CHAPTER IV

PROCESSING FACTORS AFFECTING PHYSICAL PROPERTIES OF COMPOSITE PARTICLES OF RICE STARCH AND MICROCRYSTALLINE CELLULOSE

Introduction

Base on the evaluation of powder, tablet properties, and proper quantity of MCC in the formulation, the composite particles composed of RS and VJM in the ratio of 7 : 3 was, therefore, chosen for further investigation and development as the direct compression excipient. Due to the processing variables of spray drying technique, also affect the physical properties of both powder and tablets. Therefore, processing factors such as concentration of feed suspension, feed rate, temperature, and atomizing pressure were assessed to identify the effect of these factors on the physical properties of the resulting powder by using full factorial design. The objectives of the study described in this chapter are:

1. To determine the effect of processing factors on the physical properties of powder and tablets obtained from previous selected formula (i.e. RS : VJM at 7 : 3)
2. To select the proper processing condition for future investigation of the scale up and reproducibility studies in chapter V

Materials and Methods

Materials

Rice starch	(Cho Heng Co., Ltd., Thailand)
Microcrystalline cellulose	(Vivapur®101, Lot No. 5610102917, J.Rettenmaier & Söhne, Germany)
Deionized water	

Methods

1. Preparation of Formulations

Rice starch and VJM in the ratio of 7 : 3 were weighed and mixed with deionized water to obtain the total weight of 1 kg. Then the suspension was mixed thoroughly with the aid of homoginizer for 10 minutes to obtain homogeneous suspension. The suspension was subsequently spray dried. Full factorial design was used for spray drying the formulations. The conditions varied were concentration, feed rate, inlet temperature, and atomizing pressure and are shown in detail in Table 4-1.

2. Evaluation of Spray Dried Powders

2.1 Physical Properties of Powder

Percent LOD, morphology and flow property were evaluated by using moisture analyzer, SEM and powder characteristics tester, respectively. The testing details used were the same as previously described.

2.2 Particle Size and Size Distribution

Condition and equipment used were the same as previously described.

3. Tablet Evaluation

500 ± 5 mg of the powders obtained from each processing condition were weighed and compressed by using hydraulic press at compression force of 2000 lb. Flat- faced punches and die (12.7 mm in diameter) were used for tabletting. The resulted

Table 4-1 Full factorial design of spray drying process for the preparation of composite particles.

Formulations Code	Experiment	Factors				Run Order
		A	B	C	D	
F1	--	-	-	-	-	8
F2	a	+	-	-	-	11
F3	b	-	+	-	-	1
F4	ab	+	+	-	-	13
F5	c	-	-	+	-	14
F6	ac	+	-	+	-	4
F7	bc	-	+	+	-	9
F8	abc	+	+	+	-	6
F9	d	-	-	-	+	16
F10	ad	+	-	-	+	7
F11	bd	-	+	-	+	3
F12	abd	+	+	-	+	15
F13	cd	-	-	+	+	12
F14	acd	+	-	+	+	2
F15	bcd	-	+	+	+	10
F16	abcd	+	+	+	+	5

Factors		**Low [-]**	**High [+]**
A	Concentration (%w/w)	10% w/w	20% w/w
B	Feed rate (g/min.)	20 g/min	30 g/min
C	Inlet temperature (°C)	130°C	150°C
D	Atomizing pressure	1 bar	3 bar

tablets were determined as follows: hardness, thickness, and diameter of tablets prepared were evaluated by tablet hardness Tester. Percent friability and disintegration time were determined by using Roche Friabilator and USP disintegration apparatus, respectively. The number of tested tablets and conditions were the same as mentioned earlier.

4. Data Analysis

Factors and responses data were analyzed by using Design - Expert® 6 for windows program. Statistical evaluation was performed using ANOVA test and $p < 0.05$ was considered to be statistically significant.

Results and Discussion

Processing factors affecting physical properties of spray-dried powder were examined by using single experiment of full factorial design at two levels. The experiment was run at random as shown in Table 4–1. Independent factors used in this study were concentration of feed suspension, feed rate, inlet temperature, and atomizing pressure. Percent yield, flowability index, % LOD of resulted powder formulations, hardness of prepared tablet from spray dried powder, and spray drying time were dependent variables and used to calculate the effect of independent factors. From preliminary study, inlet temperature, which was lower than 130 °C could not dry the atomized droplets from rotary wheel and leaded to wet the chamber of the spray dryer. The inlet temperature exceeding 150 ° C would give outlet temperature too high (higher than 95 °) which might damage the spray drying apparatus employed in this experiment. Moreover, previous report by other researchers indicated that the excessive high outlet temperature (over 100 °C) caused discoloration of the spray-dried product between hydroxypropyl starch and cellulose (Ohno, 1986; Ohno and Ikeda, 1991). They also suggested for keeping the outlet temperature around 40 ° ± 5 °C by regulating the flow rate of the drying air and inlet temperature up to the level of 400 °C could be used without causing any problem. Due to the limitation of regulating of the drying air in this work, then the temperature at 130 ° and 150 ° C were used as low and high level. Concentration more than 20% w/w could not produce a smooth and continuous spray due to nozzle clogging especially during the last period of spray drying process of formulation with the lowest feed rate and the highest inlet temperature. Feed rate more than 30 g/minute made the chamber too wet and the yield lower than 40 % by the adhesion of the product to the wall of drying chamber was obtained. Then the low and high level of concentration were 10 % and 20 %w/w, and the feed rate of 20 and 30 g/minute were selected. The last independent factor, atomizing pressure was set at 1 and 3 bar for low and high level. The atomizing pressure over 3 bar produced particle size too small and led to a reduction in flowability of the powder which was not suitable to be used as directly compressible diluent.

SEM photomicrographs of F1 to F16 are shown in Figures 4–1 to 4–4. The composite particles of all formulations were in spherical forms. At high magnification, MCC and rice starch particles were partial combined at the contacted point of the aggregated particles. Physical properties of powder are tabulated in Table 4–2. Percent yield, and percent LOD of the all formulations were around 44.82 –73.10% and 3.55 – 7.83 %, respectively. Angle of repose, % compressibility and flowability index of all formulations were around 28.2 – 43.2, 17.42 – 23.75%, and 59.5 – 70.7, respectively. The upper half of the formulations (F1 – F8) seemed to have lower % yield but higher flowability than the lower half of the formulations (F9 – F16) as could be seen by the lower value of % yield, angle of repose, and % compressibility but higher value of flowability index. One reason for the higher flowability was due to the larger particle size of the spray dried powder as indicated in Table 4–3. This was due to the lower atomizing pressure was used in these formulations (F1-F8). It should be noted that the upper half of the formulations had the tendency to have larger particle size and narrower distribution (smaller span value) than the lower half one. Hardness, % friability, and DT of prepared tablets were around 146.6 – 209.4 N, 0.20 – 0.40%, and 2.15 – 3.09 minutes, respectively as indicated in Table 4-4. Only hardness values were fluctuated according to the formulations while % friability and DT values were slightly different in all formulations.

To investigate factors, which would affect the physical properties of powder and tablets. Percent yield, % LOD, flowability index, hardness, and spray drying time are shown in Table 4–5 and used as responses. Due to this experiment was single replicate then the data were treated and analyzed as described by Montgomery, 1991. The estimated effects of factors on response were calculated by Yates's algorithm (Box and Hunter, 1978). The estimated effects were plotted on normal probability scale to classify the important effect of factors. The effects that are normally distributed and tend to fall along a straight line on this plot are negligible while significant effects will far from the line. From the large effects determined by normal probability plot, all of negligible effects were combined as an error term in ANOVA table to determine the significant

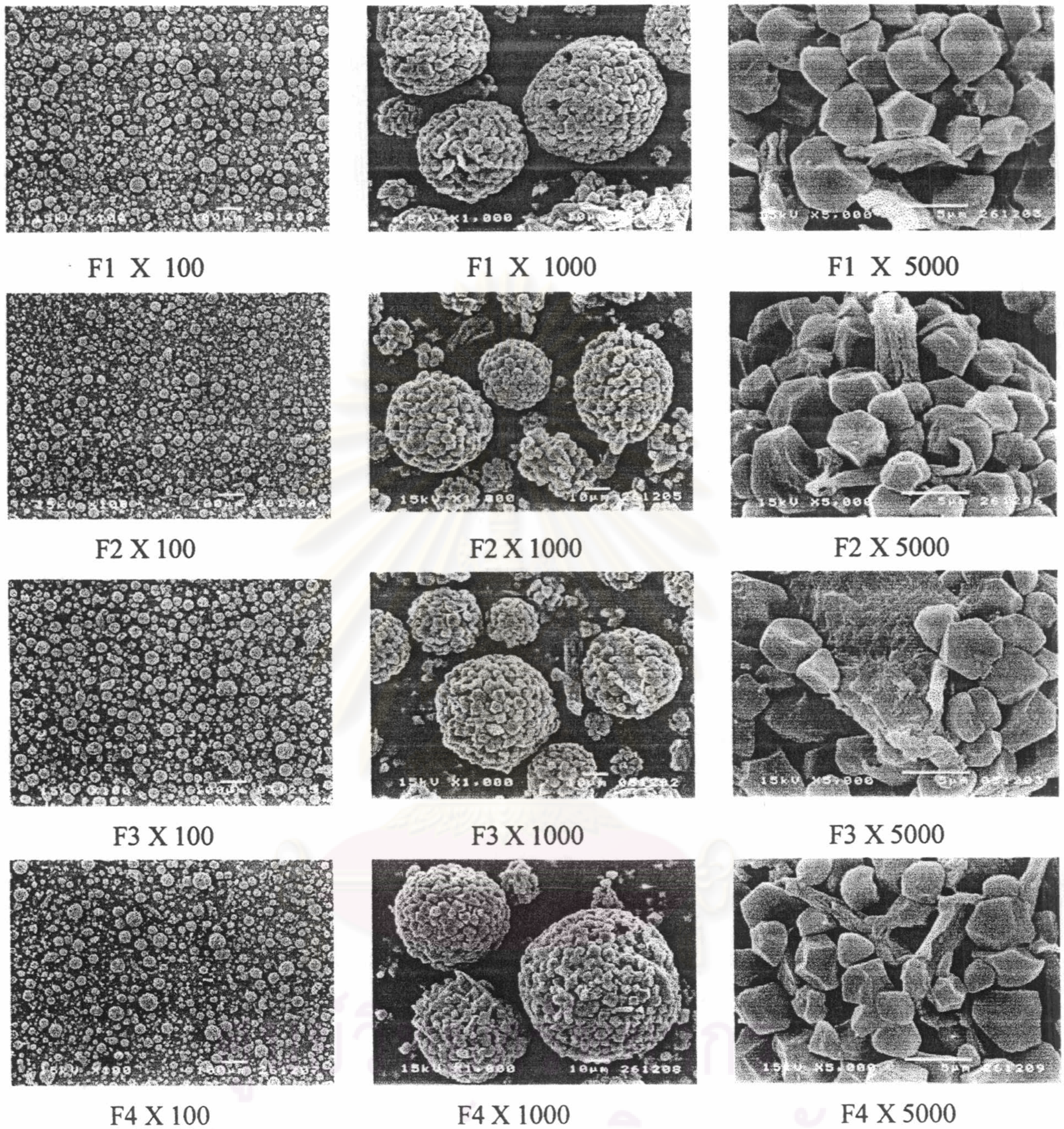
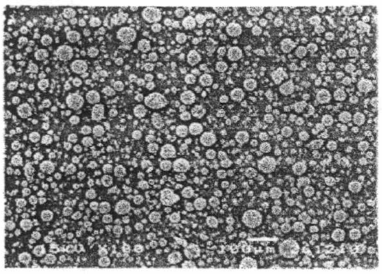
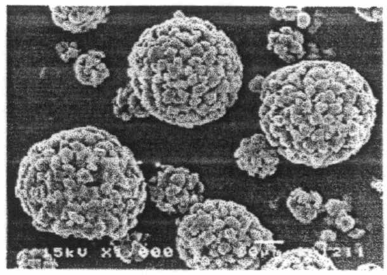


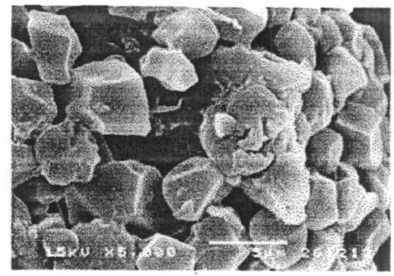
Figure 4-1 SEM photomicrographs of F1 to F4.



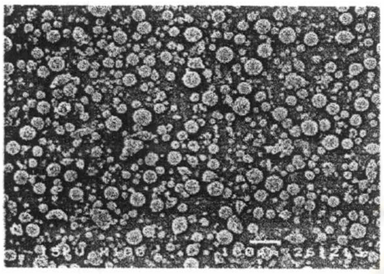
F5 X 100



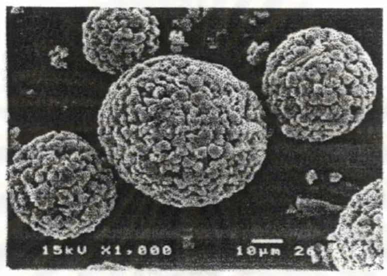
F5 X 1000



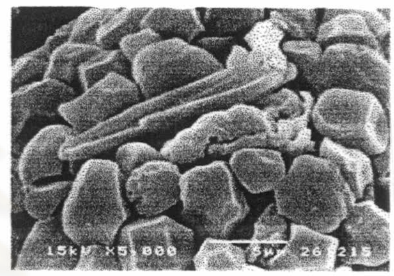
F5 X 5000



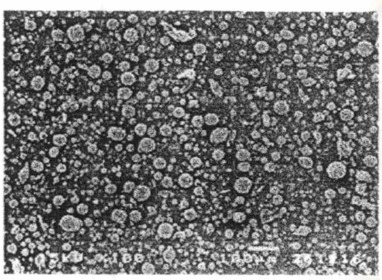
F6 X 100



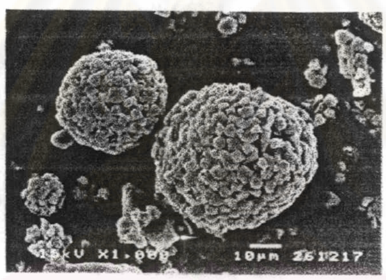
F6 X 1000



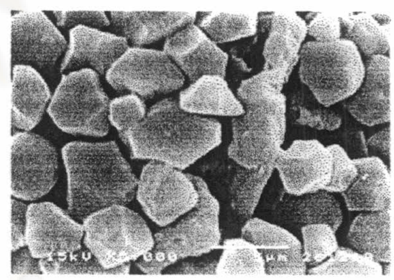
F6 X 5000



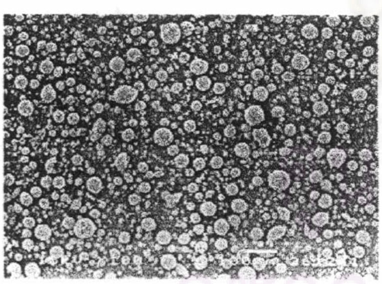
F7 X 100



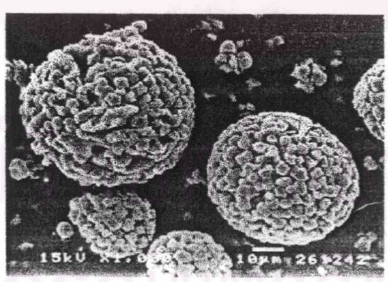
F7 X 1000



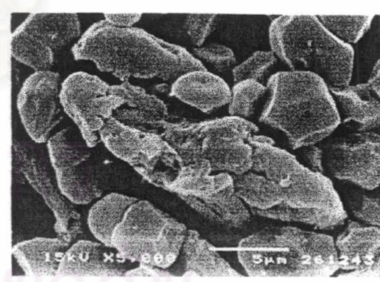
F7 X 5000



F8 X 100

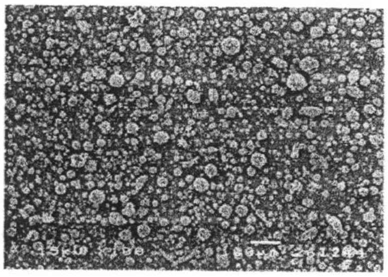


F8 X 1000

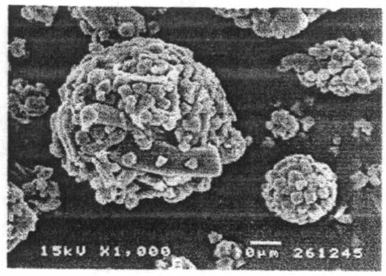


F8 X 5000

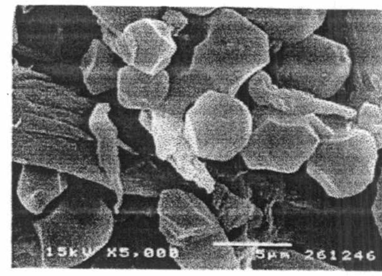
Figure 4-2 SEM photomicrographs of F5 to F8.



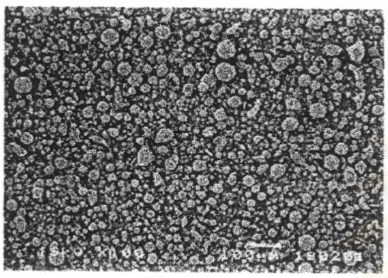
F9 X 100



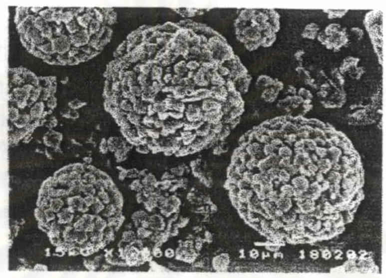
F9 X 1000



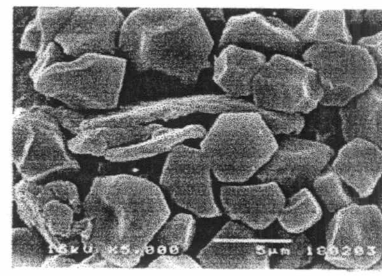
F9 X 5000



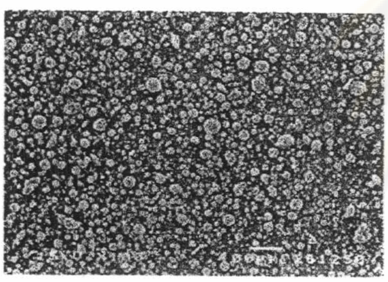
F10 X 100



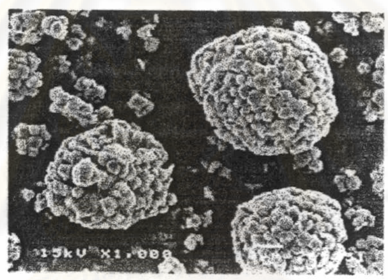
F10 X 1000



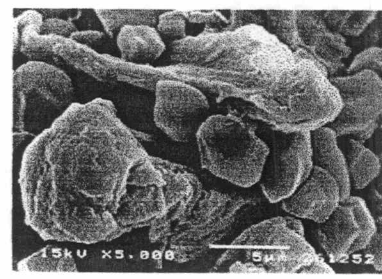
F10 X 5000



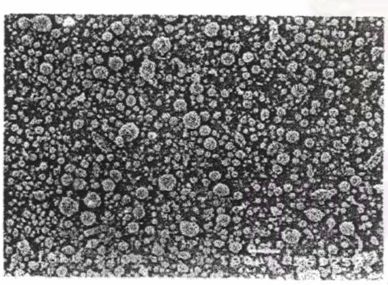
F11 X 100



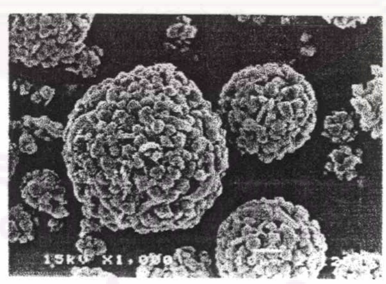
F11 X 1000



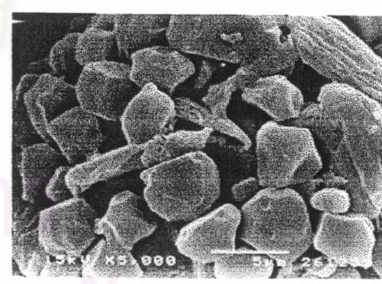
F11 X 5000



F12 X 100

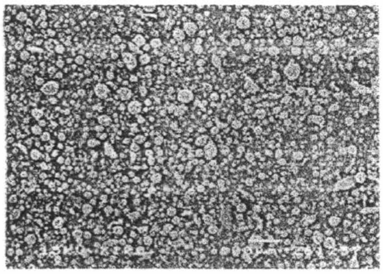


F12 X 1000

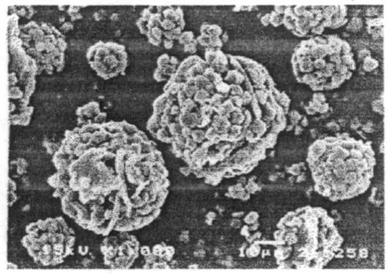


F12 X 5000

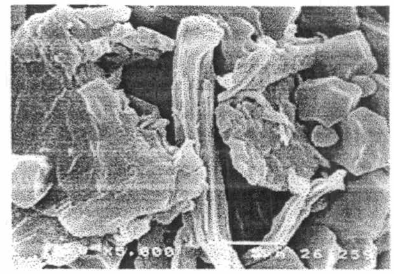
Figure 4-3 SEM photomicrographs of F9 to F12.



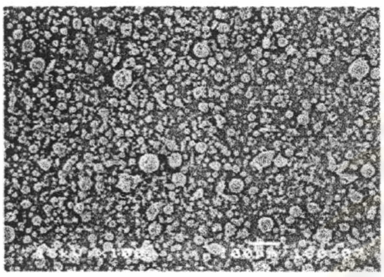
F13 X 100



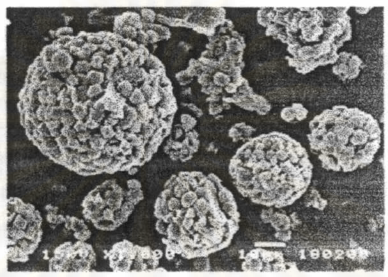
F13 X 1000



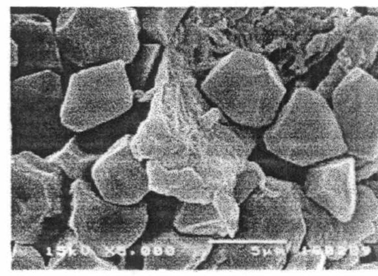
F13 X 5000



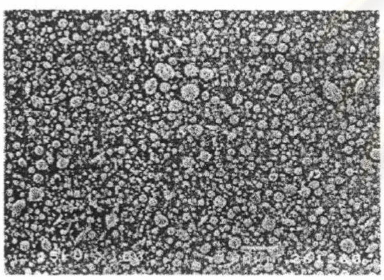
F14 X 100



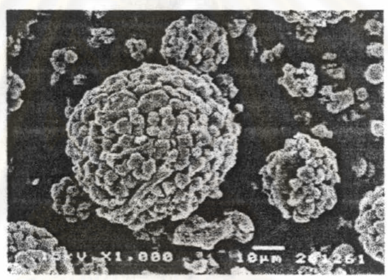
F14 X 1000



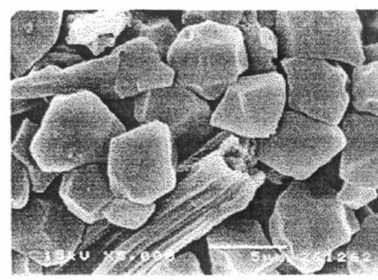
F14 X 5000



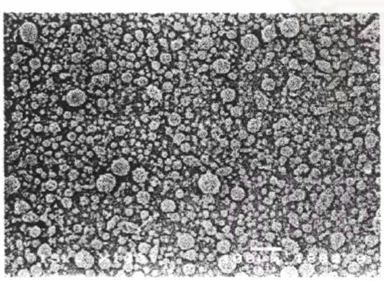
F15 X 100



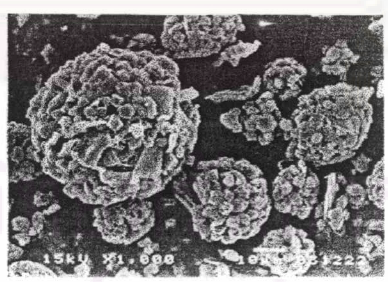
F15 X 1000



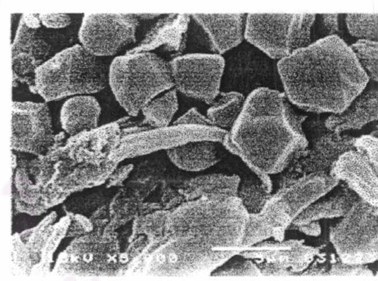
F15 X 5000



F16 X 100



F16 X 1000



F16 X 5000

Figure 4-4 SEM photomicrographs of F13 to F16.

Table 4-2 Physical properties of powder of F1 to F16.

Formula	Yield (%)	LOD (%) average (SD)	Angle of Repose (degree) average (SD)	Angle of Spatula (degree) average (SD)	Bulk Density (g/ml) average (SD)	Packed Density (g/ml) average (SD)	Compressibility (%) average (SD)	Cohesion (%) average (SD)	Flowability Index average (SD)
F1	60.59	5.62 (0.20)	37.6 (2.80)	56.4 (0.57)	0.423 (0.01)	0.530 (0.00)	20.25 (0.49)	4.7 (0.01)	66.7 (1.61)
F2	48.27	4.92 (0.25)	29.7 (2.58)	58.1 (2.11)	0.436 (0.00)	0.540 (0.01)	19.14 (0.90)	4.8 (0.02)	71.0 (1.80)
F3	53.52	6.25 (0.13)	31.7 (2.29)	58.1 (0.68)	0.417 (0.00)	0.521 (0.01)	19.90 (0.85)	4.9 (0.00)	70.3 (0.58)
F4	48.33	6.12 (0.23)	28.2 (1.50)	59.9 (2.94)	0.441 (0.01)	0.536 (0.00)	17.72 (1.24)	3.6 (0.00)	70.7 (2.08)
F5	60.96	5.06 (0.28)	32.9 (2.41)	65.1 (2.41)	0.409 (0.00)	0.521 (0.01)	21.44 (1.46)	5.0 (0.01)	64.5 (0.50)
F6	47.99	4.38 (0.20)	30.4 (2.37)	58.5 (3.36)	0.432 (0.00)	0.532 (0.00)	18.73 (0.87)	7.9 (0.00)	69.5 (0.58)
F7	50.84	6.97 (0.13)	32.7 (1.89)	64.4 (6.33)	0.409 (0.01)	0.524 (0.01)	21.97 (2.60)	3.6 (0.01)	66.7 (1.76)
F8	44.82	6.07 (0.38)	30.0 (0.70)	65.4 (1.91)	0.442 (0.01)	0.536 (0.01)	17.42 (0.40)	5.8 (0.01)	67.3 (0.29)
F9	72.47	5.68 (0.12)	39.6 (1.85)	67.8 (3.72)	0.395 (0.01)	0.505 (0.00)	21.78 (1.89)	6.0 (0.01)	60.8 (0.29)
F10	59.63	5.15 (0.40)	36.9 (1.15)	64.4 (2.34)	0.414 (0.01)	0.528 (0.00)	21.65 (0.95)	5.8 (0.00)	62.7 (0.76)
F11	67.97	6.62 (0.28)	40.3 (1.87)	68.6 (4.02)	0.390 (0.01)	0.500 (0.00)	22.00 (1.73)	1.3 (0.02)	60.7 (0.29)
F12	64.08	6.02 (0.20)	39.7 (1.10)	66.0 (2.45)	0.416 (0.02)	0.536 (0.00)	22.39 (2.96)	2.1 (0.01)	60.5 (1.00)
F13	73.10	5.78 (0.25)	41.1 (1.17)	69.8 (2.90)	0.387 (0.01)	0.505 (0.00)	23.37 (1.08)	2.3 (0.00)	59.8 (0.76)
F14	63.49	3.55 (0.30)	37.3 (1.95)	62.2 (3.44)	0.406 (0.01)	0.532 (0.00)	23.75 (1.84)	6.0 (0.01)	62.0 (2.29)
F15	69.51	7.83 (0.26)	43.2 (2.55)	70.2 (1.76)	0.394 (0.02)	0.498 (0.00)	20.87 (3.03)	0.8 (0.01)	59.5 (1.80)
F16	64.14	6.25 (0.03)	38.1 (2.87)	63.2 (1.42)	0.419 (0.00)	0.526 (0.00)	20.28 (0.77)	1.8 (0.01)	62.5 (1.80)

Table 4-3 Particle size distribution of F1 to F16 (Appendix 30).

Formulations Code	D (v, 0.1) (μm) average (SD)	D (v, 0.5) (μm) average (SD)	D (v, 0.9) (μm) average (SD)	Span (D90 – D10)/D50 (μm) average (SD)
F1	11.76 (0.11)	41.48 (0.23)	78.26 (0.62)	1.60 (0.01)
F2	17.93 (0.17)	54.23 (0.04)	103.41 (1.50)	1.58 (0.03)
F3	14.88 (0.12)	43.25 (0.12)	75.56 (0.29)	1.40 (0.00)
F4	22.94 (0.14)	52.10 (0.08)	88.30 (0.65)	1.25 (0.01)
F5	13.28 (0.16)	42.78 (0.20)	79.75 (0.20)	1.55 (0.01)
F6	17.95 (0.25)	54.51 (0.28)	100.73 (1.83)	1.52 (0.02)
F7	19.18 (4.49)	43.52 (0.53)	74.82 (1.26)	1.28 (0.15)
F8	19.37 (0.16)	51.89 (0.25)	89.25 (0.67)	1.35 (0.01)
F9	3.66 (0.35)	32.47 (0.33)	75.13 (0.74)	2.20 (0.01)
F10	12.05 (0.10)	44.48 (0.10)	88.00 (0.72)	1.71 (0.01)
F11	8.66 (0.06)	37.65 (0.03)	78.20 (0.02)	1.85 (0.00)
F12	11.58 (0.20)	43.60 (0.14)	91.57 (0.32)	1.83 (0.01)
F13	6.30 (0.33)	33.92 (0.35)	77.03 (1.53)	2.09 (0.05)
F14	11.04 (0.14)	45.00 (0.31)	95.18 (1.05)	1.87 (0.01)
F15	6.63 (0.29)	31.61 (0.57)	69.36 (3.45)	1.98 (0.07)
F16	10.32 (0.05)	42.66 (0.26)	89.72 (1.32)	1.86 (0.02)

Table 4-4 Physical properties of tablets from F1 to F16.

Formula	Hardness (N) average (SD)	Diameter (mm) average (SD)	Thickness (mm) average (SD)	Friability (%)	DT (min) average (SD)
F1	174.0 (14.32)	12.88 (0.02)	3.56 (0.04)	0.24	2.43 (0.20)
F2	146.6 (13.64)	12.90 (0.03)	3.65 (0.03)	0.26	2.70 (0.41)
F3	190.4 (13.54)	12.88 (0.02)	3.55 (0.07)	0.28	2.15 (0.21)
F4	189.2 (15.89)	12.88 (0.06)	3.52 (0.09)	0.40	2.56 (0.26)
F5	157.7 (16.19)	12.89 (0.02)	3.60 (0.06)	0.38	2.26 (0.22)
F6	153.7 (16.38)	12.90 (0.02)	3.63 (0.06)	0.30	2.50 (0.24)
F7	191.1 (14.32)	12.85 (0.02)	3.49 (0.05)	0.32	2.40 (0.13)
F8	182.2 (14.22)	12.87 (0.01)	3.51 (0.08)	0.38	2.48 (0.20)
F9	184.6 (16.38)	12.88 (0.02)	3.59 (0.03)	0.30	2.23 (0.40)
F10	163.6 (13.54)	12.88 (0.02)	3.63 (0.06)	0.20	2.67 (0.49)
F11	209.2 (11.67)	12.88 (0.02)	3.50 (0.04)	0.30	2.51 (0.19)
F12	200.5 (12.56)	12.86 (0.01)	3.53 (0.06)	0.30	2.64 (0.21)
F13	164.4 (15.01)	12.88 (0.02)	3.57 (0.05)	0.40	2.44 (0.28)
F14	160.5 (17.85)	12.89 (0.03)	3.67 (0.04)	0.39	2.80 (0.11)
F15	209.4 (12.75)	12.85 (0.01)	3.45 (0.06)	0.40	2.55 (0.29)
F16	181.9 (15.01)	12.87 (0.02)	3.55 (0.08)	0.20	3.09 (0.37)

Table 4-5 Responses of F1 to F16.

Formula	Spray Drying Time (min)	Yield (%)	LOD (%) average (SD)	Hardness (N) average (SD)	Flowability Index average (SD)
F1	53	60.59	5.62 (0.20)	174.0 (14.32)	66.7 (1.61)
F2	50	48.27	4.92 (0.25)	146.6 (13.64)	71.0 (1.80)
F3	33	53.52	6.25 (0.13)	190.4 (13.54)	70.3 (0.58)
F4	32	48.33	6.12 (0.23)	189.2 (15.89)	70.7 (2.08)
F5	53	60.96	5.06 (0.28)	157.7 (16.19)	64.5 (0.50)
F6	50	47.99	4.38 (0.20)	153.7 (16.38)	69.8 (0.58)
F7	33	50.84	6.97 (0.13)	191.1 (14.32)	66.7 (1.76)
F8	30	44.82	6.07 (0.38)	182.2 (14.22)	67.3 (0.29)
F9	53	72.47	5.68 (0.12)	184.6 (16.38)	60.8 (0.29)
F10	52	59.63	5.15 (0.40)	163.6 (13.54)	62.7 (0.76)
F11	32	67.97	6.62 (0.28)	209.2 (11.67)	60.7 (0.29)
F12	30	64.08	6.02 (0.20)	200.5 (12.56)	60.5 (1.00)
F13	54	73.10	5.78 (0.25)	164.4 (15.01)	59.8 (0.76)
F14	50	63.49	3.55 (0.30)	160.5 (17.85)	62.0 (2.29)
F15	34	69.51	7.83 (0.26)	209.4 (12.75)	59.5 (1.80)
F16	32	64.14	6.25 (0.03)	181.9 (15.01)	62.5 (1.80)

effects. By substitution the variables as the formulation run in model equation, the predicted response was calculated and determined the residual from the observed value.The residuals were plotted on normal probability plot as diagnostic checking. The points of residuals lie closely to a straight line, indicating support to the model conclusion. One factor plot and interaction plots were also constructed for explanation of response in the range of factors studied.

% Yield

The normal probability plot of the effect estimates was depicted in Table 4–6 and Figure 4–5 indicating factor A, B, D and AB deviated from the line. The analysis of variance is summarized in Table 4–7 and factor with p value lower than an $\alpha = 0.05$ is statistical significance. In this case the effects of A, B, D, AB, and BD were significant and important effects. The points of residual on the normal probability plot lie reasonably close to the straight line as shown in Figure 4-6, supporting the previous conclusion. From the estimated effects in Table 4–6, one factor plot, and interaction plots in Figures 4–7 to 4-9, the similar results were obtained. An increase in concentration from 10% w/w to 20% w/w and feed rate from 20 g/minute to 30 g/minute reduced % yield by about 8.5% and 3%, respectively. High concentration and feed rate would increase in droplet size of the atomization that was not dried when contacted to hot air and then adhered to the chamber wall resulting in lower %yield. While an increase in atomizing pressure from 1 to 3 bars increased % yield by about 15%. This is because the high atomizing pressure would result in higher velocity of the atomized wheel leading to decrease in the droplet size of the atomization that was dried immediately when contact the hot air. As there were two interaction factors between concentration and feed rate (AB), between feed rate and atomizing pressure (BD), therefore, the effects of these variables must be considered together. For AB (see Figure 4–9), increasing feed rate at low concentration would reduce % yield while feed rate did not influence on % yield at high concentration. The highest % yield was obtained at low concentration and low feed rate. For feed rate and atomizing pressure (BD) as shown in Figure 4–9, increasing atomizing pressure at either low or high feed rate would increase % yield. At low

Table 4-6 Calculated estimated effect and sum of squares (SS) of % yield by Yates's algorithm.

Exp.	%Yield	1	2	3	4	Divisor	Estimated Effect	SS	Exp.	Estimated Effect	P
1	60.59	108.86	210.71	415.32	949.71	16	59.36	--	1	59.36	
a	48.27	101.85	204.61	534.39	-68.21	8	-8.53	290.79	d	14.88	96.7
b	53.52	108.95	264.15	-36.50	-23.29	8	-2.91	33.90	ab	3.41	90.0
ab	48.33	95.66	270.24	-31.71	27.27	8	3.41	46.48	bd	2.16	83.3
c	60.96	132.10	-17.51	-20.30	-0.01	8	0.00	0.00	cd	1.52	76.7
ac	47.99	132.05	-18.99	-2.99	0.27	8	0.03	0.00	ad	0.60	70.0
bc	50.84	136.59	-16.73	14.08	-9.17	8	-1.15	5.26	bcd	0.42	63.3
abc	44.82	133.65	-14.98	13.19	-4.89	8	-0.61	1.49	acd	0.40	56.7
d	72.47	-12.32	-7.01	-6.10	119.07	8	14.88	886.10	ac	0.03	50.0
ad	59.63	-5.19	-13.29	6.09	4.79	8	0.60	1.43	c	0.00	43.3
bd	67.97	-12.97	-0.05	-1.48	17.31	8	2.16	18.73	abd	-0.11	36.7
abd	64.08	-6.02	-2.94	1.75	-0.89	8	-0.11	0.05	abcd	-0.57	30.0
cd	73.10	-12.84	7.13	-6.28	12.19	8	1.52	9.29	abc	-0.61	23.3
acd	63.49	-3.89	6.95	-2.89	3.23	8	0.40	0.65	bc	-1.15	16.7
bcd	69.51	-9.61	8.95	-0.18	3.39	8	0.42	0.72	b	-2.91	10.0
abcd	64.14	-5.37	4.24	-4.71	-4.53	8	-0.57	1.28	a	-8.53	3.3

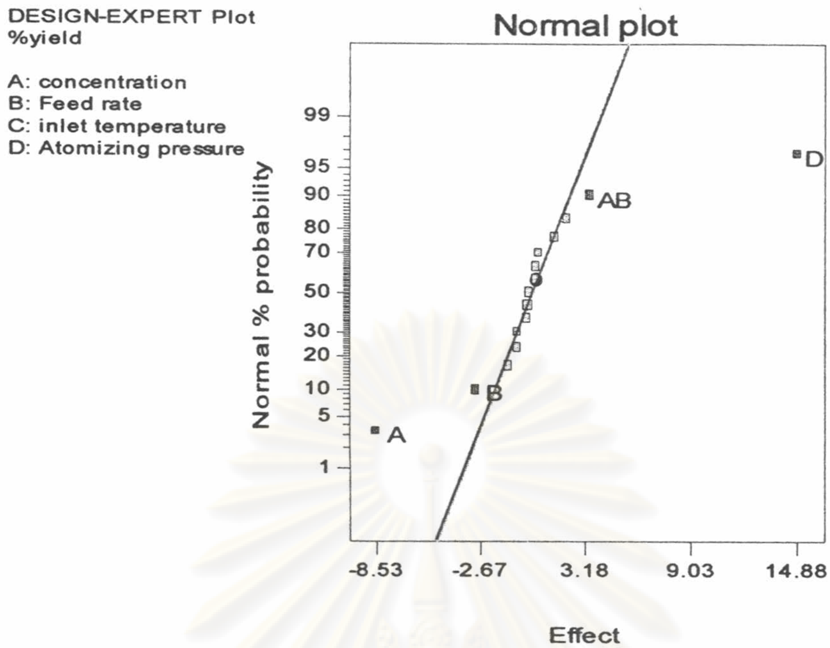


Figure 4-5 Normal probability plot of effect of % yield.

Table 4-7 ANOVA of response % yield.

Response: %yield
ANOVA for Selected Factorial Model
Analysis of variance table [Partial sum of squares]

Source	Sum of Squares	DF	Mean Square	F Value	Prob > F	
Model	1277.48	7	182.50	78.10	< 0.0001	significant
A	*290.79*	*1*	*290.79*	*124.44*	*< 0.0001*	
B	*33.90*	*1*	*33.90*	*14.51*	*0.0052*	
D	*886.10*	*1*	*886.10*	*379.19*	*< 0.0001*	
AB	*46.48*	*1*	*46.48*	*19.89*	*0.0021*	
AD	*1.43*	*1*	*1.43*	*0.61*	*0.4560*	
BD	*18.73*	*1*	*18.73*	*8.01*	*0.0221*	
ABD	*0.050*	*1*	*0.050*	*0.021*	*0.8879*	
Residual	18.69	8	2.34			
Cor Total	1296.18	15				

$F_{0.05\,(1,\,8)}$ = 5.32

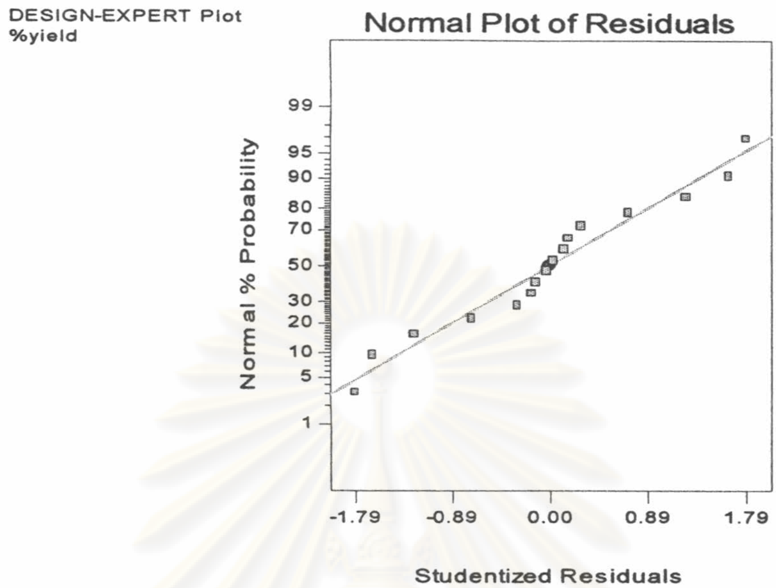


Figure 4-6 Normal probability plot of residuals of % yield.

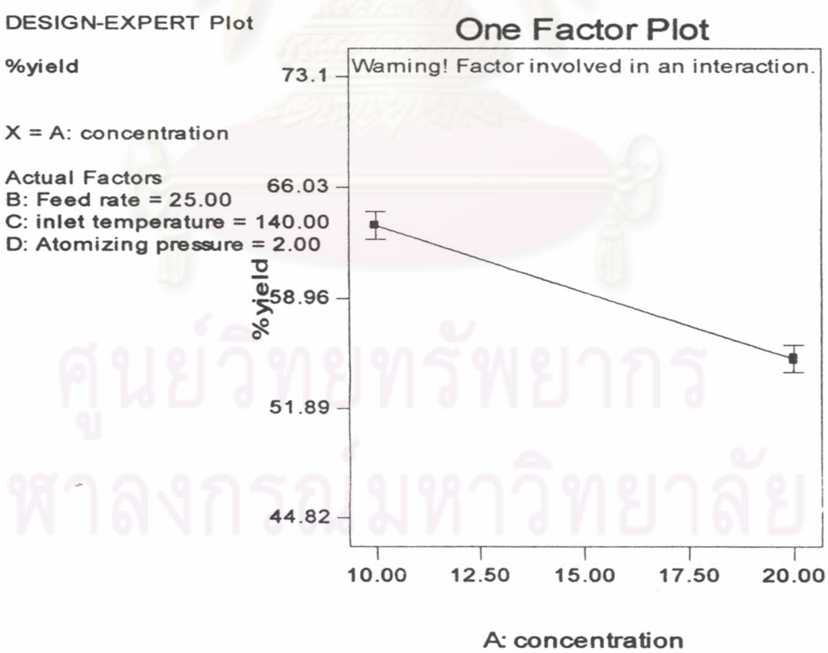


Figure 4-7 One factor plot of concentration on % yield.

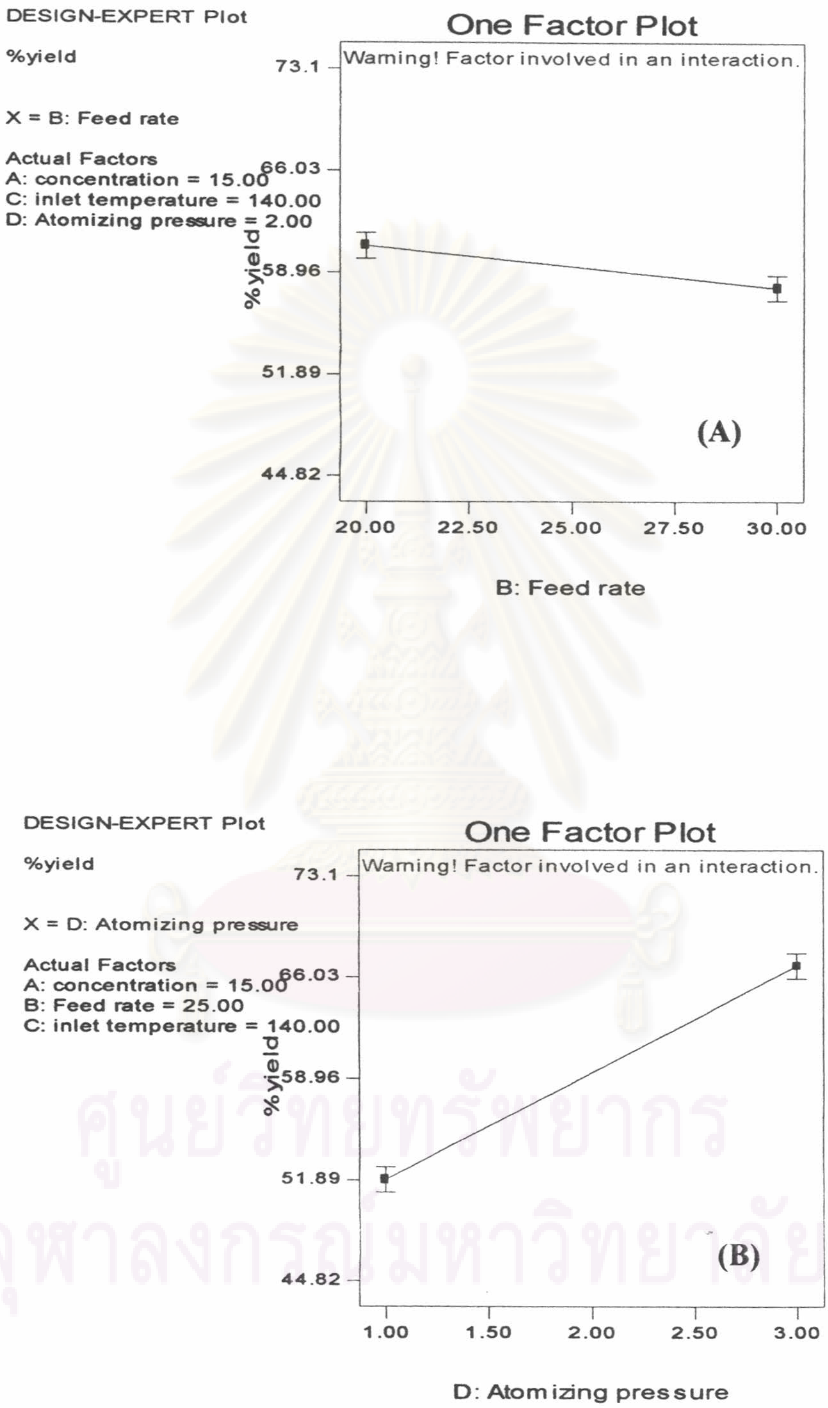


Figure 4-8 One factor plot of (A) : feed rate and (B) : atomizing pressure on % yield.

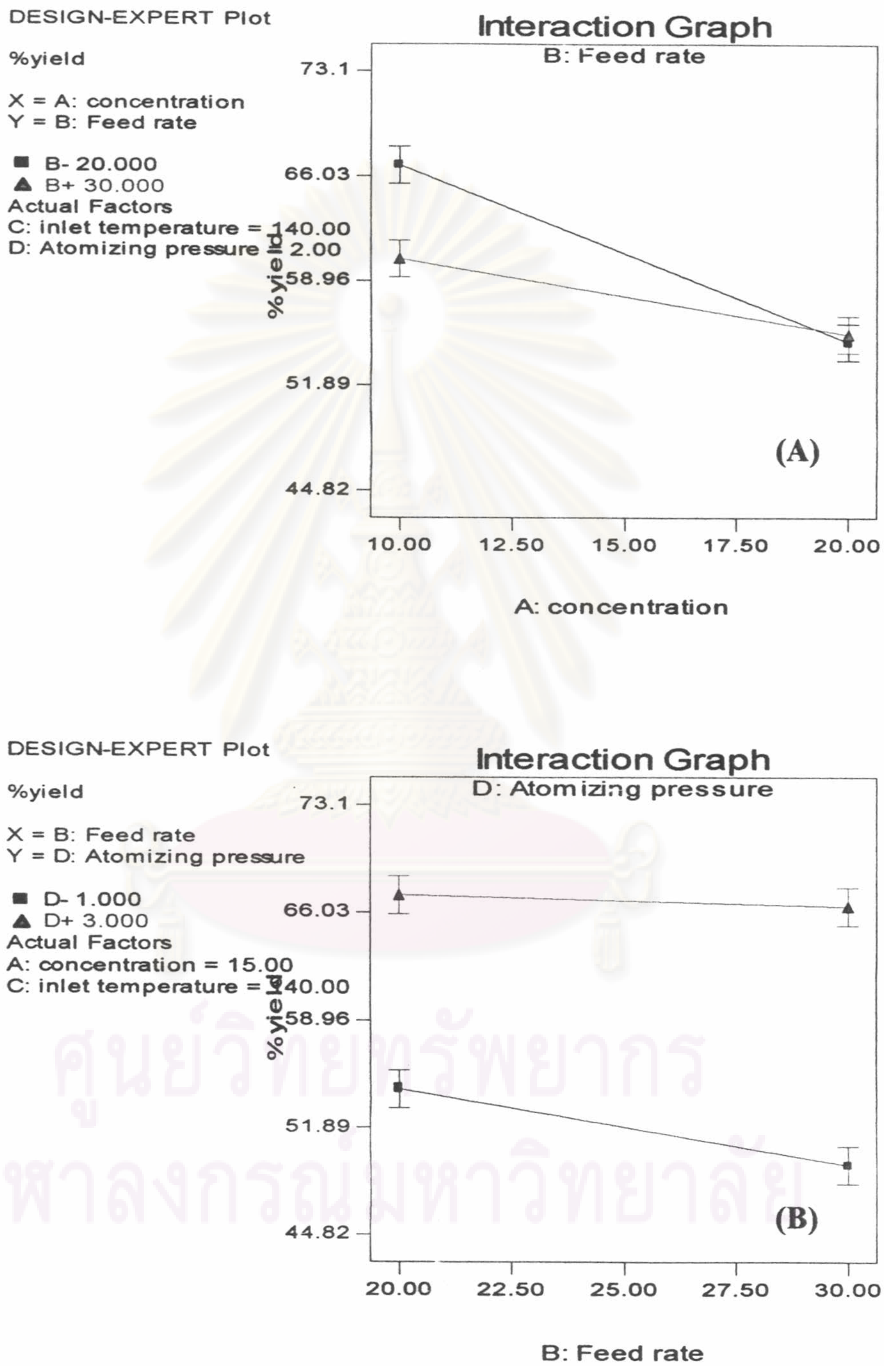


Figure 4-9 Interaction plot (A) : between concentration and feed rate and (B) : between feed rate and atomizing pressure on % yield.

atomization pressure, higher feed rate affected on the decrease of % yield while did not at high atomizing pressure. Therefore, the high % yield would be obtained when atomizing pressure and the feed rate would set at high level for high concentration. However, the feed rate should be decreased at low concentration to get higher in percent yield.

% LOD

The estimated effects of factor on % LOD, normal probability plot, and ANOVA are shown in Table 4–8, Figure 4-10, and Table 4–9, respectively. Factors A and B were only significant effects, so factors C, D and all interactions of them were negligible. To confirm the analysis, the normal probability plot of residuals was evaluated and shown in Figure 4-11. All of the residuals points lie close to the line, confirming the effects other than A and B were readily explained by random noise. One factor plot of % LOD is illustrated in Figure 4–12 and shows that the increasing in concentration would decrease in % LOD while the reverse result was obtained in increasing feed rate. Changing in concentration from 10% to 20% decreased % LOD by about 1% while increasing in feed rate from 20 g/minute to 30 g/minute increased % LOD by about 1.5%. This was due to increase feed rate led to increase atomizing droplets, which did not dry completely as in small atomizing droplets. And the formulations with higher feed rate got higher in percent LOD. Although higher concentration also caused large atomizing droplets as the effect of feed rate, the amount of water in droplets of higher concentration was more than that of in droplets of lower concentration. Then an increase in concentration caused decrease in percent LOD.

Flowability Index

The estimated effects on flowability index, normal probability plot, and ANOVA are exhibited in Table 4–10, Figure 4-13, and Table 4–11, respectively. Only the factor D significantly affected on flowability index. The diagnostic checking by normal probability plot of residual is illustrated in Figure 4–14 and all residuals were lie close to the straight line. One factor plot of flowability index is shown in Figure 4–15 and gave the high value at low atomizing pressure. Increasing atomizing pressure from 1 bar to 3 bars decrease the flowability index by about 7 units. The higher atomizing pressure

Table 4 - 8 Calculated estimated effect and SS of % loss on drying (LOD) by Yates's algorithm.

Exp.	% LOD	1	2	3	4	Divisor	Estimated effect	SS	Exp.	Estimated effect	P
1	5.62	10.54	22.91	45.39	92.27	16	5.77	--	1	5.77	
a	4.92	12.37	22.48	46.88	-7.35	8	-0.92	3.38	b	1.50	96.7
b	6.25	9.44	23.47	-2.41	11.99	8	1.50	8.99	bc	0.59	90.0
ab	6.12	13.04	23.41	-4.94	0.93	8	0.12	0.05	abcd	0.19	83.3
c	5.06	10.83	-0.83	5.43	-0.49	8	-0.06	0.02	d	0.19	76.7
ac	4.38	12.64	-1.58	6.56	-3.43	8	-0.43	0.74	bcd	0.15	70.0
bc	6.97	9.33	-1.13	0.35	4.71	8	0.59	1.39	bd	0.14	63.3
abc	6.07	14.08	-3.81	0.58	-0.07	8	-0.01	0.00	ab	0.12	56.7
d	5.68	-0.70	1.83	-0.43	1.49	8	0.19	0.14	cd	0.05	50.0
ad	5.15	-0.13	3.60	-0.06	-2.53	8	-0.32	0.40	abd	0.03	43.3
bd	6.62	-0.68	1.81	-0.75	1.13	8	0.14	0.08	abc	-0.01	36.7
abd	6.02	-0.90	4.75	-2.68	0.23	8	0.03	0.00	c	-0.06	30.0
cd	5.78	-0.53	0.57	1.77	0.37	8	0.05	0.01	acd	-0.24	23.3
acd	3.55	-0.60	-0.22	2.94	-1.93	8	-0.24	0.23	ad	-0.32	16.7
bcd	7.83	-2.23	-0.07	-0.79	1.17	8	0.15	0.09	ac	-0.43	10.0
abcd	6.25	-1.58	0.65	0.72	1.51	8	0.19	0.14	a	-0.92	3.3

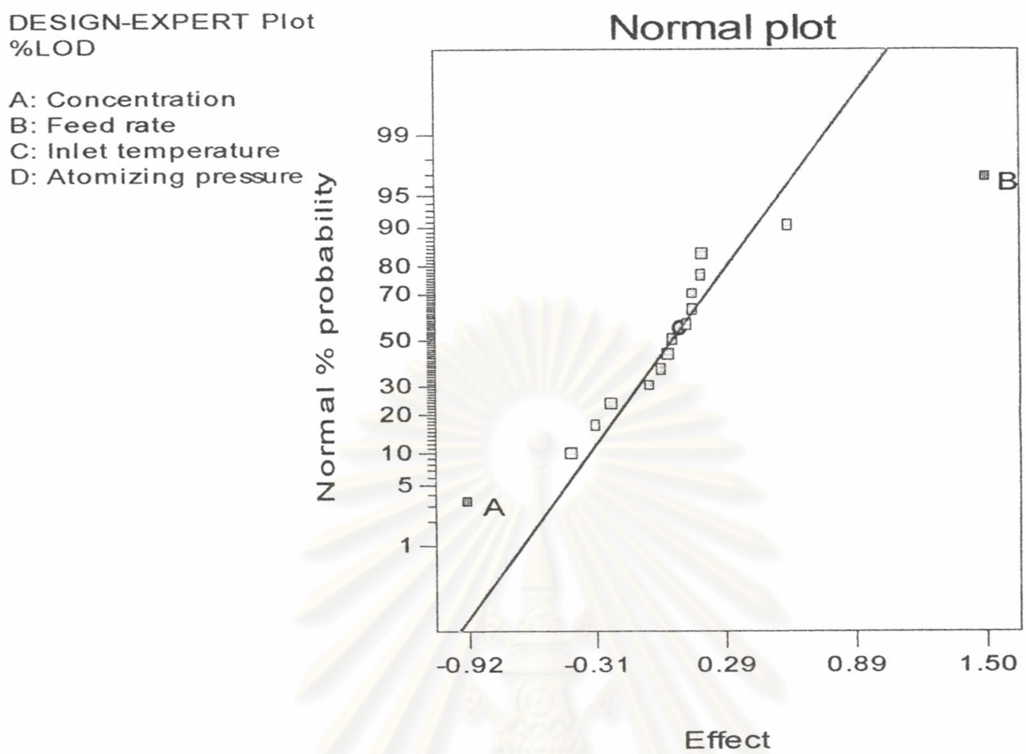


Figure 4 - 10 Normal probability plot of effect of % LOD.

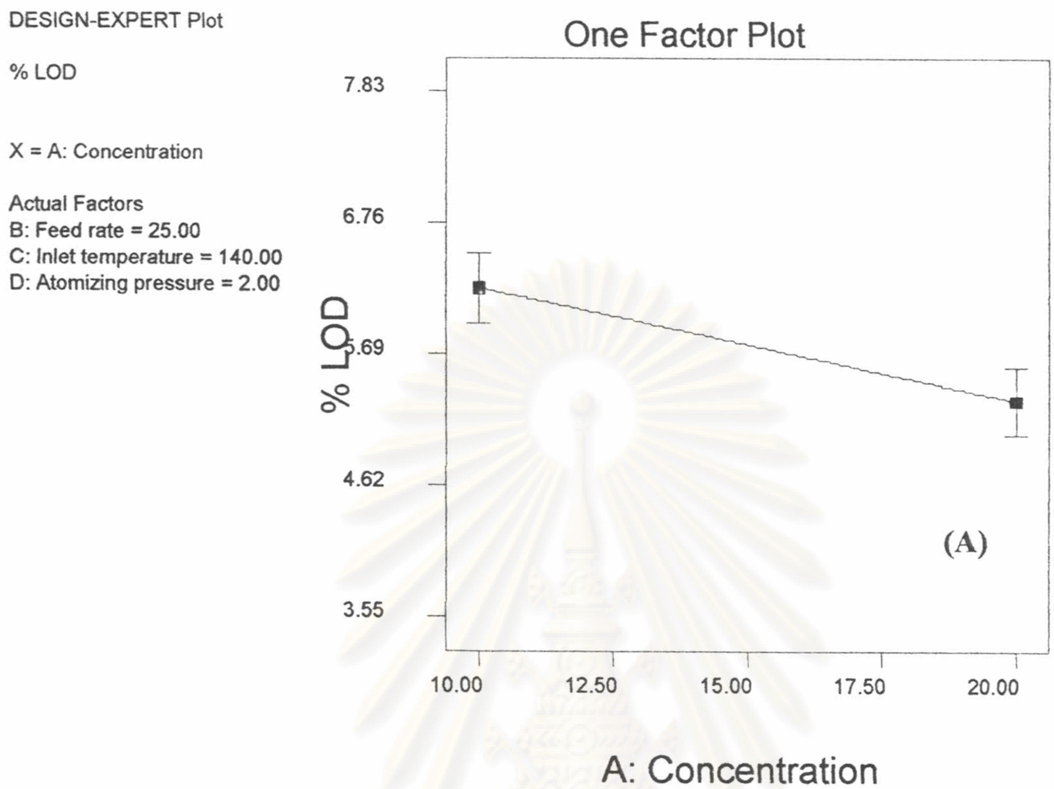
Table 4 - 9 ANOVA of response % LOD.

Response: %LOD
ANOVA for Selected Factorial Model
Analysis of variance table [Partial sum of squares]

Source	Sum of Squares	DF	Mean Square	F Value	Prob > F	
Model	12.42	3	4.14	15.38	0.0002	significant
A	*3.38*	*1*	*3.38*	*12.55*	*0.0041*	
B	*8.99*	*1*	*8.99*	*33.40*	*< 0.0001*	
AB	*0.054*	*1*	*0.054*	*0.20*	*0.6620*	
Residual	3.23	12	0.27			
Cor Total	15.64	15				

$F_{0.05\,(1,\,12)}$ = 4.75

Figure 4 - 11 Normal probability plot of residuals of % LOD.



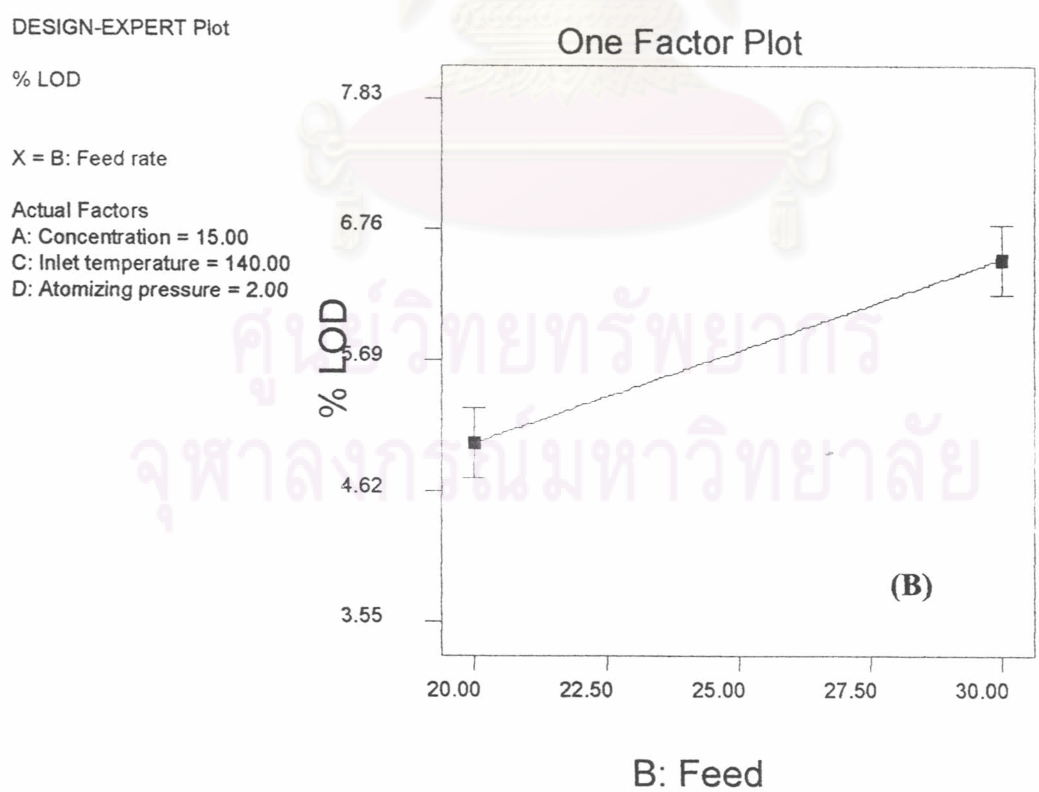


Figure 4 – 12 One factor plot of (A) : concentration and (B) : feed rate on % LOD.

Table 4 - 10 Calculated estimated effect and SS of flowability index by Yates's algorithm.

Exp.	Flow index	1	2	3	4	Divisor	Estimated effect	SS	Exp.	Estimated effect	P
1	66.60	137.60	278.60	546.90	1035.20	16	64.70	--	1	64.70	
a	71.00	141.00	268.30	488.30	17.40	8	2.18	18.92	a	2.18	96.7
b	70.30	134.30	244.70	10.70	1.20	8	0.15	0.09	cd	1.15	90.0
ab	70.70	134.00	243.60	6.70	-9.80	8	-1.23	6.00	abd	0.95	83.3
c	64.50	123.50	4.80	3.10	-11.40	8	-1.43	8.12	bcd	0.80	76.7
ac	69.80	121.20	5.90	-1.90	4.40	8	0.55	1.21	ac	0.55	70.0
bc	66.70	121.60	1.70	-8.70	-1.00	8	-0.13	0.06	abcd	0.48	63.3
abc	67.30	122.00	5.00	-1.10	2.40	8	0.30	0.36	abc	0.30	56.7
d	60.80	4.40	3.40	-10.30	-58.60	8	-7.33	214.62	acd	0.28	50.0
ad	62.70	0.40	-0.30	-1.10	-4.00	8	-0.50	1.00	b	0.15	43.3
bd	60.70	5.30	-2.30	1.10	-5.00	8	-0.62	1.56	bc	-0.13	36.7
abd	60.50	0.60	0.40	3.30	7.60	8	0.95	3.61	ad	-0.50	30.0
cd	59.80	1.90	-4.00	-3.70	9.20	8	1.15	5.29	bd	-0.62	23.3
acd	61.80	-0.20	-4.70	2.70	2.20	8	0.28	0.30	ab	-1.23	16.7
bcd	59.50	2.00	-2.10	-0.70	6.40	8	0.80	2.56	c	-1.43	10.0
abcd	62.50	3.00	1.00	3.10	3.80	8	0.48	0.90	d	-7.33	3.3

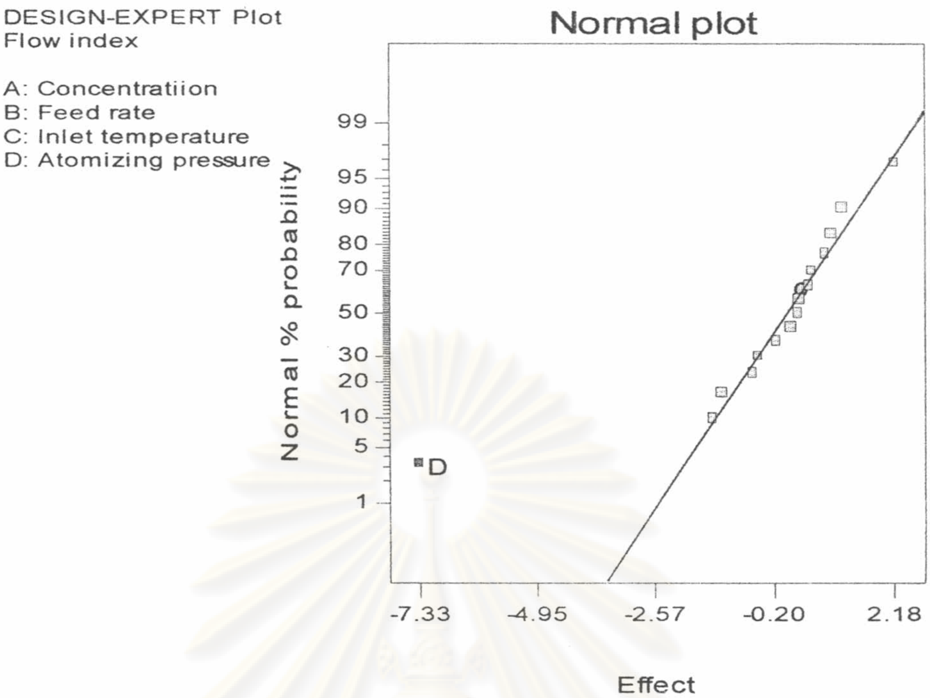


Figure 4 - 13 Normal probability plot of effect of flowability index.

Table 4 - 11 ANOVA of response flowability index.

Response: Flowability index
ANOVA for Selected Factorial Model
Analysis of variance table [Partial sum of squares]

Source	Sum of Squares	DF	Mean Square	F Value	Prob > F	
Model	214.62	1	214.62	60.10	< 0.0001	significant
D	*214.62*	*1*	*214.62*	*60.10*	*< 0.0001*	
Residual	50.00	14	3.57			
Cor Total	264.62	15				

$F_{0.05\,(1,\,14)}$ = 4.60

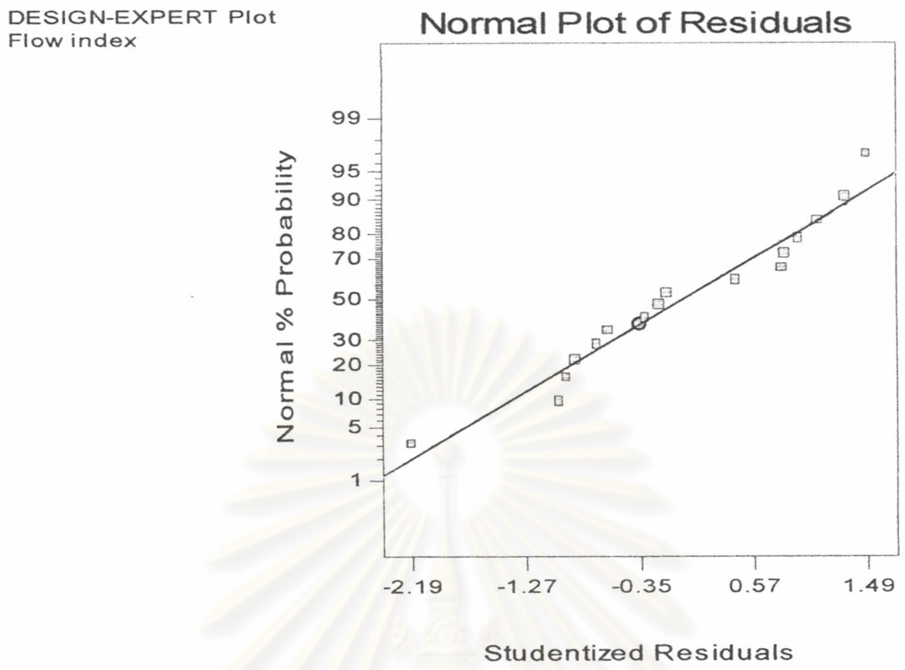


Figure 4 - 14 Normal probability plot of residuals of flowability index.

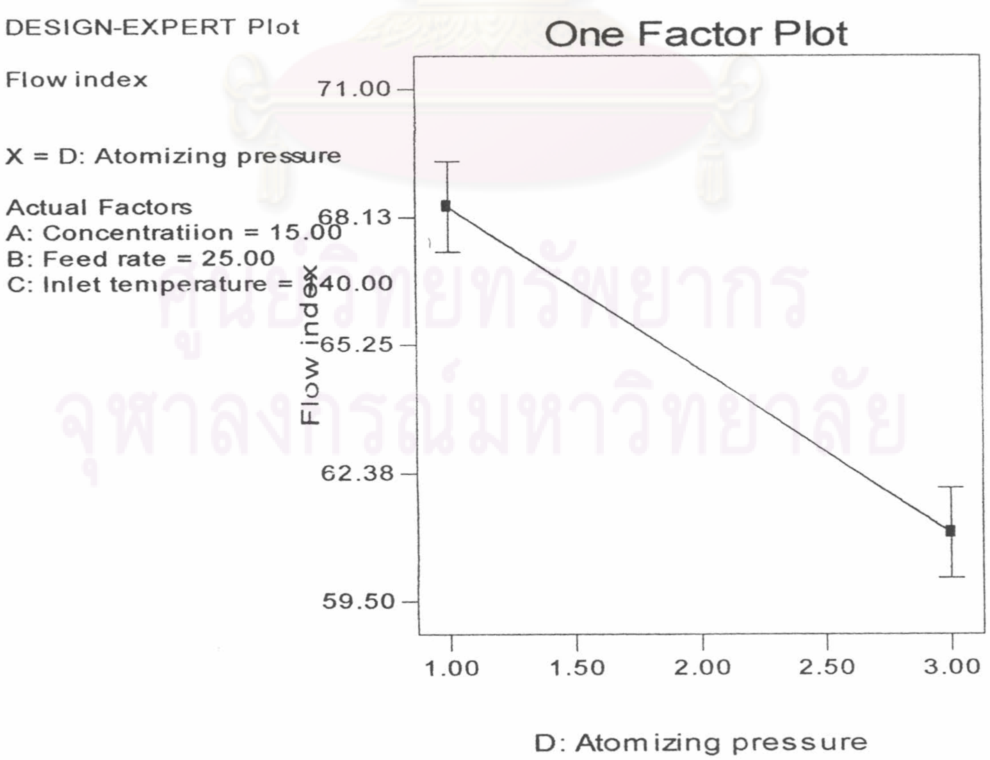


Figure 4 – 15 One factor plot of atomizing pressure on flowability index.

resulted in the higher speed rotation of atomizing wheel leading to produce the smaller droplet size of atomization and then small particle size was obtained as in Table 4–3 and SEM photomicrographs (Figure 4-1 to 4-4). These small particles would decrease the flowability of the powder.

Hardness

The estimated effect by Yates's algorithm and normal probability plot are shown in Table 4-12 and Figure 4-16. From this plot, only factor B and D were not along the straight line indicated the significantly effects. When analyzing by using analysis of variance in Table 4–13, factor A, C and all other interactions of them were negligible and combined as an estimate of error. The data showed only factor B was significant effect. Normal probability plot of residual in Figure 4 – 17 were used as diagnostic check. The residuals lie closely to the straight line confirming the significant effect of factor B. One factor plot is illustrated in Figure 4 – 18. Increasing in feed rate from 20 g/minute to 30 g/minute would increase the hardness by about 31 units. This was due to the increasing of feed rate led to increase in droplet size and then an increased in % LOD of the spray-dried powder. The tablet strength of starch and cellulose depended on theirs moisture content and maximum tablet strength of various starches were obtained at 60 – 70% relative humidity (Bos et al., 1987). At this relative humidity, the equilibrium moisture content of all starches was about 10% w/w. Water sorption of starches and celluloses occurs in different stages (Zografi and Kontny, 1986). Firstly, the water is tightly bound to anhydroglucose units until 1 : 1 (water : anhydroglucose unit) stoichiometry is obtained (11.1% w/w water). Between 1 : 1 and 2 : 1 stoichiometry the water molecules is less tightly bound on the water molecules that already bound to anhydroglucose units. At stoichiometry larger than 2 : 1 is even less tightly bound and has the properties of bulk water. Water absorbed within the starch and cellulose influences the compacting properties. Water levels below 1 : 1 stoichiometry reduce the compactibility while that of between 1 : 1 and 2 : 1 is needed to provide plasticity to the system. At stoichiometry higher than 2 : 1, the ability to form bonds was reduced, maybe due to the formation of a water film (Zografi and Kontny, 1986 ; Bos et al., 1987). Then the varying in hardness of

Table 4 – 12 Calculated estimated effect and SS of hardness by Yates's algorithm.

Exp.	Hardness	1	2	3	4	Divisor	Estimated effect	SS	Exp.	Estimated effect	P
1	174.0	320.6	700.2	1384.9	2859.0	16	178.69	--	1	178.69	
a	146.6	379.6	684.7	1474.1	-102.6	8	-12.83	657.92	b	31.10	96.7
b	190.4	311.4	757.9	-41.5	248.8	8	31.10	3868.84	d	11.15	90.0
ab	189.2	373.3	716.2	-61.1	10.0	8	1.25	6.25	ac	1.75	83.3
c	157.7	348.2	-28.6	120.9	-57.2	8	-7.15	204.49	ab	1.25	76.7
ac	153.7	409.7	-12.9	127.9	14.0	8	1.75	12.25	bc	0.98	70.0
bc	191.1	324.9	-29.7	21.3	7.8	8	0.98	3.80	bd	0.88	63.3
abc	182.2	391.3	-31.4	-11.3	-67.0	8	-8.38	280.56	bcd	0.25	56.7
d	184.6	-27.4	59.0	-15.5	89.2	8	11.15	497.29	abcd	-0.60	50.0
ad	163.6	-1.2	61.9	-41.7	-19.6	8	-2.45	24.01	acd	-2.18	43.3
bd	209.2	-4.0	61.5	15.7	7.0	8	0.88	3.06	ad	-2.45	36.7
abd	200.5	-8.9	66.4	-1.7	-32.6	8	-4.08	66.42	cd	-3.27	30.0
cd	164.4	-21.0	26.2	2.9	-26.2	8	-3.27	42.90	abd	-4.08	23.3
acd	160.5	-8.7	-4.9	4.9	-17.4	8	-2.18	18.92	c	-7.15	16.7
bcd	209.4	-3.9	12.3	-31.1	2.0	8	0.25	0.25	abc	-8.38	10.0
abcd	181.9	-27.5	-23.6	-35.9	-4.8	8	-0.60	1.44	a	-12.83	3.3

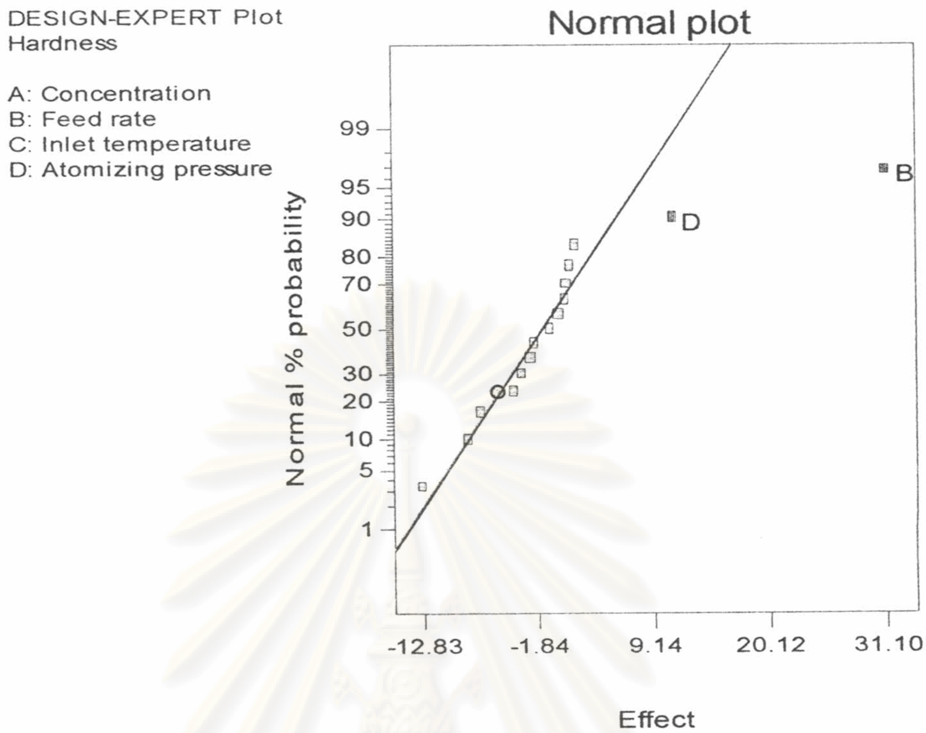


Figure 4 - 16 Normal probability plot of effect of hardness.

Table 4 – 13 ANOVA of response hardness.

Response: Hardness
ANOVA for Selected Factorial Model
Analysis of variance table [Partial sum of squares]

Source	Sum of Squares	DF	Mean Square	F Value	Prob > F	
Model	4369.19	3	1456.40	13.25	0.0004	significant
B	*3868.84*	*1*	*3868.84*	*35.19*	*< 0.0001*	
D	*497.29*	*1*	*497.29*	*4.52*	*0.0549*	
BD	*3.06*	*1*	*3.06*	*0.028*	*0.8702*	
Residual	1319.23	12	109.94			
Cor Total	5688.42	15				

$F_{0.05\,(1,\,12)}$ = 4.75

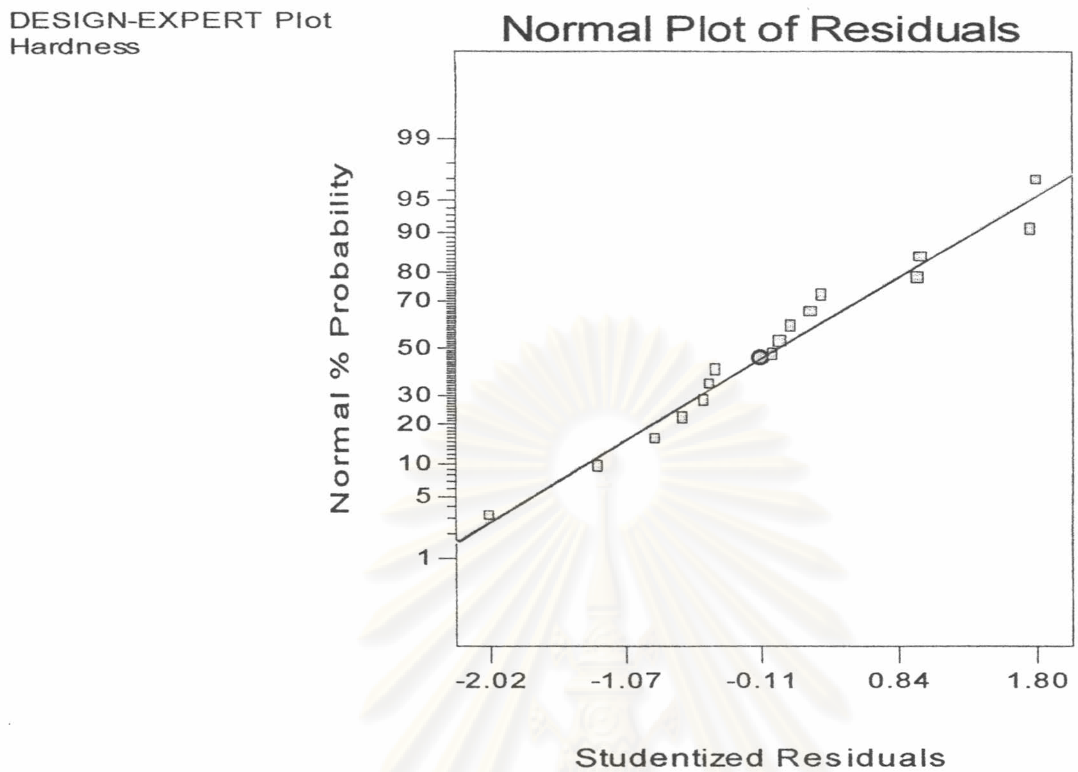


Figure 4 - 17 Normal probability plot of residuals of hardness.

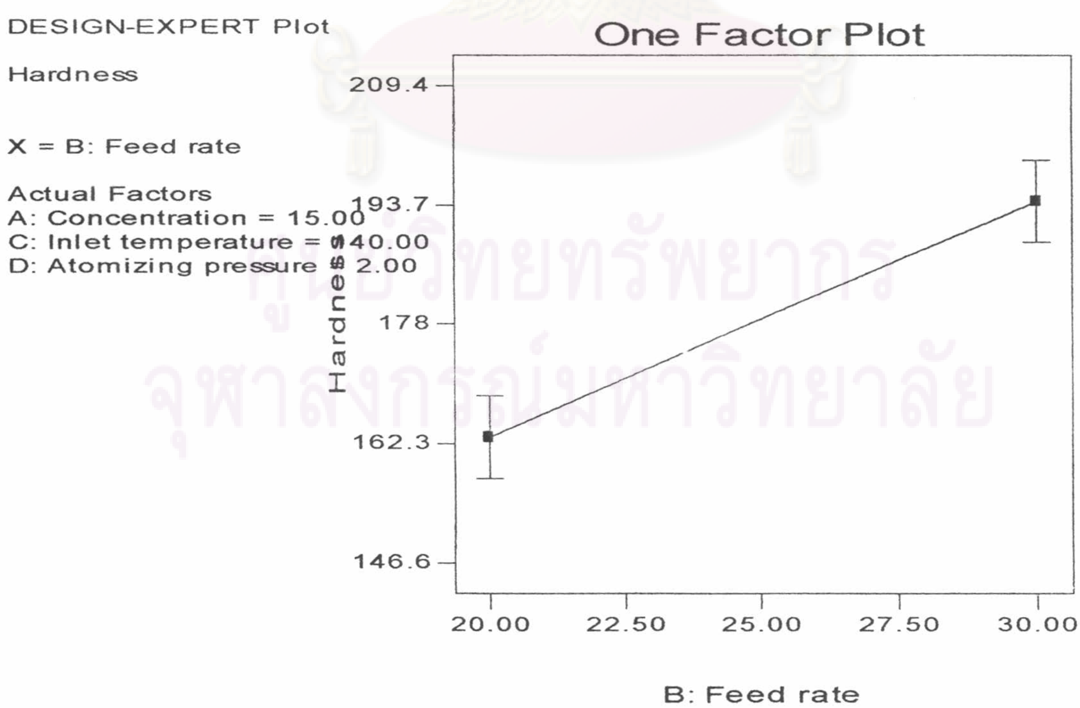


Figure 4 – 18 One factor plot of feed rate on hardness.

spray-dried formulation might be due to the different in moisture content of them. To investigate the effect of moisture content in composite particles on tablet strength, the spray-dried powder of all formulations were kept at the room temperature (around 25 ° – 27 °C and 55 – 62 %RH) for three days. Then these powders were determined % LOD, produced tablets and evaluated the hardness. % LOD and hardness value of all formulations in Table 4 – 14 were nearly the same and the values were around 9.36 – 10.13 % and 188.1 – 198.1 N, respectively. This indicated moisture content in composite particles affected on the strength of tablet. Due to the amount of rice starch in composite particles was greater than that of MCC, therefore, the effect of moisture content on compactibility from starch would then be dominant.

Spray Drying Time

The estimated effects, normal probability plot and ANOVA are illustrated in Table 4 –15, Figure 4 – 19, and Table 4 – 16, respectively. Factor A and B were significant effect. Diagnostic check and one factor plot are shown in Figure 4 – 20 and Figure 4-21, respectively. Increasing either feed rate or concentration would reduce the spray drying time. Changing concentration from 10% w/w to 20% w/w and feed rate from 20 g/minute to 30 g/minute reduced the spray drying time by about 2 and 20 units, respectively. The effect of feed rate was higher than that of concentration. These two factors at high level caused higher quantity of feed suspension to get in spray dryer chamber than the lower level and then reduction in spray drying time. Therefore, the shortest spray drying time could be obtained at high feed rate and high concentration.

The selected formulation for scale up in next chapter was determined from these previous responses. Owing to hardness and flowability (flowability index) are the important features of directly compressible diluent. Then all formulations were sorted by descending of hardness in Table 4 – 17 and flowability index in Table 4 – 18. The high hardness values were obtained in F15, F11, F12, F7, F3, and F4. Their values were in the range of 189.2 to 209.4 N. When consideration was taken on the basis of the flowability index, only F4 and F3 were the highest values of both values. All responses of these two

Table 4 – 14 Physical properties of powder and tablets of F1–F16, which stored at room temperature for three days.

Formulations	LOD (%) average (SD)	Hardness (N) average (SD)	Diameter (mm) average (SD)	Thickness (mm) average (SD)
F1	9.63 (0.29)	196.1 (6.97)	12.82 (0.03)	3.37 (0.04)
F2	9.68 (0.29)	198.1 (11.09)	12.81 (0.02)	3.36 (0.04)
F3	9.78 (0.11)	194.0 (12.56)	12.83 (0.02)	3.34 (0.04)
F4	9.60 (0.36)	193.2 (7.36)	12.82 (0.02)	3.32 (0.04)
F5	9.97 (0.24)	194.6 (9.03)	12.81 (0.02)	3.41 (0.08)
F6	10.13 (0.63)	191.9 (7.75)	12.80 (0.02)	3.35 (0.03)
F7	9.82 (0.11)	190.7 (7.46)	12.81 (0.02)	3.36 (0.06)
F8	9.82 (0.34)	188.1 (9.32)	12.83 (0.03)	3.32 (0.03)
F9	9.54 (0.19)	195.4 (3.83)	12.82 (0.02)	3.34 (0.04)
F10	9.83 (0.20)	193.6 (5.49)	12.84 (0.01)	3.38 (0.06)
F11	9.36 (0.11)	196.8 (7.06)	12.85 (0.01)	3.34 (0.04)
F12	9.55 (0.12)	192.5 (9.03)	12.84 (0.02)	3.32 (0.06)
F13	9.47 (0.18)	191.6 (7.36)	12.84 (0.02)	3.36 (0.05)
F14	9.76 (0.18)	196.8 (7.46)	12.85 (0.01)	3.32 (0.04)
F15	9.54 (0.15)	195.7 (8.34)	12.84 (0.01)	3.32 (0.06)
F16	9.61 (0.17)	196.7 (4.71)	12.84 (0.01)	3.31 (0.04)

Conditions: Room temperature = 25 °– 27 °C

RH = 55 – 62 %

Table 4 –15 Calculated estimated effect and SS of spray drying time by Yates's algorithm.

Exp.	Time (min)	1	2	3	4	Divisor	Estimated Effect	SS	Exp.	Estimated Effect	P
1	53	103.00	168.00	334.00	671.00	16	41.94	--	1	41.94	
a	50	65.00	166.00	337.00	-19.00	8	-2.38	22.56	bcd	0.88	96.7
b	33	103.00	167.00	-10.00	-159.00	8	-19.88	1580.06	cd	0.63	90.0
ab	32	63.00	170.00	-9.00	3.00	8	0.38	0.56	abcd	0.63	83.3
c	53	105.00	-4.00	-78.00	1.00	8	0.13	0.06	ab	0.38	76.7
ac	50	62.00	-6.00	-81.00	-5.00	8	-0.63	1.56	bc	0.38	70.0
bc	33	104.00	-3.00	2.00	3.00	8	0.38	0.56	d	0.38	63.3
abc	30	66.00	-6.00	1.00	1.00	8	0.13	0.06	c	0.13	56.7
d	53	-3.00	-38.00	-2.00	3.00	8	0.38	0.56	abc	0.13	50.0
ad	52	-1.00	-40.00	3.00	1.00	8	0.13	0.06	ad	0.13	43.3
bd	32	-3.00	-43.00	-2.00	-3.00	8	-0.38	0.56	abd	-0.13	36.7
abd	30	-3.00	-38.00	-3.00	-1.00	8	-0.13	0.06	acd	-0.13	30.0
cd	54	-1.00	2.00	-2.00	5.00	8	0.63	1.56	bd	-0.38	23.3
acd	50	-2.00	0.00	5.00	-1.00	8	-0.13	0.06	ac	-0.63	16.7
bcd	34	-4.00	-1.00	-2.00	7.00	8	0.88	3.06	a	-2.38	10.0
abcd	32	-2.00	2.00	3.00	5.00	8	0.63	1.56	b	-19.88	3.3

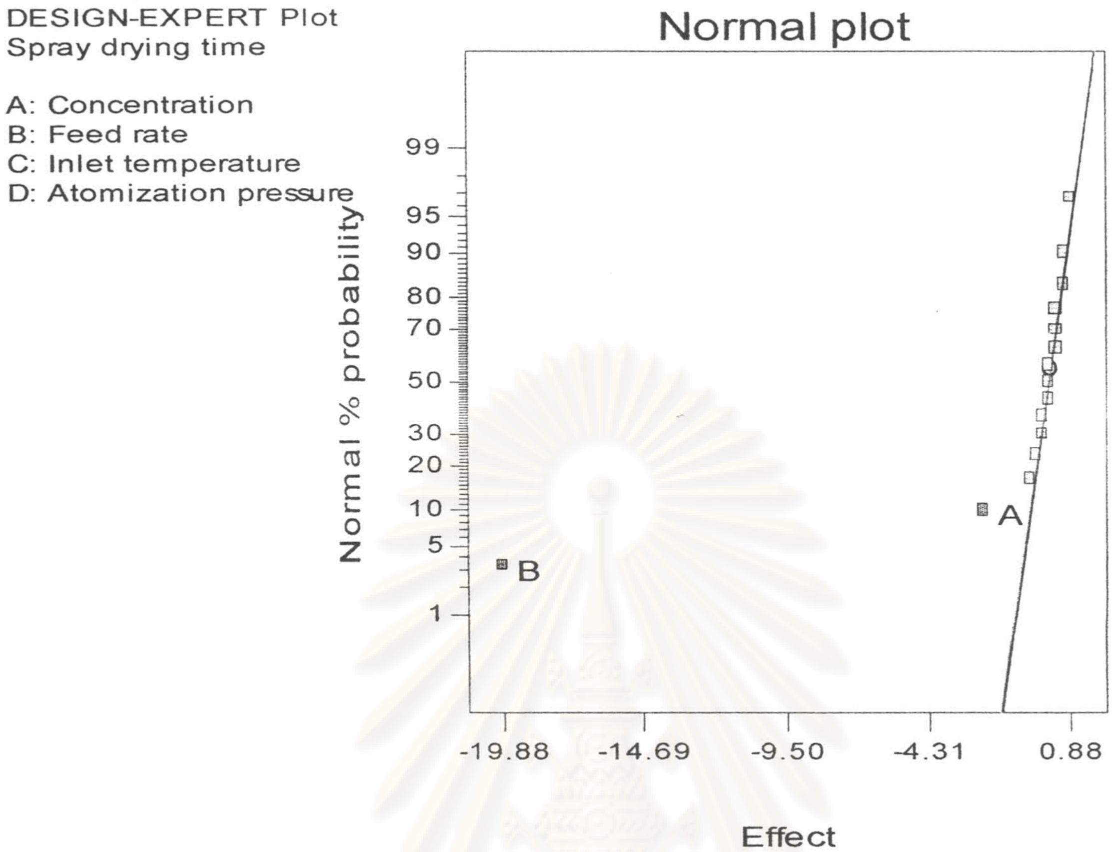


Figure 4 - 19 Normal probability plot of effect of spray drying time.

Table 4 – 16 ANOVA of response spray drying time.

Response: Spray drying time

ANOVA for Selected Factorial Model

Analysis of variance table [Partial sum of squares]

Source	Sum of Squares	DF	Mean Square	F Value	Prob > F	
Model	1603.19	3	534.40	657.72	< 0.0001	significant
A	*22.56*	*1*	*22.56*	*27.77*	*0.0002*	
B	*1580.06*	*1*	*1580.06*	*1944.69*	*< 0.0001*	
AB	*0.56*	*1*	*0.56*	*0.69*	*0.4216*	
Residual	9.75	12	0.81			
Cor Total	1612.94	15				

$F_{0.05\,(1,\,12)}$ = 4.75

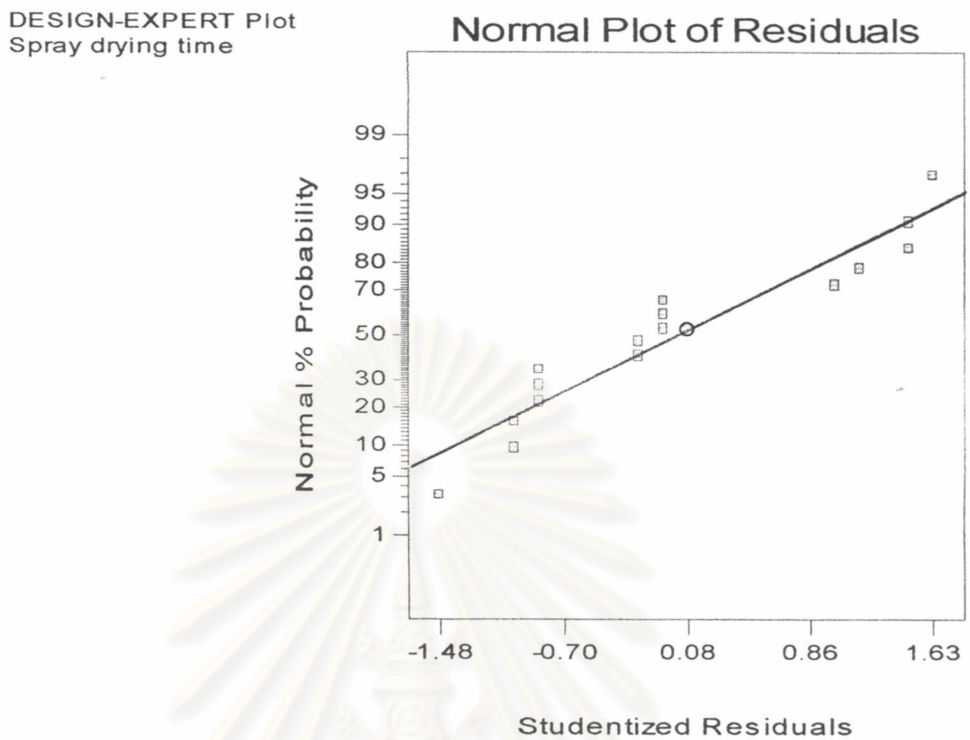
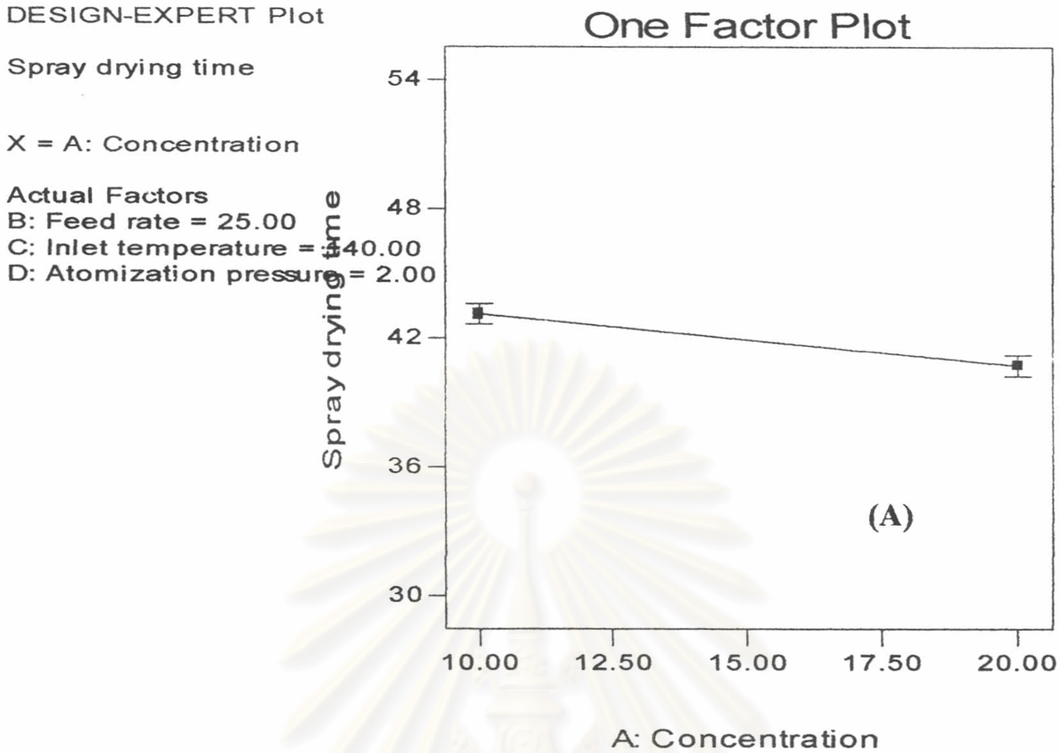


Figure 4 - 20 Normal probability plot of residuals of spray drying time.



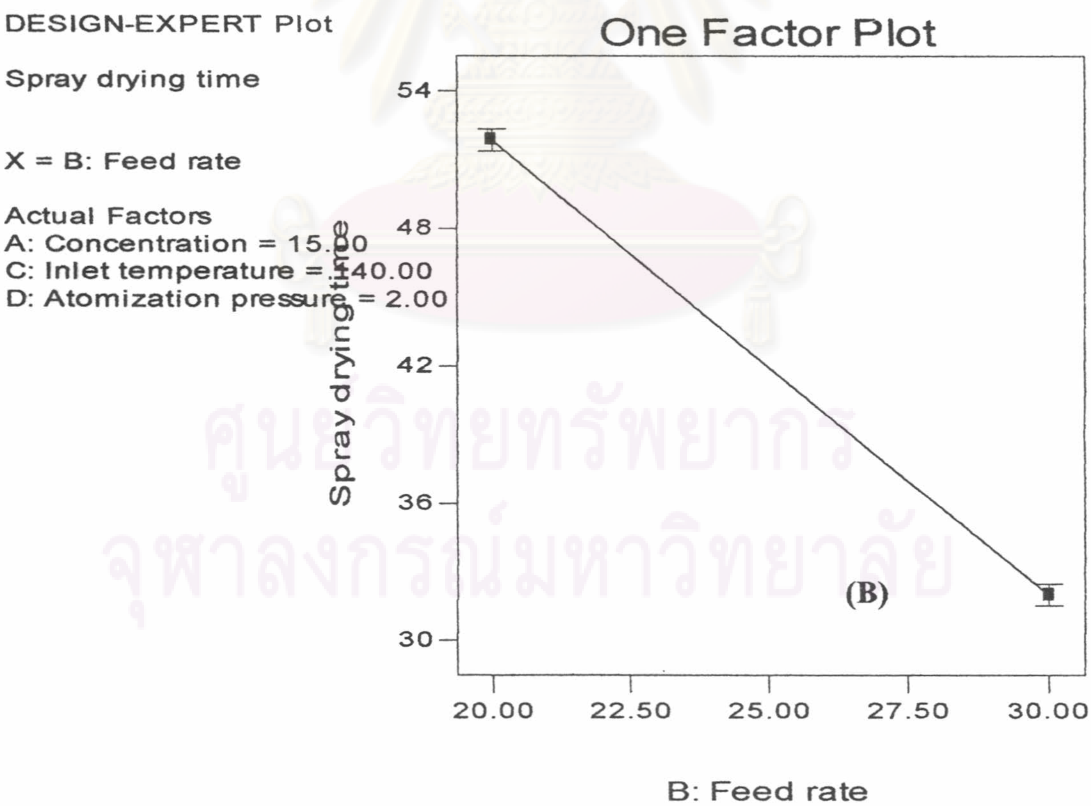


Figure 4 – 21 One factor plot of (A) : concentration and (B) : feed rate on spray drying time.

Table 4 - 17 Responses of F1 – F16 sorted by descendent hardness.

Formula	Spray Drying Time (min)	Yield (%)	LOD (%) average (SD)	Hardness (N) average (SD)	Flowability Index average (SD)
F15	34	69.51	7.83 (0.26)	209.4 (12.75)	59.5 (1.80)
F11	32	67.97	6.62 (0.28)	209.2 (11.67)	60.7 (0.29)
F12	30	64.08	6.02 (0.20)	200.5 (12.56)	60.5 (1.00)
F7	33	50.84	6.97 (0.13)	191.1 (14.32)	66.7 (1.76)
F3	33	53.52	6.25 (0.13)	190.4 (13.54)	70.3 (0.58)
F4	32	48.33	6.12 (0.23)	189.2 (15.89)	70.7 (2.08)
F9	53	72.47	5.68 (0.12)	184.6 (16.38)	60.8 (0.29)
F8	30	44.82	6.07 (0.38)	182.2 (14.22)	67.3 (0.29)
F16	32	64.14	6.25 (0.03)	181.9 (15.01)	62.5 (1.80)
F1	53	60.59	5.62 (0.20)	174.0 (14.32)	66.7 (1.61)
F13	54	73.10	5.78 (0.25)	164.4 (15.01)	59.8 (0.76)
F10	52	59.63	5.15 (0.40)	163.6 (13.54)	62.7 (0.76)
F14	50	63.49	3.55 (0.30)	160.5 (17.85)	62.0 (2.29)
F5	53	60.96	5.06 (0.28)	157.7 (16.19)	64.5 (0.50)
F6	50	47.99	4.38 (0.20)	153.7 (16.38)	69.8 (0.58)
F2	50	48.27	4.92 (0.25)	146.6 (13.64)	71.0 (1.80)

Table 4 - 18 Responses of F1 – F16 sorted by descendent flowability index.

Formula	Spray Drying Time (min)	Yield (%)	LOD (%) average (SD)	Hardness (N) average (SD)	Flowability Index average (SD)
F2	50	48.27	4.92 (0.25)	146.6 (13.64)	71.0 (1.80)
F4	32	48.33	6.12 (0.23)	189.2 (15.89)	70.7 (2.08)
F3	33	53.52	6.25 (0.13)	190.4 (13.54)	70.3 (0.58)
F6	50	47.99	4.38 (0.20)	153.7 (16.38)	69.8 (0.58)
F8	30	44.82	6.07 (0.38)	182.2 (14.22)	67.3 (0.29)
F7	33	50.84	6.97 (0.13)	191.1 (14.32)	66.7 (1.76)
F1	53	60.59	5.62 (0.20)	174.0 (14.32)	66.7 (1.61)
F5	53	60.96	5.06 (0.28)	157.7 (16.19)	64.5 (0.50)
F10	52	59.63	5.15 (0.40)	163.6 (13.54)	62.7 (0.76)
F16	32	64.14	6.25 (0.03)	181.9 (15.01)	62.5 (1.80)
F14	50	63.49	3.55 (0.30)	160.5 (17.85)	62.0 (2.29)
F9	53	72.47	5.68 (0.12)	184.6 (16.38)	60.8 (0.29)
F11	32	67.97	6.62 (0.28)	209.2 (11.67)	60.7 (0.29)
F12	30	64.08	6.02 (0.20)	200.5 (12.56)	60.5 (1.00)
F13	54	73.10	5.78 (0.25)	164.4 (15.01)	59.8 (0.76)
F15	34	69.51	7.83 (0.26)	209.4 (12.75)	59.5 (1.80)

formulations were similar except % Yield of F3 had little higher than that of F4. Owing to F4 had the higher concentration (20%) than F3 (10%). Then at the same spray drying time, F4 not only gave the higher quantity of spray dried product but also the larger particle size than that of F3. Therefore, only F4 was chosen for further studying to be developed as newly introduced as directly compressible excipient.

Conclusions

The aim of this study was to study the variables of spray drying conditions on the physical properties of powder and their tablets by using 2^4 factorial design. Concentration, feed rate, inlet temperature, and atomizing pressure were used as independent variables. Percent yield, % LOD, flowability index, hardness, and spray drying time were the responses. Factors that influenced each of responses were summarized as follows.

1. % Yield

Main factors of concentration, feed rate, atomizing pressure and interaction factors between concentration and feed rate, and feed rate and atomizing pressure did affect % yield. To obtain the high % yield at high level concentration, the feed rate and atomizing pressure should be set at high level but for low level concentration, only the level of feed rate should be decreased.

2. % LOD

Only main effect of concentration and feed rate influenced on % LOD. Increasing the level of concentration decreased % LOD while feed rate increased this response. However, feed rate gave rather more effect on % LOD than concentration.

3. Flowability Index

Atomizing pressure had the significant effect on flowability index. This response would be reduced when atomizing pressure was at the highest level.

4. Hardness

Hardness of tablets obtained from spray dried powder was affected by feed rate. An increase in this factor, led to an increase in hardness due to the high % LOD of the spray dried powders.

5. Spray Drying Time

Concentration and feed rate affected the spray drying time. That is, when both of concentration and feed rate were at their high level, spray drying time is shorten, but concentration exhibited less effect.