CHAPTER III

RESULTS

A. Properties of Griseofulvin Tablets* (Formula 1-7, and Formula 22-24)

A.1 Weight Variation of Tablets

The average weight, standard deviation, and the coefficient of variation of tablets weight are listed in table 8. Each formula of griseofulvin tablets possessed the weight variation in the limit of USP standard[61].

A.2 Thickness of Tablets

Although the thickness of tablet is not official in quality control of tablet, but the uniformity of tablet thickness can predict the uniformity of tablet content. The average thickness and standard deviation of tablets thickness are demonstrated in table 9.

A.3 Hardness of Tablets

The average hardness, standard deviation, and the coefficient of variation of tablets hardness are demonstrated in table 10.

A.4 Friability of Tablets

The friability of griseofulvin tablets is listed in table 11. It was found that the friability of tablets was slightly increased as the concentration of Ac-Di-Sol^{R} increased. Tablets manufactured by dry granulation seem to have higher friability than those manufactured by wet

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* Griseofulvin tablets manufactured by dry granulation with the hardness of 9-11 kg were capped and were not evaluated.

Table 8 Effect of Disintegrants on Weight Variation of Griseofulvin Tablets.

Formula Number	Wet granulation Tablet Hardness 5-7 Kp		Wet granulation Tablet Hardness 9-11 Kp		Dry granulation Tablet Hardness 5-7 Kp	
	Average weight (gm $\pm$ S.D.)	% C.V.	Average weight (gm $\pm$ S.D.)	% C.V.	Average weight (gm $\pm$ S.D.)	% C.V.
1	0.3110 $\pm$ 0.0024	0.76	0.3109 $\pm$ 0.0005	0.18	0.3112 $\pm$ 0.0007	0.23
2	0.3104 $\pm$ 0.0002	0.06	0.3125 $\pm$ 0.0025	0.79	0.3121 $\pm$ 0.0037	1.19
3	0.3157 $\pm$ 0.0017	0.53	0.3124 $\pm$ 0.0004	0.14	0.3139 $\pm$ 0.0029	0.91
4	0.3147 $\pm$ 0.0010	0.33	0.3149 $\pm$ 0.0003	0.10	0.3138 $\pm$ 0.0010	0.33
5	0.3180 $\pm$ 0.0012	0.37	0.3179 $\pm$ 0.0008	0.28	0.3159 $\pm$ 0.0004	0.14
6	0.3218 $\pm$ 0.0009	0.28	0.3210 $\pm$ 0.0014	0.44	0.3230 $\pm$ 0.0026	0.83
7	0.3239 $\pm$ 0.0004	0.13	0.3330 $\pm$ 0.0078	2.36	0.3219 $\pm$ 0.0038	1.19
22	0.3116 $\pm$ 0.0007	0.22	0.3116 $\pm$ 0.0007	0.22	0.3118 $\pm$ 0.0004	0.14
23	0.3119 $\pm$ 0.0003	0.09	0.3120 $\pm$ 0.0003	0.10	0.3120 $\pm$ 0.0003	0.10
24	0.3121 $\pm$ 0.0002	0.06	0.3121 $\pm$ 0.0002	0.07	0.3119 $\pm$ 0.0003	0.08

Table 9 Effect of Disintegrants on Thickness of Griseofulvin Tablets

Formula Number	Wet granulation Tablet Hardness 5-7 Kp Average Thickness (mm ± S.D.)	Wet granulation Tablet Hardness 9-11 Kp Average Thickness (mm ± S.D.)	Dry granulation Tablet Hardness 5-7 Kp Average Thickness (mm ± S.D.)
1	4.84 ± 0.0565	4.77 ± 0.0360	4.73 ± 0.0500
2	5.21 ± 0.0141	4.89 ± 0.0100	4.79 ± 0.0223
3	5.27 ± 0.0141	4.98 ± 0.0282	4.86 ± 0.0500
4	5.32 ± 0.0360	5.30 ± 0.0100	4.80 ± 0.0223
5	5.37 ± 0.0282	5.49 ± 0.0282	4.86 ± 0.0424
6	5.43 ± 0.0500	5.58 ± 0.0282	4.93 ± 0.0360
7	5.68 ± 0.0282	5.63 ± 0.0761	4.94 ± 0.0282
22	5.10 ± 0.0158	4.86 ± 0.1126	4.81 ± 0.0574
23	5.35 ± 0.0264	4.97 ± 0.0223	4.78 ± 0.0223
24	5.10 ± 0.0324	4.77 ± 0.0946	4.83 ± 0.0556

Table 10 Effect of Disintegrants on Tablet Hardness of Griseofulvin Tablets

Formula Number	Wet granulation Tablet Hardness 5-7 Kp		Wet granulation Tablet Hardness 9-11 Kp		Dry granulation Tablet Hardness 5-7 Kp	
	Hardness (Kp ± S.D.)	% C.V.	Hardness (Kp ± S.D.)	% C.V.	Hardness (Kp ± S.D.)	% C.V.
1	6.57 ± 0.3465	5.27	9.25 ± 0.2368	2.56	4.98 ± 0.2177	4.45
2	6.92 ± 0.1686	2.43	11.09 ± 0.1744	1.57	5.48 ± 0.3293	6.00
3	6.72 ± 0.3155	4.69	10.93 ± 0.3128	2.86	5.21 ± 0.1523	2.92
4	6.71 ± 0.3212	4.78	10.65 ± 0.3439	3.23	5.47 ± 0.2983	5.45
5	7.03 ± 0.1710	2.43	9.76 ± 0.2859	2.93	6.26 ± 0.2796	4.46
6	6.79 ± 0.1946	2.86	10.94 ± 0.1429	1.30	5.77 ± 0.5167	8.95
7	6.76 ± 0.2221	3.28	11.05 ± 0.1080	0.97	6.30 ± 0.5185	8.23
22	4.62 ± 0.3269	7.07	8.35 ± 0.3439	4.11	7.09 ± 0.2223	3.13
23	5.29 ± 0.5237	9.89	11.01 ± 0.1595	1.44	6.93 ± 0.1702	2.45
24	5.15 ± 0.4737	9.19	11.21 ± 0.3281	2.92	5.28 ± 0.2820	6.59

Table 11 Effect of Disintegrants on the Friability of Griseofulvin Tablets

Formula Number	Wet granulation Tablet Hardness 5-7 Kp Friability %	Wet granulation Tablet Hardness 9-11 Kp Friability %	Dry granulation Tablet Hardness 5-7 Kp Friability %
1	0.32	0.28	0.64
2	0.33	0.29	0.66
3	0.36	0.29	0.65
4	0.38	0.30	0.67
5	0.36	0.31	0.68
6	0.40	0.32	0.70
7	0.42	0.33	0.72
22	0.30	0.24	0.60
23	0.30	0.26	0.60
24	0.32	0.27	0.62

granulation. Tablets with lower hardness also showed a higher friability. However, all tablets exhibited less than 1.0 % friability

A. 5 Disintegration Time of Tablets

The disintegration times of griseofulvin tablets containing different concentrations of Ac-Di-Sol^{R} in 1:100 HCl in aqueous solution are shown in figure 6 and figure 7. At the hardness of 5-7 kp, the disintegration times of tablets manufactured by wet granulation were ranked as the following : formula 1 ($>$60 min) $>$ formula 2 (15.08 $\pm$ 0.3705) $>$ formula 3 (5.12 $\pm$ 0.1173) $>$ formula 4 (0.43 $\pm$ 0.0409) $\sim$ formula 5 (0.36 $\pm$ 0.0376) $\sim$ formula 6 (0.32 $\pm$ 0.0279) $\sim$ formula 7 (0.21 $\pm$ 0.0376). For tablets manufactured by dry granulation, the disintegration time of tablets was less than the tablets manufactured by wet granulation at every level of Ac-Di-Sol^{R} concentration. Their disintegration times of tablets were ranked as the following : formula 1 ($>$ 60 min) $>$ formula 2 (0.14 $\pm$ 0.0279) $\sim$ formula 3 (0.12 $\pm$ 0.0289) $\sim$ formula 4 (0.11 $\pm$ 0.0240) $\sim$ formula 5 (0.10 $\pm$ 0.0126) $\sim$ formula 6 (0.10 $\pm$ 0.0126) $\sim$ formula 7 (0.10 $\pm$ 0.0154).

When the hardness of tablets was increased to 9-11 kp, the disintegration times of tablets were prolonged as shown in figure 6. The disintegration times of tablets were ranked as the following : formula 1 ($>$ 60 min) $>$ formula 2 (17.51 $\pm$ 0.1942) $>$ formula 3 (14.38 $\pm$ 0.1048) $>$ formula 4 (2.27 $\pm$ 0.0937) $\sim$ formula 5 (2.28 $\pm$ 0.4050) $\sim$ formula 6 (2.20 $\pm$ 0.0836) $\sim$ formula 7 (2.06 $\pm$ 0.1076).

For tablets manufactured by wet granulation and dry granulation and tablet hardness high or low, the disintegration time was markedly decreased when Ac-Di-Sol^{R} was used as a tablet disintegrant at the

Table 12 Effect of Different Disintegrants on Disintegration Time of Griseofulvin Tablets

Formula Number	Disintegration Time, min ± S.D.		
	Wet granulation Tablet Hardness 5-7 kp	Wet granulation Tablet Hardness 9-11 kp	Dry granulation Tablet Hardness 5-7 kp
# 1 (Non-disintegrant)	> 60	> 60	> 60
# 3 (1% Ac-Di-Sol^{R})	5.12 ± 0.1173	14.38 ± 0.1048	0.12 ± 0.0289
# 22 (1% Avicel^{R} PH101)	> 60	> 60	> 60
# 23 (1% Polyplasdone XL)	5.37 ± 0.0691	14.56 ± 0.1972	0.31 ± 0.0296
# 24 (1% Explotab^{R})	5.56 ± 0.1569	15.44 ± 0.0861	0.41 ± 0.0286

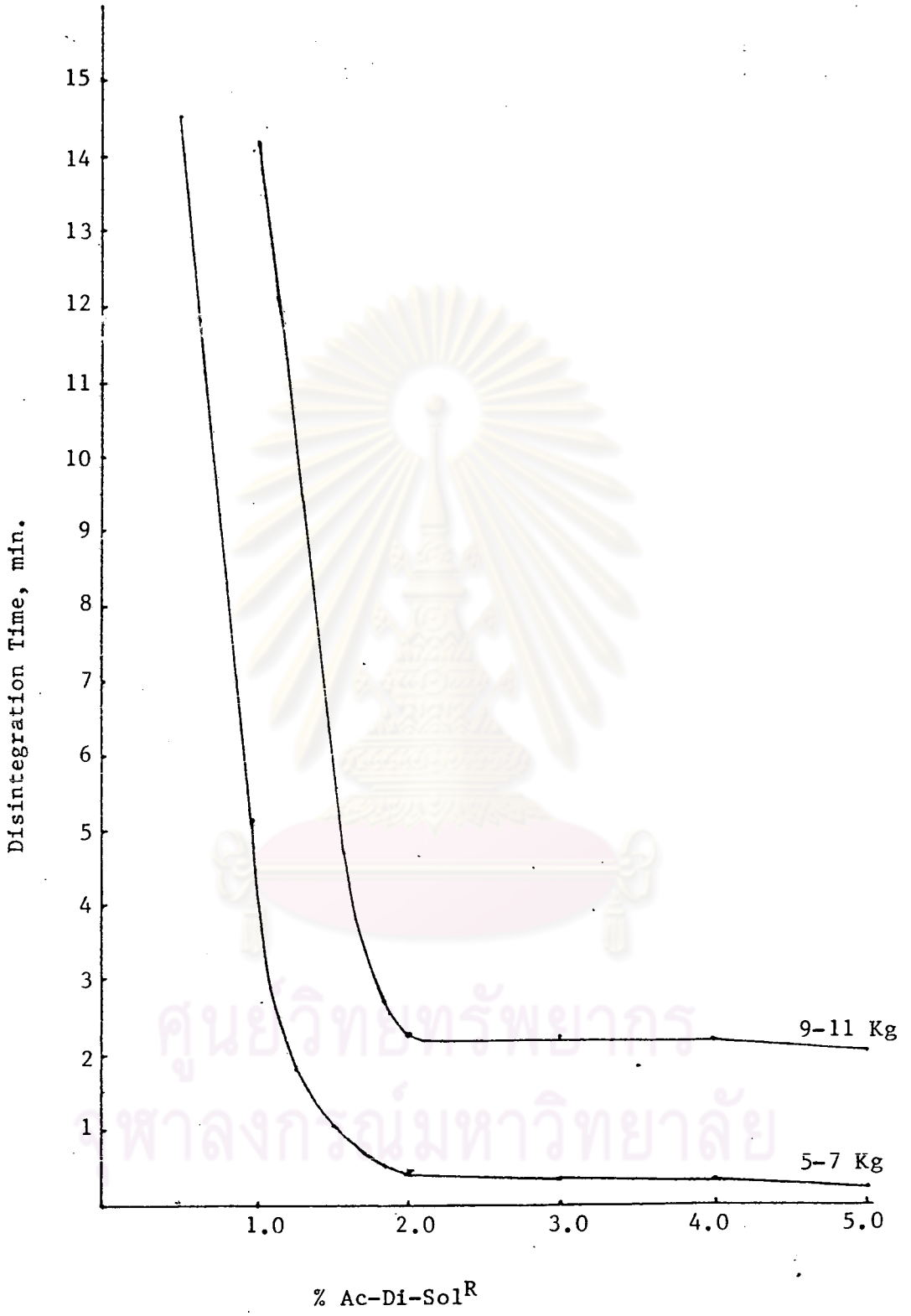

Figure 6. Effect of extent of disintegrant on disintegration time of griseofulvin tablets made by wet granulation

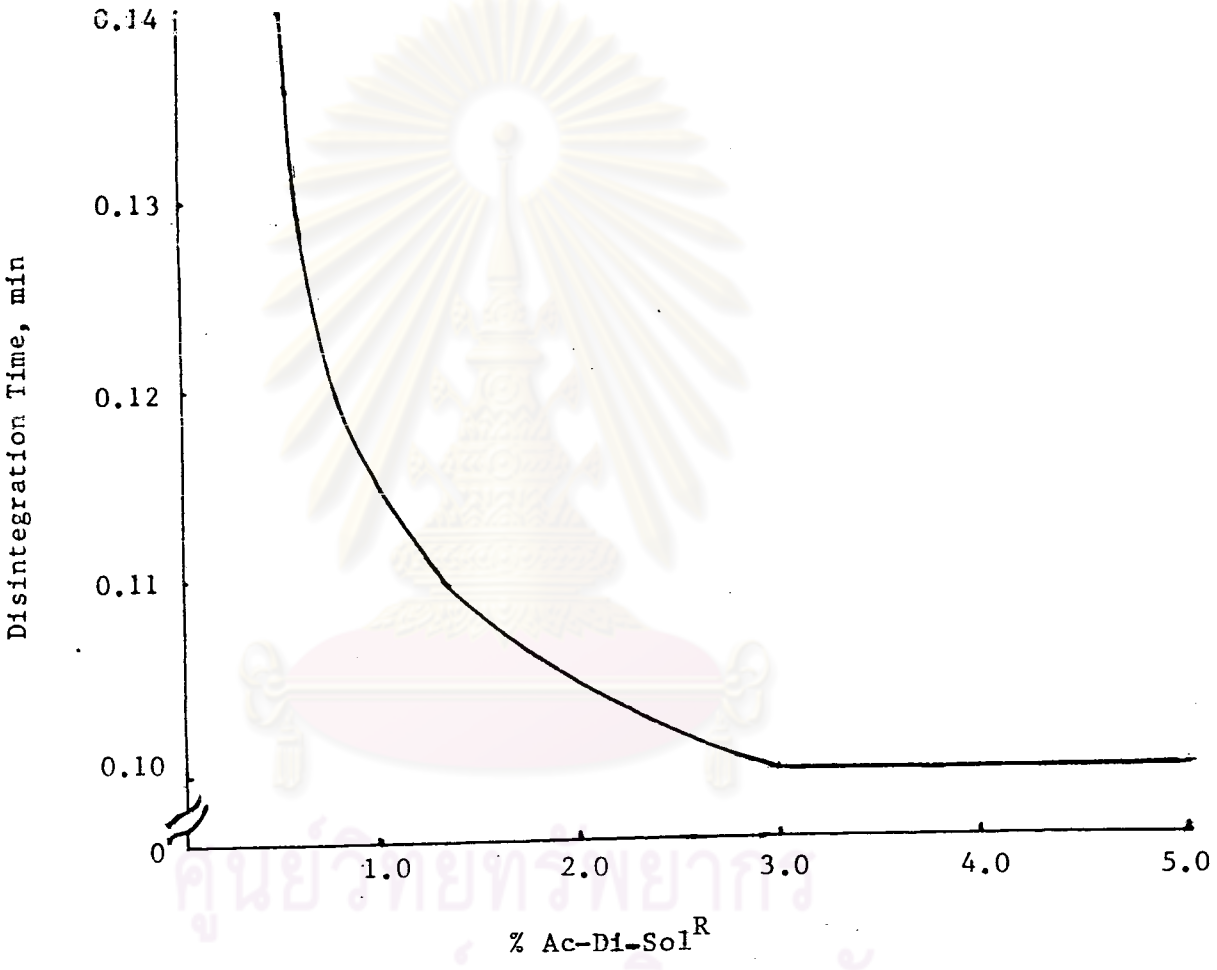

Figure 7 Effect of extent of disintegrant on disintegration time of griseofulvin tablets made by dry granulation, hardness 5-7 kp.

concentration as low as 0.5 % . However when the concentration of Ac-Di-Sol^{R} increased from 2.0 % to 5.0 %, the disintegration time was non-significantly decreased.

Table 12 shows the effects of four disintegrants : Ac-Di-Sol^{R}, Avicel^{R} PH 101, Polyplasdone^{R}XL , and Explotab^{R} on disintegration time of tablets. With the hardness of 5-7 kp, the comparison of tablets containing the same diluents but different disintegrants of 1 % concentration, the disintegration times of tablets were ranked as the following : formula 22 (1% Avicel^{R} PH 101) > formula 24 (1 % Explotab^{R}) > formula 23 (1 % Polyplasdone^{R}XL) > formula 3 (1 % Ac-Di-Sol^{R}) both in wet and dry granulation. When the hardness of tablets was increased to 9-11 kp, the disintegration times of tablets were prolonged as demonstrated in table 12.

A.6 Dissolution Rates of Tablets

A.6.1 Effect of Disintegrant on Dissolution Rates

The dissolution profiles of griseofulvin tablets are demonstrated in figure 8, 9 , and 10. The tablets containing Ac-Di-Sol^{R} as tablet disintegrant showed higher dissolution rates than those containing no disintegrant in both wet and dry granulation.

Ac-Di-Sol^{R} also increased the dissolution rates of griseofulvin tablets both in high tablet hardness (9-11 kp) and low tablet hardness (5-7 kp).

The dissolution times of tablets in this study, expressed as the time required for 85 % of griseofulvin to dissolve[62], were demonstrated in figure 11.

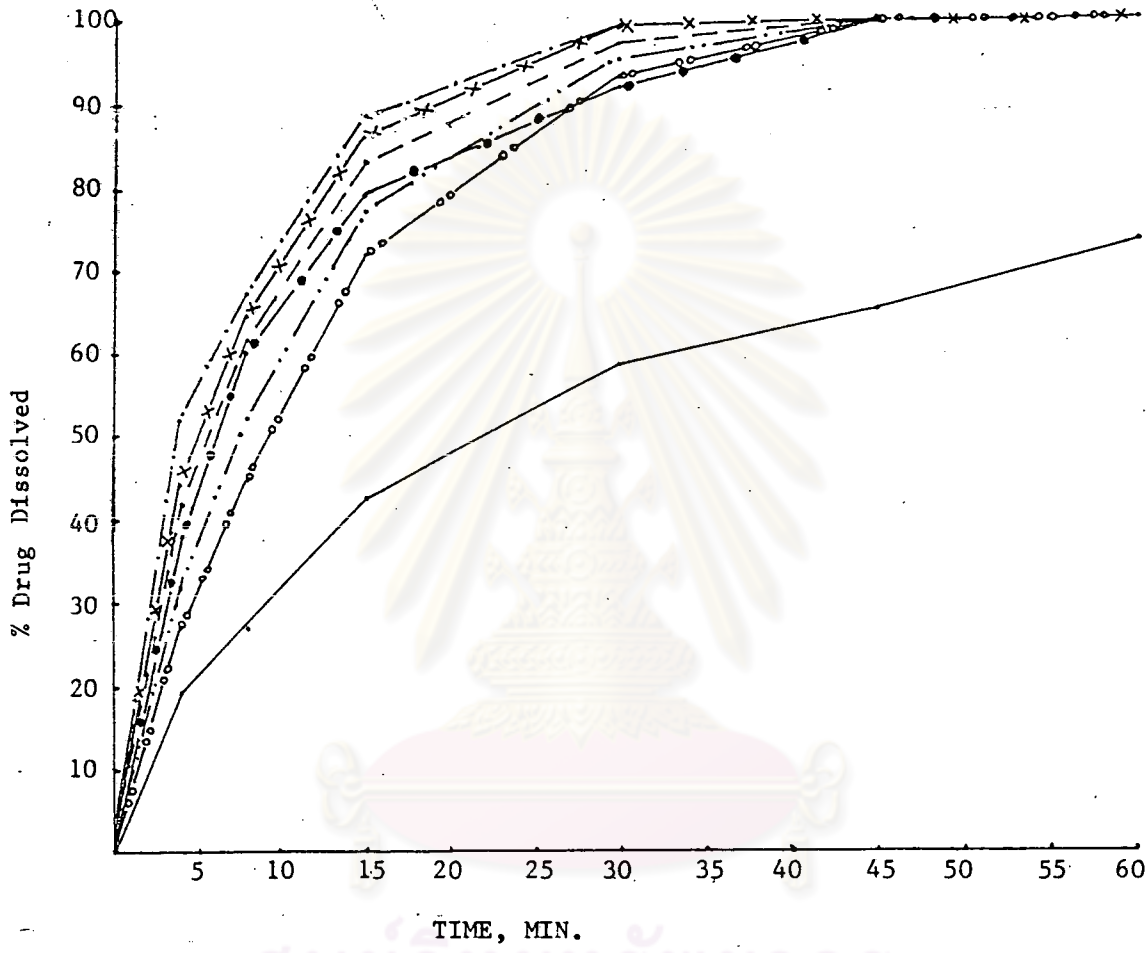

Figure 8. Dissolution profiles of griseofulvin tablets, formula 1-7, hardness 5-7 Kp (Wet granulation).

Key :

formula 1 (No disintegrant)

formula 2 (0.5% Ac-Di-Sol^{R})

formula 3 (1.0 % Ac-Di-Sol^{R})

formula 4 (2.0 % Ac-Di-Sol^{R})

formula 5 (3.0 % Ac-Di-Sol^{R})

formula 6 (4.0 % Ac-Di-Sol^{R})

formula 7 (5.0 % Ac-Di-Sol^{R})

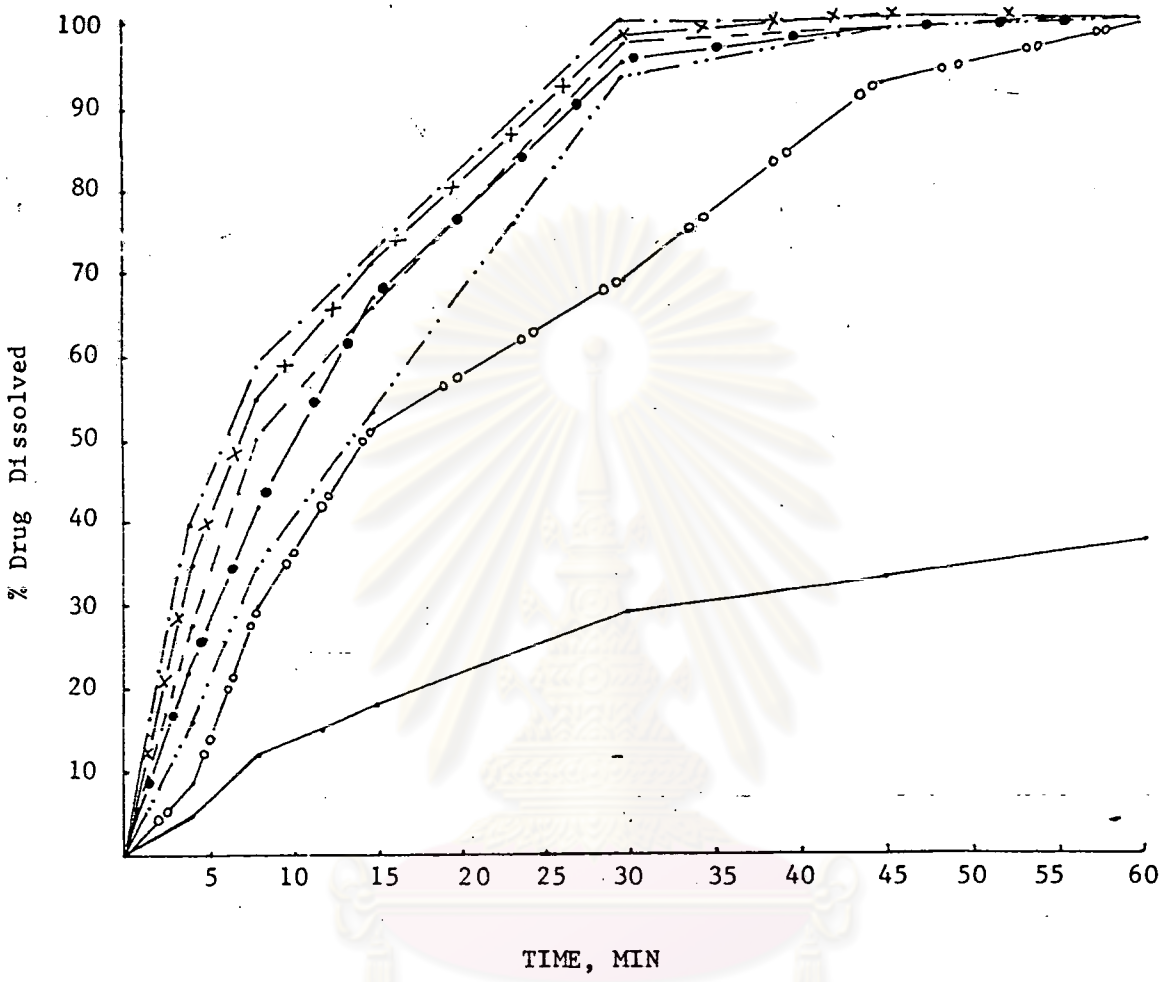

Figure 9 Dissolution profiles of griseofulvin tablets, formula 1-7, hardness 9-11 Kp (Wet granulation).

Key :

formula 1 (No Disintegrant)

formula 2 (0.5 % Ac-Di-Sol^{R})

formula 3 (1.0 % Ac-Di-Sol^{R})

formula 4 (2.0 % Ac-Di-Sol^{R})

formula 5 (3.0 % Ac-Di-Sol^{R})

formula 6 (4.0 % Ac-Di-Sol^{R})

formula 7 (5.0 % Ac-Di-Sol^{R})

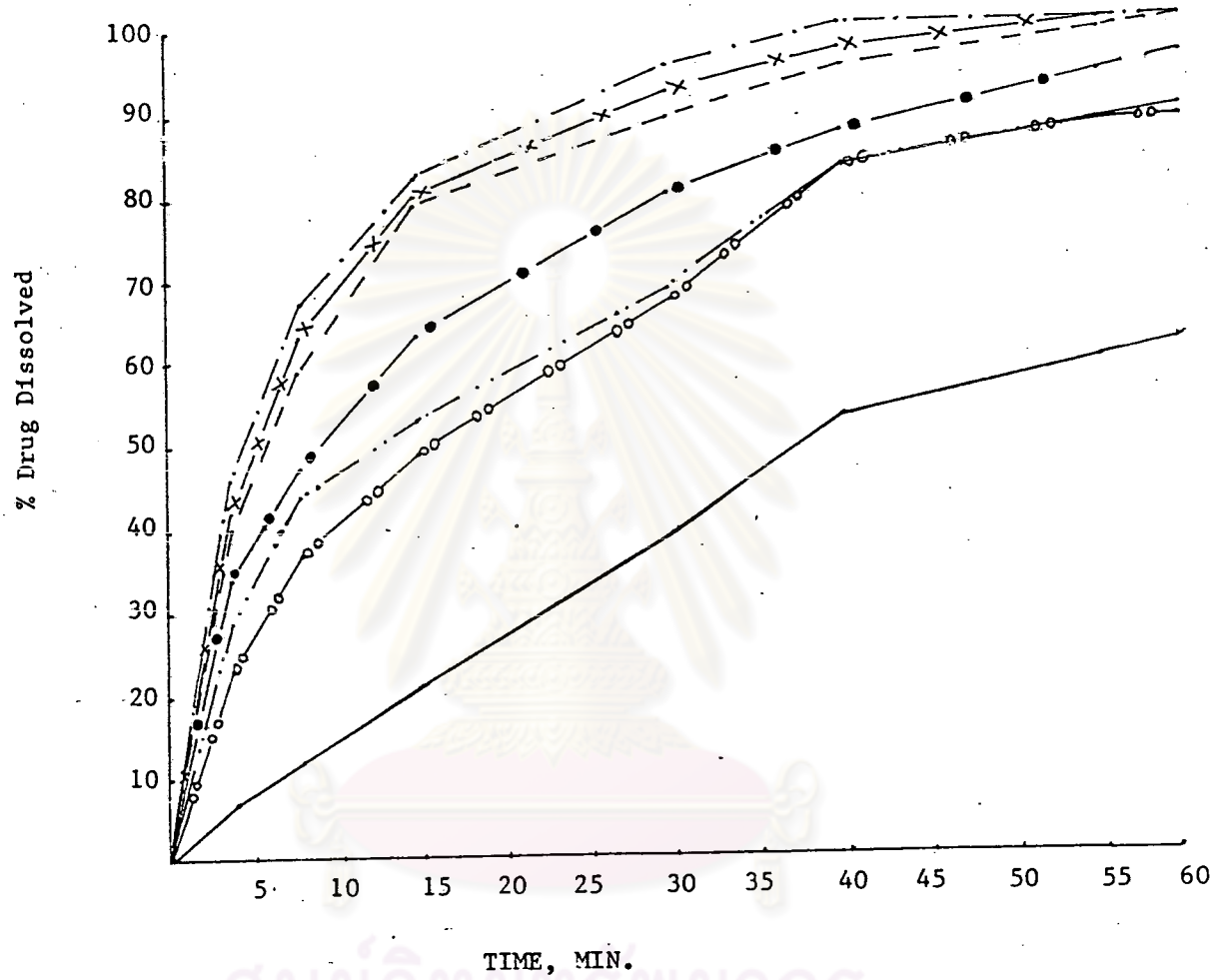

Figure 10 Dissolution profiles of griseofulvin tablets, formula 1-7, hardness 5-7 Kp (Dry granulation).

Key:

formula 1 (No Disintegrant)

formula 2 (0.5 % Ac-Di-Sol^{R})

formula 3 (1.0 % Ac-Di-Sol^{R})

formula 4 (2.0 % Ac-Di-Sol^{R})

formula 5 (3.0 % Ac-Di-Sol^{R})

formula 6 (4.0 % Ac-Di-Sol^{R})

formula 7 (5.0 % Ac-Di-Sol^{R})

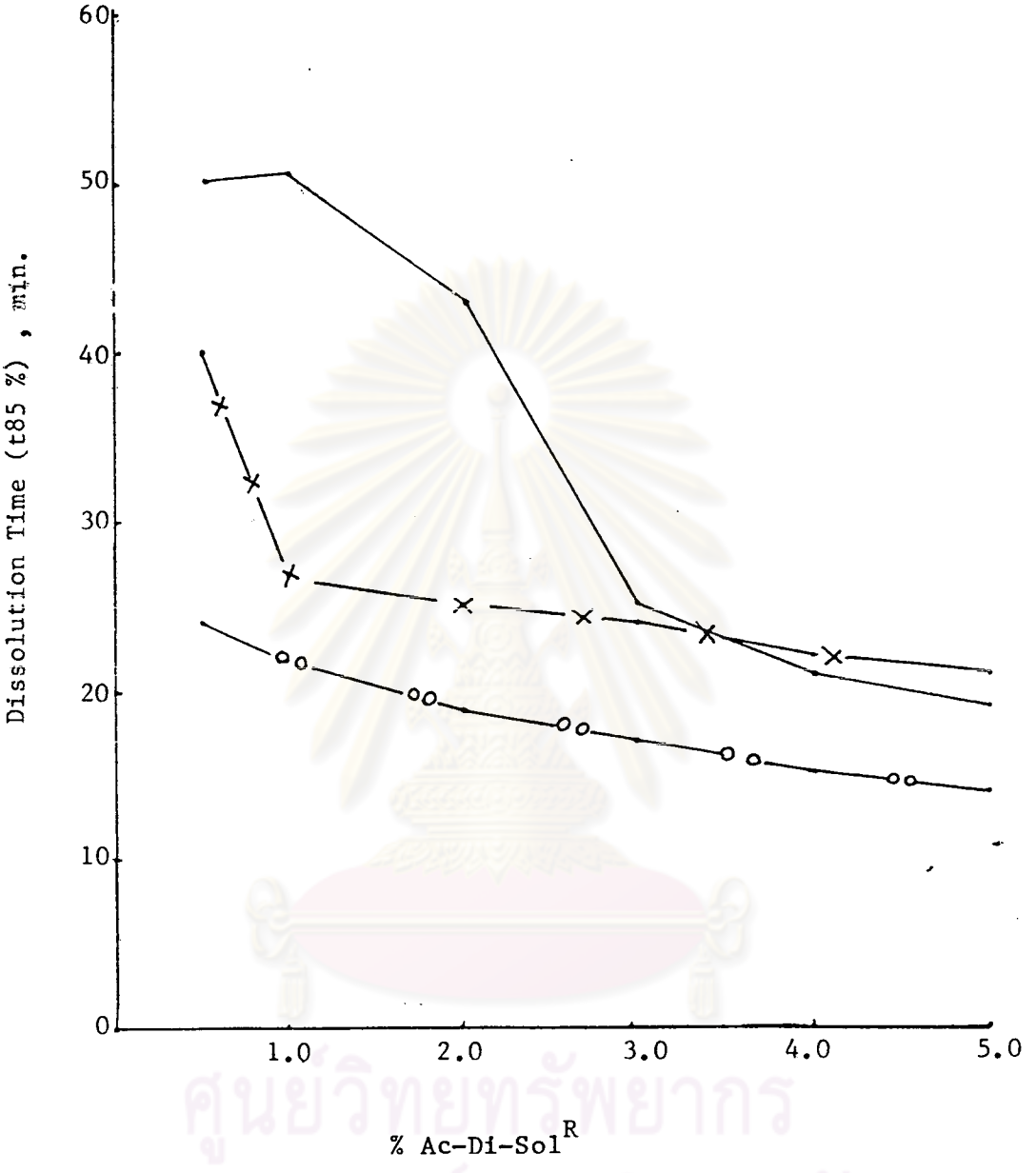

Figure 11. Relationship between extent of disintegrant and dissolution time (t 85 %) of griseofulvin tablets.

Key :

———— Dry granulation, hardness 5-7 Kp.

—x—x— Wet granulation, hardness 9-11 Kp.

—oo—oo— Wet granulation, hardness 5-7 Kp.

A.6.2 Effect of Different Disintegrants on Dissolution Rates

The effect of four tablet disintegrants : Ac-Di-Sol^{R}, Avicel^{R} PH 101, Polyplasdone^{R} XL, and Explotab^{R} on dissolution rates of griseofulvin tablets had been studied. The dissolution profiles of griseofulvin tablets, containing 1 % of different disintegrants were shown in figure 12, 13, and 14. Table 13 shows the dissolution times of tablet containing 1 % Ac-Di-Sol^{R} (formula 3) , 1 % Avicel^{R} PH 101 (formula 22), 1 % Polyplasdone^{R} XL (formula 23), and 1 % Explotab^{R} (formula 24) as tablet disintegrant. It can be seen that tablets containing Ac-Di-Sol^{R} were superior than tablets containing other disintegrants whether manufactured by wet or dry granulation methods with 5-7 or 9-11 kp of hardness. The dissolution times(t 85 %) of tablets manufactured by wet granulation and hardness of 5-7 kp were ranked as the following : formula 22 (53.25 ± 3.8890) = formula 24 (53.25 ± 3.8890) > formula 23 (47.25 ± 2.8284) > formula 3 (22.25 ± 1.4142). When the hardness was changed to 9-11 kp, the dissolution times(t 85 %) were ranked as the following : formula 22 (>60 min) = formula 24 >formula 23 (56.25 ± 1.7677) > formula 3. (27.15 ± 1.6263).

By dry granulation , the dissolution rates of tablets containing different disintegrants were less than those obtained from tablets manufactured by wet granulation as shown in figure 12 and 14. Their dissolution times (t 85 %) were ranked as the following : formula 22 (> 60 min) = formula 24 = formula 23 > formula 3 (51.25 ± 2.4748).

Table 13 Effect of Different Disintegrants on Dissolution Time (t85 %) of Griseofulvin tablets

Formula No.	Dissolution Time (t85%), min $\pm$ S.D.		
	Wet granulation Tablet Hardness 5-7 kp	Wet granulation Tablet Hardness 9-11 kp	Dry granulation Tablet Hardness 5-7 Kp
# 1 (No disintegrant)	> 60	> 60	> 60
# 3 (1 % Ac-Di-Sol^{R})	22.25 $\pm$ 1.4142	27.15 $\pm$ 1.6263	51.25 $\pm$ 2.4748
# 22 (1 % Avicel^{R} PH 101)	53.25 $\pm$ 3.8890	> 60	> 60
# 23 (1% Polyplasdone^{R}XL)	47.25 $\pm$ 2.8284	56.25 $\pm$ 1.7677	> 60
# 24 (1% Explotab^{R})	53.25 $\pm$ 3.8890	> 60	> 60

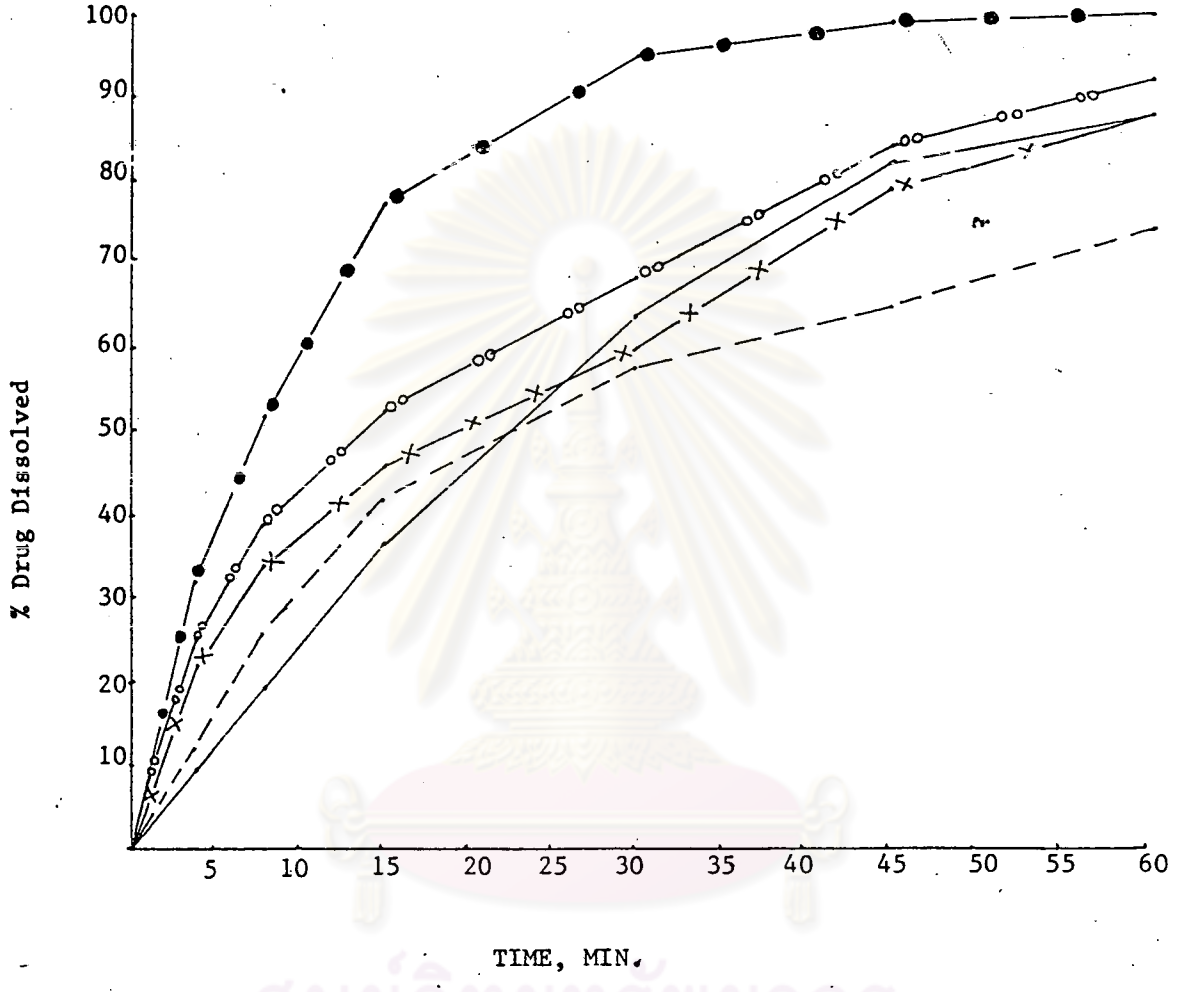

Figure 12 Effect of different disintegrants on dissolution of griseofulvin from tablets made by wet granulation, hardness 5–7 kp.

Key :

- formula 1 (No Disintegrant)
- formula 22 (1% Avicel^{R} PH 101)
- formula 23 (1 % Polyplasdone^{R} XL)
- formula 24 (1 % Explotab^{R})
- formula 3 (1% Ac-Di-Sol^{R})

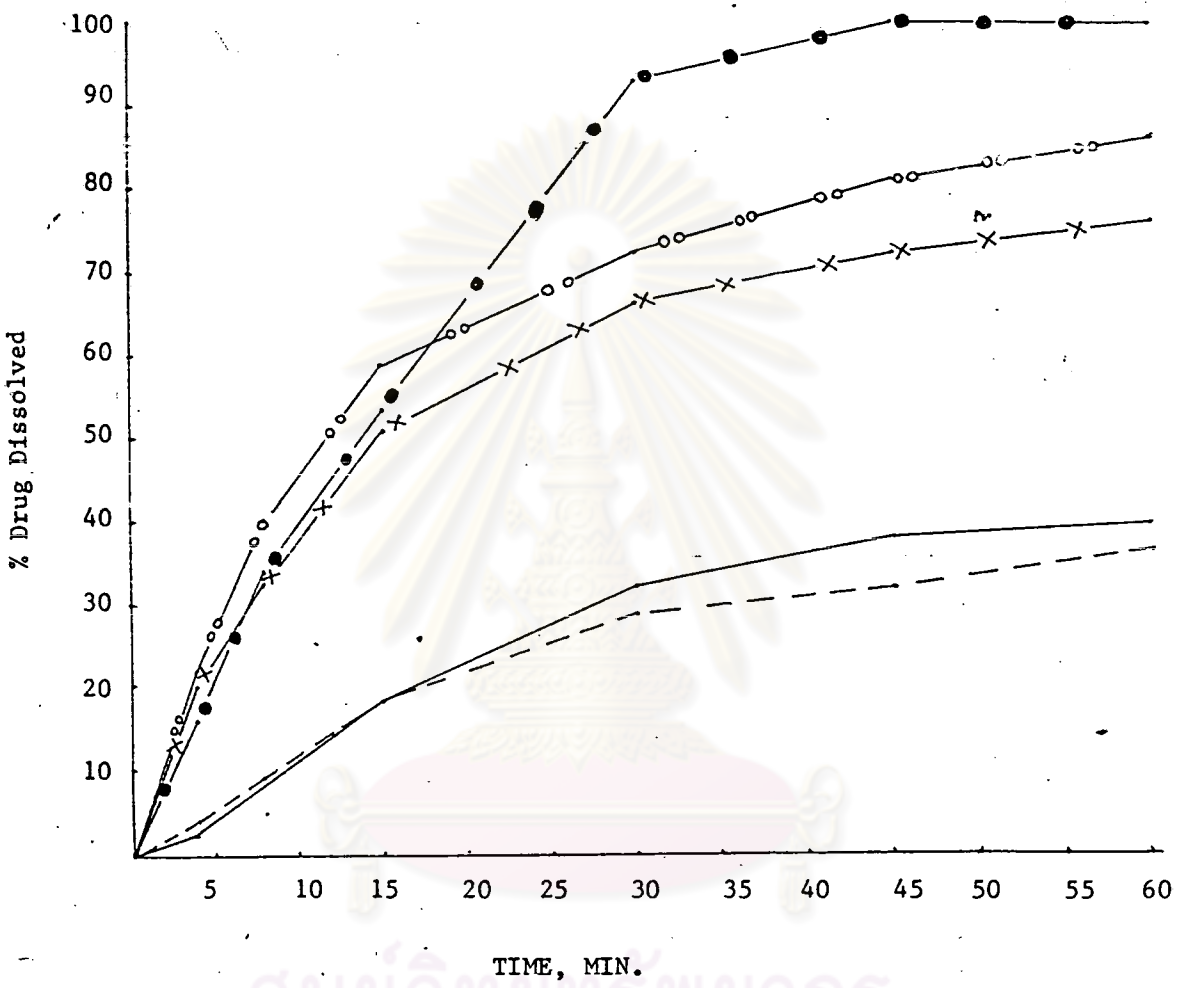

Figure 13 Effect of different disintegrants on dissolution of griseofulvin from tablets made by wet granulation, hardness 9-11 kp.

Key :

- formula 1 (No Disintegrant)
- formula 22 (1 % Avicel^{R} PH 101)
- formula 23 (1 % Polyplasdone^{R} XL)
- formula 24 (1 % Explotab^{R})
- formula 3 (1 % Ac-Di-Sol^{R})

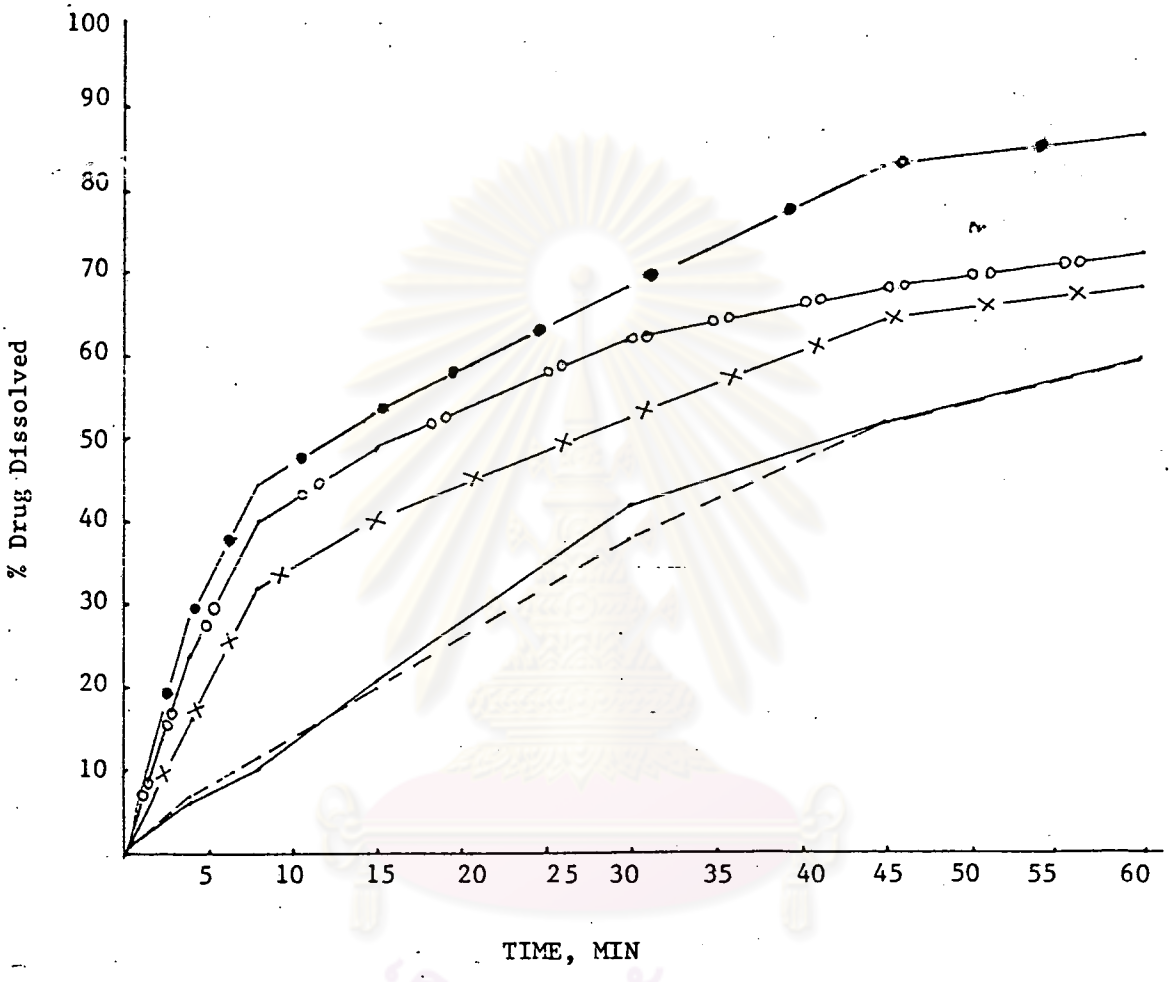

Figure 14 Effect of different disintegrants on dissolution of griseofulvin from tablets made by dry granulation, hardness 5-7 kp.

Key :

- formula 1 (No Disintegrant)
- formula 22 (1 % Avicel^{R} PH 101)
- formula 23 (1 % Polyplasdone^{R} XL)
- formula 24 (1 % Explotab^{R})
- formula 3 (1 % Ac-Di-Sol^{R})

Both in wet granulation and dry granulation, and high or low tablet hardness, Ac-Di-Sol^{R} was considered satisfactory and found to be the best among four tablet disintegrants for dissolution study of griseofulvin tablets.

A.6.3 Effect of Tablet Hardness on Dissolution Rates

The effect of two different ranges of tablet hardness : 5-7 kp and 9-11 kp on dissolution rates of tablets was shown in figure 15 and 16. The hardness of tablet did not significantly affect the dissolution rate of griseofulvin tablets containing Ac-Di-Sol^{R} as tablet disintegrant, ($t_{2,0.05} = 4.303, \pm t_{observed} = 3.220$). Conversely, increasing the hardness of tablet containing no disintegrant or Avicel^{R} PH 101 as tablet disintegrant decreased the dissolution rate as shown in figure 15,16

A.6.4 Effect of Processing on Dissolution Rates

The effect of two different procedures of tablet manufacturing : wet granulation and dry granulation on the dissolution rates of griseofulvin tablets have been studied. The dissolution profiles of the effect of processing on dissolution rate of tablets were shown in figure 17. The tablets manufactured by wet granulation had better dissolution profiles than those manufactured by dry granulation. The dissolution times (t 85 %) were significantly different ($t_{2,0.05} = 4.303, \pm t_{observed} \leq 14.388$).

A.6.5 Effect of the Methods of Incorporating Disintegrant on Dissolution Rates

The effect of three different methods of incorporating disintegrant into granules : intragranular, extragranular, and 50 % intragranular plus 50 % extragranular on dissolution rates have been

studied. The dissolution profiles of griseofulvin tablets manufactured by different methods of incorporating disintegrant into granules were shown in figure 18. Extragranular method seemed to exhibit the highest dissolution at the first 20 minutes, follow by intragranular and 50 : 50 intragranular : extragranular. However, after 20 minutes 50 : 50 intragranular : extragranular exhibited the highest dissolution, and about 100 % of the drug was dissolved at 60 minutes. The dissolution times(t 85 %) of griseofulvin tablets manufactured by three different methods of incorporating disintegrant into granules were not significantly different ($F_{2,3,0.05} = 9.55$, $F_{ratio} = 4.85$).

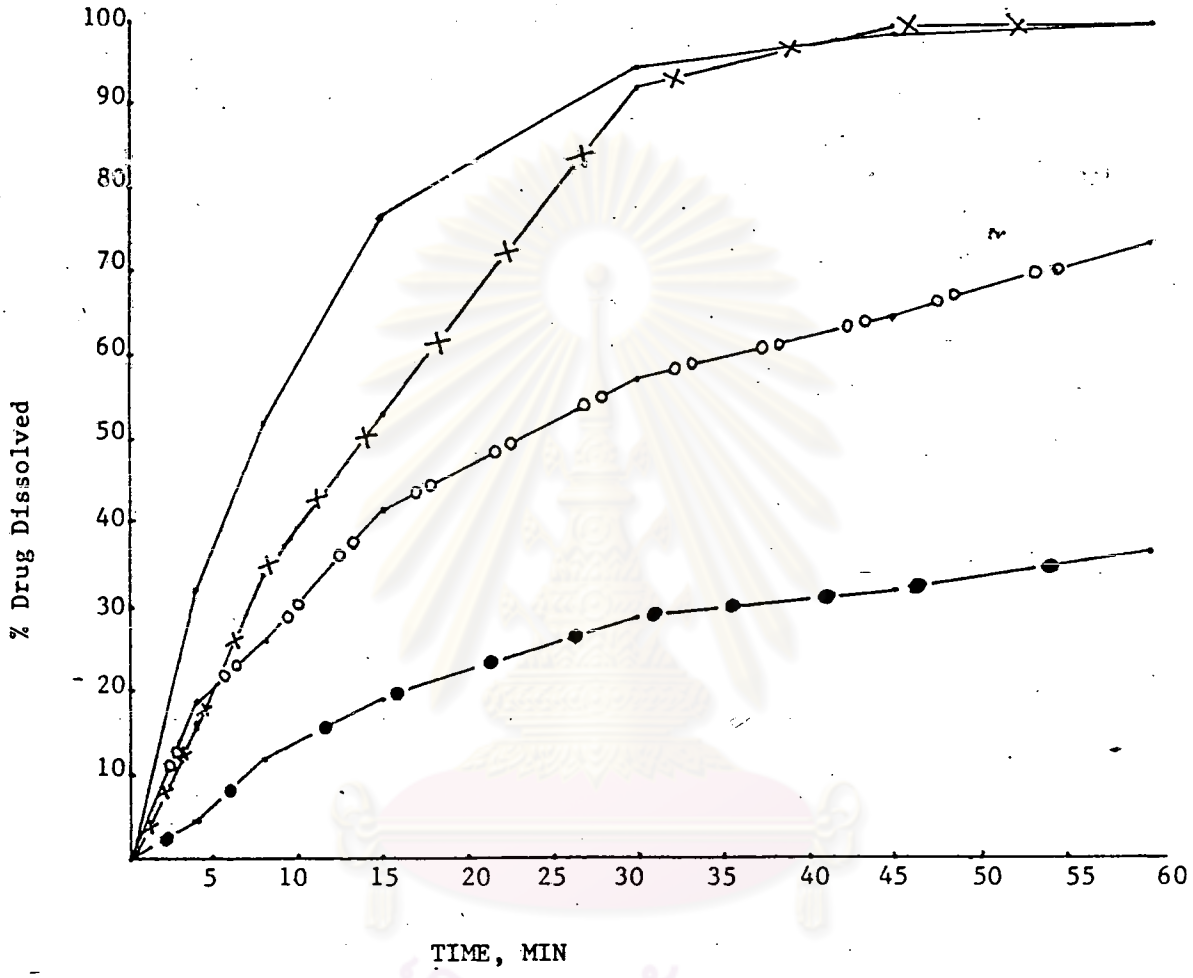

Figure 15 Effect of tablet hardnesses on dissolution of griseofulvin tablets (Wet granulation).

Key :

—o—o— formula 1 (No Disintegrant, hardness 5-7 Kp)

—●—● formula 1 (No Disintegrant, hardness 9-11 Kp)

——— formula 3 (1 % Ac-Di-Sol^{R}, hardness 5-7 Kp)

—x—x— formula 3 (1 % Ac-Di-Sol^{R}, hardness 9-11 Kp)

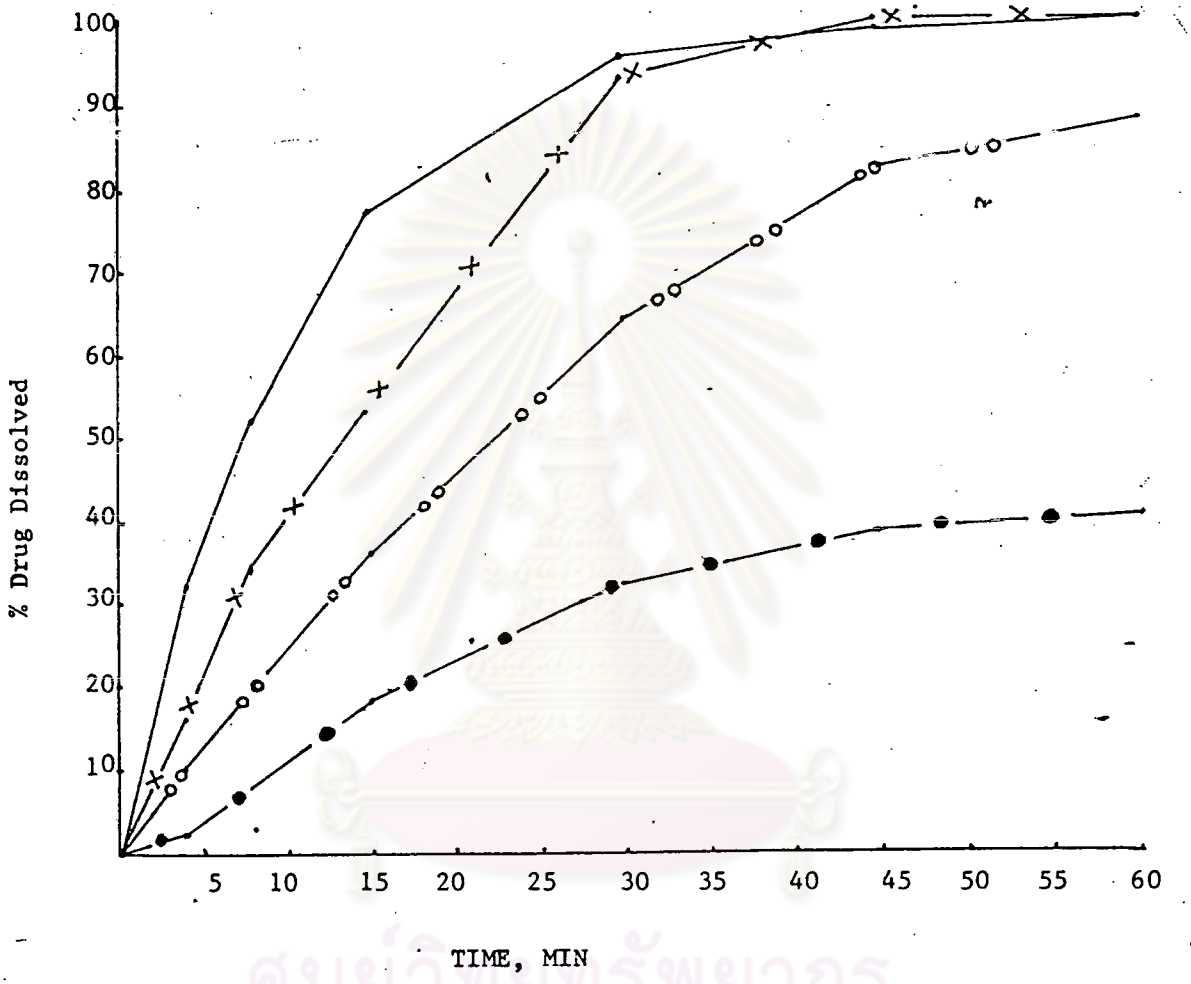

Figure 16 Effect of tablet hardnesses on dissolution of griseofulvin tablets(Wet granulation).

Key :

——— formula 3 (1 % Ac-Di-Sol^{R}, hardness 5–7 Kp)

—X—X— formula 3 (1 % Ac-Di-Sol^{R}, hardness 9–11 Kp)

—o—o— formula 22 (1 % Avicel^{R} PH 101, hardness 5–7 Kp)

—●—● formula 22 (1 % Avicel^{R} PH 101, hardness 9–11 Kp)

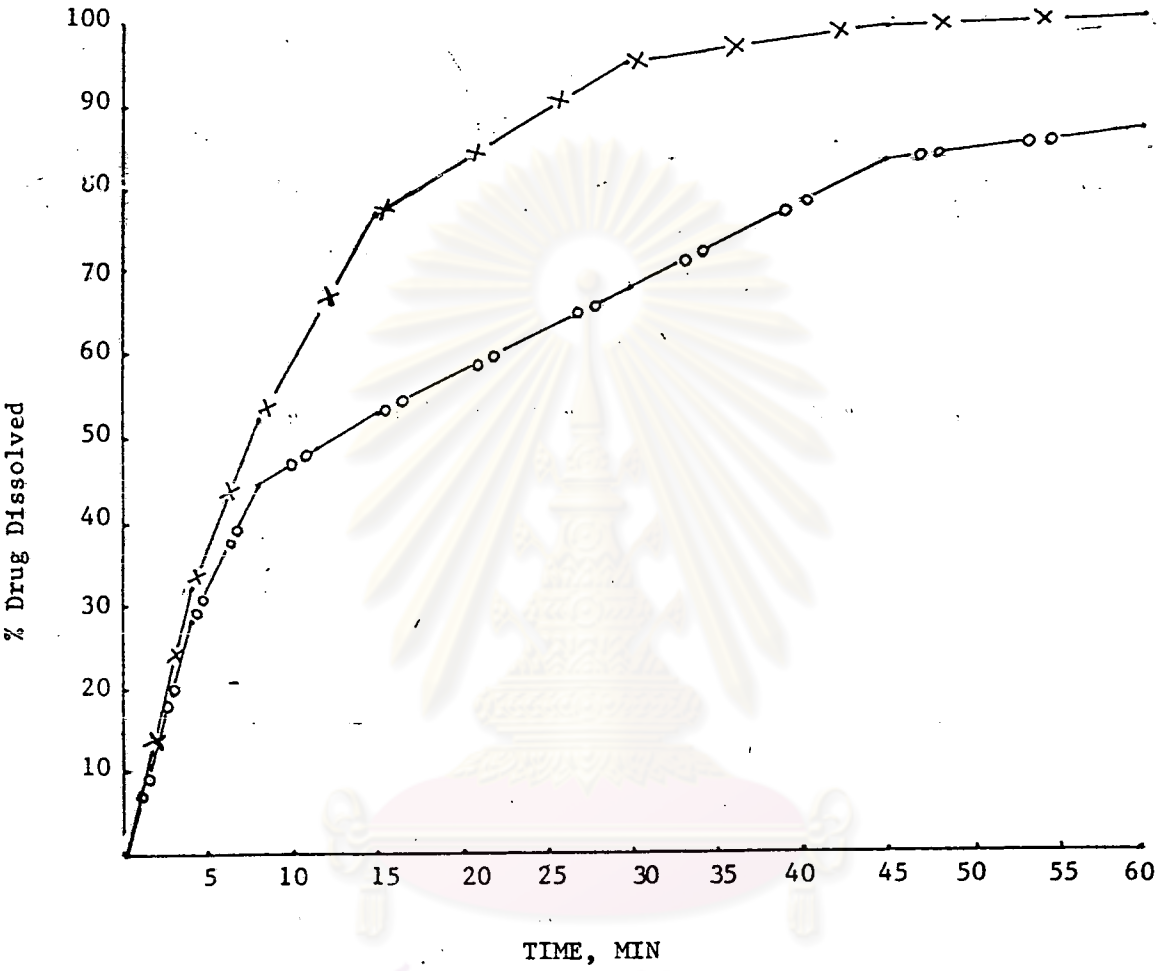

Figure 17 Effect of processing on dissolution of griseofulvin tablets, hardness 5–7 Kp.

Key :

—X—X— formula 3 (wet granulation)

—o—o— formula 3 (Dry granulation)

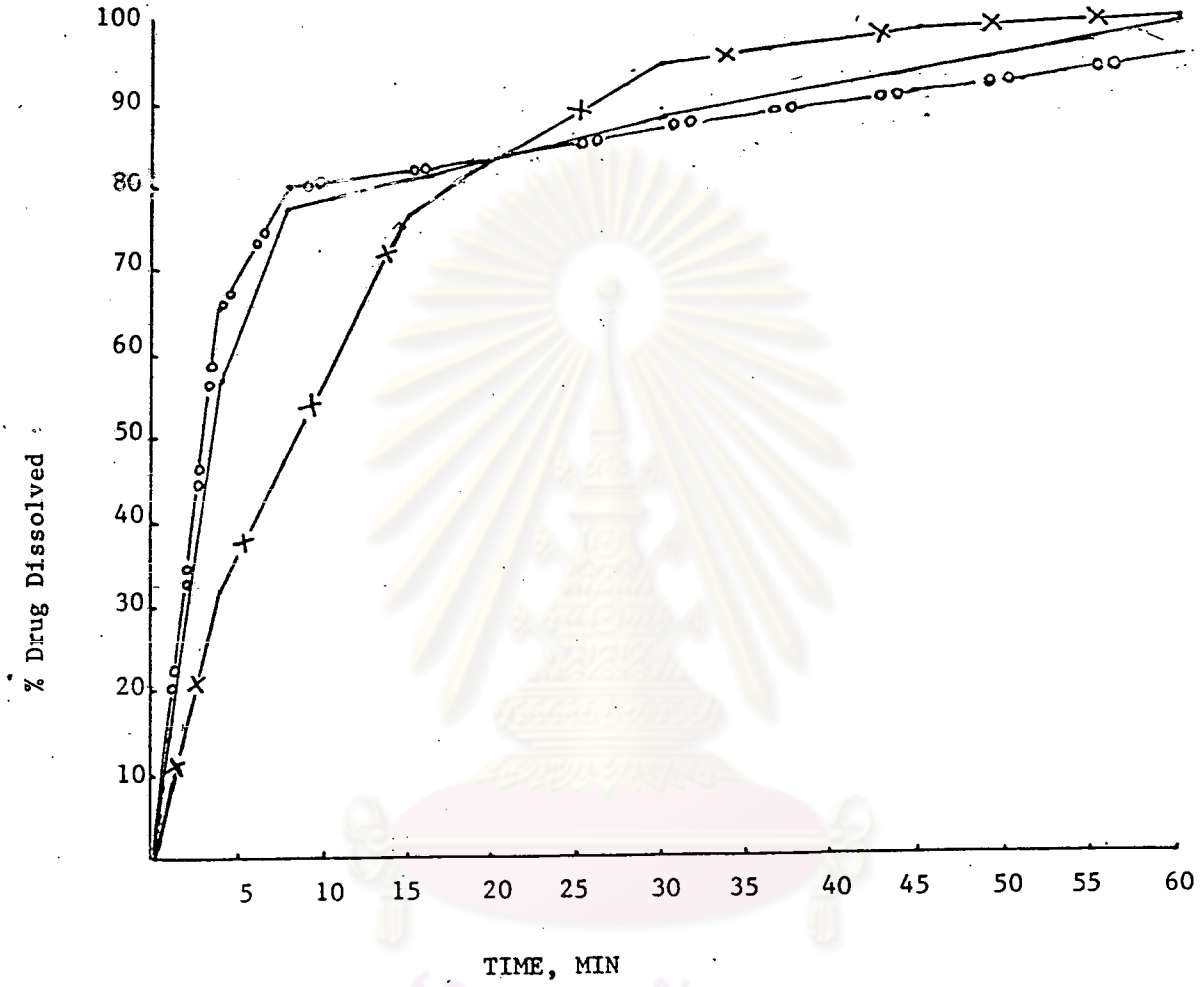

Figure 18 Effect of the methods of incorporating disintegrant into granules on dissolution of griseofulvin from tablets made by wet granulation, hardness 5-7 Kp.

Key :

——— formula 3 (Intragranular)

—oo—oo— formula 3 (Extragranular)

—x—x—formula 3 (50 : 50 Intragranular ; Extragranular)

B. Properties of Prednisolone Tablets** (Formula 8-14 and Formula 25-27)

B.1 Weight Variation of Tablets

The average weight, standard deviation, and the coefficient of variation of tablets weight are listed in table 14. Each formula of prednisolone tablets possessed the weight variation in the limit of USP standard[61].

B.2 Thickness of Tablets

The average thickness and standard deviation of tablets thickness are tubulated in table 15.

B.3 Hardness of Tablets

The average hardness, standard deviation, and the coefficient of variation of tablets hardness are listed in table 16.

B.4 Friability of Tablets

The friability of prednisolone tablets is listed in table 17.

B.5 Disintegration Time of Tablets

The disintegration times of prednisolone tablets containing different concentration of Ac-Di-Sol^{R} in 1:100 HCl in aqueous solution are shown in figure 19 and figure 20. At the hardness of 1-2 kp, the disintegration times of tablets manufactured by wet granulation were

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** Prednisolone tablets manufactured by dry granulation with the hardness of 3-5 kg were capped and were not evaluated.

Table 14 Effect of Disintegrants on Weight variation of Prednisolone Tablets

Formula Number	Wet granulation Tablet Hardness 1-2 Kp		Wet granulation Tablet Hardness 3-5 Kp		Dry granulation Tablet Hardness 1-2 Kp	
	Average weight (gm ± S.D.)	% C.V.	Average weight (gm ± S.D.)	% C.V.	Average weight (gm ± S.D.)	% C.V.
8	0.1318 ± 0.0005	0.41	0.1318 ± 0.0005	0.41	0.1315 ± 0.0011	0.89
9	0.1314 ± 0.0014	1.10	0.1304 ± 0.0004	0.34	0.1328 ± 0.0003	0.23
10	0.1339 ± 0.0009	0.66	0.1316 ± 0.0007	0.53	0.1347 ± 0.0009	0.70
11	0.1339 ± 0.0009	0.66	0.1328 ± 0.0004	0.33	0.1353 ± 0.0005	0.40
12	0.1352 ± 0.0011	0.84	0.1369 ± 0.0003	0.23	0.1354 ± 0.0004	0.33
13	0.1373 ± 0.0001	0.04	0.1369 ± 0.0003	0.23	0.1365 ± 0.0003	0.21
14	0.1388 ± 0.0007	0.50	0.1374 ± 0.0016	1.21	0.1404 ± 0.0023	1.67
25	0.1325 ± 0.0005	0.41	0.1331 ± 0.0008	0.62	0.1335 ± 0.0008	0.66
26	0.1328 ± 0.0004	0.33	0.1329 ± 0.0006	0.47	0.1332 ± 0.0005	0.41
27	0.1336 ± 0.0010	0.74	0.1333 ± 0.0007	0.53	0.1334 ± 0.0007	0.58

Table 15 Effect of Disintegrants on Thickness of Prednisolone Tablets

Formula Number	Wet granulation Tablet Hardness 1-2 Kp Average Thickness (mm ± S.D.)	Wet granulation Tablet Hardness 3-5 Kp Average Thickness (mm ± S.D.)	Dry granulation Tablet Hardness 1-2 Kp Average Thickness (mm ± S.D.)
8	3.85 ± 0.0100	3.73 ± 0.0479	4.01 ± 0.0324
9	3.90 ± 0.0200	3.73 ± 0.0406	4.04 ± 0.0529
10	4.24 ± 0.0574	3.77 ± 0.0200	4.07 ± 0.0234
11	4.25 ± 0.0458	3.80 ± 0.0681	4.09 ± 0.0223
12	4.31 ± 0.0158	4.12 ± 0.0648	4.10 ± 0.0100
13	4.38 ± 0.0264	4 13 ± 0.0264	4.12 ± 0.0254
14	4.59 ± 0.0200	4.34 ± 0.0839	4.12 ± 0.0200
25	4.16 ± 0.0360	4.04 ± 0.0514	4.11 ± 0.0324
26	4.51 ± 0.0316	4.38 ± 0.0158	4.45 ± 0.0458
27	4.12 ± 0.0254	4.05 ± 0.0608	4.15 ± 0.0353

Table 16 Effect of Disintegrants on Tablet Hardness of Prednisolone Tablets

Formula Number	Wet granulation Tablet Hardness 1-2 Kp		Wet granulation Tablet Hardness 3-5 Kp		Dry granulation Tablet Hardness 1-2 Kp	
	Hardness (Kp ± S.D.)	% C.V.	Hardness (Kp ± S.D.)	% C.V.	Hardness (Kp ± S.D.)	% C.V.
8	1.05 ± 0.0978	9.31	3.80 ± 0.3436	9.04	1.02 ± 0.0421	4.13
9	1.48 ± 0.1255	8.47	4.04 ± 0.1577	3.90	1.06 ± 0.0843	7.95
10	1.86 ± 0.1646	8.85	4.93 ± 0.2110	4.28	1.01 ± 0.0875	8.66
11	1.00 ± 0.0947	9.47	3.87 ± 0.3165	8.17	1.69 ± 0.1566	9.26
12	1.95 ± 0.0971	4.98	3.80 ± 0.3480	9.15	1.01 ± 0.0737	7.30
13	1.80 ± 0.5099	8.32	3.75 ± 0.3516	9.37	1.17 ± 0.1066	9.11
14	1.18 ± 0.0951	8.05	4.13 ± 0.3808	9.22	1.05 ± 0.0849	8.09
25	2.03 ± 0.1888	9.30	5.00 ± 0.1763	3.52	2.16 ± 0.1712	7.92
26	1.18 ± 0.1140	9.66	4.96 ± 0.1897	3.82	2.06 ± 0.1776	8.62
27	1.23 ± 0.1146	9.32	3.12 ± 0.2097	6.72	1.04 ± 0.1808	7.38

Table 17 Effect of Disintegrants on the Friability of Prednisolone Tablets

Formula Number	Wet granulation Tablet Hardness 1-2 Kp Friability %	Wet granulation Tablet Hardness 3-5 Kp Friability %	Dry granulation Tablet Hardness 1-2 Kp Friability %
8	0.53	0.32	0.71
9	0.54	0.33	0.82
10	0.56	0.35	0.74
11	0.62	0.37	0.75
12	0.66	0.40	0.78
13	0.69	0.43	0.80
14	0.72	0.45	0.83
25	0.51	0.28	0.69
26	0.50	0.30	0.68
27	0.54	0.33	0.70

ranked as the following : formula 8 (30.33 ± 0.2984) > formula 9 (0.21 ± 0.0240) > formula 10 (0.08 ± 0.0275) ~ formula 11 (0.07 ± 0.0275) = formula 12 (0.07 ± 0.0178) ~ formula 13 (0.06 ± 0.0118) ~ formula 14. (0.05 ± 0.0109). When the hardness of tablets was changed to 3-5 kp, the disintegration times of tablets(min) were ranked as the following : formula 8 (41.66 ± 0.5164) > formula 9 (1.27 ± 0.0783) > formula 10 (0.30 ± 0.0562) ~ formula 11 (0.27 ± 0.0238) ~ formula 12 (0.25 ± 0.0343) ~ formula 13 (0.20 ± 0.0256) ~ formula 14. (0.18 ± 0.0352). When the hardness of tablets was increased, the disintegration times of tablets was also increased as shown in figure 19.

The disintegration times of prednisolone tablets manufactured by dry granulation was less than those obtained from tablets manufactured by wet granulation, the disintegration times(min) were ranked as the following : formula 8 (1.17 ± 0.0236) > formula 9 (0.15 ± 0.0412) ~ formula 10 (0.10 ± 0.0154) ~ formula 11 (0.09 ± 0.0346) ~ formula 12 (0.08 ± 0.0167) = formula 13 (0.08 ± 0.0167) = formula 14 (0.08 ± 0.0200).

It was noted that Ac-Di-Sol^{R} was shown to be very effective as a tablet disintegrant in prednisolone tablets at level as low as 0.5 %. When the concentration increased from 1 % to 5 % the disintegration time was non-significantly decreased.

Table 18 shows the effects of four disintegrants : Ac-Di-Sol^{R} Avicel^{R} PH 101, Polyplasdone^{R}XL, and Explotab^{R} on disintegration time of tablets. With the hardness of 1-2 kg, the comparison of the tablets containing the same diluents but different disintegrants of 1 % concentration, disintegration times of tablets were ranked as the following : formula 25 (1 % Avicel^{R} PH 101) > formula 27 (1 % Explotab^{R}) > formula 26 (1 % Polyplasdone^{R}XL) > formula 10, (1 % Ac-Di-Sol^{R}), both in wet granulation and dry granulation. When the

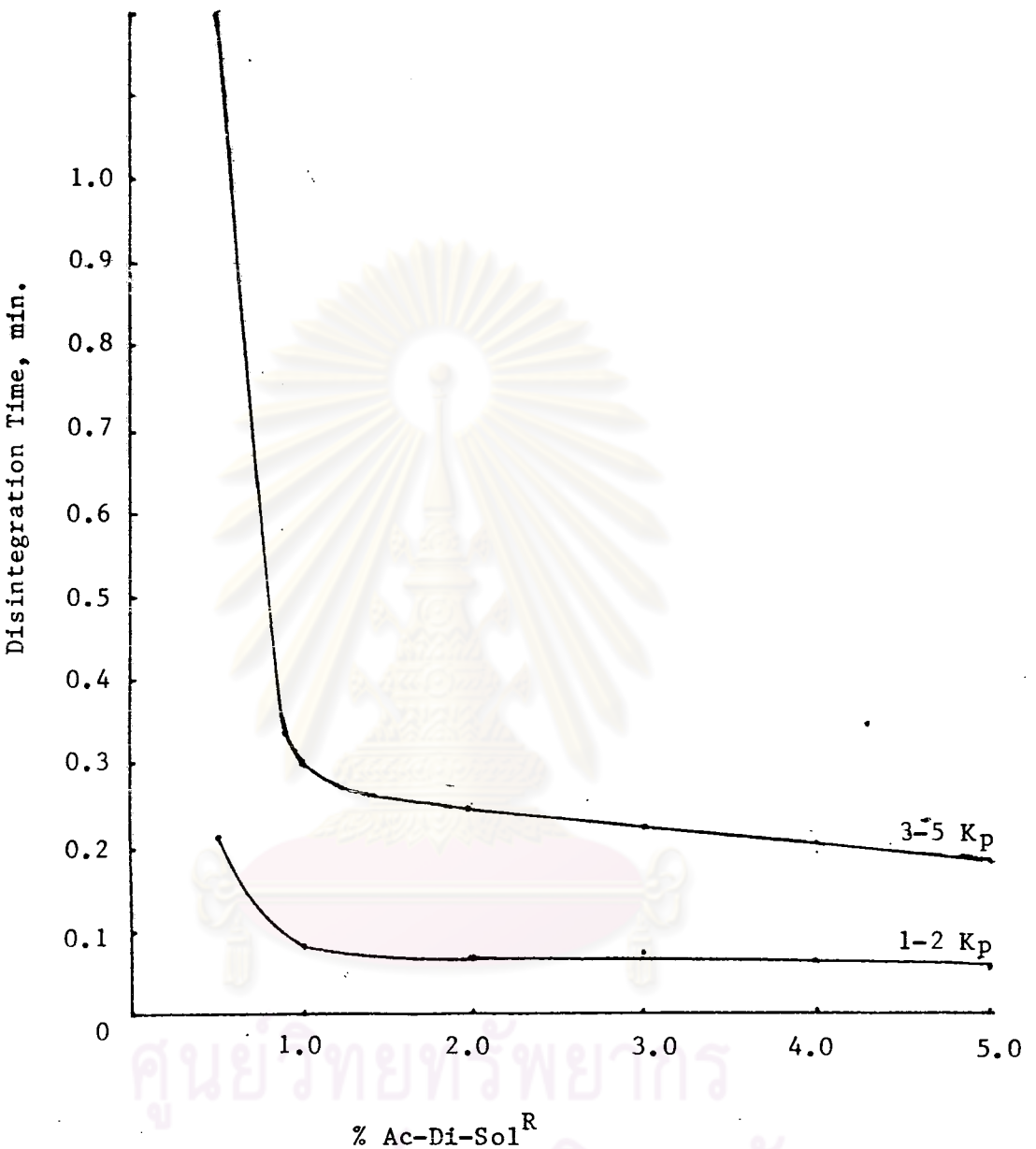

Figure 19 Effect of extent of disintegrant on disintegration time of prednisolone tablets made by wet granulation.

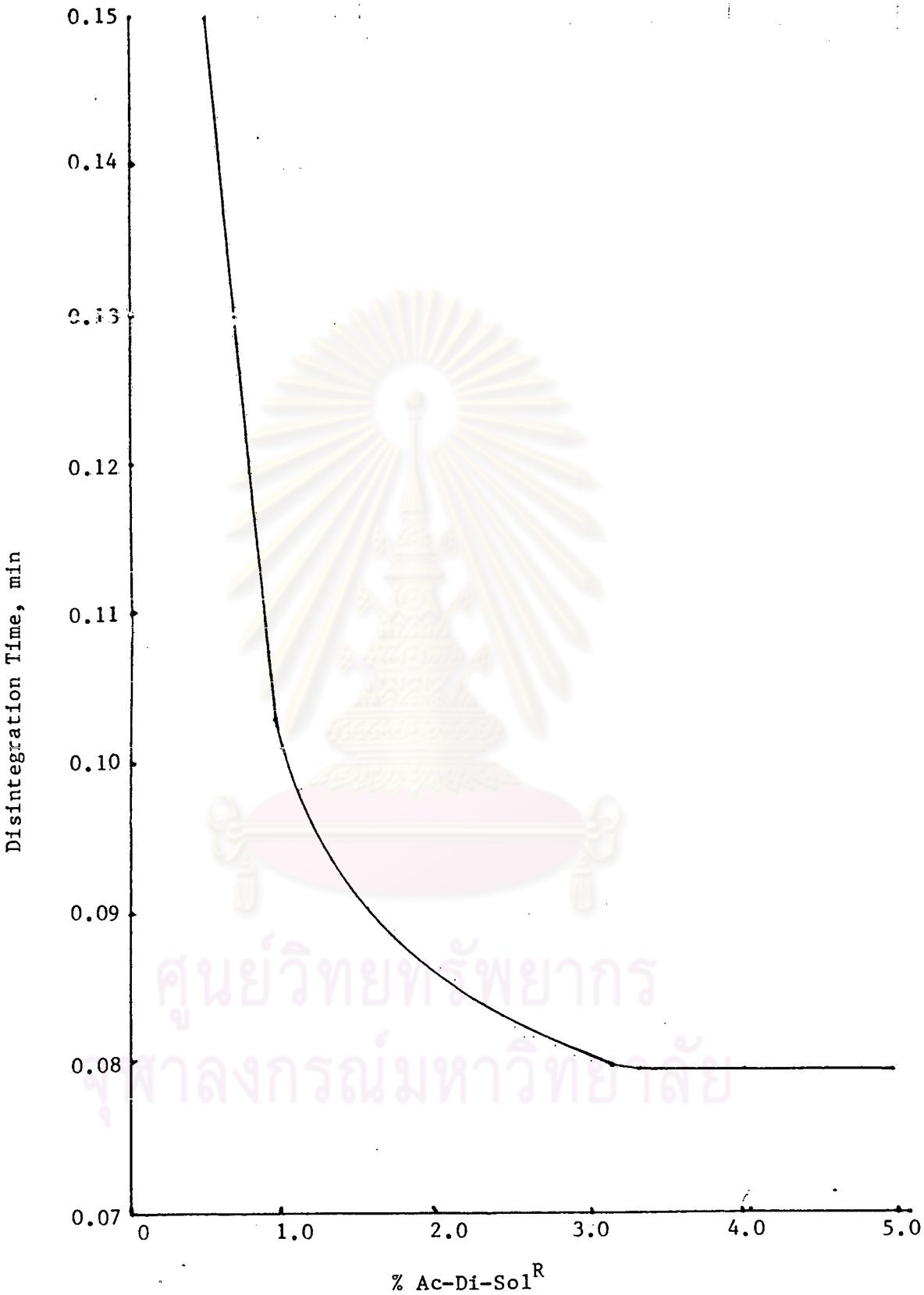

Figure 20 Effect of extent of disintegrant on disintegration time of prednisolone tablets made by dry granulation, hardness 1-2 kp.

Table 18 Effect of Different Disintegrants on Disintegration Time of Prednisolone Tablets

Formula No.	Disintegration Time, min $\pm$ S.D.		
	Wet granulation Tablet Hardness 1-2 k_p	Wet granulation Tablet Hardness 3-5 k_p	Dry granulation Tablet Hardness 1-2 k_p
# 8 (No disintegrant)	30.33 $\pm$ 0.2984	41.66 $\pm$ 0.5164	1.17 $\pm$ 0.0236
# 10(1% Ac-Di-Sol^R)	0.08 $\pm$ 0.0275	0.40 $\pm$ 0.0562	0.10 $\pm$ 0.0154
# 25(1% Avicel^R PH101)	14.45 $\pm$ 0.1300	44.66 $\pm$ 0.5164	10.50 $\pm$ 0.8366
# 26(1% Polyplasdone^R XL)	0.58 $\pm$ 0.0387	2.15 $\pm$ 0.1830	0.13 $\pm$ 0.0346
# 27(1% Explotab^R)	1.00 $\pm$ 0.0707	2.35 $\pm$ 0.0591	0.15 $\pm$ 0.0155

hardness of tablets was increased to 3-5 kp, the disintegration times of tablets were increased as demonstrated in table 18.

B.6 Dissolution Rates of Tablets.

B.6.1 Effect of Disintegrant on Dissolution Rates

The dissolution profiles of prednisolone tablets are shown in figure 21, 22, and 23. The tablets containing Ac-Di-Sol^{R} as tablet disintegrant showed higher dissolution rates than the tablets containing no disintegrant in both wet and dry granulation.

Ac-Di-Sol^{R} also increased the dissolution rates of prednisolone tablets both in high tablet hardness (3-5 kp) and low tablet hardness (1-2 kp).

The dissolution time of tablets in this study, expressed as the time required for 70 % of prednisolone to dissolve,[63] were demonstrated in figure 24.

B.6.2 Effect of Different Disintegrants on Dissolution Rates

The effect of four tablet disintegrants : Ac-Di-Sol,^{R} Avicel^{R} PH 101, Polyplasdone^{R} XL, and Explotab^{R} on dissolution rates of prednisolone tablets had been studied. The dissolution profiles of prednisolone tablets, containing 1 % of different disintegrants were shown in figure 25, 26 and 27. Table 19 shows the dissolution times of tablet containing 1 % Ac-Di-Sol^{R} (formula 10), 1 % Avicel^{R} PH 101 (formula 25), 1 % Polyplasdone^{R}XL (formula 26) and 1 % Explotab (formula 27) as tablet disintegrants . It can be seen that tablets containing Ac-Di-Sol^{R} were superior than tablets containing other disintegrants whether manufactured by wet granulation or dry granulation methods with 1-2 or 3-5 kp of hardness. The dissolution

times(t 70 %) of tablets manufactured by wet granulation and hardness 1-2 kp were ranked as the following : formula 25 (33.25 $\pm$ 3.8890) > formula 27 (20.10 $\pm$ 1.2727) > formula 26 (15.20 $\pm$ 0.8485) > formula 10 (12.25 $\pm$ 1.0606). When the hardness was changed to 3-5 kp, the dissolution times(t 70 %) were ranked as the following : formula 25 (45.25 $\pm$ 5.3033) > formula 27 (30.10 $\pm$ 2.6870) > formula 26 (22.05 $\pm$ 2.8284) > formula 10 (20.10 $\pm$ 2.6870)

By dry granulation, the dissolution rates of tablets containing various disintegrants were less than those obtained from tablet manufactured by wet granulation as shown in figure 25 and 27. Their dissolution times (t 70 %) were ranked as the following : formula 25 (> 60 min) = formula 26 = formula 27 > formula 10 (59.25 $\pm$ 1.4142).

Both in wet granulation and dry granulation, and high or low tablet hardness, Ac-Di-Sol^{R} was considered satisfactory and found to be the best among four tablet disintegrants for dissolution study of prednisolone tablets.

B.6.3 Effect of Tablet Hardness on Dissolution Rates

The effect of two different ranges of tablet hardness : 1-2 kp and 3-5 kp on dissolution rates of tablets was shown in figure 28 and 29. The hardness of tablet did not significantly affect the dissolution rate of prednisolone tablets containing Ac-Di-Sol^{R} as tablet disintegrant, ($t_{2,\ 0.05} = 4.303$, $\pm\ t_{observed} = 3.843$). Conversely, increasing the hardness of tablet containing no disintegrant or Avicel^{R} pH 101 as tablet disintegrant decreased the dissolution rate as shown in figure 28 and 29 .

Table 19 Effect of Different Disintegrants on Dissolution Times (t 70%) of Prednisolone Tablets

Formula No.	Dissolution Time (t 70%), min ± S.D.		
	Wet granulation Tablet Hardness 1-2 kp	Wet granulation Tablet Hardness 3-5 kp	Dry granulation Tablet Hardness 1-2 kp
# 8 (No disintegrant)	38.25 ± 2.4748	> 60	> 60
#10 (1 % Ac-Di-Sol®)	12.25 ± 1.0606	20.10 ± 2.6870	59.25 ± 1.4142
#25 (1% Avicel® PH 101)	33.25 ± 3.8890	45.25 ± 5.3033	> 60
#26 (1% Polyplasdone® XL)	15.20 ± 0.8485	22.05 ± 2.8284	> 60
#27 (1 % Explotab®)	20.10 ± 1.2727	30.10 ± 2.6870	> 60

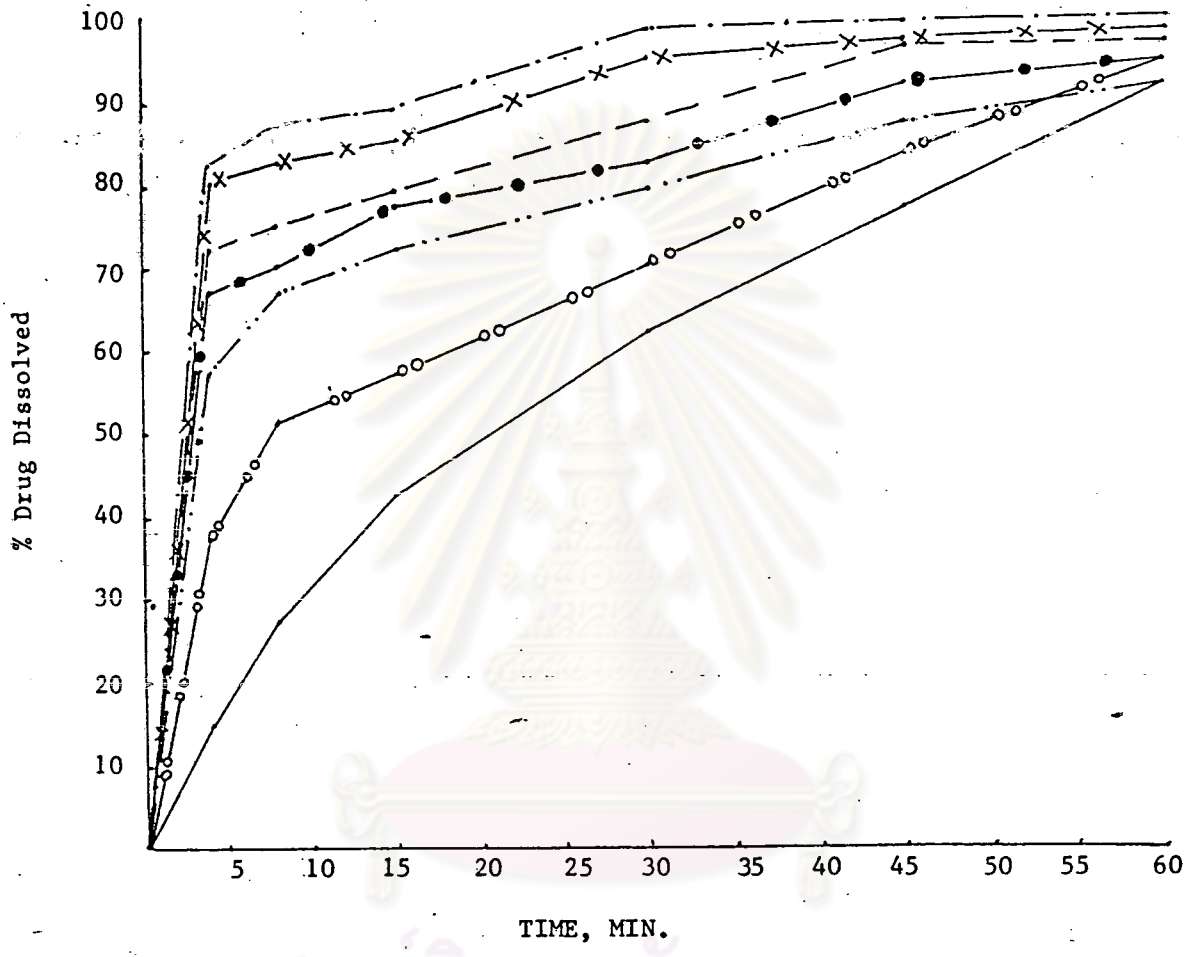

Figure 21. Dissolution profiles of prednisolone tablets, formula 8-14, hardness 1-2 kp (Wet granulation).

Key :

——————— formula 8 (No Disintegrant)

—oo—oo— formula 9 (0.5 % Ac-Di-Sol^{R})

—·· —·· — formula 10(1.0 % Ac-Di-Sol^{R})

—●—●— formula 11(2.0 % Ac-Di-Sol^{R})

- - - - - - formula 12(3.0 % Ac-Di-Sol^{R})

—x—x— formula 13(4.0 % Ac-Di-Sol^{R})

—·—·— formula 14(5.0 % Ac-Di-Sol^{R})

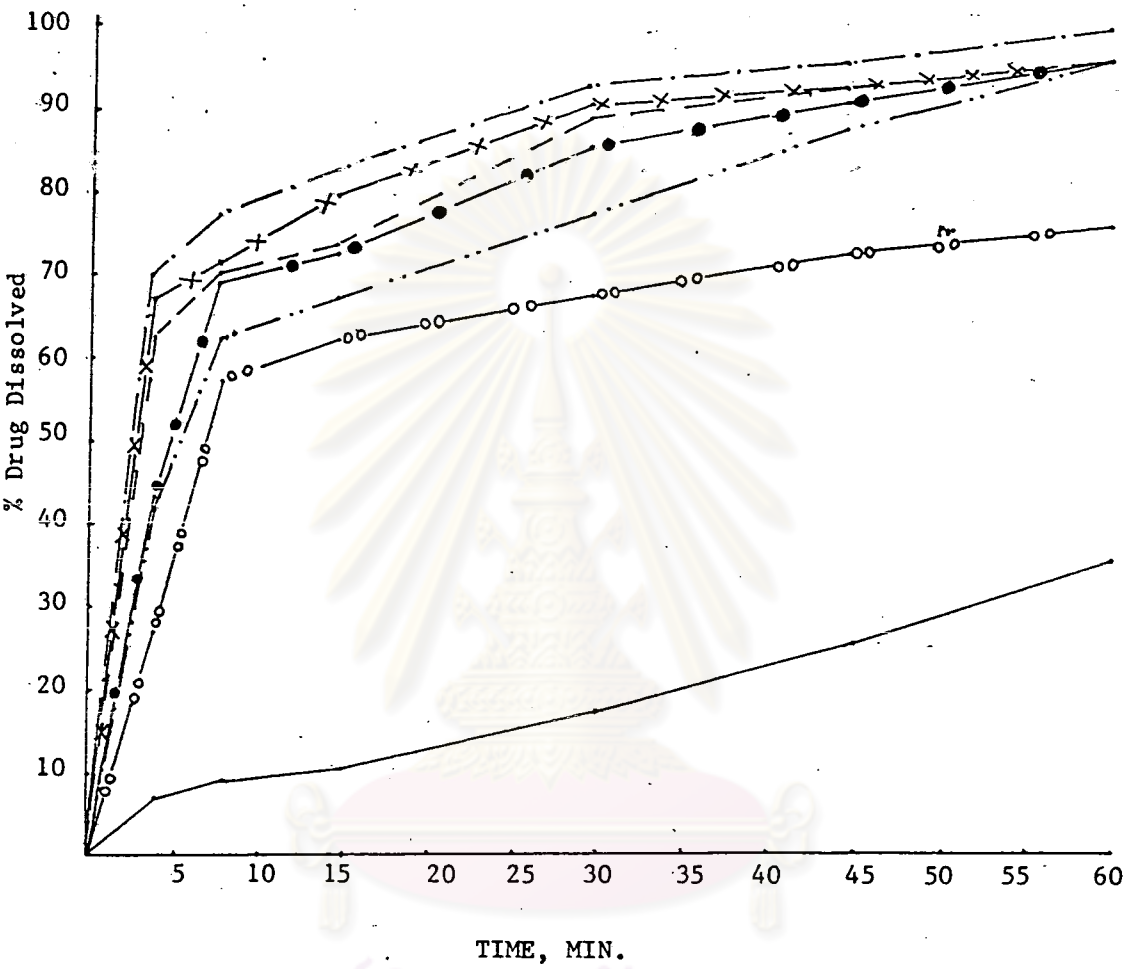

Figure 22 Dissolution profiles of prednisolone tablets, formula 8-14, hardness 3-5 K_p (Wet granulation).

Key :

formula 8 (No Disintegrant)

formula 9 (0.5 % Ac-Di-Sol^R)

formula 10(1.0 % Ac-Di-Sol^R)

formula 11(2.0 % Ac-Di-Sol^R)

formula 12(3.0 % Ac-Di-Sol^R)

formula 13(4.0 % Ac-Di-Sol^R)

formula 14(5.0 % Ac-Di-Sol^R)

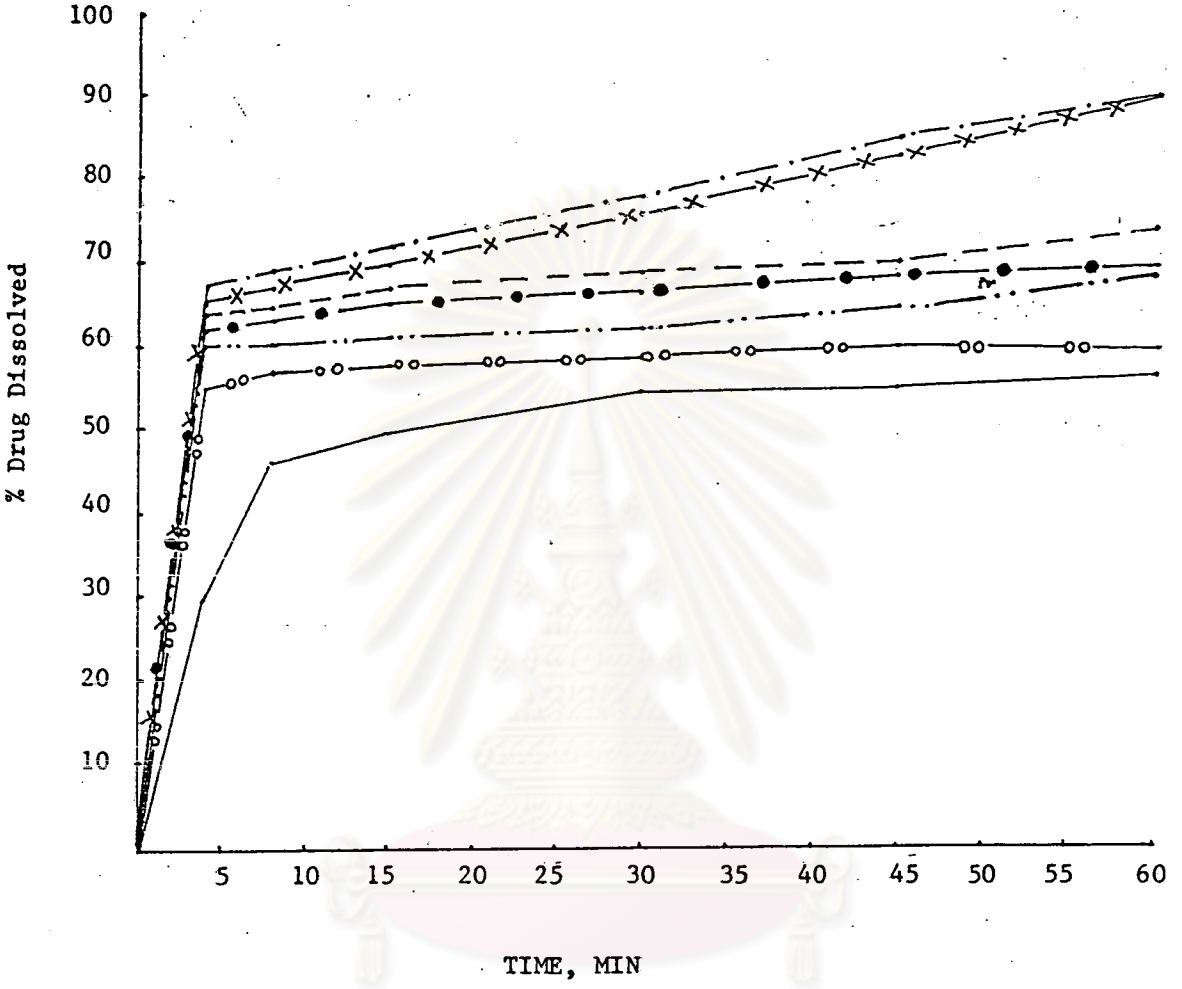

Figure 23 Dissolution profiles of prednisolone tablets, formula 8-14, hardness 1-2 Kp (Dry granulation).

Key :

——— formula 8 (No Disintegrant)

—oo—oo— formula 9 (0.5 % Ac-Di-Sol^{R})

—··—·· formula 10(1.0 % Ac-Di-Sol^{R})

—●—● formula 11(2.0 % Ac-Di-Sol^{R})

- - - - - - formula 12(3.0 % Ac-Di-Sol^{R})

—X—X— formula 13(4.0 % Ac-Di-Sol^{R})

—·—·— formula 14(5.0 % Ac-Di-Sol^{R})

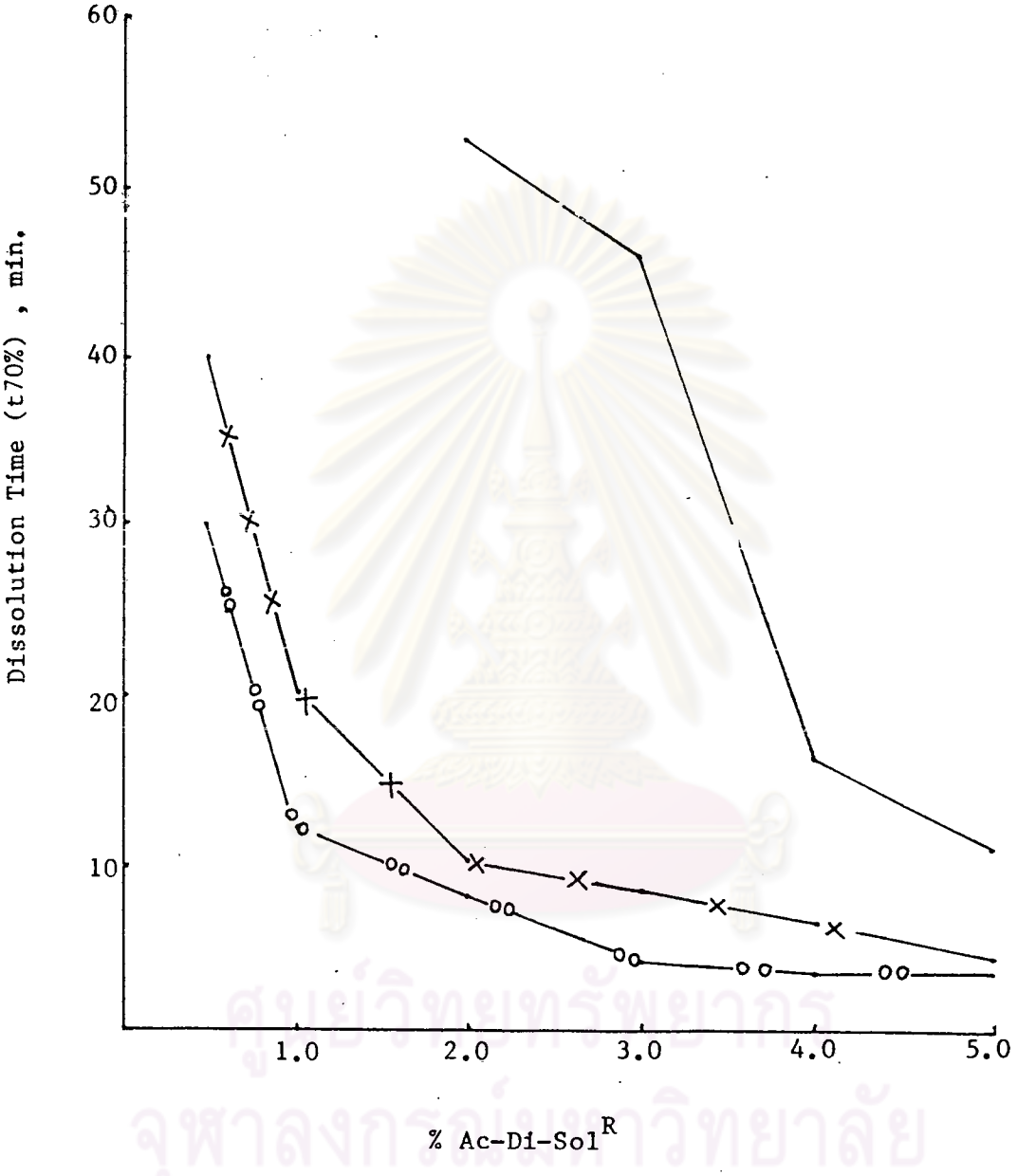

Figure 24 Relationship between extent of disintegrant and dissolution time (t 70 %) of prednisolone tablets

Key :

——— Dry granulation, hardness 1-2 Kp

—x—x— Wet granulation, hardness 3-5 Kp

—o—o— Wet granulation, hardness 1-2 Kp

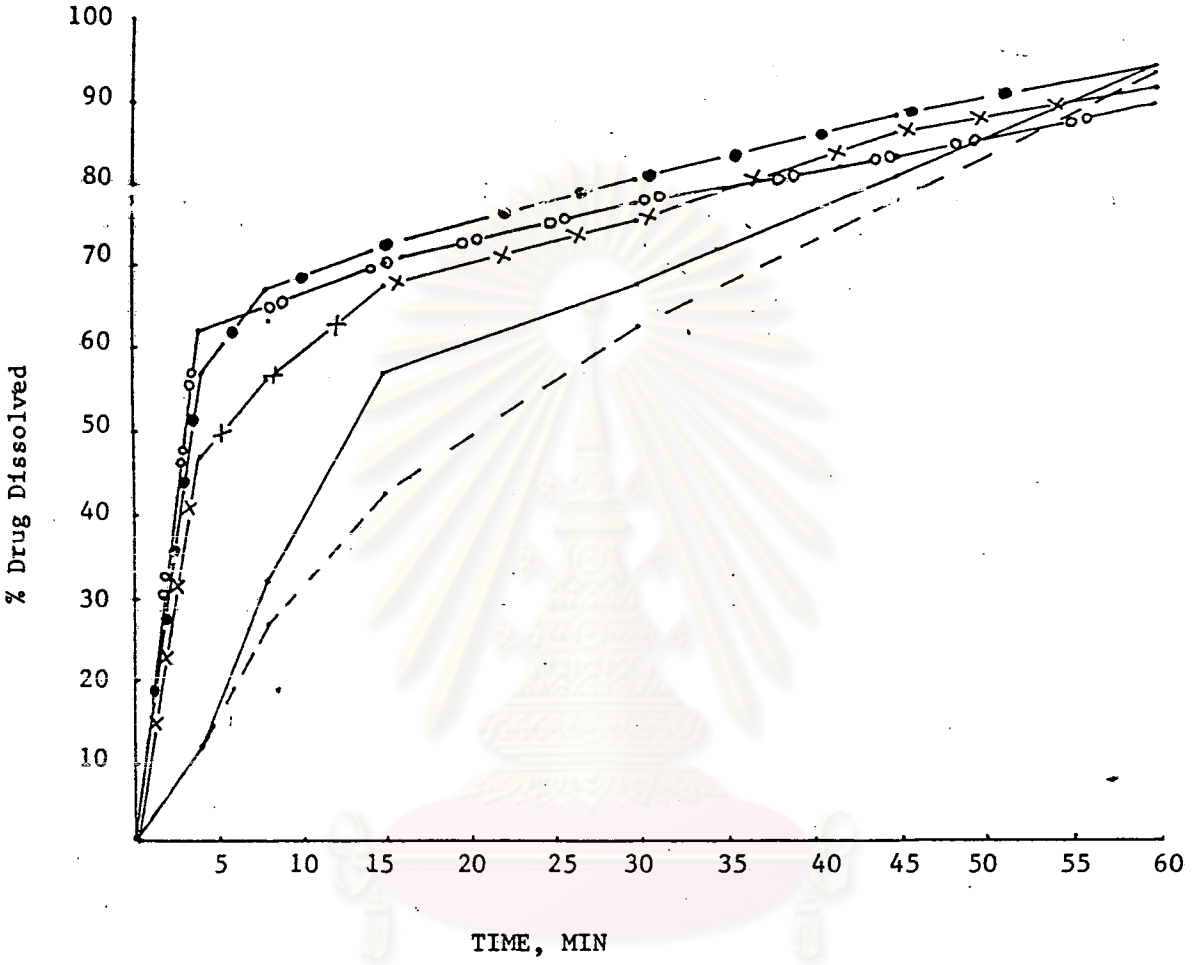

Figure 25 Effect of different disintegrants on dissolution of prednisolone from tablets made by wet granulation, hardness 1-2 kp.

Key :

- formula 8 (No Disintegrant)
- formula 25 (1.0 % Avicel ^{R} PH 101)
- formula 26 (1.0 % Polyplasdone^{R} XL)
- formula 27 (1.0 % Explotab^{R})
- formula 10 (1.0 % Ac-Di-Sol^{R})

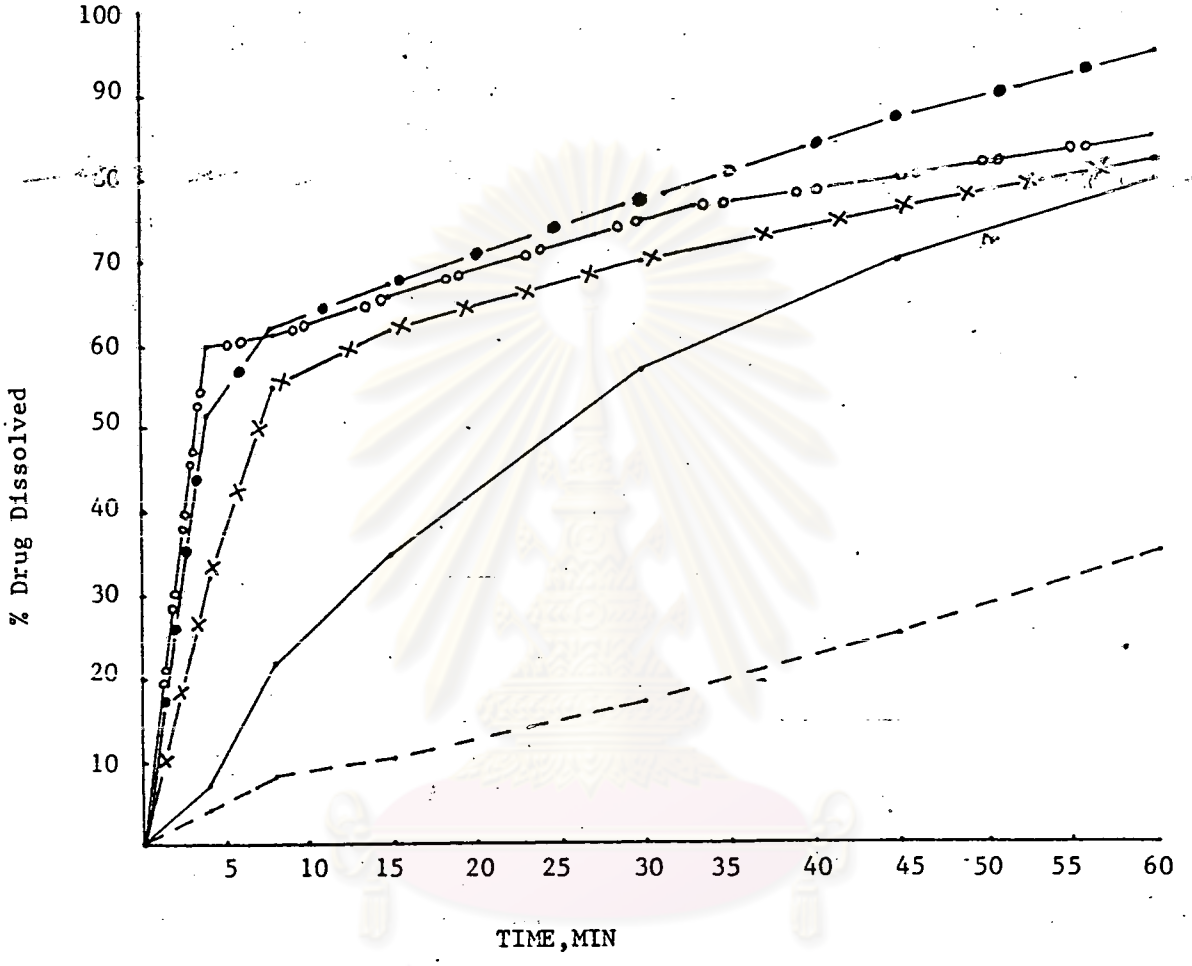

Figure 26 Effect of different disintegrants on dissolution of prednisolone from tablets made by wet granulation, hardness 3-5 kp.

Key :

- - - - - formula 8 (No Disintegrant)

——— formula 25 (1.0 % Avicel^{R} PH 101)

—oo—oo— formula 26 (1.0 % Polyplasdone^{R} XL)

—x—x— formula 27 (1.0 % Explotab^{R})

—●—●— formula 10 (1.0 % Ac-Di-Sol^{R})

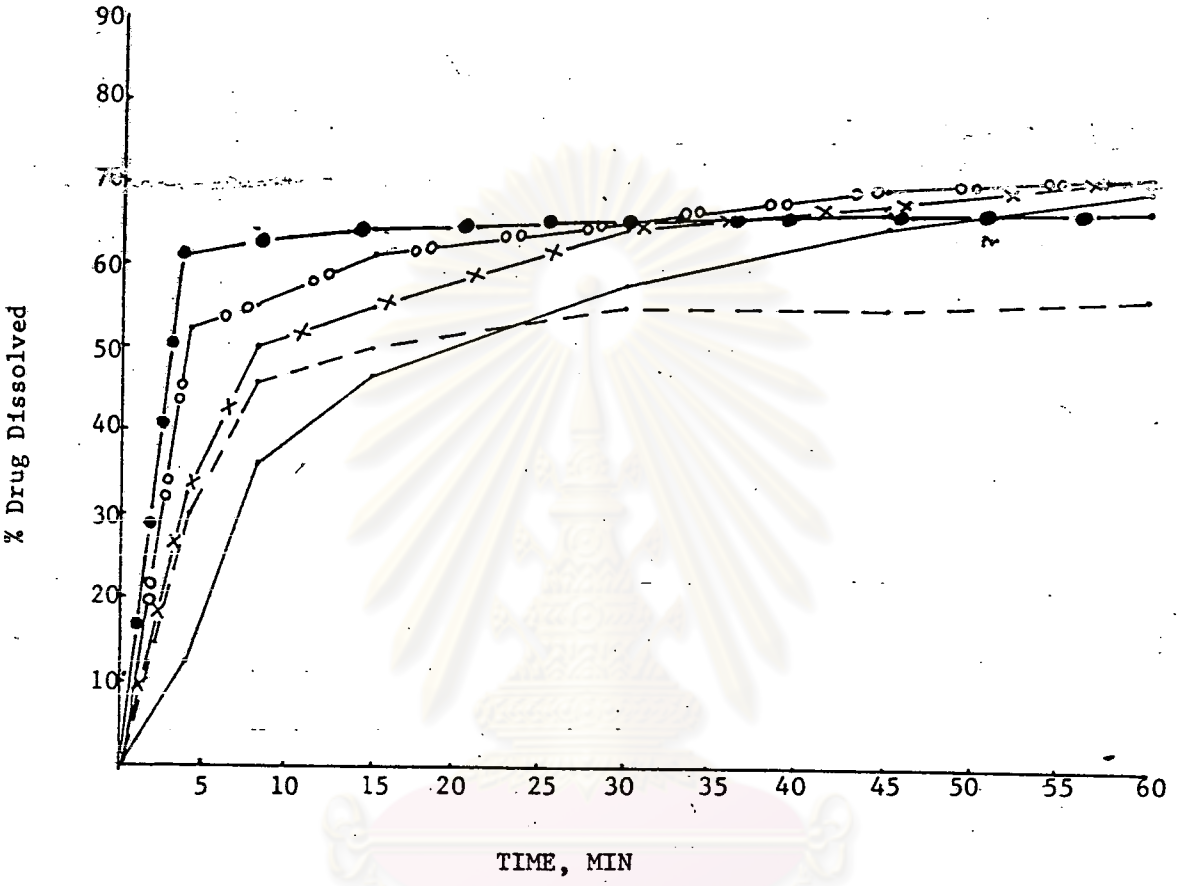

Figure 27 Effect of different disintegrants on dissolution of prednisolone from tablets made by dry granulation, hardness 1-2 kp.

Key :

- formula 8 (No Disintegrant)
- formula 25 (1 % Avicel^{R} PH 101)
- formula 26 (1 % Polyplasdone^{R} XL)
- formula 27 (1 % Explotab^{R})
- formula 10 (1 % Ac-Di-Sol^{R})

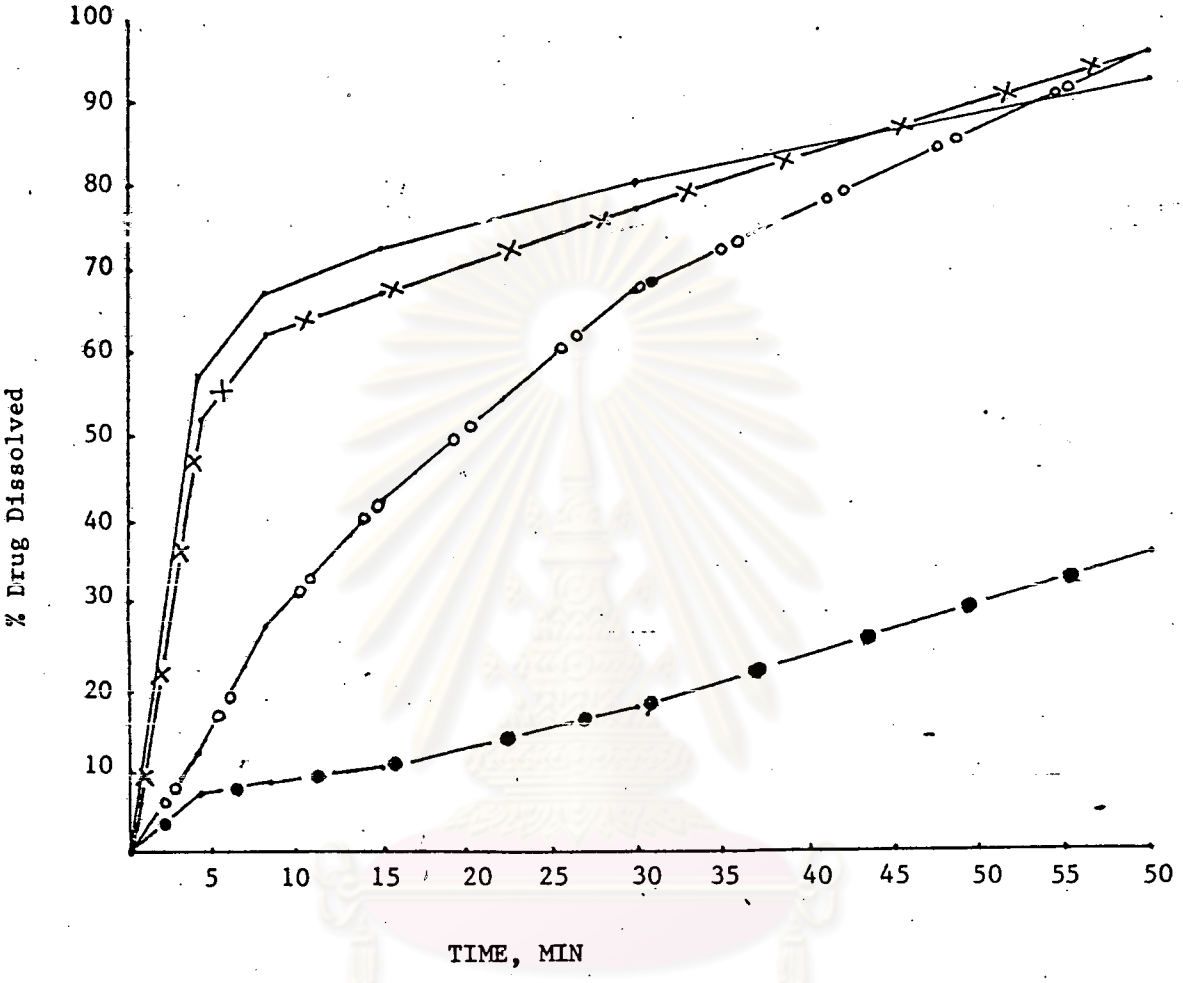

Figure 28 Effect of tablet hardnesses on dissolution of prednisolone tablets (Wet granulation)

Key :

—oo—oo— formula 8 (No Disintegrant, hardness 1-2 Kp)

—●—●— formula 8 (No Disintegrant, hardness 3-5 Kp)

———— formula 10 (1 % Ac-Di-Sol^{R}, hardness 1-2 Kp)

—X—X— formula 10 (1 % Ac-Di-Sol^{R}, hardness 3-5 Kp)

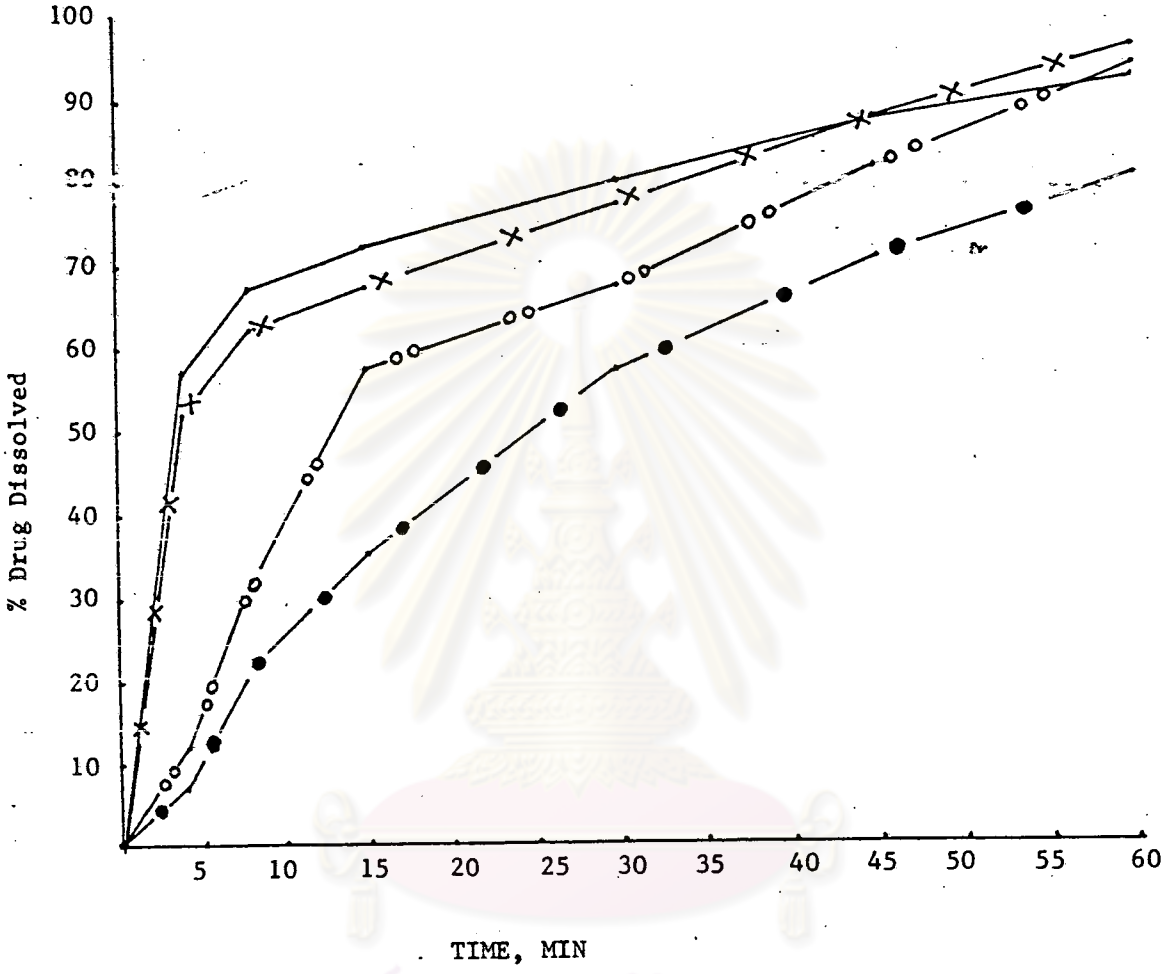

Figure 29 Effect of tablet hardnesses on dissolution of prednisolone tablets (Wet granulation).

Key :

——————— formula 10 (1 % Ac-Di-Sol^{R}, hardness 1-2 Kp)

—x—x— formula 10 (1 % Ac-Di-Sol^{R}, hardness 3-5 Kp)

—o—o— formula 25 (1 % Avicel^{R} PH 101, hardness 1-2 Kp)

—●—●— formula 25 (1 % Avicel^{R} PH 101, hardness 3-5 Kp)

B.6.4 Effect of Processing on Dissolution Rates

The effect of two different processing of tablet manufacturing : wet granulation and dry granulation on dissolution rates of prednisolone tablets have been studied. The dissolution profiles of the effect of processing on dissolution rate of tablets were shown in figure 30.

The tablets manufactured by wet granulation had better dissolution profiles than those manufactured by dry granulation. The dissolution times (t 70%) were significantly different ($t_{2,\ 0.05} = 4.303, \pm t_{observed} = 37.603$)

B.6.5 Effect of The Methods of Incorporating Disintegrant on Dissolution Rates

The effect of three different methods of incorporating disintegrant into granules : intragranular, extragranular, and 50 % intragranular plus 50 % extragranular on dissolution rates have been studied. The dissolution profiles of prednisolone tablets manufactured by different methods of incorporating disintegrant into granules were shown in figure 31. The dissolution times(t 70%) of prednisolone tablets manufactured by three different methods of incorporating disintegrant into granules were not significantly different ($F_{2,\ 3,0.05} = 9.55$, F ratio = 5.43).

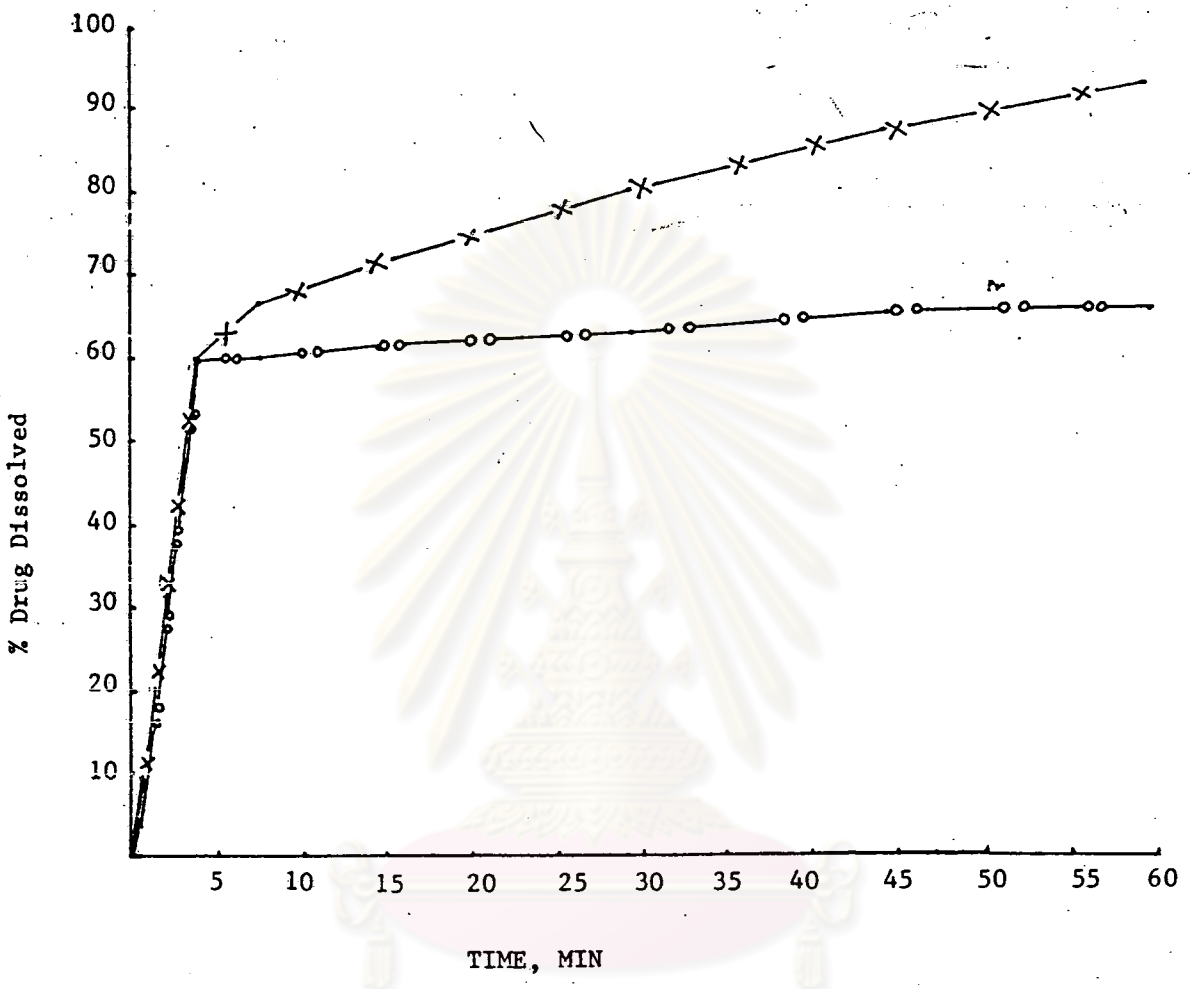

Figure 30 Effect of processing on dissolution of prednisolone tablets hardness 1-2 Kp.

Key :

—X—X— formula 10 (Wet granulation)

—oo—oo— formula 10 (Dry granulation)

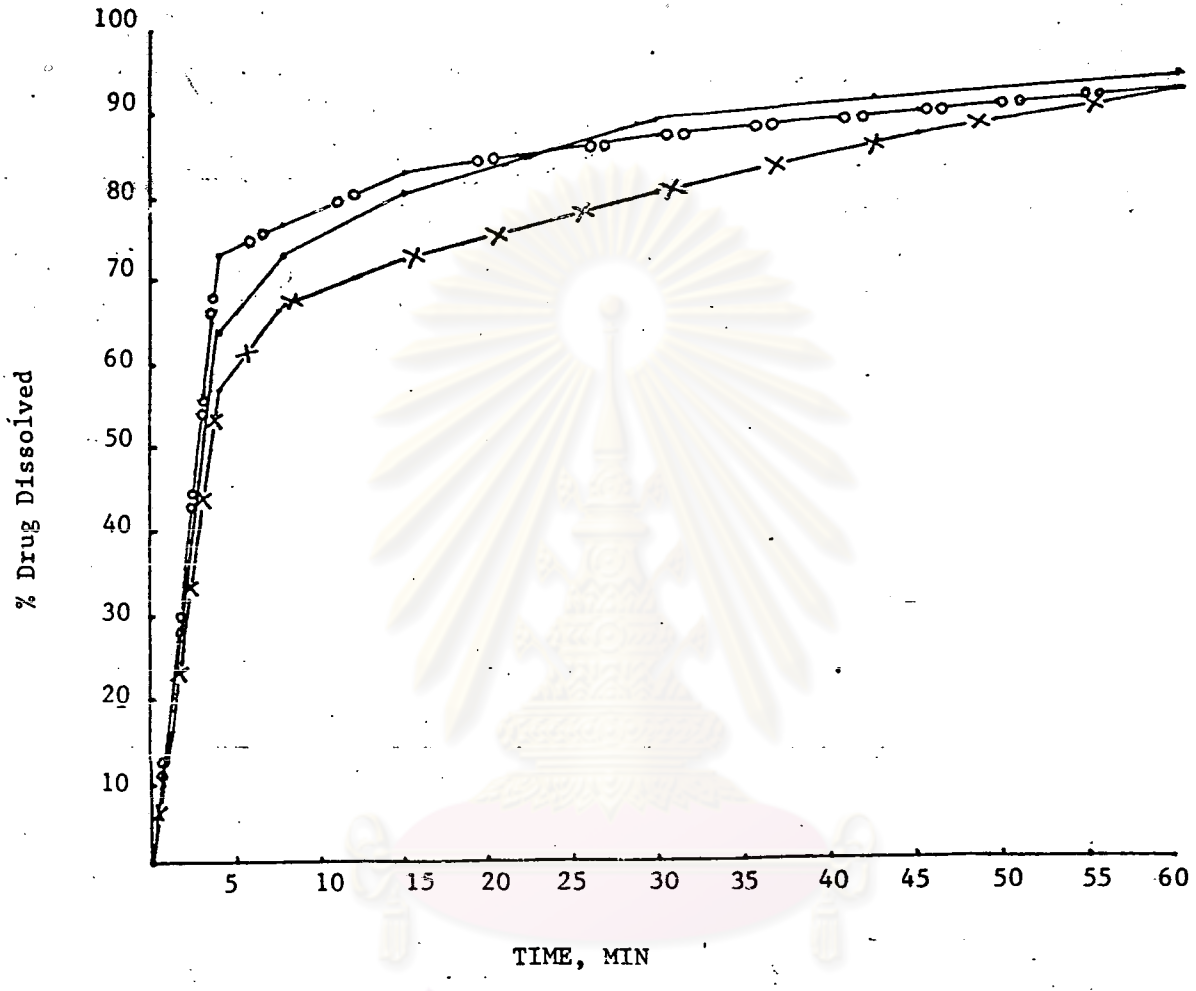

Figure 31 Effect of the methods of incorporating disintegrant into granules on dissolution of prednisolne from tablets made by wet granulation, hardness 1-2 K.p.

Key :

——————— formula 10 (Intragranular)

—oo—oo— formula 10 (Extragranular)

—x—x— formula 10 (50:50 Intragranular:Extragranular)

C. Properties of Furosemide Tablets*** (Formula 15-21 and Formula 28-30)

C.1 Weight Variation of Tablets

The average weight, standard deviation, and the coefficient of variation of tablets weight are listed in table 20. Each formula of furosemide tablets possessed the weight variation in the limit of USP standard(61).

C.2 Thickness of Tablets

The average thickness and standard deviation of tablets thickness are tubulated in table 21.

C.3 Hardness of Tablets

The average hardness, standard deviation, and the coefficient of variation of tablets hardness are listed in table 22.

C.4 Friability of Tablets

The friability of furosemide tablets is listed in table 23. It was found that the tablets manufactured by dry granulation seems to have higher friability than those manufactured by wet granulation. However all tablets exhibited less than 1.0 % friability.

*** Furosemide tablets manufactured by dry granulation with the hardness of 8-11 kg were capped and were not evaluated.

Table 20 Effect of Disintegrants on Weight Variation of Furosemide Tablets

Formula Number	Wet granulation Tablet Hardness 4-6 Kp		Wet granulation Tablet Hardness 8-11 Kp		Dry granulation Tablet Hardness 4-6 Kp	
	Average weight (gm ± S.D.)	% C.V.	Average weight (gm ± S.D.)	% C.V.	Average weight (gm ± S.D.)	%C.V.
15	0.1460 ± 0.0009	0.64	0.1451 ± 0.0015	1.04	0.1460 ± 0.0019	1.30
16	0.1459 ± 0.0005	0.37	0.1485 ± 0.0006	0.42	0.1461 ± 0.0014	1.01
17	0.1463 ± 0.0009	0.64	0.1465 ± 0.0020	1.43	0.1481 ± 0.0015	1.06
18	0.1487 ± 0.0010	0.70	0.1477 ± 0.0004	0.30	0.1480 ± 0.0015	1.06
19	0.1484 ± 0.0010	0.70	0.1498 ± 0.0013	0.87	0.1499 ± 0.0010	0.69
20	0.1500 ± 0.0006	0.42	0.1553 ± 0.0044	2.85	0.1521 ± 0.0014	0.92
21	0.1514 ± 0.0005	0.36	0.1537 ± 0.0035	2.32	0.1524 ± 0.0004	0.29
28	0.1488 ± 0.0007	0.52	0.1495 ± 0.0007	0.47	0.1488 ± 0.0008	0.56
29	0.1486 ± 0.0013	0.92	0.1493 ± 0.0006	0.42	0.1487 ± 0.0008	0.60
30	0.1497 ± 0.0004	0.29	0.1494 ± 0.0007	0.47	0.1490 ± 0.0010	0.67

Table 21 Effect of Disintegrants on Thickness of Furosenide Tablets

Formula Number	Wet granulation Tablet Hardness 4-6 Kp Average Thickness (mm. ± S.D.)	Wet granulation Tablet Hardness 8-11 Kp Average Thickness (mm ± S.D.)	Dry granulation Tablet Hardness 4-6 Kp Average Thickness (mm. ± S.D.)
15	4.06 ± 0.0529	3.94 ± 0.0591	3.47 ± 0.0308
16	4.07 ± 0.0308	4.00 ± 0.0353	3.57 ± 0.0308
17	4.09 ± 0.0100	4.01 ± 0.0158	3.71 ± 0.0781
18	4.11 ± 0.0100	4.00 ± 0.0141	3.73 ± 0.0380
19	4.14 ± 0.0100	4.01 ± 0.0212	3.79 ± 0.0158
20	4.09 ± 0.0070	4.04 ± 0.0514	3.80 ± 0.0173
21	4.08 ± 0.0223	4.04 ± 0.0552	3.86 ± 0.0173
28	4.18 ± 0.0173	4.05 ± 0.0458	3.73 ± 0.0731
29	4.82 ± 0.0648	4.74 ± 0.1000	4.51 ± 0.0300
30	4.22 ± 0.0254	4.08 ± 0.0353	3.66 ± 0.1382

Table 22 Effect of Disintegrants on Tablet Hardness of Furosemide Tablets

Formula Number	Wet granulation - Tablet Hardness 4-6 Kp		Wet granulation Tablet Hardness 8-11 Kp		Dry granulation Tablet Hardness 4-6 Kp	
	Hardness (Kp ± S.D.)	% C.V.	Hardness (Kp ± S.D.)	% C.V.	Hardness (Kp ± S.D.)	% C.V.
15	4.28 ± 0.2609	6.09	9.09 ± 0.6822	7.50	6.04 ± 0.1646	2.72
16	4.05 ± 0.0849	2.09	7.72 ± 0.2485	3.21	4.62 ± 0.4289	9.28
17	5.37 ± 0.3529	6.57	10.39 ± 0.4458	4.29	5.28 ± 0.5067	9.59
18	4.12 ± 0.1626	3.94	9.35 ± 0.8449	9.03	5.09 ± 0.5078	9.97
19	4.20 ± 0.2054	4.89	7.86 ± 0.1897	2.41	4.85 ± 0.3597	7.41
20	5.57 ± 0.4835	8.68	9.62 ± 0.9021	9.37	4.13 ± 0.1337	3.23
21	4.17 ± 0.1946	4.66	8.63 ± 0.7874	9.12	4.39 ± 0.2884	6.57
28	6.35 ± 0.3719	5.85	11.55 ± 0.4478	3.87	5.95 ± 0.2013	3.38
29	6.51 ± 0.2766	4.25	11.97 ± 0.2110	1.76	8.05 ± 0.2173	2.69
30	5.19 ± 0.1728	3.33	10.04 ± 0.2458	2.44	6.70 ± 0.2867	4.27

Table 23 Effect of Disintegrants on the Friability of Furosemide Tablets

Formula Number	Wet granulation Tablet Hardness 4-6 Kp Friability %	Wet granulation Tablet Hardness 8-11 Kp Friability %	Dry granulation Tablet Hardness 4-6 Kp Friability %
15	0.18	0.14	0.66
16	0.18	0.14	0.70
17	0.20	0.15	0.72
18	0.23	0.16	0.77
19	0.24	0.17	0.80
20	0.26	0.17	0.83
21	0.27	0.18	0.87
28	0.16	0.10	0.54
29	0.16	0.12	0.55
30	0.18	0.14	0.60

C.5 Disintegration Time of Tablets

The disintegration times of furosemide tablets containing different concentration of Ac-Di-Sol^{R} in 1:100 HCl in aqueous solution are shown in figure 32 and 33 . At the hardness of 4-6 kp, the disintegration times of tablets manufactured by wet granulation were ranked as the following : formula 15 (> 60 min) > formula 16 (0.40 ± 0.0340) ~ formula 17 (0.36 ± 0.0240) > formula 18 (0.20 ± 0.0240) = formula 19 (0.20 ± 0.0240) ~ formula 20 (0.19 ± 0.0240) ~ formula 21 (0.15 ± 0.0236). When the hardness of tablets was changed to 8-11 kp, the disintegration times of tablets were ranked as the following : formula 15 (> 60 min) > formula 16 (8.54 ± 0.5657) > formula 17 (2.27 ± 0.1038) > formula 18 (1.31 ± 0.0376) ~ formula 19 (1.26 ± 0.0878) ~ formula 20 (1.19 ± 0.0734) ~ formula 21 (1.12 ± 0.0440) . When the hardness of tablets was increased, the disintegration times of tablets were increased as shown in figure 32. The disintegration times of furosemide tablets manufactured by dry granulation were less than those obtain from tablets manufactured by wet granulation, the disintegration times were ranked as the following : formula 15 (2.14 ± 0.0813) > formula 16 (0.10 ± 0.0126) > formula 17 (0.05 ± 0.0077) ~ formula 18 (0.04 ± 0.0063) = formula 19 (0.04 ± 0.0077) = formula 20 (0.04 ± 0.0063) ~ formula 21 (0.03 ± 0.0109).

It was noted that Ac-Di-Sol^{R} was shown to be very effective as a tablet disintegrant in furosemide tablets at level as low as 0.5 to 1.0 %. When the concentration increased from 2.0 % to 5.0 % the disintegration times were non-significantly decreased.

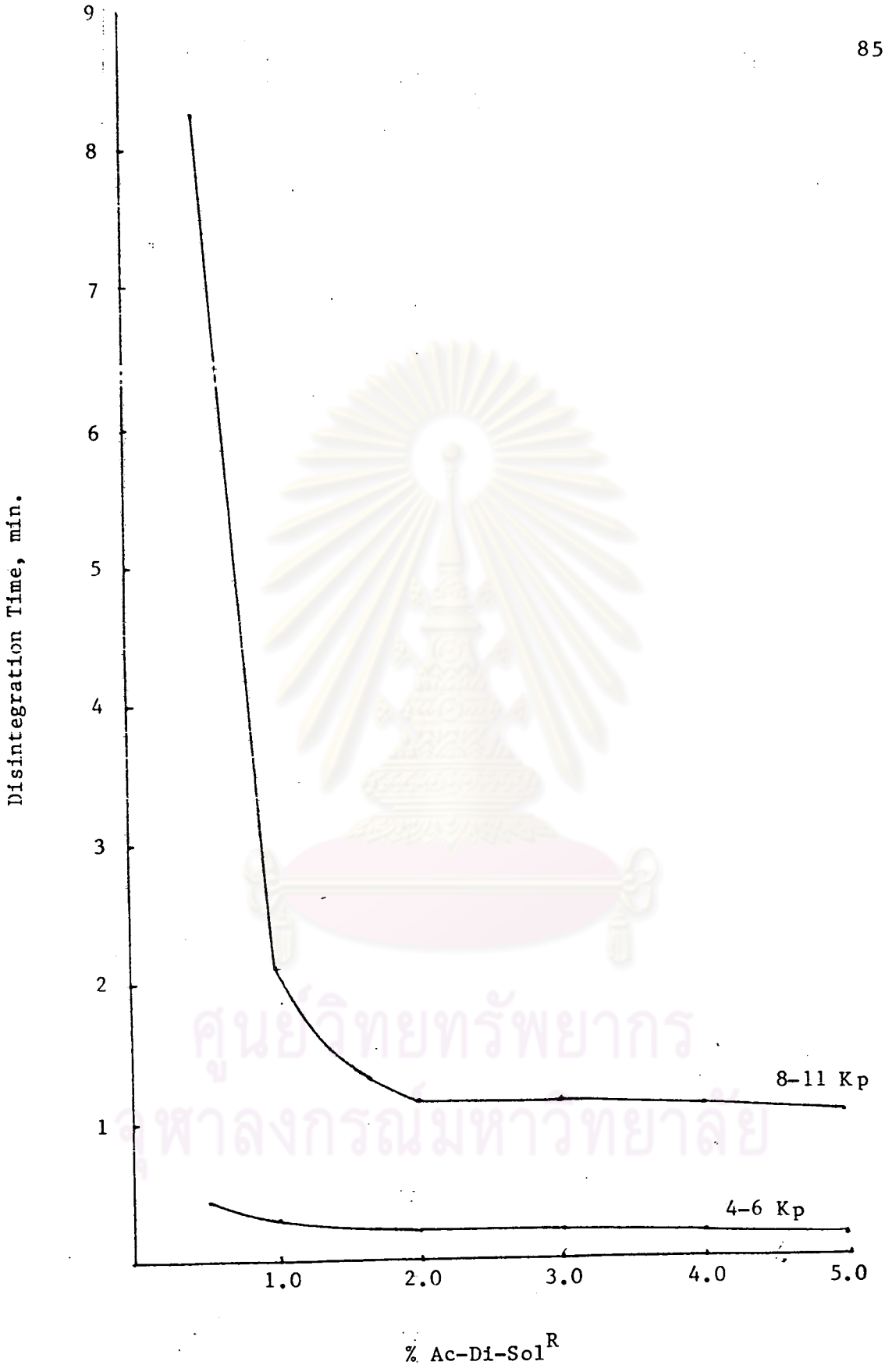

Figure 32 Effect of extent of disintegrant on disintegration time of furosemide tablets made by wet granulation

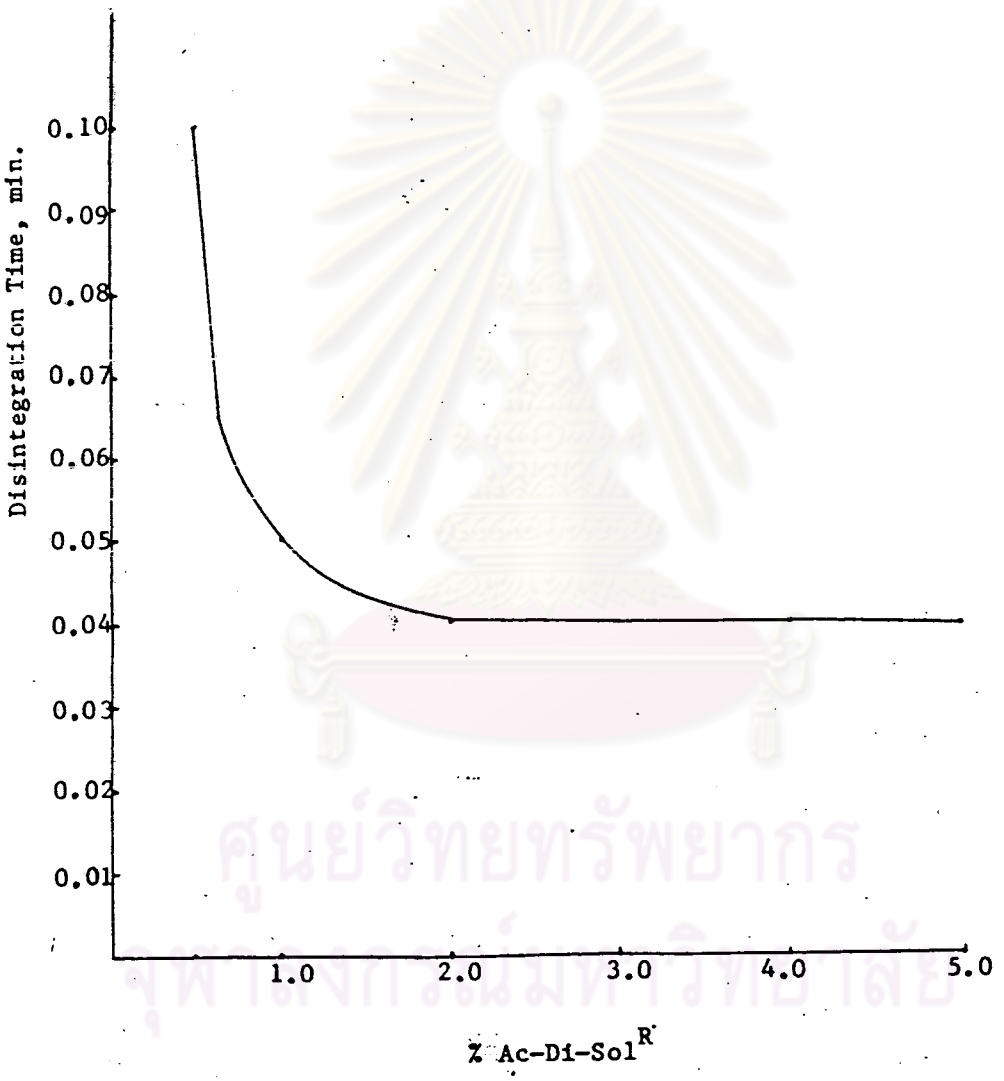

Figure 33 Effect of extent of disintegrant on disintegration time of furosemide tablets made by dry granulation, hardness 4-6 kp.

Table 24 shows the effects of four disintegrants : Ac-Di-Sol^{R}, Avicel^{R} PH 101, Polyplasdone^{R} XL, and Explotab^{R} on disintegration time of tablets. With the hardness of 4-6 kp, the comparison of tablets containing the same diluents but different disintegrants, of 1 % concentration, the disintegration times of tablets were ranked as the following : formula 28 (Avicel^{R} PH 101) > formula 30 (1% Explotab^{R}) ~ formula 29 (1 % Polyplasdone^{R} XL) > formula 17, (1 % Ac-Di-Sol^{R}) both in wet granulation and dry granulation. When the hardness of tablets was increased to 8-11 kp, the disintegration times of tablets were increased as demostrated in table 24.

C.6 Dissolution Rates of Tablets

C.6.1 Effect of Disintegrant on Dissolution Rates

The dissolution profiles of furosemide tablets are shown in figure 34, 35 and 36. The tablets containing Ac-Di-Sol^{R} as tablet disintegrant showed higher dissolution rates than the tablets containing no disintegrant in both wet and dry granulation. Ac-Di-Sol^{R} also increased the dissolution rates of furosemide tablets both in high tablet hardness (8-11 kg) and low tablet hardness (4-6 kg).

The dissolution rates of tablets in this study, expressed as the time required for 65 % of furosemide to dissolve[64], were demonstrated in figure 37.

C.6.2 Effect of Different Disintegrants on Dissolution Rates

The effect of four tablet disintegrants : Ac-Di-Sol^{R}, Avicel^{R} PH 101, Polyplasdone^{R} XL, and Explotab^{R} on dissolution rates of furosemide tablets had been studied. The dissolution profiles of furosemide tablets, containing 1 % of different disintegrants were

Table 24 Effect of Different Disintegrants on Disintegration Time of Furosemide Tablets

Formula No.	Disintegration Time, min ± S.D.		
	Wet granulation Tablet Hardness 4-6 kp	Wet granulation Tablet Hardness 8-11 kp	Dry granulation Tablet Hardness 4-6 kp
# 15 (No disintegrant)	> 60	> 60	2.14 ± 0.0813
# 17 (1% Ac-Di-Sol®)	0.36 ± 0.0240	2.27 ± 0.1038	0.05 ± 0.0077
# 28 (1% Avicel® PH 101)	> 60	> 60	25.05 ± 0.5039
# 29 (1% Polyplasdone® XL)	0.39 ± 0.0334	7.46 ± 0.1540	0.22 ± 0.0394
# 30 (1% Explotab®)	0.40 ± 0.0387	10.33 ± 0.5164	0.24 ± 0.0272

shown in figure 38, 39 and 40. Table 25 shows the dissolution times of tablet containing 1 % Ac-Di-Sol^{R} (formula 17), 1 % Avicel^{R} PH 101 (formula 28), 1 % Polyplasdone^{R} XL (formula 29), and 1 % Explotab (formula 30) as tablet disintegrants. It can be seen that tablets containing Ac-Di-Sol^{R} were superior than those containing other disintegrants whether manufactured by wet or dry granulation methods with 4-6 or 8-11 kp of hardness. The dissolution times ($t_{65\%}$) of tablets manufactured by wet granulation and hardness 4-6 kp were ranked as the following : formula 29 (17.45 ± 2.1000) > formuls 30 (11.10 ± 1.2727) > formula 29 (9.45 ± 1.4142) > formula 17 (8.45 ± 1.5556). When the hardness was changed to 8-11 kp, the dissolution times (t 65 %) were ranked as the following : formula 28 (> 60 min) > formula 30 (24.25 ± 2.4748) > formula 29 (22.25 ± 1.7677) > formula 17 (16.45 ± 2.8284).

By dry granulation, the dissolution rates of tablets containing various disintegrants were less than those obtained from tablets manufactured by wet granulation as shown in figure 38 and 40. Their dissolution times (t 65 %) were ranked as the following : formula 28 (>60 min) > formula 30 (47.45 ± 4.2426) > formula 29 (45.25 ± 1.7677) > formula 17 (43.20 ± 3.9597).

Both in wet granulation and dry granulation, and high or low tablet hardness, Ac-Di-Sol^{R} was considered satisfactory and found to be the best among four tablet disintegrants for dissolution study of furosemide tablets.

C.6.3 Effect of Tablet Hardness on Dissolution Rates

The effect of two different ranges of tablet hardness: 4-6 kp and 8-11 kp on dissolution rates of tablets were shown in figure 41 and 42. The hardness of tablet did not significantly affect

Table 25 Effect of Different Disintegrants on Dissolution Time (t65%) of Furosemide Tablets

Formula Number	Dissolution Time (t 65%), min ± S.D.		
	Wet granulation Tablet Hardness 4-6 kp	Wet granulation Tablet Hardness 8-11 kp	Dry granulation Tablet Hardness 4-6 kp
# 15 (No Disintegrant)	20.10 ± 2.6870	> 60	> 60
# 17 (1% Ac-Di-Sol^{R})	8.45 ± 1.5556	16.45 ± 2.8284	43.20 ± 3.9597
# 28 (1% Avicel^{R} PH 101)	17.45 ± 2.1000	> 60	> 60
# 29 (1% Polyplasdone^{R} XL)	9.45 ± 1.4142	22.25 ± 1.7677	45.25 ± 1.7677
# 30 (1% Explotab^{R})	11.10 ± 1.2727	24.25 ± 2.4748	47.45 ± 4.2426

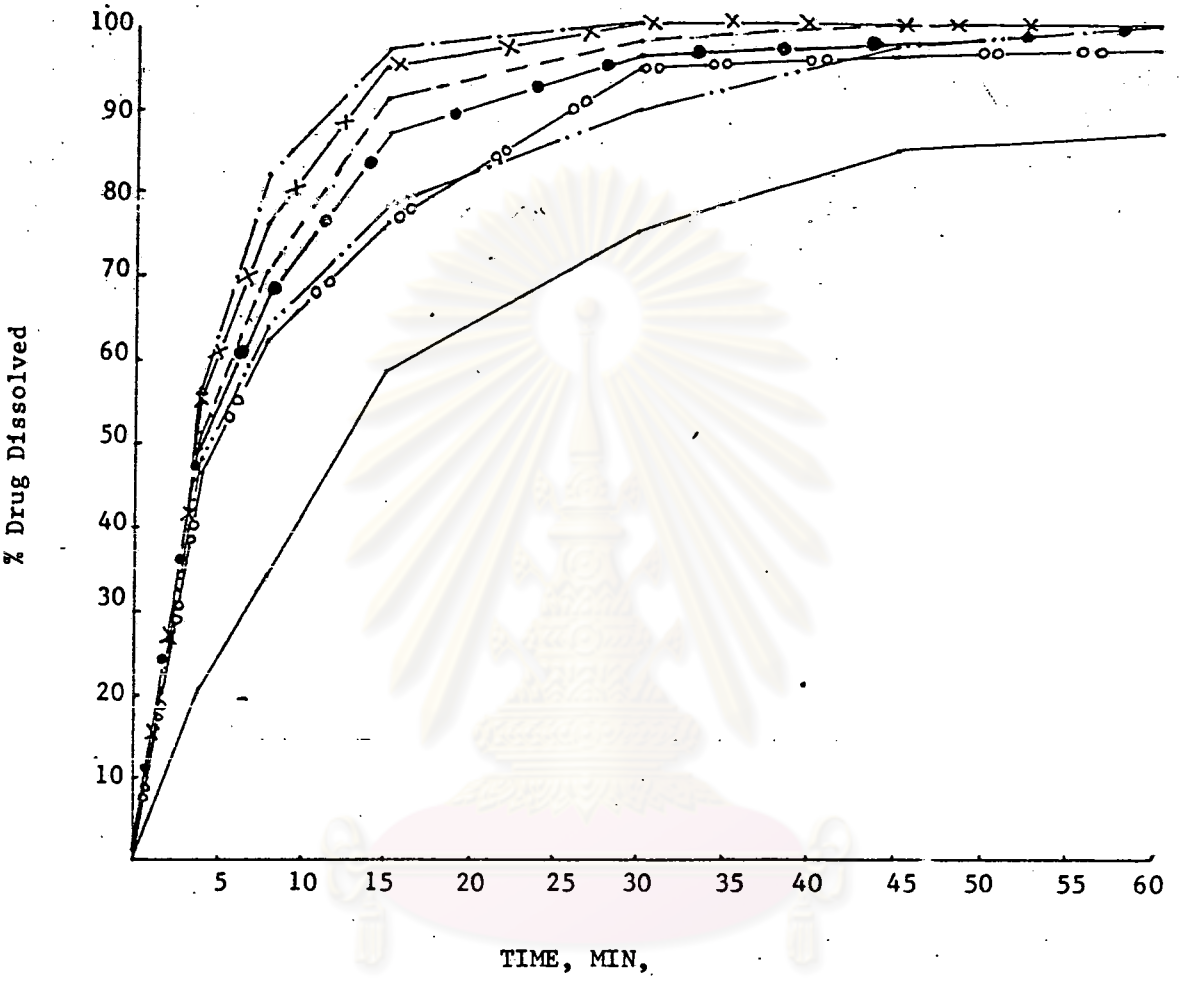

Figure 34 Dissolution profiles of furosemide tablets, formula 15-21, hardness 4-6 Kp. (Wet granulation)

Key :

formula 15 (No Disintegrant)

formula 16 (0.5 % Ac-Di-Sol^{R})

formula 17 (1.0 % Ac-Di-Sol^{R})

formula 18 (2.0 % Ac-Di-Sol^{R})

formula 19 (3.0 % Ac-Di-Sol^{R})

formula 20 (4.0 % Ac-Di-Sol^{R})

formula 21 (5.0 % Ac-Di-Sol^{R})

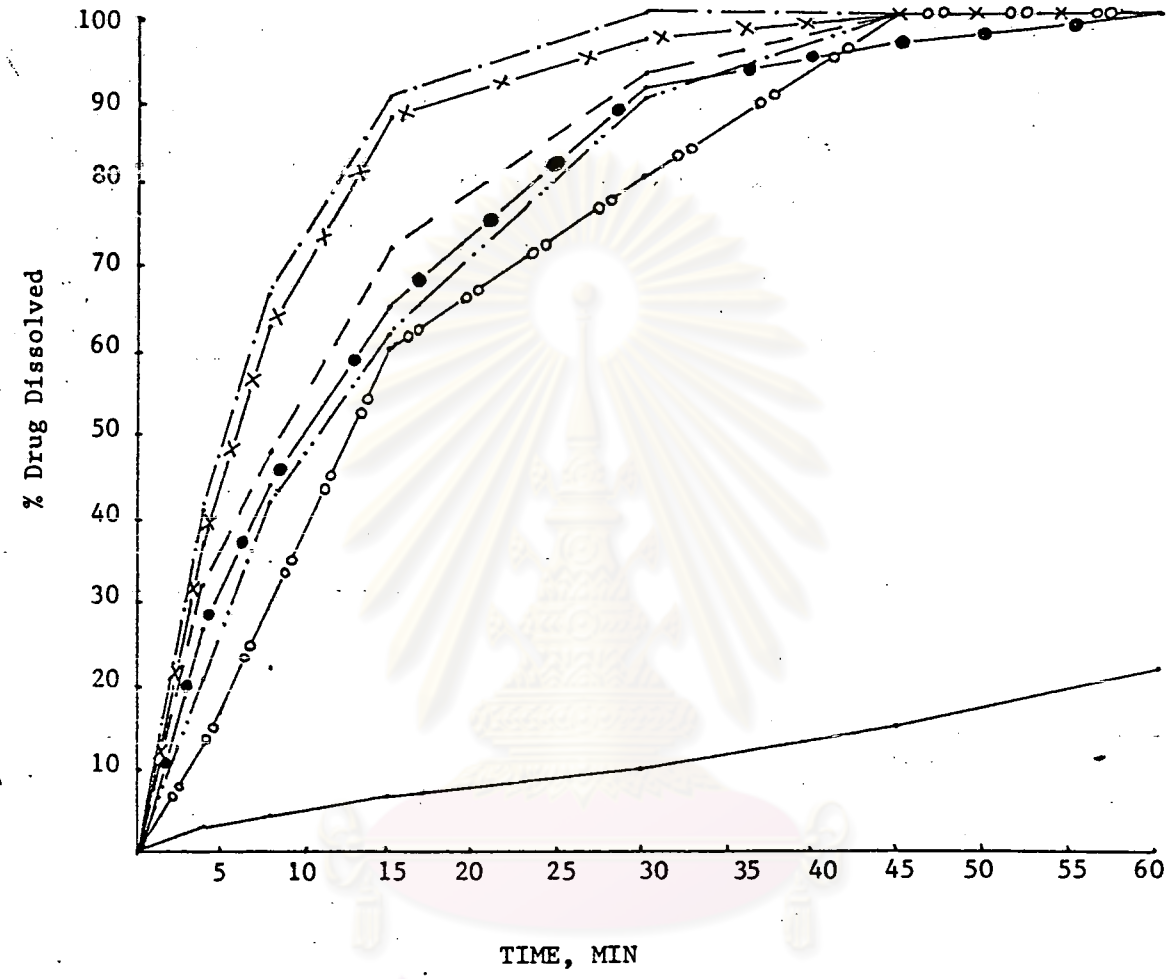

Figure 35 Dissolution profiles of furosemide tablets, formula 15-21, hardness 8-11 Kp (Wet granulation)

Key :

formula 15 (No Disintegrant)

formula 16 (0.5 % Ac-Di-Sol^{R})

formula 17 (1.0 % Ac-Di-Sol^{R})

formula 18 (2.0 % Ac-Di-Sol^{R})

formula 19 (3.0 % Ac-Di-Sol^{R})

formula 20 (4.0 % Ac-Di-Sol^{R})

formula 21 (5.0 % Ac-Di-Sol^{R})

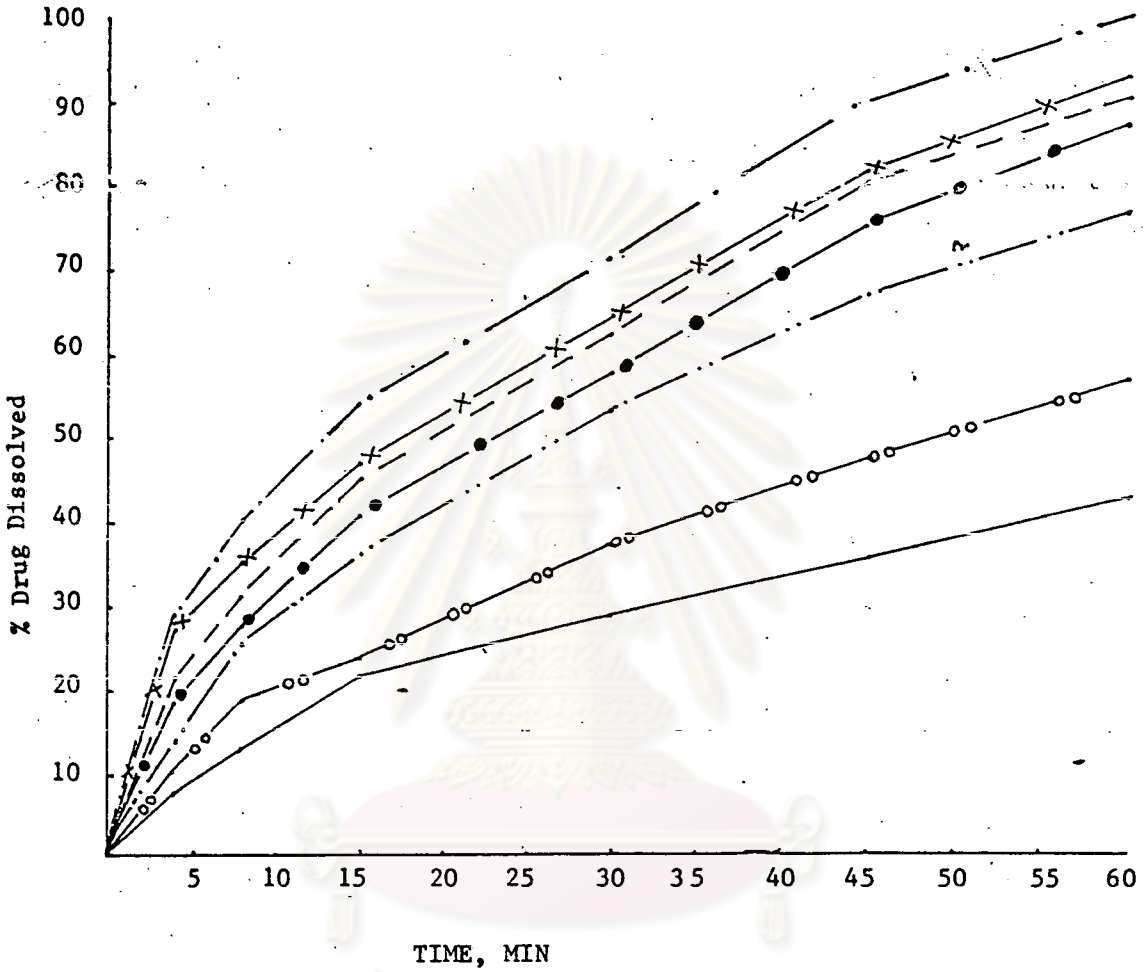

Figure 36 Dissolution profiles of furosemide tablets, formula 15-21, hardness 4-6 Kp (Dry granulation)

Key :

formula 15 (No Disintegrant)

formula 16 (0.5 % Ac-Di-Sol^{R})

formula 17 (1.0 % Ac-Di-Sol^{R})

formula 18 (2.0 % Ac-Di-Sol^{R})

formula 19 (3.0 % Ac-Di-Sol^{R})

formula 20 (4.0 % Ac-Di-Sol^{R})

formula 21 (5.0 % Ac-Di-Sol^{R})

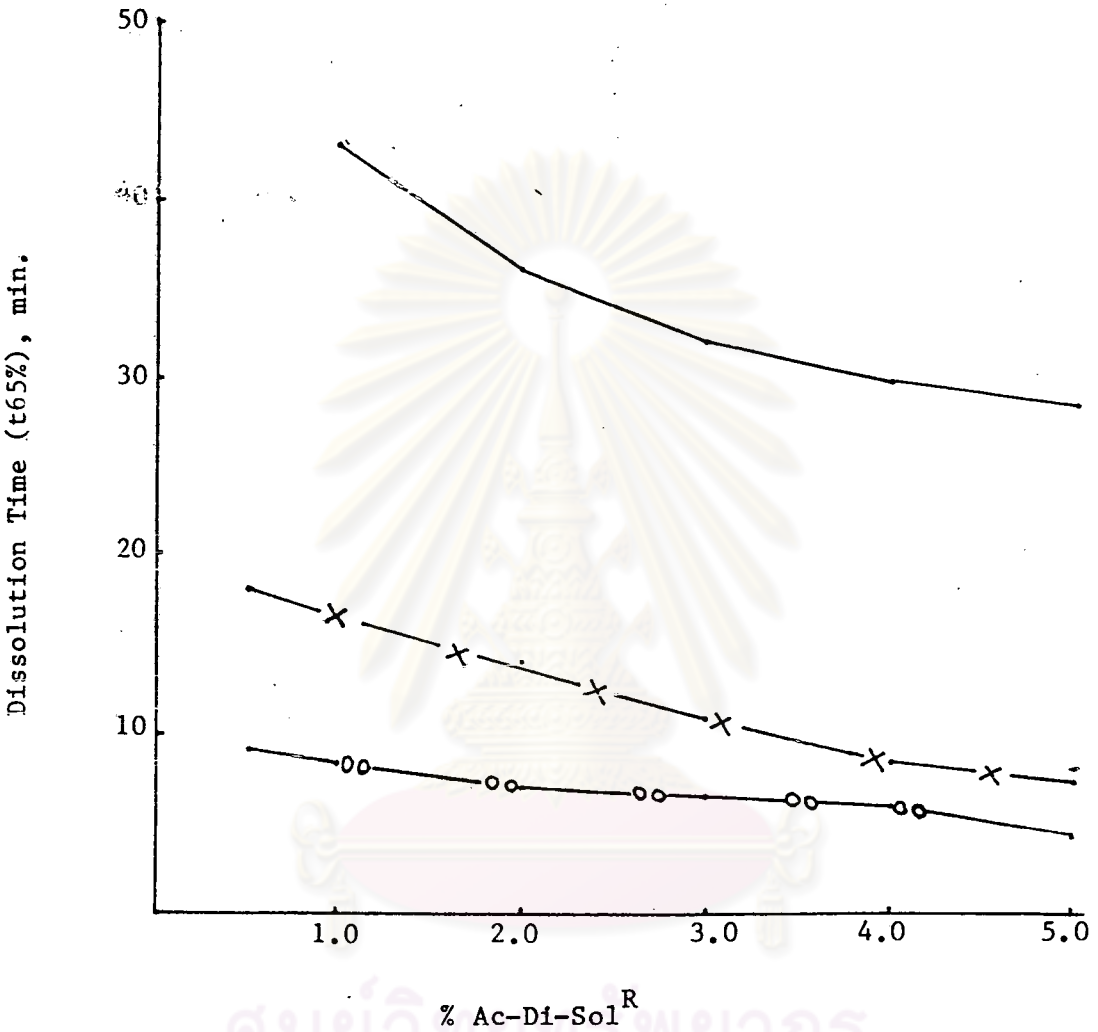

Figure 37 Relationship between extent of disintegrant and dissolution time (t 65%) of furosemide tablets.

Key :

——— Dry granulation, hardness 4-6 Kp

—x—x— Wet granulation, hardness 8-11 Kp

—oo—oo— Wet granulation, hardness 4-6 Kp

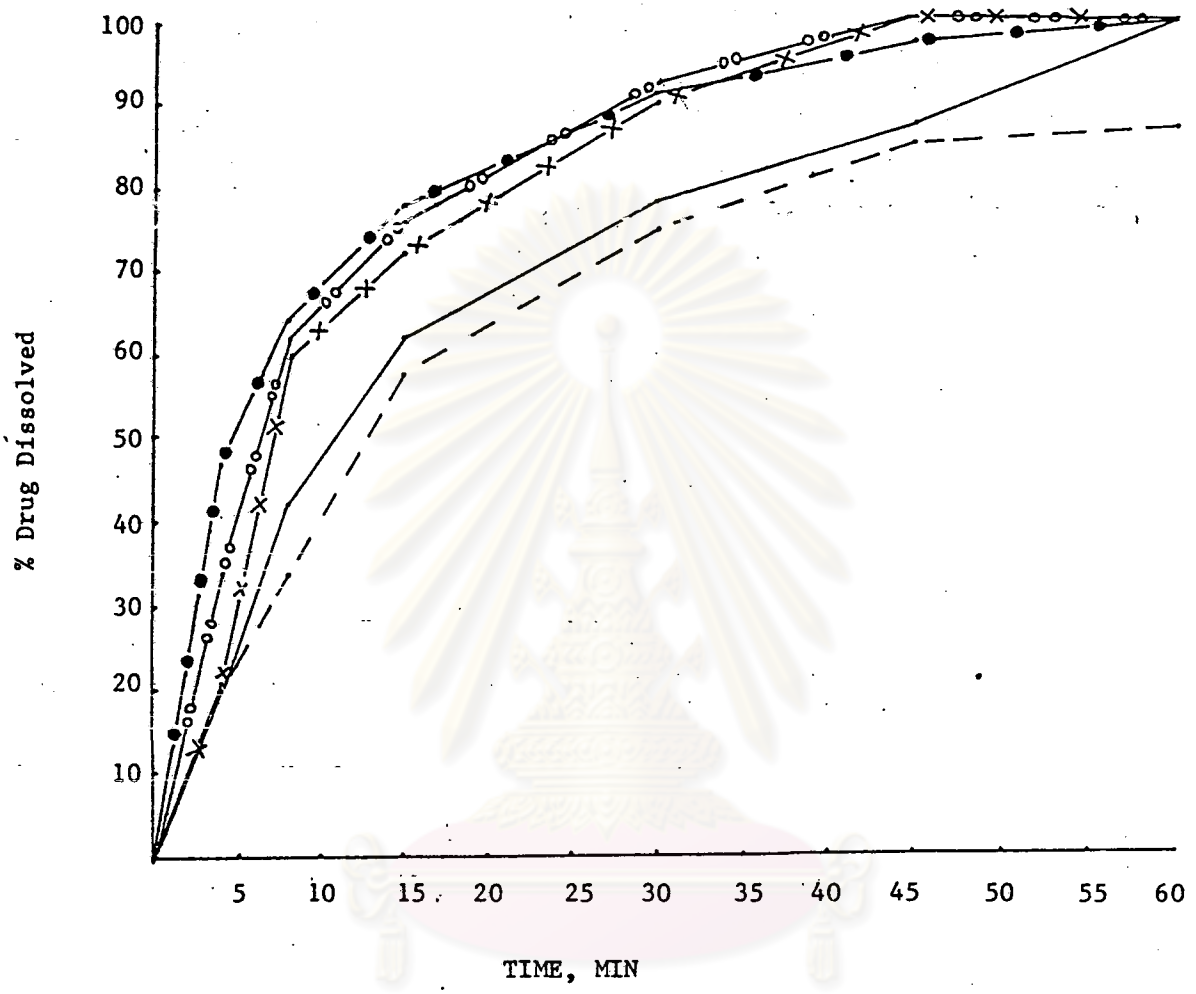

Figure 38 Effect of different disintegrants on dissolution of furosemide from tablets made by wet granulation, hardness 4-6 kp.

Key :

- formula 15 (No Disintegrant)
- formula 28 (1 % Avicel^{R} PH 101)
- formula 29 (1 % Polyplasdone^{R} XL)
- formula 30 (1 % Explotab^{R})
- formula 17 (1 % Ac-Di-Sol^{R})

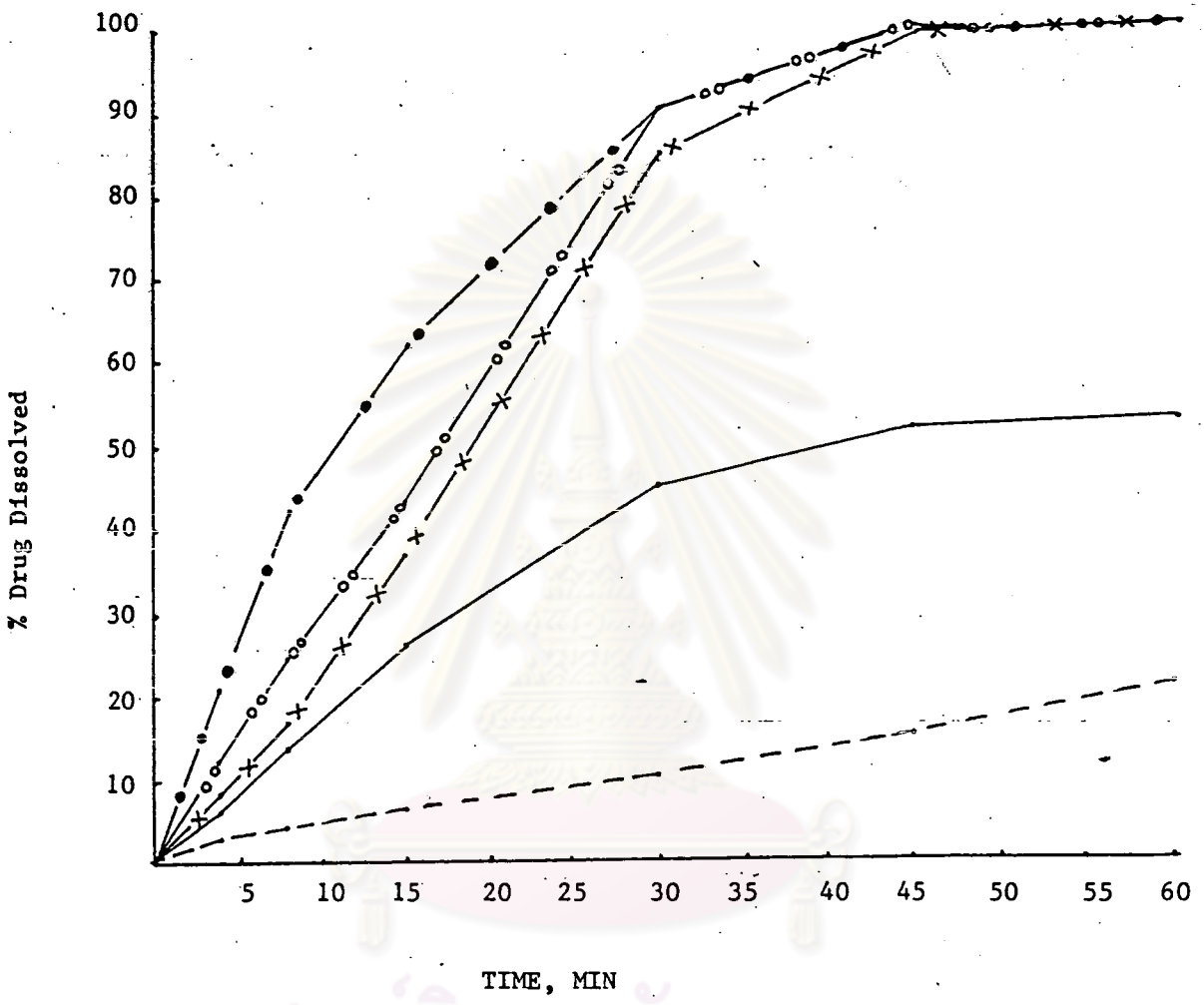

Figure 39 Effect of different disintegrants on dissolution of furosemide from tablets made by wet granulation, hardness 8-11 kp.

Key :

- – – – – formula 15 (No Disintegrant)
- ——— formula 28 (1 % Avicel^{R} PH 101)
- —oo—oo— formula 29 (1 % Polyplasdone^{R} XL)
- —x—x— formula 30 (1 % Explotab^{R})
- —●—●— formula 17 (1 % Ac-Di-Sol^{R})

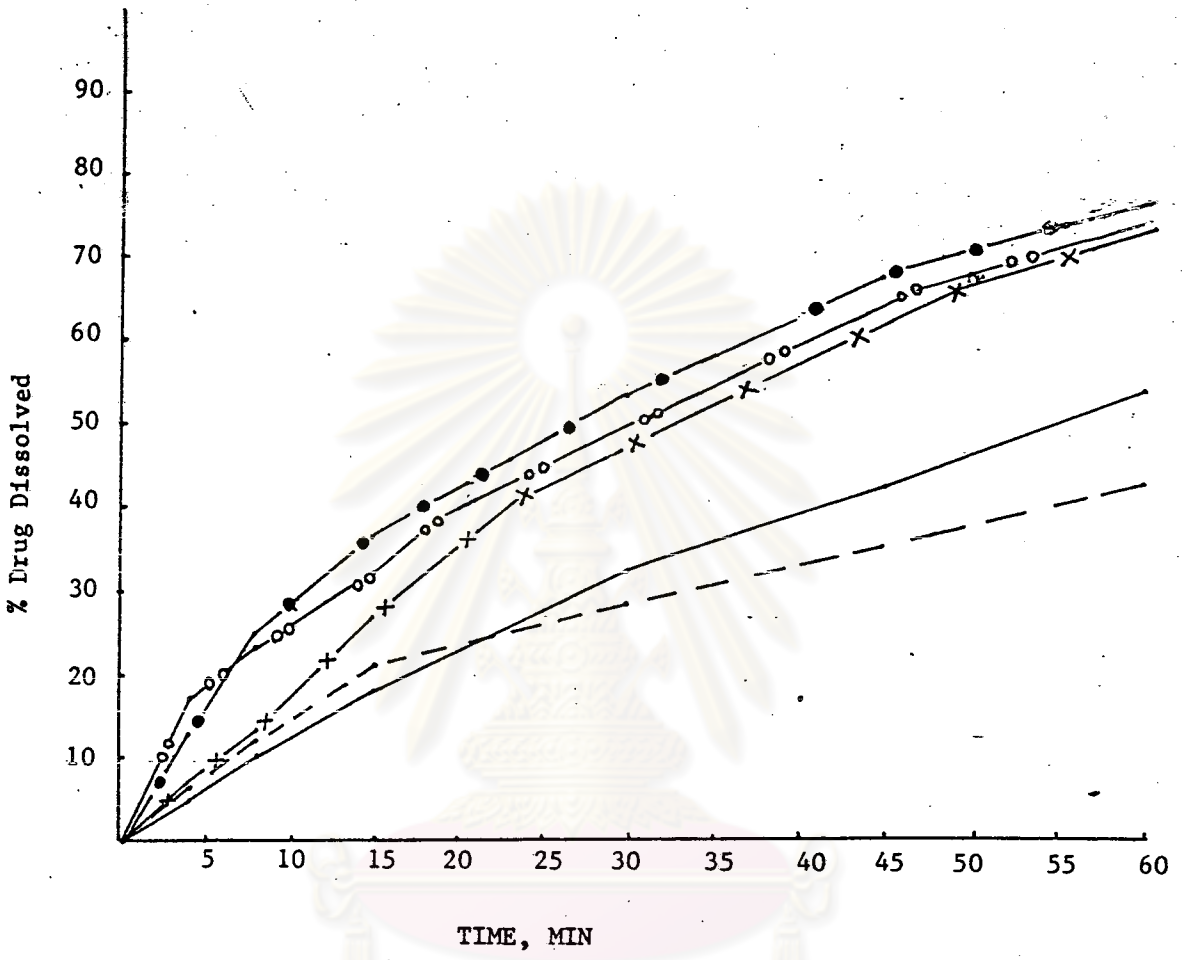

Figure 40 Effect of different disintegrants on dissolution of furosemide from tablets made by dry granulation, hardness 4-6 kp.

Key :

- – – – formula 15 (No Disintegrant)
- ——— formula 28 (1 % Avicel^{R} PH 101)
- —oo—oo— formula 29 (1 % Polyplasdone^{R} XL)
- —x—x— formula 30 (1 % Explotab^{R})
- —●—●— formula 17 (1 % Ac-Di-Sol^{R})

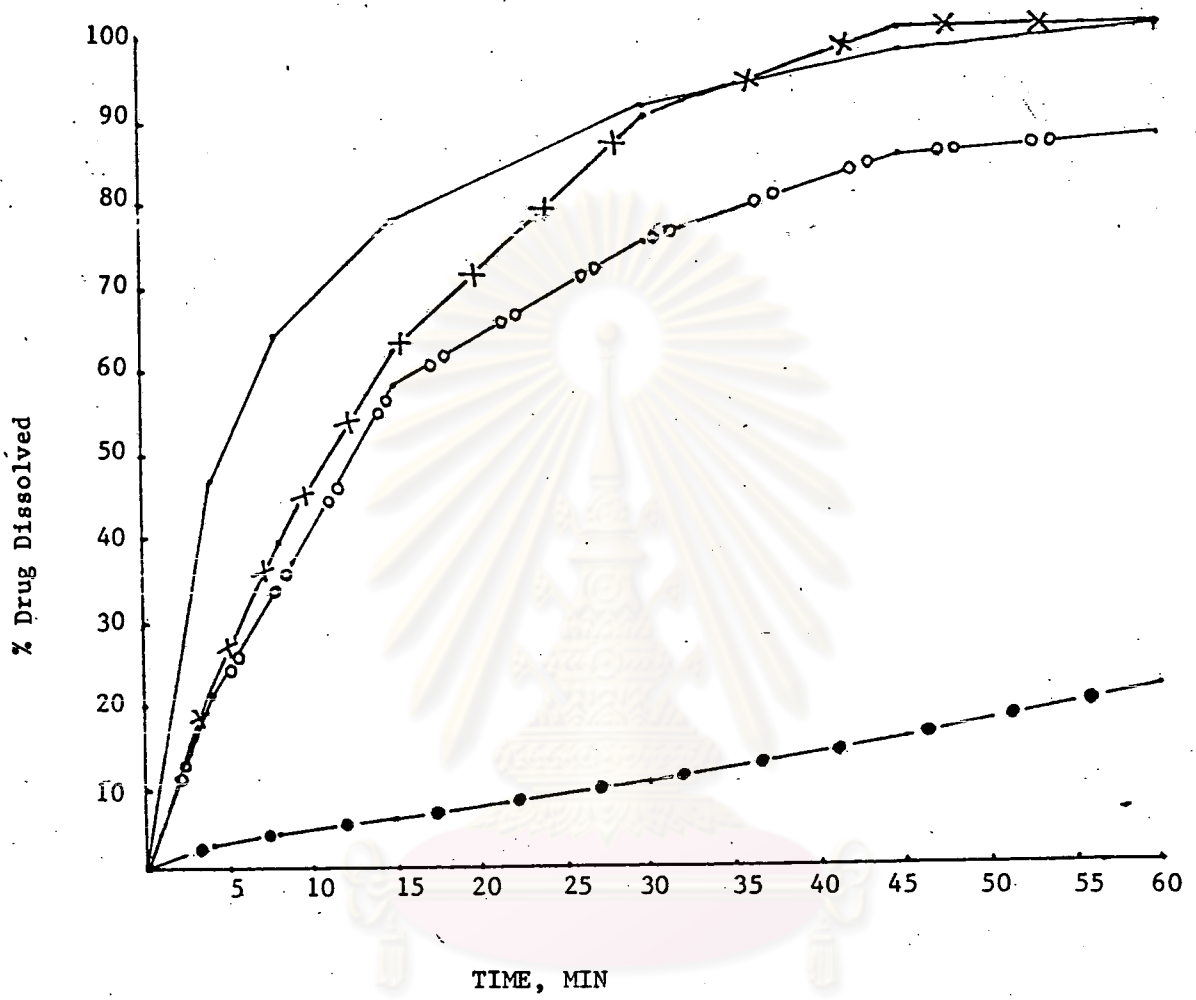

Figure 41 Effect of tablet hardnesses on dissolution of furosemide tablets(Wet granulation)

Key :

—oo—oo— formula 15 (No Disintegrant, hardness 4–6 Kp)

—●—●— formula 15 (No Disintegrant, hardness 8–11 Kp)

——————— formula 17 (1 % Ac-Di-Sol^{R}, hardness 4–6 Kp)

—x—x— formula 17 (1 % Ac-Di-Sol^{R}, hardness 8–11 Kp)

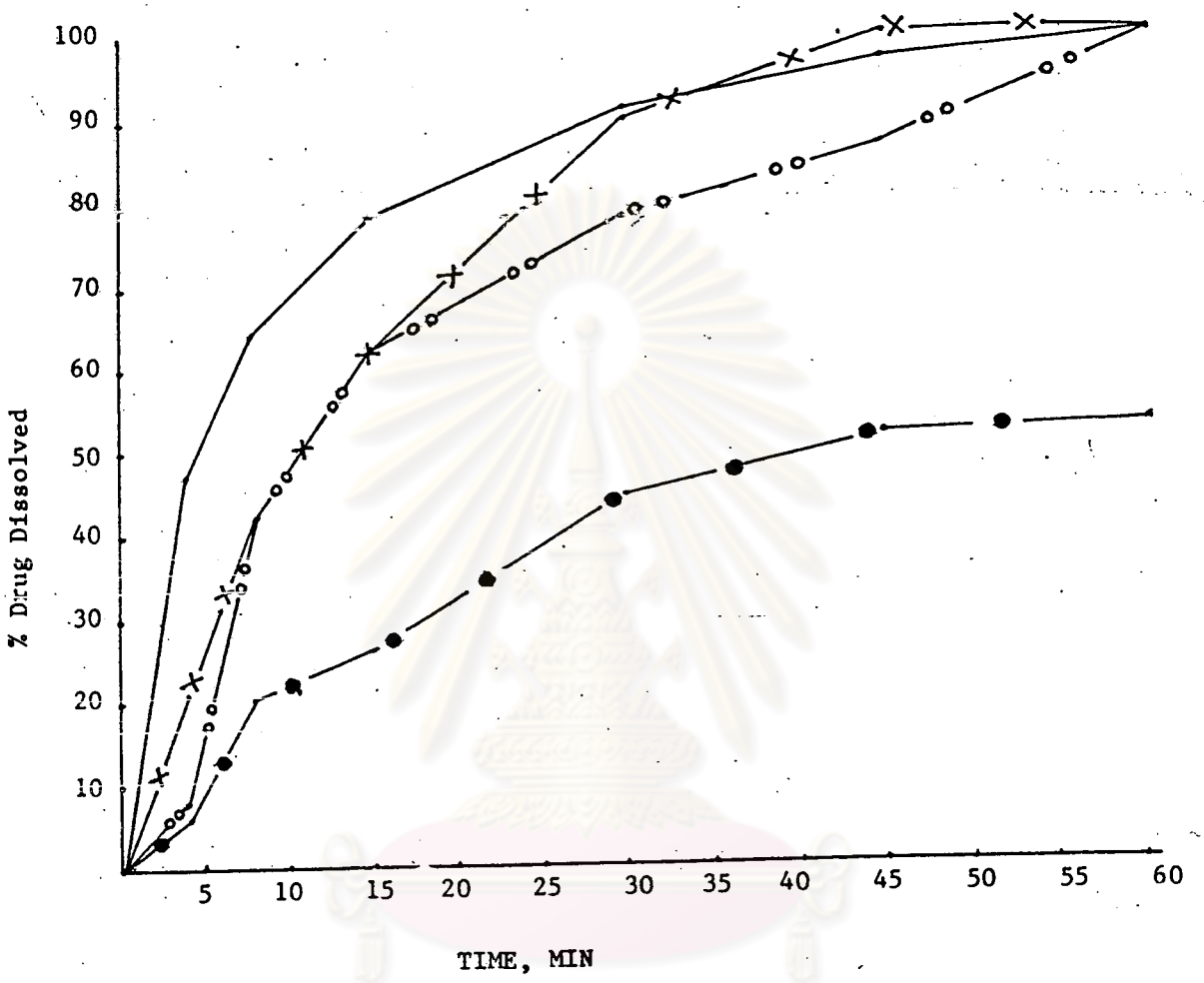

Figure 42 Effect of tablet hardnesses on dissolution of furosemide tablets(Wet granulation)

Key :

———— formula 17 (1 % Ac-Di-Sol^{R}, hardness 4-6 Kp)

—X—X— formula 17 (1 % Ac-Di-Sol^{R}, hardness 8-11 Kp)

—oo—oo— formula 28 (1 % Avicel^{R}, hardness 4-6 Kp)

—●—●— formula 28 (1 % Avicel^{R}, hardness 8-11 Kp)

the dissolution rate of furosemide tablets containing Ac-Di-Sol^{R} as tablet disintegrant, ($t_{2,0.05}$ = 4.303, $\pm$ $t_{observed}$ = 3.506). On the other hand, increasing the hardness of tablet containing no disintegrant or Avicel^{R} PH 101 as tablet disintegrant decreased the dissolution rate as shown in figure 41 and 42.

C.6.4 Effect of Processing on Dissolution Rates

The effect of two different processing of tablet manufacturing : wet granulation and dry granulation on dissolution rates of furosemide tablets have been studied. The dissolution profiles of the effect of processing on dissolution rate of tablets were shown in figure 43. The tablets manufactured by wet granulation had better dissolution profiles than the tablets manufactured by dry granulation. The dissolution times ($t_{65\ \%}$) were significantly different ($t_{2,0.05}$=4.303, $\pm$ $t_{observed}$ = 11.5517)

C.6.5 Effect of The Methods of Incorporating Disintegrant on Dissolution Rates

The effect of three different methods of incorporating disintegrant into granules : intragranular, extragranular, and 50 % intragranular plus 50 % extragranular on dissolution rates have been studied. The dissolution profiles of furosemide tablets manufactured by different methods of incorporating disintegrant into granules were shown in figure 44. The dissolution times(t 65%) of furosemide tablets manufactured by three different methods of incorporating disintegrant into granules were not significantly different ($F_{2,3,0.05}$ = 9.55, F_{ratio} = 5.43).

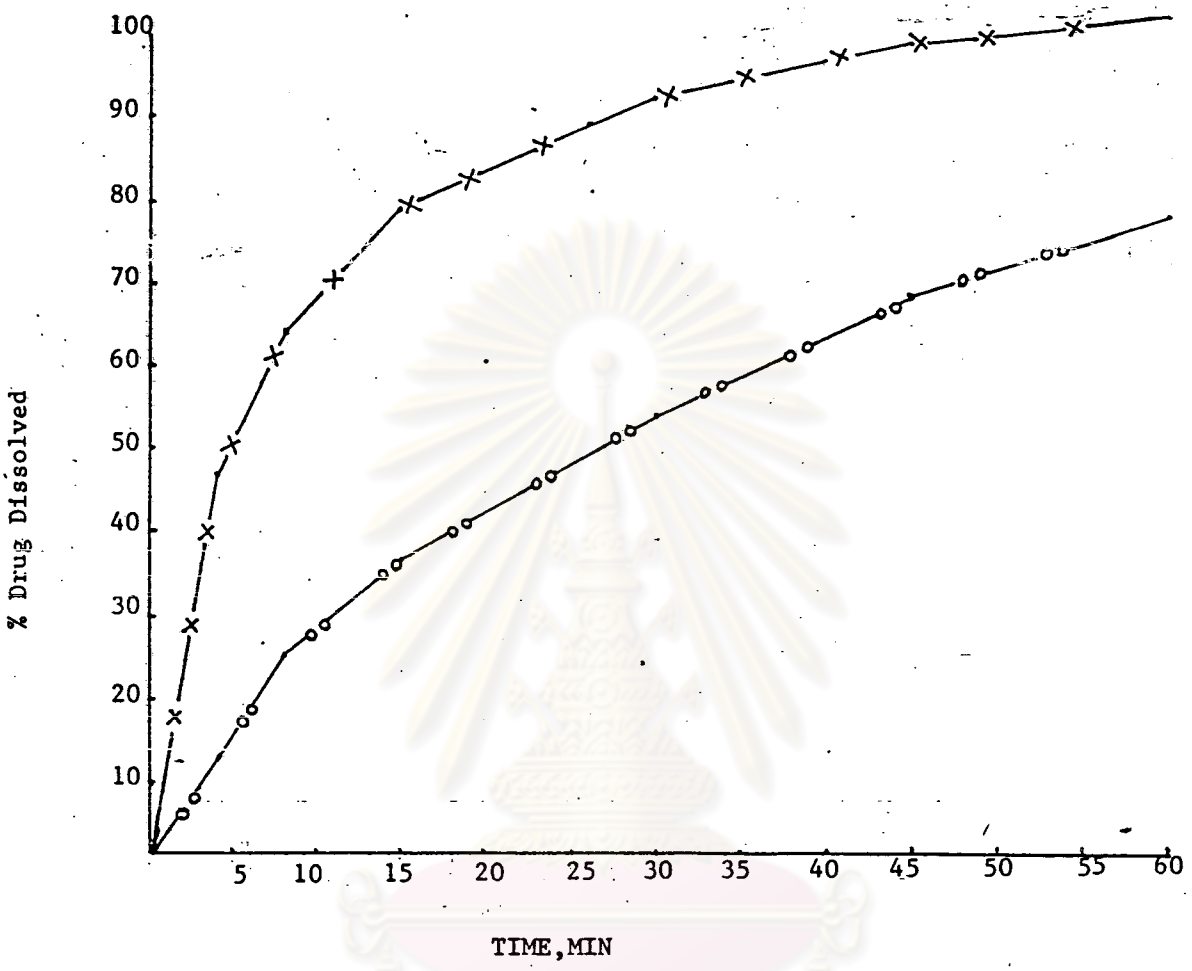

Figure 43 Effect of processing on dissolution of furosemide tablets, hardness 4-6 Kp.

Key :

—X—X— formula 17 (Wet granulation)

—o—o— formula 17 (Dry granulation)

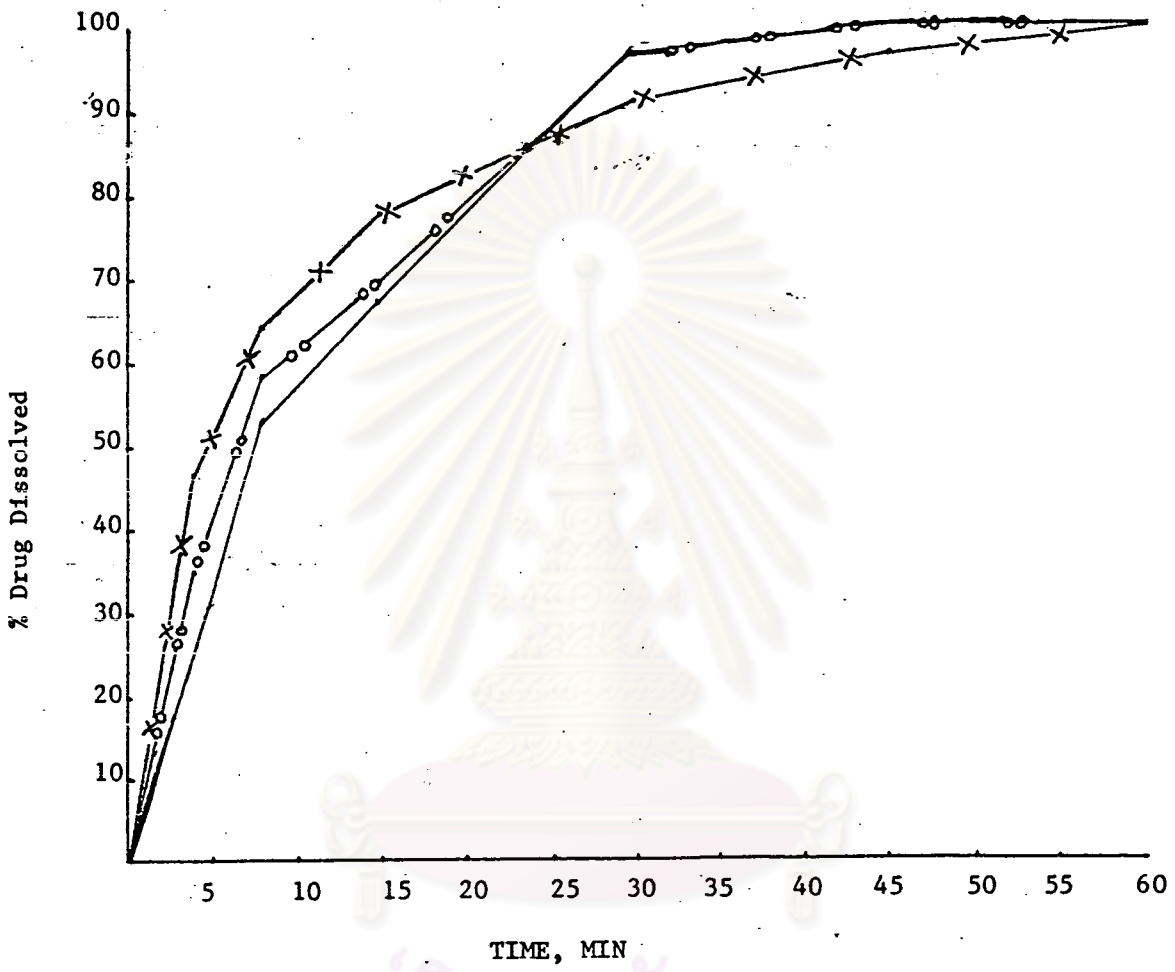

Figure 44 Effect of the methods of incorporating disintegrant into granules on dissolution of furosemide from tablets made by wet granulation, hardness 4-6 K_p.

Key :

——————— formula 17 (Intragranular)

—o—o— formula 17 (Extragranular)

—x—x— formula 17 (50:50 Intragranular : Extragranular)