CHAPTER III

RESULTS

3.1 Particle Size Distribution

Table 3.1 and Figure 3.1 showed the particle size distribution of each component. Approximately 90 % of DCP particle was more than 125 μm. Aspirin had nearly 90 % of size in range of 45-212 μm. More than 80 % of chitin had the particle size less than 90 μm. Corn starch had rather fine particle (< 45 μm) about 70 %.

Table 3.1 The Percent of Weight Retained on Each Sieve Size

Component	Sieve Size (μm)					
	212	180	125	90	45	pan
Aspirin	9.05	19.44	32.92	20.06	18.42	0.10
DCP	40.14	28.23	23.12	8.0	0.5	0.0
CS	1.22	4.29	4.80	5.10	15.61	68.98
CT	1.62	2.53	4.95	6.27	44.29	40.34

DCP : Dibasic calcium phosphate

CS : Corn starch

CT : Chitin

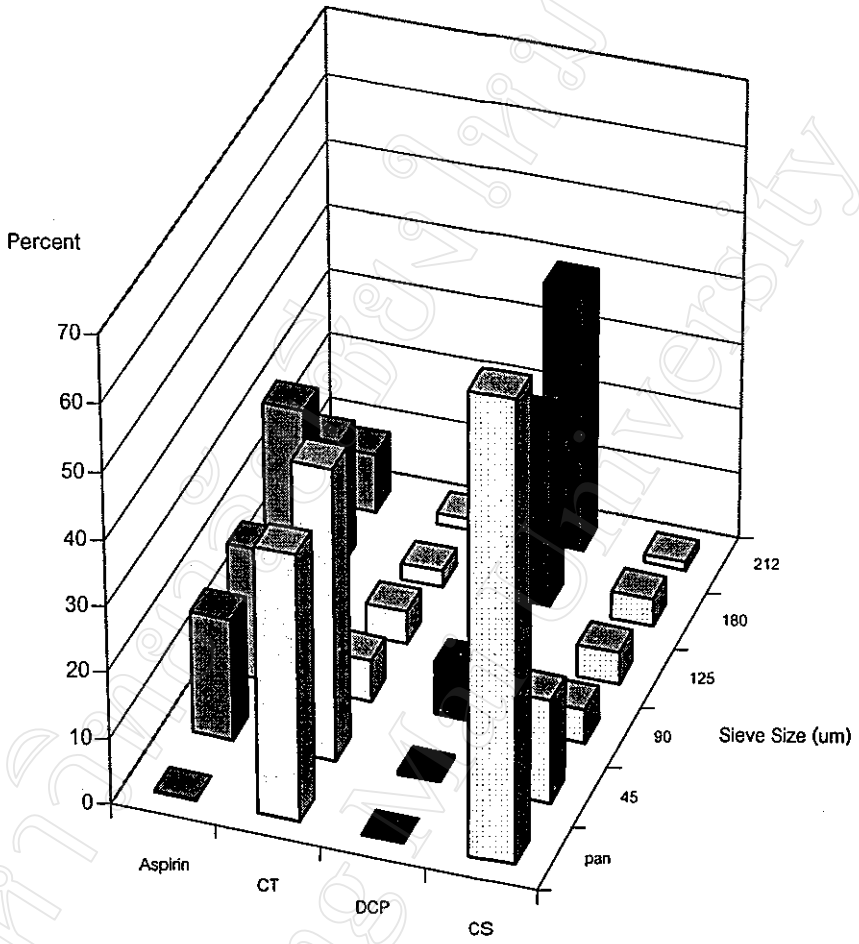

Figure 3.1 Particle Size Distribution of Each Component

3.2 Determination of the Formulation Properties

3.2.1 The Studies of Powder Properties

- Angle of Repose

In this experiment, the powder mixture of all formulations (F1 to F10) were determined in angle of repose and percent compressibility. In angle of repose, it was showed that the maximum angle of repose was F3 as 44.59 ° and the minimum was F5 as 33.84° that showed in Table 3.2. However, almost formulations had angle of repose

Table 3.2 The Flowability of Powder Mixture of Each Formulation

Formulation	Property					
	AOR			% Compressibility		
	Mean	S.D.	Flow	Mean	S.D.	Flow
F1	35.50	3.01	P	16.73	1.08	G-F
F2	37.59	0.95	P	10.87	2.61	E
F3	44.59	1.45	V	15.94	0.6	G
F4	39.13	0.47	P	19.63	0.99	F
F5	33.84	2.41	P	19.05	0.83	F
F6	40.31	2.65	V	24.04	2.15	P
F7	39.36	2.15	P	24.8	1.93	P
F8	35.42	1.42	P	21.76	1.16	F-P
F9	37.32	1.54	P	18.98	1.45	F
F10	40.16	0.56	V	23.57	1.72	P
Abbreviations	P = Passable V = Very Poor			E = Excellent G = Good F = Fair to Passable P = Poor		

in the range between 30-40 that showed the flowability of powder mixture was range passable (Wells, 1988) as showed in Table 3.2 and Figure 3.2 .

- **Percent Compressibility**

In percent compressibility, it was found that F7 was the highest percent compressibility as 24.8 and the lowest was F2 as 10.87. The flowability of powder mixture was varying when determined by percent compressibility as seen in Table 3.2 and Figure 3.3.

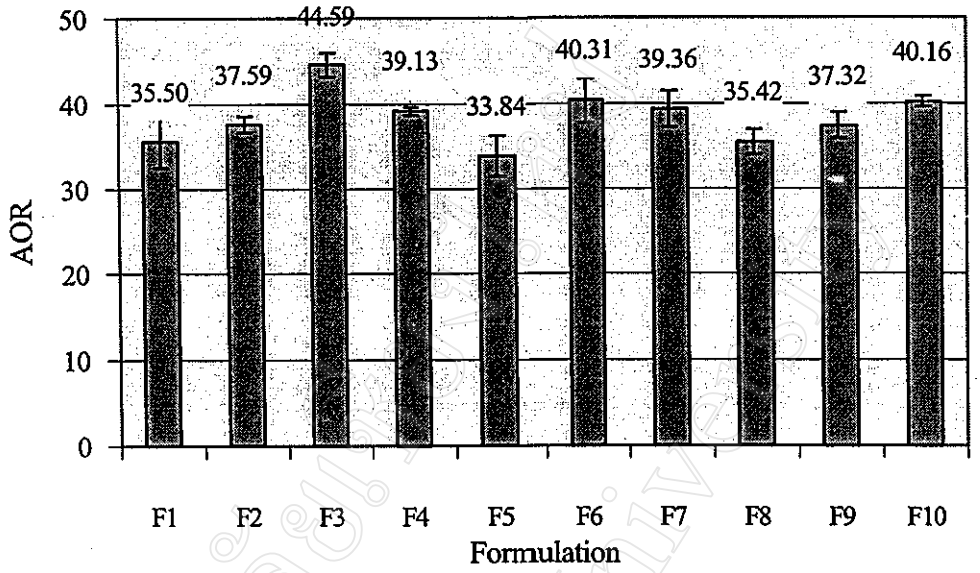

Figure 3.2 The Angle of Repose of Formulations F1- F10

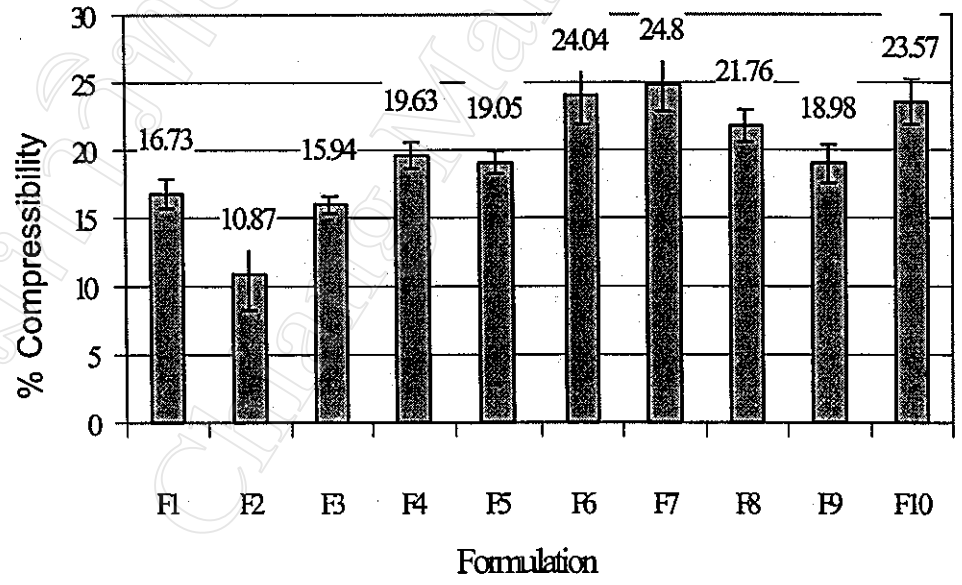

Figure 3.3 The Percent Compressibility of Formulations F1- F10

F1 = CT 1.0000/ DCP 0.0000/ CS 0.0000*
F2 = CT 0.0000/ DCP 1.0000/ CS 0.0000
F3 = CT 0.0000/ DCP 0.0000/ CS 1.0000
F4 = CT 0.5000/ DCP 0.5000/ CS 0.0000
F5 = CT 0.0000/ DCP 0.5000/ CS 0.5000
F6 = CT 0.5000/ DCP 0.0000/ CS 0.5000
F7 = CT 0.1666/ DCP 0.1666/ CS 0.6667
F8 = CT 0.6667/ DCP 0.1666/ CS 0.1666
F9 = CT 0.1666/ DCP 0.6667/ CS 0.1666
F10 = CT 0.3333/ DCP 0.3333/ CS 0.3333

*The proportion of each excipient used

3.2.2 The Studies of Tablet Properties

In this study, the formulations F1-F10 and F11- F20 were used as the same component, but their compressional pressure were different. Formulations F1-F10 were tableted with 1.0 ton compressional pressure and formulations F11-F20 were tableted with 1.5 tons compressional pressure. Table 3.3 showed the summary of tablet properties of formulations F1-F20.

- Hardness

In Table 3.3, at 1.0 ton compressional pressure (F1-F10), the maximum hardness of aspirin tablet was formulation F1 as 64.8 N and the minimum hardness was F5 as 16.63 N. Similarly, at 1.5 tons compressional pressure (F11-F20), the highest hardness was F11 as 73.83 N, but the lowest was F13 as 16.07 N. The comparative hardness of aspirin tablet at 1.0 and 1.5 tons can be seen in Figure 3.4, it was found that almost formulations, the hardness of 1.5 tons tablet were higher than 1.0 ton tablet.

- Percent Friability

In Table 3.3, at 1.0 ton compressional pressure (F1-F10), the tablet of F3 was the highest percent friability as 8.12 % and F8 was the lowest as 0.18 %. At 1.5 tons compressional pressure (F11-F20), the maximum tablet friability was F13 as 6.39 % and the minimum was F11 as 0.16 %. To compare the friability of tablet at 1.0 ton and 1.5 tons, the Figure 3.5 was illustrated. The percent friability of tablets at 1.5 tons compressional pressure were less than at 1.0 ton compressional pressure except formulation 8 (and 18) however, the both formulations had similar friability as 0.18 and 0.22 %, respectively.

- Disintegration Time

The disintegration time of aspirin tablet can be seen in the last column in Table 3.3, almost formulations had the similar disintegration time which less than 30 seconds. However, there are two formulations (F2 and F12) that had disintegration time more than 3600 seconds (>1 hour).

Table 3.3 The Tablet Properties of Formulations F1- F20

Formulation	Tablet Property					
	Hardness* (N)		% Dissolution**		% Friability	DI (s)
	Mean	S.D.	Mean	S.D.		
F1	64.80	4.55	88.31	0.87	0.26	11
F2	50.63	2.15	10.12	0.91	0.46	> 3600
F3	20.93	2.65	58.26	13.91	8.12	22
F4	37.33	0.81	78.75	7.3	0.47	11
F5	16.63	2.03	59.62	11.85	1.77	23
F6	28.73	4.67	76.68	12.04	1.32	15
F7	21.7	1.01	69.08	10.36	3.03	20
F8	48	2.85	88.76	0.46	0.18	11
F9	36.33	1.03	83.18	6.83	0.47	13
F10	38.57	1.65	81.10	4.02	0.68	19
F11	73.83	4.51	88.68	1.28	0.16	22
F12	61.27	0.5	10.90	0.34	0.44	> 3600
F13	16.07	2.04	54.94	14.83	6.39	27
F14	57.4	2.78	76.20	12.07	0.3	15
F15	35.57	2.65	63.61	14.35	1.05	20
F16	46.67	1.66	88.31	1.16	0.69	19
F17	38.03	1.69	66.65	14.06	1.1	19
F18	57.83	1.35	86.68	1.20	0.22	12
F19	43.77	3.37	66.11	12.19	0.38	13
F20	41.47	3.44	82.45	3.79	0.61	13

* three determinations

** six determinations

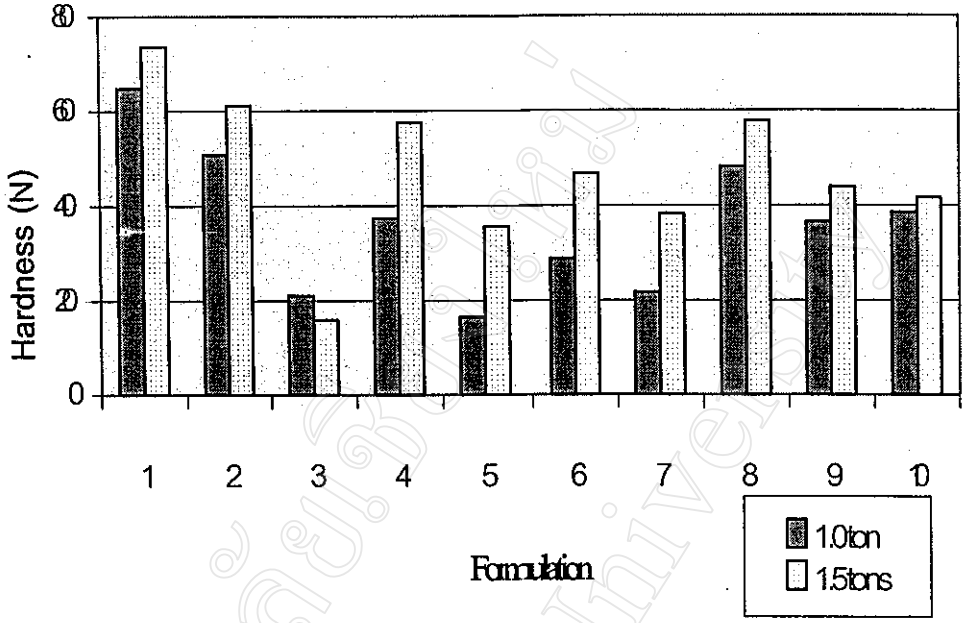

Figure 3.4 The Comparative Tablet Hardness at Different Compressional Pressure

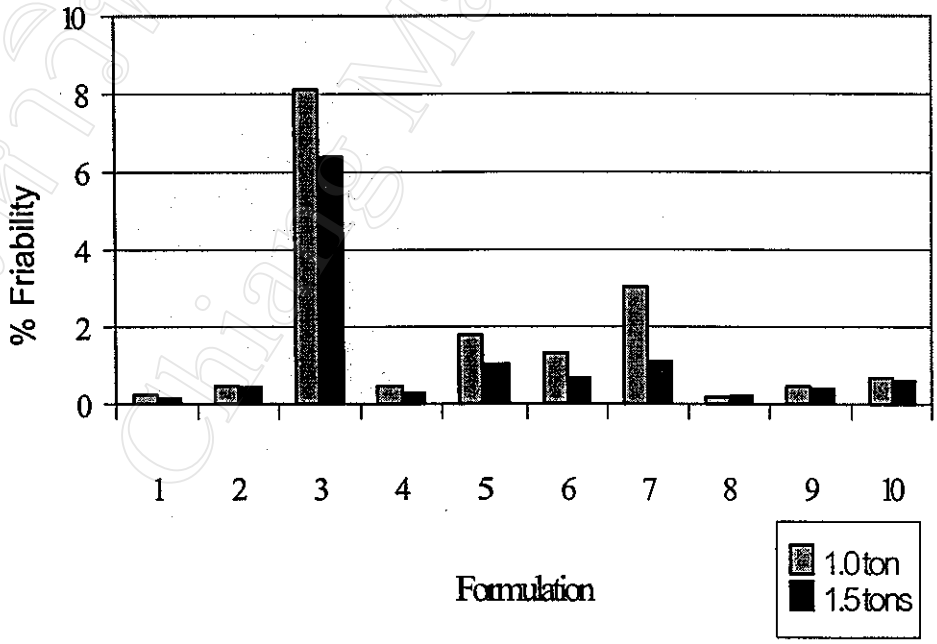

Figure 3.5 The Comparative Percent Tablet Friability at Different Compressional Pressure

- Dissolution

The dissolution of tablet is known as drug release profile that can be seen in Table 3.3. At 1.0 ton compressional pressure (F1-F10), the F8 was the highest percent drug release as 88.76 % and F2 was the lowest as 10.12 %. At 1.5 tons compressional pressure (F11-F20), F11 was the maximum percent drug release as 88.67 % and F12 was the minimum as 10.90 %. In Figure 3.6, when compare the percent drug release at different compressional pressure, it was found that the similar percent drug release was found in both groups of formulations (1.0 ton and 1.5 tons compressional pressure). Table 3.4 showed the Weibull distribution parameter of all formulations. It can be noted that, almost formulations had Td < 1.5 hours, but F2 (and F12) had Td > 24 hours, however b parameter of all formulations were less than one.

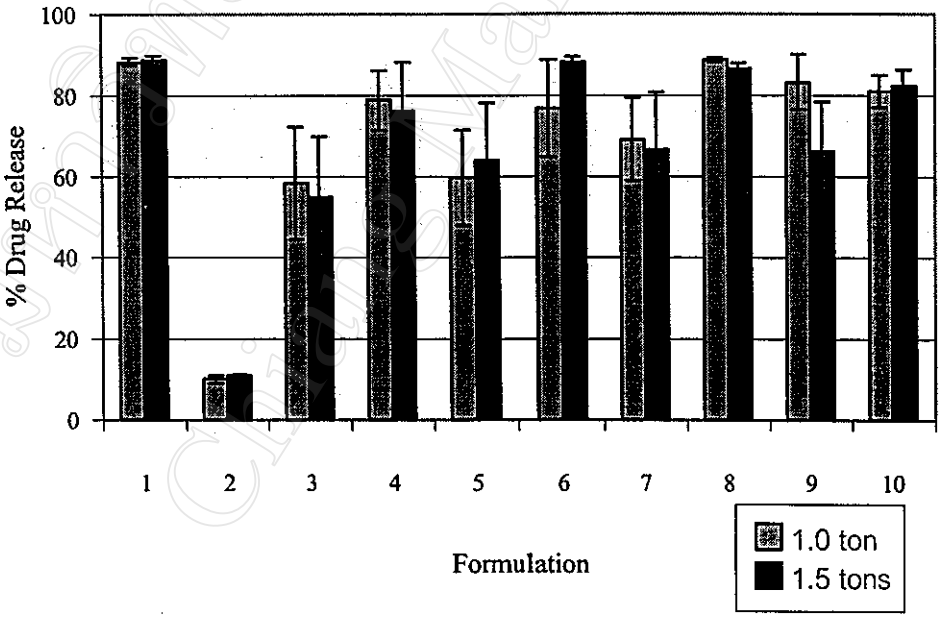

Figure 3.6 The Comparative Percent Drug Release at 45 Minutes of Different Compressional Pressure

Table 3.4 The Weibull Dissolution Parameter of Formulations F1-F20

Formulation	Td (minute)		b		R^2
	Mean	S.D.	Mean	S.D.	
F1	4.80	1.54	0.71	0.10	0.954
F2	1470.60	303.37	0.66	0.02	0.989
F3	64.80	49.67	0.56	0.06	0.978
F4	18.37	8.09	0.67	0.07	0.952
F5	55.27	34.16	0.67	0.10	0.987
F6	12.82	11.63	0.54	0.13	0.934
F7	34.40	16.88	0.58	0.08	0.983
F8	6.20	1.90	0.83	0.18	0.916
F9	16.24	5.52	0.78	0.17	0.962
F10	10.66	7.47	0.48	0.10	0.927
F11	6.75	3.43	0.75	0.11	0.923
F12	1482.17	272.83	0.63	0.03	0.995
F13	83.37	65.66	0.69	0.10	0.982
F14	26.62	12.89	0.82	0.07	0.979
F15	39.32	26.33	0.66	0.06	0.926
F16*	8.00	3.78	0.66	0.07	0.907
F17	42.73	30.25	0.58	0.07	0.973
F18	6.44	2.88	0.62	0.06	0.931
F19	38.45	23.80	0.68	0.13	0.974
F20	10.94	7.15	0.46	0.11	0.915

* Five determinations

3.3 Optimization of Formulations Properties

3.3.1 Limitation the Optimal Range of Each Property

Because the results of each property in different formulation were varying, so the optimal range of each property was limited. The limited range of each property can be seen in Table 3.5.

Table 3.5 The Limited Range of the Formulation Properties

Response	Limited Range	Reason
Angle of Repose	< 40	More passable flowability
Percent Compressibility	< 21	More passable flowability
Hardness (N)	> 40	General requirement
Percent Friability	< 1	According to USP 24
Log Disintegration Time*	< 2.5	< 5.27 minutes
Percent Drug Release	> 70	According to BP 1998

* Log disintegration time (Log DI) was used to evaluate the model substituent to disintegration time (DI) because to adjust the high range data of disintegration time that resulting to more appropriate data. The transformation of DI to Log DI, can be seen in Table B3 (in Appendix B).

3.3.1.1 Statistical Analysis

To evaluate the response surface model, SAS® software program version 6.12 was used. The angle of repose (response) is selected as an example for this statistical analysis (the other responses were evaluated as the same manner). Many standard statistical softwares, include SAS®, do not provide the correct analysis of a mixture experiment because (Leesawat, 1999)

1. the standard model is required to contain a constant term and the mixture models do not, or

2. if a no-constant term option is available in the analysis, then the regression or fitted model sum of squares in the ANOVA table is not corrected for the overall mean.

The SAS input statements for analysis the Scheffe' cubic model without a constant term is tabulated in Table 3.6.

Table 3.6 The SAS Input Statements of Angle of Repose

```
option is=70;
data a;
input formu chitin dcp starch AOR COMP;
response=AOR;
card;
1    1        0        0        35.18  17.72
1    1        0        0        32.66  16.88
1    1        0        0        38.66  15.58
2    0        1        0        37.23   8.51
2    0        1        0        36.87  13.68
2    0        1        0        38.66  10.42
3    0        0        1        43.23  16.05
3    0        0        1        44.42  15.29
3    0        0        1        46.12  16.47
4    0.5      0.5      0         39.6  20.65
4    0.5      0.5      0        38.66  18.68
4    0.5      0.5      0        39.14  19.57
5    0        0.5      0.5      32.88  20.00
5    0        0.5      0.5      32.06  18.48
5    0        0.5      0.5      36.59  18.68
6    0.5      0        0.5      39.93  26.14
6    0.5      0        0.5      43.13  24.14
6    0.5      0        0.5      37.87  21.84
7    0.1666   0.1666   0.6667   41.47  26.88
7    0.1666   0.1666   0.6667   39.42  23.08
7    0.1666   0.1666   0.6667   37.18  24.44
8    0.6667   0.1666   0.1666   33.80  21.59
8    0.6667   0.1666   0.1666   36.43  20.69
8    0.6667   0.1666   0.1666   36.03  22.99
9    0.1666   0.6667   0.1666   38.24  20.21
9    0.1666   0.6667   0.1666   35.54  17.39
9    0.1666   0.6667   0.1666   38.18  19.35
10   0.3333   0.3333   0.3333   40.80  25.27
10   0.3333   0.3333   0.3333   39.87  21.84
10   0.3333   0.3333   0.3333   39.81  23.6
;

proc glm data=a;
      model response = chitin dcp starch chitin*dcp chitin*starch dcp*starch chitin*dcp*starch
/noint ;
run;
```

The output of SAS analysis is shown in Table 3.7. In this table there are three parameter terms (CHITIN*DCP, CHITIN*STARCH, and CHITIN*DCP*STARCH) that had β-coefficient more than 0.05 (non-significant). It can be seen that the CHITIN*STARCH term had more clearly not significant than the other two so that this term was the first excluded. The SAS input statements were analyzed again without the excluded term (as seen in Table 3.8). The output of first excluded was showed in Table 3.9. As the result, the β-coefficient of CHITIN*DCP and CHITIN*DCP*STARCH were not significant, but the last term was excluded in the this step because this term was higher than the other one. The SAS input after excluded and CHITIN*DCP*STARCH term was shown in Table 3.10. The output of second exclude can be seen in Table 3.11. In this table, all term had the significant β-coefficient. The model fitted of angle of repose is

$$\text{Angle of Repose} = 34.955CT + 37.661DCP + 44.773CS + 12.349CT*DCP - 25.536\ DCP*CS \quad (3.1)$$

However, as Equation 3.1 the degree of freedom (DF) and the sum of squares for the "Model" and " Uncorrected Total" value in Table 3.11 are not corrected for overall mean of 30 data values. Because the fitted model was not contain a constant term ($\beta 0$) (the NOINT option was used in the model statements which is the first model statements listed in Table 3.6). To obtain the correct DF and sum of squares, the input data without the NOINT and deleted one of the linear blending terms was analyzed, as the statements in the block of Table 3.12. Since SAS automatically insert a constant term in the model unless one specifies NOINT statement, so the deletion of one of the linear blending terms in the model is necessary. Table 3.13, with the addition of the intercept term in the model and the deletion of one of the linear terms, the DF and sum of squares for the model and corrected total values are adjusted for the overall mean (Leesawat, 1999).

Table 3.7 The SAS Output of Angle of Repose without NOINT Option

General Linear Models Procedure

Dependent Variable: RESPONSE

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	7	44284.74015214	6326.39145031	1448.66	0.0001
Error	23	100.44264786	4.36707165		
Uncorrected Total	30	44385.18280000			

R-Square	C.V.	Root MSE	RESPONSE Mean
0.997737	5.453144	2.08975397	38.32200000

NOTE: No intercept term is used: R-square is not corrected for the mean.

Source	DF	Type I SS	Mean Square	F Value	Pr > F
CHITIN	1	22202.70356776	22202.70356776	5084.12	0.0001
DCP	1	12181.53512972	12181.53512972	2789.41	0.0001
STARCH	1	9769.69232981	9769.69232981	2237.13	0.0001
CHITIN*DCP	1	23.75266969	23.75266969	5.44	0.0288
CHITIN*STARCH	1	1.23208893	1.23208893	0.28	0.6004
DCP*STARCH	1	98.87277977	98.87277977	22.64	0.0001
CHITIN*DCP*STARCH	1	6.95158646	6.95158646	1.59	0.2197

Source	DF	Type III SS	Mean Square	F Value	Pr > F
CHITIN	1	3885.69644032	3885.69644032	889.77	0.0001
DCP	1	4585.50941821	4585.50941821	1050.02	0.0001
STARCH	1	6388.34693338	6388.34693338	1462.84	0.0001
CHITIN*DCP	1	11.08164268	11.08164268	2.54	0.1248
CHITIN*STARCH	1	0.01329887	0.01329887	0.00	0.9565
DCP*STARCH	1	103.14473232	103.14473232	23.62	0.0001
CHITIN*DCP*STARCH	1	6.95158646	6.95158646	1.59	0.2197

Parameter	Estimate	T for H0: Parameter=0	Pr > |T|	Std Error of Estimate
CHITIN	34.78952789	29.83	0.0001	1.16629727
DCP	37.79269785	32.40	0.0001	1.16629727
STARCH	44.60754756	38.25	0.0001	1.16629727
CHITIN*DCP	9.35252308	1.59	0.1248	5.87113243
CHITIN*STARCH	-0.32399190	-0.06	0.9565	5.87113243
DCP*STARCH	-28.53318447	-4.86	0.0001	5.87113243
CHITIN*DCP*STARCH	48.84729585	1.26	0.2197	38.71628879

Table 3.8 The SAS Input Statements of Angle of Repose (First Excluded)

```
option is=70;
data a;
input formu chitin dcp starch AOR COMP;
response=AOR;
card;
1    1        0       0        35.18   17.72
1    1        0       0        32.66   16.88
1    1        0       0        38.66   15.58
2    0        1       0         37.23    8.51
2    0        1       0        36.87   13.68
2    0        1       0        38.66   10.42
3    0        0       1        43.23   16.05
3    0        0       1        44.42   15.29
3    0        0       1        46.12   16.47
4    0.5      0.5     0         39.6   20.65
4    0.5      0.5     0        38.66   18.68
4    0.5      0.5     0        39.14   19.57
5    0        0.5     0.5      32.88   20
5    0        0.5     0.5      32.06   18.48
5    0        0.5     0.5      36.59   18.68
6    0.5      0       0.5      39.93   26.14
6    0.5      0       0.5      43.13   24.14
6    0.5      0       0.5      37.87   21.84
7    0.1666   0.1666  0.6667   41.47   26.88
7    0.1666   0.1666  0.6667   39.42   23.08
7    0.1666   0.1666  0.6667   37.18   24.44
8    0.6667   0.1666  0.1666   33.8    21.59
8    0.6667   0.1666  0.1666   36.43   20.69
8    0.6667   0.1666  0.1666   36.03   22.99
9    0.1666   0.6667  0.1666   38.24   20.21
9    0.1666   0.6667  0.1666   35.54   17.39
9    0.1666   0.6667  0.1666   38.18   19.35
10    0.3333  0.3333  0.3333   40.8    25.27
10    0.3333  0.3333  0.3333   39.87   21.84
10    0.3333  0.3333  0.3333   39.81   23.6
;

proc glm data=a;
      model response = chitin dcp starch chitin*dcp chitin*starch dcp*starch chitin*dcp*starch
/noint ;
run;

proc glm data=a;
      model response = chitin dcp starch chitin*dcp dcp*starch chitin*dcp*starch /noint ;
run;
```

Table 3.9 The SAS Output of Angle of Repose (First Excluded) with NOINT Option

General Linear Models Procedure

Dependent Variable: RESPONSE

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	6	44284.72685327	7380.78780888	1763.35	0.0001
Error	24	100.45594673	4.18566445		
Uncorrected Total	30	44385.18280000			

R-Square	C.V.	Root MSE	RESPONSE Mean
0.997737	5.338682	2.04588965	38.32200000

NOTE: No intercept term is used: R-square is not corrected for the mean.

Source	DF	Type I SS	Mean Square	F Value	Pr > F
CHITIN	1	22202.70356776	22202.70356776	5304.46	0.0001
DCP	1	12181.53512972	12181.53512972	2910.30	0.0001
STARCH	1	9769.69232981	9769.69232981	2334.08	0.0001
CHITIN*DCP	1	23.75266969	23.75266969	5.67	0.0255
DCP*STARCH	1	99.00651631	99.00651631	23.65	0.0001
CHITIN*DCP*STARCH	1	8.03663999	8.03663999	1.92	0.1786

Source	DF	Type III SS	Mean Square	F Value	Pr > F
CHITIN	1	4822.42557106	4822.42557106	1152.13	0.0001
DCP	1	4587.98443759	4587.98443759	1096.12	0.0001
STARCH	1	7931.25064048	7931.25064048	1894.86	0.0001
CHITIN*DCP	1	11.54974234	11.54974234	2.76	0.1097
DCP*STARCH	1	105.82977496	105.82977496	25.28	0.0001
CHITIN*DCP*STARCH	1	8.03663999	8.03663999	1.92	0.1786

Parameter	Estimate	T for H0: Parameter=0	Pr > |T|	Std Error of Estimate
CHITIN	34.76106598	33.94	0.0001	1.02410037
DCP	37.79408717	33.11	0.0001	1.14155042
STARCH	44.57908565	43.53	0.0001	1.02410037
CHITIN*DCP	9.40783601	1.66	0.1097	5.66351161
DCP*STARCH	-28.47787155	-5.03	0.0001	5.66351161
CHITIN*DCP*STARCH	47.97806186	1.39	0.1786	34.62482984

Table 3.10 The SAS Input Statements of Angle of Repose (Second Excluded)

```
option is=70;
data a;
input formu chitin dcp starch AOR COMP;
response=AOR;
card;
1    1        0        0        35.18  17.72
1    1        0        0        32.66  16.88
1    1        0        0        38.66  15.58
2    0        1        0        37.23  8.51
2    0        1        0        36.87  13.68
2    0        1        0        38.66  10.42
3    0        0        1        43.23  16.05
3    0        0        1        44.42  15.29
3    0        0        1        46.12  16.47
4    0.5      0.5      0        39.6   20.65
4    0.5      0.5      0        38.66  18.68
4    0.5      0.5      0        39.14  19.57
5    0        0.5      0.5      32.88  20
5    0        0.5      0.5      32.06  18.48
5    0        0.5      0.5      36.59  18.68
6    0.5      0        0.5      39.93  26.14
6    0.5      0        0.5      43.13  24.14
6    0.5      0        0.5      37.87  21.84
7    0.1666   0.1666   0.6667   41.47  26.88
7    0.1666   0.1666   0.6667   39.42  23.08
7    0.1666   0.1666   0.6667   37.18  24.44
8    0.6667   0.1666   0.1666   33.8   21.59
8    0.6667   0.1666   0.1666   36.43  20.69
8    0.6667   0.1666   0.1666   36.03  22.99
9    0.1666   0.6667   0.1666   38.24  20.21
9    0.1666   0.6667   0.1666   35.54  17.39
9    0.1666   0.6667   0.1666   38.18  19.35
10   0.3333   0.3333   0.3333   40.8   25.27
10   0.3333   0.3333   0.3333   39.87  21.84
10   0.3333   0.3333   0.3333   39.81  23.6
;

proc glm data=a;
      model response = chitin dcp starch chitin*dcp chitin*starch dcp*starch chitin*dcp*starch
/noint ;
run;

proc glm data=a;
      model response = chitin dcp starch chitin*dcp dcp*starch chitin*dcp*starch /noint ;
run;

proc glm data=a;
      model response = chitin dcp starch chitin*dcp dcp*starch /noint ;
run;
```

Table 3.11 The SAS Output of Angle of Repose (Second Excluded) with NOINT Option

General Linear Models Procedure

Dependent Variable: RESPONSE

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	5	44276.69021328	8855.33804266	2040.54	0.0001
Error	25	108.49258672	4.33970347		
Uncorrected Total	30	44385.18280000			

R-Square	C.V.	Root MSE	RESPONSE Mean
0.997556	5.436030	2.08319549	38.32200000

NOTE: No intercept term is used: R-square is not corrected for the mean.

Source	DF	Type I SS	Mean Square	F Value	Pr > F
CHITIN	1	22202.70356776	22202.70356776	5116.18	0.0001
DCP	1	12181.53512972	12181.53512972	2807.00	0.0001
STARCH	1	9769.69232981	9769.69232981	2251.23	0.0001
CHITIN*DCP	1	23.75266969	23.75266969	5.47	0.0276
DCP*STARCH	1	99.00651631	99.00651631	22.81	0.0001

Source	DF	Type III SS	Mean Square	F Value	Pr > F
CHITIN	1	4968.59107481	4968.59107481	1144.91	0.0001
DCP	1	4588.28000145	4588.28000145	1057.28	0.0001
STARCH	1	8151.73460983	8151.73460983	1878.41	0.0001
CHITIN*DCP	1	23.15504777	23.15504777	5.34	0.0294
DCP*STARCH	1	99.00651631	99.00651631	22.81	0.0001

Parameter	Estimate	T for H0: Parameter=0	Pr > |T|	Std Error of Estimate
CHITIN	34.95451946	33.84	0.0001	1.03303904
DCP	37.66071521	32.52	0.0001	1.15822687
STARCH	44.77253913	43.34	0.0001	1.03303904
CHITIN*DCP	12.34946121	2.31	0.0294	5.34632305
DCP*STARCH	-25.53624635	-4.78	0.0001	5.34632305

Table 3.12 The SAS Input Statements of Angle of Repose without $\beta 1^*$ CHITIN Term and No NOINT Option

```
option is=70;
data a;
input formu chitin dcp starch AOR COMP;
response=AOR;
card;
1    1        0        0        35.18  17.72
1    1        0        0        32.66  16.88
1    1        0        0        38.66  15.58
2    0        1        0        37.23  8.51
2    0        1        0        36.87  13.68
2    0        1        0        38.66  10.42
3    0        0        1        43.23  16.05
3    0        0        1        44.42  15.29
3    0        0        1        46.12  16.47
4    0.5      0.5      0        39.6   20.65
4    0.5      0.5      0        38.66  18.68
4    0.5      0.5      0        39.14  19.57
5    0        0.5      0.5      32.88  20
5    0        0.5      0.5      32.06  18.48
5    0        0.5      0.5      36.59  18.68
6    0.5      0        0.5      39.93  26.14
6    0.5      0        0.5      43.13  24.14
6    0.5      0        0.5      37.87  21.84
7    0.1666   0.1666   0.6667   41.47  26.88
7    0.1666   0.1666   0.6667   39.42  23.08
7    0.1666   0.1666   0.6667   37.18  24.44
8    0.6667   0.1666   0.1666   33.8   21.59
8    0.6667   0.1666   0.1666   36.43  20.69
8    0.6667   0.1666   0.1666   36.03  22.99
9    0.1666   0.6667   0.1666   38.24  20.21
9    0.1666   0.6667   0.1666   35.54  17.39
9    0.1666   0.6667   0.1666   38.18  19.35
10   0.3333   0.3333   0.3333   40.8   25.27
10   0.3333   0.3333   0.3333   39.87  21.84
10   0.3333   0.3333   0.3333   39.81  23.6
;

proc glm data=a;
      model response = chitin dcp starch chitin*dcp chitin*starch dcp*starch chitin*dcp*starch
/noint ;
run;

proc glm data=a;
      model response = chitin dcp starch chitin*dcp dcp*starch chitin*dcp*starch /noint ;
run;

proc glm data=a;
      model response = chitin dcp starch chitin*dcp dcp*starch /noint ;
run;
```

```
proc glm data=a;
      model response = dcp starch chitin*dcp dcp*starch ;
run;
```

Table 3.13 The SAS Output without $\beta 1^*$ CHITIN Term and No NOINT Option

General Linear Models Procedure

Dependent Variable: RESPONSE

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	4	219.43043780	54.85760945	12.64	0.0001
Error	25	108.48184220	4.33927369		
Corrected Total	29	327.91228000			

R-Square	C.V.	Root MSE	RESPONSE Mean
0.669174	5.435761	2.08309234	38.32200000

Source	DF	Type I SS	Mean Square	F Value	Pr > F
DCP	1	25.85021040	25.85021040	5.96	0.0221
STARCH	1	70.78781768	70.78781768	16.31	0.0004
DCP*CHITIN	1	23.72257317	23.72257317	5.47	0.0277
DCP*STARCH	1	99.06983655	99.06983655	22.83	0.0001

Source	DF	Type III SS	Mean Square	F Value	Pr > F
DCP	1	13.93968773	13.93968773	3.21	0.0852
STARCH	1	159.05994354	159.05994354	36.66	0.0001
DCP*CHITIN	1	23.12324754	23.12324754	5.33	0.0295
DCP*STARCH	1	99.06983655	99.06983655	22.83	0.0001

Parameter	Estimate	T for H0: Parameter=0	Pr > |T|	Std Error of Estimate
INTERCEPT	34.95384907	33.84	0.0001	1.03296696
DCP	2.70706080	1.79	0.0852	1.51035838
STARCH	9.81797339	6.05	0.0001	1.62162324
DCP*CHITIN	12.34125870	2.31	0.0295	5.34617983
DCP*STARCH	-25.54433780	-4.78	0.0001	5.34604299

3.3.2 Evaluation of Response Surface Models

The models of the response and R-square of the formulation properties were showed in Table 3.14.

Table 3.14 The Response Surface Model of Each Property

Response	Response Surface Model	R^2
Angle of Repose	34.955CT+37.661DCP+44.773CS+12.349CT*DCP-25.536DCP*CS	0.669
% Compressibility	16.340CT+10.713DCP+16.505CS+24.008CT*DCP+32.950CT*CS+25.176DCP*CS	0.872
Hardness-1*	65.437CT+50.476DCP+20.268CS-80.576CT*DCP-56.591CT*CS-78.244DCP*CS+446.975CT*DCP*CS	0.978
Hardness-2**	74.944CT+58.177DCP+17.235CS-47.9CT*DCP	0.941
%Drug Release-1* at 45 min	88.244CT+15.2DCP+57.271CS+138.462CT*DCP+120.346DCP*CS	0.792
%Drug Release-2** at 45 min	87.853CT+13.775DCP+52.854CS+104.049CT*DCP+54.525CT*CS+119.314DCP*CS	0.835
Log DI-1*	1.134CT+3.363DCP+1.449CS-4.909CT*DCP-4.201DCP*CS	0.899
Log DI-2**	1.365CT+3.399DCP+1.489CS-5.246CT*DCP-4.855DCP*CS	0.923
Friability-1*	0.333CT+0.553DCP+8.064CS-11.415CT*CS-9.975DCP*CS	0.999
Friability-2**	0.676DCP+6.055CS-9.385CT*CS-9.520DCP*CS	0.955

1* = at 1.0 ton compressional pressure

2 **= at 1.5 tons compressional pressure

The contour plot of each response was obtained by using JMP® software program version 3.6.1.2. In the contour plot, the boundary lines (dotted line) in figure indicated the limit value of response. The area, which labeled the alphabet (surrounded with thick dotted line) illustrated the selected area that mentioned in Table 3.5. In Figure 3.7, the selected area were consist of area that had angle of repose less than 40, so the area with higher angle of repose was excluded. Also, the other selected areas were selected in the same manner. In Figure 3.8-3.12 showed the contour plots of formulations F1-F10 of percent compressibility, hardness, percent friability, log disintegration time, and percent drug release at 45 minutes, respectively. The selected areas (A-F) of angle of repose, percent compressibility and other responses of formulations F1-F10 (Figure 3.7-3.12) were superimposed, so the final area which combine with all response was obtained. The optimal area (area which surrounded with thick dotted line) of all responses in 1.0 ton compressional pressure was shown in Figure 3.13. In compressional pressure of 1.5 tons, the Figure 3.14-3.17 demonstrated the contour plots of hardness, percent friability, log disintegration time and percent drug release at 45 minutes, respectively. In Figure 3.18, showed the optimal area of combined response (area A, B, and G-J) in compressional pressure of 1.5 tons (included the angle of repose and percent compressibility). In this area, the formulation had optimal properties, that in appropriate range.

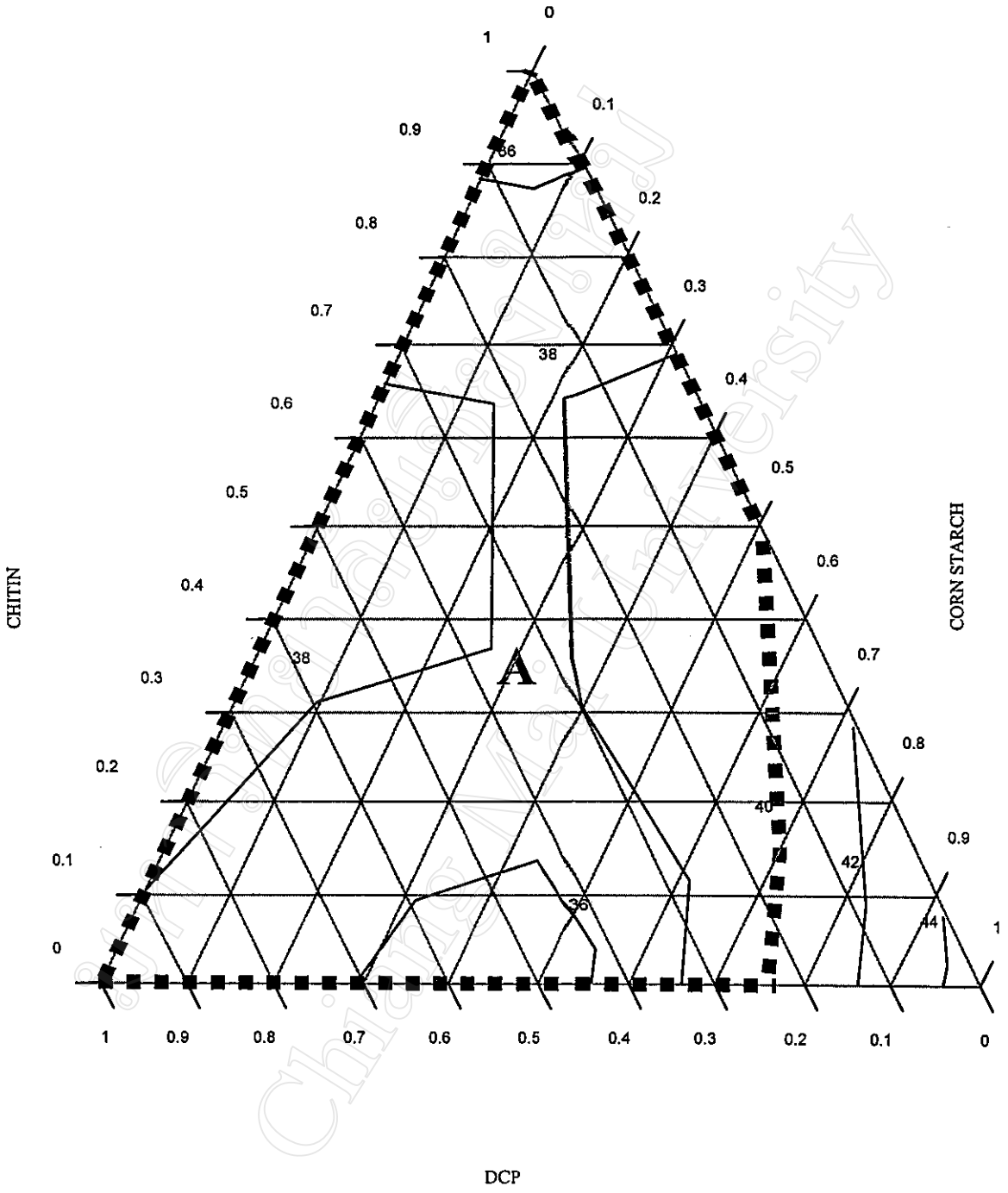

Figure 3.7 The Contour Plot of Angle of Repose

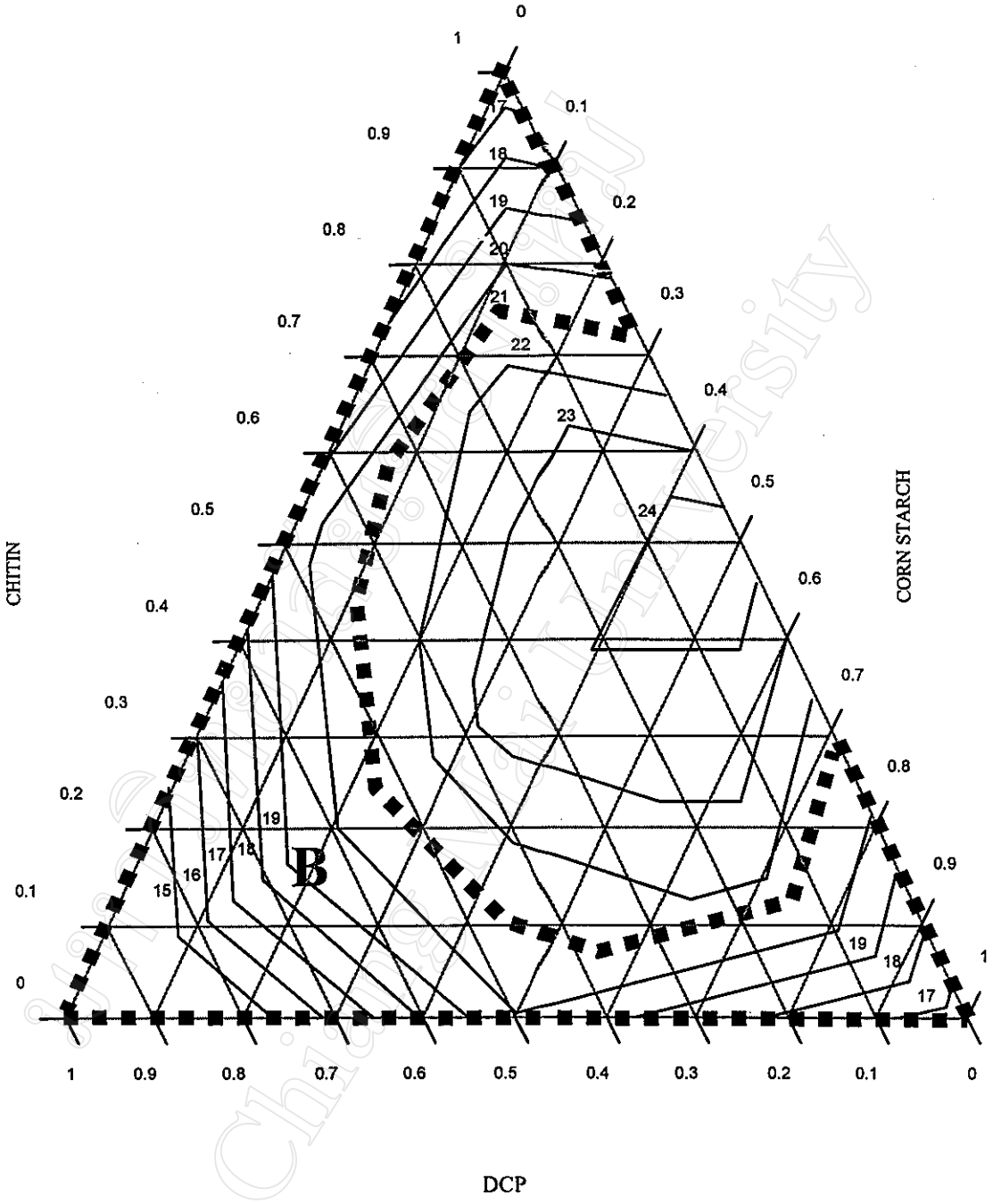

Figure 3.8 The Contour Plot of Percent Compressibility

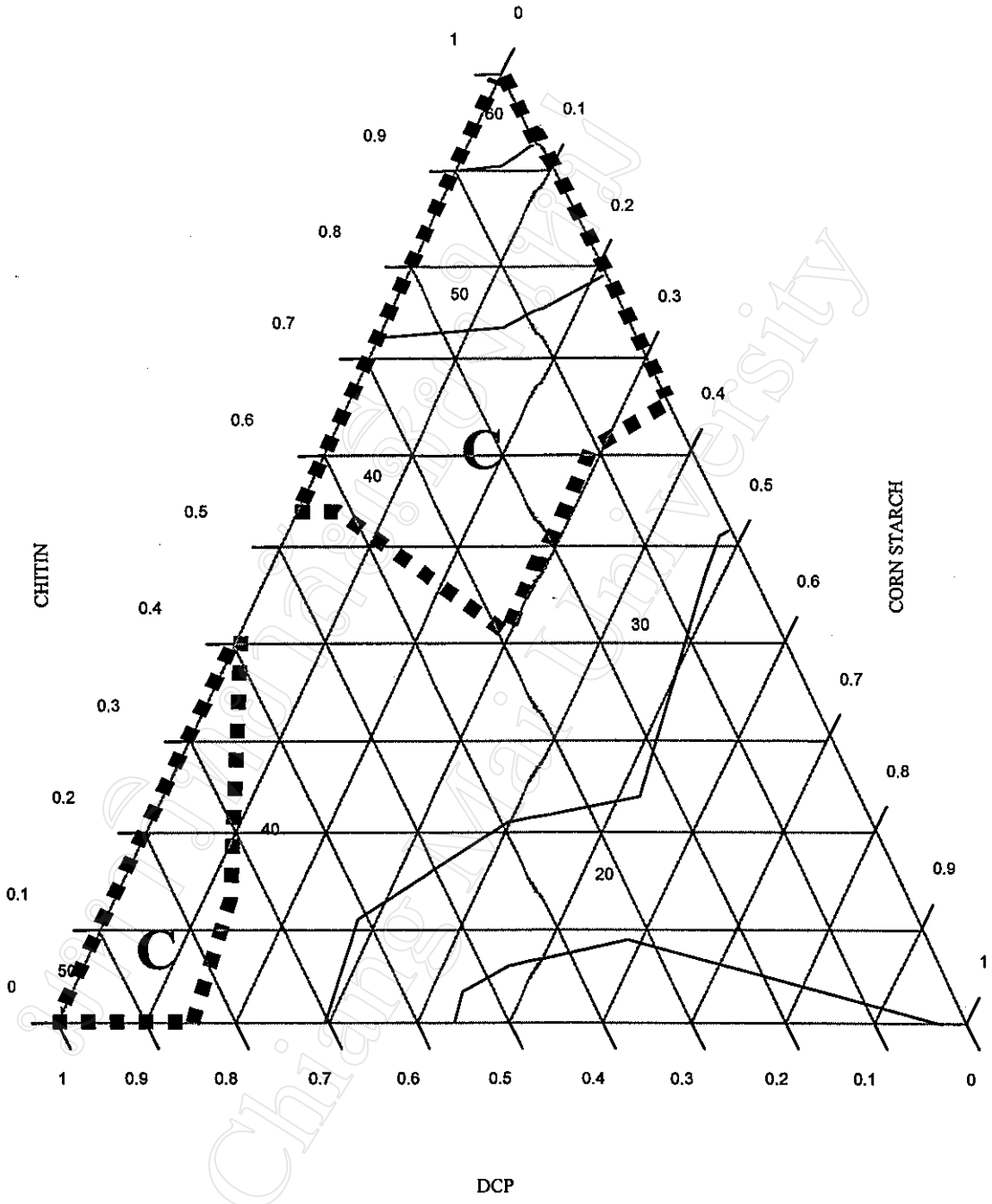

Figure 3.9 The Contour Plot of Hardness at 1.0 Ton Compressional Pressure

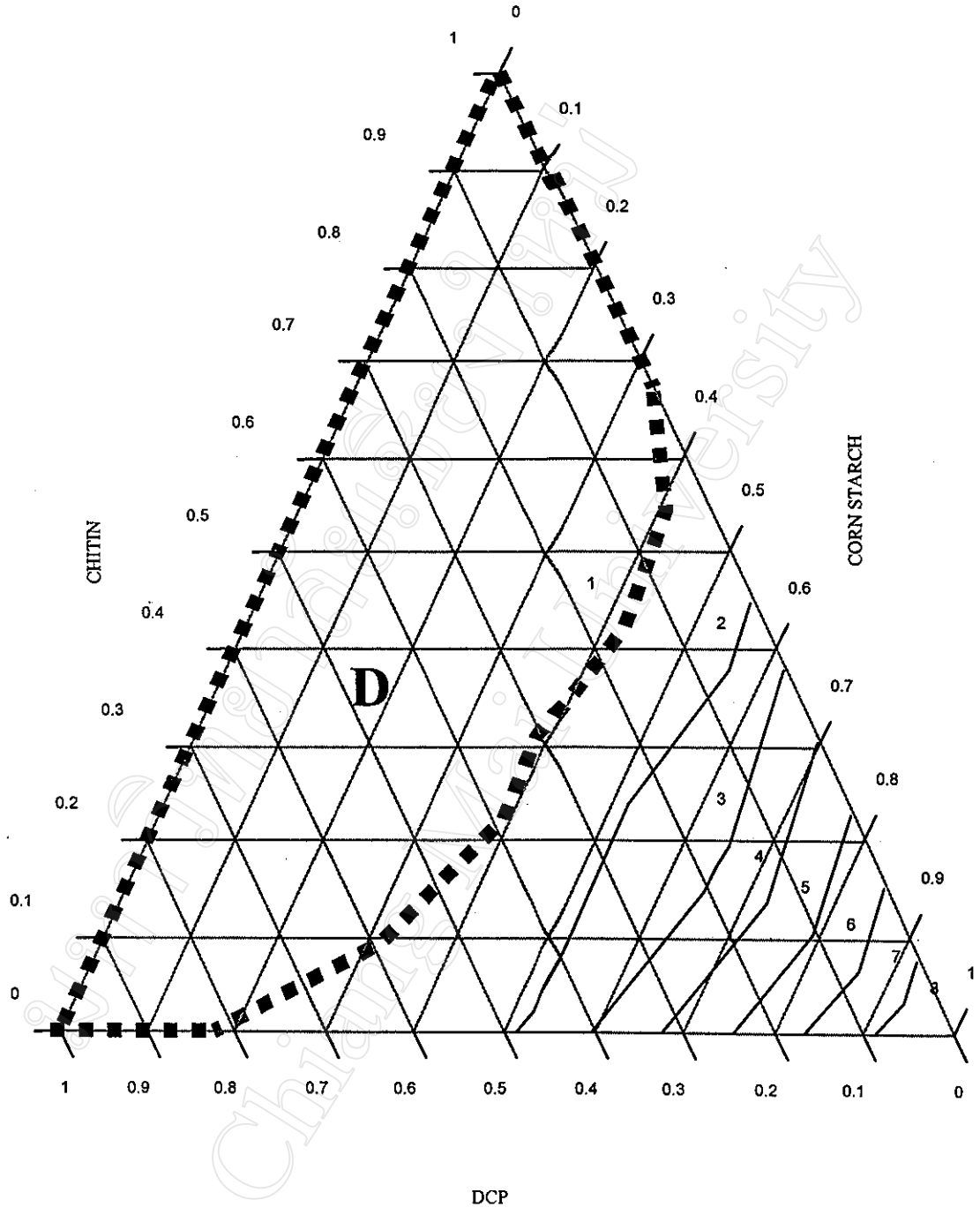

Figure 3.10 The Contour Plot of Percent Friability at 1.0 Ton Compressional Pressure

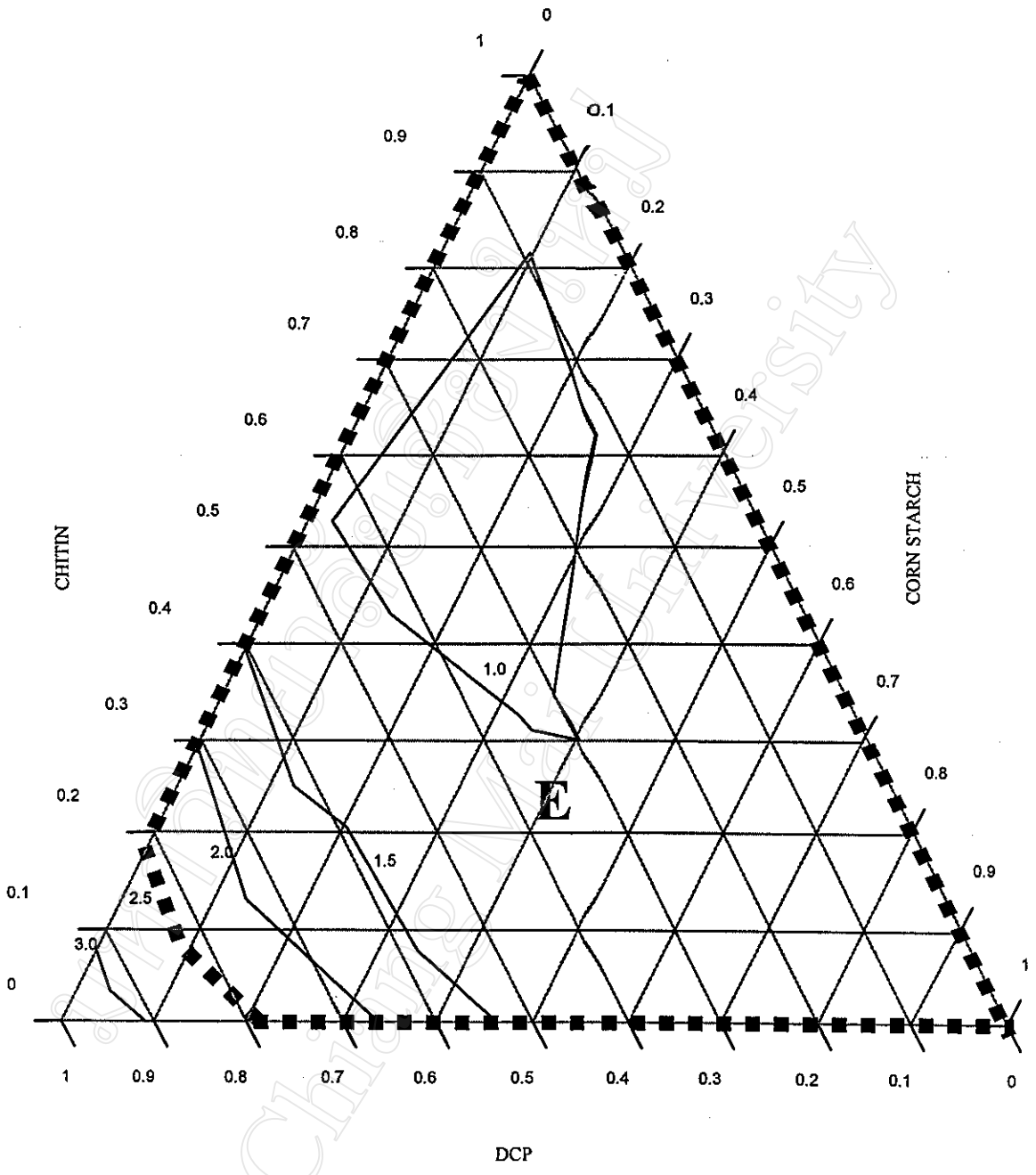

Figure 3.11 The Contour Plot of Log Disintegration Time at 1.0 Ton Compressional Pressure

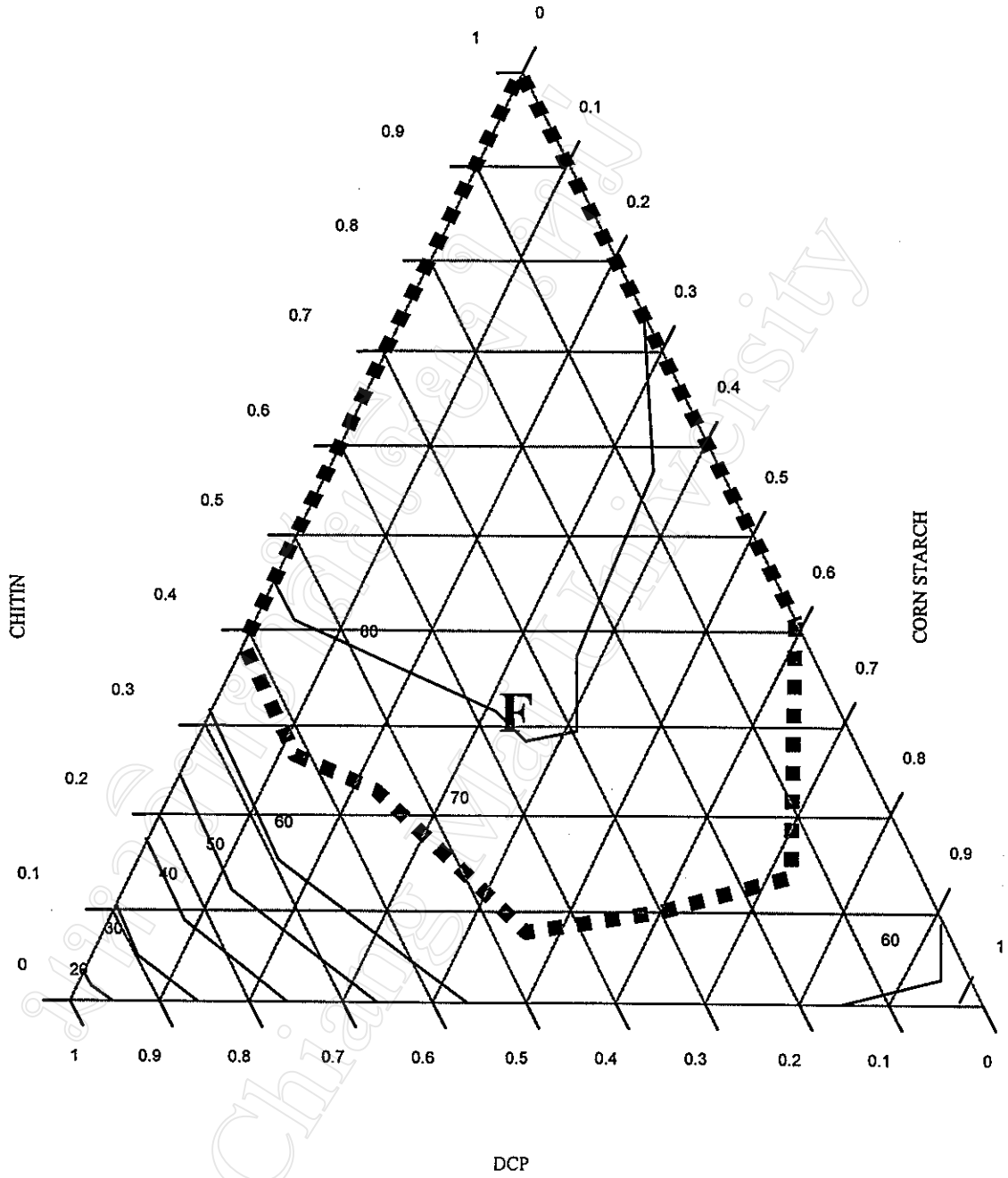

Figure 3.12 The Contour Plot of Percent Drug Release at 45 Minutes of 1.0 Ton Compressional Pressure

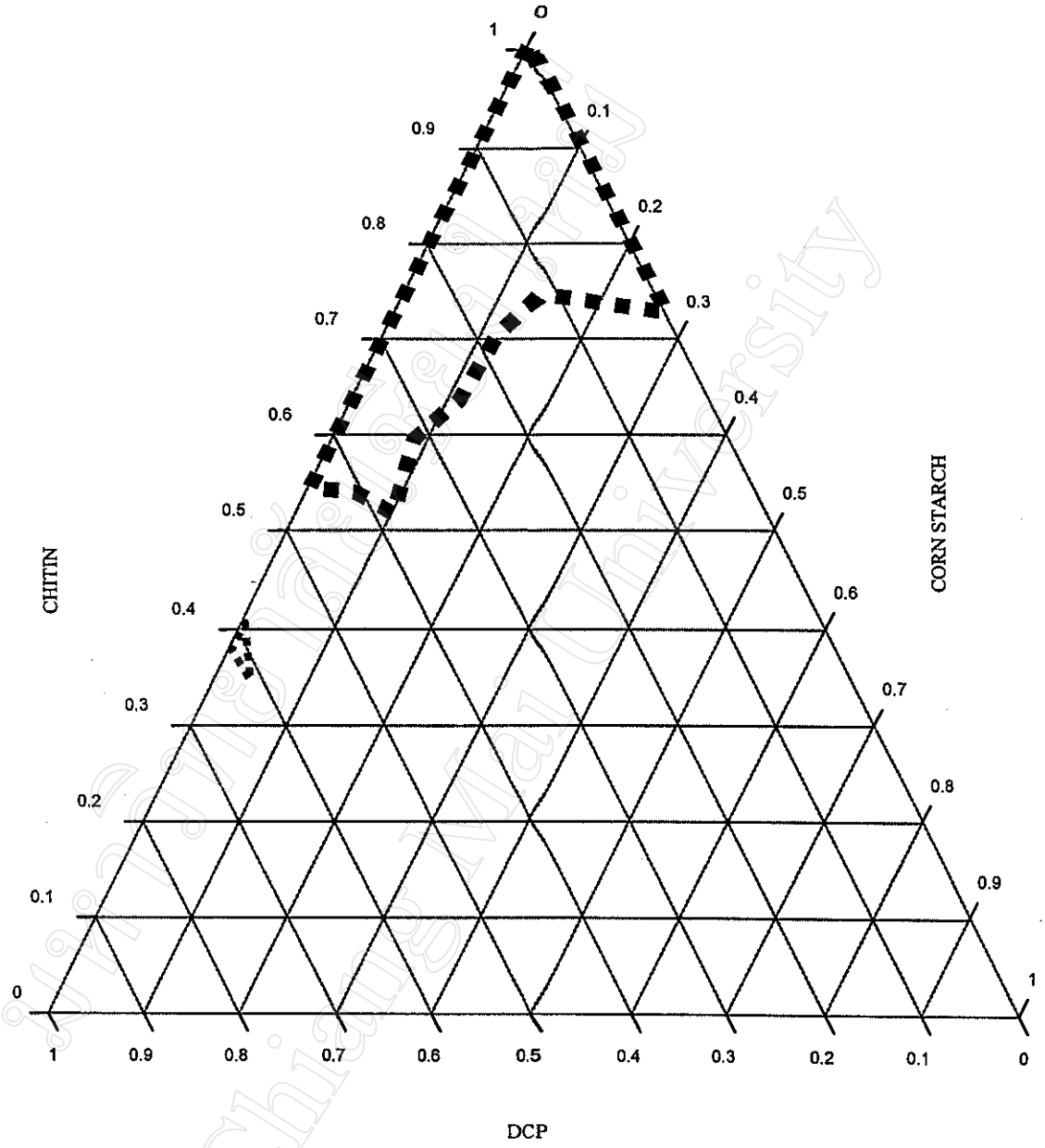

Figure 3.13 The Optimized Area at 1.0 Ton Compressional Pressure

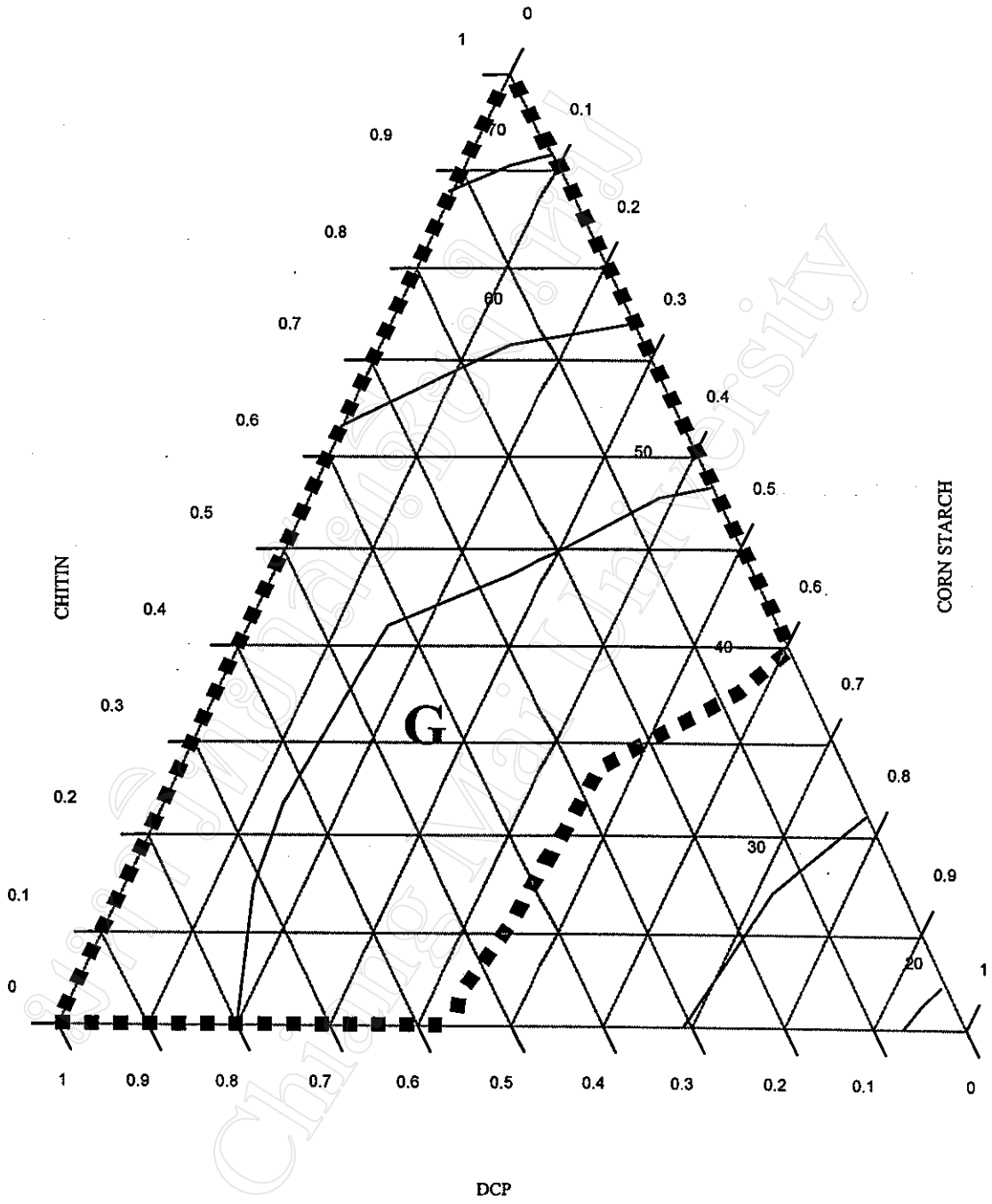

Figure 3.14 The Contour Plot of Hardness at 1.5 Tons Conpressional Pressure

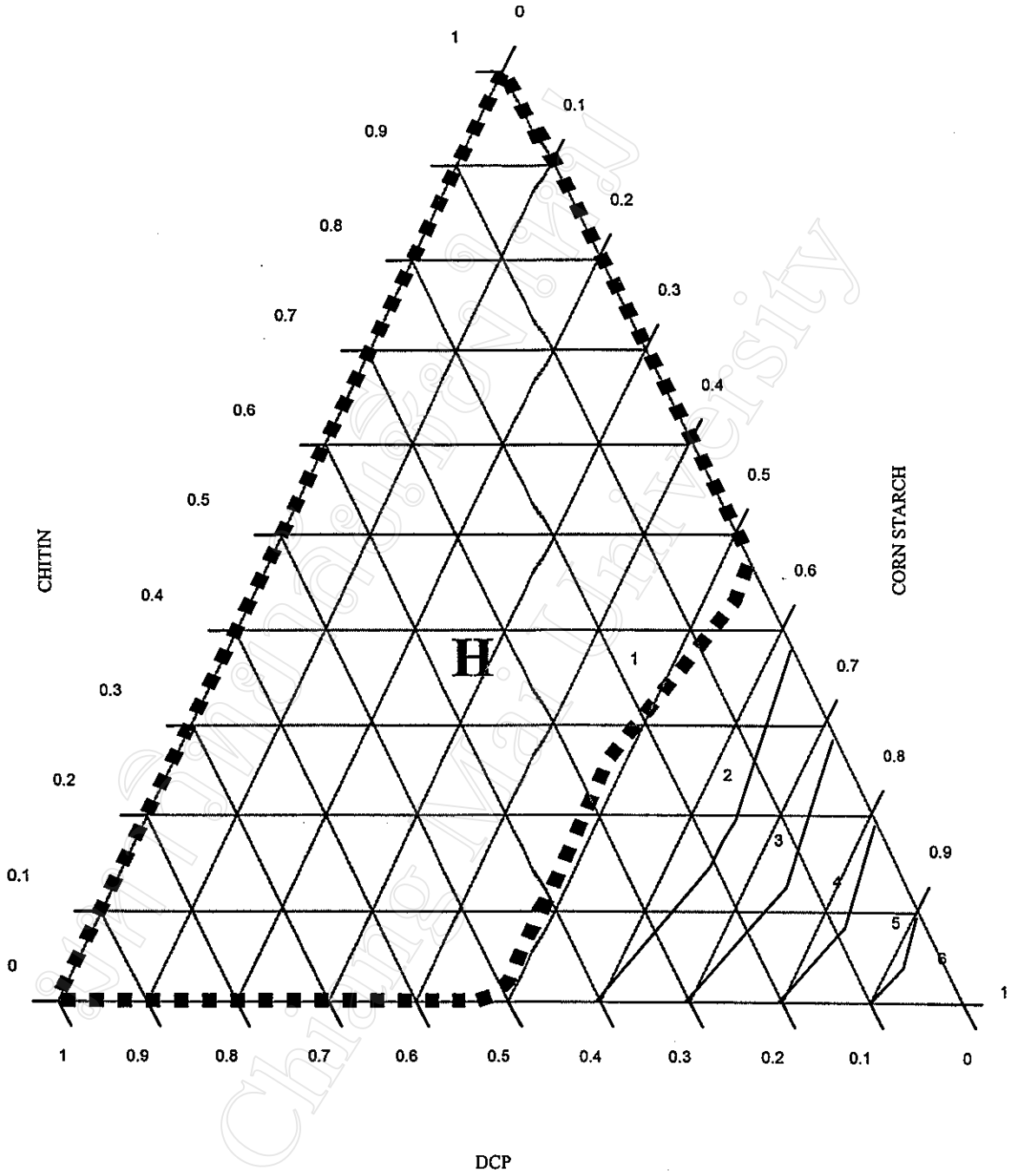

Figure 3.15 The Contour Plot of Percent Friability at 1.5 Tons Compressional Pressure

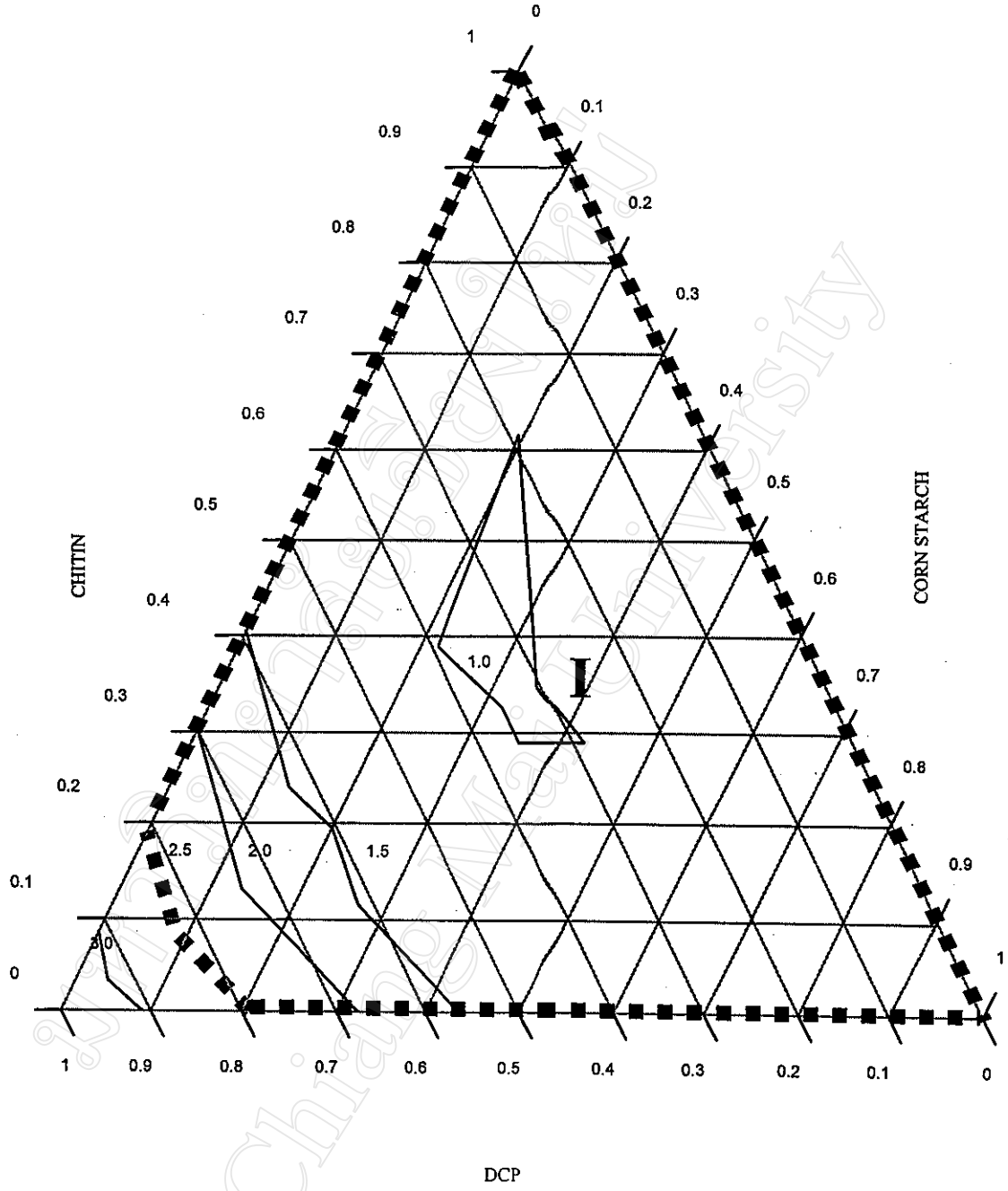

Figure 3.16 The Contour Plot of Log Disintegration Time at 1.5 Tons Compressional Pressure

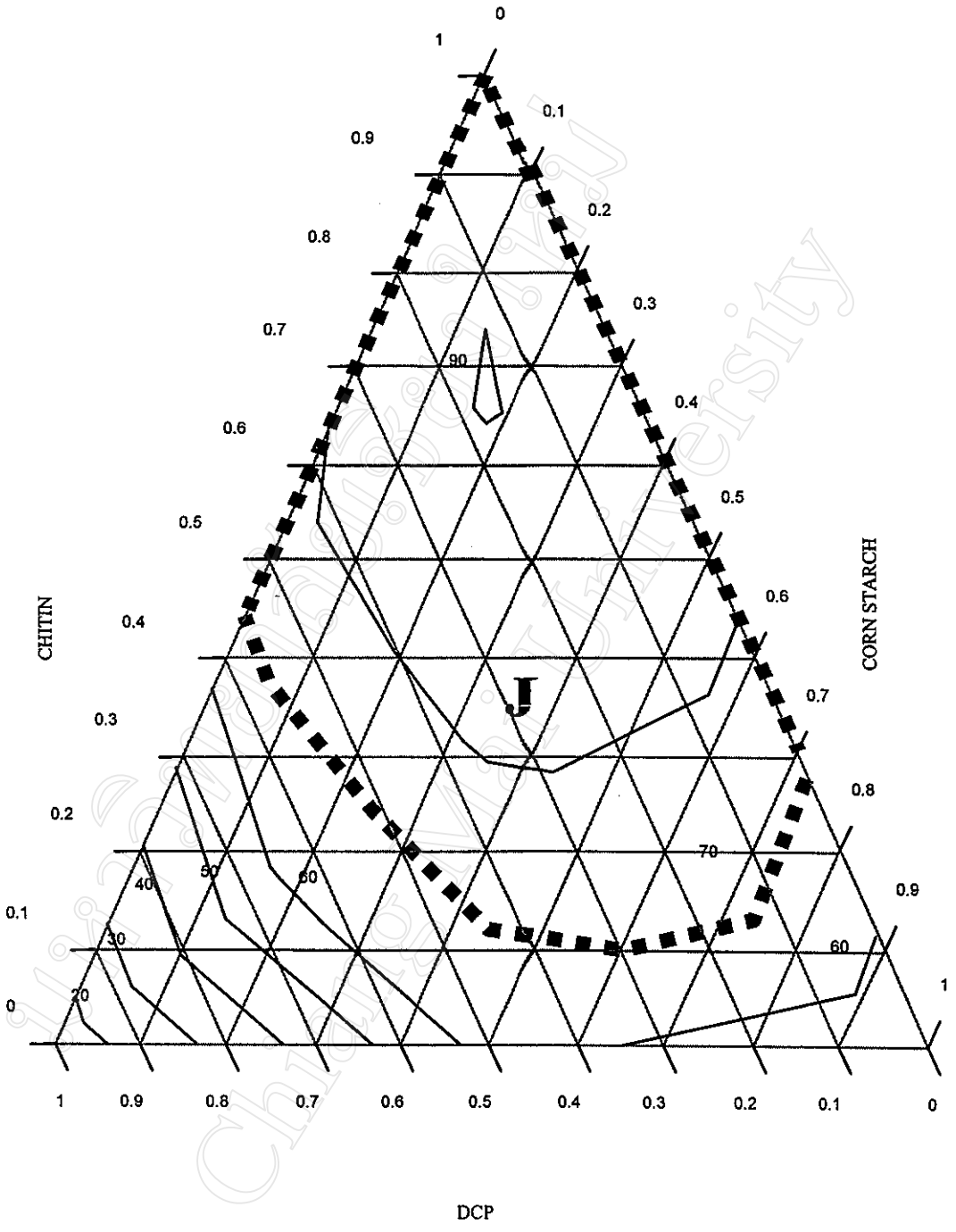

Figure 3.17 The Contour Plot of Percent Drug Release at 45 Minutes of 1.5 Tons Compressional Pressure

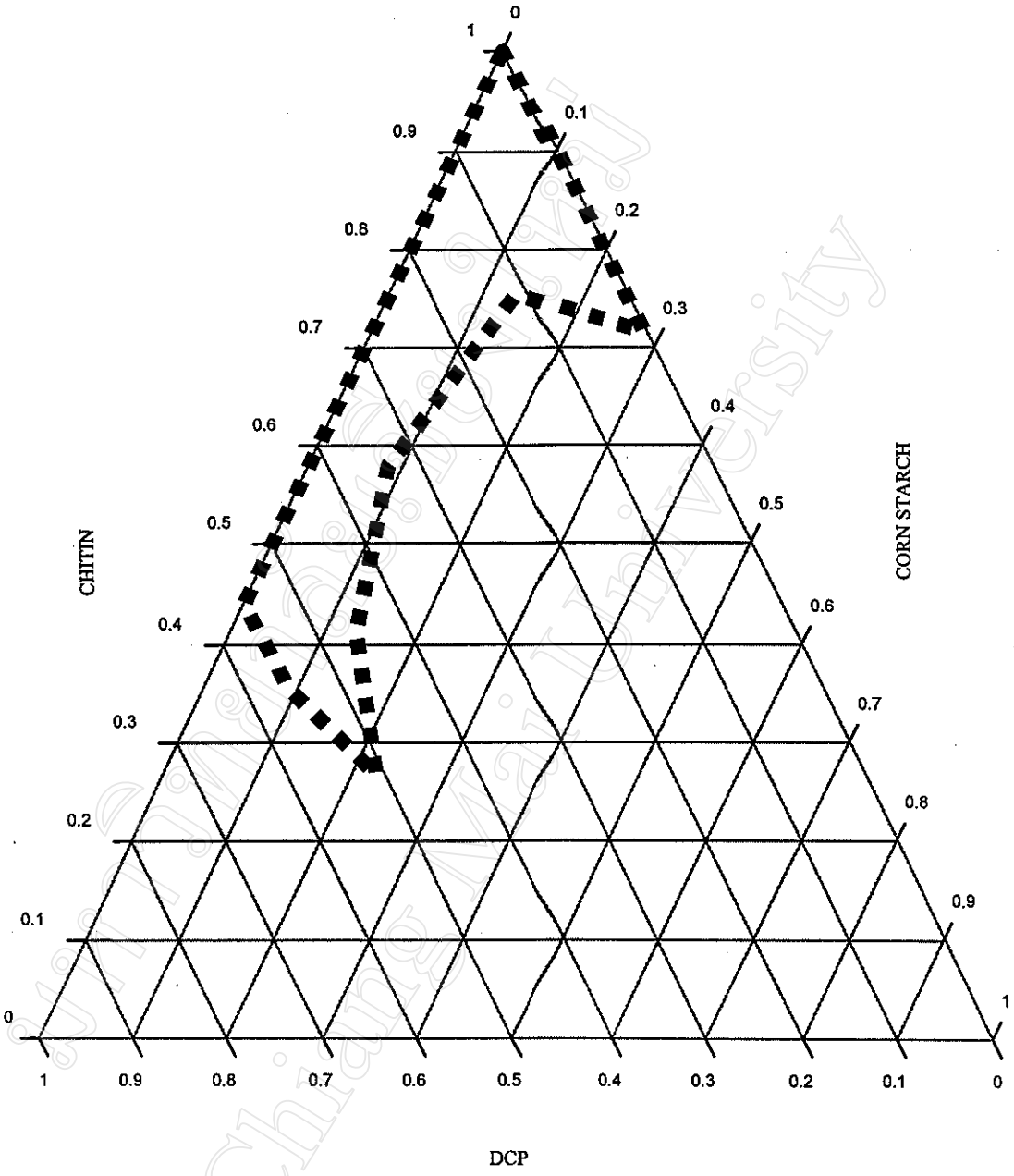

Figure 3.18 The Optimized Area at 1.5 Tons Compressional Pressure

3.4 Scale Up the Direct Compression Tablet

From the optimal area of 1.0 ton compressional pressure, the point X1 was selected for scale up formulation (Figure 3.19). And also, in 1.5 tons compressional pressure, the point X2 was selected as seen in Figure 3.20. The two selected points consist of three components. The proportion of three excipients in both formulations were showed in Table 3.15.

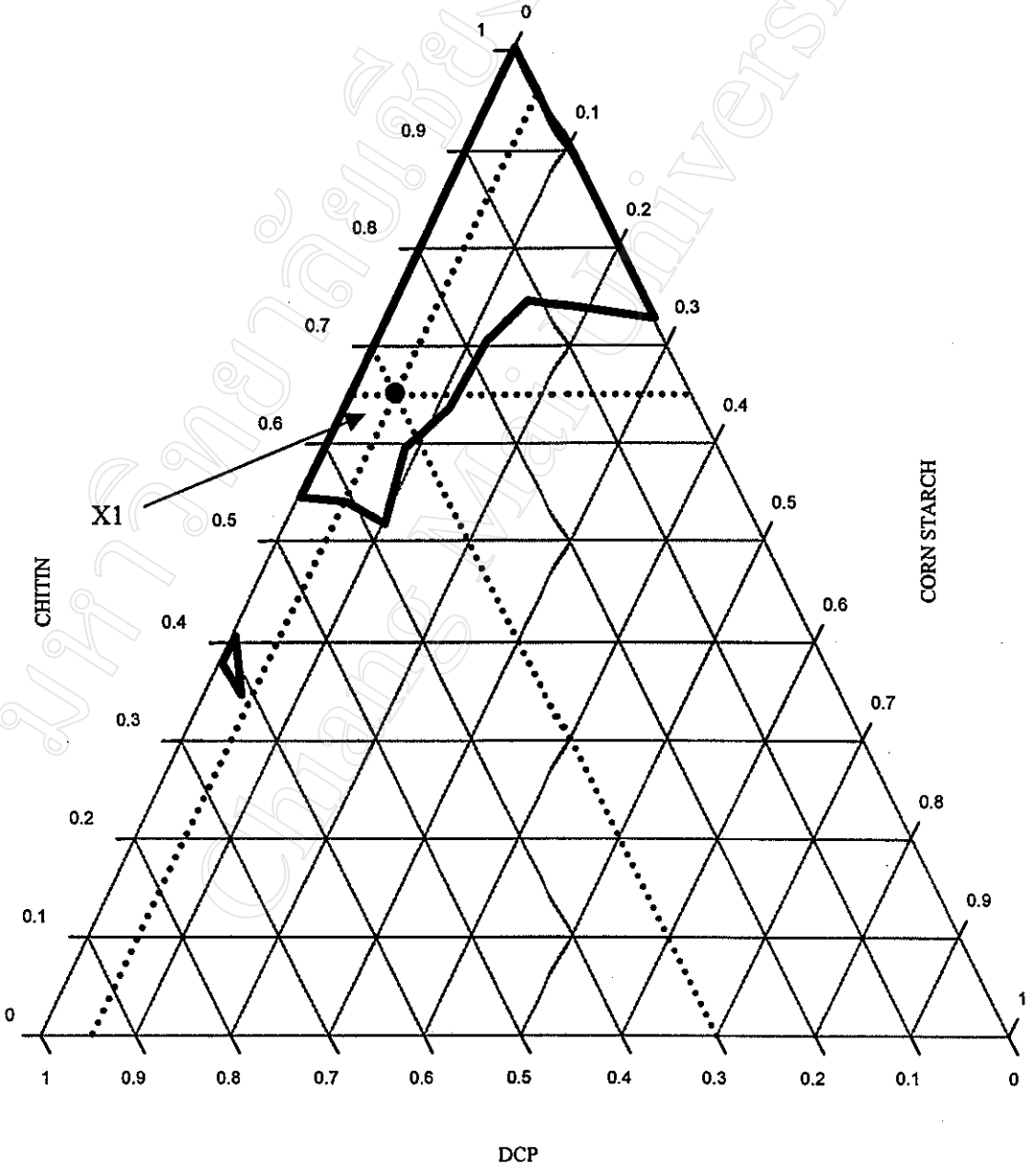

Figure 3.19 The Selected Point ;X1 at 1.0 Ton Compressional Pressure

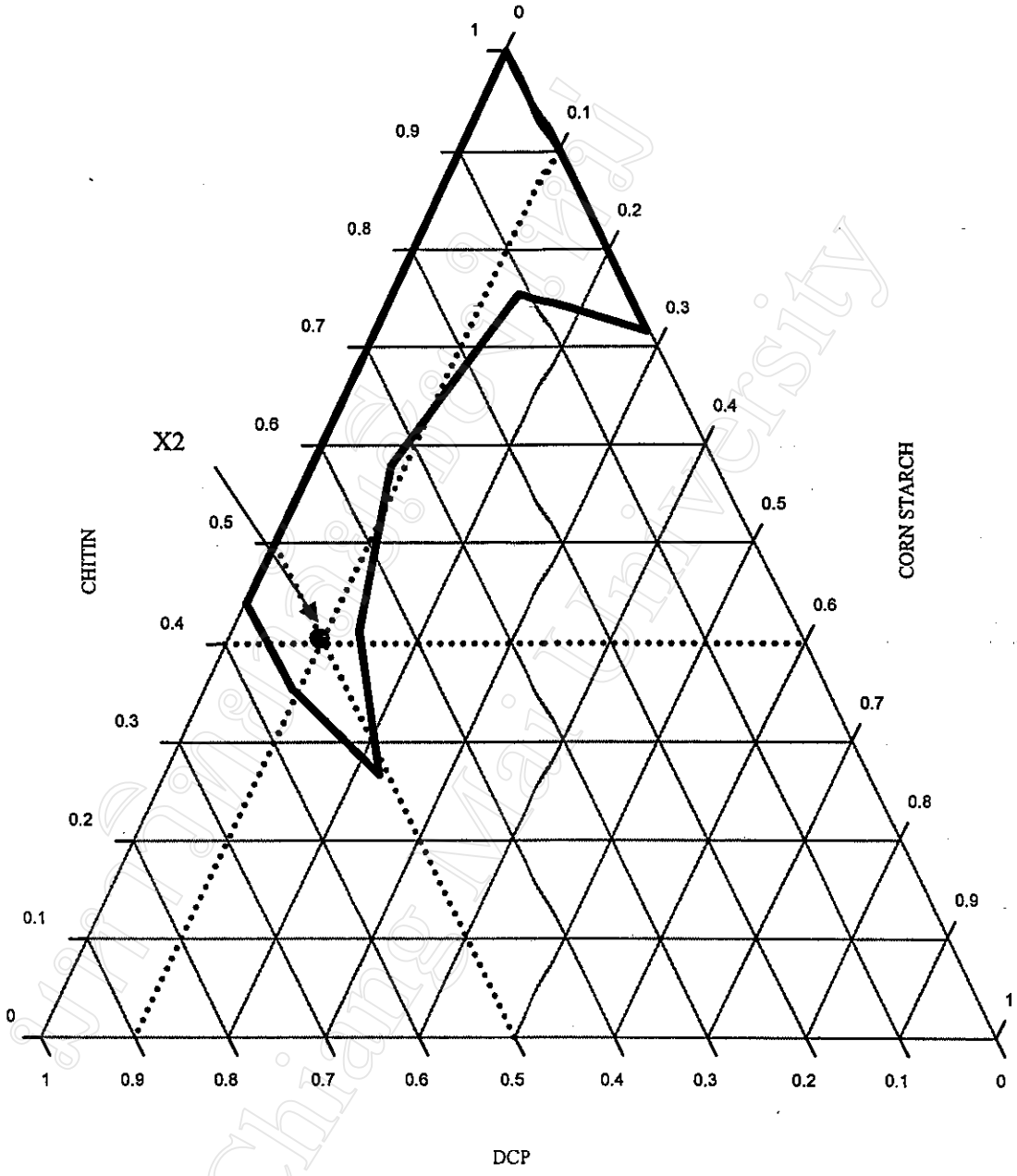

Figure 3.20 The Selected Point; X2 at 1.5 Tons Compressional Pressure

Table 3.15 The Proportion of Three Excipients in Each Formulation

Composition	Formulation	
	X1 (%)	X2 (%)
Chitin	65	40
Dibasic Calcium Phosphate	30	50
Corn Starch	5	10
Total	100	100

The method of making direct compression aspirin tablet was mentioned in previous chapter.

3.5 Comparision the Scale Up Direct Compression Aspirin Tablets with Commercial Tablets

The comparative properties of aspirin formulations between optimized formulation and commercial tablet were showed in Table 3.15. The value of predicted column of each response was obtained by substituent of the proportion of chitin, dibasic calcium phosphate and corn starch (in Table 3.15) to the statistical response model (in Table 3.14). And, the experiment values were derived by determination of experiment formulation. Then, the experiment value of each property was compared with the predicted value.

- Angle of Repose

In Figure 3.21, showed the angle of repose of X1 and X2. The significant difference ($p < 0.05$) between the experimental and the predicted value was observed in X1 but in X2 no significant difference was attained. However, when compare the experimental angle of repose of X1 and X2, no significant different ($p > 0.05$) was found.

- Percent Compressibility

The percent compressibility of X1 and X2 can be seen in Figure 3.22. The experiment values of both formulations were 22.05 and 23.07, respectively. In

formulation X1, it was found that the experimental and predicted value was no significant difference ($p > 0.05$) but the significant difference ($p < 0.05$) was found in formulation X2. When compare the experimental value of both formulations, no significance difference was observed ($p > 0.05$).

Table 3.16 Comparative Aspirin Formulation from the Optimized and Commercial Formulations

Property	Commercial		X1			X2		
	Mean	S.D.	Predicted	Experiment		Predicted	Experiment	
				Mean	S.D.		Mean	S.D.
Angle of Repose	-	-	38.28	41.09	0.88	38.48	38.69	1.36
Percent Compressibility	-	-	20.79	22.05	1.37	20.92	23.07	1.08
Hardness (N)	61.61	4.67	44.32	91.81	6.49	51.21	87.32	8.24
Thickness (mm)	4.70	0.07	-	3.96	0.04	-	3.86	0.09
Percent Friability	0.08	-	0.26	0.07	-	0.09	0.13	-
Disintegration Time (s)	70	-	6.3	12	-	12.6	13	-
Weight (mg)	571.99	6.47	-	440.89	5.86	-	436.63	7.74
Percent Drug Release	84.23	16.28	93.59	86.39	2.74	76.27	71.31	4.76

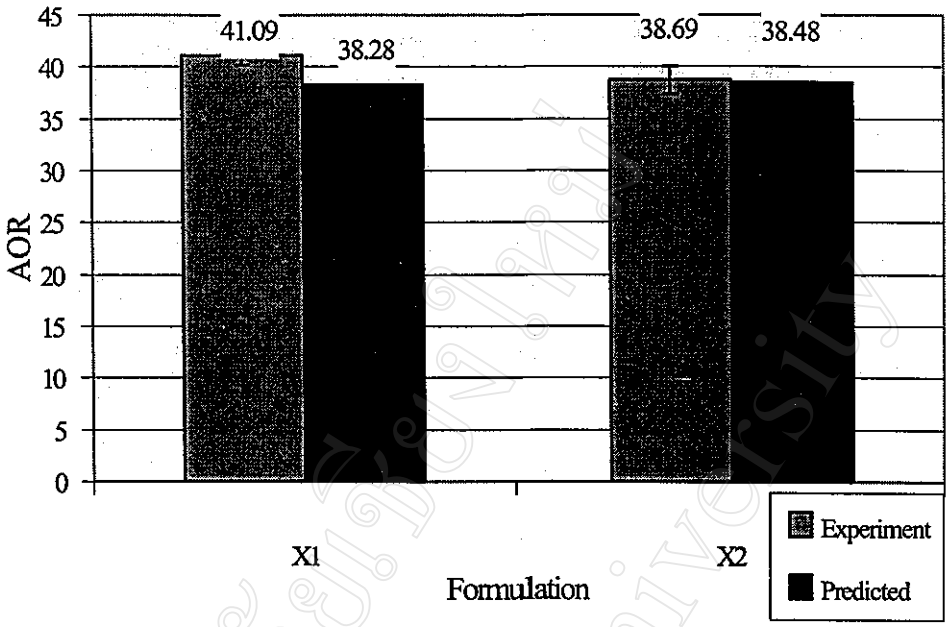

Figure 3.21 The Angle of Repose of Formulations X1 and X2

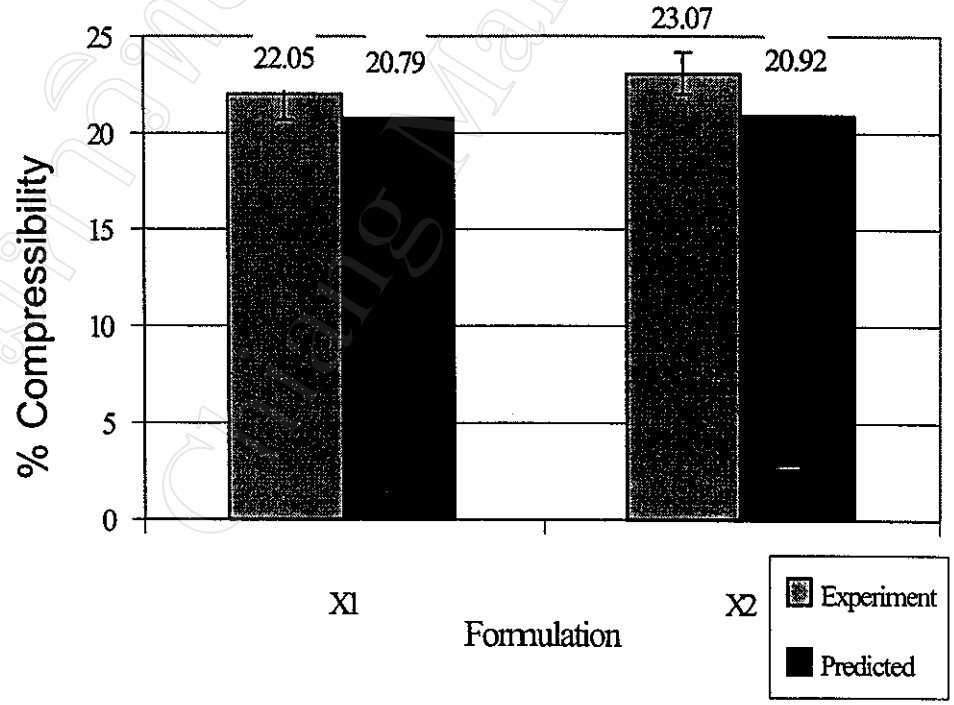

Figure 3.22 The Percent Compressibility of Formulations X1 and X2

- Hardness

In Figure 3.23, demonstrated the hardness of commercial aspirin tablet and the X1 and X2 tablets. The results were that, the hardness of commercial product, the experimental value of X1 and X2 were 61.61, 91.81 and 87.32 N, respectively. The predicted value of X1 and X2 were 44.32 and 51.21 N, respectively. The hardness of commercial product was significant lower ($p < 0.05$) than the experimental value of X1 and X2. In formulation X1 and X2, the experimental value of hardness showed the significant higher than the predicted at 95 % confidence.

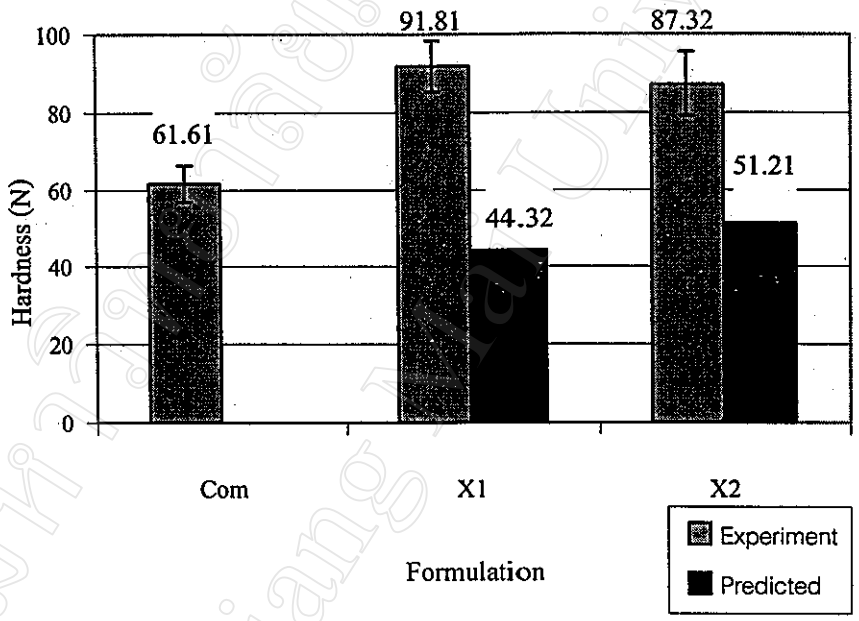

Figure 3.23 The Hardness of Three Formulations

- Percent Friability

The comparative of percent friability of each formulation can be seen in Figure 3.24. The percent friability of commercial tablet, X1 and X2 were 0.08, 0.07 and 0.13, respectively. In formulation X1, the experimental friability was lower than the predicted value as 0.07 and 0.26 % respectively but in formulation X2, the experimental value was higher than the predicted at 0.13 and 0.09 %, respectively.

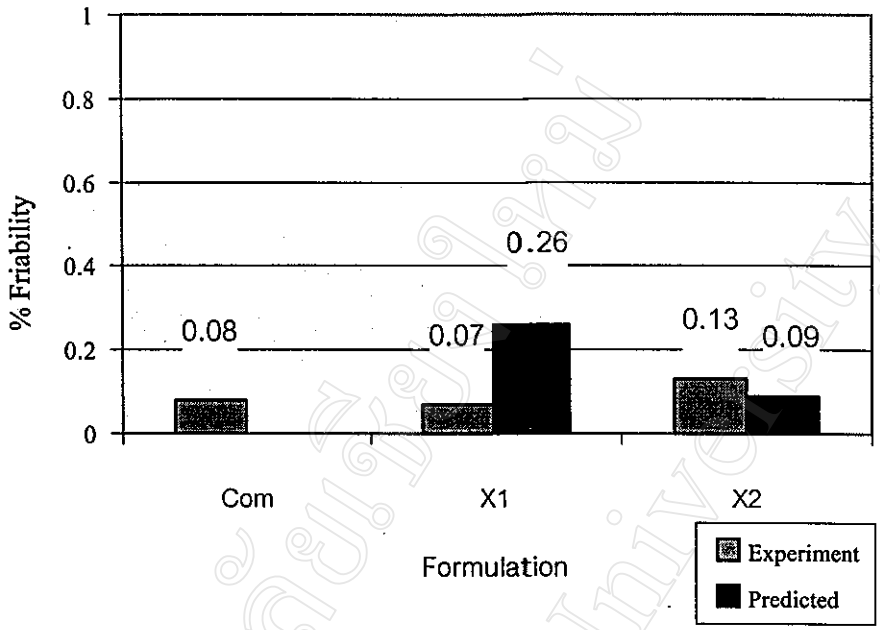

Figure 3.24 The Percent Friability of Three Formulations

- **Disintegration Time**

Figure 3.25 depicted the disintegration time of three tablet formulations. The results were that the disintegration time of commercial tablet was higher than the others. The disintegration time of commercial was 70 seconds, while formulation X1 and X2 were 12 and 13 seconds, respectively. When compare the predicted disintegration time with the experimental data, it was found that, the predicted of X1 was lower than the experiment, at 6.3 seconds, while in formulation X2, the predicted was similar with the experiment at 12.6 seconds.

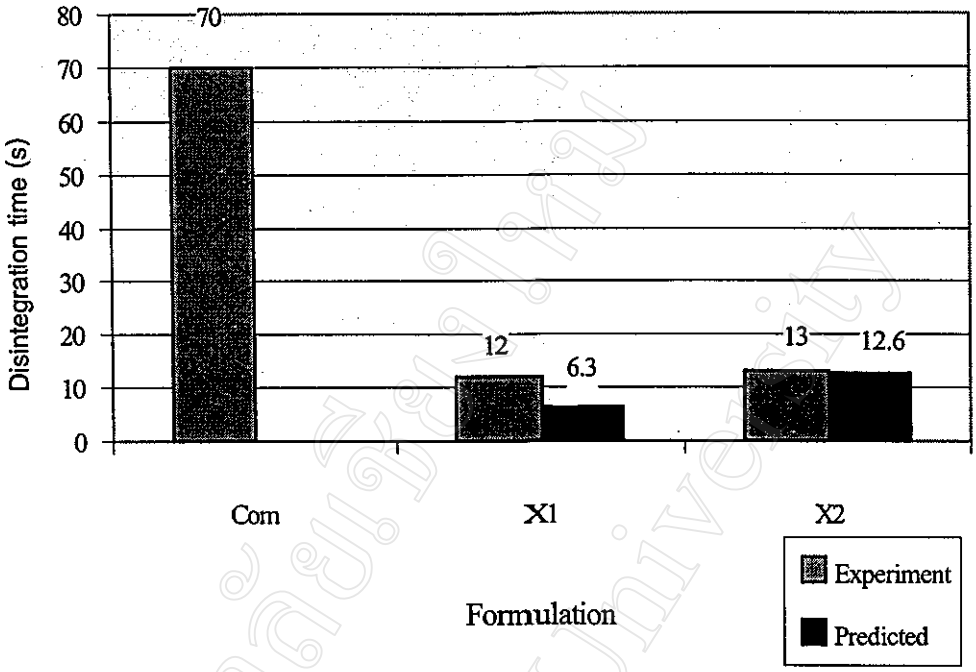

Figure 3.25 The Disintegration Time of Three Formulations

- Percent Drug Release

In dissolution of tablet, Figure 3.26 showed the percent drug release of commercial, X1 and X2 tablets. It can be observed that, the mean percent drug release of the three formulation had significant difference ($p < 0.05$) at 84.23, 86.39 and 71.31, respectively. The experimental dissolution of X1 was significant lower than the predicted value, but the formulation X2, the percent drug release of experiment and predicted was not significant difference ($p > 0.05$). The Td and b parameter of X1, X2 and commercial tablets can be seen in Table 3.16. From the results, it was showed that the Td of X1 were significant difference ($p < 0.05$) from X2 and commercial, but X2 and commercial was no significant difference ($p > 0.05$). However, b parameter of X1 and X2 were less than one while the value of this parameter of commercial tablet was more than one.

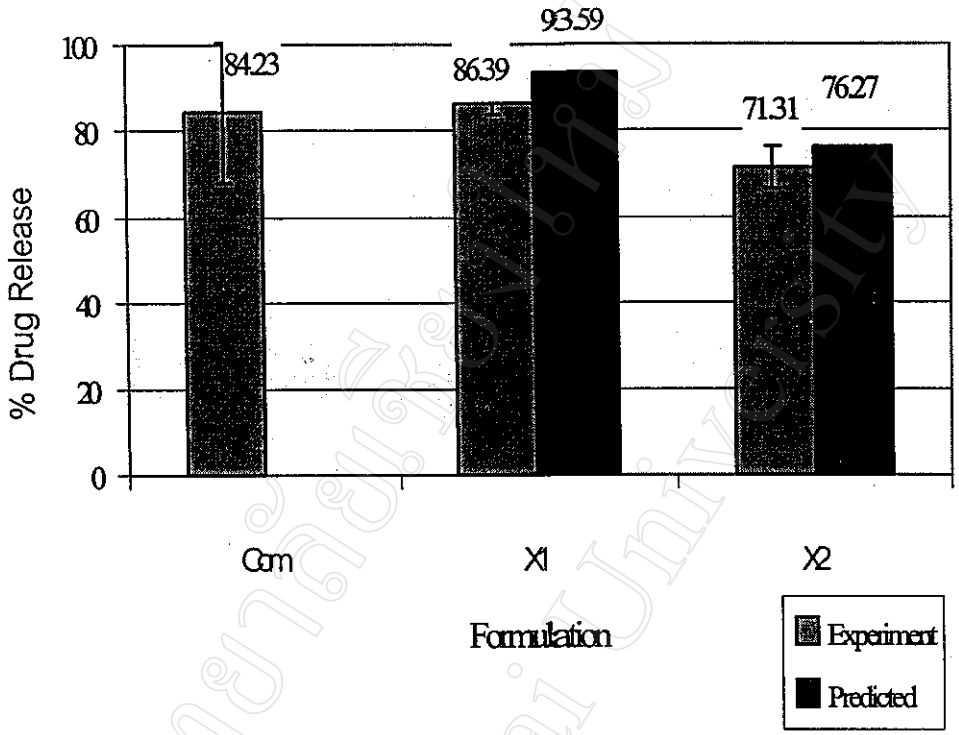

Figure 3.26 The Percent Drug Release of Three Formulations

Table 3.16 The Weibull Dissolution Parameter of X1, X2, and Commercial Tablets

Formulation	Td		b		R^2
	Mean	S.D.	Mean	S.D.	
X1	12.10	2.24	0.62	0.02	0.957
X2	29.34	7.53	0.58	0.05	0.984
Commercial	31.61	12.61	1.34	0.18	0.973

- Tablet Weight

Figure 3.27 depicted the average weight of tablets from the commercial, X1 and X2. It can be seen that, the average weight of commercial tablets > X1 > X2 as 571.99 > 440.89 > 436.63 mg, respectively.

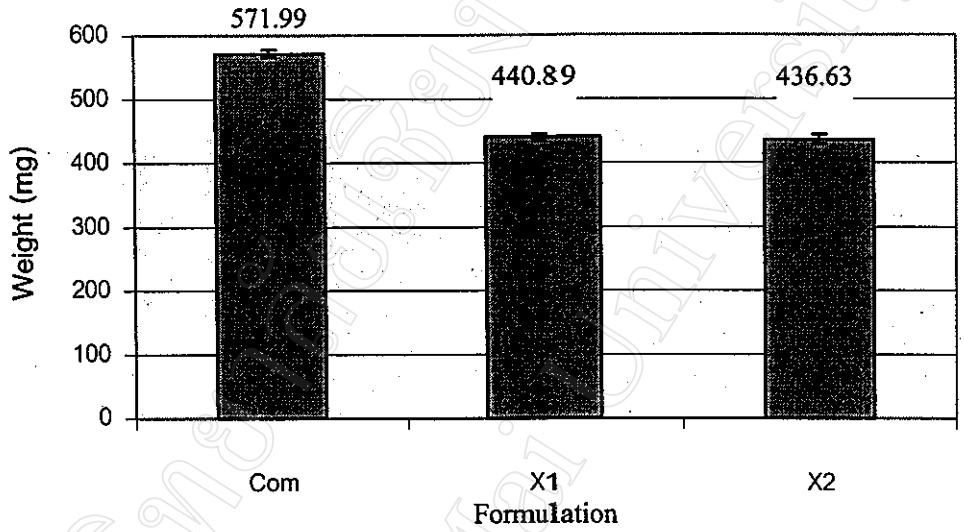

Figure 3.27 The Weight of Three Formulations

- Thickness

Figure 3.28 showed the tablet thickness of commercial, X1 and X2. The results were that, the thickness of all formulations was significant difference ($p < 0.05$) at 4.7 mm, 3.96 and 3.86 mm, respectively.

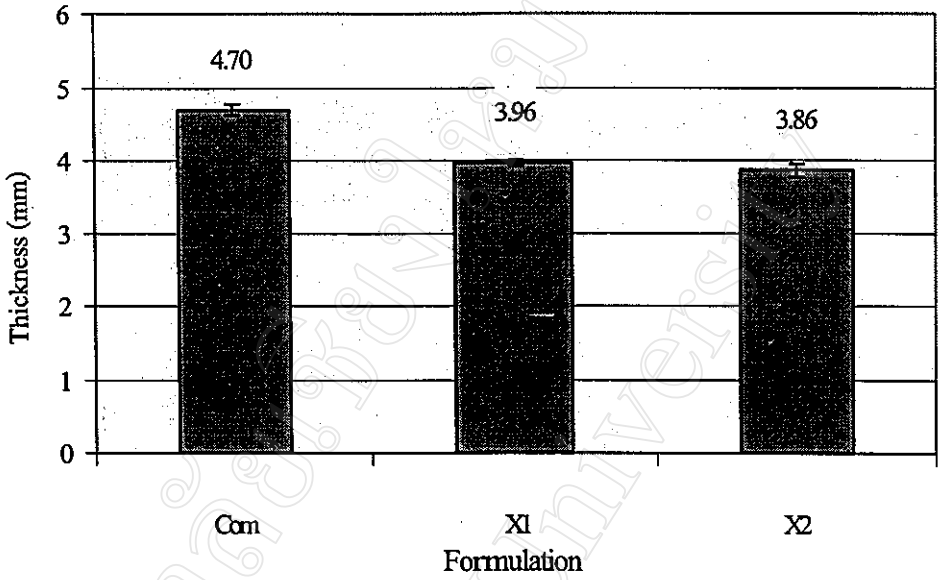

Figure 3.28 The Thickness of Three Formulations