CHAPTER IV

DISCUSSION AND CONCLUSIONS

In Pharmaceutical industries, product development is one of the most important function of research and development section. It is generally recognizing that the design of product formulation may be considered as the key role of research and development pharmacist. For instance, in the case of formulating a new tablet, the researcher must give his thought on the way how to produce a readily dissolvable tablet. This is a lead to a topic of our following discussion.

The objective of this study aims to provide an appropriate means for the development of dipyrone tablet to have therapeutic effectiveness and inexpensive formulation by way of studying the effects of various additives on the dissolution behaviour of the product. As it is obvious that certain additive may produce inhibitory effect on dissolution. As a result, care must be taken in the selection of additives to use in order to ensure that physiological availability and therapeutic efficacy of the drugs will not be hindered. All additives used in the experiments are commonly employed in the local pharmaceutical manufactures. The amount of additives used are also limited in the practical range. The sequence of preparation of granules and tablets are the same as in the actual manufacturing practices. We designed our experiments in such a way that the total

effects of additives that incorporated into the tablets were studied and analyzed at the same time. Therefore, we trust that the results of this work may be useful for the manufacturers in order to develop their own formulations.

Our discussion are divided into two parts. The first part will discuss about the effect of each additive on the dissolution behaviour of dipyrone tablets and how to select single optimum additive. The effect of hardness of tablets on dissolution behaviour will also be discussed. The second part will touch upon the results of factorially designed experiments and the effect of selected additives concentrations on the dissolution behaviour of dipyrone tablets.

Preliminary experiment aimed to select single optimum additive that enhances the dissolution of tablets. Various properties of tablets such as weight variation, friability, percent labeled amount, have been evaluated in such a way that tablets must pass all the requirement of standard tablets. The tablets containing corn starch as diluent and granulating with corn starch paste when incorporated with corn starch or sodium alginate as extragranular disintegrant (Formulas 2 and 3, tablet hardness 5-6 kg.), the friability of tablets were higher than the level of acceptibility (the value of friability of tablets of 0.8%-1.0% are frequently qouted as the upper level of acceptibility of pharmaceutical products). This was probably due to the reduction of binding property between the granules when the extragranular disintegrant was added. An increase in the hardness

of tablets granulating with polyvinylpyrrolidone (Formula 6, tablet hardness 9.26 kg.) resulted in the reduction of binding property of binder. Therefore, the tablets were capping during the friability test. From the results of friability of tablets, those formulas were not satisfactory formulations. The friability of tablets granulating with corn starch paste are generally higher than the other two binders. When the tablets incorporated with corn starch or sodium alginate as disintegrant, the friability was higher than the tablets incorporated with the other two disintegrants. These results were mostly due to the different effects of binders and disintegrants on the binding properties of tablets.

By using the disintegration time of tablets as an indicator, all formulas of dipyrone tablets were considered satisfactory. The highest disintegration time of tablets was only 7.92 $\pm$ 0.10 minutes (Formula 18, tablet hardness 9.85 kg.), while the lowest disintegration time of tablets was 4.88 $\pm$ 0.10 minutes (Formula 7, tablet hardness 5.58 kg.). Therefore, the disintegration time of tablets can not be used as an index in product development for the rejection of unsuitable formulations. Although, there was no distinct difference in the disintegration time of dipyrone tablets prepared by various formulations. However, the dissolution time of tablets was very different among those formulations employed. It may be concluded that there was no correlation between disintegration time and dissolution time of dipyrone tablets.

The effects of diluents, binding agents and disintegrating

agents on the dissolution of dipyrone tablets will be elaborated as the followings :

Disintegrant is one of the tablet component that affects the dissolution behaviour. The disintegrants facillitate the dissolution of the active drug in the tablets by propagated the tablets to disintegrate into granules and then into primary solid particles. Several types of disintegrants have different mechanisms. Thus, the effects of disintegrants on the dissolution of tablets are also different. In our experiment, four tablet disintegrants had been primarily selected in the comparative study. Corn starch is widely used and remains the most popular disintegrant of all. Sodium alginate is alginic acid derivative which possesses one of the best combinations of sufficient swelling with minimum stickiness and concentration as low as 4% or 5% are often adequate[30]. Sodium carboxymethylcellulose, Nymcel®, is specially modified cellulose which renders maximum swelling in water without dissolving. The use of only 1% - 3% of sodium carboxymethylcellulose can cause the breakdown of even the hardest tablets[31]. Sodium starch glycolate or carboxymethyl starch, Explotab®, is a sodium glycolate of potato starch. The particle can swell up to 300 times their intial size[21]. The sodium starch glycolate 5% is approximately the optimum concentration[32].

Among four tablet disintegrants, sodium carboxymethylcellulose provided the tablets with the lowest dissolution time ($t_{90\%}$). The dissolution time of tablets was reduced to nearly the half of the controlled tablets when sodium carboxymethylcellulose had been used.

The three binding agents had been included in this experiment. The most frequently employed binder is starch paste and normally prepared in the concentration 10% W/W. The corn starch paste was compared with 10% W/W solution of polivinylpyrrolidone and 10% W/W solution of gelatin. The results indicated that the tablets granulated with corn starch paste exhibited the highest dissolution time. This was probably due to the insoluble viscous film is expected to be form when the tablets containing starch paste expose to dissolution medium and this would inhibit diffusion of the active ingredient. When compared between polyvinylpyrrolidone and gelatin, we found that polyvinylpyrrolidone gave much faster dissolution of the active drug than gelatin. Therefore, polyvinylpyrrolidone was the binder of choice for dipyrone tablets. When sodium carboxymethylcellulose was incorporated into the tablets granulating with polyvinylpyrrolidone or gelatin, the dissolution time of tablets was no significant difference. Therefore, polyvinylpyrrolidone or gelatin may be selected as binder in the latter experiment when the sodium carboxymethylcellulose are included. But polyvinylpyrrolidone was considered more satisfactory than gelatin because of its convenience in the preparation of solution and granules.

Corn starch and lactose were normally used as diluent in the tablet making because they have the good tableting qualities and low cost than other diluents. Although, corn starch that used as diluent was considered as intragranular disintegrant at the same time. But the dissolution time of tablets containing corn starch and granulating with starch paste was not lower than the tablets contain-

ing lactose. This was probably due to lactose has rapid solubility and has no retarding effect. As it had been found that the greater the quantity of lactose as diluent in tablet dosage form, a more rapid dissolution was obtained[9]. But the dissolution time of tablet containing corn starch and granulating with polyvinylpyrrolidone or gelatin was lower than the tablets containing lactose and granulating with the same binders. The results indicated that corn starch that used as diluent did not enhance the dissolution of drug when granulated with corn starch paste. While this effect did not occure when the tablets granulated with polyvinylpyrrolidone or gelatin. So that, our experiment decided to use corn starch as diluent because polyvinylpyrrolidone was selected to be used as binder and the cost of corn starch was lower than lactose. Although, there was non-significant between lactose and corn starch in the dissolution time of tablets containing sodium carboxymethylcellulose.

The effects of hardness on the dissolution time of dipyrone tablets have been studied. An increase in the hardness of tablets caused a reduction in pore size, porosity and liquid penetration rate but had increased in the interparticulate bonding. Therefore, the dissolution time of tablets increased, except the formula 7; tablet hardness 8.72 $\pm$ 0.47 kg., the dissolution time of tablets decreased with increasing the hardness. This may be due to the fracturing of drug granules at higher compressional pressure, yielding smaller primary granules[11]. The tablets granulated with corn starch paste, an increase in the hardness of tablets, the dissolution time of tablets was dramatically increased. While the

tablets granulated with polyvinylpyrrolidone or gelatin, the dissolution time of tablets was slightly increased when the hardness of tablets increased. When sodium carboxymethylcellulose or sodium starch glycolate was used as disintegrant in the tablets granulating with polyvinylpyrrolidone, the hardness of tablets had a little effect on the dissolution time of tablets.

The factorially designed experiment was performed to study the effects of corn starch, polyvinylpyrrolidone and sodium carboxymethylcellulose on the dissolution of dipyrone form tablets. Only the effect produced by corn starch was found to be statistically significant. The results indicated that the amount of corn starch had pronounced the dissolution of dipyrone from tablet. Therefore, our experiments were conducted to study the effects of additive concentrations on the dissolution of dipyrone tablets. Sodium carboxymethylcellulose was found to be effective when used as a low concentration as 1% of active ingredient. When the amount of sodium carboxymethylcellulose increased from 1% to 3% and 5%, the dissolution time of tablets increased except the formulations of tablets containing 5% corn starch and granulating with 10% W/W solution of polyvinylpyrrolidone. Therefore, the optimum quantity of sodium carboxymethylcellulose in tablet was 1% of active ingredient. The concentration of polyvinylpyrrolidone had no effect on the dissolution time of dipyrone tablets. The dissolution time of tablets granulating with 20% W/W solution of polyvinylpyrrolidone was slightly lower than the tablets granulating with 10% W/W solution of polyvinylpyrrolidone. This result may be due to the polyvinylpyrrolidone made the surface

of drug more hydrophillic and the amount of polyvinylpyrrolidone had no retarding effect on the dissolution of drug. The amount of corn starch was considered satisfactory at the concentrations 10% and 15% of active ingredient when the tablets granulated with 10% W/W solution of polyvinylpyrrolidone. But the tablets granulated with 20% W/W solution of polyvinylpyrrolidone, the corn starch 15% of active ingredient was found to be better than 5% and 10% corn starch.

Therefore, the formulation of dipyrone tablet that should be used in the manufacturing production by considering the therapeutic effectiveness and the low cost of production, the following additives should be used as the following : corn starch 10%, polyvinylpyrrolidone 10% W/W solution, and sodium carboxymethylcellulose 1% of active ingredient, respectively.

The effects of lubricants on the dissolution of dipyrone tablets had been studied by factorially designed experiments. Magnesium stearate and talc are hydrophobic lubricants but they give different effects on the dissolution rate of tablets[26]. Magnesium stearate retarded the dissolution of drug from tablets by softening and spreading out under compression to provide impervious surface barrier which would decrease the effective solid-solvent interface. Thus the concentration of magnesium stearate in tablet formulation should be employed as little as possible to prevent a marked decrease in dissolution rate. If the amount of magnesium stearate used is small, say less than 1%, the retarding effect may be negligible[1]. Talc showed lesser effect in comparing with magnesium stearate, in

retarding the dissolution of drug. Since talc was more rapidly wetted by dissolution medium and the insoluble particles could be splitted from the surface of the tablets.

Considerable interest had been developed in study the effects of two lubricants because the combination of talc and magnesium stearate are commonly employed in tablet formulation. It was found to be statistically non-significant when the combination of talc and magnesium stearate were used in our combination, an increase in the amount of one lubricant did not interfere the effect of the other.

Conclusions

From previous study of the dissolution profiles of twenty commercial dipyrone tablets from different manufacturers, the results showed that different brands of dipyrone tablets labeled to have the same quantity of active ingredient possessed different dissolution characteristics. Extensive literature survey reveals that the different dissolution characteristics of dipyrone tablets are most likely to be caused by the different product formulations and product processes. For this reason, the experiments had been performed with an aim to develop the formulation of dipyrone tablet which possess both therapeutic effectiveness and inexpensive recipe. The additives those are commonly used in tablet formulation have been selected to be comparatively studied of the effects on the dissolution behaviour of dipyrone tablets. The results of the experiments may be concluded as following :

1. At an initial stage, two diluents; three binders; four tablet disintegrants were selected to compare the effects on the dissolution of dipyrone tablets. Corn starch, polyvinylpyrrolidone and sodium carboxymethylcellulose were selected to be used as diluent, binder and disintegrant respectively in the factorially designed experiments by judging from their more pronounced effects on the dissolution time and the economy of costs.

2. From factorially designed experiments indicated that only the effect of diluent is statistically significant.

3. For corn starch 10% concentration was found to be the optimum concentration. The effect of sodium carboxymethylcellulose was found to be more pronounced when used at a low concentration of 1% of active ingredient. The two different concentrations of polyvinylpyrrolidone had no different effect on the dissolution time of dipyrone tablets.

4. The dissolution time of tablets increased linearly parallel to the increase in the hardness of tablets, especially if the tablets were granulated with corn starch paste.

5. Effects produced by talc and magnesium stearate in combination was found to be statistically non-significant.

6. No correlation was found between the disintegration time and the dissolution time ($t_{90\%}$) of dipyrone tablets.

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