Optimization of Direct Compression Aspirin Tablet Using Statistical Mixture Design

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ABSTRACT

The objective of this study was to optimize aspirin tablet by using statistical mixture design based on three tablet excipients: chitin (CT), dibasic calcium phosphate (DCP) and corn starch (CS) and to compare the optimized formulation with the commercial one. The direct compression method was used to prepare the tablets since it is the most efficient process. The appropriate experimental design was a statistical mixture design. Ten formulations from the experimental design were determined for angle of repose, percent compressibility, tablet hardness, percent friability, log disintegration time and drug release profile. All data were analyzed by using statistical programs. Contour plots of each response were depicted, based on the equation given by the statistical-fitted models. With the optimization of more than one criterion, a combined contour plot was made so that the optimum formulation to satisfy the overall goal was obtained. The scale up formulation was selected from the optimized area of the combined properties. The results suggested that the selected formulation had clearly higher hardness and shorter disintegration time than the commercial tablet. The dissolution study showed no significant difference between the optimized formulation and the commercial tablet. It can be concluded that optimization is an effective technique which can be used to obtain the pharmaceutical formulation with the required characteristics.

Key Words: Aspirin, Augmented Simplex Centroid Design, Direct Compression, Mixture Design, Optimization

INTRODUCTION

A pharmaceutical formulation is composed of several composition factors and process variables. These factors and variables not only affect the characteristic property of the dosage form but also make it difficult to formulate. Consequently, expertise and experience are required to design any pharmaceutical formulation. Formulation experience with pharmaceutical preparation generally can guide a formulation expert to select those variables that most likely have an effect on those corresponding responses.

In the development stage of a direct compression tablet, several variables may need to be considered simultaneously to achieve the optimum result. Traditional formulation designs were based on trial and error. It is time-consuming, unreliable, costly and often

unsuccessful. The rapid development of statistical experimental designs, optimization techniques and computer technologies provide an effective method for modeling complicated multivariate drug formulations. Pharmaceutical formulation thus has been brought into a new era.

Since a process is normally characterized by multiple objectives, quantitative prediction of the system behavior from basic physical and chemical principles is often difficult. Optimization of drug formulation can be sought, using a response surface methodology. A mixture design is a special type of response surface experiment in which the factors are the components of a mixture and the response is a function of the proportions of each component (Duineveld et al., 1993). This method is dependent on predetermined statistical significance levels which means less significant terms are not included in the models (Lewis et al., 1999).

In a direct compression, the tablets are compressed directly from powder blends of the active ingredient and suitable excipients (Shangraw, 1989). It is the most efficient process because it is fastest and simplest for the tablet manufacturing and protects the drug from heat and moisture. Although this technique seems quite simple, it requires good flowability and compressibility of the powder which will flow uniformly into a die cavity and form into a firm compact (Göczo et al., 2000). When the formulation consists of more than one excipient and each excipient varies in its properties, this problem can be solved by using computer optimization technique which optimizes pharmaceutical response relating to the properties of the formulation.

Chitin is a naturally-occurring polymer that is found widely in nature as a main constituent in exoskeletons of crustaceans (Muzzarelli, 1977). Next to cellulose, chitin is the most abundant polysaccharide on earth and for this reason, there is continuing interest in finding new commercial uses for what is now essentially a waste product from crab and shrimp industry. Not surprisingly, Thailand with extensive commercial shellfish industries has been at the forefront of chitin funding and research (Chen and Chen, 1998).

The general aim of this study was to exhibit the application of statistical experimental design in the tablet optimization. The specific objective was to find optimum formulations for direct compression tablet, using aspirin 150 mg as a model drug and to compare with commercial aspirin tablets. Three excipients, chitin, dibasic calcium phosphate and corn starch play different roles in tablet formulation. Sawayanagi et al., (1982) reported that chitin had good properties as an excipient for direct compression. Chitin had also been reported as a disintegrant (Ritthidej et al., 1994). Corn starch was employed as diluent, disintegrant and glidant (Wade and Weller, 1994). Dibasic calcium phosphate was used as a direct compression excipient (Wade and Weller, 1994). By varying the proportions of the excipient mixture, it is expected that the properties of the dosage form could be well controlled. In this study, a concentration of excipient mixture in the tablet was fixed at a specific amount. A suitable design for this restriction is statistical mixture designs (Johnson et al., 1990). All mixture designs have a constraint, that is, the sum of all component proportions must add up to one. As a result of this constraint, a change in the amount of one component requires an adjustment in the amount of other components to keep the sum of the components equal to one. The response surface methodology (RSM) was applied for optimization of the study

formulations. This method can combine the multiple objectives and find optimization areas for overall objectives, using a combined contour plot.

MATERIALS AND METHODS

Materials

Chitin (Unicord, Thailand), dibasic calcium phosphate (Emcompress®, USA) and corn starch (O. V. Chemical, Thailand) were used as excipients. Aspirin (Aspirin BP 1988, China) and magnesium stearate (O. V. Chemical, Thailand) were used as a model drug and a lubricant, respectively. Sodium acetate trihydrate (AnalaR®, USA) and acetic acid (AnalaR®, USA) were used to prepare acetate buffer pH 4.5 as dissolution medium. A commercial 325 mg aspirin tablet (Aspaco®, Thailand) was used to compare with the optimized formulation.

Research Design and Method

Response Surface Methodology (RSM)

In pharmaceutical formulations, the 'one variable at a time method' requires many experiments and there is no guarantee that an optimal formulation can be achieved. Moreover, the interaction between different factors, which can influence the target responses, may not be detected. The use of an experimental design can be helpful in the optimization of pharmaceutical formulations (Turkoglu and Sakr, 1992).

Response surface methodology (RSM) is a collection of statistical and mathematical techniques, useful for developing, improving and optimizing processes (Myers and Montgomery, 1995). It also has an important application in the design, development and formulation of new products as well as in the improvement of existing product designs. The basic components of response surface methodology include experimental design, regression analysis and optimization algorithms which are used to investigate the empirical relationship between one or more measured responses and a number of independent variables, with the ultimate goal of obtaining an optimal problem solution.

The Mixture Design

In mixture experiment which is a special type of response surface experiments, the factors are the components or ingredients of a mixture, and consequently, their levels are not independent (Hirata et al., 1992). For the three-component mixture, then

$$0 \le x_i \le 1 \qquad ...(1)$$

where i = 1, 2, 3 and

$$x_1+x_2+x_3 = 1 \qquad ...(2)$$

The Augmented Simplex Centroid Design

To accommodate a polynomial equation to represent the response surface over the entire mixture region, a natural choice for the design would be one whose points are spread evenly over the whole mixture factor space.

Simplex designs are used to study the effects of mixture components on the response variable (Marti-Mestres et al., 1997). The simplex centroid design has 2^p-1 points,

corresponding to the p permutations of (1,0,0,...,0), the $\binom{p}{2}$ permutations of ($^1/_2$, $^1/_2$, 0, ..., 0), the $\binom{p}{3}$ permutations of ($^1/_3$, $^1/_3$, $^1/_3$, 0, ..., 0), ..., and the overall centroid $\left(\frac{1}{p}, \frac{1}{p}, ..., \frac{1}{p}\right)$. In Figure 1, the simplex centroid design consists of the point numbers 1,2,3,4,5,6, and 10. A criticism of the simplex centroid design is that most of the experimental runs occur on the boundary of the region and, consequently, include only p-1 of the p components. It is usually desirable to augment the simplex centroid with additional points in the interior of the region where the blends will consist of all p mixture components. In augmented simplex centroid design (JMP Statistics and Graphic Guide, Version 3.1, 1995), the point numbers 7, 8 and 9 are added into the design.

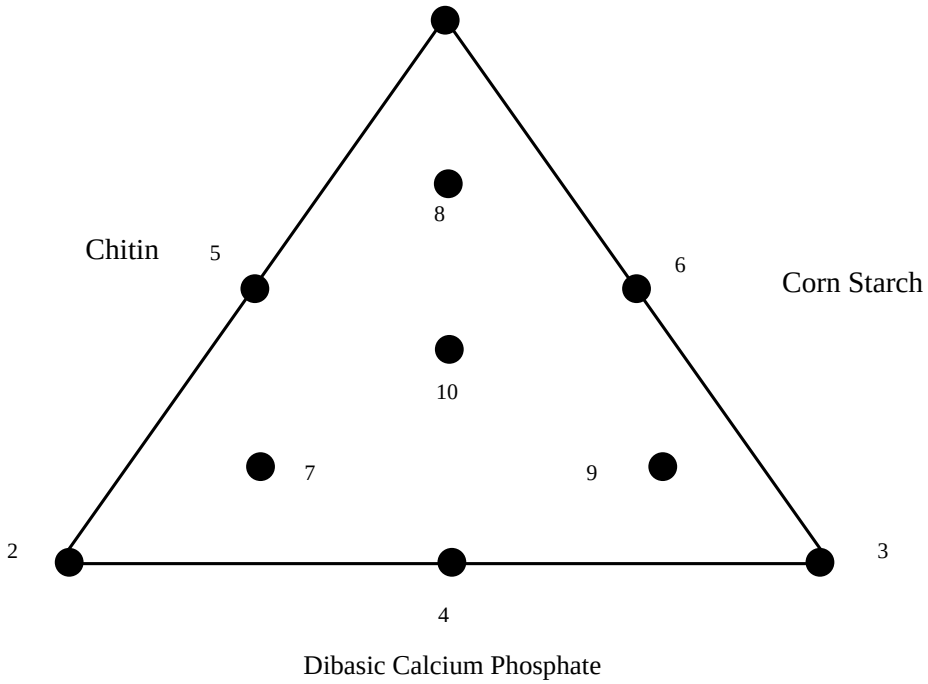

Figure 1. The Augmented Simplex Centroid Design.

The response can be related to the mixture composition with the use of a special-cubic equation (Lahdenpää et al., 1996):

$$y = \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_{12} x_1 x_2 + \beta_{13} x_1 x_3 + \beta_{23} x_2 x_3 + \beta_{123} x_1 x_2 x_3 \quad ...(3)$$

where y is the modeled response, β_1 to β_{123} are the regression coefficients and x_1, x_2, and x_3 are the fractions of the three mixture components.

The seven regression coefficients in this model can be estimated by use of multiple regression. This requires at least seven measurements of each response, located in the experimental space. After calculating the models for each criterion, the values of the response can be predicted at every mixture composition within the experimental space.

It should be noted that in this model, the intercept, present in normal model equations, has disappeared. As a consequence, it is not possible to evaluate Scheffe' models with linear regression, using standard regression software. Special regression algorithms can, however,

be implemented in some software packages, for example, SAS®. Algorithms for implementation in SAS® have been given by Cornell (1990).

Preparation of Powder Mixtures and Tablets

The mixture design, based on augmented simplex centroid design, was employed. This design has 10 formulations that spread evenly over the whole mixture factor space. The weight of powder mixture was 30g. The weights of components in each formulation were fixed as three-excipient (CT/DCP/CS) at 24.5%, lubricant (magnesium stearate) at 0.5% and the model drug (aspirin) at 75.0%. The percentages of each component are tabulated in Table 1 and the proportion of three-excipient in each formulation is shown in Figure 1.

Table 1. The percentage of each component in each formulation.

Formulation	Aspirin	Mg St	Excipients		
			CT	DCP	CS
1	75	0.5	24.5	0	0
2	75	0.5	0	24.5	0
3	75	0.5	0	0	24.5
4	75	0.5	12.25	12.25	0
5	75	0.5	0	12.25	12.25
6	75	0.5	12.25	0	12.25
7	75	0.5	4.08	4.08	16.33
8	75	0.5	16.33	4.08	4.08
9	75	0.5	4.08	16.33	4.08
10	75	0.5	8.17	8.17	8.17

Mg St = magnesium stearate
DCP = dibasic calcium phosphate
CT = chitin
CS = corn starch

Chitin and corn starch were dried by hot-air oven at 60˚C for 3 hours before use. Aspirin, chitin and magnesium stearate were sieved by using laboratory sieve No. 60 mesh. Each component in each formulation was mixed by using mortar and pestle for 10 minutes. The powder mixtures were used to evaluate for powder flowability: angle of repose and percent compressibility. Then the 433.33 mg powder was tableted by Carver Laboratory Press (Model C, USA) at 1.0 ton compressional pressure, using 10.3 mm flat faced bevel edge, circular punch. The compression pressure was maintained for 7 seconds. The tablets were used to evaluate for tablet properties: hardness, percent friability, disintegration time and percent drug release at 45 minutes.

Evaluation of Formulation Properties

Angle of Repose

The angle of repose is known as the angle between the surface of the cone and the horizontal plane (Gold et al., 1966). It was calculated from equation:

$$\text{Tan } \theta = H/R \quad ...(4)$$

where H = the height of cone-like pile + $^1/_4$ inch,
R = the radius of circle

Percent Compressibility

The percent compressibility was measured and calculated from equation (Carr, 1965):

$$\%Compressibility = \frac{(Tapped\ density - Bulk\ density)}{Tapped\ density} \times 100 \quad ...(5)$$

Where : Tapped density = the density after being tapped for 1,000 times (Jolting volumeter, Germany)
Bulk density = the density after being tapped for three times

Tablet Hardness

The hardness was examined by using Hardness tester (Pharma Test Model PTB-31, Ser. No. I-4390/B). The mean and standard deviation were calculated from three determinations.

Percent Friability

The friability of tablets was determined by using Erweka Abrasion Tester (Model 1AP No.24438, Germany). The method of determination was according to British Pharmacopoeia 1998 (BP 1998). The percent friability was obtained from 20-tablet sample.

Disintegration Time

The disintegration time was measured by using USP XXIV disintegration apparatus (Pharma Test, Model PTZ1 No. 1-3869/A) with purified water at 37˚C as disintegration medium. The mean and standard deviation were calculated from six determinations.

Percent Drug Release

The dissolution study was followed as stated in BP 1998. Five-hundred milliliters of acetate buffer was used as dissolution medium. The paddle was rotated at 50 rpm. The release profile of tablet was determined from six tablets. The five milliliters of sample were withdrawn and passed through 0.45 μm filter at the time interval of 2, 5, 8, 10, 15, 20, 25, 30, 35, 40 and 45 minutes. Acetate buffer was replaced into the vessel in equal volume to maintain the constant volume of dissolution medium. The absorbance of sampling solution was determined by using spectrophotometer (Spectronic Genesys TM 5, USA) at 265 nm. Some collections were diluted with dissolution medium to obtain the appropriate absorption.

Statistical Analysis

The data of powder flowability and tablet properties were used to evaluate for the model response and R-square by using SAS® software program (Version 6.12, USA). The model search was started with a full model as shown in Equation 3. The non-significant terms of the model were excluded. Only significant terms ($\alpha = 0.05$) were used in the fitted model. The contours of response model were plotted by using JMP® software (Version 3.6.1.2, USA).

Then, the range of optimal value of each property was selected. All selected response surface areas were superimposed and the optimal range for all properties was obtained.

Laboratory Scale Up

The selected formulation in the optimized area was chosen for scale up. The proportion of three-excipient (CT/DCP/CS) was calculated from the point and other components were fixed (aspirin 75% and magnesium stearate 0.5%) and the scale of powder blend was 200 g. Aspirin and three-excipient (CT, DCP and CS) were mixed in the cube mixer (Erweka-Apparatebau, Model KU1 No. 3142560, Germany) for 10 minutes. Then, magnesium stearate was added and mixed further for 2 minutes. The tablets were produced from the powder mixture by using Hanseaten Single Stroke (Model EI No. 359, Germany) with the same set of punch and die as in Carver Press. The tablet properties of the selected formulation were compared with those of the commercial aspirin tablet.

RESULTS AND DISCUSSION

The data of powder flowability and tablet properties of ten formulations were evaluated as shown in Table 2. Table 3 shows the response surface model of each property which was obtained from statistical analysis by using SAS® software program.

Table 2. Powder and tablet properties of the experimental design formulation.

Formulation	Powder Properties		Tablet Properties			
	Angle of Repose	%Com-pressibility	Hardness (N)	%Friability	Disintegration Time (sec)	Drug Release (%)
1	35.50	16.73	64.80	0.26	11	88.31
2	37.59	10.87	50.63	0.46	> 3600	10.12
3	44.59	15.94	20.93	8.12	22	58.26
4	39.13	19.63	37.33	0.47	11	78.75
5	33.84	19.05	16.63	1.77	23	59.62
6	40.31	24.04	28.73	1.32	15	76.68
7	39.36	24.80	21.70	3.03	20	69.08
8	35.42	21.76	48.00	0.18	11	88.76
9	37.32	18.98	36.33	0.47	13	83.18
10	40.16	23.57	38.57	0.68	19	81.10

Table 3. 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	65.437CT+50.476DCP+20.268CS-80.576CT*DCP-56.591CT*CS-78.244DCP*CS+446.975CT*DCP*CS	0.978
% DR at 45 Mins	88.244CT+15.2DCP+57.271CS+138.462CT*DCP+120.346DCP*CS	0.792
Log DI	1.134CT+3.363DCP+1.449CS-4.909CT*DCP-4.201DCP*CS	0.899
% Friability	0.333CT+0.553DCP+8.064CS-11.415CT*CS-9.975DCP*CS	0.999

CT = chitin
DCP = dibasic calcium phosphate
CS = corn starch
DR = drug release
DI = disintegration time

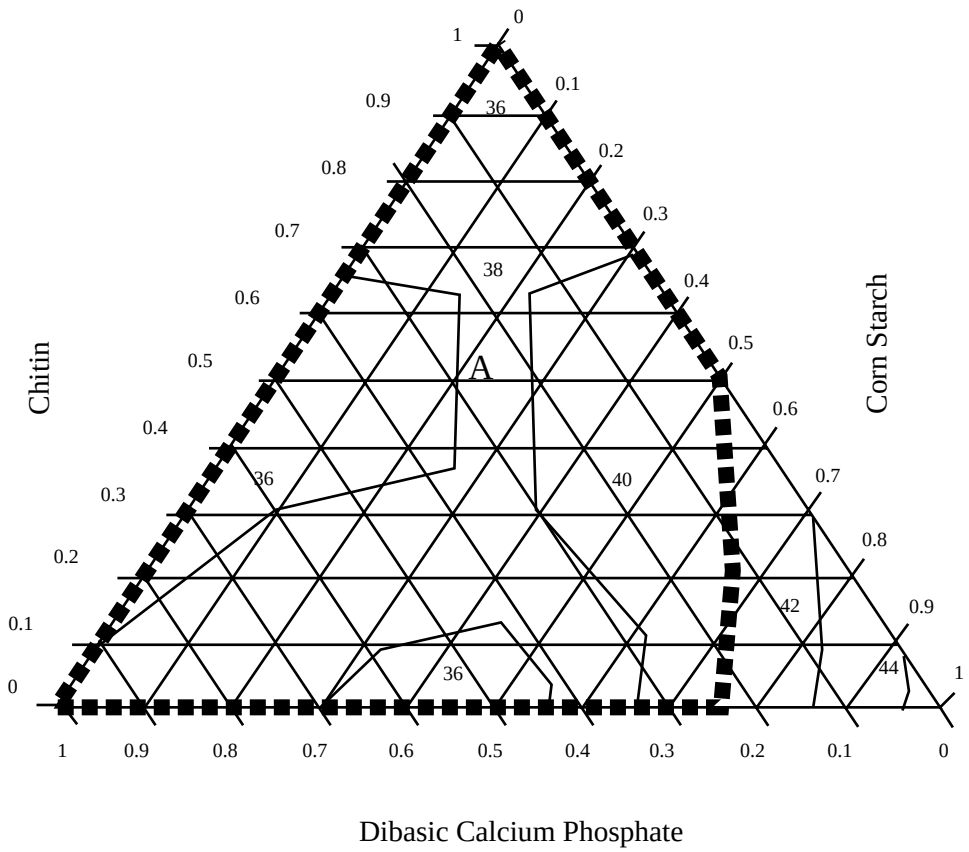

Figure 2. The Contour Plot of Angle of Repose (Degree).

Powder Mixture Properties

The contour plot of each property was drawn by using JMP® software program. Figure 2 shows the contour plot of angle of repose from a fitted statistical model in Table 3. The effect of excipient mixtures on the powder flowability is significant. The powder flowability of these formulations can be categorized into three groups: poor, passable, and fairly good flow. The powder flowability increased with an increase in the amount of chitin and/or dibasic calcium phosphate in the mixtures, while a high proportion of corn starch in the mixtures resulted in reducing the powder flowability.

The flow property of powder was necessary in direct compression because the appropriate flowability of material was required so that the correct amount of drug may be fed into a die cavity. The lower angle of repose of material indicates that the material is more flowable (Carr, 1965). The selected area of angle of repose (area A) was chosen only when the angle of repose was less than 40o and classified as passable flow. In Figure 3, the percent compressibility was selected as less than 21% (area B) for passable flow.

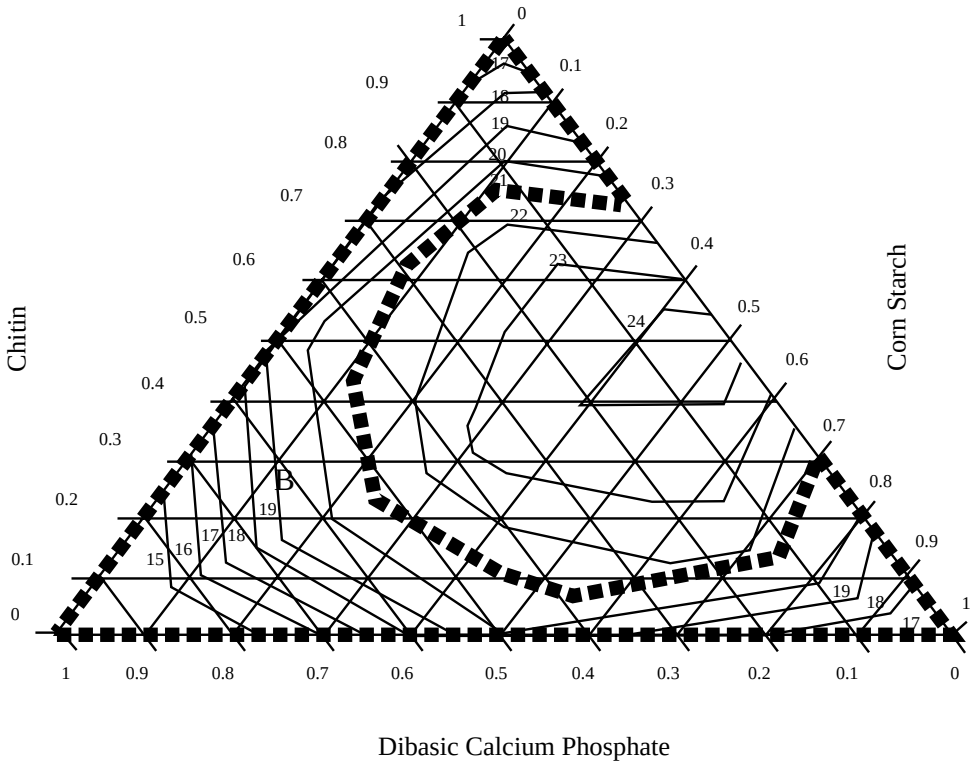

Figure 3. The Contour Plot of Percent Compressibility (%).

Tablet Properties

Each excipient had great influence on the tablet hardness as seen in Figure 4. An increase in corn starch resulted in a decrease in tablet hardness. The opposite effect was found in chitin and dibasic calcium phosphate. The binding strength of dibasic calcium phosphate was less than that of chitin. In pharmaceutical industry, the hardness of tablet about 4 kilograms is considered to be a minimum permit for a satisfactory tablet (Ansel, 1985). Also in this study, the selected range of hardness was more than 40 N (area C) as seen in Figure 4.

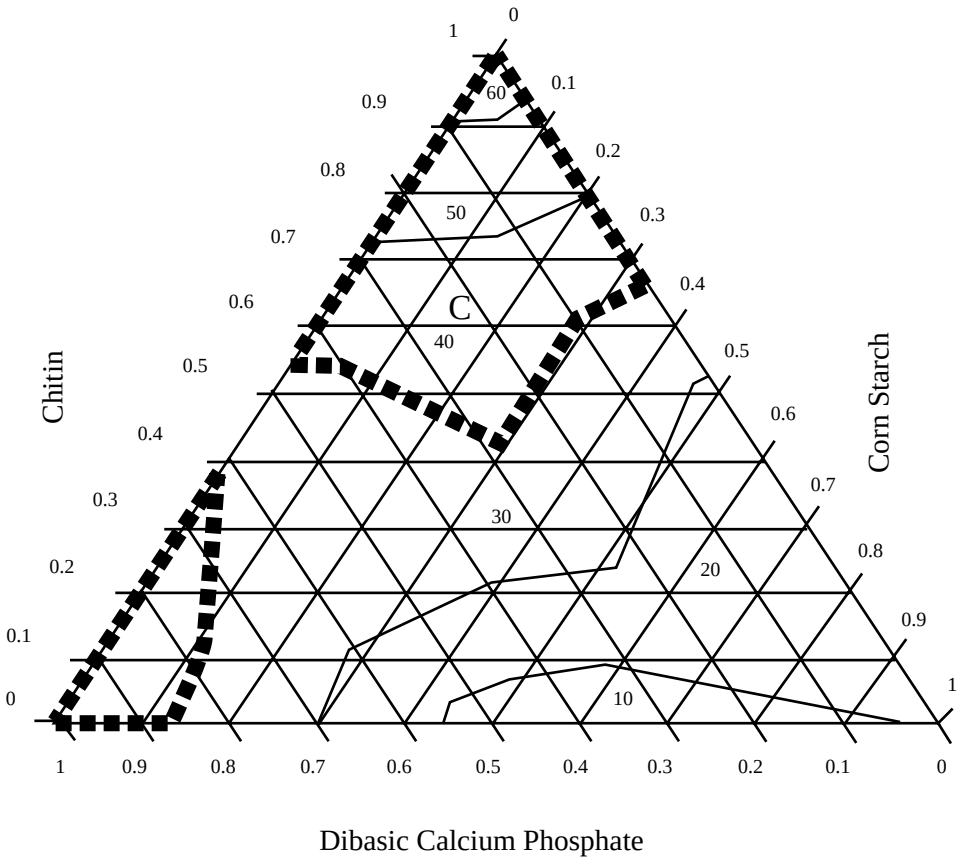

Figure 4. The Contour Plot of Hardness (Newton).

The percent friability of corn starch system (100% corn starch) was greatest among these ten formulations as seen in Figure 5. The reason may be due to poor binding properties of corn starch. The tablet friability decreased as chitin or dibasic calcium phosphate was increased in the excipient mixtures. The percent friability of tablet is the term that is widely used to indicate mechanical strength (Marshall and Rudnic, 1990). Figure 5 shows the contour plot of the percent friability of tablet, the accepted friability of tablet was less than 1% (according to BP 1998) as seen in the area D.

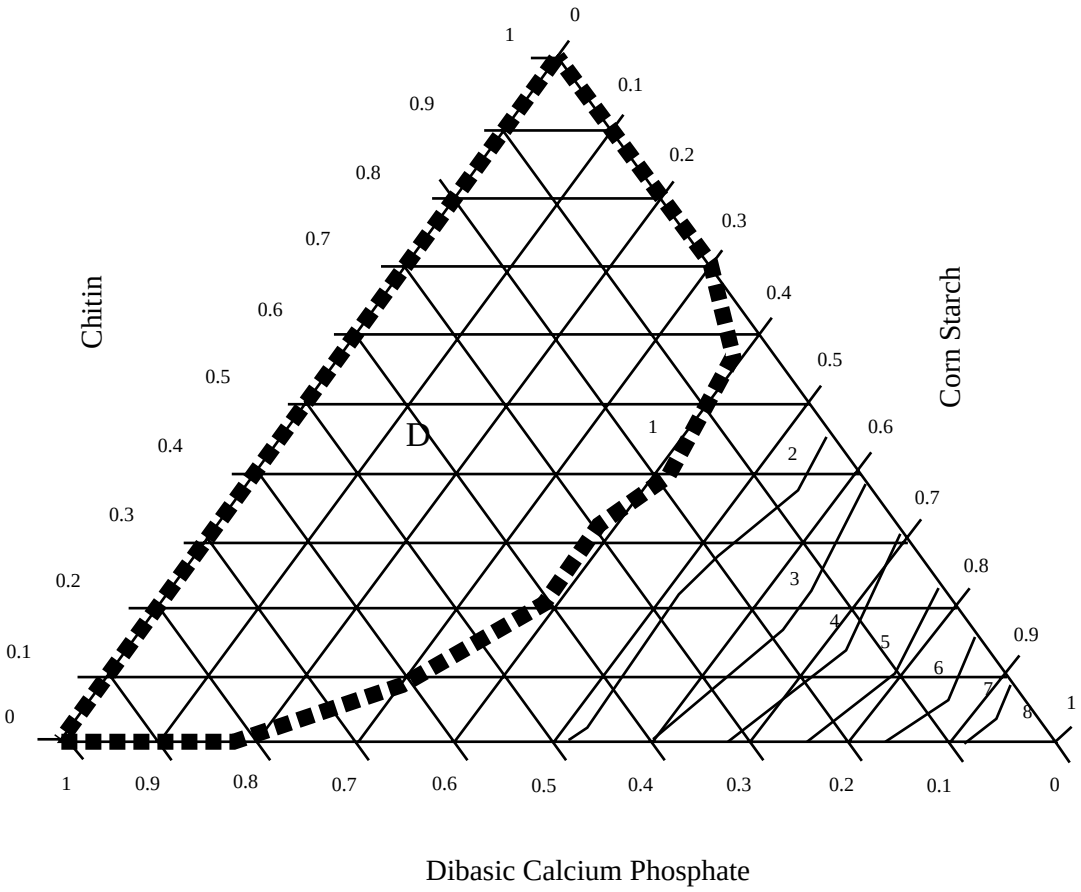

Figure 5. The Contour Plot of Percent Friability (%).

Disintegration and Dissolution Study

In this study, the real disintegration time was transformed to logarithmic data because the wide distribution of data needed adjustment to more appropriate distribution (Judd and McClelland, 1989). These transformed data were used to evaluate for the statistical model. The chosen log disintegration time was less than 2.5 that limited only area with disintegration time less than 316 seconds or 5.27 minutes as seen in area E (Figure 6). Area F (Figure 7), with the percent drug release of more than 70%, was selected based on BP 1998.

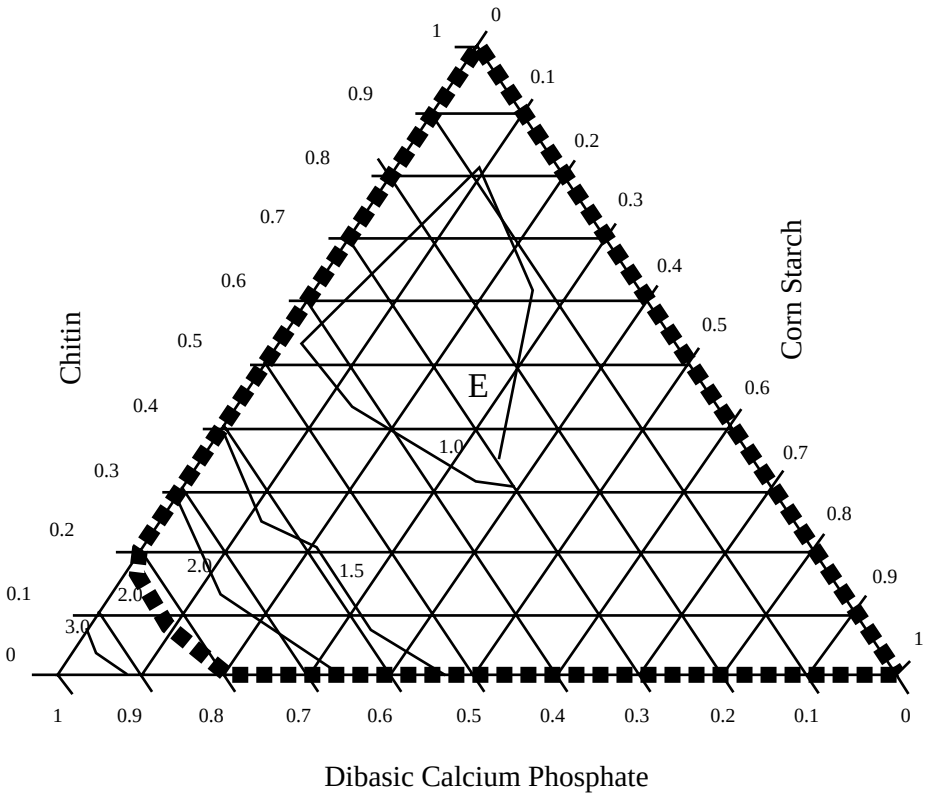

Figure 6. The Contour Plot of Log Disintegration Time (Log sec).

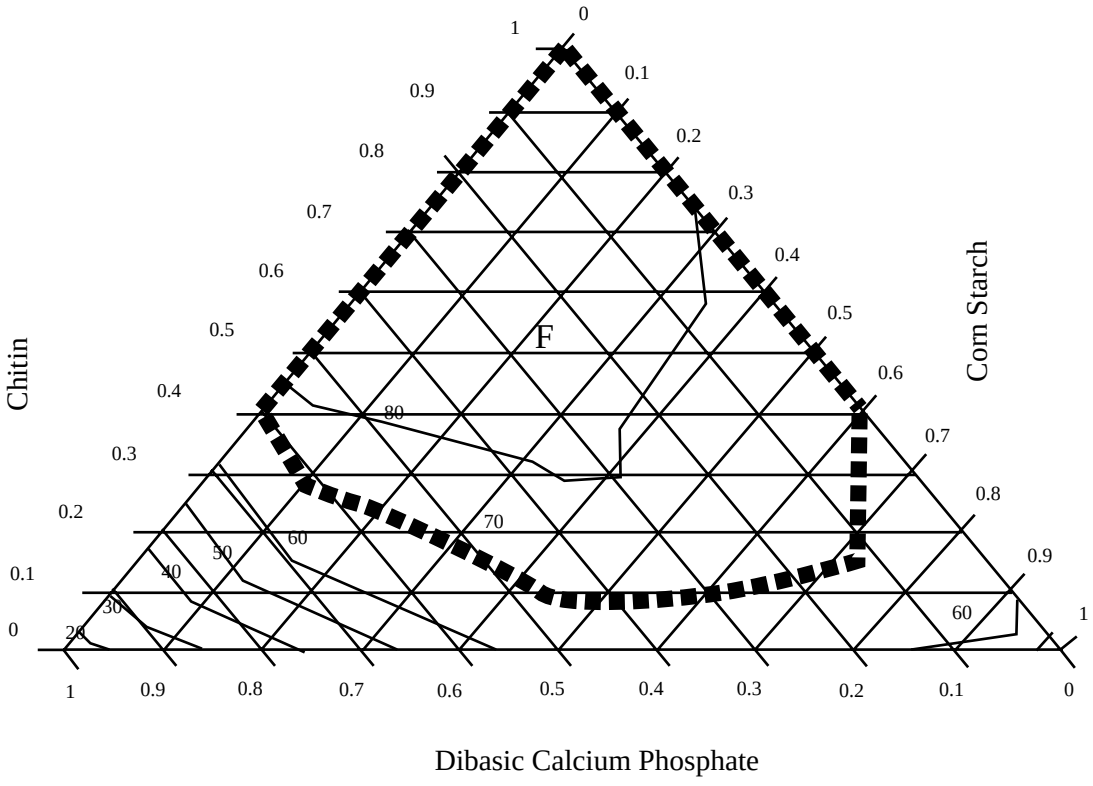

Figure 7. The Contour Plot of Percent Drug Release at 45 Minutes (%).

Optimization Technique

To obtain optimized area of all properties, the selected areas (A-F) of all properties were superimposed. Figure 8 shows the optimized area which had all properties in the selected criteria. The point X is the selected point for scale up formulation. At this point, the proportion of CT: DCP:CS was 65:30:5. The tablet properties of formulation X were determined and compared with the commercial tablet as seen in Table 4. As the result, it can be seen that the selected formulation X had clearly shorter disintegration time and higher hardness than the commercial tablet. The dissolution study showed no significant difference between the optimized formulation and the commercial tablet.

Table 4. Comparative optimized aspirin tablet (formulation x) with commercial aspirin tablet.

Property	Optimized Aspirin Tablet	Commercial Aspirin Tablet
Strength (mg)	325	325
Weight [a] (mg)	433.33	571.99
Thickness [a] (mm)	3.96	4.74
Diameter [a] (mm)	10.50	11.12
Hardness [a] (N)	91.81	61.61
Percent Friability (%)	0.07	0.08
Disintegration Time (sec)	12	70
Drug Release at 45 Minutes (%)	86.39	84.23

[a] ten determinations

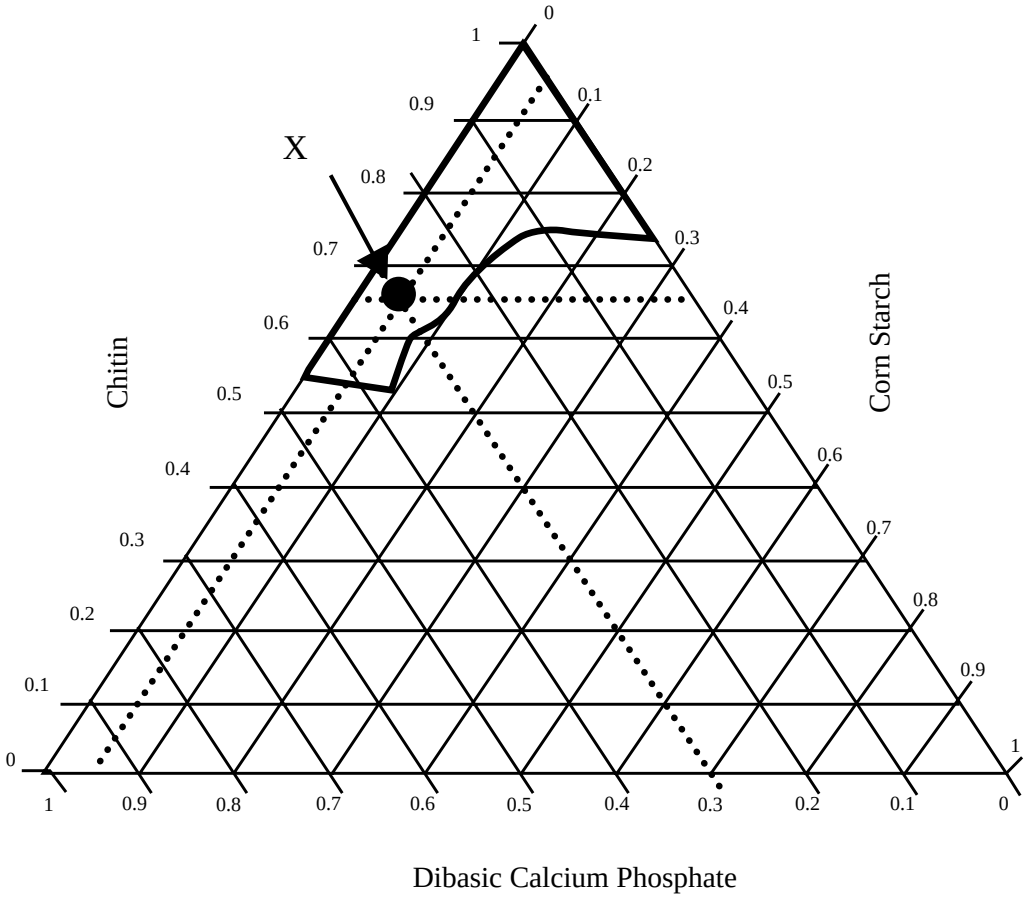

Figure 8. The Optimized Area of Aspirin Tablet and the Selected Point. (X = the selected point)

CONCLUSION

Based on the results from this study, the following conclusions are reached:

1. The mixtures of these three excipients not only improve powder flowability but also modify tablet friability and tablet hardness. The mixtures of these three excipients have high influence on drug release profiles and at a proper ratio of the excipients, it produced a better drug release profile.
2. The criteria for optimization of powder properties, tablet properties and drug release profiles were established, based on rational criteria. The optimum area for the powder properties, tablet properties and drug release profile were located, using the statistical fitted models and the contour plot of responses.
3. The statistical mixture design has the advantage of performing a small number of experiments and the fitted model from the statistical analysis can be used to predict values of responses at any point inside the experimental space. The mixture design can be successfully used to optimize the direct compression tablet formulation.
4. The graphical procedure is an important tool for understanding the change of responses and locating the area of interest. A graphical method can be easily used to locate the overall optimum zone. The formulation containing 65% of chitin, 30% of dibasic calcium phosphate and 5% of corn starch was in the optimum zone and was

considered as an optimum formulation. The design and evaluation of the formulations in this study resulted in successful product development.

5. The evaluation of the laboratory scale-up formulation showed that the powder mixture had acceptable flow properties. The laboratory scale-up tablets were evaluated and their tablet properties were acceptable. The laboratory scale-up process produced the tablets with good physical properties. The percent drug release of the laboratory scale-up formulation was higher than that of the commercial tablet and passed the requirement in BP. The formulation was successfully scaled up from the mortar scale to laboratory batch size. At the appropriate proportion of each excipient that is obtained from the optimized area, it is possible to produce the better formulation than the commercial one.

One distinct advantage of RSM is that the response surface is fitted by a continuous function and can be drawn as a contour plot. The optimal area in each contour plot can be located easily by reading the value from the plot. The combination of each response can be made and the overall optimal zone can be obtained, using the intersection area of each optimal response.

A pharmaceutical scientist needs to understand the theoretical formulation and target processing parameters, as well as the ranges for each excipient and processing parameter. With a rational approach to the selection of the several excipients and manufacturing processes for a given product, one can establish a set of experiments to obtain the optimum formulation. The statistical mixture design and the combined contour plot are powerful tools and lead to the optimum formulation. The final product meets not only the requirements placed on it, but also the practical mass production criteria of process and product reproducibility.

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