CHAPTER IV

DISCUSSION AND CONCLUSIONS

In pharmaceutical industry, product development is very important to improve the efficacy of pharmaceutical dosage forms especially solid dosage forms, because sometimes they seem to be unreliable delivery systems. However, solid dosage forms appear to be simple to manufacture , to control and to administer. They are usually designed for oral ingestion and this means of administration can often result in inefficient and erratic drug therapy. The popular oral solid dosage forms are tablet and capsule. It should be considered that while solid dosage form development is a scientific exercise, it is also a compromise between cost and benefit. The cost of development required to meet the higher standards of quality and performance is also likely to be higher. As the standards of regulatory requirements and quality increase, the task of balancing various factors e.g. patient acceptability, efficacy, stability, large scale manufacture etc. will become more difficult.

The objective of this study aimed to provide an appropiate means for developing diazepam capsule to have therapeutic effectiveness and inexpensive formulation by way of studying the influence of dispersion method in various diluents on dissolution rate of diazepam capsule.

The dispersion methods used in the experiment were simple and may be used in the local pharmaceutical manufactures. The dispersion methods were simple blending method, solvent deposition method and ball-milling or frictional deposition method.

As it is obvious that diluent may produce some effects on dissolution, care must be taken in the selection of diluents in order to ensure that bioavailability of the drugs will not be hindered. The diluents used in the experiment were divided into two groups, water-soluble groups and water-insoluble groups. Mannitol and sucrose were selected for water-soluble groups. Dibasic calcium phosphate and microcrystalline cellulose were for water-insoluble groups. All diluents used in the experiment, are commonly employed in the local pharmaceutical manufacturers. The amounts of diluent used were also limited in the practical range. Therefore, it was trusted that the results of this investigation may be useful for the manufacturers in order to develop their own pharmaceutical products.

A solid substance can be classified as being crystalline, non-crystalline, or a mixture of the two forms. In crystalline materials, the molecular or atomic species are ordered in a three-dimensional array, called a lattice within the solid particles. This ordering of molecule components is lacking in non-crystalline material. Non-crystalline solids sometimes are referred to as glasses or amorphous solids. Most of drugs are crystalline and hence show some symmetry and regularity. This can be made visible by X-Ray diffraction or diffractometry. Every crystal form of a compound produces its own characteristic X-Ray diffraction patterns

as a "fingerprint". The spacing between and the relative intensities of the diffracted maxima can be used for qualitative and quantitative analysis of crystalline materials. When analysing a mixture, X-Ray diffraction patterns show the typical lines of each component separately. These diffraction patterns can be derived either from single crystal or form a powdered sample (containing numerous crystals) of the material. In this experiment , the powder method was chosen because an advantage over other means of analysis in that they were non-destructive in nature and simple.

During manufacturing procedure, the drug substance is subjected to a variety of unit operations. These include grinding, in order to produce the drug powder exhibiting a high surface area available for dissolution and also to ensure homogeneity of drug to provide dosage uniformity. These fine drug powder produced must then be mixed together with diluents in order to ease dispersion of the drug so that a correct dose will be available in a capsule or tablet . It has been reported that a strong grinding force gave to a solid increased the activation energy on the surface and the distortion of the crystal lattice together with reducing the particle size (37). The field of research including these studies is called "mechanochemistry" (37). Hersey (40) proposed that grinding could induce "mechanical activation" which could increase in solubility and dissolution rate of drug. In pharmaceutical processes, mechanical activation may be occured during milling, granulating and tabletting. These processes, particulary that of milling can cause a mechanical activation of drug, where by the crystal structure of the drug molecule can be disturbed. Such lattice changes or disorder of the crystal can be manifest through out the entire crystal or at

at the surface of the drug particle only. The crystalline changes can be readily demonstrated by using a variety of techniques including X-Ray diffraction, electronmicroscopy, density determination, dilation on melting, differential thermal analysis, differential scanning calorimetry. A number of indirect method including rate of hydrolysis and water absorption can also be used. In this experiment, X-Ray diffraction technique was selected to determined the change in crystallinity of diazepam in the mixtures of diazepam and diluents, because of the advantage over other techniques in that the sample was examined as presented, very small amounts of sample were needed, the sample could be recovered since the method was non-destructive and finally the technique was simple to operate comparing to the other techniques which might be needed an experienced person.

In the experiment, it was found that the major portion of diazepam in the drug-diluent mixtures of all diluents prepared by simple blending and solvent deposition method were in crystalline form, because the diazepam diffraction peaks could be observed obviously in the X-Ray diffraction patterns of the diazepam-diluent mixtures. However, some portions of the diazepam in the diazepam-diluent mixtures of all diluents may be changed in crystallinity, especially in solvent deposition method, because there are partially decreased in intensity of diazepam diffraction peaks compared to simple blending method. There was a change in crystallinity of diazepam during grinding of diazepam in all diluents. It was found that at the ratio of 1:20 and 1:10 of diazepam in all diluents, the diazepam diffraction peaks in the X-Ray diffraction patterns of diazepam-diluent mixtures

were disappeared after twenty-hour grinding and thirty-hour grinding respectively. It seemed to be that the crystallinity of diazepam in the diazepam-diluent mixtures were destroyed and changed to an amorphous state. At the ratio of 1:5 of diazepam in all diluents, the diazepam diffraction peaks in the X-Ray diffraction patterns of diazepam-diluent mixtures were not disappeared after sixty hour grinding, however the diazepam diffraction peaks were decreased in the intensity with the increasing of grinding time. The decomposition did not appear to be a major factor for the decrease in peak intensity of diazepam. It was likely that the crystalline portions of diazepam were remained in the ground mixture.

Owing to the varied ratio of diazepam in diluents, it was also understandable that there was the critical ratio of drug to diluents above which grinding did not produce a phase change. For all diluents, a non-crystalline state of the diazepam was obtained when the percentage of diazepam in the ground mixture was 10 percent or less. If the percentage of diazepam in the ground mixture was above 10 percent, the non-crystalline state of the diazepam was difficult to obtained after grinding by ball milling method.

According to table 46, the approximate time required for grinding 1:20 ratio of diazepam in dibasic calcium phosphate appeared to indicate the amorphous nature of diazepam was five hours shorter than the other diluents at the same ratio. The mechanism of ball milling, impact type comminution is the impaction of grinding media and particles. Abrasion will also produce a comminution during ball milling. Dibasic calcium phosphate is hard and abrasive, comparing

to the other diluents used in the experiment . Since the abrasive property of dibasic calcium phosphate may induce the destructive process of the crystalline property of diazepam faster than the other diluents, therefore the approximate time required for milling the 1:20 ratio of diazepam in dibasic calcium phosphate dihydrate appeared to indicate amorphous nature of diazepam was shorter than the other diluents.

As described before, when a crystalline powder of diazepam was grinding with diluents used in the experiment in the percentage of diazepam less than ten, the non-crystalline state of the diazepam could be obtained. When a crystalline powder of diazepam was grinding in similar manner, but in the absence of diluents, the X-Ray diffraction peaks of diazepam had a little change. This phenomena may be resulted from the agglomeration of diazepam after grinding, where no further destructive process of the crystalline diazepam and the non-crystalline state of the diazepam could not be obtained.

From the previous study, we found that the dissolution characteristics of drug could be altered by dispersing it on the surface of certain material. In the experiment , three dispersion methods were chosen, simple blending method, solvent deposition method and ball-milling method. It was found that ball milling method gave the shorter dissolution time than solvent deposition method and simple blending method in all of four diluents used. According to simple blending method,simple blending method of milled diazepam gave the shorter dissolution time than simple blending method of unmilled diazepam in all of four diluents used.

And it was found that solvent deposition method gave the shorter dissolution time than simple blending method of unmilled diazepam in all of four diluent used.

As described before, it was found that the major portion of diazepam in the diazepam-diluent mixtures prepared by simple blending method and solvent deposition method were in crystalline form. The major portion of diazepam in the 1:20 and 1:10 ratio of diazepam in diazepam-diluent mixtures prepared by ball milling method were in amorphous form after grinding for 20 hours and 30 hours respectively, however the major portion of diazepam in the 1:5 ratio of diazepam in diazepam-diluent mixtures prepared by ball milling method were in crystalline form after grinding for 60 hours.

The significant different in dissolution rate of diazepam from diazepam capsule prepared by the three different dispersion methods were concerned with the crystallinity of diazepam in the drug-diluent mixtures. The apparent amorphous nature of diazepam in the drug-diluent mixtures could be considered to be mainly responsible for the enhanced dissolution rate.

The dissolution profile of diazepam capsules were presented in the Figure 32-43. In the experiment, it was found that the four diluents produced some effects on dissolution rate of diazepam in the diazepam capsule concerning to the three diapersion methods.

I. Simple Blending Method

According to the dissolution rate of unmilled diazepam capsules at the first interval (approx. 0-25 min.) of dissolution profiles, prepared by simple blending method, it was found that the diazepam capsule prepared from drug-diluent mixtures, the diluent which gave faster dissolution rate was ranked as follow : mannitol> microcrystalline cellulose> dibasic calcium phosphate> sucrose. Mannitol and sucrose are the soluble diluents. Shah et. al. (44) demonstrated that in-vitro dissolution test, soluble diluents, release the digoxin more rapidly than the insoluble ones. In the experiment, at the first interval of dissolution profiles mannitol gave the fastest dissolution rate, however sucrose, soluble diluent gave the slowest dissolution rate. The failure of sucrose as diluent to enhance the dissolution rate of diazepam from diazepam capsules may be due to the agglomeration of sucrose after milling and absorbing moisture.

The superiority of mannitol over the microcrystalline cellulose was that mannitol was a soluble diluent hence had solubilization effect. Among microcrystalline cellulose and dibasic calcium phosphate in the first interval of dissolution profiles, microcrystalline cellulose gave the faster dissolution rate than dibasic calcium phosphate. This result may be due to the superior wettability of microcrystalline cellulose over dibasic calcium phosphate.

The second interval of dissolution profiles (approx. 25-60 min.) dibasic calcium phosphate gave the fastest dissolution rate. The performance of dibasic calcium phosphate in this case was unexpected. The solubility of dibasic calcium phosphate in dissolution media likely accounted for these observation, since after the dibasic calcium phosphate dissolved, calcium salt of diazepam may be occured hence enhanced dissolution rate rate of diazepam around the dibasic calcium phosphate particles. In the second intervals of dissolution profiles, the diluent that gave the faster dissolution rate of diazepam was ranked as follow : dibasic calcium phosphate〉 mannitol〉 microcrystalline cellulose〉 sucrose.

According to the dissolution rate of milled diazepam from the diazepam capsule at the first interval of dissolution profiles (approx. 0-25 min.), prepared by simple blending method, it was found that the diazepam capsule prepared from drug-diluent mixtures, the diluent which gave faster dissolution rate was ranked as follow : microcrystalline cellulose〉 mannitol〉 dibasic calcium phosphate〉 sucrose. As decribed before, reduction of particle size of poorly water-soluble drug resulted in aggregation and agglomeration of the fine drug particles due to their increased surface energy. The milled diazepam was expected to aggregate much more than the unmilled diazepam. In this case, the aggregation of the diazepam seemed to be the greater effect on dissolution rate of diazepam than the poor wettability of milled diazepam resulting from particle size reduction. The superiority of microcrystalline cellulose over the mannitol in this case may by due to the higher efficiency in reduction of aggregation of milled diazepam.

The second interval of dissolution profiles (approx. 25-60 min.) the diluents that gave faster dissolution rate of diazepam was ranked as follow: dibasic calcium phosphate dihydrate> microcrystalline cellulose> mannitol> sucrose. The superiority of dibasic calcium phosphate over microcrystalline cellulose in the second interval of dissolution profiles was not expected. The solubility of dibasic calcium phosphate dihydrate in dissolution media likely accounted for these observation. After the dibasic calcium phosphate dissolved, calcium salt of diazepam may be occured hence enhanced dissolution rate of diazepam around the dibasic calcium phosphate particles.

From the experiments, it may be concluded that the mechanism in dissolution enhancement of the simple blending method was depended on the agglomeration tendency and wettability or solubility of the diluent used. The ideal diluent that gave the maximum dissolution enhancement in this method should

1. not aggregate or agglomerate after preparing the drug-diluent mixture

2. be wetted easily by dissolution media or dissolved in the dissolution media

3. not cause drug-diluent interactions.

II. Solvent Deposition Method.

According to the dissolution rate of diazepam capsule at the first interval (approx. 0-25 min.) of dissolution profiles, prepared by solvent deposition method, it was found that the diazepam capsule prepared from drug-diluent mixtures in which mannitol and microcrystalline cellulose were used as diluents gave the insignificant difference in dissolution rate. The diazepam capsule, prepared from the drug-diluent mixtures in which mannitol and microcrystalline cellulose were used as diluents gave faster dissolution rate than dibasic calcium phosphate. The diazepam capsule, prepared from the drug-diluent mixtures, in which mannitol was used as diluent gave the fastest dissolution rate, where as sucrose used as diluent gave the slowest dissolution rate. The failure of sucrose as diluent to enhance the dissolution rate of the diazepam from diazepam capsule may be due to the agglomeration of sucrose in the diazepam-sucrose mixtures. The insignificant difference in dissolution rate of diazepam from diazepam capsule using mannitol and microcrystalline cellulose as diluents may be due to the small difference in specific surface area of mannitol and microcrystalline cellulose as shown in table 15. The specific surface area of mannitol and microcrystalline cellulose were 0.44 m^2/gm and 0.37 m^2/gm, respectively. Among microcrystalline cellulose and dibasic calcium phosphate in the first interval of the dissolution profiles, microcrystalline cellulose gave the faster dissolution rate than dibasic calcium phosphate. This result may be due to the superior wettability of microcrystalline cellulose over dibasic calcium phosphate dihydrate.

The second interval of dissolution profiles (approx. 25-60 min.), dibasic calcium phosphate gave the fastest dissolution rate. The performance of dibasic calcium phosphate dihydrate in this case was unexpected. The solubility of dibasic calcium phosphate dihydrate in dissolution media likely accounted for these observation. After the dibasic calcium phosphate dihydrate dissolved, calcium salt of diazepam may be occured hence enhanced dissolution rate of diazepam around the dibasic calcium phosphate particles.

From the experiment , it may be concluded that the mechanism in dissolution enhancement of the solvent deposition method was depended on the surface area, agglomeration tendency and wettability of the diluent used. The ideal diluent that gives the maximum dissolution enhancement in this method should

1. own large surface area
2. not aggregate or agglomerate after preparing the drug-diluent mixture.
3. be wetted easily by dissolution media
4. not cause drug-diluent interactions

III. Ball milling method

Milling or comminution operations are used to produce fine particulates having increased surface area available for dissolution. Milling produces particle size reduction, but as the particle size is reduced, it becomes increasingly more difficult to obtain furthur reduction size. Eventually a practical grind limit attained (65). The most important factor limiting size reduction is the tendency for the fine product particles produced by milling to reaggregate and establish a dynamic equilibrium situation between the two operation of agglomeration and fragmentation as shown in Figure 44.

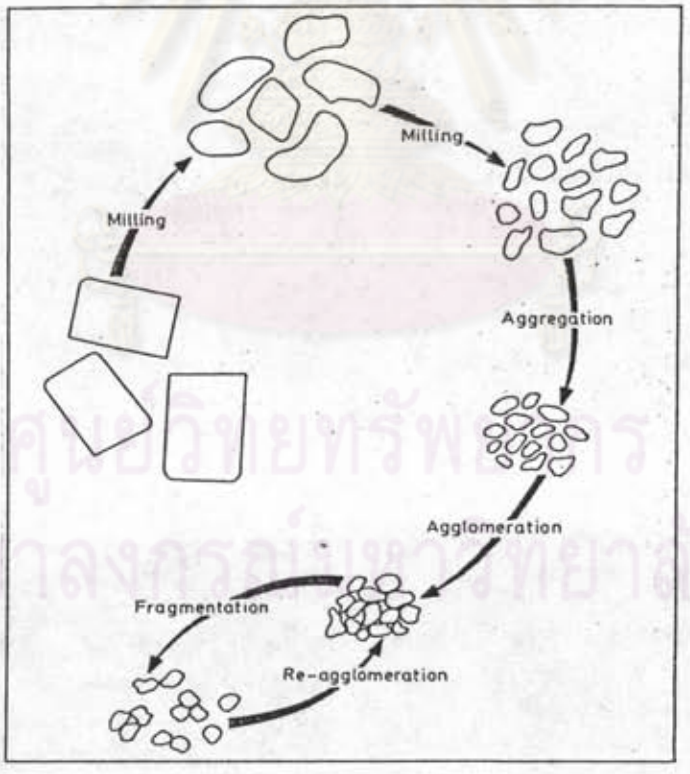

Figure 44 Diagrammatic representation of the mechanism of milling equilibrium.

It was found that comminution consisted of three phase as shown in Figure 45. The phase was nominal grinding phase or Rittinger's stage. At this stage the particles were beginning to break down. The second phase was aggregation phase resulting in crystal clevage and formation of platelets. This stage of aggregation was due to Van der Waal's forces and could be mechanically reversed since the energy involved amounts to 0.04-4.0 kJ/mole. The third phase was agglomeration phase resulting in a decreased incidence of size reduction due to welding or solid formation of particle resulting from much higher energy levels (40-400 kJ/mole). At this agglomerative stage the process is irreversible (65).

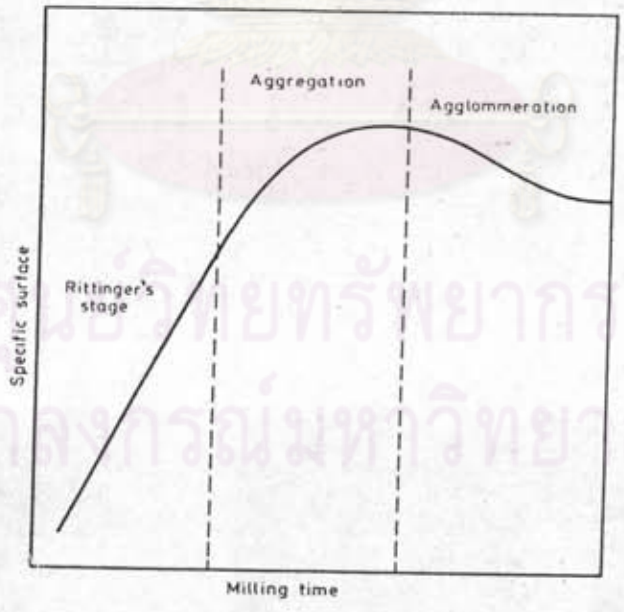

Figure 45 Theoretical diagram illustrating the three phases of fine dry grinding.

The agglomeration process in the ball mill was characterized as a "balling up", where the material appeared damp (65). Prior to balling-up, the powders took on a fluffy appearance and ultimately became completely caked. It was found that grinding of many materials in a ball mill for long periods, resulted in agglomeration, where no further size reduction could be attained. The irreversibility of agglomeration operations after prolonged milling times suggested that milling could not proceed indefinitely. Agglomeration was likely to be the major problem of milling, thus delaying the agglomeration might be resulted in the production of finer particles. To overcome the agglomeration problem, the following methods were used to solve this problem.

a. If wet milling could be utilised, agglomeration could be delayed resulting, in the production of finer particles.

b. If dry milling were utilised, it was necessary to decrease the energy input to defer the onset of agglomeration. This might be achieved by reducing the mill diameter, the size of the grinding media or the time of grinding.

c. Using the grinding aids e.g. surface active agents, inorganic salts with multivalent ions. The use of grinding aids to delay the onset of agglomeration appeared to be effective only during the aggregative phase.

d. Mechanical removal the fine powders as soon as they reached the desired degree of fineness was a most practical way of eliminating agglomeration.

In fine, dry grinding of solids considerable energy was supplied to the material, of which only a fraction was used in the formation of new surfaces. The remainder was converted directly into heat or stored in the material, causing plastic deformation, "mechanical activation" and "amorphisation" (40, 65). On prolonged grinding atoms or ions were removed from the surface of the crystal lacttice, creating mechanically activated chemically unbound defect sites. The individual activated particles agglomerated, but maintained their high energy content.

In the experiment , it was found that grinding of diazepam-diluent mixture in ball mill, a large increase in dissolution rate of diazepam was detected, thereby supporting the concept of "mechano-activation". Mannitol, sucrose and dibasic calcium phosphate dihydrate were tended to agglomerate after milling with diazepam. For microcrystalline cellulose, the tendency to agglomerate after milling with diazepam was less than the three diluents. As aforementioned there was a change in crystallinity of diazepam during ball milling of diazepam-diluent mixtures. It was found that the approximate time required for milling 1:20 ratio of diazepam in dibasic calcium phosphate to the amorphous state was five hours shorter than the other diluents at the same ratio. In this case the hardness and abrasive property of dibasic calcium phosphate dihydrate likely accounted for these observation. According to ball milling method, the hardness and abrasive property of diluents were considered as well as the agglomeration tendency of diluents in selecting the most suitable diluents. From the dissolution profiles of diazepam capsule prepared

by ball milling method, the diazepam capsules prepared from drug-diluent mixture, the diluent which gave faster dissolution rate was ranked as follow : microcrystalline cellulose〉 mannitol〉 dibasic calcium phosphate〉 sucrose. The diazepam in the diazepam-diluent mixtures at the ratio of 1:20 and 1:10, was found in an amorphous state after milling for 20 hours and 30 hours respectively, however some portions of diazepam in the 1:5 ratio of diazepam in diazepam-diluent mixtures prepared by ball milling were remained in crystalline form after milling for 60 hours. The results may be due to the high percentage of diazepam in the diazepam-diluent mixtures, and the agglomeration of the diazepam-diluent mixtures after prolonged grinding.

From the experiment , it may be concluded that the mechanism in dissolution enhacement of the ball-milling method was depended on the amounts of diazepam in diazepam-diluent mixture, the milling time, the agglomeration tendency of diluents after prolonged grinding. The ideal diluents used in ball-milling method should be compromised among the following properties.

1. hard and abrasive
2. the agglomeration tendency of diluents after prolonged grinding.
3. does not cause drug-diluent interactions.

The combination of two or more diluents in order to get the ideal desirable properties of diluents may be succeeded in enhancement of dissolution rate by this method.

Conclusion

Diazepam is a psychotropic benzodiazepine, exhibiting poorly water-soluble and absorption irregularities (62). For this reason, the experiment had been performed with an aim to develop the manufacturing process of diazepam capsule which possesses therapeutic effectiveness, inexpensive and ease to manufacture.

As previous study, many methods have been used to enhance the dissolution rate of poorly water-soluble drugs. It was believed that the solid dispersion technique was the one of pharmaceutical techniques which effective in increasing dissolution rate of many poorly water-soluble drugs (22-35). However the techniques were limited to manufacture, because of the processing problems of solid dispersions, which tend to be wax like sticky masses (32) and poor flowability. The process of preparing solid dispersion system might cause degradation of drugs or excipient used. In the experiment, the solid surface dispersion system was selected to overcome this problems of solid dispersion system. An known before, the solid surface dispersion system was achieved by two methods, solvent deposition method and frictional deposition or mechanical deposition method. In this study, both methods were selected and compared with the simple blending method to accomplish the best way that gave the highest dissolution rate of drug and ease to manufacture.

The results of the experiment may be concluded that:-

1. Among the three dispersion methods, mechanical deposition method exhibited the highest dissolution rate, followed by solvent deposition and simple blending method.

2. Each diluents used in preparing drug-diluent mixtures own its dissolution behavior of diazepam from diazepam capsule according to the dispersion method.

3. A greater amount of diluent increased a higher dissolution rate of diazepam from diazepam capsule in the three dispersion method, however the amount of diluent was limited in the practical rage.

4. The mechanism of simple blending method was depended on the agglomeration tendency and wettability or solubility of the diluent used.

5. The mechanism of solvent deposition method was depended on the surface area, agglomeration tendency and wettability or solubility of the diluent used.

6. The mechanism of mechanical deposition method was depended on the amounts of drug in drug-diluent mixture, the milling time, the agglomeration tendency of diluent and abrasive property of the diluent used.

7. According to the mechanism of the three dispersion method the suitable diluent may be selected to achieve the highest dissolution rate of the drug.

The solid surface dispersion method was successful to overcome some processing problems of solid dispersion system especially in the production of wax like sticky mass and poor flowability. However the other problems such as, the limitation of solid dispersion method in large dose drug and the generally poor stability of solid dispersions had not been solved by solid surface dispersion systems. Since the solid surface dispersion system, the drug molecule were activated to higher energy level, the activation energy of drug may be reduced after storage for a long time, thus the further experiments about the stability of the system were suggested.

It is hoped that these finding would be useful to research and development pharmacist in order to develop the appropriate formulation of diazepam capsule to employed in the manufacturing practices.