CHAPTER IV

DISCUSSION AND CONCLUSION

In industrial pharmacy, the product development is one of the best role for industrial pharmacist. In general , one of the development of new formulation is to achieve a better quality of product and to produce a readily dissolvable tablet .

The objective of this study aimed to improve the dissolution rate of tablet containing poorly soluble drugs : griseofulvin, prednisolone, and furosemide, to have therapeutic effectiveness and inexpensive formulation by studying the effect of a disintegrant : croscarmellose sodium (Ac-Di-Sol^{R}) on the dissolution behavior of tablet. The additives used in the experiments are commonly employed in pharmaceutical manufacture and the amount are limited in the practical range. The sequence of preparation of tablet is the same as practice in pharmaceutical industry.

The tablets containing poorly soluble drug showed a poor dissolution profile in 1 : 100 HCl solution in water which containing 0.02% Polysorbate 80, due to its poorly disintegration (>60 min in 1:100 HCl solution in water) and its hydrophobicity and clumping together of fine powder

When the Ac-Di-Sol^{R} was used as a tablet disintegrant at concentration as low as 0.5 %, the disintegration times of tablets were markedly decreased, both in wet granulation and dry granulation, and both in high and low tablet hardnesses. This can be attributed the relative rapid disintegration to the strong elastic relaxation of cellulose fibers, which may leave large pores in the tablet matrix,

facilitating rapid water penetration and the rupture of hydrogen bonds[42].

A comparative study the effect of Ac-Di-Sol^{R} on disintegration time of tablets with various disintegrants : Avicel^{R} PH 101, Polyplasdone^{R} XL. and Explotab^{R}. Ac-Di-Sol^{R} showedthe best disintegrating property among the four disintegrants, both in wet granulation and dry granulation and both in high tablet hardness and low tablet hardness. It was found that Ac-Di-Sol^{R} exhibited the same result in griseofulvin, prednisolone and furosemide tablets.

The effect of Ac-Di-Sol^{R} on the dissolution rates of tablets containing poorly soluble drug have been studied. With poorly soluble drugs (griseofulvin, prednisolone, and furosemide), tablets which containing Ac-Di-Sol^{R}, whether manufactured by wet granulation or dry granulation methods, extensively increased in dissolution rates of tablet. This is correlated to the disintegration properties. Both in high tablet hardness and low tablet hardness, the tablets containing Ac - Di - Sol^{R} showed the dissolution profile higher than the tablets containing non-disintegrant, due to its more rapid disintegration. It can be reasoned that the disintegrant facillitates the dissolution of active drug by propagating the tablets to disintegrate into granules and then into primary solid particles.

Due to the reason that the dissolution times of griseofulvin tablets (t 85 %) , prednisolone tablets (t 70 %) and furosemide tablets (t 65 %) were within 60 minutes when 1 % Ac-Di-Sol^{R} was used as tablet disintegrant, and the aim of this investigation is to study the effect of Ac-Di-Sol^{R} on dissolution rate at the low concentration of disintegrant to eliminate the detrimental effect of the disintegrant to tablet

parameters such as weight variation, hardness, and thickness[64] and to eliminate the detrimental effect of disintegrant on viscosity of the surrounding environment, the tablet containing 1 % of Ac-Di-Sol^R as tablet disintegrant was the candidate to study the dissolution rate of tablets compared to the tablets containing other disintegrants . Avicel^R PH 101, Polyplasdone^R XL, and Explotab^R.

Ac-Di-Sol^R (Croscarmellose Sod.) is internally cross-linked sodium carboxymethyl cellulose which greatly reduces its water solubility while permitting the material to swell and to absorb many times its weight in water without losing individual fiber integrity. The cross-linked cellulose was also shown to be very effective as low as 0.5 %[42].

Avicel^R PH 101, a microcrystalline cellulose, exhibits very good disintegrant property at level of 10 %.It functions by allowing water to enter the tablet matrix by mean of capillary pores, which breaks the hydrogen bonding between adjacent bundles of cellulose microcrystal[65].

Polyplasdone^R XL is cross-linked polyvinylpyrrolidone which is insoluble in water but is highly hydrophilic. As water is absorbed the lattice structure of polymer expands and particle swell, causing tablet disintegrate. This can be attributed its superiority to the substances' cavity to absorb more than 50 % of its own weight in water. Because of its low bulk density (0.26g/ml), it tends to distribute itself evenly in tablet matrix, increasing surface area and number of sites for capillary action. The mechanism of action was reported to be capillary action with a secondary swelling effect . Cross-linked PVP is effective as disintegrant at 2-5 % level[42].

Explotab^{R} is sodium carboxymethyl starch, which is hydrophilic but not completely water soluble. When exposed to water, the modified starch grains swell without losing individual their integrity, causing tablet disintegrate. Sodium carboxymethyl starch appears to be most effective at levels between 4 % and 8 %. Levels above 8 % increased the disintegration time, due to viscosity producing effect[42].

Among the four disintegrants, the tablets containing Ac-Di-Sol^{R} exhibited the highest dissolution rate, both in wet granulation and dry granulation because they disintegrated into primary solid particles most rapidly among the four disintegrants. The superiority of cross-linked cellulose can be attributed to its fibrous nature, which swells and absorbs many times its weight and allows intraparticulate as well as extraparticulate wicking of water, and its strong elastic relaxation structure, which leave large pore in tablet matrix facilitate rapid water penetration and rapid disintegration[42,68].

An increased in the hardness of any tablet caused a reduction in pore size, porosity and liquid penetration rate but increased the interparticulate bonding. However the hardness of tablet did not appear to have any significantly effect on dissolution rates of griseofulvin, prednisolone, and furosemide tablets, which containing Ac-Di-Sol^{R} as tablet disintegrant. This can be attributed to the internal wicking of water into the tablet matrix by cellulose fiber regardless of the degree of tablet porosity resulting from different hardness level[67].

The process of tablet manufacturing is one of the factors that affect the dissolution behavior. The effects of processing on the dissolution rate of poorly soluble drugs tablets have been studied. These dissolution times (t85 % for griseofulvin, t 70% for

prednisolone, and t 65 % for furosemide) of tablets which containing 1% Ac-Di-Sol^{R} manufactured by wet granulation exhibited higher dissolution rate than those manufactured by dry granulation, in spite of the tablets manufactured by dry granulation disintegrated more rapidly than the tablets manufactured by wet granulation. The causation of this phenomena was due to the tablets manufactured by dry granulation compacted together with solid bridge (interlock mechanism), which in turn, produced numerous pores in the tablet matrix, so the liquid could easily penetrate into tablet matrix. However the tablet manufactured by dry granulation disintegrated not only into tiny particle but also into flake form which was small enough to pass through the seive of disintegration tester. The flakes, which caused the problem in solubilization, must need some time to disintegrate into smaller particles and then into primary solid particles before dissolving may occur. Therefore, the decrease in dissolution rate may occur. The causation of the formed flakes was due to the slugging to prepare dry granules. The fine powder of drug, additives and dry binder were compressed to slug. The slugs were granulated into granules. Then the dry granules were compressed again into tablet. The cohesive force of powder in the first compression (slugging) was higher than the cohesive force of granules in the second compression. And the powder of poorly soluble drug was double compressed to compact form, the surface area of the drug was reduced, resulted in decreasing in dissolution rate of poorly soluble drug followed Noyes-Whitney's relationship[13].

The effect of the methods of incorporating the disintegrant into granules on dissolution rates of tablets have been studied. The tablets,

containing poorly soluble drugs : griseofulvin, prednisolone, and furosemide, which prepared by incorporating Ac-Di-Sol^{R} as tablet disintegrant into granules by three different methods : intragranular, extragranular, and 50 % intragranulas plus 50 % extragranular showed the same dissolution rates. The dissolution times (t 85 % for griseofulvin, t 70 % for prednisolone, t 65 % for furosemide) were the same. This suggested that the methods of incorporating disintegrant (1 % Ac-Di-Sol^{R}) into granules did not appear to have any significantly effect on dissolution of these poorly soluble drugs. This can be attributed to its fibrous nature, which allows intraparticulate as well as extraparticulate wicking of water even at low concentration levels[68].

In conclusion, it has been shown that croscarmellose sodium (Ac-Di-Sol^{R}) can markedly increase the dissolution rates of poorly soluble drugs : griseofulvin, prednisolone, and furosemide, both in tablets manufactured by wet granulation and dry granulation and even the hardness of tablet at high or low level. One percentage of croscarmellose (Ac-Di-Sol^{R}), as tablet disintegrant, appeared to be superior to Avicel^{R} PH101, Polyplasdone^{R}XL, and Explotab^{R}.

Whether Ac-Di-Sol^{R} was incorporated into granules by any method, it clearly showed an increase in dissolution rates of the poorly soluble drugs.

Croscarmellose sodium (Ac-Di-Sol^{R}) was found to be excellent disintegrant for the poorly soluble drugs : griseofulvin, prednisolone, and furosemide and it can extensively increase the dissolution rates of these poorly soluble drugs at the concentration of 0.5- 1.0 %.