (1%) and starch/lactose granules was approximately 15 minutes and an increased in the microfine salicylic acid to 5 and 10% increased the ordered mixing time and even after 100 minutes mixing the coefficient of variation of the systems had not fallen below 10% despite an initial rapid decrease.

Staniforth et al. (29) studied a system consisting of fine potassium chloride powder which performed ordered mixes with three coarse direct compression tableting excipients; Dipac, Emdex and a recrystallized lactose. they found that when the potassium chloride was blended. with each of the three excipients, by rotation in a Y-cone blender, the resulting ordered mixes showed different degrees of segregation tendency, or stability. Furthermore, the three excipients required different times to form

ordered mixes and this also varied according to the percentage of potassium chloride in the system.

When an ordered mixture was compressed into tablets, the first important step in drug dissolution is the break down of the tablet into smaller particles or granules. This process is known as disintegration, and a scheme of the ways in which drug formulated into a tablet become available to the body is illustrates in Figure 3.

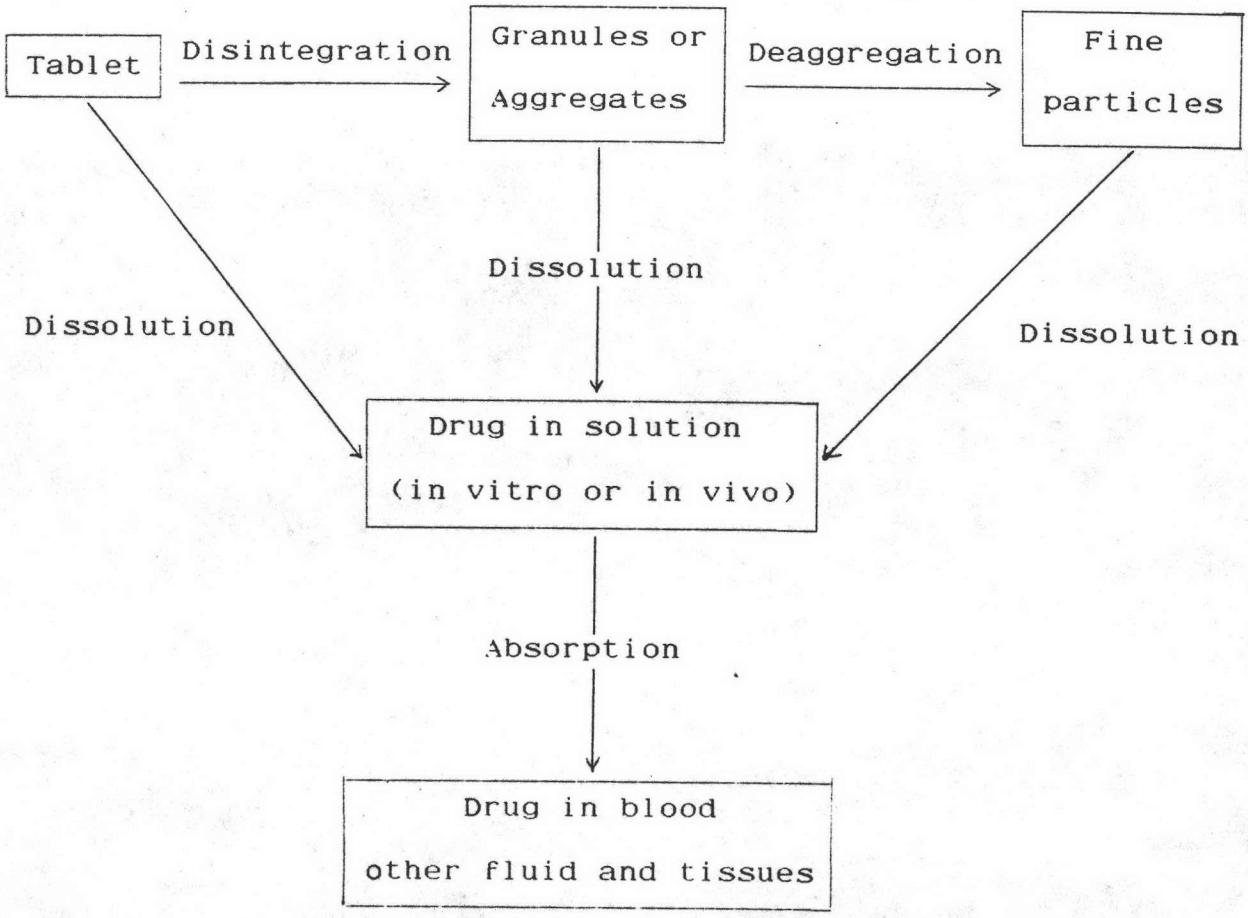

Figure 3. Process involved when a tablet is exposed to fluid water (30).

Panaggio et al. (31) found that direct compression tablet systems comprised of more than one matrix may have significant advantages over the individual matrices presently available. Especially in tablet disintegration, the tablet formulation containing two direct compression vehicles, dicalcium phosphate dihydrate and Starch 1500 corresponding to the proportion of 75:25 and 90:10% w/w gave the fastest disintegration than other proportion, especially to dicalcium phosphate dihydrate or Starch 1500 individually as a diluent in the formulation would give a markedly slower disintegration time.

In this work prednisolone (32, 33, 34) a synthetic glucocorticoid is chosen, representing a sparingly soluble drug. It occurs as a white to practically white odorless, crystalline powder with a bitter taste. The solubility of prednisolone has been included in a list of substances susceptible to biological problem. And a minimum dissolution rate for prednisolone is required by U.S.P. The U.S.P.XX requires 60% dissolution in 20 min. for prednisolone tablets. When prednisolone is reduced to micronized form, having an average particle size approximately 1-3 µm. to which intrinsic cohesional properties would occured.

The direct compression vehicles used are commercially available in the market, these are;

1. Starch 1500

Starch 1500 is a corn starch which has been physically modified to be free flowing and directly compressible. Consequently it is exceptionally adaptable in tablet and capsule formulation and widely accepted as a multipurpose excipient in all solid dosage forms. It is a partially hydrolyzed starch and can be compressed into a compact with still remaining its disintegrant properties. Generally it is used as a direct compression diluent and disintegrant. Its average particle size is approximately 50-100μm. The major advantage of Starch 1500 is that it retains the disintegrant properties of starch without decreasing the fluidity and compressibility of the total formulation, as in the case with plain starch. In adding the lubricant in the formulation, such as magnesium stearate which have been shown to cause difficulties with most direct compression excipients, should be avoided or kept below 0.25%. Otherwise this may cause reduced tablet strength and impair the dissolution process. So in this work 0.25% of aerosil L.200 was incorporated externally to the mixture of both direct compression and wet granulation just prior before compression of tablet for the aim of hardness increasement. Esezobo (35) found that in formulating paracetamol tablet when aerosil was added externally, the strength of the tablet increased while their friability, disintegration and dissolution rates decreased.

2. Elcema G.250 (36)

It is another form of cellulose in a microfine form and is preferably used as a direct compression vehicle. It is a compressible, self-disintegrating antiadherent form of cellulose which can be made into hard compacts. It is not a partially effective dry binder due to large particle size of the granules and the resistance to fracture under compression. Its average particle size is approximately 90-250 µm.

In this work 20% of Starch 1500 was incorporated in the formulation as a disintegrant and also to investigate that when these two direct compression vehicles are incorporated together would order unit segregation occur.

3. Tablettose (37,38)

It is a new variety of alpha lactose monohydrate which has been developed especially for direct compression. It is in the form of granulate, is free flowing and consists of agglomerations of very small crystals which deform easily when compressed. Its average particle size is approximately 157 µm. The differences of particle size and more of the fine have no effect on the flowability of Tablettose. It disintegrates almost the same as spray dried lactose when using the same binding agent in the formulation.

In this work 20% of Starch 1500 was incorporated in the formulation as a disintegrant and also to investigate that when these two direct compression vehicles are

incorporated together would order unit segregation occur.

The degree of homogeneity of the mixture was determined from the coefficient of variation which can be used as a measure of sample uniformity, as in the case of comparing the efficiency of two or more mixing operation and has different sample sizes or different compositions. The coefficient of variation is the standard deviation divided by the mean, that is

$$C.V. = S.D./\bar{X}$$

This value is usually expressed as a percent, by multiplying the values by 100.

Surface characteristic of drug carriers is important to study since it affects the homogeneity of the ordered mixture. A scanning electron microscope was used to examine the surface characteristic of the three direct compression vehicles used and the ordered mixture of the three formulations.

The purposes of the study were:

1. To study the possibility of using Starch 1500, Starch 1500 mixed with Elcema G.250 and Starch 1500 mixed with Tablettose as drug carriers in the formulation of prednisolone tablets prepared by ordered mixing. And to ensure a good drug content uniformity, as well as to improve the dissolution rate.

2. To study the optimum mixing time of the ordered mixture in each formulation.

3. To investigate the ordered unit segregation of the ordered mixture in each formulation.

4. To compare the dissolution rate of prednisolone tablets prepared by ordered mixing in each formulation.

5. To compare the dissolution rate of prednisolone tablets prepared by direct compression and by wet granulation.

6. To compare the stability of the prednisolone tablets prepared by ordered mixing in each formulation regarding to disintegration time, hardness and dissolution rate.