CHAPTER IV

DISCUSSION AND CONCLUSION

The Physical Properties of Active Raw Materials

The photomicrographs in Figures 5-15 revealed the size and shape of active raw materials powder from various sources used in this study. Most of the particle morphology of the same active raw materials from scanning electron microscope showed similar results except for Mefenamic Acid I, II and III, the photomicrographs showed that there were differences in shape and size of the particles from different sources of Mefenamic acid samples used in this study. This may be caused by differences in active raw material production process that may lead to variability in the properties of finished products (Timmins et al.,1986).

Particle size distribution of various active raw materials are indicated in Table 3 and Figures 19, 25, 29. The data showed that for active raw materials of Tetracycline Hydrochloride, Tetracycline III possessed the widest size distributions while Tetracycline II showed the narrowest size distribution and more than 98% of Tetracycline II particles was smaller than 150 µm, correlated with the result from SEM picture which showed the thinnest rod-shaped particles. It was noticed that the particle size distribution of five sources of

Cimetidine were not very different unlike three sources of Mefenamic Acid, Mefenamic Acid I possessed the widest range of size distribution and they were clearly seen the differences in particle shapes among Mefenamic Acid samples.

In this study, bulk density and tapped density of various samples were less than 1 g/ml. Bulk, tapped and true density within Tetracycline Hydrochloride samples were similar and within Cimetidine and Mefenamic Acid samples were slightly different. The main differences are that Cimetidine IV has a greater bulk density than most of the others, and Cimetidine V has a lower bulk density. Mefenamic Acid I also has a greater bulk density, and Mefenamic Acid II has a lower bulk density.

Tetracycline Hydrochloride III has a greater moisture content markedly, while another sources are similar.

Compressibility and angle of repose are shown in Table 4 . These two parameters were the indicators that showed flowability of powder. The highest value of percent compressibility and angle of repose of Tetracycline II was obviously different among Tetracycline Hydrochloride samples. From SEM picture in Figures 5, 6 and 7, they are clearly seen the thinnest and longest rod-shaped particle of Tetracycline II, thus causing the highest interparticular locking. For most pharmaceutical powders, the angle of repose values range from 25 to 45°, with lower values indicating better flow characteristics (Wadke et al.,1989) where the value lower than

40° indicated good flowing property (Fonner et al.,1980). The active raw materials samples in this study showed different value from 32 to 48° in Table 2. The angle of repose of all Tetracycline Hydrochloride samples were lower than 40° while the angle of repose of all Cimetidine and all Mefenamic Acid samples were greater than 40°. In addition, compressibility confirmed the result. Jones (1979) indicated correlation between compressibility and flowability as illustrated in Appendix V. From this data might be classified flowability of Tetracycline I, II and III as excellent, good and excellent, respectively. For Cimetidine I, II, III, IV and V as very very poor, very poor, very poor, very poor and very very poor, respectively. For Mefenamic Acid I, II and III as very poor, very very poor and very very poor, respectively.

The melting test is often used for routine quality control of a drug or compound. The melting point of various samples were slightly different agree with Chiou and Kyle, 1979 who studied on melting point of various sources of digoxin and digitoxin powder and showed that there were many reasons for variation in the melting range among all samples such as the presence of polymorphic and amorphous forms, crystal defects, impurities and solvate formation or combination of these factors. These reasons be also expected to alter the solubility and dissolution properties of the drug. However, in this study, there were small variation in melting ranges of the active raw materials from various

sources and they are in the range of acceptable limit (USP XXII, 1990).

Table 4 and Table 7 show the relationship between physical properties and actual formulation. The active raw materials with similar physical properties of bulk, tapped density, percent compressibility, flow rate and angle of repose such as Tetracycline I and III; Cimetidine II and III , used very similar actual formulation.

Table 3, Figures 34, 37 and 39 show the effect of active raw materials particle size on releasing of the drug from the dosage form that the smallest average particle size of Tetracycline II (98.90% smaller than 150 μm) Capsules show the fastest and highest dissolution profile among Tetracycline samples while the largest average particle size of Cimetidine V (88.78% larger than 850 um) Capsules and Mefenamic II (93.68% larger than 850 um) Capsules show the slowest and the lowest dissolution profile among Cimetidine samples and Mefenamic Acid samples, respectively.

The Chemical Content of Active Raw Materials

The values of chemical content of each active raw materials samples from this study are presented in Table 6; the listing is divided into three groups representing comparable materials and the result showed acceptable content according to USP XXII(1990) and BP 1988 which indicated that in this study there was no marked variation in chemical

content with the sources of active raw materials.

Comparison of the Physical Properties of the Hard Gelatin Capsules

Among the same drug, the actual formulas in Table 7 show different amount of diluent to fit the capsule and the quantities of diluent added were unpredictable agree with Newton, J.M. and Bader, F., 1981, who had demonstrated that there were no satisfactory prediction of the bulk densities of powder mixtures, and its relationship to the filling of hard gelatin capsules, when the capsules were filled by a process involving compression of the powder within the capsule shell.

Most of experimental capsules exhibited average weight variation, percent of relative standard deviation, content uniformity and disintegration time within the official limit except some of fixed-diluent capsules. Surprisingly, the disintegration time of Mefenamic Acid I Capsules took shorter than for the others mefenamic acid capsules (Table 9) may be because of the presence of higher level of lactose added in the formulation (Table 7).

Comparison of Disintegration time between fixed-diluent formulas and q.s-diluent formulas, the data from Table 9 and Table 10 showed very similar disintegration times.

However, results from this study showed that all the lots investigated conformed to the requirements of the pharmacopeias except when the source of active raw materials

had been altered and the physical properties of the dosage form may be effected. Therefore it may be interpreted that among the water soluble drug (Tetracycline Hydrochloride as the model drug) variation in sources of active raw materials had no effect on weight variation, content uniformity and disintegration time, unlike the slightly water soluble drug (Cimetidine as the model drug) and water insoluble drug (Mefenamic Acid as the model drug).

Comparison of the Dissolution Rate of Active Raw Materials

The dissolution behaviors of various capsule samples contain active raw material alone are compared on percent and time for the same drug to release from the capsules.

Analysis of Variance was performed to determine if the sources of active raw materials alone actually produce significantly different dissolution profiles. The data represented in Tables 11-12, 15-16 and 19 show that at all the point of times and percent drug released studied, the calculated F value for various sources of active raw materials exceeds the tabular F value at 95 percent level of confidence except raw materials of Tetracycline Hydrochloride. The results by analysis of variance indicated that sources of Tetracycline Hydrochloride I, II and III showed no statistically significant differences while Cimetidine I-V and Mefenamic Acid I-III did.

In the case of Raw Materials Cimetidine I-V, Figure

35, Cimetidine V showed the fastest rate of dissolution and the dissolution rate could be ranked as follow: Cimetidine V > Cimetidine III > Cimetidine I > Cimetidine II > Cimetidine IV.

In the case of Raw Materials Mefenamic Acid I-III, Figure 33 shows that the dissolution profiles differed markedly among the sources. Observation of the dissolution behavior of the slow-dissolving active raw material Mefenamic Acid I-III, showed that the contents of these capsules remained as a wet powder pack long after the gelatin wall had dissolved. Shinkuma et al. (1984), stated that *in vitro* dissolution of nearly insoluble drugs from hard gelatin capsules like mefenamic acid is affected markedly by various factors such as the particle size and packing of the drugs, the deaggregation rate of the capsule contents, additives and/or polymorphism of mefenamic acid. In this study too, the dissolution rate may be affected by the same factors. As a result, the dissolution rates of Mefenamic Acid I and II from capsules were markedly slower than that of Mefenamic Acid III (Figures 37, 38 and 41).

Comparison of the Dissolution Rate of the Experimental Hard Gelatin Capsules

The dissolution behaviors of various experimental hard gelatin capsule samples are compared on percent and time

for the same drug to release from the capsules.

Analysis of Variance was performed to determine if the sources of active raw materials actually produce significantly different dissolution profiles of experimental capsules. The data represented in Tables 13-14, 17-18 and 20 show that at all the point of times and percent drug released studied, the calculated F value for various experiment capsules exceeds the tabular F value at 95 percent level of confidence. Surprisingly, the calculated F value for 75% drug released of Working Formula Cimetidine I and another Fixed-diluent Formula Cimetidine(II, III, IV and V) was the only value below the tabular F. The results by analysis of variance indicated that most of experimental capsules of the same drug showed statistically significant different. The variation in drug release may be depending on level of the additives, agree with recent literature of Singla and Mediratta, 1988.

Conclusions

It may be concluded that chemically equivalent active raw materials from different suppliers do not necessarily possess comparable physical properties and dissolution profiles of the dosage form and that, when used in hard gelatin capsule formulation, active raw materials should be evaluated very carefully, especially before inclusion in existing capsule formulations. Of all the active raw materials tested from different sources, only Cimetidine I, II, III, IV

and V were found to be equivalent in existing capsule formulations at 75% drug released.

Most of the *in vitro* dissolution rate of the same drugs from the experimental capsules differed markedly from one source to another. The variation in drug released from the capsules may be attributed to various factors such as particle size of the drug contained in them and variations in the levels of the additives.

Evaluation of these data shcwed that the physical properties of active raw material are very important factors in the manufacturing of hard gelatin capsule dosage form, especially when active ingredients are used in high dose. Variation in active raw materials may occur among different suppliers of the same product or among different batches of the same supplier. Therefore, the validation of a proper process for examining the active raw materials is very important for the manufacturer to ensure consistency of drug released from the dosage form, especially with drugs of low water solubility. The source variation problem may be minimized by procuring active raw material from a single supplier.