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Original Article

Development and Optimization of Ferrous Fumarate Chewable Tablets by Simplex Experimental Design

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Abstract

Chewable ferrous fumarate tablet is the best iron dosage form for children due to better compliance and lower teeth staining compared to the oral drop. Because of the different desirable properties of chewable tablets and the opposing effects of fillers on them, the mathematical experimental design was used as the formulation approach. Different series of formulations based on single filler (Lactose granule, mannitol granule, and three Avicels) were prepared and evaluated. The total filler percentage in formulation was kept constant at 40% and simplex lattice mixture design was used with percentages of each of the three selected fillers as factors and hardness, friability, and taste of the resulted tablets as responses. The statistical analysis and optimization were performed by Design Expert software using responses in suggested experimental runs. Two-way analysis of variance and Scheffe Post-Hoc test showed that both the type and amount of fillers were effective on hardness and had interaction. Avicel PH301 was selected as the filler for imparting higher hardness, and lactose and mannitol granules for imparting good taste and mouth feel to tablets. The proper models for the relationship between the three factors and each of the three responses were determined and the regarding equations were suggested. The mathematical optimization suggested the acceptable formulations of ferrous fumarate chewable tablets. The mathematical experimental design is suggested as a promising efficient method for optimization of pharmaceutical formulation projects with multiple goals.

Keywords: Chewable Tablet, Experimental Design, Ferrous Fumarate, Formulation, Optimization, Simplex Lattice.

1. Introduction

Iron deficiency is an important concern in modern society (today medicine). Ferrous salts are usually used for prevention and treatment of iron deficiency. Different dosage forms of ferrous salts have been developed to best suit the needs

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to the crushing strength (hardness) and friability of the tablets, other factors such as taste and mouth feel would also become important concerns. In practice, the economical issues are also additional determining factors on practical formulation in pharmaceutical industry. Among these different factors, each has its own importance and weight for the pharmaceutical manufacturing companies. On the other hand, fillers have different and even opposing effects on desirable characteristics of chewable tablets. Therefore, optimization of formulation considering the different dependent variables imposes a big challenge to manufacturing companies.

Today, most of the formulation projects perform a method changing each variable at a time while keeping the other variables constant. However, the mathematical experimental design technique also called design of experiments (DOE) is a systematic and relatively new concept for planning and performing rational and informative experiments. This could lead to investigation of different variables and their effects on dependent variables while considering the weight and importance of each [2, 3]. Therefore, this would be a good approach towards formulation of different dosage forms. It provides a logical evaluation of multiple factors concomitantly influencing the important product characteristics. This technique has been used in some formulation studies to investigate the effects of excipients and/or manufacturing conditions as effective variables on product characteristics [4-12]. However, there is no report on ferrous fumarate chewable tablet formulation using the mathematical design of experiments. Therefore, this study was aimed at using mathematical experimental design for formulation of ferrous fumarate chewable tablets.

For performing this approach, the variables should first be screened and the important independent variables (factors) be selected. Then, the desirable range for each important dependent variable (responses) should be determined. Investigation on suggested formulations by the mathematical design could then lead to the desirable formulations.

Avicel imparts excellent hardness and friability and undesirable taste to tablets. On the other hand, lactose and mannitol cause good taste, lower hardness, and higher friability in tablets. Therefore, avicel PH 301 was chosen as the filler for giving good compactibility and friability to formulations, while mannitol and lactose granules were also chosen for giving good taste properties to formulations.

In this study, the composition of the different fillers was changed while keeping the total amount of the fillers constant. Therefore, the simplex lattice mixture design was used as a logical approach towards formulation of ferrous fumarate chewable tablet considering the amount of different fillers as the independent variables (factors) and hardness, friability, and taste of the tablets as dependent variables (responses).

2. Mateirals and Methods

2.1. Materials

Mannitol and α-Lactose monohydrate were obtained from Merck, Germany. Ferrous fumarate was gifted by Razak Pharmaceutical Company. Avicel PH200, PH301, and PH302 were gifted by Akbarieh Company, Iran (representative of FMC, USA).

2.2. Determination of angle of repose and Carr's Index for ferrous fumarate and fillers

The bulk and tapped densities of ferrous fumarate and each of the different fillers were obtained by using proper measures and the Erweka SVM 121 tapped density tester. The Carr's compressibility index was then calculated by using the two density values.

The angle of repose of ferrous fumarate and the fillers were determined by using the fixed cone method with a glass plate of 8.5 cm diameter.

2.3. Evaluation of the compactibility of ferrous fumarate

Ferrous fumarate was mixed with 0.5% magnesium stearate and directly compressed using a single punch tablet press (Erweka EKO AR 400, Erweka, Germany) equipped with 7 mm flat punch. The hardness (crushing strength) of the resulting tablets was measured by the Erweka TBH 28 hardness tester. The compression force was set to obtain the maximum possible hardness.

2.4. Preparation of ferrous fumarate tablets with single filler

Different series of formulations each containing one of the fillers in increasing amounts were compressed and evaluated. Each series contained 100 mg ferrous fumarate per tablet, 1% Aerosil (colloidal silicone dioxide), 0.5% magnesium stearate, and increasing amounts of the selected filler (25%, 30%, 40%, and 50% w/w of the tablets). Different grades of microcrystalline cellulose (i.e. Avicels PH 200, PH 301, and PH 302), lactose granules, and mannitol granules were used as filler. Ferrous fumarate, colloidal silicone dioxide and the filler were passed through a sieve with 0.600 µm opening and mixed for five minutes in a cubic mixer. Magnesium stearate was passed through a 0.150 µm opening sieve, added to the mixture and mixed for another two minutes in the cubic mixer. The formulations were then compressed by a single-punch pressing machine (Erweka AR 4100, Erweka, Germany) with a 7-mm flat-faced punch to obtain tablets with maximum possible hardness. The tablet hardness and percent friability were evaluated by the Erweka TBH 28 hardness tester and the Erweka TA friabilator. The minimum amount of each filler capable of introducing proper hardness and percent friability to the resulting tablets was chosen.

2.5. Evaluation of tablet properties

The hardness test was performed on ten tablets from each formulation by using Erweka TBH 28 hardness tester. The hardness values were reported as mean ± SD (Standard Deviation). The percent friability of tablets was also determined by the standard method using Erweka TA Roche-type friabilator at a speed of 25 rpm for 4 minutes.

2.6. Design of Experiments (DOE) and Optimization

Considering the results of the previous section, the total amount of filler was kept constant at 40% w/w of each formulation. The design of experiments and statistical analysis of the data was performed by the Design Expert version 7.0.0 software (Stat-Ease Inc., USA). Simplex lattice mixture design was used to design proper runs for evaluation of the effects of three factors (Avicel PH301, lactose granules, and mannitol granules) on three responses (i.e. tablet hardness, percent friability, and taste). The experimental ranges and constraints for factors and the constraints for responses are illustrated in tables 9 and 10.

In a mixture design, the independent variables (factors) of filler amounts could be changed in a manner that the sum of the percentages should remain constant and equal to 100% [13, 14]. Therefore, different ratios of the fillers were used in formulations according to the suggested runs while keeping the total filler amount at 40% w/w of formulation (Table 11). For data analysis, the best fitted mathematical model for each of the three responses was selected by the software on the basis of sum of squares and the insignificance of the lack of fit tests. The mathematical equations were also suggested including the statistically significant interactions. The numerical and graphical optimization was then performed by the multiple optimization procedure using the specific goals and the desirability function.

2.7. Taste evaluation

Taste evaluation of the formulated tablets was performed by 10 healthy volunteers 18-40 years old. All formulations were tested by the ten volunteers after enough interval time. Tablets were evaluated as undesirable (0), acceptable (1), and good (2). The mean values for each formulation were reported and the Friedman test was used for statistical analysis and discussion.

3.Results and Discussion

3.1. Evaluation of pre-formulation characteristics of ferrous fumarate and five fillers

The angle of repose and Carr's compressibility index of ferrous fumarate along with the maximum possible hardness of its compressed tablets are shown in table 1. The angle of repose and Carr's compressibility index for five different fillers, i.e. lactose granule, mannitol granule, Avicel PH 200, Avicel PH 301, and Avicel PH 302 were determined and shown in table 2.

Direct compression is the best method for tablet production form scientific and economic points of view. Good flowability and compaction properties are prerequisites for successful formulation of tablets by this method. Therefore, the flowability of ferrous fumarate was estimated using the Carr's index and angle of repose (table 1). The low values of both terms for ferrous fumarate indicated a good flowability, while the

Table 1. Evaluation of pre-formulation properties of ferrous fumarate.

Substance	Carr's Index (%)	Repose Angle (º)	Max. Hardness (N)
Fe Fumarate	6.4	13	53.9

Table 2. Evaluation of pre-formulation properties of fillers.

Substance	Lactose G.	Mannitol G.	Avicel PH 200	Avicel PH 301	Avicel PH 302
Carr's Index (%)	5.0	5.1	11.9	10.5	12.1
Repose Angle (º)	29	27	34	32	33

hardness value of 53.9 N indicated a minimum compactibility. Therefore, considering the adequate compactibility and flowability of ferrous fumarate, the direct compression method was applicable and chosen. The results for five different fillers, i.e. lactose granule, mannitol granule, Avicel PH 200, Avicel PH 301, and Avicel PH 302 are observed in table 2. Relatively low values of Carr's index and angle of repose suggested adequate flowability for all fillers, although better flowability for lactose granule and mannitol granule.

3.2. Evaluation of one-filler formulations

Table 3. Composition of the single-filler formulations.

Formul.	Fe Fumarate (%)	Filler (%)	Col. Sil. Dioxide (%)	Mg Stearate (%)
1	73.5	25	1	0.5
2	68.5	30	1	0.5
3	58.5	40	1	0.5
4	48.5	50	1	0.5

Table 4. Hardness and friability of Avicel PH 200 formulations.

Avicel PH 200 (%)	Hardness (N)	Friability (%)
25	67.7±6.8	0.74
30	74.5±9.8	0.63
40	113.8±7.8	0.42
50	145.1±10.1	0.30

Different series of formulations based on Avicels PH200, PH301, and PH302, and lactose and mannitol granules as fillers were prepared. The optimum amount of colloidal silicone dioxide and magnesium stearate as anti-adherent and lubricant were found to be 1% and 0.5% respectively. Table 3 shows the composition of these different series of formulations. The resulted hardness and friability values for each formulation series based on the above-mentioned fillers are shown in tables 4-8.

For all Avicels, a decreasing trend in percent friability and an increasing trend in hardness were observed on increasing their percentage in formulations. Avicel (microcrystalline cellulose) undergoes a plastic deformation on compression

Table 5. Hardness and friability of Avicel PH 301 formulations.

Avicel PH 301 (%)	Hardness (N)	Friability (%)
25	87.3±11.6	0.69
30	95.1±10.8	0.55
40	143.2±11.8	0.32
50	166.7±9.8	0.20

Table 6. Hardness and friability of Avicel PH 302 formulations.

Avicel PH 302 (%)	Hardness (N)	Friability (%)
25	62.8±8.8	0.75
30	78.4±7.9	0.62
40	105.9±9.8	0.42
50	157.9±9.9	0.24

Table 7. Hardness and friability of mannitol granule formulations.

Mannitol Granule (%)	Hardness (N)	Friability (%)
25	49.0±8.8	0.82
30	53.9±8.7	0.69
40	70.6±10.7	0.54
50	85.3±11.8	0.41

Table 8. Hardness and friability of lactose granule formulations.

Lactose Granule (%)	Hardness (N)	Friability (%)
25	44.1±7.6	0.86
30	49.0±5.9	0.75
40	65.7±7.7	0.57
50	80.4±11.4	0.44

and makes strong compacts by hydrogen bonds between the hydroxyl groups of cellulose branches. As observed in tables 4 and 5, a prominent increase in hardness is observed by increasing the percentage of avicels PH 200 and PH 301 from 30% to 40%, i.e. decreasing the drug content from 68.5% to 58.5% (table 3), which is speculated to be due to more avicel surfaces becoming free from the ferrous fumarate particles covering them. For formulations based on avicel PH 302, it could be observed from table 6 that this prominent change was observed from 40% to 50%, i.e. decreasing the drug content from 58.5% to 48.5%. A similar effect has previously been reported for microcrystalline cellulose and paracetamol with the prominent change observed after decreasing the drug content to below 46% [9, 15, and 16]. Tables 7 and 8 indicate that similar but much weaker trends in hardness were observed for formulations based on lactose granules and mannitol granules. The avicel formulations showed much higher hardness values than lactose/mannitol counterpart formulations. In our study, the order of regarding hardness in avicels was PH 301>PH 302>PH 200. Two-way analysis of variance (two-way ANOVA) showed significant difference in maximum hardness between different fillers ($p<0.001$). It also showed significant difference in hardness between different percentages (25% to 50%) of fillers for each filler ($p<0.001$). By using Scheffe test as the Post-Hoc test, significant difference was found between all levels of fillers ($p<0.001$). The analysis also showed that both the type and amount of vehicles were effective on hardness and had interaction with each other. Among the avicels, avicel PH 301 showed significantly higher hardness than avicels PH 302 and PH 200 ($p<0.01$), but there was no significant difference between the two latter avicels ($p>0.05$). The results showed that Avicel PH301 was the best among different Avicels with regard to hardness of the tablets. Therefore, Avicel PH301 was selected as one of the three fillers for the experimental design.

3.3. Design of Experiments (DOE)

Avicel imparts excellent hardness and friability and undesirable taste to tablets. On the other hand, lactose and mannitol cause good taste, lower hardness, and higher friability in tablets. Therefore, avicel PH 301 was chosen as the filler for giving good compactibility and friability to formulations, while mannitol and lactose granules were also chosen for giving good taste properties to formulations.

The total amount of the fillers was kept constant and the amounts of the fillers were varied in such a way that the total amount did not change. Therefore, for optimization of the three responses the mixture design was used. Among the mixture design formats, because of the number of factors (i.e. three) and the fact that all factors had the same ranges, simplex lattice mixture design was used with the experimental ranges and constraints for factors being shown in table 9 and the responses and their constraints being shown in table 10.

The 14 runs (combinational formulations) suggested by the simplex lattice mixture design are shown in table 11. Table 12 shows the 3

Table 9. Experimental ranges and constraints for the factors.

Factor	Low value (%)	High value (%)	Constraint
X_1 (Avicel)	0	100	$X_1+X_2+X_3=100\%$
X_2 (Lactose)	0	100	$X_1+X_2+X_3=100\%$
X_3 (Mannitol)	0	100	$X_1+X_2+X_3=100\%$

Table 10. Responses and their constraints.

Response	Constraint
Y_1 (Hardness)	>50 N
Y_2 (Friablity)	<0.8%
Y_3 (Taste)	>1.0

Table 11. Simplex lattice DOE factor settings for three fillers and their percentage in total filler.

Run	Avicel PH301 (%)	Lactose Gr. (%)	Mannitol Gr. (%)
1	50	50	0
2	33.3	33.3	33.3
3	16.7	16.7	66.6
4	100	0	0
5	0	100	0
6	100	0	0
7	0	0	100
8	50	50	0

Table 12. Responses (Hardness, friability, and taste) for the DOE runs.

Run	Hardness (N)	Friability (%)	Taste mark
1	72.8	0.50	0.8
2	70.5	0.55	1.2
3	67.7	0.58	1.4
4	140.4	0.32	0.2
5	63.5	0.59	1.5
6	144	0.28	0.2
7	70.7	0.51	1.9
8	77.1	0.42	0.6
9	66.4	0.57	1.9
10	65.9	0.55	1.4
11	74.3	0.50	1.2
12	66.4	0.59	1.3
13	75.5	0.56	1.0
14	98.9	0.42	0.4

responses (i.e. hardness, friability, and taste) for

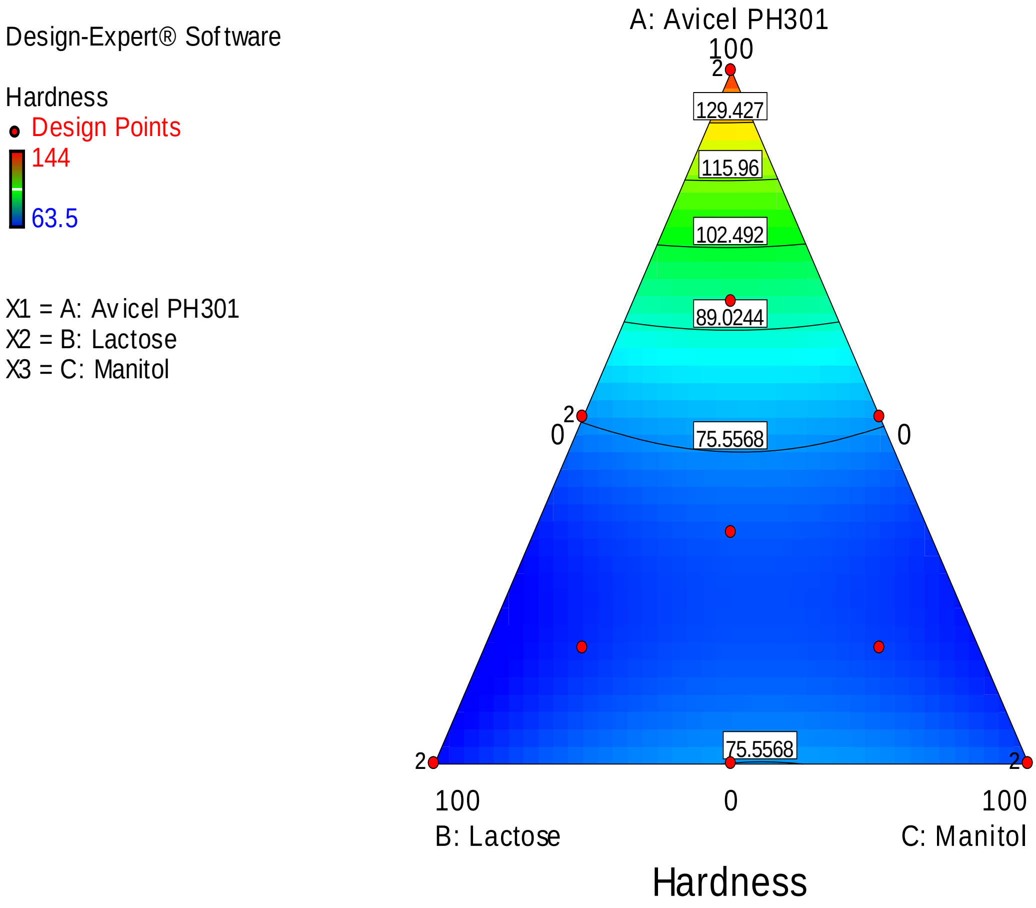

Figure 1. Contour diagram of the effect of three fillers on hardness response.

each of the suggested runs.

3.4. Analysis of the mixture data

The ingredients of the different runs of experimental design and the related responses (hardness, percent friability, and taste) are shown in tables 11 and 12. The simplex lattice mixture design was used for design of experiments since the total amount of the three selected fillers was kept constant at 40% of formulation and their composition were changed, so the total amount of the fillers would be 100%. The DOE suggested 14 combination formulations (shown in table 11) which were prepared and evaluated with regard to hardness, friability, and taste of the tablets. Table 12 shows the observed responses (hardness, percent friability, and taste).

Friedman test on the results of taste evaluation study showed very significant difference ($p<0.001$) between different runs. It could be observed that formulations with the best taste results have the least desirable values of hardness. Different models (i.e. linear, quadratic, cubic and special cubic) could be used to explain the simplex lattice design results. Statistical significance of data fitting to these models ($p<0.05$) as well as insignificance of the lack of fit tests were the basis for selecting the proper model. Figures 1 to 6 show the contour and 3D response plots (for hardness, friability, and taste) as a function of the filler composition. In contour diagrams, each corner of the equilateral triangle represents 100% of each of the three factors and the inside region represents the different combinations of the factors.

3.4.1. Effect of type and amount of filler on hardness

Figures 1 and 2 show the relationship between the tablet hardness response and the three factors (percent of Avicel PH 301, Mannitol granule, and Lactose granule). Statistical analysis suggested the Quadratic model as the best model for this relationship ($p<0.0001$). It also showed the significance of three interaction terms, i.e. X_1X_2 and X_1X_3 ($p<0.0001$), and X_2X_3 ($p<0.05$). The following equation was calculated and suggested for the hardness response in relation to type and amount of fillers:

$$Y_1 = 142.90\ X_1 + 64.39\ X_2 + 68.22\ X_3 - 110.38\ X_1 X_2 - 116.40\ X_1 X_3 + 37.34\ X_2X_3$$

X_1: Avicel percentage

X_2: Lactose percentage

X_3: Mannitol percentage

Y_1 =Hardness

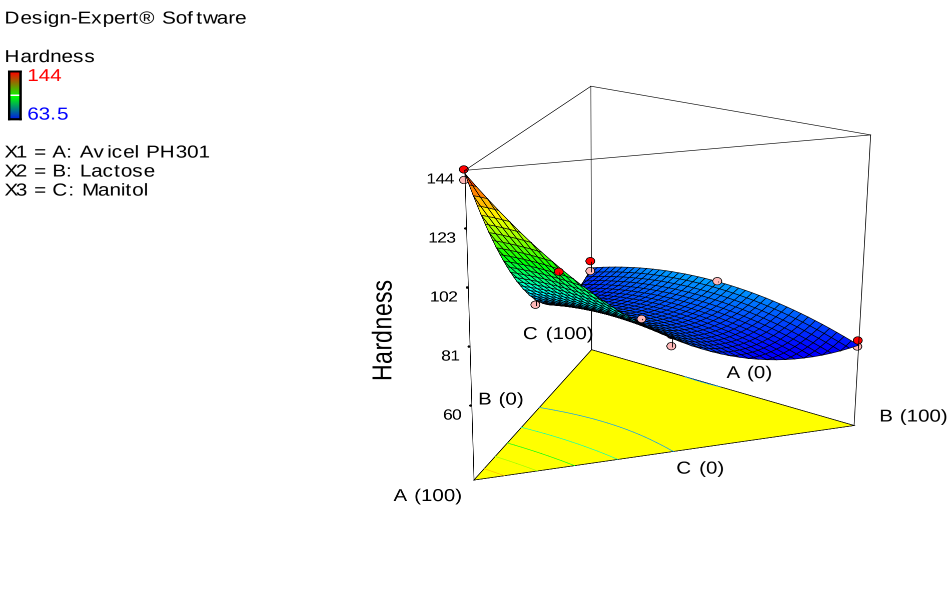

Figure 2. 3D plot of the effect of three fillers on hardness response.

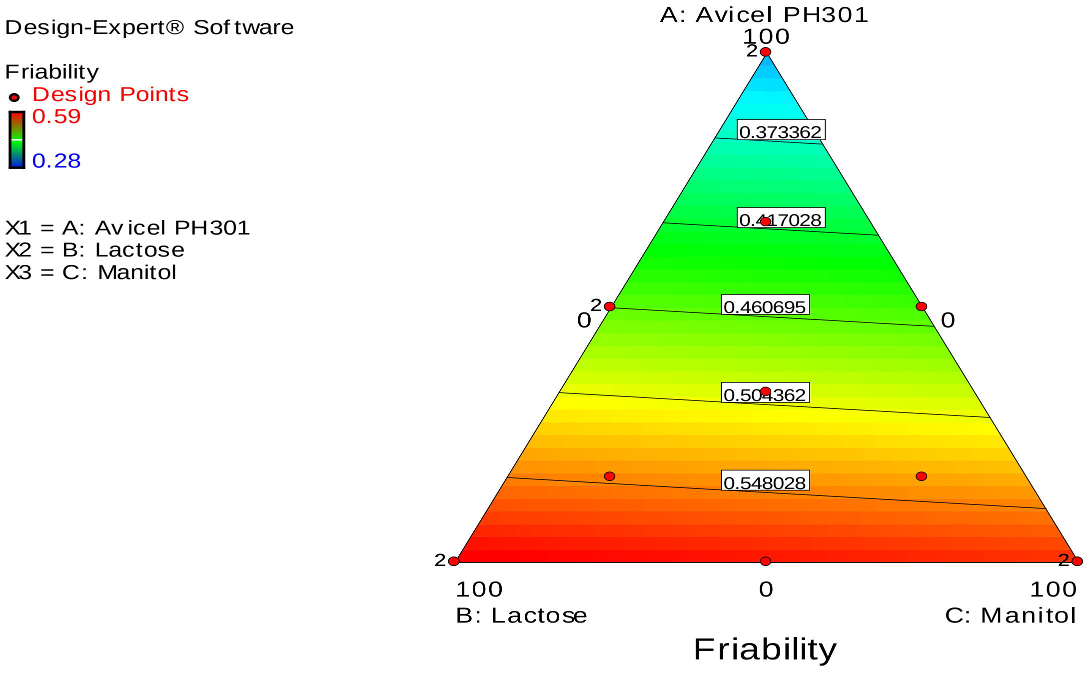

Figure 3. Contour diagram of the effect of three fillers on percent friability response.

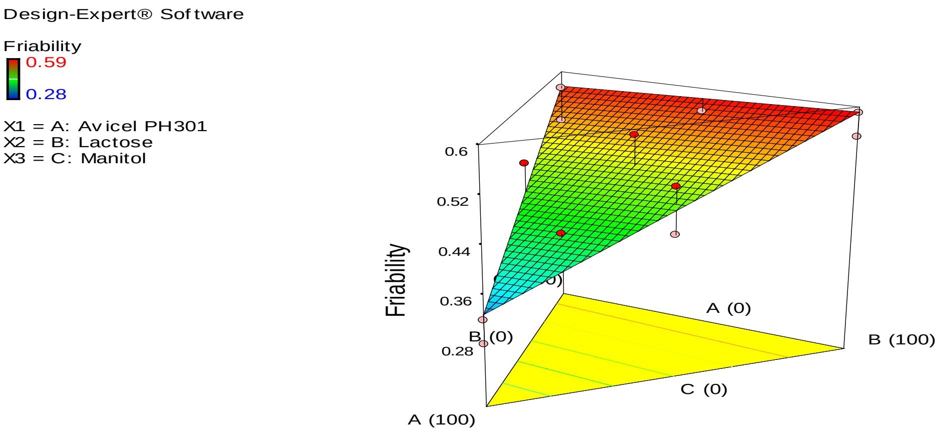

Figure 4. 3D plot of the effect of three fillers on percent friability response.

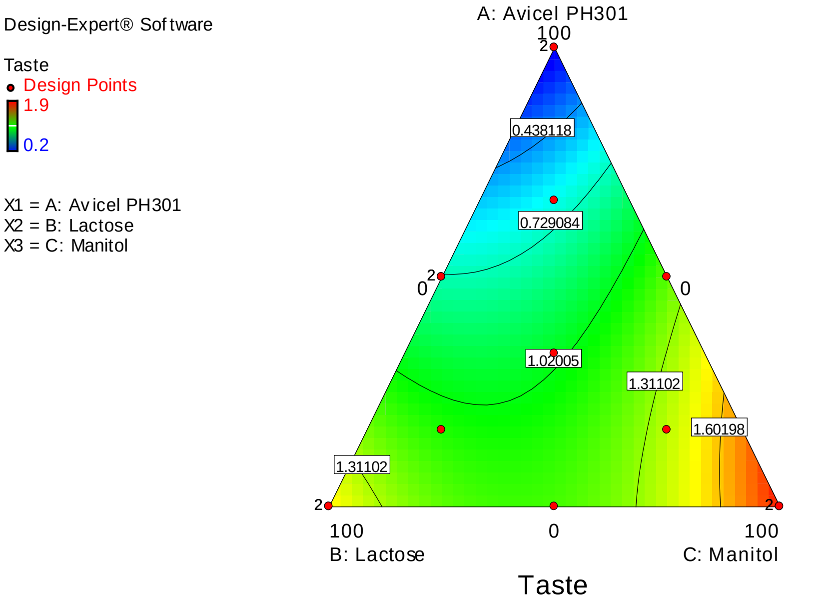

Figure 5. Contour diagram of the effect of three fillers on taste response.

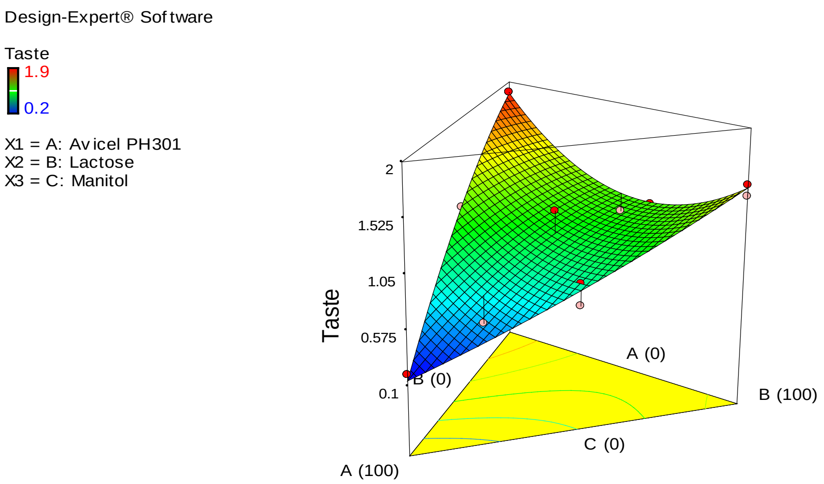

Figure 6. 3D plot of the effect of three fillers on taste response.

As the plots and the equation show, the highest hardness values are expected from formulations having only avicel as the filler. However, there is a negative interaction between avicel with each of mannitol and lactose granules, which is speculated to be due to their different mechanism of consolidation. The weak positive interaction between mannitol and lactose is suggested to be

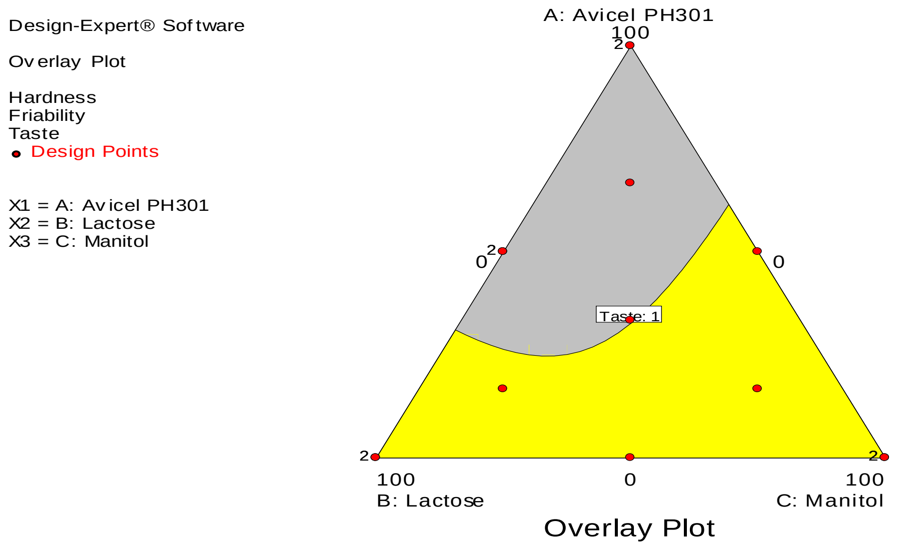

Figure 7. The overlay plot of the effect of three fillers on the three responses showing the desirable area.

due to the stronger interaction between the two fillers.

3.4.2. Effect of type and amount of filler on percent friability

Figures 3 and 4 show the relationship between the percent friability response and the three factors (percent of Avicel PH 301, Mannitol granule, and Lactose granule). The Linear model was suggested for the relationship between type and amount of filler and percent friability of the resulted tablets (p<0.001). A previous study has also reported a linear model for the relationship between friability (10).The following equation was calculated for percent friability response in relation to type and amount of fillers:

$Y_2 = 0.330\ X_1 + 0.592\ X_2 + 0.574\ X_3$

X_1: Avicel percentage

X_2: Lactose percentage

X_3: Mannitol percentage

Y_2 =Friability

As could be inferred from the response surface plot and the suggested equation, the contribution of each filler to percent friability was in the order of lactose>mannitol>avicel. Therefore, avicel would be the most and lactose the least desirable filler with regard to percent friability of the resulted tablets.

3.4.3. Effect of type and amount of filler on taste

Figures 5 and 6 show the relationship between the taste response and the three factors (percentages of Avicel PH 301, Mannitol granule, and Lactose granule). The Quadratic model was suggested as the best model for the relationship between fillers and taste (p<0.001). There was one statistically significant interaction term of X_2X_3 ($p<0.05$). Therefore, the following equation was calculated and suggested for the relationship between taste and the type and amount of fillers:

$Y_3 = 0.147\ X_1 + 1.476\ X_2 + 1.893\ X_3 - 2.065\ X_2 X_3$

X_1: Avicel percentage

X_2: Lactose percentage

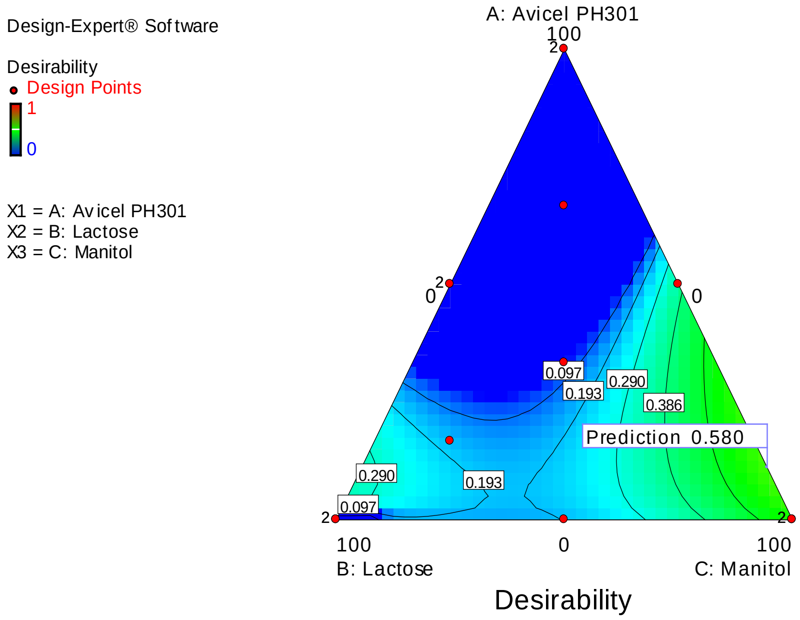

Figure 8: Contour diagram of the effect of three fillers on overall desirability.
(Maximizing hardness and taste and minimizing friability with weights of 1, 0.5 and 1, and importance values of +, +++ and +++++ for the three responses of hardness, friability and taste, respectively)

X_3: Mannitol percentage

Y_3 =Taste

As could be inferred from the taste response surface plot and the suggested equation, the contribution of each filler to desirable taste was in the order of mannitol>lactose>avicel. This is expected since avicel (microcrystalline cellulose) has a chalky taste and mouth feel, while lactose has a weak sweetness with a neutral mouth feel, and mannitol has a moderate sweetness with a desirable cooling mouth feel. However, a significant interaction between mannitol and lactose with a negative effect on taste was observed, which considering the taste suggest not using lactose and mannitol concomitantly.

3.5. Optimization of responses

The aim of the optimization process is finding suitable factor combinations resulted in optimal profile of the important responses (for chewable tablets hardness, friability, and taste). For graphical optimization by the Design Expert software, the required limits of the response values should be defined. Considering the required limits of hardness and friability for tablets, the upper and lower limits were defined. However, in chewable tablets the overall taste and mouth feel of the product is also of utmost importance to desirability. Therefore, a minimum taste value of 1.0 (assigned to a formulation having an acceptable taste) was defined as the lower limit. Figure 7 represents the resulted overlay plot of the graphical optimization indicating suggested regions in which all responses were acceptable (the light region).

For numerical optimization, the desired criteria with regard to the three responses should

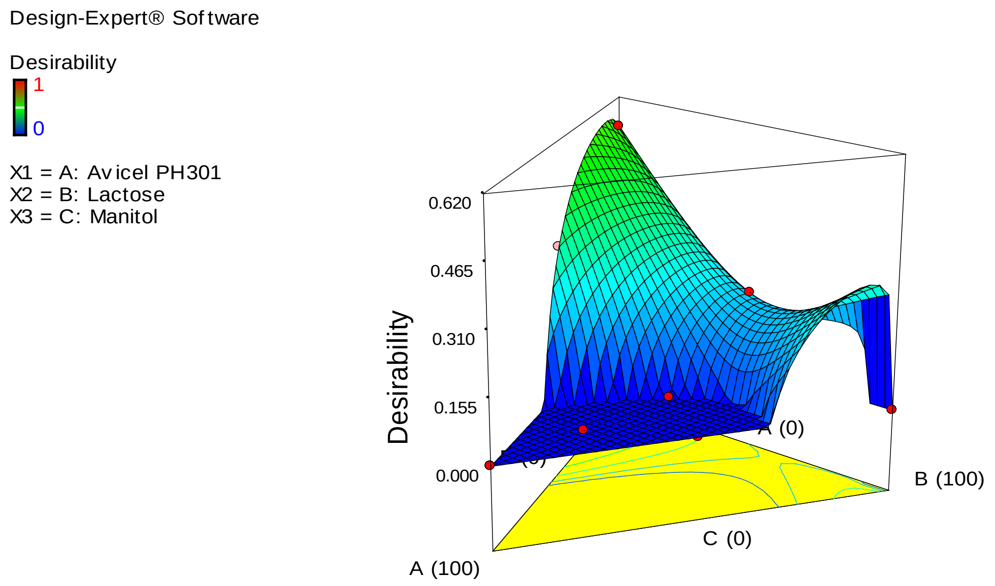

Figure 9. 3D plot of the effect of three fillers on overall desirability.
(Maximizing hardness and taste and minimizing friability with weights of 1, 0.5 and 1, and importance values of +, +++ and +++++ for the three responses of hardness, friability and taste, respectively)

be defined for the software. The goals for the three factors (i.e. each filler percentage in total filler amount) were defined as being in range (with lower and upper limits of 0 and 100%). Regarding the responses, the goals were defined for hardness to be maximized with weight and importance of 1, friability to be minimized with a weight of 0.5 and importance of 3, and taste to be maximized with a weight of 1 and importance value of 5. Figure 8 shows the contour diagram and figure 9 the 3D surface response plot for the effect of three factors (the percentages of the fillers) on the calculated overall desirability.

The best formulation with the highest desirability value of 0.580 was suggested as comprising 88.94% of mannitol and 11.06% of avicel. Of course, the region of relatively high desirability value could also be acceptable for formulation.

4. Conclusion

In our study, the simplex lattice experimental design and mathematical optimization by the Design Expert software suggested the best formulation for ferrous fumarate chewable tablets as well as an acceptable region for formulation regarding the three important characteristics of chewable tablets, i.e. hardness, friability, and taste. Having the acceptable region for formulation gives the potential to have the optimum formulation while considering some other factors as the available facilities and the final cost of products. In conclusion, the Simplex lattice mixture is suggested as a promising and efficient approach for pharmaceutical formulation projects in which multiple goals should be attained.

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