CHAPTER IV

DISCUSSION AND CONCLUSION

Particle size Distribution

The drug carriers used in this work were Starch 1500, Elcema G.250 and Tablettose. From particle size distribution studies, Starch 1500 had smallest particle size (d_{ave} = 86 μm), Elcema G.250 had largest particle size (d_{ave} = 275 μm) and Tablettose had average particle size of 171 μm.

The particle size of the drug carriers are responsible to the mixing time. The smaller particle size drug carrier would take a longer mixing time to break the drug agglomerates than the larger particle size drug carriers. The size distribution of the drug carriers is influential to the ordered unit segregation and therefore affected the homogeneity of the ordered mixture.

Scanning Electron Micrographs

Besides the particle size of the drug carrier which influences the ordered mix, the surface characteristic of the drug carrier should also be regarded. As the carrier possessing a smooth surface would not give the same degree of homogeneity and stable ordered mixture to those carriers with macroporous or indented surface

characteristic. This was reported by Staniforth (27) when using two chemically similar excipients with comparable coarse particle size distribution as Emdex and Dipac to form homogeneous powder 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 surface crystal agglomerate of sucrose. From the scanning electron micrograph studies, Starch 1500 and Tablettose have quite smooth surface comparing to Elcema G.250 which is a fibrous powder with a lot of indented on the surface, which may be a good adhesion sites to the drug, and also prevent drug segregation by the three mechanisms as mentioned in the introduction. So the drug would be more permanently adhered to Elcema G.250 than to Starch 1500.

Mixing Homogeneity

Only Starch 1500 was selected as drug carrier in formulation 1. The reason in selecting Starch 1500 as drug carriers due to the properties of directly compressible and self disintegrating agent. From the mixing profile in Figure 14, a high coefficient of variation were obtained at every interval of mixing time as compared to Elcema G.250 and Tablettose; the drug carriers used in formulation 2 and 3 respectively. Since the micronized drug did not distributed through the mixture and drug

agglomerates still occurred. As the particle size of Starch 1500 is small, thus hindered the free flowing property due to cohesive forces as well as static forces. At 50 minutes, the coefficient of variation is 12.83% which is still high, after the lubricants; magnesium stearate and aerosil L.200 were incorporated and mixing was continued for 10 minutes, the coefficients of variation became lower to 3.15%. These lubricants improved the flow property of the drug carrier to be free flowing and probably by diffusion mechanisms which caused the redistribution of particles by the random movement of particles relative one to the other.

Formulation 2 and 3 contained Elcema G.250 and Tablettose as drug carriers respectively. Formulation 2 gave the fastest homogeneity ordered mixture at 5 minutes (C.V.=2.61%), probably because of the moderately large particle size of Elcema G.250 which participated in breaking drug agglomerate, and the higest degree of homogeneity of the ordered mixture was achieved at 20 minutes to which the lowest C.V. was 1.69%. The results clearly showed that as the larger the particle size of drug carrier, the faster the ordered mixing time.

Formulation 3 contained two direct compression vehicles; Tablettose and Starch 1500, the coefficient of variation of 7.44% was obtained at 2 minutes mixing time. This fast formation of ordered mix may have been due to the excellent flow property of Tablettose. Because the granulated form of Tablettose assisted in breaking

drug agglomerates. At 5 minutes mixing time, the coefficient of variation increased to 16.87% which was due to the presence of drug agglomerates in one sample that led to a high drug content. The highest degree of homogeneity of the ordered mixture occurred at 30 minutes, obtaining a lowest C.V. of 1.0%. This was probably due to the absence of drug agglomerate in the mixture and a strong utilizing particle interaction between drug and drug carrier.

Formulation 3 resulted in a higest degree of homogeneity of the ordered mixture at the slower rate (30 minutes mixing time) than formulation 2 (20 minutes mixing time) and both at much faster rate than formulation 1 (>50 minutes mixing time).

Ordered Unit Segregation

Ordered unit segregation may be caused by a difference in particle size and density of the two direct compression vehicle in the ordered mixture.

From the result of ordered unit segregation studies during compression in Table 8. Formulation 1 gave the difference of content uniformity between the first and the last interval sampling of only 1.14%. This was because formulation 1 contained only one drug carrier component; Starch 1500. so that the ordered mixture would not prone to cause ordered unit segregation.

The result from Table 9 shows that there was a difference of 8.82% drug content between the first and the

last interval of prednisolone tablet formulation 2 during compression. The difference of the percent drug content between the two intervals in formulation 2 is more than formulation 1 and 3, but still meets the requirement of USP.

The difference of the drug content in formulation 2 during compression may be due to the difference in particle size of the two drug carriers which may led to ordered unit segregation. Although Elcema G.250 has a larger particle size than Starch 1500, but its density (0.44 g./c.c.) is less than Starch 1500 (0.62 g./c.c.). Therefore, ordered unit segregation of the ordered mixture would not be intense with regarding to particle size and density of the two drug carriers.

Formulation 3 also contained two direct compression vehicles; Tablettose and Starch 1500, there was only a slightly difference of 1.45% drug content from the two intervals of sampling during compression, since the particle size (171 μm) and density (0.55 g./c.c.) of Tablettose is not much difference from Starch 1500.

Although formulation 2 and.3 cintained two direct compression vehicles, but the two direct compression vehicles in formulation 2 is more different in particle size and density than the two direct compression vehicles in formulation 3, therefore the percent difference of drug content between the two intervals of sampling during compression of formulation 2 is more than formulation 3.

Disintegration Time

From the experiment of Panaggio et al (31), they found that the direct compression tablet containing two direct compression vehicles; Dicalcium phosphate dihydrate and Starch 1500 has significant advantages over the individual matrices presently available, especially when using at ratio 75:25 would gave the fastest disintegration time than other ratios. So in this work, formulation 2 and 3, Starch 1500 a direct compression vehicles and also a self disintegrant was added 20% in order to give the fast disintegration time. Therefore formulation 2 and 3 contained two direct compression vehicles; Elcema G.250 and Starch 1500, and Tablettose and Starch 1500 respectively at ratio 77:20.

The disintegration time of prednisolone tablets from formulation 2 and 3 are 1.31 minutes and 0.15 minute respectively, these are markedly faster than formulation 1 which is 16.5 minutes. Formulation 1 gave the slowest disintegration time because Starch 1500 when exposed to the disintegration medium formed sticky mass and mucous, thus delaying the disintegration time.

The sticky mass and mucous which formed is caused by the physical property of Starch 1500 which consists of 5% free amylose, 15% free amylopectin and 80% unmodified starch, when wetted there would be a sudden swelling of amylose plus the binding property of amylopectin thus formed mucous to tablet matrix, inhibitting water penetration.

The fast disintegration time of formulation 2 and 3 were probably due to the advantage of using Starch 1500 as a co-direct compression vehicle and self disintegrant in the formulations. When the tablet imparted to disintegration medium, the Starch 1500 which was distributed in tablet matrix would cause a double disintegration action involving the significant swelling of amylose and the deformation recovery mechanisms of the unmodified portion of the starch, thus expelling the other direct compression particles.

Dissolution Rate

From the dissolution profile as shown in Figure 15. Formulation 2 and 3 gave faster dissolution rate than formulation 1, more than 60% of prednisolone was dissolved within 20 minutes. This may be due to their faster disintegration time. Formulation 1 gave the slowest and unsatisfied drug dissolution rate, it gave only 49% prednisolone at 20 minutes and did not meet the requirement of USP XX dissolution apparatus Type I which requires 60% of prednisolone to dissolved within 20 minutes.

Prednisolone tablet formulation 3 gave the faster dissolution rate than formulation 2, this was probably due to the water solubility of Tablettose, therefore Tablettose was rapidly soluble when exposed to dissolution medium and the drug would be rapidly released enhancing the faster dissolution rate than Elcema G.250 which was insoluble in water and would released the drug at the slower rate.

The dissolution rate of prednisolone tablet formulation 2 and 3 prepared by direct compression was faster than that the tablet prepared by wet granulation method, as seen in Figure 17. As the tablet prepared by direct compression, the drug is in the extragranular position, therefore the drug was released immediately after the tablet was disintegrated, ensuring its faster dissolution rate than the wet granulation method by which the drug is situated in the intragranular position combinding with binding agent and diluent into granules which may caused a delay in drug release.

Although direct compression may be a method to increased a more drug dissolution rate than wet granulation, but this does not always true for all cased, as a faster dissolution rate of prednisolone tablet formulation 3 prepared by wet granulation than formulation 2 prepared by direct compression was observed. This faster dissolution rate was due to Tablettose which was soluble in water and would cause a more rapid in drug released rate than Elcema G.250 which was insoluble in water and therefore may retarded in drug release.

Physical Stability of Prednisolone Direct Compressed Tablets

Although both of the direct compressed tablets formulation 2 and 3 gave a satisfactory dissolution rate, their physical stability should also be considered in order to maintain its physical properties during storage

time. Therefore, the three formulations of prednisolone direct compressed tablet were performed to physical stability test regarding to disintegration time, hardness and dissolution rate by storing those tablets in polystyrene jar at room temperature which was carried on 4th, 8th, and 12th week.

The polystyrene jar was selected in this experiment because it is widely used for prescription containers, but the moisture protection is very poor.

The results show that the storage of the three formulations of prednisolone direct compressed tablets in polystyrene jar at room temperature for 12 weeks did not affected the disintegration time, hardness and dissolution rates, only a slightly decreased in disintegration time of the tablet in formulation 2, and a negligible decreased in hardness of the tablet in formulation 3 at 12 weeks of storage. So the three formulations of prednisolone direct compressed tablets were physically stable within the storage time of 12 weeks. Further study with longer time of storage is suggested.

Conclusion

The results from the experiment indicated that it is possible to prepare prednisolone ordered mixture to a high degree of homogeneity by using, Starch 1500, Elcema G.250 and Starch 1500 (77:20), and Tablettose and Starch 1500 (77:20) as drug carriers.

Ordered mixing time varies according to drug carriers used. Formulation 2 (containing Elcema G.250 and Starch 1500 at ratio 77:20) gave the highest degree of homogeneity of ordered mixture at 20 minutes mixing time (C.V.=1.69%) and the C.V.% remained constant to the end of mixing operation. Formulation 3 (containing Tablettose and Starch 1500 at ratio 77:20) resulted in the highest degree of homogeneity of ordered mixture at 30 minutes mixing time (C.V.=1.0%).

Formulation 1 (containing Starch 1500) required the longest mixing time (>50 minutes). It obtained a satisfactory degree of homogeneity of ordered mixture (C.V.=3.10%), after the lubricants were added and further mixing for 10 minutes. The three formulations studies gave the stable ordered mixture which were not prone to segregation during compression.