Chapter III

Results

I. Effect of Processing Variables of Spray Drying Technique

The powders were prepared using spray drying apparatus. The processing variables that were varied including inlet air temperatures, feed rates, atomizing air pressures and concentrations of solution.

1. Physical Properties of Spray Dried Powders Prepared by Different Spray Drying Conditions

1.1 Morphology of Spray Dried Powders

Figure 1 showed the scanning electron photomicrographs of theophylline drug powder at different magnifications. Theophylline crystals had various sizes. Each large crystal consisted of small rods.

The shape and surface topography of spray dried particles prepared at different inlet temperatures were shown in Figure 2-5. The products obtained were microspheres. The surface of microspheres was covered with microcrystals that made rough surface but some of them had rather smooth surface.

The powder produced at inlet air temperatures of 120° and 130° C (Figure 2,3) gave larger microspheres than those produced at 150° and 170° C (Figure 4,5). Higher number of agglomerates were formed when inlet air temperatures of 150° and 170° C were employed. The agglomerated particles of co-spray dried powder prepared at 150°C were more regular shape than those produced at 170° C and covered with microcrystals, while agglomerates of powder produced at 170°C were embedded with microcrystals. The product prepared at 170°C formed looser agglomerates than that prepared at 150°C.

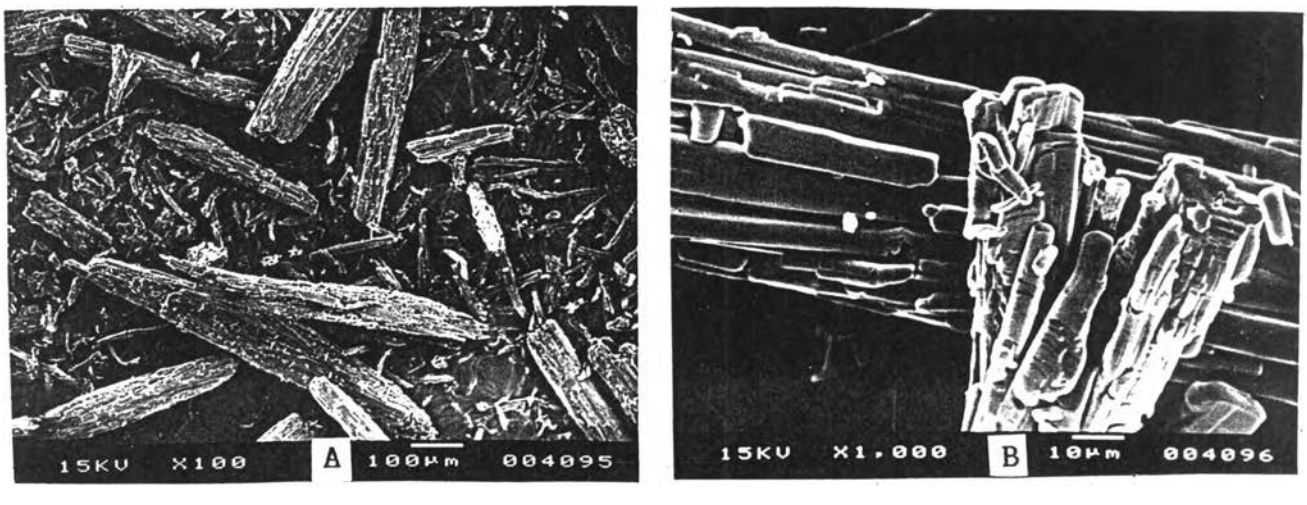


Figure 1 Photomicrographs of Original Theophylline Powders (A X 100, B X 1,000)

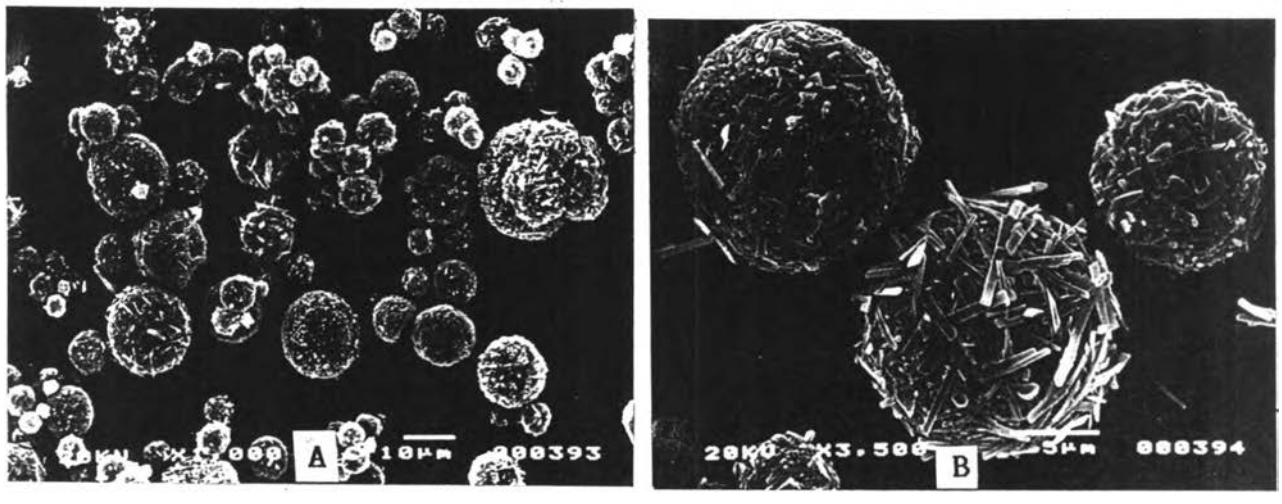


Figure 2 Photomicrographs of Spray Dried Particles Prepared at 120 °C Inlet Air Temperature (Key : A x 1,000 , B x 3,500)

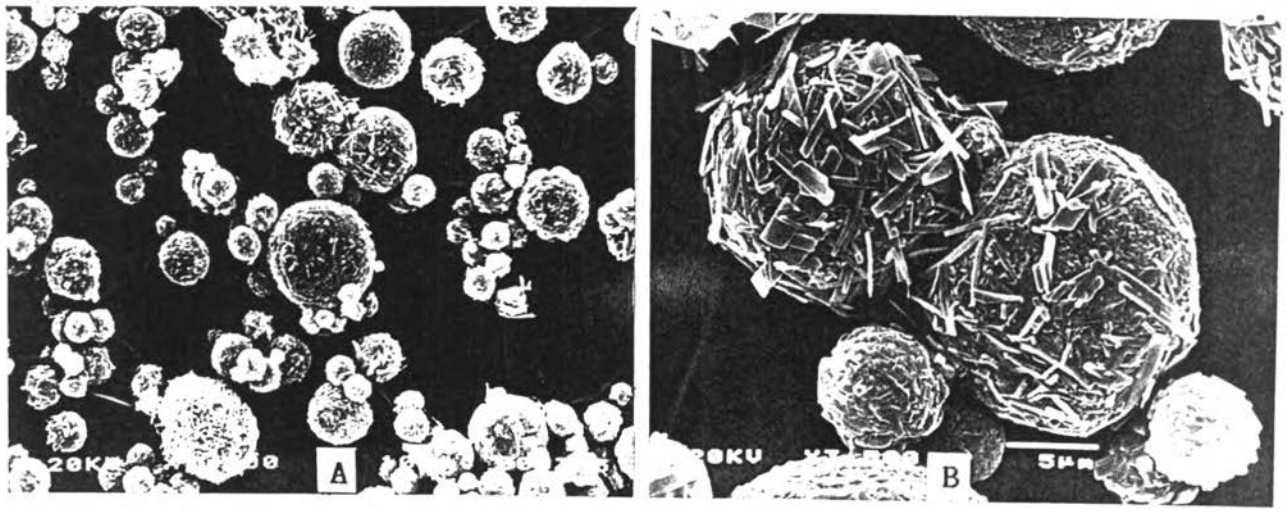


Figure 3 Photomicrographs of Spray Dried Particles Prepared at 130 °C Inlet Air Temperature (Key : A x 1,000 , B x 3,500)

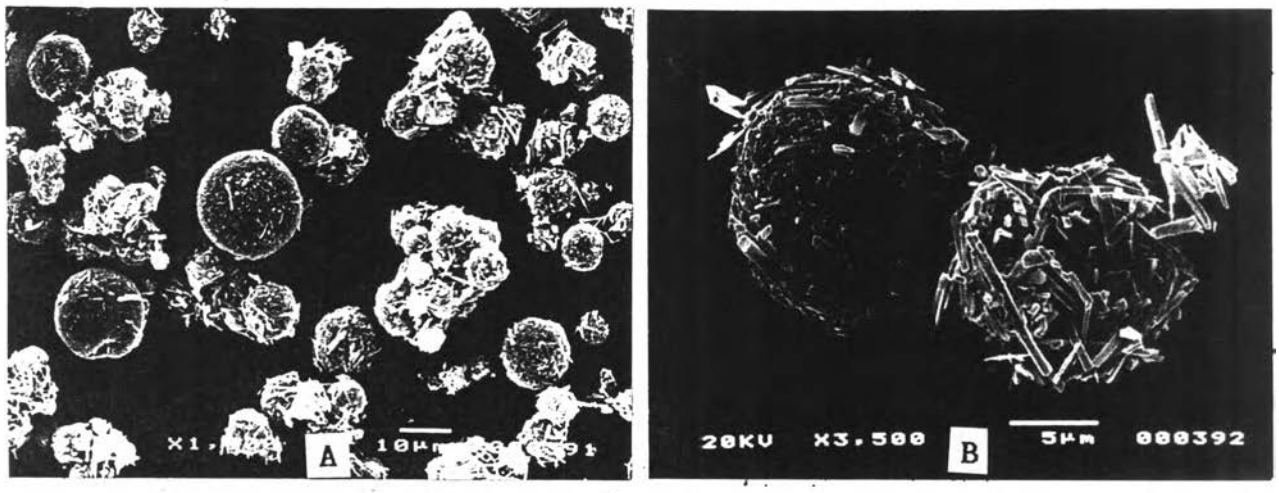


Figure 4 Photomicrographs of Spray Dried Particles Prepared at 150 °C Inlet Air Temperature (Key : A x 1,000 , B x 3,500)

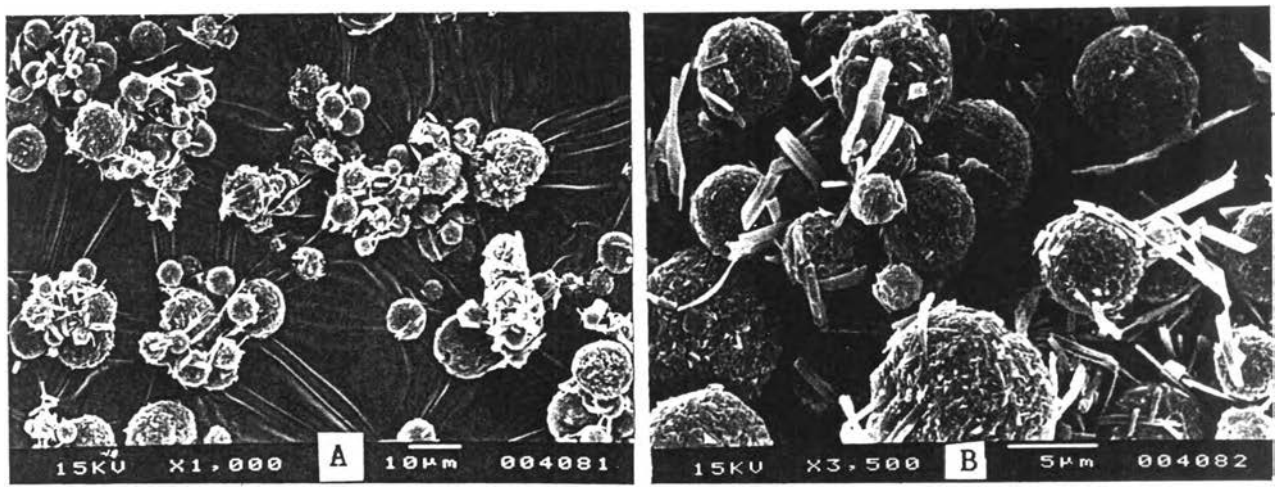


Figure 5 Photomicrographs of Spray Dried Particles Prepared at 170 °C Inlet Air Temperature (Key : A x 1,000 , B x 3,500)

The photomicrographs of spray dried powders produced at different feed rates were shown in Figure 6-9. At feed rate of 18 ml/min , most microspheres had rather smooth surface and the surface of a few powder was covered with microcrystals (Figure 6). At feed rate of 24 and 27 ml/min , the surface of microspheres was covered with microcrystals (Figure 7 and 8). Some of them had rather smooth surface. At the fastest rate, 30 ml/min, microspheres were embedded with microcrystal thus producing more rough surface.

The microscopic images of spray dried particles prepared at various atomization pressures were shown in Figure 10-13. It was found that higher atomizing air pressure produced smaller microspheres. At 2 bar, the size of some particles was less than 5 μm (Figure 10) . The surface of microspheres was rather smooth because it was covered with a few microcrystals. The powders produced at 3 bar showed more microcrystals covered on the surface (Figure 11). It appeared that agglomerates of spray dried powder prepared at 6 bar were composed of small microspheres.

The photomicrographs of spray dried particles prepared from different concentrations of solution were shown in Figure 14-17. More concentrated solutions yielded larger microspheres and less agglomerated particles. Feed solution of 10 % gave the smallest microspheres and more agglomeration formed in comparison with 13%, 20%, 25 % solutions.

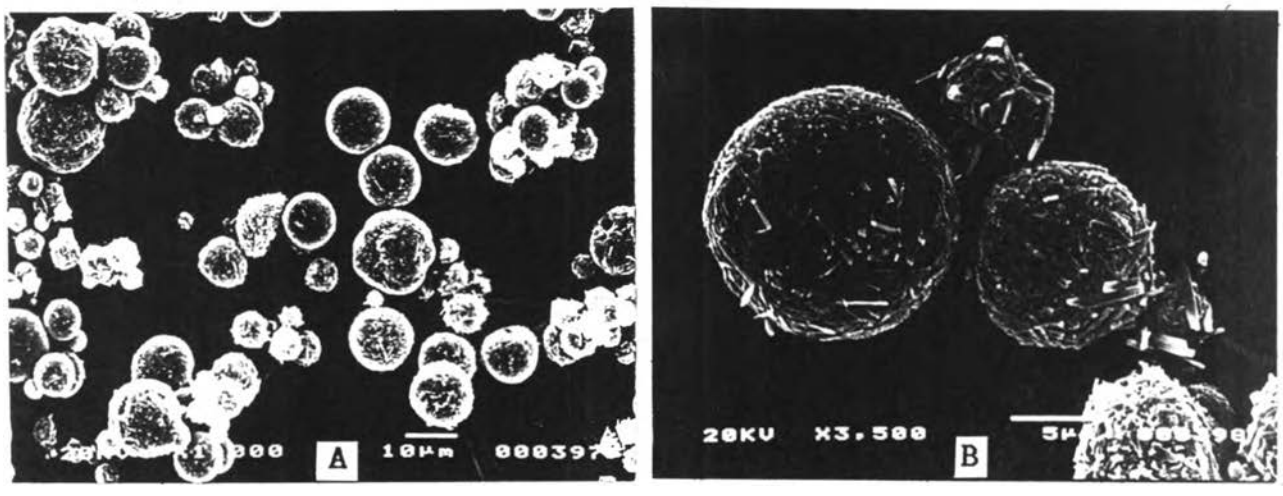


Figure 6 Photomicrographs of Spray Dried Particles Produced at the Feed Rate of 18 ml/min (Key : A x 1,000 , B x 3,500)

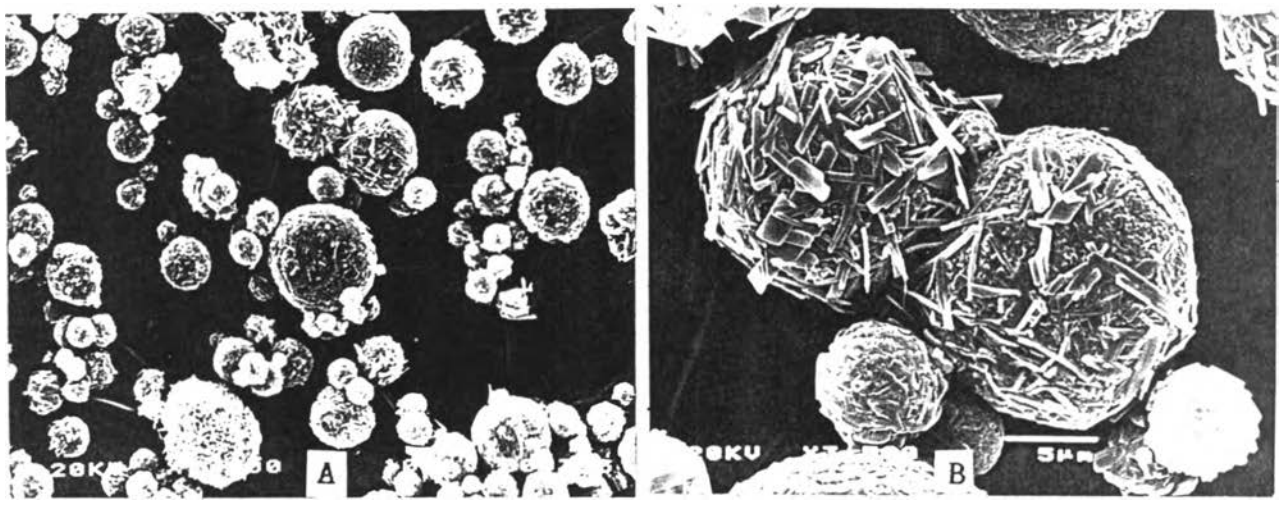


Figure 7 Photomicrographs of Spray Dried Particles Produced at the Feed Rate of 24 ml/min (Key : A x 1,000 , B x 3,500)

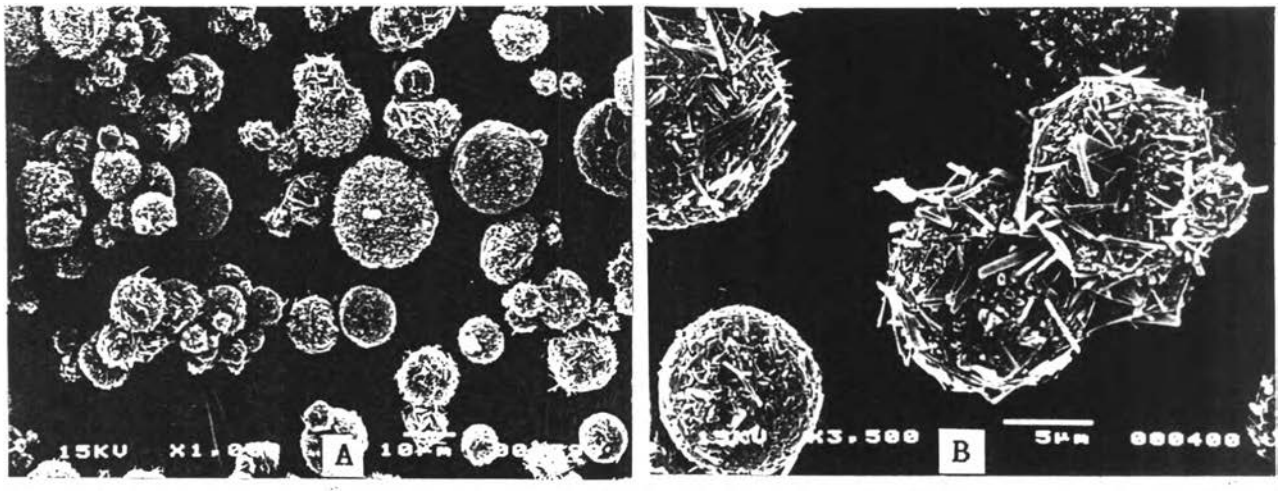


Figure 8 Photomicrographs of Spray Dried Particles Produced at the Feed Rate of 27 ml/min (Key : A x 1,000 , B x 3,500)

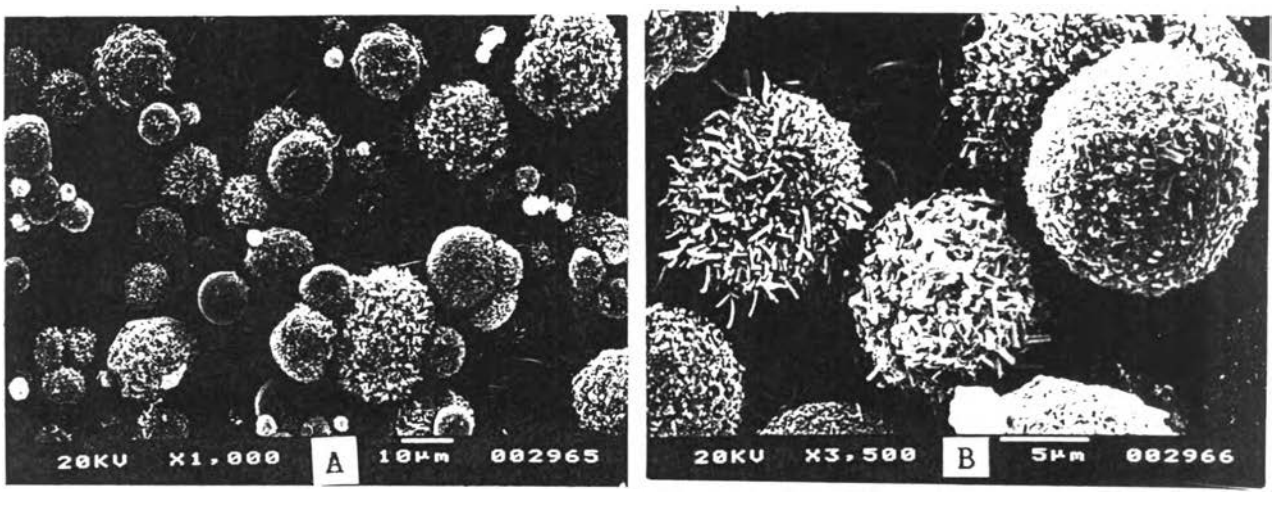


Figure 9 Photomicrographs of Spray Dried Particles Produced at the Feed Rate of 30 ml/min (Key : A x 1,000 , B x 3,500)

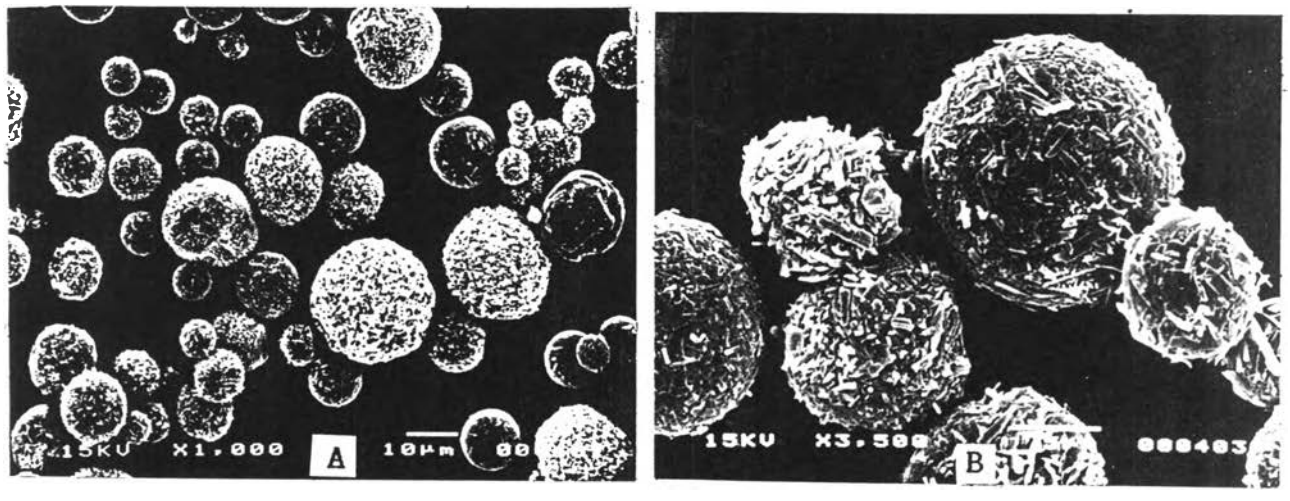


Figure 10 Photomicrographs of Spray Dried Particles Prepared using Atomization Pressure at 2 Bar (Key : A x 1,000 , B x 3,500)

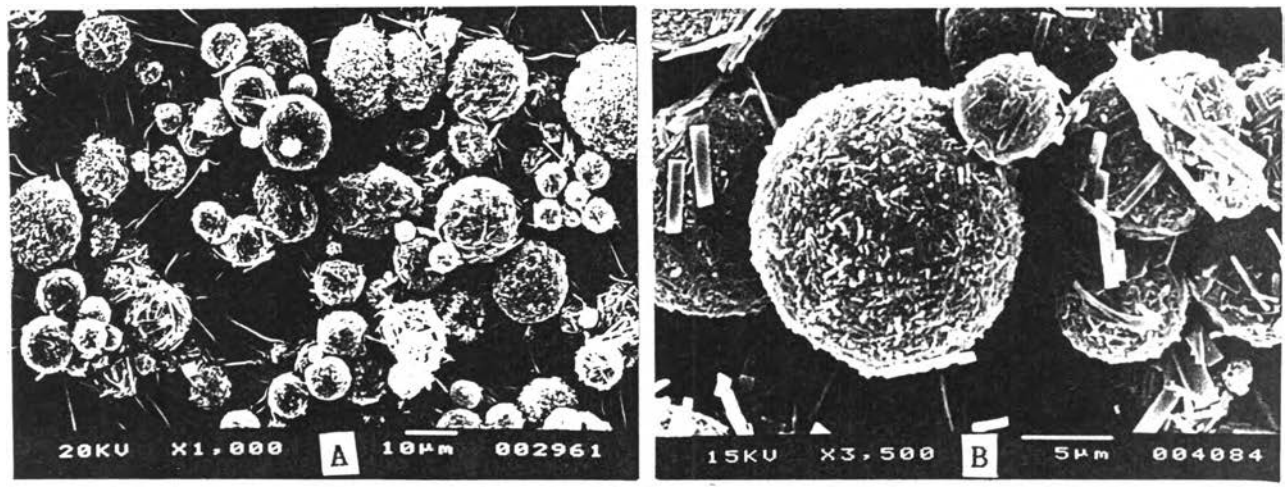


Figure 11 Photomicrographs of Spray Dried Particles Prepared using Atomization Pressure at 3 Bar (Key : A x 1,000 , B x 3,500)

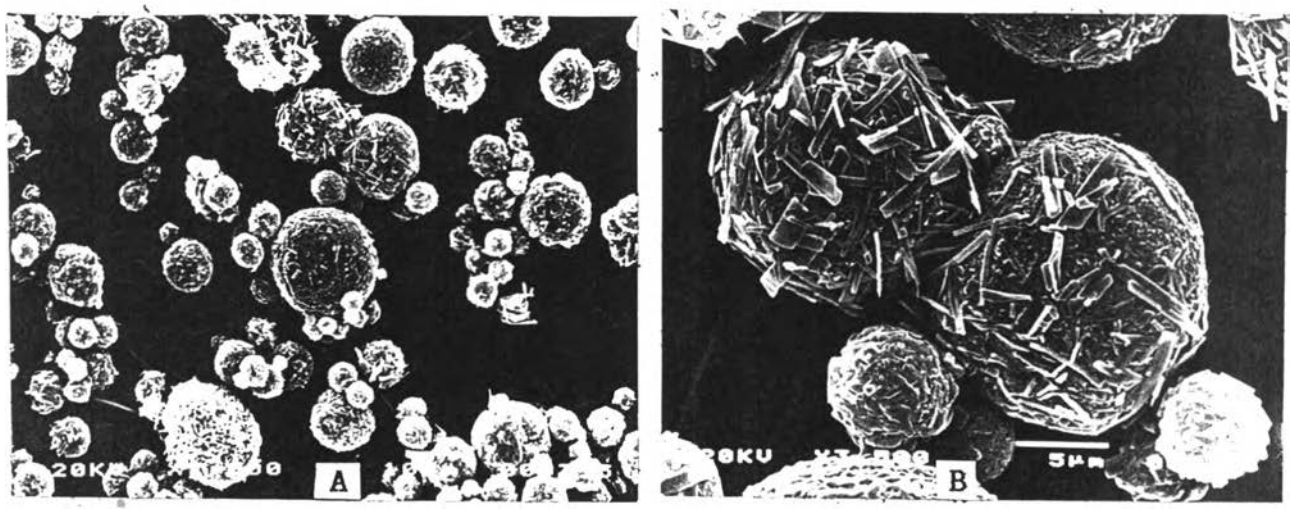


Figure 12 Photomicrographs of Spray Dried Particles Prepared using Atomization Pressure at 4 Bar (Key : A x 1,000 , B x 3,500)

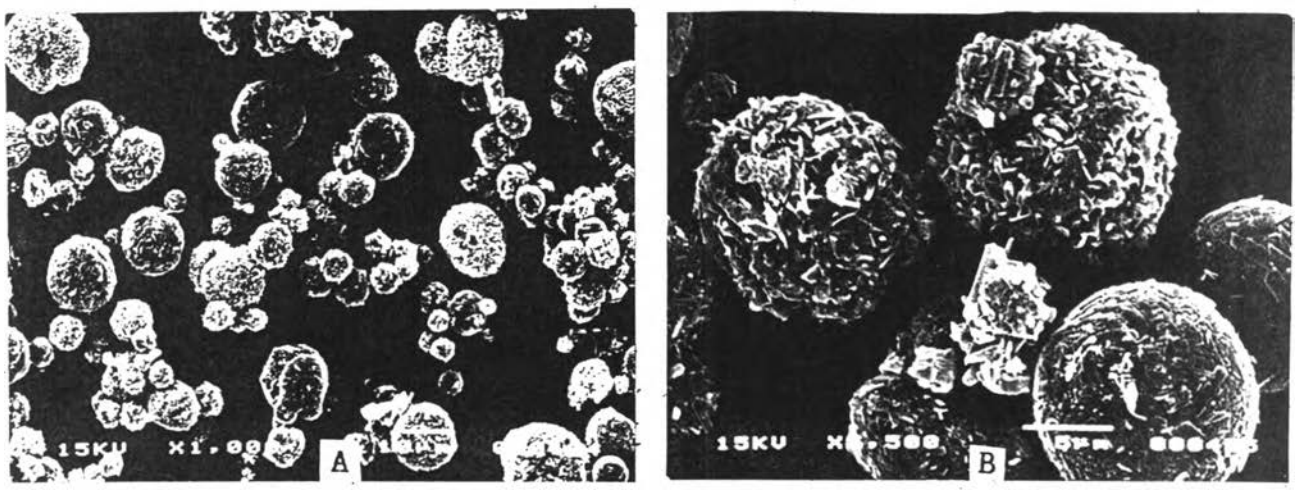


Figure 13 Photomicrographs of Spray Dried Particles Prepared using Atomization Pressure at 6 Bar (Key : A x 1,000 , B x 3,500)

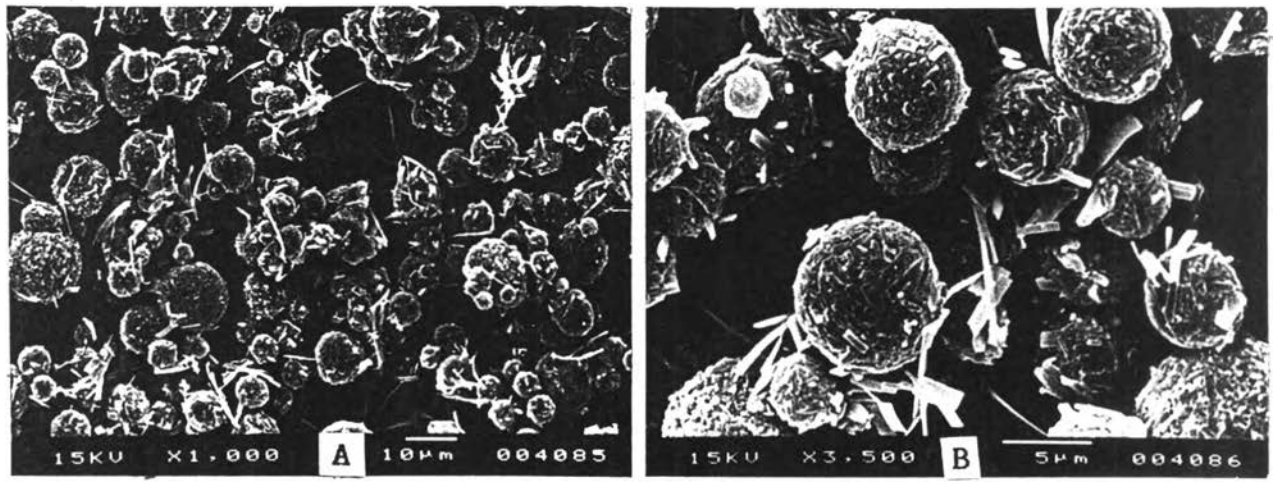


Figure 14 Photomicrographs of Spray Dried Particles
Prepared from 10 % solution
(Key : A x 1,000 , B x 3,500)

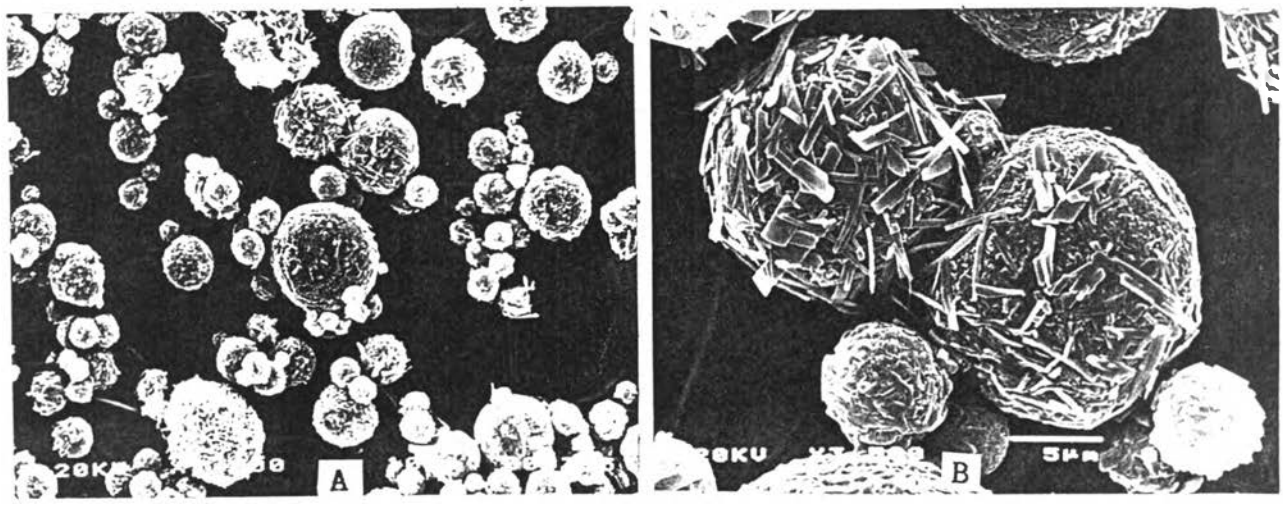


Figure 15 Photomicrographs of Spray Dried Particles
Prepared from 13 % solution
(Key : A x 1,000 , B x 3,500)

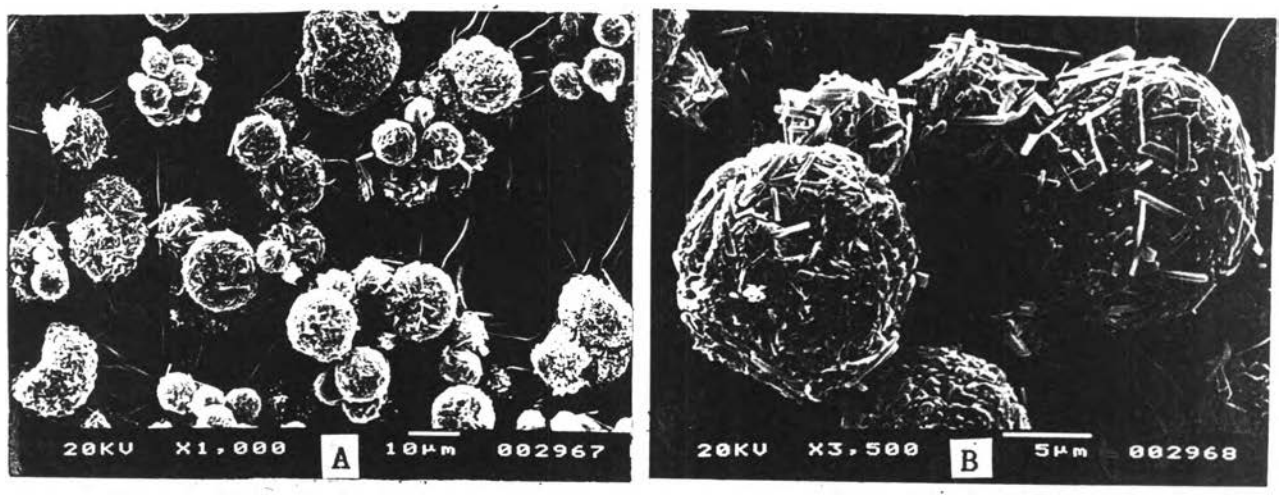


Figure 16 Photomicrographs of Spray Dried Particles Prepared from 20 % solution (Key : A x 1,000 , B x 3,500)

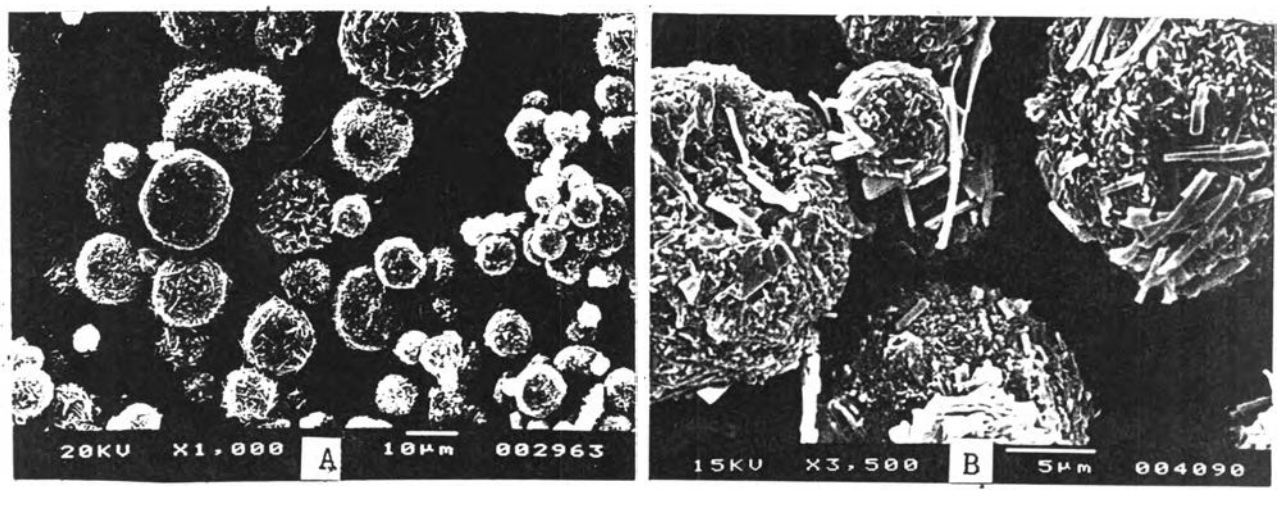


Figure 17 Photomicrographs of Spray Dried Particles Prepared from 25 % solution (Key : A x 1,000 , B x 3,500)

1.2 Drug Content

The percent drug content of spray dried powders prepared from various processing variables were shown in Table 5 . The theoretical drug content in product was 69.71% . The standard deviation shown implied The uniformity of drug distribution in spray dried powder.

The data revealed that spray drying conditions did not influence drug distribution. Inlet air temperature at 170 ° C gave slightly low drug content of the powder in the chamber (68.08%).

1.3 Moisture Content

The moisture content of spray dried powders were also presented in Table 5 . Increase of inlet air temperature gave products with lower moisture content. In case of atomizing air pressure, using higher air pressure likely produced higher moisture content in powder. Apparently, feed rate and concentration of solution had an insignificant effect on moisture content of powder.

Table 5 The Percent of Drug Content and Moisture Content of Spray-Dried Products at Various Spray Conditions

Process Variable /Level	% Drug Content*		% Moisture* Content
	Collector	Chamber	
Inlet Temperature (°C)			
120	69.66(0.66)**	69.75(0.21)	2.54(0.04)
130	69.78(0.62)	69.62(0.59)	2.27(0.16)
150	69.59(1.60)	69.89(1.40)	1.86(0.07)
170	69.67(0.32)	68.08(0.15)	1.82(0.14)
Feed rate (ml/min)			
18	69.82(0.29)	69.69(0.46)	2.67(0.06)
24	69.78(0.62)	69.62(0.59)	2.27(0.16)
27	69.74(0.13)	69.83(0.90)	2.37(0.12)
30	69.63(0.27)	69.74(0.49)	2.55(0.72)
Atomization pressure			
2 bar	69.64(0.20)	69.55(0.19)	1.99(0.11)
3 bar	69.83(0.33)	69.97(1.29)	1.77(0.07)
4 bar	69.78(0.62)	69.62(0.59)	2.27(0.06)
6 bar	69.68(0.29)	69.98(0.72)	3.21(0.09)
Concentration of Solution (%)			
10	69.70(0.07)	69.64(0.24)	1.96(0.35)
13	69.78(0.62)	69.62(0.59)	2.27(0.06)
20	69.87(0.37)	69.63(0.16)	2.49(0.19)
25	69.85(0.56)	69.69(0.35)	2.57(0.13)

* Average from three determinations
** Standard deviation

1.4 Angle of Repose, Bulk Density, Tapped Density and Compressibility

Angle of repose, bulk density, tapped density and compressibility of product prepared from different conditions were shown in Table 6. Angle of repose and compressibility indicated the flowability of powder. The lower angle of repose was obtained from powder with better flowability.

There was a trend to decrease on angle of repose value as inlet air temperature increased. It was found that feed rate seem to slightly affect angle of repose of products. At atomization pressure of 2 bar gave product with lowest repose of angle (34.17 °). When air pressure was increased from 3 bar to 6 bar, angles of repose were not much different. Powder produced at higher concentrations had lower angle of repose . Compressibility of the spray dried powders was in the range of 22.90 - 49.34 % . The highest compressibility of the product was obtained from inlet temperature at 170°C. The lowest compressibility was obtained from atomization pressure of 2 bar.

The products prepared at inlet air temperatures of 120° , 130 ° and 150 ° C had no significant difference on bulk density but the density decreased for

Table 6 Angle of Repose, Bulk Density, Tapped Density and Compressibility of Product Prepared from Different Conditions

Process Variable /Level	Angle of Repose (degree)	Bulk Density (g/ml)	Tapped Density (g/ml)	Compressibility (%)
Inlet Temperature (°C)				
120	38.92	0.454	0.647	29.83
130	38.21	0.470	0.687	31.59
150	36.44	0.447	0.612	26.96
170	36.63	0.382	0.754	49.34
Feed rate (ml/min)				
18	36.37	0.458	0.615	25.53
24	38.21	0.470	0.687	31.59
27	38.30	0.448	0.617	27.39
30	38.29	0.398	0.624	36.22
Atomization pressure				
2 bar	34.17	0.522	0.677	22.90
3 bar	38.95	0.414	0.675	38.67
4 bar	38.21	0.470	0.687	31.59
6 bar	37.66	0.426	0.583	26.93
Concentration of Solution (%)				
10	40.57	0.460	0.690	33.23
13	38.21	0.470	0.687	31.59
20	38.33	0.477	0.697	31.58
25	36.51	0.431	0.637	32.34

those of 170° C. The highest tapped density of powder was obtained when it was prepared at 170° C and it was decreased when lower air temperature was used . Feed rate at 24 ml/min yielded product with higher bulk and tapped density. At other feed rates, bulk and tapped density tended to decrease . In case of atomization pressure, the highest bulk density was obtained from the product prepared at air pressure of 2 bar. Bulk density was lower for the powder produced at atomizing pressures of 3-6 bar. Tapped density was indistinctly different for products of 2-4 bar and decreased in those of 6 bar. Feed solution concentrated at 10-20% gave products with indifferent bulk and tapped density. But it was decreased at concentration of 25 %.

1.5 Particle size distribution

The particle size distributions of the powders were shown in Table 27 (see Appendix) and depicted in Figure 18-21. Values of cumulative % frequency undersize were transformed into Z value (standard score) which presented in Table 28-31 (see Appendix) and illustrated versus particle size in Figure 65,67,69 and 71 (in Appendix). These values were plotted on probability-log scale in order to estimate D_{50} (Geometric mean diameter at Z=0) of spray dried product (see Figure 66,68,70 and 72 in Appendix). D_{50} of products at different conditions were shown in Table 32 (in Appendix).

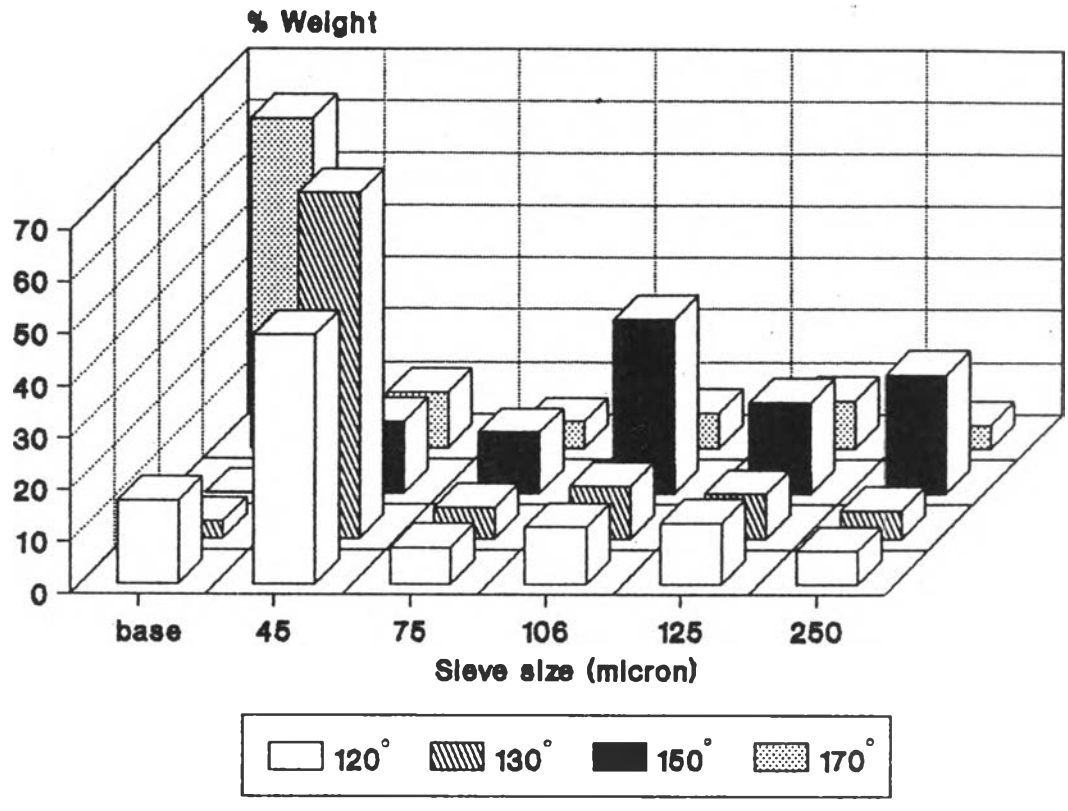


Figure 18 Effect of Inlet Air Temperature on Particle Size Distribution of Spray-Dried Powders

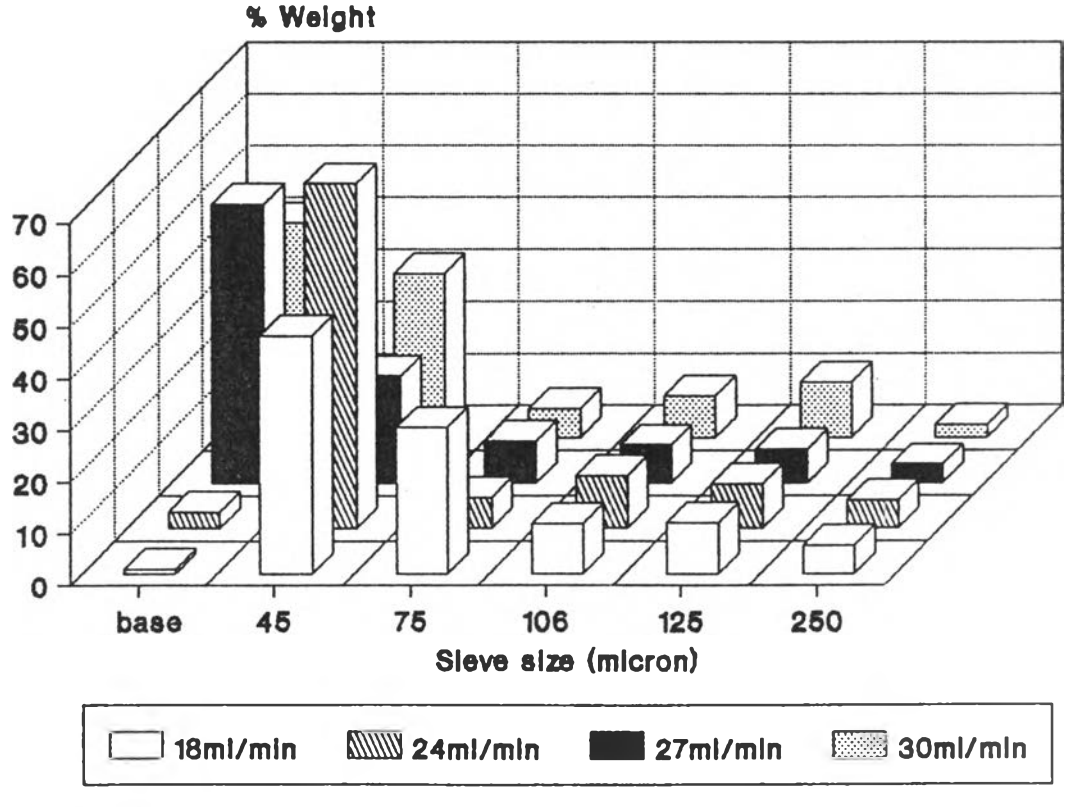


Figure 19 Effect of Feed Rate on Particle Size Distribution of Spray-Dried Powders

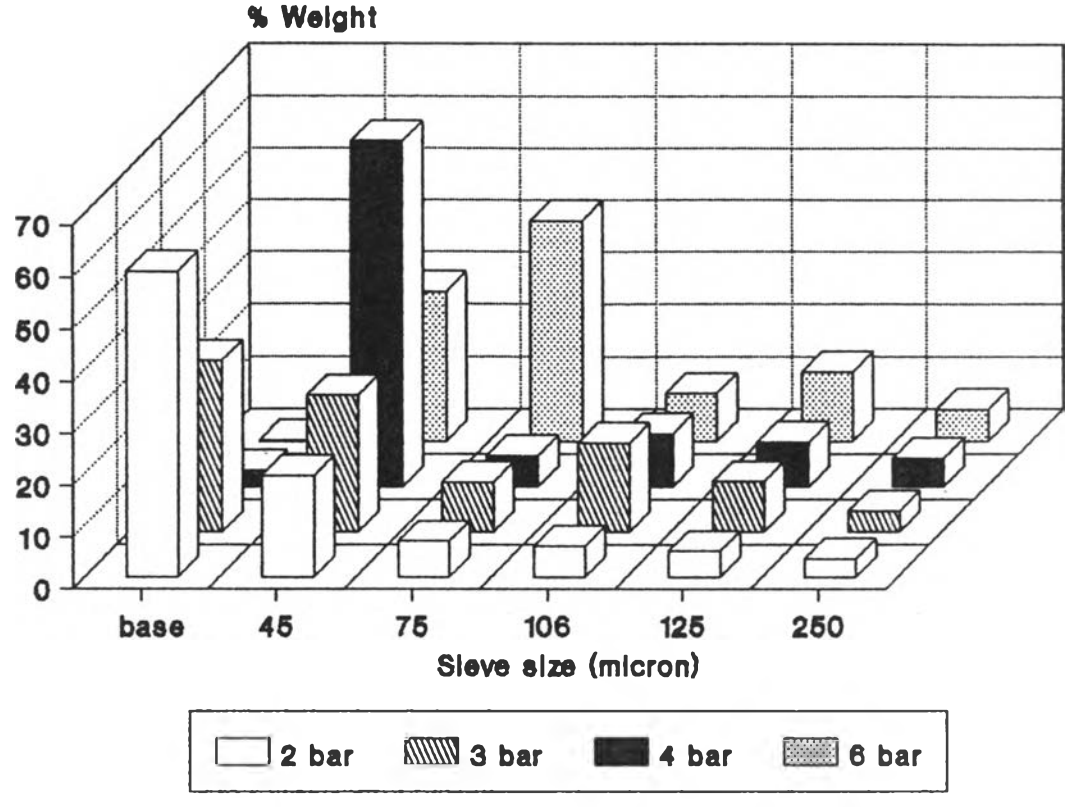


Figure 20 Effect of Atomization Pressure on Particle Size Distribution of Spray-Dried Powders

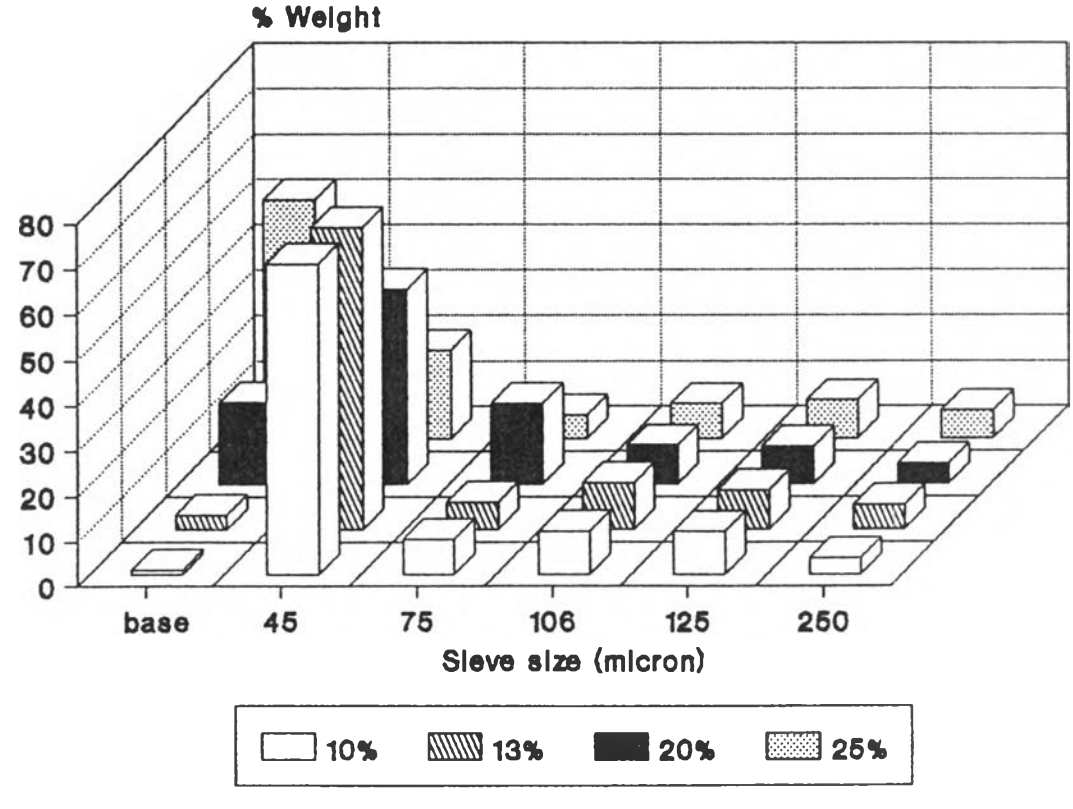


Figure 21 Effect of Concentration of Solution on Particle Size Distribution of Spray-Dried Powders

The particle size of powders prepared at inlet temperature between 120-150° C appeared to be increased when the inlet temperature increased. But particle size of spray dried powder produced at the highest inlet temperature (170° C) were smaller (most of the size of particle were less than 45 μm) (Figure 18).

At the feed rate of 18-27 ml/min, there was a trend of decrease in particle size of powder as feed rate increased, but at the feed rate of 30 ml/min gave larger particles (percent of particle size of 45-75 μm and 125-250 μm) were found higher than those of 27 ml/min (Figure 19).

When higher atomizing pressures were used, larger particle size were produced (Figure 20). The powder produced from 10 % and 13 % solution gave rather similar particle size distribution (Figure 21). The powder prepared from 20 % solution provided smaller particles (size of particles were less than 45 μm). The product prepared from 25 % solution mostly gave particles at size under 45 μm.

D_{50} of products from different inlet air temperatures were illustrated in Figure 22. At 170° C inlet air temperature gave product with lowest D_{50} value (32.30 μm). The products prepared at 120° to 150° C, higher inlet air temperature produced larger D_{50}. There was a trend to decrease the D_{50} value as the faster

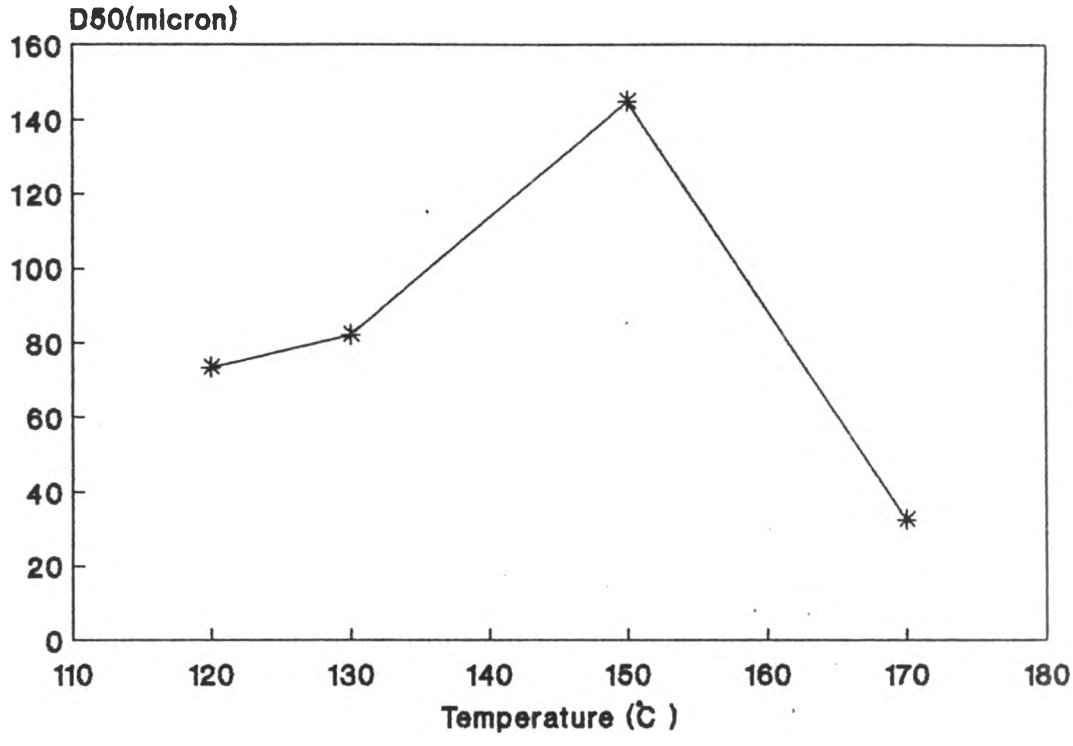


Figure 22 Effect of Inlet Air Temperature on Geometric Mean Diameter (D_{50}) of Spray-Dried Powders

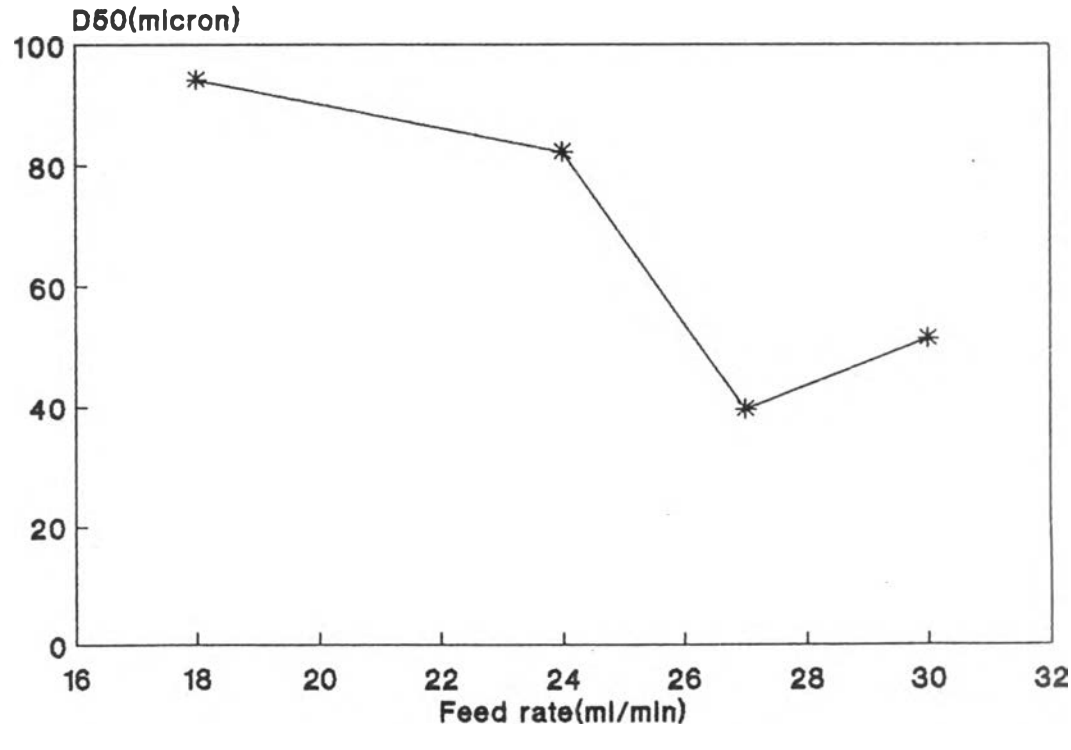


Figure 23 Effect of Feed Rate on Geometric Mean Diameter (D_{50}) of Spray-Dried Powders

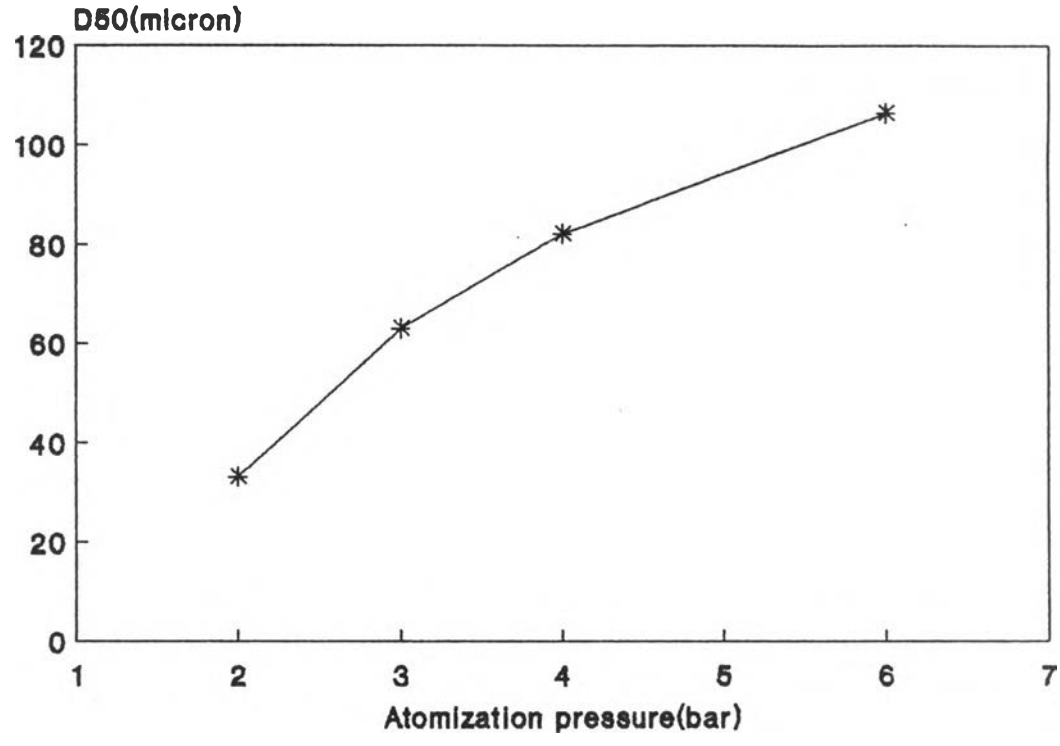


Figure 24 Effect of Atomization Pressure on Geometric Mean Diameter (D_{50}) of Spray-Dried Powders

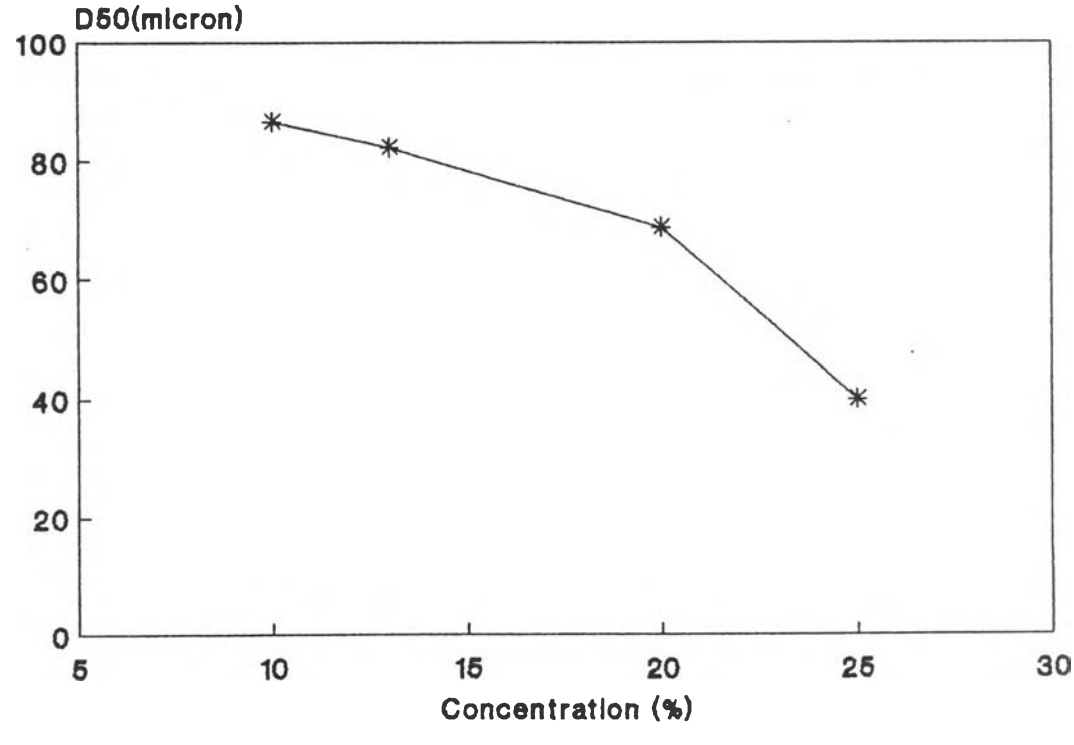


Figure 25 Effect of Concentration of Solution on Geometric Mean Diameter (D_{50}) of Spray-Dried Powders

feed rates were used except at 30 ml/min D_{50} value increased from 39.47 to 51.22 (Figure 23). In case of the effect of atomization pressure, higher air pressures yielded spray dried powder with higher D_{50} values (Figure 24). In contrary, the solution with higher concentration produced lower D_{50} value (Figure 25).

1.6 Percent Recovery

In spray drying process, the liquid was atomized into droplets and the droplets were transformed into dried particulates. The products were collected from collector and chamber. The percent recovery in chamber and collector was represented in Table 7. The type and level of process variables did not affect the total percent recovery of spray dried products.

Generally the percent recovery of the powder form collector was higher than in chamber. When inlet air temperature was increased, product in collector was also increased. The percent recovery of powder obtained not only from the chamber but also collector was not different at feed rate of 18, 24, 27 ml/min. But the percent recovery of powder in collector decreased at feed rate of 30 ml/min. When higher air pressure was used, higher percent of powder in collector was found. Products obtained from chamber and collector were not remarkably affected by various concentration of solution.

Table 7 The Percent Recovery of Spray-Dried Products at Various Spray Conditions

Process Variable /Level	Percent Recovery		
	Collector	Chamber	Total
Inlet temperature (°C)			
120	55.25	30.05	85.30
130	59.35	28.35	87.70
150	65.00	24.45	89.45
170	69.95	18.75	88.70
Feed rate (ml/min)			
18	59.00	24.40	83.40
24	59.35	28.35	87.70
27	58.90	29.80	88.80
30	31.35	49.85	81.20
Atomization pressure			
2 bar	37.30	47.25	84.55
3 bar	55.60	31.00	86.60
4 bar	59.35	28.35	87.70
6 bar	70.25	18.80	89.05
Concentration of solution (%)			
10	57.35	25.90	83.25
13	59.35	28.35	87.70
20	56.65	32.30	88.95
25	51.30	34.35	85.65

2. Physical Properties of Matrices Prepared from Spray-Dried Products

2.1 Thickness, Hardness and Disintegration Time of Matrices

Thickness, hardness and disintegration time of matrices made from spray dried products were presented in Table 8. Average value of thickness was mostly ranging from 4.166-4.297 mm. The uniform thickness of the spray-dried matrix indicated that the compressional force was uniform with the standard deviation not exceeding ± 0.045 for all the matrices. The powder obtained at the inlet air temperature of 170° C showed the least thickness of matrices. The highest thickness of matrices at 4.516 and 4.528 mm were taken from products prepared from 25% solution and feed rate of 30 ml/min respectively.

Average values of hardness were mostly ranging from 10.97-14.07 kp. The less hardness was given from product prepared at 120° C inlet air temperature and atomizing pressure of 3 bar. Product produced at 170 °C inlet air temperature showed matrices with the most hardness.

Most of disintegration times were more than 120 minutes. Some of them were ranging from 105-112 minutes. The powder obtained from 25% solution gave matrices with the least disintegration time (81 min).

Table 8 Physical Properties of the Matrices Prepared from Spray-Dried Powder Produced at Different Conditions

Process Variable /Level	Physical Properties of Matrices		
	Thickness* (mm)	Hardness* (Kp)	Disintegration Time(min)**
Inlet temperature (° C)			
120	4.243(0.035)	9.92(2.21)***	>120
130	4.262(0.027)	12.13(0.81)	>120
150	4.166(0.023)	13.95(2.96)	>120
170	3.871(0.040)	19.88(0.20)	>120
Feed rate (ml/min)			
18	4.253(0.022)	10.97(2.08)	112.3(7.6)
24	4.262(0.027)	12.13(0.81)	>120
27	4.262(0.028)	12.13(2.26)	>120
30	4.528(0.043)	13.63(0.53)	105(6.2)
Atomization pressure			
2 bar	4.255(0.028)	14.07(1.21)	>120
3 bar	4.492(0.034)	9.65(1.13)	112.8(5.6)
4 bar	4.262(0.027)	12.13(0.81)	>120
6 bar	4.297(0.023)	13.18(2.08)	>120
Concentration of solution (%)			
10	4.192(0.022)	12.03(1.11)	105.7(8.6)
13	4.262(0.027)	12.13(0.81)	>120
20	4.179(0.035)	13.32(1.10)	>120
25	4.516(0.039)	11.48(0.41)	81(7.18)

* Average from ten determinations
** Average from six determinations
*** Standard deviation

2.2 Dissolution Studies

The amount of drug release at any time interval of matrices preparing from spray-dried products at various conditions were shown in Table 33-36 (in Appendix).

2.2.1 Effect of Inlet air Temperature

The dissolution profiles of matrices prepared from spray-dried products at different inlet air temperatures were illustrated in Figure 26. Inlet air temperature notably affected dissolution of theophylline from matrices.

Higher inlet air temperature used in preparation produced slower dissolution rate of drug from the spray dried matrices. The first hour of each dissolution profiles appeared slightly different. The final amount of drug release from matrices prepared at inlet air temperatures of 120°, 130°, 150° and 170° C were 83.84%, 87.43%, 68.54%, and 66.55% respectively.

The plots of $T_{50\%}$ and $T_{80\%}$ (the times at 50% and 80% drug released) versus the inlet air temperature were shown in Figure 27 (see Table 9). It showed the same result that higher inlet air temperature increased not only time of $T_{50\%}$ but also $T_{80\%}$. It more remarkably affected $T_{80\%}$ than $T_{50\%}$. Duncan multiple

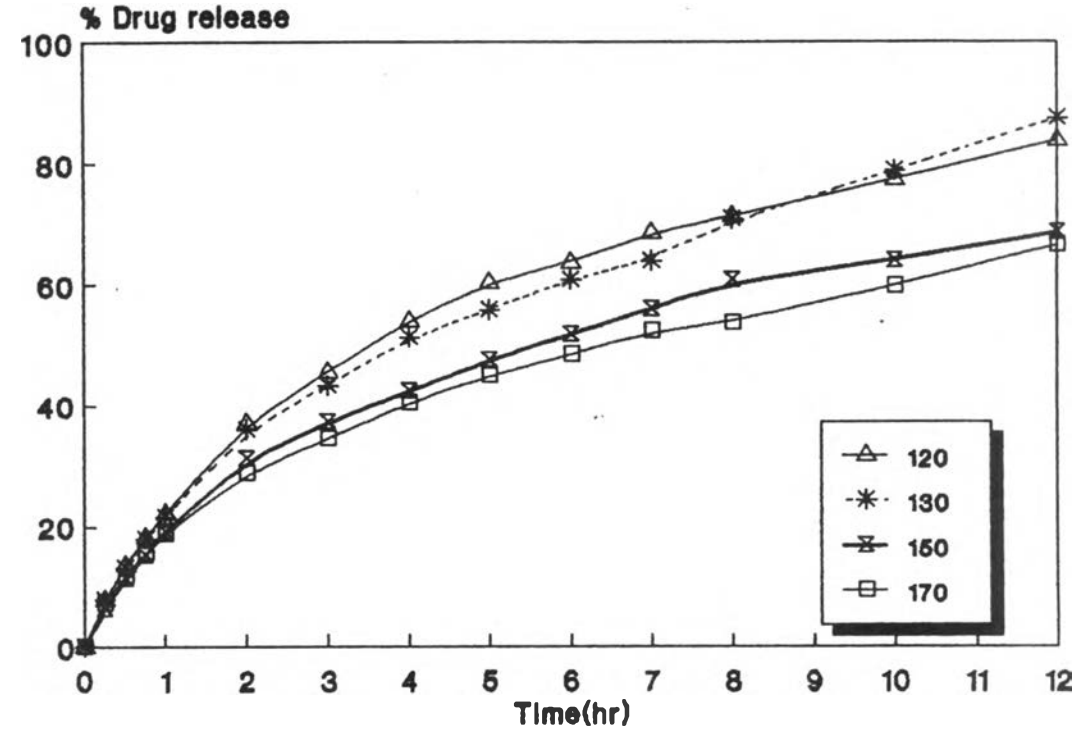


Figure 26 Effect of Inlet Air Temperature on Drug Release Profiles of Spray-Dried Matrices

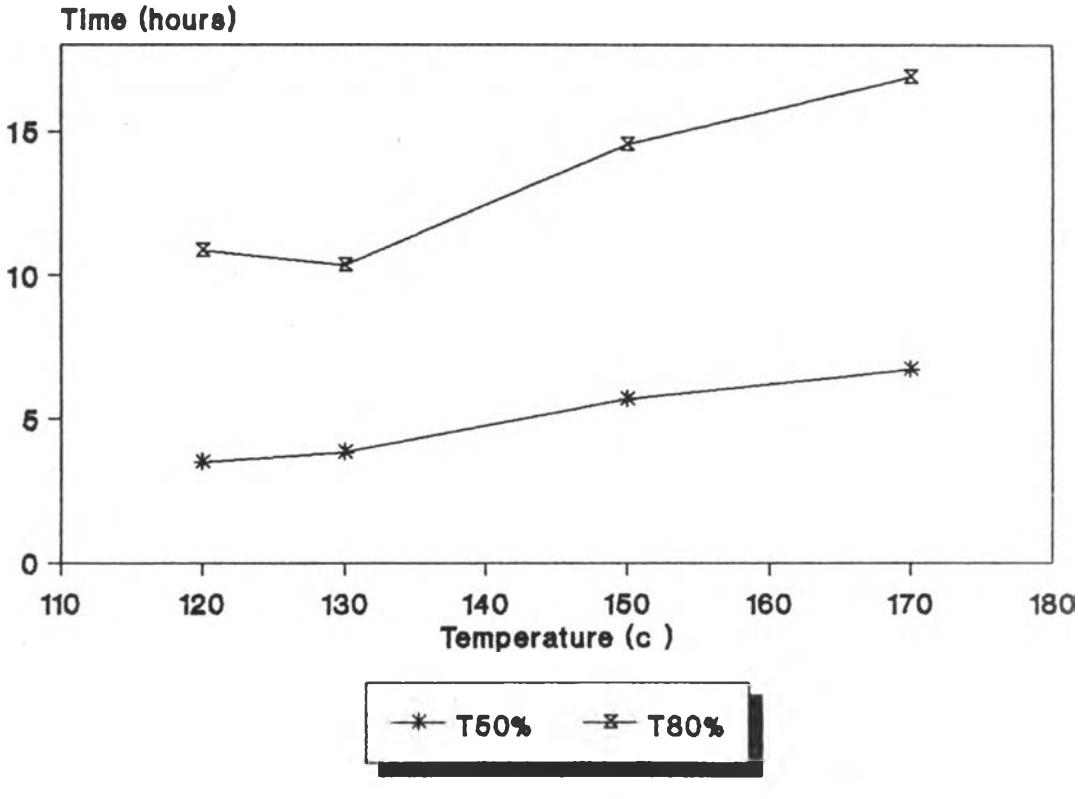
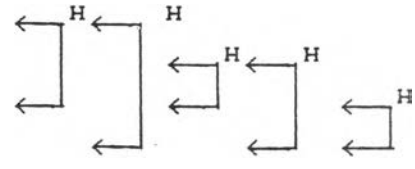
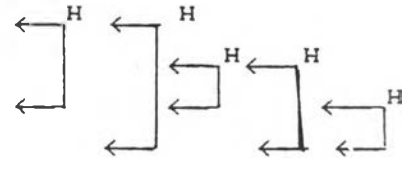


Figure 27 Effect of Inlet Air Temperature on $T_{50\%}$ and $T_{80\%}$ of Spray-Dried Matrices

Table 9 Statistical Analysis of the Effect of Inlet Air Temperature on $T_{50\%}$ and $T_{80\%}$ of the Matrices

Inlet Temperature (℃)	$T_{50\%}$ (hr.)	Significant Difference*
120	3.500(0.130)	
130	3.850(0.152)	
150	5.717(0.522)	
170	6.750(1.033)	
Inlet Temperature (℃)	**$T_{80\%}$ (hr.)**	**Significant Difference***
120	10.867(0.175)	
130	10.342(0.218)	
150	14.545(0.957)	
170	16.900(1.606)	

* The arrow sign indicated the significant difference between the variables that specified.

H = highly significant ($p<0.01$).

range test was performed to test the differences between groups of not only $T_{50\%}$ but also $T_{80\%}$ of matrices prepared at various inlet temperatures. The statistical computer program used in this analysis was SYSTAT. The significant differences between the groups were present in Table 9 (see statistical data in Appendix, Table 37-38.). It was found that not only $T_{50\%}$ but also $T_{80\%}$ of matrices prepared at temperatures of 120 ° and 130 ° C were not significantly different. On the other hand, not only $T_{50\%}$ but also $T_{80\%}$ of matrices produced at temperature of 120-130°C ,150 °C and 170°C were all significantly different from each other ($p<0.01$).

2.2.2 Effect of Feed Rate

Figure 28 illustrated the amount of drug release at various time intervals of matrices produced from spray dried powder at different feed rate. Their dissolution profiles appeared indifferent. At first hour, they seemed to be similar. Feed rate slightly affected the dissolution profiles. $T_{50\%}$ and $T_{80\%}$ were plotted versus feed rate in Figure 29. Value of $T_{50\%}$ slightly decreased when feed rate was increased (see Table 10). Analysis of variance of $T_{50\%}$ and $T_{80\%}$ were shown in Table 39-40 (in Appendix). The significant differences ($p<0.05$) of $T_{50\%}$ were observed in the groups of feed rate : 24 and 27 ml/min; 18 and 30 ml/min; 24 and 30 ml/min (Table 10). From feed

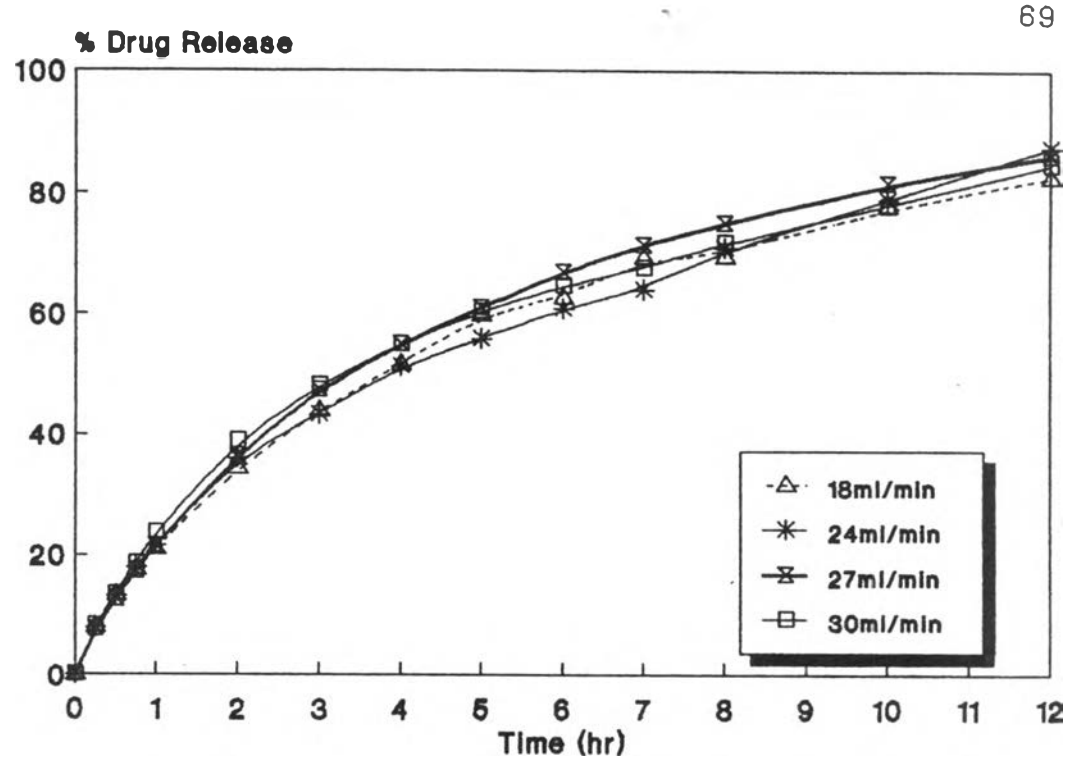


Figure 28 Effect of Feed Rate on Drug Release Profiles of Spray-Dried Matrices

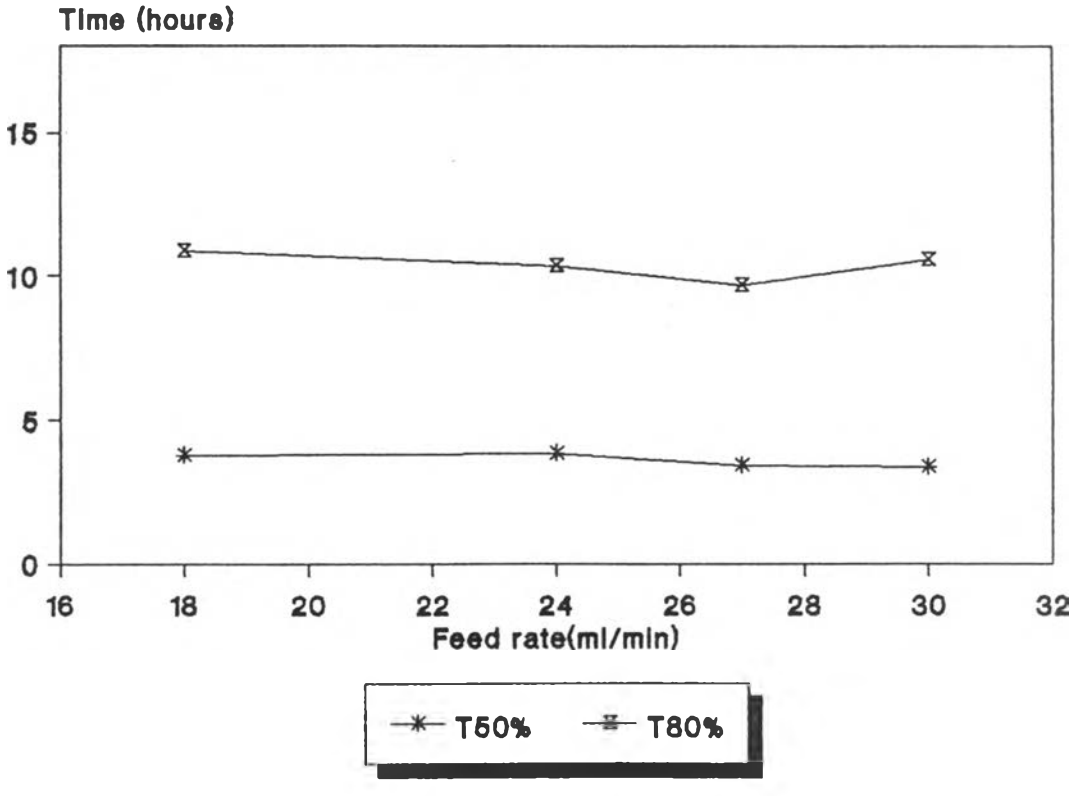


Figure 29 Effect of Feed Rate on $T_{50\%}$ and $T_{80\%}$ of Spray-Dried Matrices

Table 10 Statistical Analysis of the Effect of Feed Rate on $T_{50\%}$ and $T_{80\%}$ of the Matrices

Feed Rate (ml/min)	$T_{50\%}$ (hr.)	Significant Difference*
18	3.792(0.36)	
24	3.850(0.152)	
27	3.433(0.298)	
30	3.383(0.354)	

Feed Rate (ml/min)	$T_{80\%}$ (hr.)	Significant Difference*
18	10.858(0.737)	H
24	10.342(0.218)	
27	9.700(0.326)	
30	10.583(0.697)	

* The arrow sign indicated the significant difference between the variables that specified.

H = highly significant ($p<0.01$).

rate 18 to 27 ml/min , value of $T_{80\%}$ decreased when feed rate increased. However, it was conversely increased at feed rate 30 ml/min. Statistical analysis of $T_{80\%}$ showed that they were significantly different between the groups of feed rate: at 18 and 27 ml/min ($p < 0.01$), 27 and 30 ml/min ($p<0.05$).

2.2.3 Effect of Atomization Pressure

The dissolution profiles of matrices produced from spray dried powder at various atomizing air pressures were shown in Figure 30, Dissolution profiles were seemed not different. The plots of $T_{50\%}$ and $T_{80\%}$ versus atomization pressure were shown in Figure 31 (see Table 11). The plot of $T_{50\%}$ seemed to be straight line. Statistical data indicated that no significantly difference (at $p=0.05$) of $T_{50\%}$ and $T_{80\%}$ was found at various atomization pressures (Table 11). Analysis of variance were shown in Table 41 and 42 (in Appendix).

2.2.4 Effect of Concentration of Solution

Figure 32 showed the dissolution profiles of matrices produced from spray dried solutions at different concentrations. At first hours, all dissolution rates seemed to be similar. The dissolution profiles of matrices prepared from 10-20% solution were similar. Nevertheless, matrices prepared from 25% solution produced

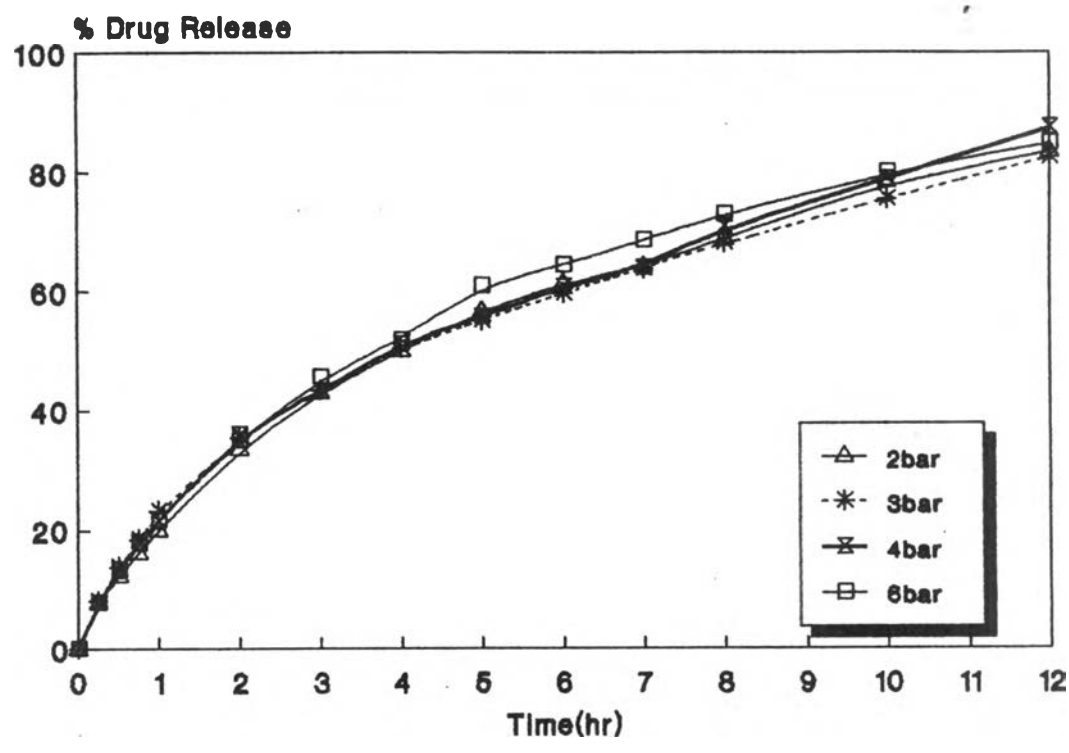


Figure 30 Effect of Atomization Pressure on Drug Release Profiles of Spray-Dried Matrices

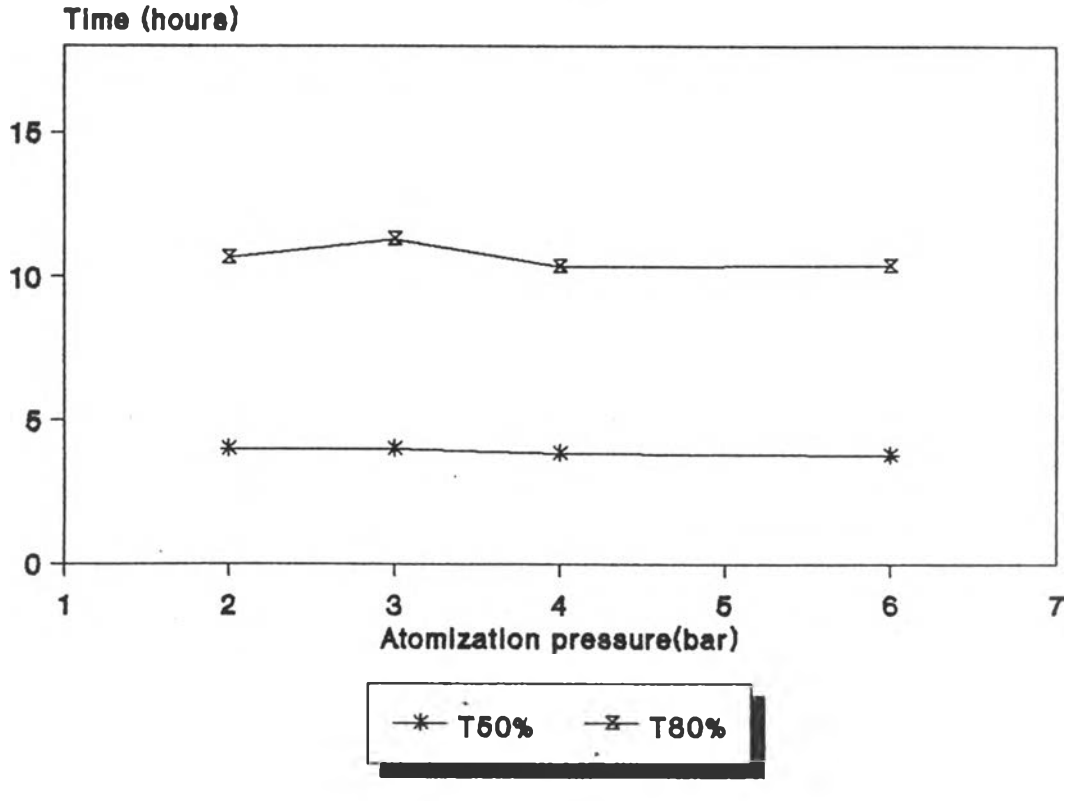


Figure 31 Effect of Atomization Pressure on $T_{50\%}$ and $T_{80\%}$ of Spray-Dried Matrices

Table 11 Statistical Analysis of the Effect of Atomization Pressure on $T_{50\%}$ and $T_{80\%}$ of the Matrices

Atomization Pressure (bar)	$T_{50\%}$ (hr.)	Significant Difference
2	4.008(0.102)	
3	4.008(0.347)	None*
4	3.850(0.152)	
6	3.783(0.209)	
Atomization Pressure (bar)	**$T_{80\%}$ (hr.)**	**Significant Difference**
2	10.675(0.639)	
3	11.292(0.777)	None*
4	10.342(0.218)	
6	10.375(0.735)	

* The value of those groups were not significantly different.

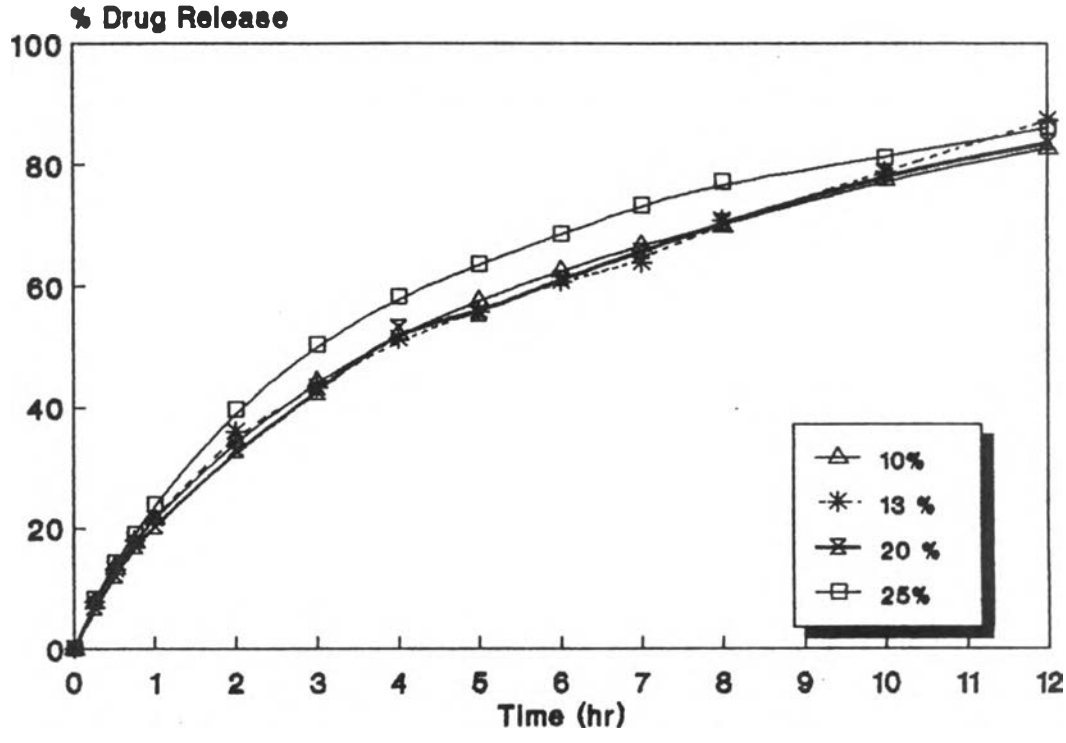


Figure 32 Effect of Concentration of Solution on Drug Release Profiles of Spray-Dried Matrices

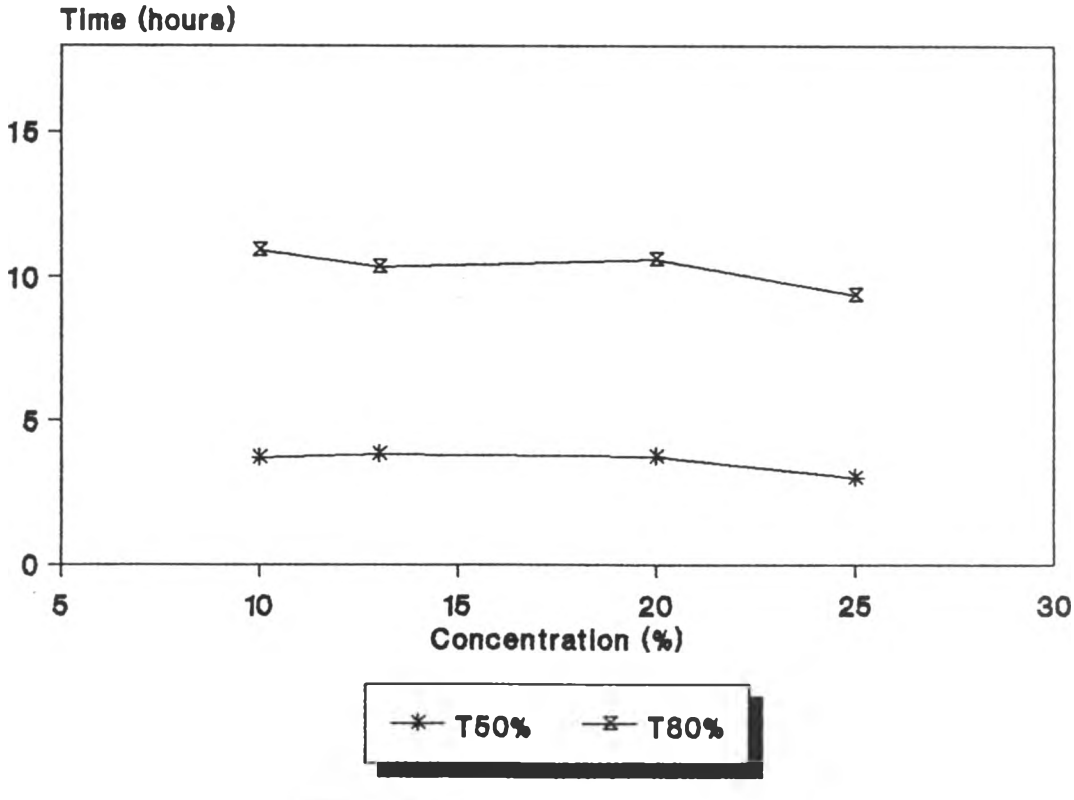


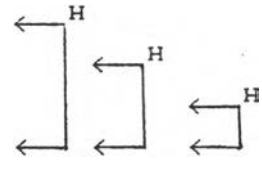
Figure 33 Effect of Concentration of Solution on $T_{50\%}$ and $T_{80\%}$ of Spray-Dried Matrices

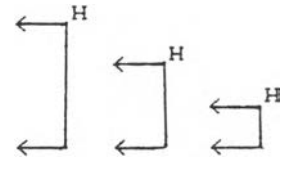
faster dissolution rate. The plots of $T_{50\%}$ and $T_{80\%}$ versus concentrations of solution were shown in Figure 33 (see data in Table 12). It showed that the 25% solution yielded matrices with shorter $T_{50\%}$ and $T_{80\%}$ The significant differences between the groups were shown in Table 12 (see statistical data in Appendix, Table 43-44.). It showed that not only $T_{50\%}$ but also $T_{80\%}$ of matrices prepared from the 25% solution was significantly different ($p=0.01$) from those of other groups.

II. Effect of Tabletting Process on Properties of the Spray Dried Matrices

The suitable spray drying conditions were selected and employed to prepare co-spray dried powder for further study. The previous data of effects of processing variables were used. The selected spray drying conditions were employed according to Table 13. Matrices prepared from inlet air temperature at 130° C gave higher dissolution rate than at 150 ° and 170 ° C. Matrices prepared from inlet temperature at 120° C released theophylline at 8-12 hours in lower amount than at 130° C. For these reasons, 130 ℃ inlet air temperature was used. Atomizing air pressure insignificantly affected dissolution profile. The advantage of atomization pressure at 2 bar was that it provided the best flowability of powders. Matrices prepared from 10-20% solution provided similar dissolution profile. In

Table 12 Statistical Analysis of the Effect of Concentration of solution on $T_{50\%}$ and $T_{80\%}$ of the Matrices

Concentration of Solution (%)	$T_{50\%}$ (hr.)	Significant Difference*
10	3.733(0.082)	
13	3.85(0.152)	
20	3.742(0.049)	
25	3.033(0.289)	

Concentration of Solution (%)	$T_{80\%}$ (hr.)	Significant Difference*
10	10.933(0.593)	
13	10.342(0.218)	
20	10.617(0.643)	
25	9.375(0.549)	

* The arrow sign indicated the significant difference between the variables that specified.

H = highly significant ($p<0.01$).

production, 20% solution took shorter time of spray drying process. In case of 25% solution, the matrices gave faster-release drug in 0.1N.HCl. Feed rate of 27 ml/min. was used because their matrices gave similar dissolution rate in 0.1N.HCl as feed rate of 18 and 24 ml/min and the advantage of feed rate at 27 ml/min was the shorter processing time. Feed rate of 30 ml/min provided higher dissolution rate in 0.1N.HCl than feed rate of 18, 24 and 27 ml/min.

Table 13 Spray Drying Condition During Study on the Effect of Tabletting Processing on Properties of the Matrices

Inlet Air Temperature : 130° C
Atomizing Air Pressure : 2 bar
Concentration of Solution : 20%
Feed Rate : 27 ml/min

The effects of tabletting processing on the dissolution profiles of matrices were investigated into three categories.

1. Effect of Magnesium Stearate

The spray dried powders were mixed with 0.75% or 1.5% magnesium stearate respectively. Then matrices were

produced. The amount of drug release at any time interval of those matrices were shown in Figure 34 (see data in Appendix, Table 45). The plots of $T_{50\%}$ and $T_{80\%}$ versus magnesium stearate percent were illustrated in Figure 35 (see data in Table 14). The dissolution rate at 1-2 hours of spray dried matrices and spray dried matrices with 0.75 % magnesium stearate seemed to be similar. But dissolution rate in phosphate buffer pH 6.8 of spray dried matrices with 0.75% magnesium stearate was decreased. The percent of theophylline release at 12 hours was decreased from 88.41% to 85.45% when 0.75% magnesium stearate was added. When 1.5% magnesium stearate was mixed, dissolution rate was notably decreased. The percent of theophylline release at 12 hours of those matrices was 57.31%.

$T_{50\%}$ of spray dried matrices, spray dried matrices with 0.75% and 1.5% magnesium stearate were 3.480, 4.013 and 9.265 hours respectively. $T_{80\%}$ of spray dried matrices, spray dried matrices with 0.75% and 1.5% magnesium stearate were 9.867, 10.518 and 22.021 hours respectively. Statistical analysis data (Table 50 and 51 in Appendix) reported that not only $T_{50\%}$ but also $T_{80\%}$ of the spray dried matrices with various magnesium stearate percents was significantly different ($p<0.01$). The significant differences between the groups were shown in Table 14. Higher percentage of magnesium stearate provided longer $T_{50\%}$ and $T_{80\%}$ of matrices.

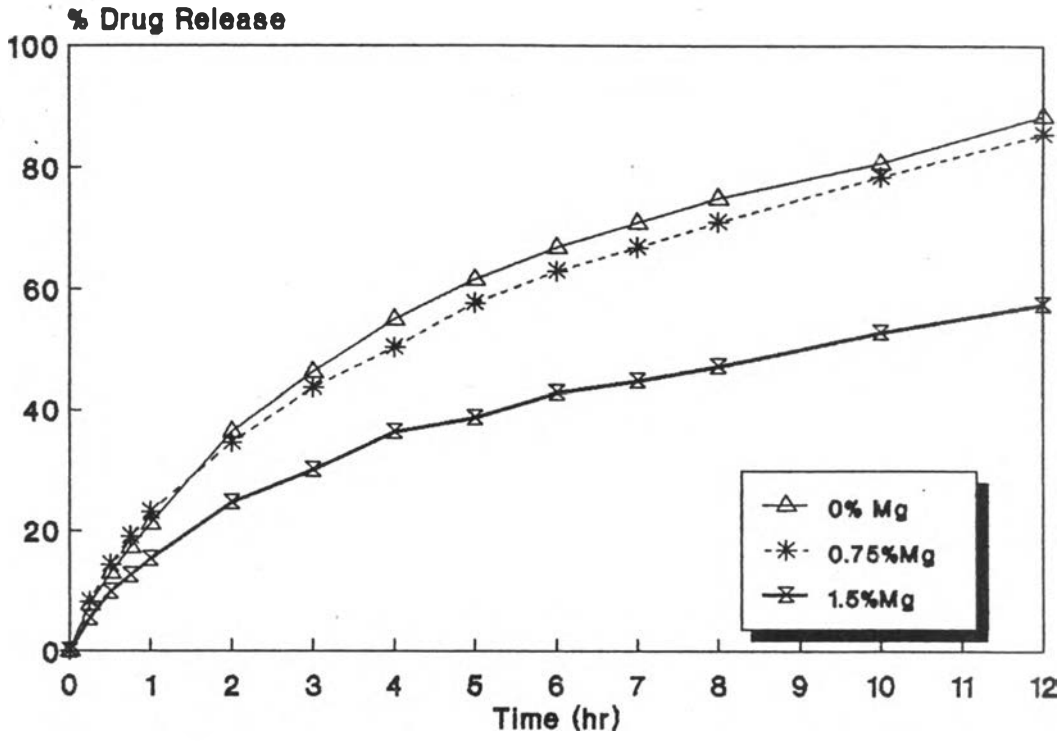


Figure 34 Effect of Magnesium Stearate on Dissolution Profiles of Spray-Dried Matrices

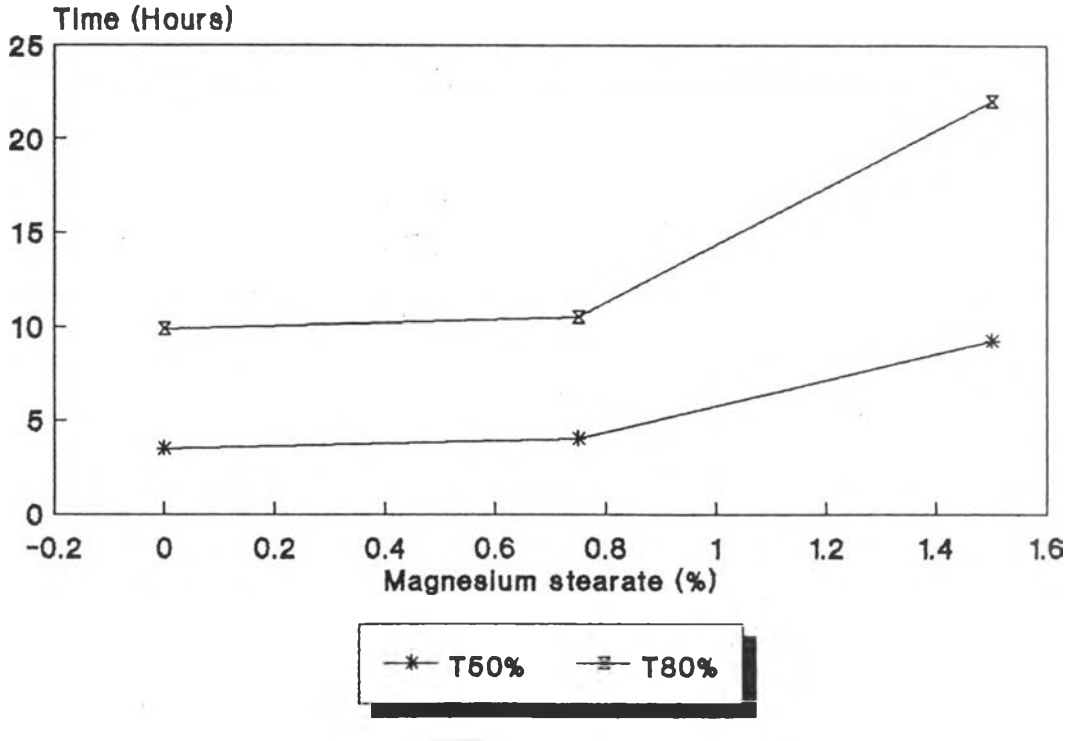


Figure 35 Effect of Magnesium Stearate on $T_{50\%}$ and $T_{80\%}$ of Spray-Dried Matrices

Table 14 Statistical Analysis of the Effect of Magnesium Stearate Concentration on $T_{50\%}$ and $T_{80\%}$ of the Matrices

Magnesium Stearate (%)	$T_{50\%}$ (hr.)	Significant Difference*
0	3.480(0.103)	← H ← H
0.75	4.013(0.150)	← H
1.5	9.265(0.088)	

Magnesium Stearate (%)	$T_{80\%}$ (hr.)	Significant Difference*
0	9.867(0.266)	← H ← H
0.75	10.518(0.189)	← H
1.5	22.021(0.284)	

* The arrow sign indicated the significant difference between the variables that specified.

H = highly significant ($p<0.01$).

2. Effect of Compressional Force on Matrices Prepared by Carver Laboratory Press

The spray dried powders were compressed into matrices with the following compressional pressures: 500 lbs, 1,000 lbs and 1,500 lbs by Carver Laboratory Press. The amount of drug release at any time interval of three-level compressional force matrices were illustrated in Figure 36 (see Appendix, Table 46). The plots of $T_{50\%}$ and $T_{80\%}$ versus those compressional force were showed in Figure 37. When compressional pressure was increased from 500 lbs to 1,000 lbs, dissolution rate in the first 6 hours was increased. But at 6-12 hours, dissolution rate was corresponding. For 1,500 lbs compressional pressure, dissolution rate was reduced.

$T_{50\%}$ of matrices at 500 lbs, 1,000 lbs and 1,500 lbs were 3.480, 3.038 and 3.797 hours respectively . $T_{80\%}$ of matrices at 500 lbs, 1,000 lbs and 1,500 lbs were 9.867, 9.514 and 11.650 hours respectively. The significant differences between the groups were presented in Table 15 (see analysis of variance in Appendix, Table 52-53). It showed that $T_{50\%}$ of matrices at various compressional forces were significantly different ($p<0.01$). $T_{80\%}$ of matrices at 500 lbs and 1,000 lbs were not significantly different from each other. $T_{50\%}$ and $T_{80\%}$ at 1,500 lbs were longest. On the other hand, $T_{50\%}$ and $T_{80\%}$ at 1,000 lbs were shortest.

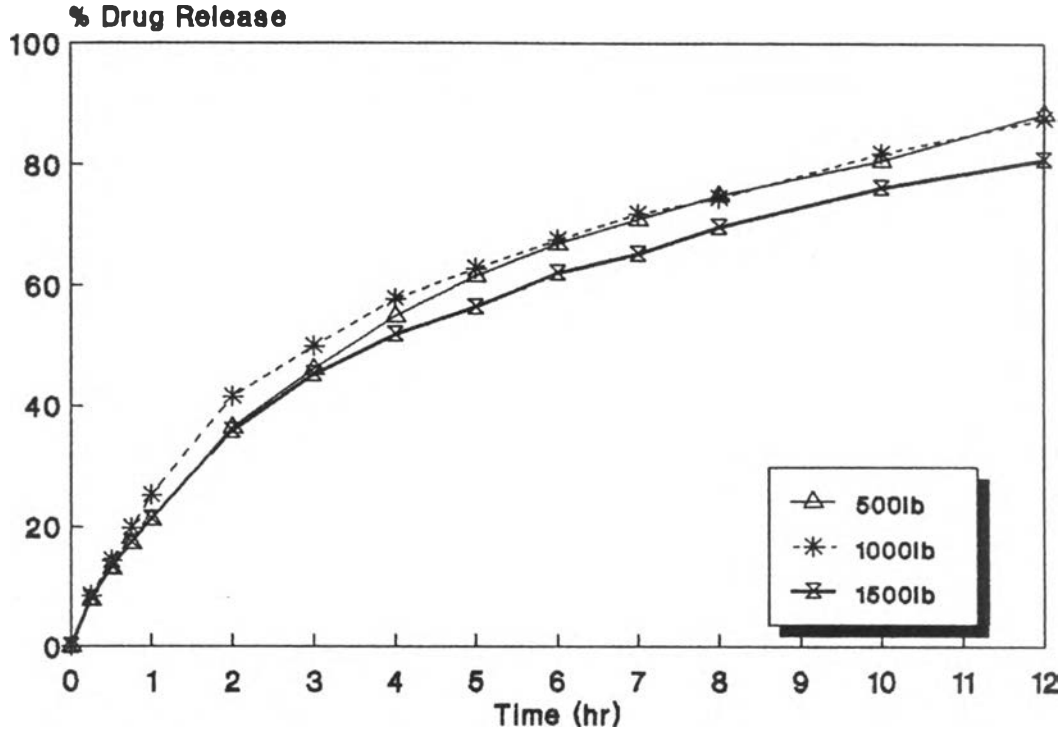


Figure 36 Effect of Compressional Force on Dissolution Profiles of Matrices Prepared by Carver Laboratory Press

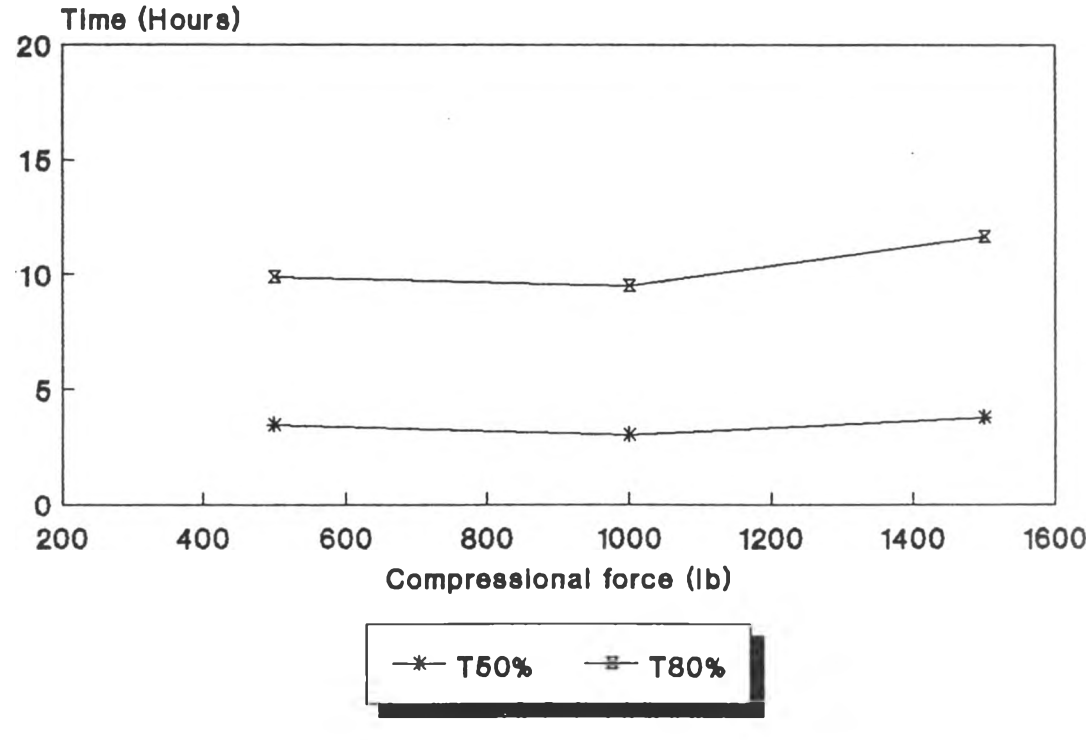


Figure 37 Effect of Compressional Force on $T_{50\%}$ and $T_{80\%}$ of Matrices Prepared by Carver Laboratory Press

Table 15 Statistical Analysis of the Effect of Compressional Force on $T_{50\%}$ and $T_{80\%}$ of the Matrices Prepared by Carver Laboratory Press

Compressional Force (lb)	$T_{50\%}$ (hr.)	Significant Difference*
500	3.480(0.103)	←H ←H
1000	3.038(0.048)	←H
1500	3.797(0.245)	

Compressional Force (lb)	$T_{80\%}$ (hr.)	Significant Difference*
500	9.867(0.266)	←H
1000	9.514(0.077)	←H
1500	11.650(0.488)	

* The arrow sign indicated the significant difference between the variables that specified.

H = highly significant ($p<0.01$).

3. Effect of Compressional Force on Matrices Prepared by Instrumented Single Punch Machine

The spray dried powders were mixed with 0.75% magnesium stearate and then compressed into matrices with instrumented single punch machine at compressional pressure : 300 lbs, 500 lbs and 700 lbs. The amount of drug release at any time interval of those matrices were presented in Figure 38 (see data in Appendix, Table 47). Dissolution profiles in the first 4 hours of three-level compressional pressure matrices were not different. After four hours, dissolution rate was orderly increased when compressional pressure at 300 lbs, 500 lbs and 700 lbs were used.

The plots of $T_{50\%}$ and $T_{80\%}$ versus this compressional force were shown in Figure 39. $T_{50\%}$ of matrices at 300 lbs, 500 lbs and 700 lbs were 3.747, 3.606 and 3.638 hours respectively. $T_{80\%}$ of matrices at 300 lbs, 500 lbs and 700 lbs were 11.624, 11.374 and 9.926 hours respectively. The significant differences between the groups were shown in Table 16 (see analysis of variance in Appendix, Table 54-55). It was revealed that compressional pressure did not significantly affected $T_{50\%}$ of matrices at 300-700 lbs. $T_{80\%}$ of matrices at 300 lbs and 500 lbs were not significantly different. $T_{80\%}$ of matrices at 700 lbs was shortest.

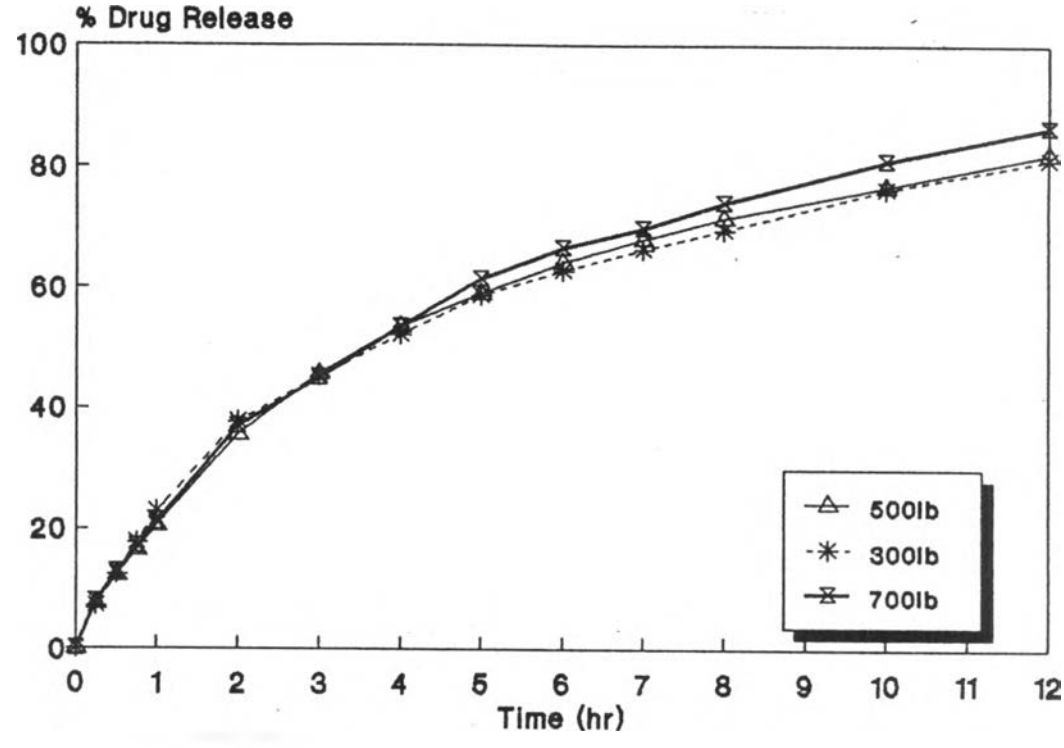


Figure 38 Effect of Compressional Force on Dissolution Profiles of Matrices Prepared by Instrumented Single Punch Machine

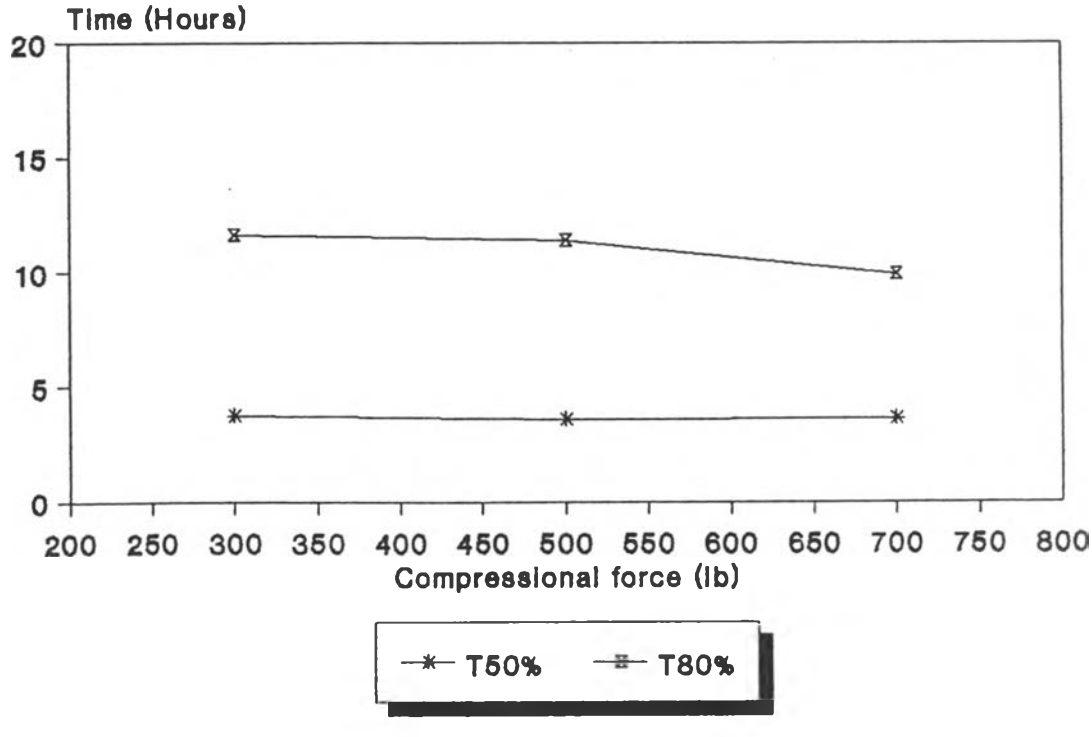


Figure 39 Effect of Compressional Force on $T_{50\%}$ and $T_{80\%}$ of Matrices Prepared by Instrumented Single Punch Machine

Table 16 Statistical Analysis of the Effect of Compressional Force on $T_{50\%}$ and $T_{80\%}$ of the Matrices Prepared by Instrumented Single Punch Machine

Compressional Force (lb)	$T_{50\%}$ (hr.)	Significant Difference
300	3.747(0.101)	
500	3.606(0.151)	None*
700	3.638(0.219)	

Compressional Force (lb)	$T_{80\%}$ (hr.)	Significant Difference**
300	11.624(0.257)	←H
500	11.374(0.349)	←H
700	9.926(0.652)	

* The value of those groups were not significantly different.

** The arrow sign indicated the significant difference between the variables that specified.

H = highly significant ($p<0.01$).

III. Reproducibility of Drug Release Pattern of Matrices Prepared by Spray Drying Technique

1. Batch to Batch Variation of Spray-Dried Matrices

The co-spray dried powders were prepared in the same condition. The powder were mixed with 0.75% magnesium stearate before compression on instrumented single punch tabletting machine at a force of 500 lbs. Consecutive three batches were produced. The amount of drug release at any time interval of consecutive three batches of matrices were plotted in Figure 40 (see data in Appendix, Table 48). Batch I matrices provided slightly lower dissolution rate between 2-10 hours than Batch II and III matrices. Dissolution rate of Batch II and III matrices were similar.

The plots of $T_{50\%}$ and $T_{80\%}$ were shown in Figure 41. $T_{50\%}$ of batch I, II and III were 3.806, 3.606 and 3.505 hours respectively. $T_{80\%}$ of Batch I, II and III were 11.350 11.374 and 10.476 hours respectively. The significant differences between the groups were shown in Table 17 (see analysis of variance in Appendix, Table 56-57). It expressed that $T_{50\%}$ of batch II and III were not significantly different. But those of batch I was significantly different from other groups. $T_{80\%}$ of batch I and II were not significantly different but those of batch III was significantly different from other groups.

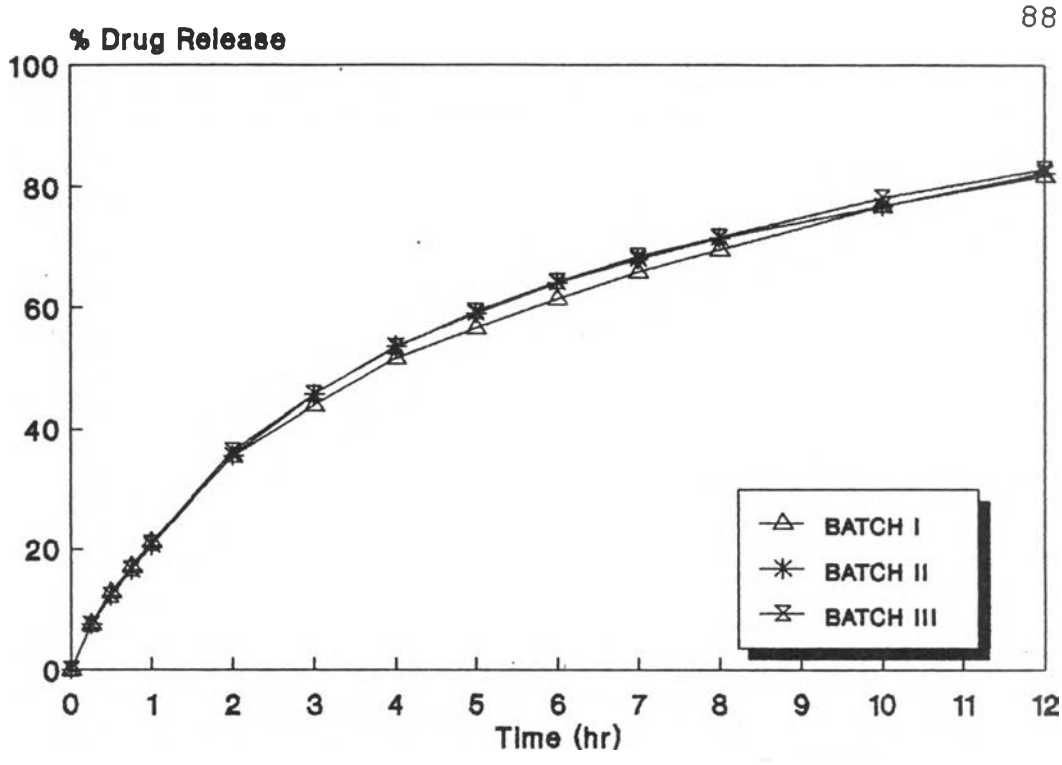


Figure 40 Comparison Dissolution Profiles of Consecutive-Three Batch

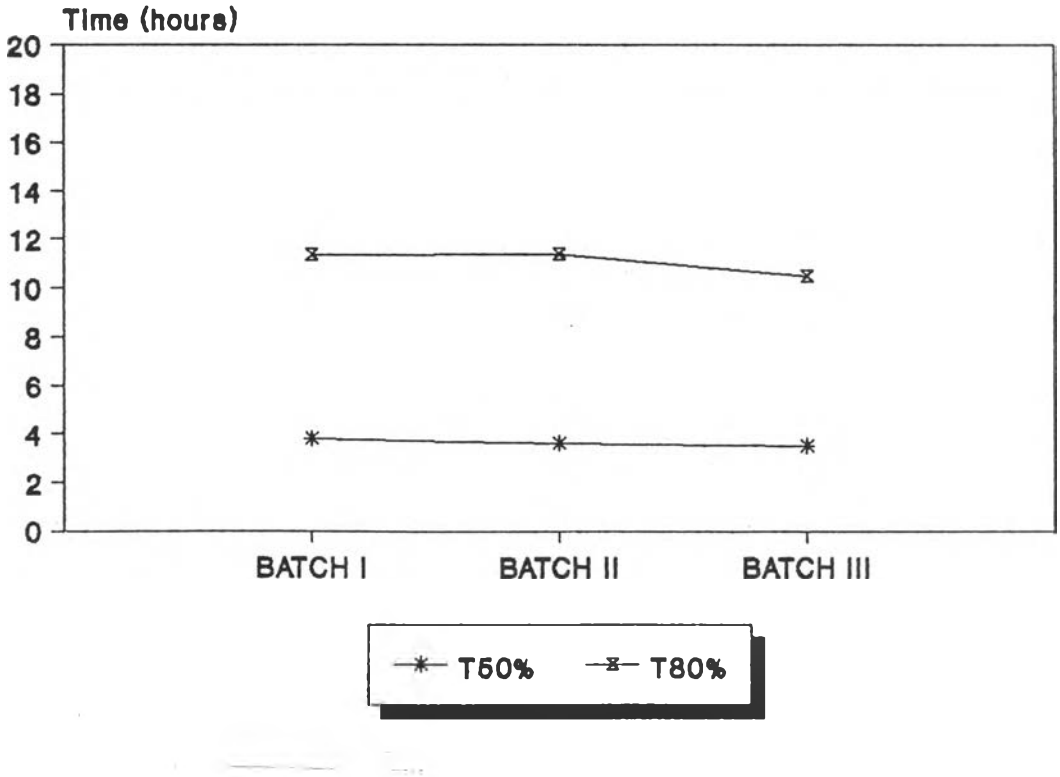


Figure 41 Comparison $T_{50\%}$ and $T_{80\%}$ of Consecutive Three Batch

Table 17 Statistical Analysis on the Variation of $T_{50\%}$ and $T_{80\%}$ of Consecutive Three Batches

Batch	$T_{50\%}$ (hr.)	Significant Difference*
I	3.806(0.071)	←H ←H
II	3.606(0.151)	←
III	3.505(0.187)	←

Batch	$T_{80\%}$ (hr.)	Significant Difference*
I	11.350(0.459)	←H
II	11.374(0.349)	←H
III	10.476(0.494)	←

* The arrow sign indicated the significant difference between the variables that specified.

H = highly significant ($p<0.01$).

Scale-up batch was prepared to yield 0.5 kg product. The amount of drug release at any time interval of scale-up batch matrices were reported in Table 49 (in Appendix). Their dissolution profiles were plotted to compare with consecutive-three batches in Figure 42. Dissolution rate in 0.1N.HCl of scale-up batch matrices was sightly higher than the consecutive three batches. But the dissolution rate in phosphate buffer pH 6.8 was similar to batch II and III.

The plots of $T_{50\%}$ and $T_{80\%}$ versus three-consecutive batches and scale-up batch were shown in Figure 43. $T_{50\%}$ and $T_{80\%}$ of scale-up batch were 3.682 and 10.571 hours respectively. The significant differences between scale-up batch and other batches were presented in Table 18 (see analysis of variance in Appendix, Table 58-59). It reported that $T_{50\%}$ of scale-up batch was not significantly different from those of batch I-III. $T_{80\%}$ of scale-up batch was not significantly different from those of batch III but different from those of batch I and II.

2. Commercial Products

Commercial products used were Nuelin$^{(R)}$ 250 mg and Theodur$^{(R)}$ 300 mg. The amount of drug release at any time interval were presented in Table 49 (in Appendix). Their dissolution profiles were plotted with spray dried matrices in Figure 44. Dissolution rate in 0.1N.HCl of

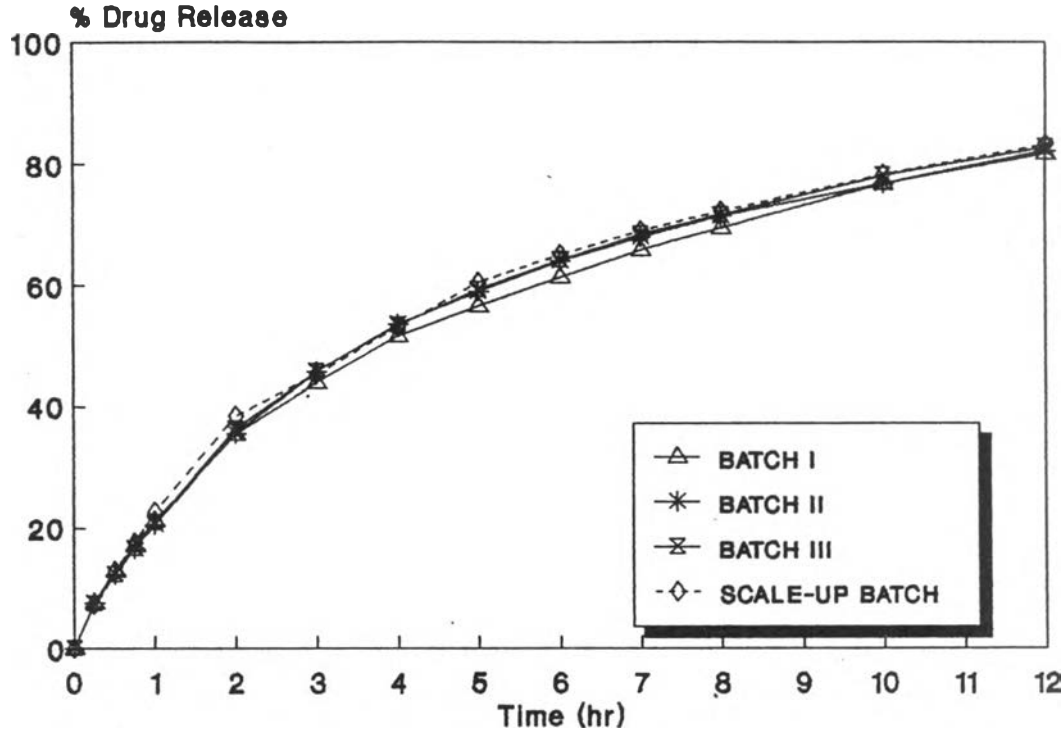


Figure 42 Comparison Dissolution Profiles of Consecutive-Three Batch and Scale-up Batch

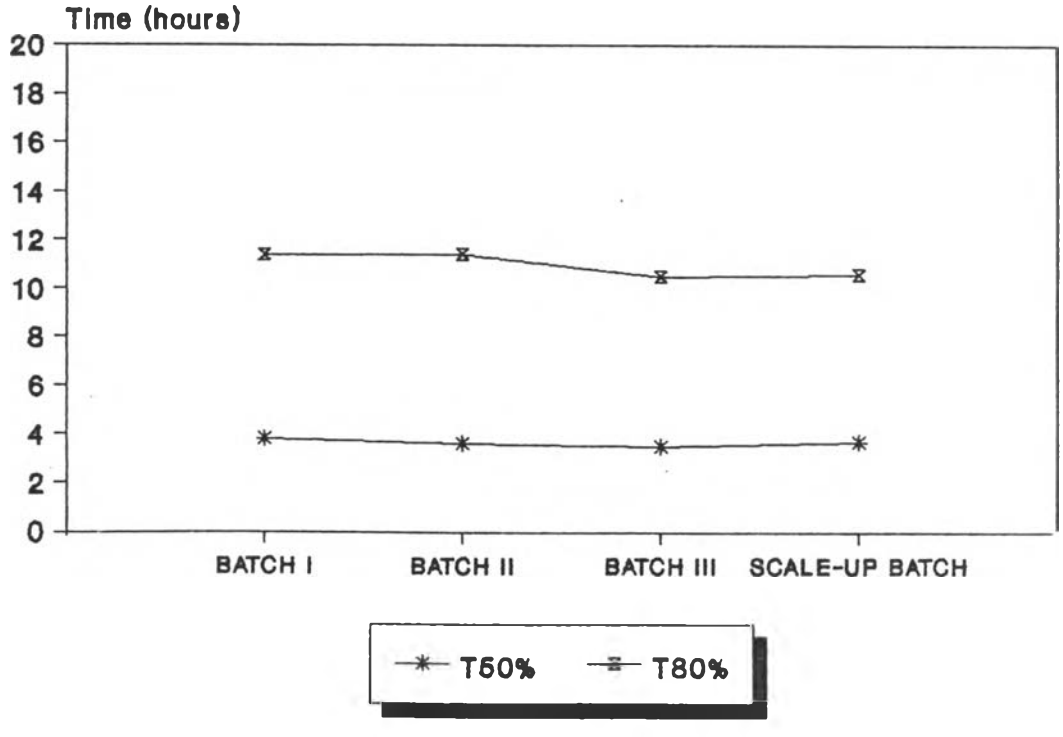


Figure 43 Comparison $T_{50\%}$ and $T_{80\%}$ of Consecutive Three Batch and Scale-up Batch

Table 18 Statistical Analysis on the Variation of $T_{50\%}$ and $T_{80\%}$ of Consecutive Three Batches and Scale-up Batch

Batch	$T_{50\%}$ (hr.)	Significant Difference*
I	3.806(0.071)	←H
II	3.606(0.151)	←
III	3.505(0.187)	←
Scale-up	3.682(0.231)	

Batch	$T_{80\%}$ (hr.)	Significant Difference*
I	11.350(0.459)	← ←
II	11.374(0.349)	← ← ←
III	10.476(0.494)	← ←
Scale-up	10.571(0.681)	←

* The arrow sign indicated the significant difference between the variables that specified.

H = highly significant ($p<0.01$).

spray dried matrices, Nuelin(R) and Theoduf(R) were orderly decreased. Patterns of Dissolution profile of spray dried matrices and Nuelin(R) were similar.

$T_{50\%}$ and $T_{80\%}$ of spray-dried matrices, Theodur(R) and Nuelin(R) were plotted in Figure 45. $T_{50\%}$ of spray-dried matrices, Theodur(R) and Nuelin(R) were 3.682, 5.124 and 5.369 hours respectively. $T_{80\%}$ of spray-dried matrices, Theodur(R) and Nuelin(R) were 10.571, 10.156 and 12.950 hours respectively. The significant differences between the groups were shown in Table 19 (see analysis of variance in Appendix, Table 60 and 61). It indicated that $T_{50\%}$ of Theodur(R) and Nuelin(R) were not significantly different. $T_{80\%}$ of Theodur(R) was not significantly different from spray-dried matrices but different from Nuelin(R).

3. Variation within Batch of Spray-Dried Matrices and Commercial Products

The amount of minimum-maximum drug release percent and differential percent from spray dried matrices and commercial products at any interval time were shown in Table 20. Differential drug release percent of six matrices prepared from Batch I at any interval time were between 0.48%-3.63%. In case of Batch II matrices, those values were between 1.25-4.97%. Differential drug release percent

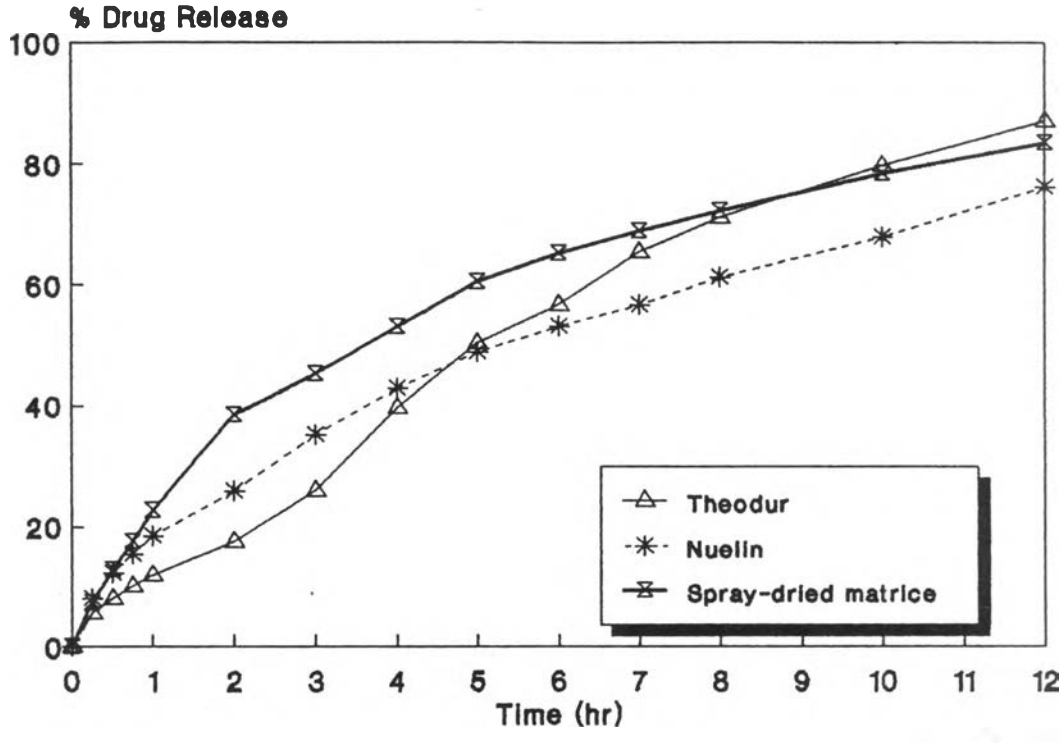


Figure 44 The Drug Release Profiles of Theodur (R), Nuelin (R) and Spray-Dried Matrices

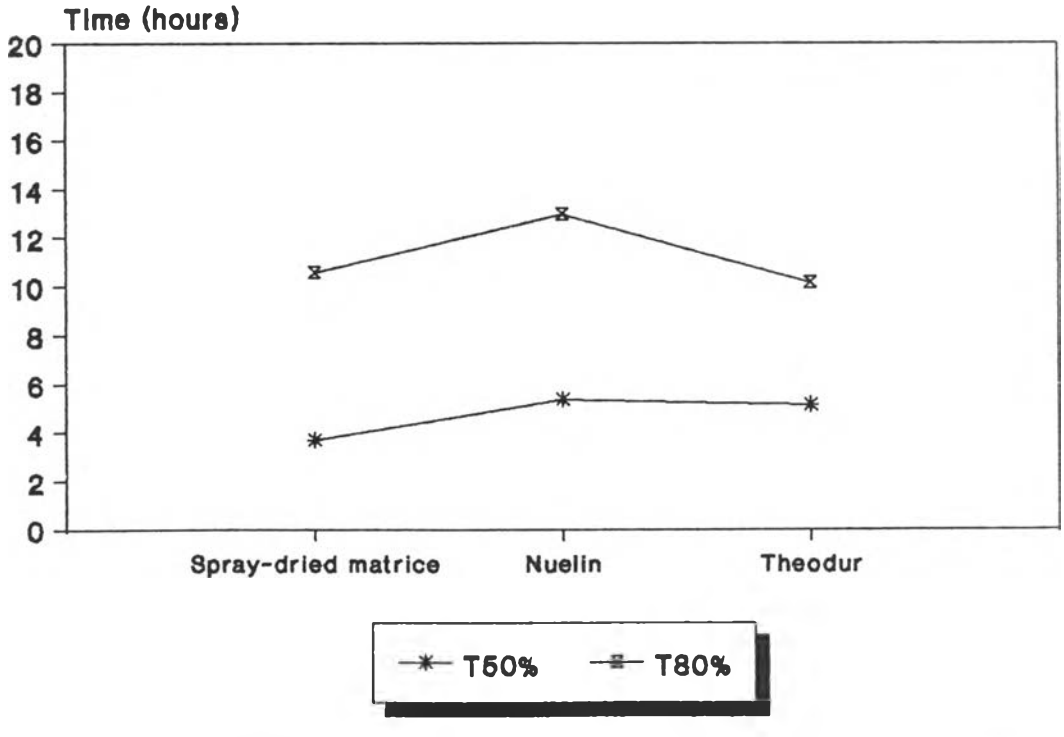


Figure 45 Comparison $T_{50\%}$ and $T_{80\%}$ of Theodur (R), Nuelin (R) and Spray-Dried Matrices

Table 19 Satistical Analysis on $T_{50\%}$ and $T_{80\%}$ of Spray Dried Matrices and Commercial Products

Formulation	$T_{50\%}$ (hr.)	Significant Difference*
Spray-Dried Matrice	3.682(0.231)	← H ← H
Nuelin (R)	5.369(0.288)	←
Theodur (R)	5.124(0.319)	←

Formulation	$T_{80\%}$ (hr.)	Significant Difference*
Spray-Dried Matrice	10.571(0.681)	← H
Nuelin (R)	12.950(0.592)	← H
Theodur (R)	10.156(0.974)	

* The arrow sign indicated the significant difference between the variables that specified.

H = highly significant ($p<0.01$).

Table 20 The Amount of Minimum-Maximum Drug Release Percent and Differential Percent from Spray-Dried Matrices and Commercial Products at any Interval Time

Formulation / Time (hr.)	Theodur (R)		Nuelin (R)	
	Min-Max*	DP**	Min-Max	DP
0.25	5.04-5.99	0.95^{L}	7.67-8.53	0.86^{L}
0.50	7.44-8.91	1.47	11.68-12.73	1.05
0.75	9.55-11.07	1.52	15.03-15.98	0.95
1	11.43-12.75	1.32	17.97-19.06	1.09
2	16.53-18.69	2.16	25.07-26.40	1.33
3	24.52-28.09	3.57	33.44-36.87	3.43
4	35.79-42.59	6.80	41.12-45.46	4.34
5	47.79-54.43	6.64	46.33-51.19	4.86
6	52.21-60.23	8.02	51.74-54.53	2.79
7	59.35-69.56	10.21	54.44-59.50	5.06
8	65.45-77.79	12.34^{H}	59.24-62.51	3.27
10	75.72-84.45	8.73	64.88-69.77	4.89
12	84.25-89.55	5.30	72.17-78.75	6.58^{H}

Formulation / Time (hr.)	Batch I		Batch II	
	Min-Max	DP	Min-Max	DP
0.25	7.47-7.95	0.48^{L}	7.02-8.27	1.25^{L}
0.50	12.55-13.19	0.64	11.75-13.29	1.54
0.75	16.81-17.60	0.79	15.69-17.36	1.67
1	20.46-22.01	1.55	19.90-21.26	1.36
2	34.27-37.14	2.87	34.75-36.64	1.89
3	42.74-45.02	2.28	43.44-47.05	3.61
4	50.80-52.27	1.47	51.43-56.40	4.97^{H}
5	55.94-57.62	1.68	57.58-60.86	3.28
6	60.35-62.59	2.24	62.46-66.10	3.64
7	65.11-66.82	1.71	66.43-70.08	3.65
8	68.82-70.68	1.86	70.41-73.54	3.13
10	75.68-78.34	2.66	75.36-79.03	3.67
12	79.80-83.43	3.63^{H}	80.60-84.00	3.40

Formulation / Time (hr.)	Batch III		Scale-up Batch	
	Min-Max	DP	Min-Max	DP
0.25	7.38-8.02	0.64^{L}	6.46-8.34	1.88^{L}
0.50	11.90-13.10	1.20	11.84-14.20	2.36
0.75	16.32-17.44	1.12	16.06-19.11	3.05
1	20.23-22.73	2.50	20.73-24.61	3.88
2	34.44-39.10	4.66	36.30-40.03	3.73
3	44.48-48.03	3.55	43.30-46.99	3.69
4	53.11-57.19	4.08	51.00-56.09	5.09
5	57.96-62.96	5.00	58.89-62.40	3.51
6	63.25-68.01	4.76	63.20-67.57	4.38
7	67.65-71.91	4.26	67.32-71.70	4.39
8	70.43-75.54	5.11^{H}	69.59-74.51	4.92
10	77.14-81.19	4.05	75.10-81.22	6.12^{H}
12	82.66-83.98	1.32	81.48-86.62	5.14

* Minimum-Maximum drug release percent at any interval time
** Differential percent of minimum and maximum drug release percent
^{L} = Lowest value ; ^{H} = Highest value

of six matrices prepared from Batch III and scale-up batch were between 0.64-5.11% and 1.88-6.12% , respectively. The commercial products, Theodur(R) and Nuelin(R), provided differential drug release percent between 0.95-12.34% and between 0.86-6.58% , respectively. Theodur(R) provided the highest differential drug release percent (12.34%). Generally, spray dried matrices gave rather low amount of differential drug release. The values of differential drug release percent of scale-up batch and Nuelin(R) were similar.

The drug release patterns of six spray dried matrices from each of batch I-III and scale-up batch were shown in Figure 46-49, respectively. The commercial products, Theodur(R) and Nuelin(R), their dissolution profiles were illustrated in Figure 50 and 51, respectively. Each dissolution profiles of six matrices of batch I seemed to be similar (Figure 45). Not only those of batch II but also batch III were slightly different. In case of scale-up batch, each dissolution profiles showed greater difference in the interval of 8-12 hours. The drug release patterns of six tablets of Theodur(R) were most different especially in phosphate buffer pH 6.8 (Figure 50). The six dissolution profiles of Nuelin(R) were slightly different (Figure 51).

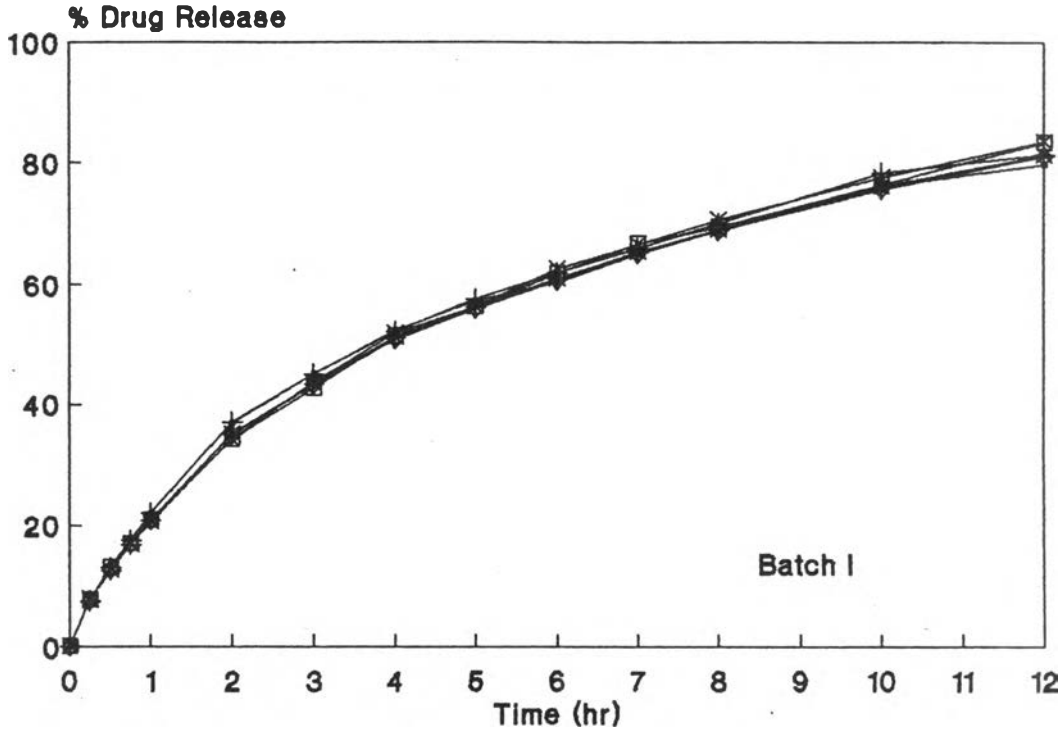


Figure 46 The Drug Release Profiles from Six Spray Dried Matrices of Batch I

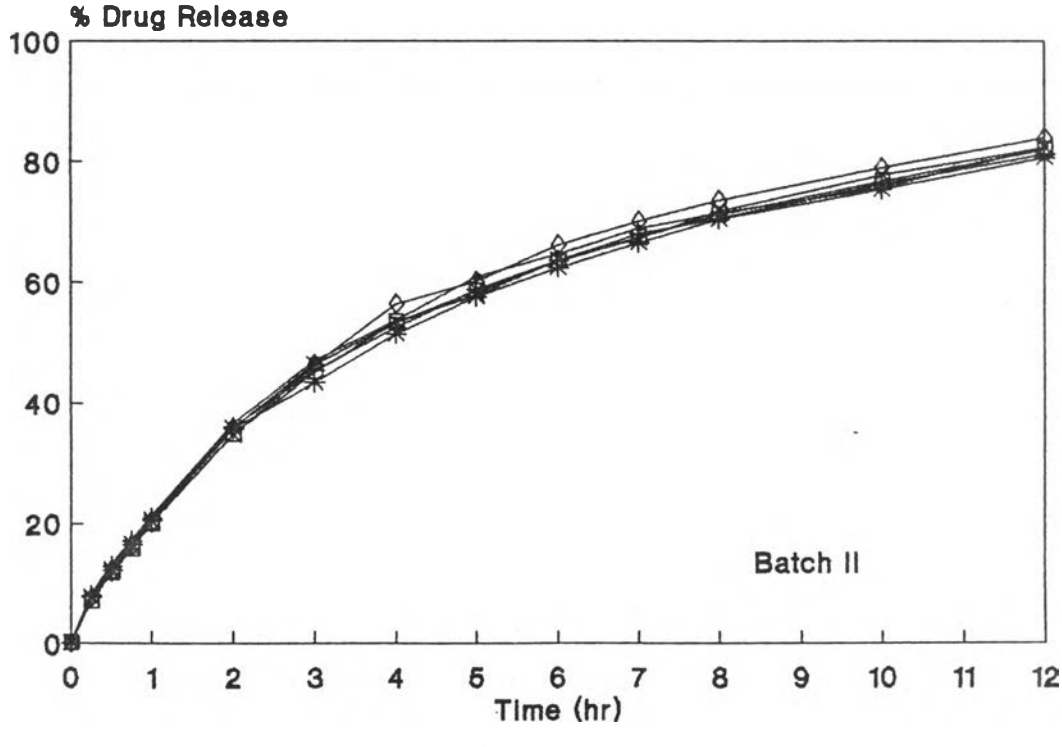


Figure 47 The Drug Release Profiles from Six Spray Dried Matrices of Batch II

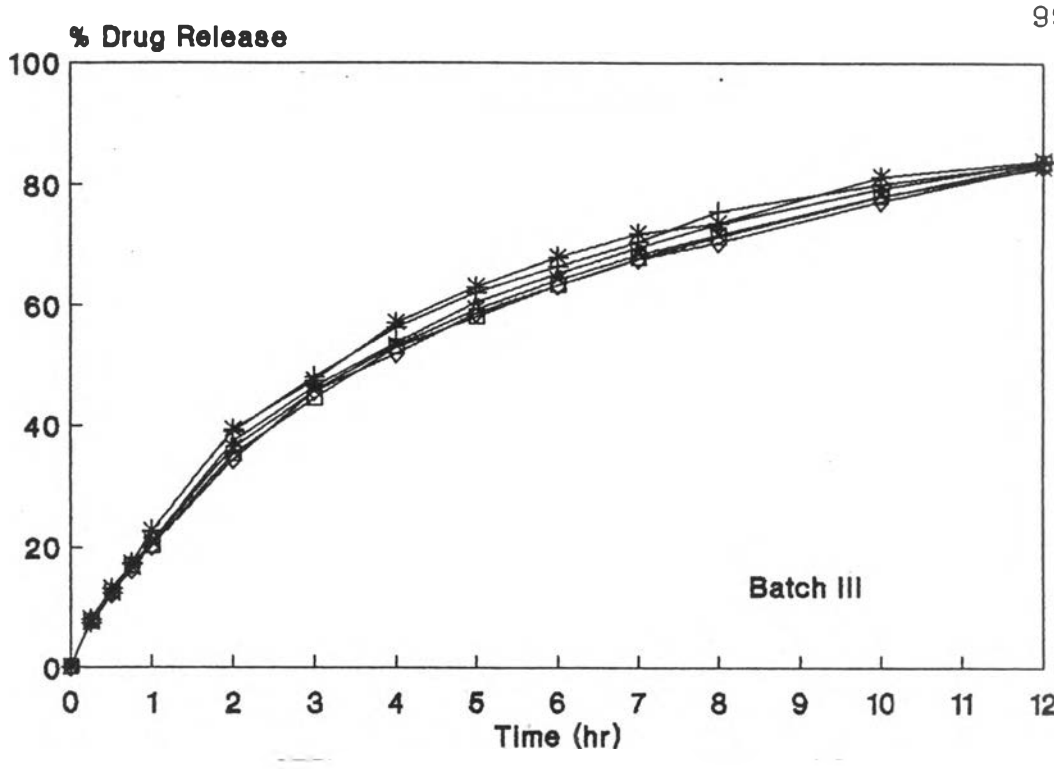


Figure 48 The Drug Release Profiles from Six Spray Dried Matrices of Batch III

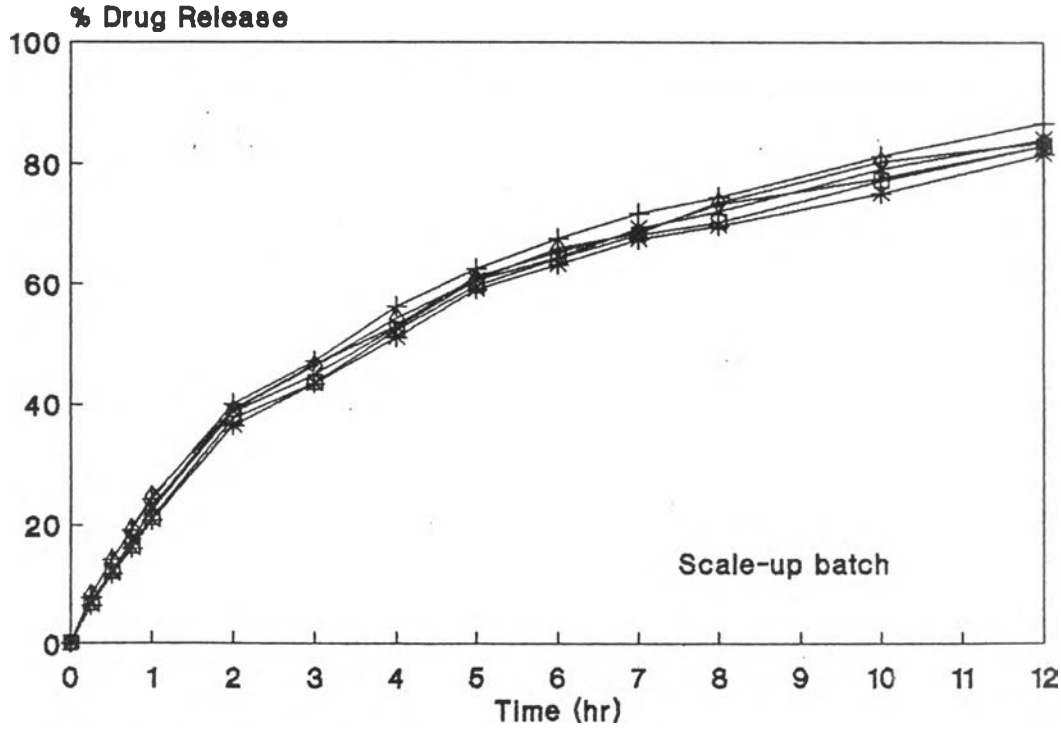


Figure 49 The Drug Release Profiles from Six Spray Dried Matrices of Scale-up Batch

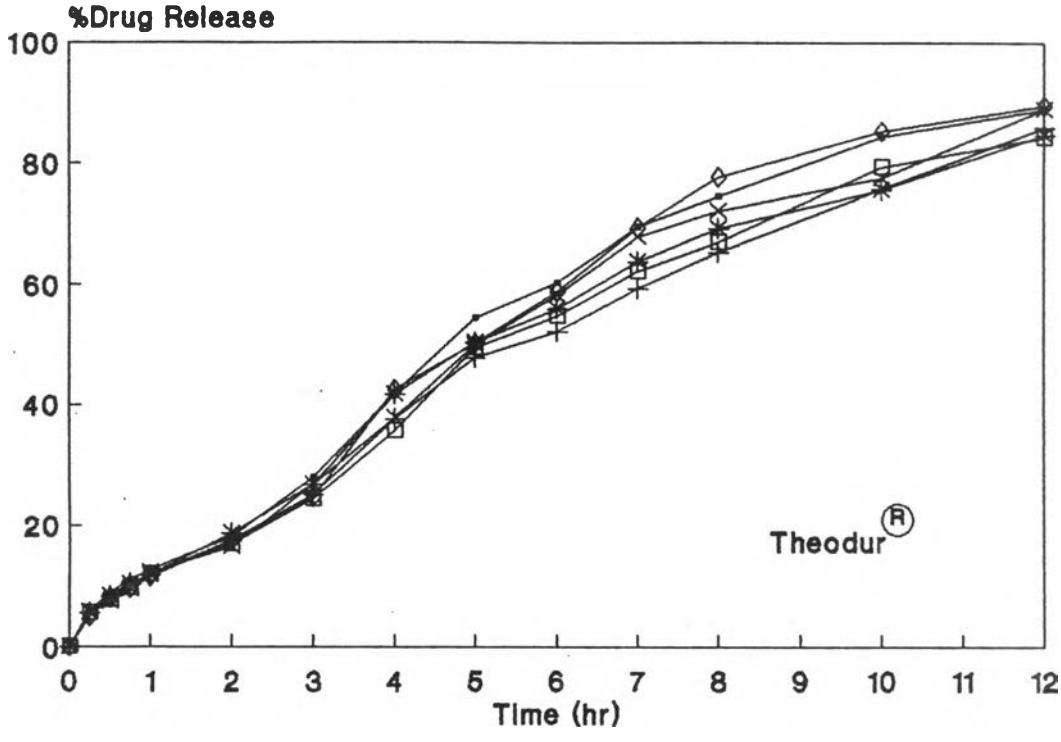


Figure 50 The Drug Release Profiles from Six Tablets of Theodur (R)

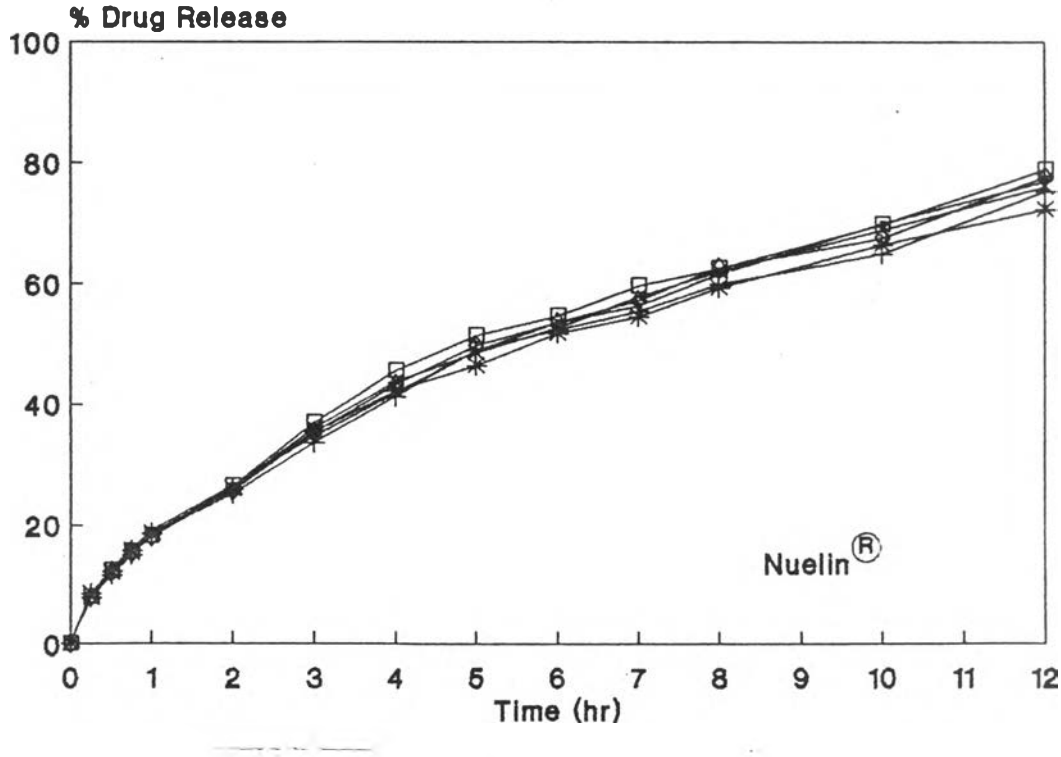


Figure 51 The Drug Release Profiles from Six Tablets of Nuelin (R)

4. Weight Variation, Thickness, Hardness, Disintegration Time of Matrices Prepared from Spray-Dried Products and of Commercial Products

Weight variation, thickness, hardness, disintegration time of matrices prepared from spray-dried products according to the study in II, III and commercial products were shown in Table 21. Average weight and standard deviation of consecutive three batches and scale-up batch ranged from 432.81-438.33 mg and 7.94-8.91 respectively. Average weight and standard deviation of Theodur(R) were 626.19 and 13.09 respectively. Average weight and standard deviation of Nuelin(R) were 493.04 and 3.98 respectively. Increase percentage of magnesium stearate produced less thickness and less hardness of matrices. Higher compressional pressure increased hardness but decreased thickness. The compressional pressure higher than 500 lbs yielded more than 20 kp hardness of matrices. Hardness and thickness of consecutive three batches and Scale-up batch were ranging from 18.48-19.53 kp and 4.474-4.531 mm respectively. Nuelin(R) exhibited the least hardness (3.80 kp) . Theodur(R) gave matrices with 12.02 kp hardness. Disintegration time of all product were more than 120 minutes.

Table 21 Physical Properties of the Matrices Prepared from Spray-Dried Powders and Commercial Products

Formulation	Physical Properties of Matrices			
	Weight‡	Thickness‡‡ (mm)	Hardness‡‡ (Kp)	Disintegration Time(min)‡‡‡
EFFECT OF MAGNESIUM STEARATE (according to the study in II(1))				
+0% Mg	427.09(1.12)‡‡‡‡	4.226(0.033)	15.38(1.90)	>120
+0.75% Mg	433.75(0.65)	4.059(0.021)	13.37(1.12)	>120
+1.5% Mg	436.23(0.98)	4.015(0.045)	10.74(0.94)	>120
EFFECT OF COMPRESSIONAL FORCE (by Carver Laboratory Press according to the study in II(2))				
500 lbs	427.09(1.12)	4.226(0.033)	15.38(1.90)	>120
1000 lbs	432.57(1.73)	4.038(0.047)	>20	>120
1500 lbs	432.21(0.64)	3.921(0.027)	>20	>120
EFFECT OF COMPRESSIONAL FORCE (by Instrumented Single Punch Machine according to the study in II(3))				
300 lbs	438.68(5.74)	4.945(0.291)	8.812(0.99)	>120
500 lbs	432.81(8.44)	4.474(0.038)	18.83(1.40)	>120
700 lbs	431.09(5.64)	4.363(0.036)	>20	>120
CONSECUTIVE AND SCALE-UP BATCH (according to the study III)				
Batch I	438.33(7.94)	4.526(0.035)	18.48(2.21)	>120
Batch II	432.81(8.44)	4.474(0.038)	18.83(1.40)	>120
Batch III	435.62(8.37)	4.486(0.057)	19.86(0.36)	>120
Scale-up batch	435.20(8.91)	4.531(0.066)	19.53(1.19)	>120
Theodur	626.19(13.09)	7.546(0.089)	12.02(1.58)	>120
Nuelin	493.04(3.98)	5.772(0.039)	3.80(0.24)	>120

‡ Average from twenty determinations
‡‡ Average from ten determinations
‡‡‡ Average from six determinations
‡‡‡‡ Standard deviation

5. Physical Properties of Spray-Dried Powders of Consecutive-Three Batches and Scale-up Batch

5.1 Morphology of Spray-Dried Powders

The photomicrographs of spray-dried powder of batch I-III and scale-up batch according to the study in III were shown in Figure 52-55 respectively. All spray dried powders had apparently similar characteristics. The size of particles were generally larger than 10 um.

5.2 Angle of Repose, Bulk Density , Tapped Density and Compressibility

Angle of repose, bulk density, tapped density and compressibility of consecutive three batches and scale-up batch were shown in Table 22. Angle of repose of batch I-III and scale-up batch was in the range of 31.99-34.14 °. Bulk and tapped density were ranging from 0.459-0.475 g/ml and 0.655-0.668 g/ml respectively. %Compressibility was ranging from 28.89-29.92%. The highest and lowest values of bulk and tapped density were obtained from batch II and scale-up batch respectively.

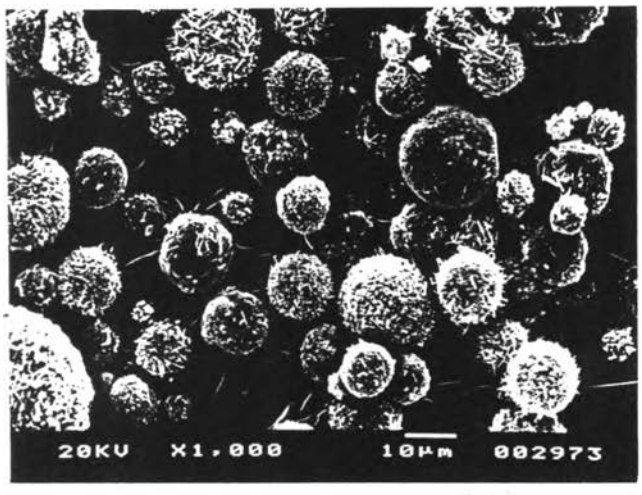


Figure 52 Photomicrograph of Spray Dried Particles of Batch I

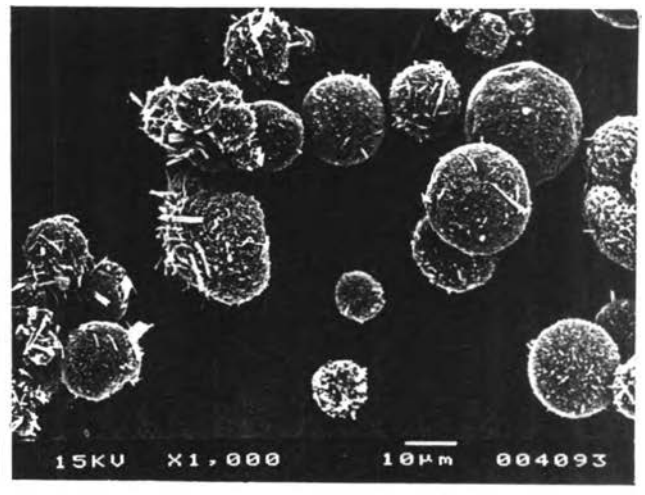


Figure 53 Photomicrograph of Spray Dried Particles of Batch II

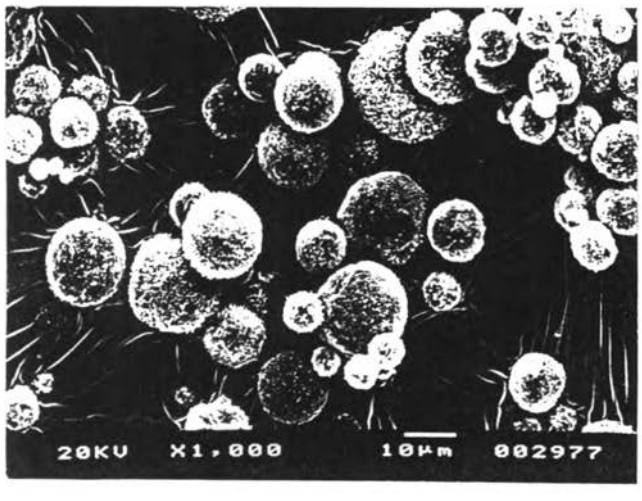


Figure 54 Photomicrograph of Spray Dried Particles of Batch III

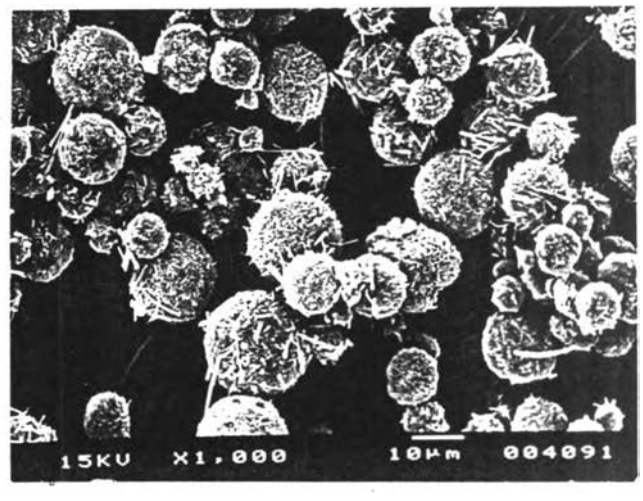


Figure 55 Photomicrograph of Spray Dried Particles of Scale-up Batch

Table 22 Angle of Repose, Bulk Density, Tapped Desity and Compressibility of Products from Consecutive-Three Batches and Scale-up Batch

Formulation	Angle of Repose (degree)	Bulk Density (g/ml)	Tapped Density (g/ml)	Compressibility (%)
Batch I	31.99	0.462	0.657	29.68
Batch II	33.97	0.475	0.668	28.89
Batch III	34.14	0.463	0.656	29.42
Scale-up Batch	32.34	0.459	0.655	29.92

5.3 Particle size distribution

The particle size distribution of the powders was shown in Table 62 (see Appendix). The particle size distribution was depicted in Figure 56 . Values of cumulative % frequency undersize were transformed into Z value (standard score) which presented in Table 63 (see Appendix) and plotted versus particle size in Figure 73-74 (in Appendix). D_{50} of products was shown in Table 23.

Particle size distribution of consecutive three batches and scale-up batch was not much different (Figure 56). The size of those particles were mostly less than 45 μm. D_{50} of consecutive three batches ranged from 22.71-31.41 μm. The Largest D_{50} (37.57 μm) was taken from scale-up batch.

Table 23 Geometric Mean Diameter of Spray-Dried Product from Consecutive-Three Batches and Scale-up Batch

Formulation	D50* (μm)
Batch I	22.71
Batch II	31.41
Batch III	27.69
Scale-up Batch	37.57

*Geometric mean diameter

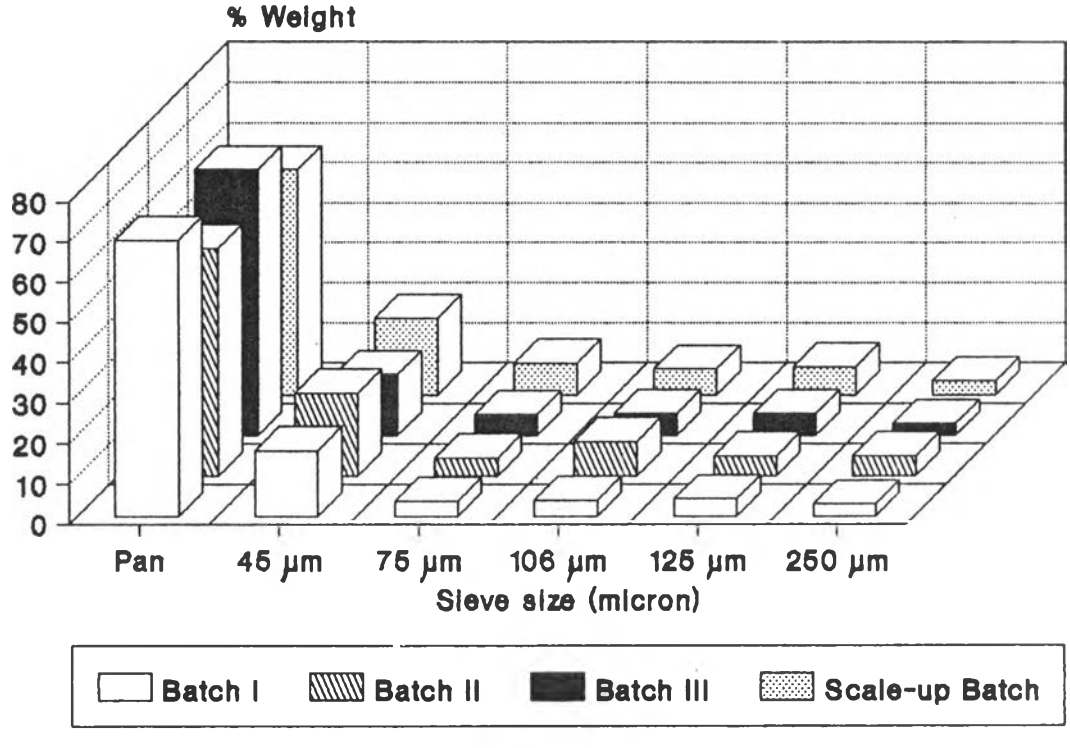


Figure 56 The Particle Size Distribution of Consecutive Three Batch and Scale-up Batch

5.4 Percent Recovery

The percent recovery of spray-dried products of the three consecutive batches and scale-up batch were shown in Table 24. The total percent recovery of batch I-III was approximately 84%. The total percent recovery was increased in scale-up batch. The percent recovery of batch I-III not only in collector but also in chamber was similar. The percent recovery in collector of scale-up batch was higher than those of batch I-III.

Table 24 The Percent Recovery of Spray-Dried Product from Consecutive-Three Batches and Scale-up Batch

Formulation	Percent Recovery		
	Collector	Chamber	Total
Batch I	33.30	51.10	84.40
Batch II	33.45	49.45	82.90
Batch III	35.30	49.00	84.30
Scale-up Batch	43.40	48.08	91.48

6. Morphology of Spray Dried Matrices and Nuelin(R) Before and After Release

The photomicrographs of spray-dried matrices and Nuelin(R) (before release testing) in surface view and cross section were shown in Figure 57-58(A,B). Surface view of spray dried matrices in Figure 57(A,B) showed that the matrices was composed of compressed microspheres. The microcrystals of theophylline could be found on them. More interparticular spaces were found than those of Nuelin(R). Surface view of Nuelin(R) had rather smooth surface (Figure 58). Cross section of spray dried matrices could be clearly seen the whole compressed microsphere and the more interparticular space, Cross section of Nuelin(R) was rough.

The photomicrographs of Nuelin (R) (after release testing) on surface view and cross section were shown in Figure 59-60 (A,B). In Figure 59 A, the larger spaces were found and their surface was very rough. More spaces were found on the cross section of Nuelin(R) than before the release testing. However, they were less than those of the surface view (Figure 59 A). Low amount of crystals were found as shown in Figure 60 B.

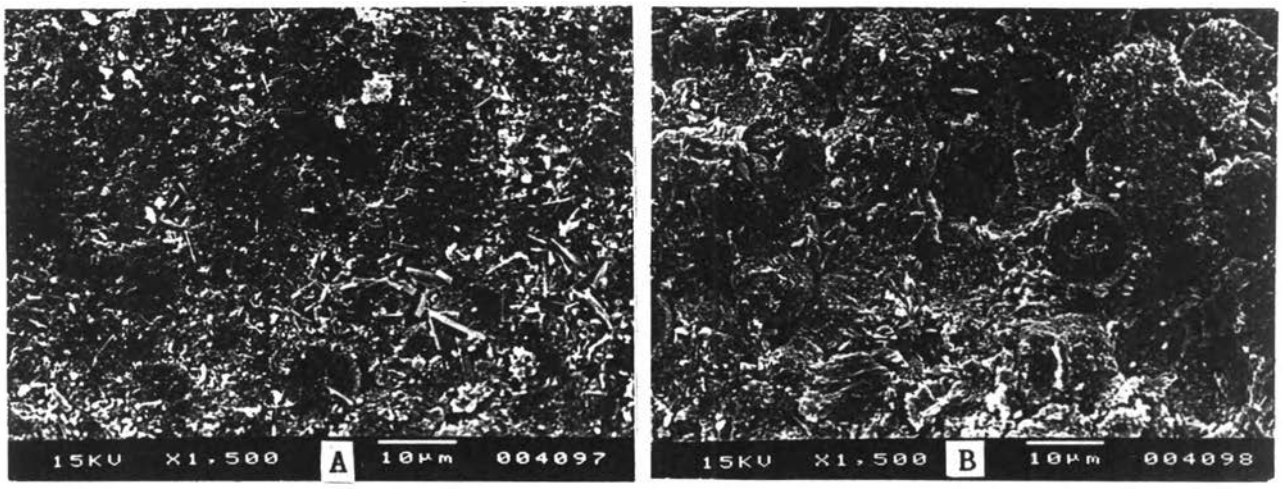


Figure 57 Photomicrographs of Spray-Dried Matrices before Release Testing

Key A: Surface View x 1,500

B: Cross Section x 1,500

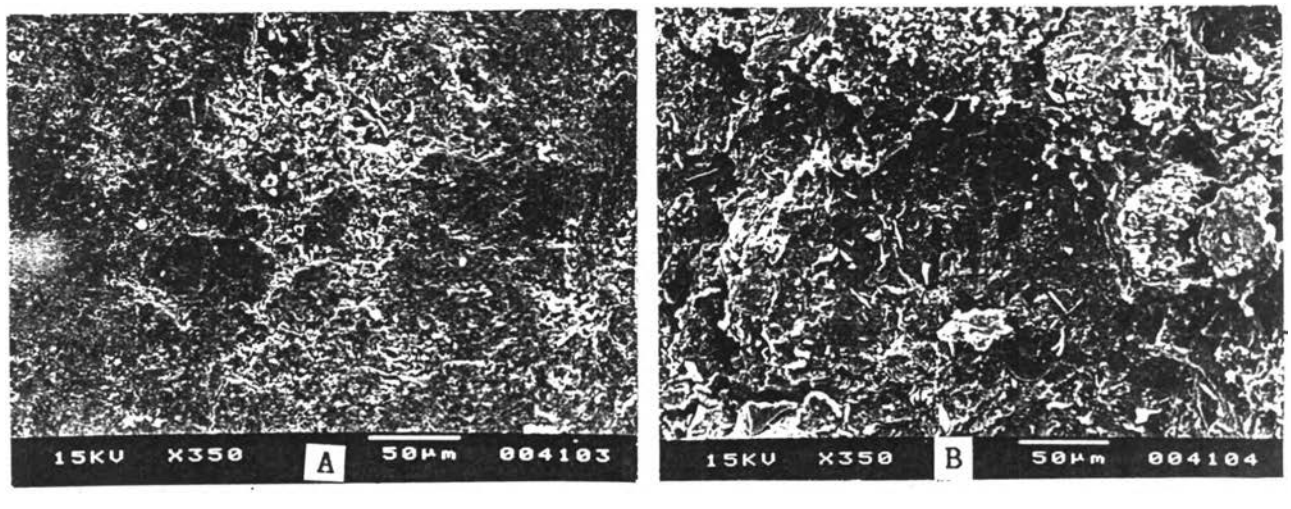


Figure 58 Photomicrographs of Nuelin(R) before Release Testing

Key A: Surface View x 350

B: Cross Section x 350

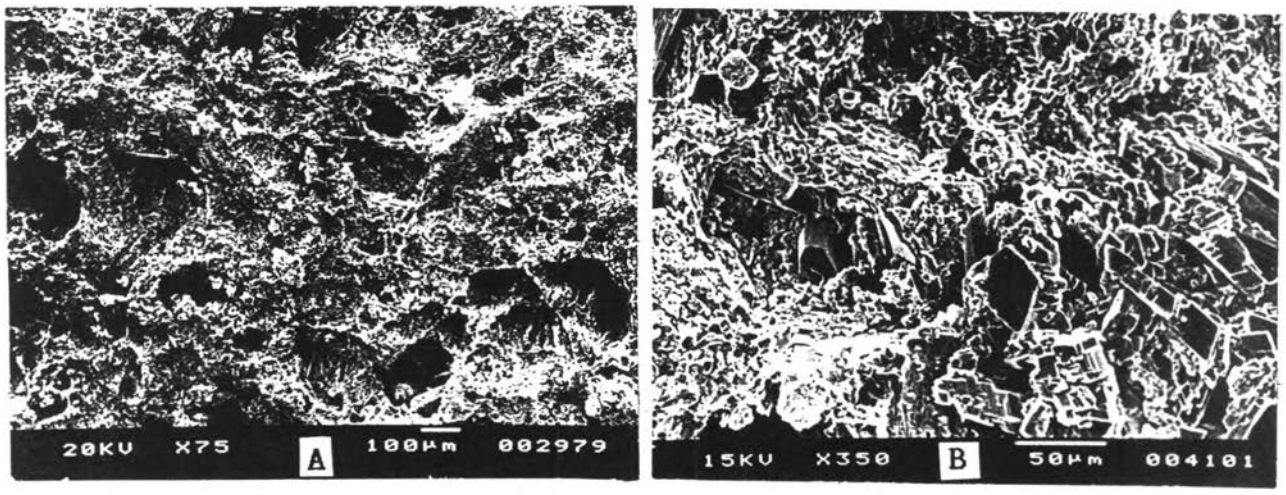


Figure 59 Photomicrographs of Nuelin(R) after Release Testing (Surface View)
Key (A x 75 , B x 350)

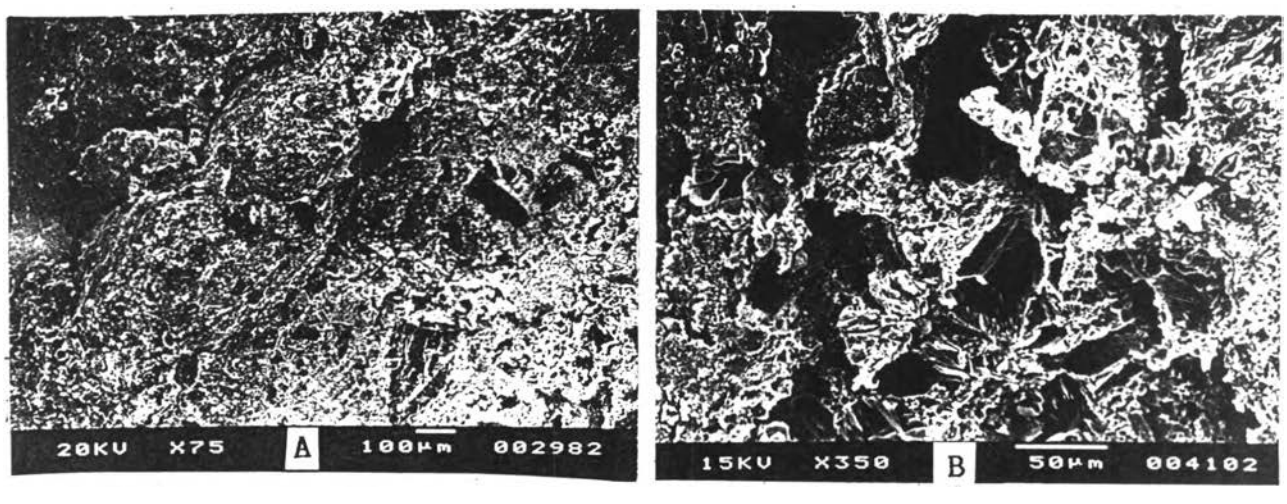


Figure 60 Photomicrographs of Nuelin(R) after Release Testing (Cross Section)
Key (A x 75 , B x 350)

The photomicrographs of spray dried matrices after release testing on surface view and cross section were shown in Figure 61-62(A,B). A lot of spaces could be seen (Figure 61). The microcrystals of theophylline were embedded in the surface. Those microcrystals might be connected with residual polymer in formulation. Figure 62 depicted the cross section of spray dried matrices, the space and the microcrystals also could be found.

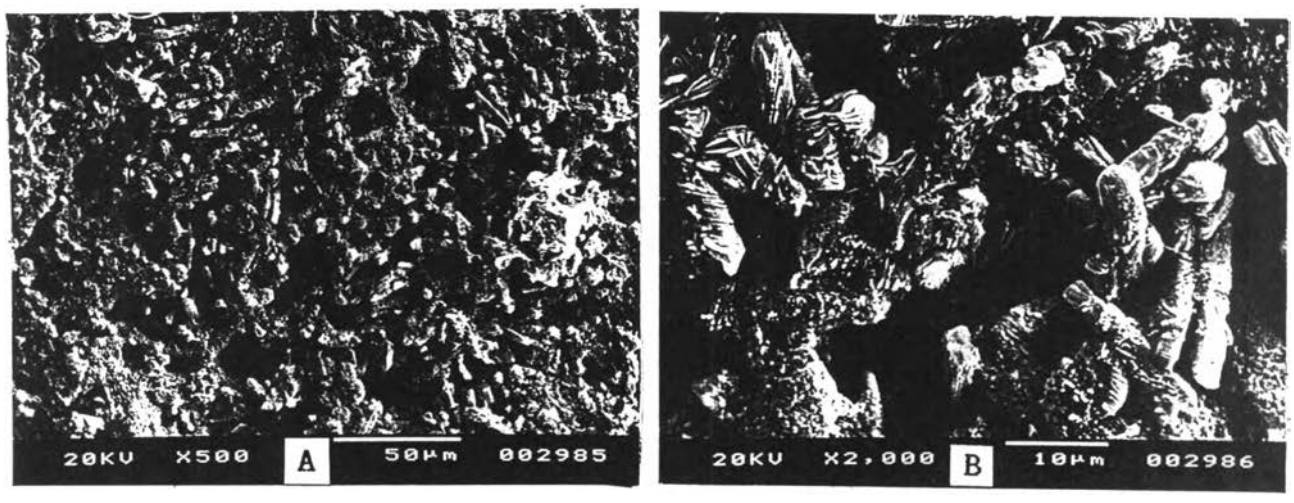


Figure 61 Photomicrographs of Spray-Dried Matrices after Release Testing (Surface View) Key (A x 500 , B x 2,000)

Figure 62 Photomicrographs of Spray-Dried Matrices after Release Testing (Cross Section) Key (A x 500 , B x 2,000)