

# Application of Sequential Design of Experiments to Develop Ibuprofen (400 mg) Tablets by Direct Compression

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## Abstract

A strategy based on sequential design of experiments (screening, optimization and confirmation) was used to develop a tablet formulation of ibuprofen (400 mg) that is manufactured by direct compression. This formulation has a high content of ibuprofen (76%), in spite of the poor flowability of the drug substance. Sequential design of experiments proved to be an effective and efficient strategy in formulation development.

**Keywords:** Central-Composite Design, Design Of Experiments, Direct Compression, Ibuprofen, Simplex-Screening Design

## 1. Introduction

Ibuprofen, a Non-Steroidal Anti-Inflammatory Drug (NSAID), is widely used as an analgesic, anti-inflammatory and anti-pyretic agent. It is supplied as tablets with strengths of 200 to 800 mg<sup>1</sup>. Ibuprofen has the disadvantage of showing poor flowability which implies tableting problems, such as its high tendency of sticking to the punches<sup>2</sup>. The direct compression method is a desirable alternative for wet granulation, because it requires fewer processing stages, eliminates heat and moisture effects on hygroscopic and thermo-sensitive substances and increases productivity. An important problem of this method is the use of more than 30% of the drug substance in the formulation, mainly for drug substances that present low flowability, such as ibuprofen<sup>3</sup>.

The objective of this research was to address the challenge of developing tablets containing a high content of ibuprofen (400 mg) by a direct compression method.

Because of the complex challenges encountered during formulation development, it is critical to use an effective and efficient strategy. Design of experiments has been widely applied to formulation development. Design of

experiments allows the study of formulation components and manufacturing factors in a systematic and efficient way to optimize the formulation and its manufacturing process<sup>4,5</sup>.

In particular, the strategy of sequential design of experiments is essential for addressing complex problems<sup>5</sup>. In order to address the objective, a strategy based on the sequential design of experiments was applied in three stages: screening optimization and confirmation. In the screening stage, the potential components that are suspected to affect the performance of the product are included to ensure that no important component is overlooked. The focus at this stage is on identifying the most critical components. In the optimization stage, the above mentioned components are subsequently studied to identify the best formulations. In the confirmation stage, the identified best formulations are manufactured and tested to determine whether or not they meet the results predicted by the optimization model. In this work, a sequential design of experiments was applied to the development of ibuprofen (400 mg) tablets by a direct compression method.

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## 2. Materials and Methods

### 2.1 Materials

The following materials were used: racemic ibuprofen was kindly gifted by P & G (Mexico), microcrystalline cellulose (Avicel® PH-200; FMC Corporation, USA), anhydrous lactose (Meggle, Germany), fumed silica (Aerosil® 200, Wacker Mexicana, S.A de C.V., Mexico), croscarmellose sodium (Ac-Di-Sol®, FMC Corporation, USA), sodium starch glycolate (Explotab®, J Rettenmaier & Söhne, México) and magnesium stearate (DVA.-Mexico, Mexico).

Henceforth these excipients will be designated as follows: Cellulose microcrystalline as Avicel, anhydrous lactose as lactose, fumed silica as Aerosil, croscarmellose sodium as Acdisol, sodium starch glycolate as Explotab and magnesium stearate as Mg-stearate.

### 2.2 Powder Mixtures

For the screening stage, powder mixtures of 300 g were obtained by mixing the necessary amounts of their components using a stainless steel cube blender with a load capacity of one kg during 8 minutes.

### 2.3 Angle of Repose

For the purposes of this research, the angle of repose (repose angle) was used as a surrogate variable of powder flowability because the flowability of a powder is of key importance in the manufacturing of tablets<sup>3</sup>.

The repose angle of powder mixtures was determined by the funnel method. The end of a funnel was placed 10 cm above a flat base. Powder mixtures (10 g) were filled into the funnel, and the powder mixtures were allowed to flow through the funnel onto its surface. The repose angle was calculated by

$$\theta = \tan^{-1}(h/r).$$

where  $h$  is the height of pile;  $r$  is the radius of the base of the pile; and  $\theta$  is the repose angle

Smaller values of the repose angle indicate better flowability.

### 2.4 General Method for Manufacturing Ibuprofen Tablets

The specified amounts of ibuprofen and other excipients

were accurately weighed. Ibuprofen, Aerosil and Mg-stearate were passed through 40# mesh screen prior to mixing. Ibuprofen was then mixed with Avicel using the above-mentioned cube blender during 8 minutes (mixture A). Acdisol was added to mixture A and mixed during 8 minutes (mixture B). Mg-stearate was added to mixture B and mixed using during 3 minutes to obtain mixture C.

Powder mixture C was compressed into tablets by using single-punch tablet press machine (KILLIAN Tableting GmbH, Germany) using 10-mm-flat surface punches. The compression force was adjusted to give tablet hardness in the range of 7 to 11 kp.

### 2.5 Hardness and Friability Tests

The hardness and friability tests were performed by using a hardness tester (Schleuniger Pharmatron, model 6D, USA) and a friability tester (Elecsa, model F30A, Mexico), respectively.

### 2.6 Statistical Analysis

All of the experimental designs (screening and optimization) were generated and analyzed by using Design-Expert® software (version 6, Stat-Ease, Inc., USA).

For the screening stage, a simplex-screening design (3q+1, where q is the number of components, also known as ABCD design) was used<sup>6</sup>. The mixtures were prepared and tested in a randomized order. A Scheffé linear regression model was fitted to the resulting data.

For the optimization stage, the central composite design (CCD, a response surface method) was used<sup>7</sup>. Randomization was also applied. Quadratic regression models were evaluated for fitting the resulting data and the best-fitting model was selected by using backward stepwise regression<sup>8</sup>.

## 3. Results

### 3.1 Ibuprofen

The repose angle of the ibuprofen powder was  $40.41^\circ \pm 2.217^\circ$  (mean  $\pm$  standard deviation,  $n = 10$ ). This value indicated poor flowability.

### 3.2 Screening Stage

In order to improve the flowability of ibuprofen, the following 6 excipients were considered (Table 1).

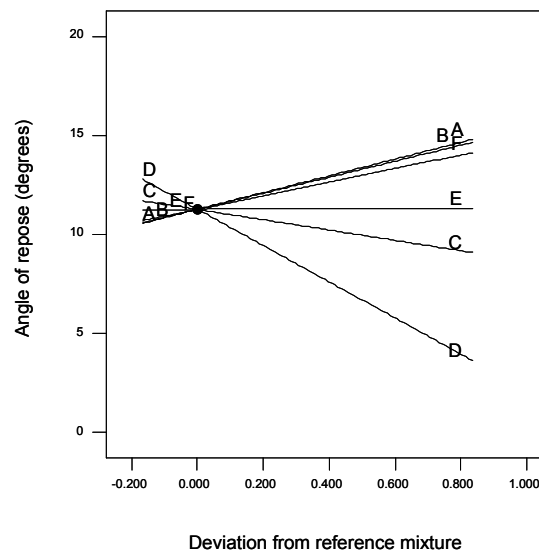
**Table 1.** Excipients (components) evaluated in the screening stage

Excipient	Function
Avicel PH-200	Direct compression agent
Aerosil	Glidant
Lactose	Diluent
Mg-stearate	Lubricant
Acdisol	Disintegrant
Explotab	Disintegrant

These six components were evaluated using a simplex-screening design (3q+1), which required a minimum of 19 mixtures (3x6+1), and the equi-proportional mixture (1/6, 1/6, 1/6, 1/6, 1/6, 1/6, reference mixture) was duplicated to obtain a design with 20 formulations.

Table 2 shows the design and the results.

The interpretation of the results was facilitated by using the component-effects graph (Figure 1).

**Figure 1.** Component-effects graph. A = Avicel, B = Aerosil, C = Lactose, D= Mg-stearate, E = Acdisol and F = Explotab.**Table 2.** Simplex-screening design (3q+1)

Avicel	Aerosil	Lactose	Mg stearate	Acdisol	Explotab	Repose angle (degrees)
1.00	0.00	0.00	0.00	0.00	0.00	18.54
0.00	1.00	0.00	0.00	0.00	0.00	16.77
0.00	0.00	1.00	0.00	0.00	0.00	10.99
0.00	0.00	0.00	1.00	0.00	0.00	6.68
0.00	0.00	0.00	0.00	1.00	0.00	12.89
0.00	0.00	0.00	0.00	0.00	1.00	16.03
0.58	0.08	0.08	0.08	0.08	0.08	13.09
0.08	0.58	0.08	0.08	0.08	0.08	13.9
0.08	0.08	0.58	0.08	0.08	0.08	11.84
0.08	0.08	0.08	0.58	0.08	0.08	5.93
0.08	0.08	0.08	0.08	0.58	0.08	13.28
0.08	0.08	0.08	0.08	0.08	0.58	14.38
0.00	0.20	0.20	0.20	0.20	0.20	13.09
0.20	0.00	0.20	0.20	0.20	0.20	7.22
0.20	0.20	0.00	0.20	0.20	0.20	8.99
0.20	0.20	0.20	0.00	0.20	0.20	7.76
0.20	0.20	0.20	0.20	0.00	0.20	7.96
0.20	0.20	0.20	0.20	0.20	0.00	8.05
0.17	0.17	0.17	0.17	0.17	0.17	9.44
0.17	0.17	0.17	0.17	0.17	0.17	8.48

The component-effects graph illustrates the effects of incrementing the proportions of the 6 excipients on the estimated repose angle as one move away from the reference mixture (the centroid).

The examination of this graph suggested that the effects of Mg-stearate and lactose were to improve flowability by decreasing the repose angle, whereas the effects of Avicel, Aerosil and Explotab were not to improve flowability because they increased the repose angle. On the other hand, Acdisol behaved as an inactive component regarding flowability by maintaining almost a constant repose angle.

These results allowed us to choose Acdisol over Explotab as the disintegrant because Explotab appeared to have an unfavorable effect on flowability.

Based on these results and on subject-matter knowledge (including supplier recommendations), we decided to include, for the optimization stage, Mg-stearate at a fixed and small proportion (<1%) because it is a hydrophobic excipient that may delay the dissolution of a drug substance from the tablet; thus the lowest possible proportion is preferred. In a similar manner, Aerosil was included at a fixed and small proportion (<1%) because it appeared that high proportions of this excipient imply unfavorable flowability.

Avicel and Acdisol were identified as the critical components to be optimized because Avicel is the direct-compression agent and Acdisol is important to improve the disintegration of the tablet, which may imply better dissolution of the drug substance.

### 3.3 Optimization Stage

In the optimization stage, the focus was on optimizing the proportions of Avicel and Acdisol in formulations containing fixed proportions of Mg-stearate and Aerosil. In these formulations the proportion of lactose (a major and an inert component) was adjusted so that the proportions of all the excipients in each mixture add up to one (or 100%). In this case, the proportions of Avicel and Acdisol could be varied independently (as factors). In this situation, the inert component (lactose) is designated as the slack variable.

Using the slack variable approach, the classical and widely used response surface methods such as the Central Composite Design (CCD) may be applied to experimentation with mixtures<sup>9,10</sup>.

In this way, a central composite design for two factors and with an axial distance to the center of the design ( $\alpha$ ) equal to the square root of 2 (1.414) was used to optimize the repose angle<sup>8</sup>.

The design and the results are shown in Table 3.

This design requires a total of 13 formulations corresponding to 4 factorial points (coded as -1,+1), 4 axial points (coded as -1.414,+1.414) and 5 center points (coded as 0,0). In addition to the required points, two additional points were added to serve as check points, corresponding to a duplicate of a mixture containing Avicel (22.8%) and Acdisol (0.2%).

Using backward stepwise regression, the following quadratic model was fitted to the data.

**Table 3.** Central composite design for 2 factors

Avicel (%)	Avicel (coded level)	Acdisol (%)	Acdisol (coded level)	Repose angle (degrees)
15.0	-1	0.10	-1	21.2
30.0	+1	0.10	-1	32.1
15.0	-1	0.50	+1	30.1
30.0	+1	0.50	+1	23.5
11.9	-1.414	0.30	0	30.1
33.1	+1.414	0.30	0	27.7
22.5	0	0.02	-1.414	17.1
22.5	0	0.58	+1.414	28.9
22.5	0	0.30	0	21.2
22.5	0	0.30	0	21.8
22.5	0	0.30	0	27.6
22.5	0	0.30	0	21.8
22.5	0	0.30	0	24.2
22.8	+0.04	0.20	-0.5	26.1
22.8	+0.04	0.20	-0.5	26.1

$$RA = 23.604 - 1.094 (\text{Avicel}) + 74.907 (\text{Acdisol}) - 2.935 (\text{Avicel})(\text{Acdisol}) + 0.044(\text{Avicel})^2$$

where  $RA$  is the estimated repose angle. This model is for actual values of Avicel and Acdisol.

The corresponding Analysis Of Variance (ANOVA) of this model is shown in Table 4.

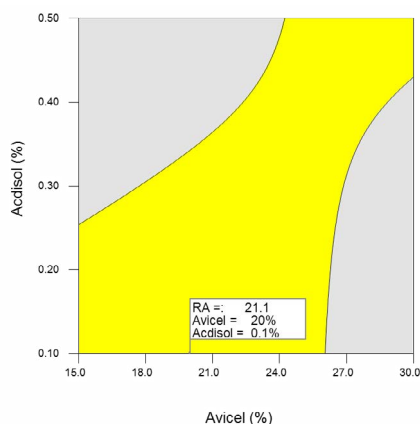
**Table 4.** ANOVA for the quadratic model

Source	Sum of squares	df	Mean square	F-value	p-value
Model	156.10	4	39.03	4.27	0.028
Avicel	0.16	1	0.16	0.02	0.897
Acdisol	26.36	1	26.36	2.89	0.120
Avicel*Acdisol	77.56	1	77.56	8.49	0.015
Avicel <sup>2</sup>	47.78	1	47.78	5.23	0.045
Residual	91.32	10	9.13		
Lack of Fit	63.11	5	12.62	2.24	0.199
Pure Error	28.21	5	5.64		
Total	247.42	14			

The ANOVA indicated that the quadratic model resulted significant ( $p = 0.028$ ) and with an adequate fit because the lack of fit test results were not significant ( $p = 0.199$ ). In addition, the interaction term ( $p = 0.015$ ) indicated that the effect of Avicel on the repose angle depended on the levels of Acdisol and viceversa, and the quadratic term for Avicel ( $p = 0.045$ ) indicated that the resulting response surface is not planar instead, it has curvature.

The criterion for selecting acceptable formulations was set at a repose angle  $<25^\circ$ .

The formulation selection was facilitated using a contour graph (Figure 2).



**Figure 2.** Contour graph for the repose angle. Contour lines were set at  $25^\circ$ .

The contour graph shows two areas, the yellow area corresponds to the operational area (sweet spot), and the grey areas correspond to non-operational areas.

The flag in the contour plot indicates the selected mixture (formulation) to be investigated in the next stage of experimentation. This formulation containing Avicel 20% and Acdisol 0.1% was selected based on cost considerations and previous experience with other products.

The optimization model predicted for the selected formulation a repose angle of  $21.1^\circ$ .

### 3.4 Confirmation Stage

After the optimization stage, four replicates of the selected formulation were prepared their repose angle values were  $18.23^\circ$ ,  $18.43^\circ$ ,  $17.23^\circ$  and  $19.23^\circ$  with a mean value of  $18.28^\circ$ .

This mean value was well within the 95% prediction interval of  $16.40^\circ$  to  $25.73^\circ$ , confirming the predictive power of the optimization model.

Based on these confirmatory results, three pilot batches (600 g each) of the following formulation were manufactured by direct compression.

Component	%
Ibuprofen	76.19
Avicel	20.00
Acdisol	0.100
Mg-stearate	0.323
Aerosil	0.476
Lactose	2.911

Table 5 shows the performance of these batches with respect to in-process specifications.

**Table 5.** Pilot batches produced using the selected formulation

Characteristic	Specification	Batch 1	Batch 2	Batch 3
Average weight	499-551mg	520.96	520.02	518.89
Hardness	7.0-11.0 kp	8.76	9.71	9.53
Friability	$\leq 1\%$	0.76	1.00	0.80

The three batches met the in-process specifications.

## 4. Discussion

Using the methods regarding sequential design of experiments, we were able to overcome the limitation

of not more than 30% of the drug substance for tablets manufactured by direct compression. The selected formulation had a high content of ibuprofen (76%), in spite of the poor flowability of the drug substance. Moreover, the ibuprofen raw material was not previously treated to improve its flowability characteristics, and the selected tablet formulation was manufactured by using conventional excipients and equipment,

Considering together the screening and optimization stages, the selected formulation was obtained with only 35 experimental trials, which proves the great efficiency obtained by using the sequential design of experiments.

Although we were able to obtain a formulation of ibuprofen (400 mg) tablets by direct compression, from which three pilot batches were consistently produced, it is acknowledged that the batch size was very small and manufactured with a single-punch tablet machine. In addition, the performance of this formulation was evaluated only in terms of physical characteristics. Thus, we cannot yet predict at this time whether or not this formulation can be scaled up to production scales.

It is important to point out that we did not designate the selected formulation as the optimized formulation, because there are many other formulations that can meet the criterion of a repose angle of  $<25^\circ$ , which could have been selected from the operational area depicted in the contour graph. This provides flexibility to the future development efforts, for example, assuming that the selected formulation is not suitable for production scales, or that it may fail to meet certain specifications. We will still be able to improve this formulation by considering the knowledge gained from the optimization stage.

Therefore, further research is needed to obtain a production scale product. Based on the results of the present research, we think that this new challenge can be accomplished in an efficient manner by using design of experiments.

## 5. Conclusion

The sequential design of experiments proved to be a very valuable strategy for the efficient development of ibuprofen (400 mg) tablets obtained by the direct compression method.

A tablet formulation with a high content of ibuprofen

(76%) was developed, in spite to the poor flowability of the drug substance.

Further research is needed to obtain a manufacturable product at production scales.

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