Iranian Journal of Pharmaceutical Sciences
2013: 9 (4): 23- 38
www.ijps.ir

Original Article

A Statistical Approach Towards Development and Optimization of Conventional Immediate Release Tablet of Nimorazole by Wet Granulation Technique

Aditi Paul, Trishna Bal, Ram Dubey, Manik Ghosh*

Department of Pharmaceutical Sciences and Technology, Birla Institute of Technology, Mesra-835215 , India

Abstract

Till date, most of the drugs have been given in conventional immediate release dosage form. Nimorazole is an anticancer drug, used as a hypoxic radiosensitizer in patients undergoing radiotherapy and no formulation has been available in the market till now. Hence, for the purpose to develop an immediate release dosage form, a statistical optimization process has been employed to quantify the effect of two primary excipient MCC and maize starch on its immediate release characteristics. A series of combinations by varying the composition of the two excipients were prepared and their effect on tablet property such as disintegration time, hardness and friability were analyzed using statistical design software. An optimized formulation generated by the software, was evaluated for tablet properties and drug-excipient compatibility study was carried out by FT-IR analysis and DSC thermogram analysis. A SEM image of the granules was recorded to study surface morphology. A 70:50 combination of MCC and starch was found to be the best optimized formulation for an immediate release tablet without affecting its hardness and stability. Disintegration time increased with increasing amount of starch, but decreased with increasing amount of MCC. The low prediction error observed during evaluation of the final formulation indicated the high prognostic capability of the RSM methodology. FT-IR and DSC study confirmed the compatibility of the drug with excipients.

Keywords: nimorazole, MCC, maize starch, disintegration time, hardness, friability.

Corresponding Author: Manik Ghosh, Department of Pharmaceutical Sciences and Technology, Birla Institute of Technology, Mesra-835215.
Tel: 09430360991
E-Mail: manik@bitmesra.ac.in
Cite this article as: Paul A, Bal T, Dubey R, Ghosh M. A Statistical Approach Towards Development and Optimization of Conventional Immediate Release Tablet of Nimorazole by Wet Granulation Technique
Iranian Journal of Pharmaceutical Sciences, 2013, 9 (4): 23-38.

1. Introduction

Nimorazole is a nitroimidazole group of drug containing a morpholine moiety in its chemical structure [1]. The drug is primarily indicated in amoebiosis and giardiasis as anti-infective agent [2]. It has been recently investigated as an anticancer agent in squamus

cell carcinoma of the oral region. The drug has undergone several phase III clinical studies and has been evaluated as hypoxic radiosensitizer of primary radiotherapy in supraglottic larynx and pharynx carcinoma [3,4].

When a new chemical compound possessing promising pharmacological activity comes to the market, the development of an effective dosage form becomes necessary for its delivery in patients. Of the several other dosage forms available, oral solid dosage form is still considered to be the most popular in terms of patient acceptability and ease of large scale low cost production [5]. Out of the two most commonly employed methods, i.e. wet granulation and direct compression, the former was proven better with drugs with poor flowability [5]. On the other hand, this method of tablet manufacturing suffers from several disadvantages of drug-excipients interactions induced by granulating fluid. In most of the cases, water being used as granulating agent accelerated the chemical interaction between drug and excipients and thereby, changes in drug's activity was observed [6]. Thus, choice of excipient was considered to be of utmost importance when wet granulation method was to be applied. Micro crystalline cellulose (MCC) was one of the most versatile excipient used in tableting of poorly flowable drugs. MCC showed an outstandingly high compactability which has made it possible to produce tablets strong enough to withstand tooling wear at reasonably low compaction forces without affecting much its disintegration property [7]. When a disintegrating agent was incorporated in the formulation with MCC in proper ratio, tablet disintegrated at a much faster rate giving high bioavailability of the active substances. Thus, a proper combination of diluent and disintegrating agent was the most important parameter to be considered in poorly flowable drugs and an optimization of these excipients is necessary for the development of an effective formulation.

Recently, response surface methodology (RSM) has widely been used as an accurate and highly precise statistical method for the development and optimization of process variables. RSM can be defined as a combination of mathematical and statistical processes which enables the design of a series of formulation with several process variables that are believed to affect the final product efficiency [8]. A statistical approach is always advantageous when several variables are involved as it generates less number of mathematically significant models to optimized variables based on the analysis of responses obtained , thus , avoiding evaluation of all the possible combinations [9,10].

This present study has been undertaken to develop a conventional immediate release formulation of nimorazole and to optimize the formulation, based on a statistical design to obtain the most effective drug-excipient combination. Prior to development of formulation, a preformulation study had been conducted to evaluate several parameters,

knowledge of which is necessary for excipient selection and choice of tableting method. This study focused on the effect of two excipients, MCC (diluent) and starch (binder) on the tablet parameters,mainly hardness, disintegration time and friability as these three parameters are likely to affect the immediate release property of the desired formulation. A statistical optimization method has been employed in order to determine the best combination of the stated variables and the optimized product is further subjected to release profile evaluation.

2. Materials and Methods

2.1. Materials

Nimorazole was a gift from Centaur Pharmaceutical (Pune, India), MCC was purchased from sigma-aldrich (St. Louis, MO, USA) and maize starch was purchased from Roquette (Lestrem, France). Polyvinyl pyrrolidone was purchased from CDH laboratory (New Delhi, India).

2.2. Method

2.2.1. Preformulation Evaluation

Knowledge of preformulation parameters before tableting, are of extreme importance. Several preformulation characteristics e.g. solubility, melting point, PK_a, bulk density, tapped density, angle of repose, compressibility index and particle size distribution are likely to influence tablet property, andthe choice of manufacturing methodlargely depends on these above stated parameters. Prior to development and design of formulation, a preformulation study was conducted and results were listed in Table 1. Solubility of nimorazole was determined in water, methanol and acetone as per the specification prescribed in British Pharmacopoeia [11]. PK_a of the drug was determined by spectrophotomertic method [12]. Bulk and tap density were determined using tap density tester [13] and angle of repose was determined by fixed funnel and free standing cone method [14]. Compressibility index and Hausner's Ratio were calculated from the data

Table 1. Results of preformulation study of the drug nimorazole.

Parameter	**Results**
Solubility	The drug is highly soluble in water, methanol and acetone.
PK_a	5 - 5.8
Melting point(°c)	109-110°C
Bulk density (gm/cc)	0.45± 0.03
Tap density (gm/cc)	0.73± 0.04
Compressibility index (%)	38.3 %
Hausner's Ratio	1.62
Angle of repose (°c)	43.56 ± 1.55

obtained from bulk and tap density measurement [15].

2.2.2. Experimental design

To optimize the formulation, a 3^2 central composite design (CCD) was employed using the Design-Expert® Software (Version-7.0.0, Stat-Ease Inc., Minneapolis, MN), which included 9 experimental runs. The amount of MCC used as diluent (X_1, mg) and the amount of maize starch used as disintegrating agent (X_2, mg) were considered to be independent variables. Statistical design is used to generate 9 experimental models to evaluate the effect of these independent variables on dependent variables or responses. For immediate release formulation, disintegration time (Y_1, second) and tablet hardness (Y_2, kg/cm^2) and friability (Y_3, percentage) were selected as responses which mainly depend on the independent variables stated above. Table 2 listed the minimum and maximum values of independent factors along with the median value and the range is selected on the basis of series of preliminary trial batches. The responses obtained after each run was analysedby Design-Expert® Software. Linear, cross product contribution (2FI), quadratic and cubic models were generated for the responses and best fit model was established by analysis of adjusted R^2, predicted R^2 and PRESS value. Minimum difference between adjusted R^2 and predicted R^2 (within 0.2), higher value of adjusted and predicted R^2 and small PRESS value indicates a best fitted model for the particular response [16–19]. Regression analysis of the data and estimation of regression coefficient is also performed by the software and regression equation is validated by ANOVA test. Two-dimensional (2D) contour plots and three-dimensional (3D) response plots were plotted in order to determine individual and interactive effect of independent variables on responses.

2.2.3. Preparation of nimorazole tablet

Immediate release tablets of nimorazole containing 150mg of drug were prepared by wet granulation method. All the ingredients including drug and excipients except lubricant were mixed thoroughly and pass through a suitable sieve.A Binder solution (providone K30 in water) was then added slowly and granules were passed through a 22 mesh sieve. The

Table 2. Independent variables of central composite design and their upper, middle and lower limits.

Independent variables	**symbols**	**Levels**		
		-1	0	1
MCC as diluent (mg)	X_1	50	75	100
Maize starch as binder (mg)	X_2	30	40	50

Table 3. A 3^2 central composite design with independent variable X_1= amount of MCC (mg), X_2= amount of maize starch (mg) and responses Y_1= disintegration time (second),Y_2= hardness (kg/cm^2) and Y_3= friability (percentage)**.**

Run	Coded variables				Coded responses
	X_1	X_2	Y_1	Y_2	Y_3
1	110	40	186.52±3.57	8.263±1.077	0.33
2	50	50	80.53±4.82	5.722±0.645	0.93
3	40	40	52.33±4.36	4.152±1.023	1.58
4	100	50	150.00±3.50	8.055±0.596	0.37
5	75	40	128.16±5.34	6.821±0.849	0.55
6	100	30	189.5±3.20	7.541±0.573	0.42
7	50	30	109.54±7.11	4.985±0.492	1.52
8	75	54	90.34±3.07	7.052±0.481	0.50
9	75	26	155.67±2.16	6.140±0.345	0.66

granules were allowed to dry at 60°c for 2 hrs. Lubricants were added to the dried granules and again sifted through the sieve and then compressed into a tablet using cadmach CMD3 rotary tablet punching machine.

2.2.4. Estimation of responses

2.2.4.1. Determination of disintegration time

Disintegration test is performed in disintegration apparatus USP (ED-2L, Electrolab, India). One tablet was introduced into each tube of disintegration apparatus and placed in a 1-L beaker containing water and disintegration time was recorded. The study was conducted at temperature 37°C±2°C [5, 20].

2.2.4.2. Determination of tablet hardness

Hardness is considered a function of the compressive force applied during tablet punching and a significant relationship with disintegration time and dissolution rate can be established. Pfizer hardness tester was used for measuring the hardness of tablets. The hardness of 20 tablets of each formulation was recorded [5, 20].

2.2.4.3. Friability testing

20 tablets from each batch were weighed accurately and placed in Friabilator **(**EF-2, electrolab, India). After 100 rotations tablets were weighed and percentage friability was calculated (5, 20). All the batches were additionally tested for weight variation and dug content to check that the pharmacopoeial specifications were within limit.

2.2.4.4.Weight variation test

The weight variation of individual tablets indicated non-uniformity in drug content. The averageweight of 20 tablets was determined using an analytical balance (AB104-S, METTLER, TOLEDO, Switzerland). The average weight and standard deviations of each batch is mentioned in table 6 [5,20].

Table 4. Model Summery Statistic of responses

Response	Model	Std.Dev	R^2	Adjusted R^2	Predicted R^2	PRESS	significance
Y_1	Linear	7.55	0.9686	0.9624	0.9310	1255.89	suggested
	2FI	7.77	0.9701	0.9602	0.8897	2006.47	-
	Quadratic	8.66	0.9712	0.9506	0.7949	3730.53	-
	cubic	7.07	0.9863	0.9670	0.1208	15991.87	-
Y_2	Linear	0.26	0.9575	0.9491	0.9200	1.26	-
	2FI	0.27	0.9583	0.9444	0.9088	1.44	-
	quadratic	0.15	0.9894	0.9818	0.9245	1.19	suggested
	cubic	0.11	0.9962	0.9908	0.7547	3.88	-
Y_3	Linear	0.20	0.7900	0.7480	0.5928	0.81	-
	2FI	0.20	0.8268	0.7691	0.5673	0.86	-
	Quadratic	0.061	0.9866	0.9771	0.9049	0.19	suggested
	cubic	0.027	0.9982	0.9956	0.8831	0.23	-

Y_1= disintegration time (second), Y_2= hardness (kg/cm^2) and Y_3= friability (percentage)

2.2.4.5. Drug content

Content uniformity test is applied to assure the uniform distribution of the drug in the tablet. 10 tablets were weighed and crushed to powder. Powder equivalent to100mg of nimorazole was weighed and dissolved in distilled water. Different concentrations of drug were prepared and analyzed spectrophotometrically (UV- 1800, Shimadzu Corporation, Japan) [5].

2.2.5. Compatibility study

2.2.5.1.FT-IR analysis

FT-IR spectra of pure drug, MCC, maize starch, physical mixture and granules were recorded (FT-IR, 8400-S, shimadzu, Japan) by KBr disc method (2mg of sample with 200mg of KBr) and analyzed for possible interaction. The scanning was performed from wave number 400-4000 cm^{-1} with a resolution of 2cm^{-1}.

2.2.5.2. DSC thermogram analysis

Approximately 5mg of pure drug and tablet formulation were taken in an aluminum crucible for DSC analysis (DSC-60, Shimadzu Corporation, Japan). Heat flow rate was 10^0c per minute and samples were heated upto 150^0c to detect possible interaction between drug and polymer.

2.2.6. Surface morphology study

Surface morphology of drug particle and granules were examined by Scanning electron microscopy (JSM-6390LV, SEM, JEOL). The particles were observed for size, shape and surface characteristics.

2.2.7. Optimization and Validation of Model

The goal of this statistical design was to find a better optimized formulation with optimum parameters, i.e. a reasonably low disintegration

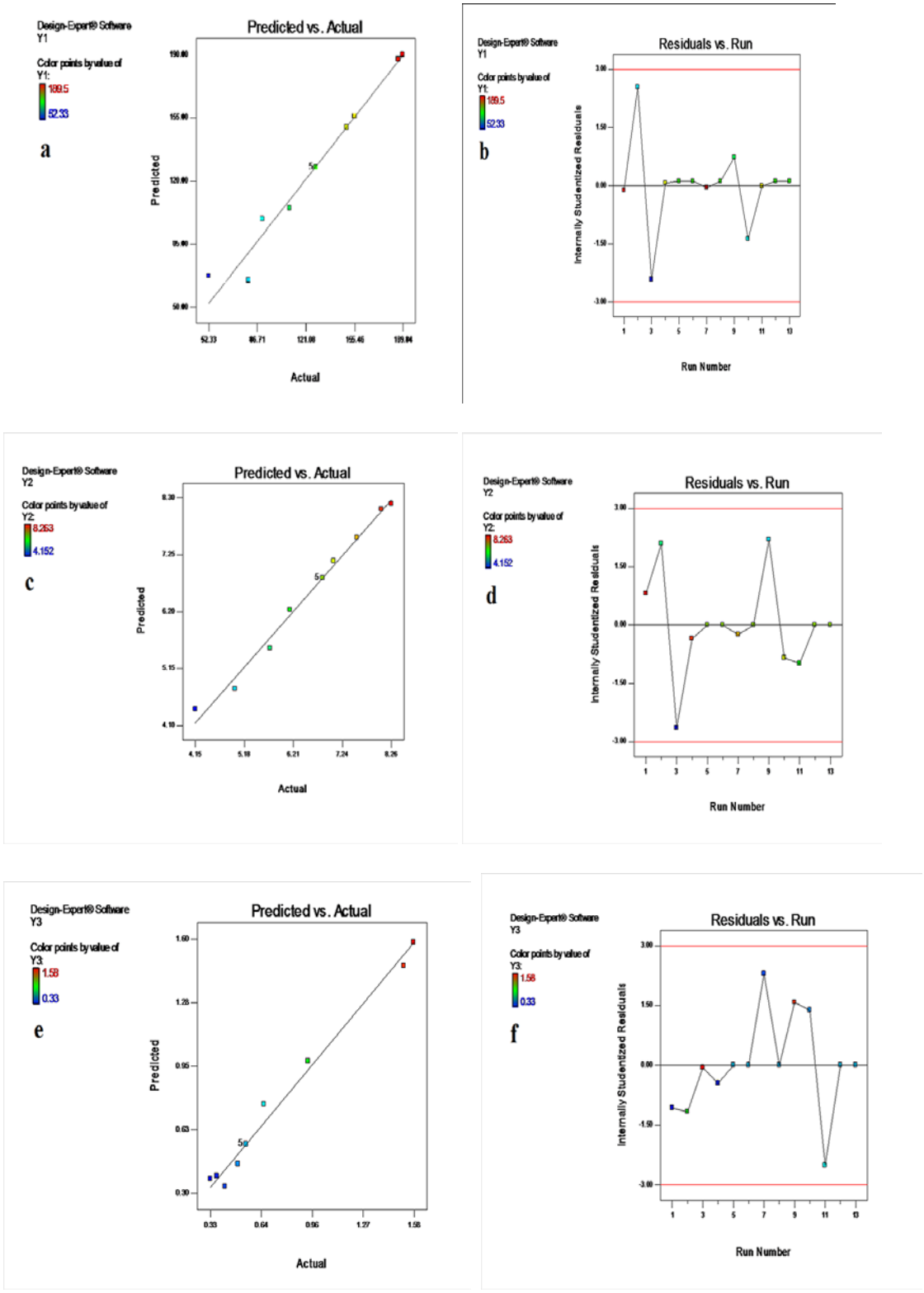

Figure.1. Linear plot of correlation (a, c, e) showing difference between actual value and predicted value and their corresponding residual plots (b, d, f) for the three responses.

time but retaining its hardness at the same time After analysis of all responses an extensive grid

obtained from the dissolution study were fitted into several release kinetic models (zero order,

Table 5. ANOVA results for response surface linear model for all three responses.

Response	Variables	Sum of squares	Mean square	F value	p value
	Model	17618.49	8809.24	154.39	<0.0001*
	X_1	14382.36	14382.36	252.06	<0.0001*
Y_1	X_2	3236.12	3236.12	56.72	<0.0001*
	Model	15.63	3.13	130.51	<0.0001*
	X_1	14.32	14.32	597.85	<0.0001*
Y_2	X_2	0.81	0.81	33.69	0.0007*
	X_1X_2	0.01	0.01	0.52	0.4946
	X_1^2	0.48	0.48	20.13	0.0028*
	X_2^2	0.033	0.03	1.38	0.2781
	Model	1.95	0.39	103.25	<0.0001*
	X_1	1.47	1.47	388.54	<0.0001*
Y_3	X_2	0.094	0.09	24.82	0.0016*
	X_1X_2	0.073	0.07	19.29	0.0032*
	X_1^2	0.32	0.32	83.59	<0.0001*
	X_2^2	0.024	0.024	1.21	0.3080

dissolution medium (0.1 N HCl) was taken and the temperature was kept constant at 37°C±0.5°C throughout the experiment. The

and Hausner's ratio of 1.62.The measurement of angle of repose also indicated poor flow property of the drug.

Table 6. Results of weight variation and drug content.

Run	1	2	3	4	5	6	7	8	9
Average Weight (mg)	302.75 ±2.67	248.35 ±1.25	232.48 ±2.78	306.32 ±2.55	273.64 ±1.98	288.45 ±1.23	235.58 ±2.23	281.52 ±1.88	256.45 ±1.35
Drug content (percent)	99.65%	100.18%	98.76%	98.3%	99.98%	1002.12%	98.75%	99.92%	99.5%

speed of the paddle was set at 100 RPM. Sampling was done at regular intervals. The samples were filtered and diluted with 0.1N HCl and then analyzed by UV spectrophotometer (UV-1800 Shimadzu).The absorbance was measured at 306nm and % drug release was calculated.In order to determine the mechanism of drug release from the tablet matrix, data

3.2. Statistical Analysis of Data

To investigate the effect of two independent variables on three dependent responses, a 3^2 factorial design model comprising of a total of 9 runs has been carried out. Analyzing the responses obtained after 9 runs, one linear model and two quadratic models were generated by the software for evaluation of the responses.

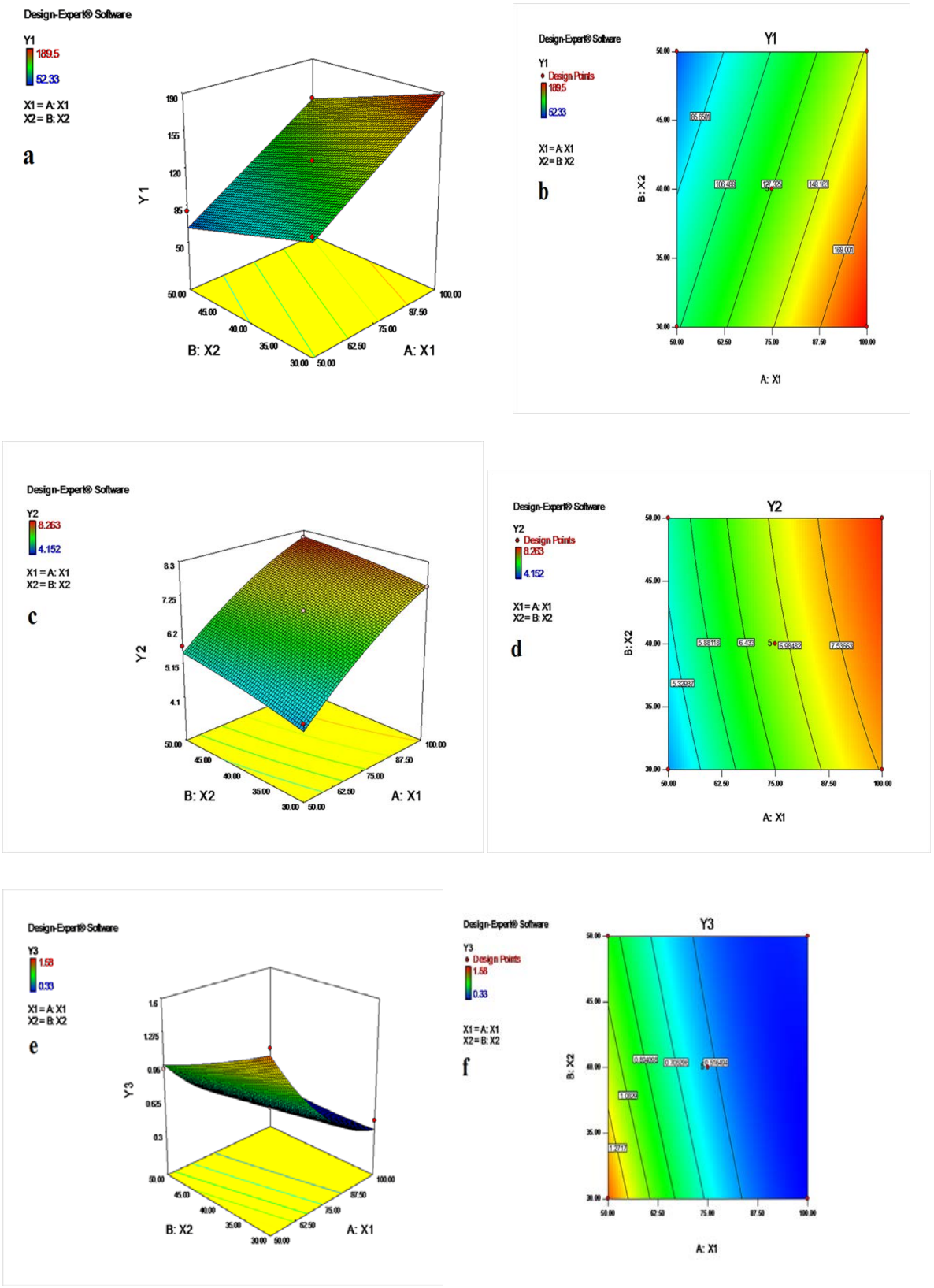

Figure 2. Response surface 3- D plots (a, c, e) and contour plots (b, d, f) showing linear effect of independent variables on responses.

Linear models were suggested for response Y_1 and Y_2. The following equation best express a linear model with two independent variables.

$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2$ ..... (1)

In this equation, β_0 is the intercept and β_1 and β_2 are coefficients corresponding to the factor $X_1$and X_2. The results of the 9 runs are shown in table 3. The linear model suggested that formulation variations have direct effect on the responses and the two equations for two responses generated by the equation is as follows

$Y_1 = +127.33 + 42.40\times X_1 - 20.11\times X_2$..... (2)

The model generated for the responses Y_2 andY_3 suggested a quadratic pattern and the equation it followed can be written as

$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_1 X_2 + \beta_4 X_1^2 + \beta_5 X_2^2$…….(3)

In this equation,β_3 is the coefficient associated with interaction andβ_4, $\beta_5$are the quadratic terms. The actual equations were as follow

$Y_2 = 6.82 + 1.34X_1 + 0.32X_2 - 0.056X_1X_2 - 0.26X_1^2 - 0.069X_2^2$…… (4)

$Y_3 = 0.55 - 0.43X_1 - 0.11X_2 + 0.14X_1X_2 + 0.21X_1^2 + 0.026X_2^2$…….(5)

The equation represents the quantitative effects of factor (X_1 and X_2) upon the responses (Y_1, Y_2 and Y_3). All the values of actual vs. predicted coefficient are reported for each response Y_1, Y_2 and Y_3in Fig1. A positive coefficient indicates a response is increased when the particular factor shifts from lower (-1) range to higher range (1), and on the other hand, reverse effect is observed in case of negative response. Table 5 shows the ANOVA results and p values of each factor for the measured responses. Significant factors affecting the

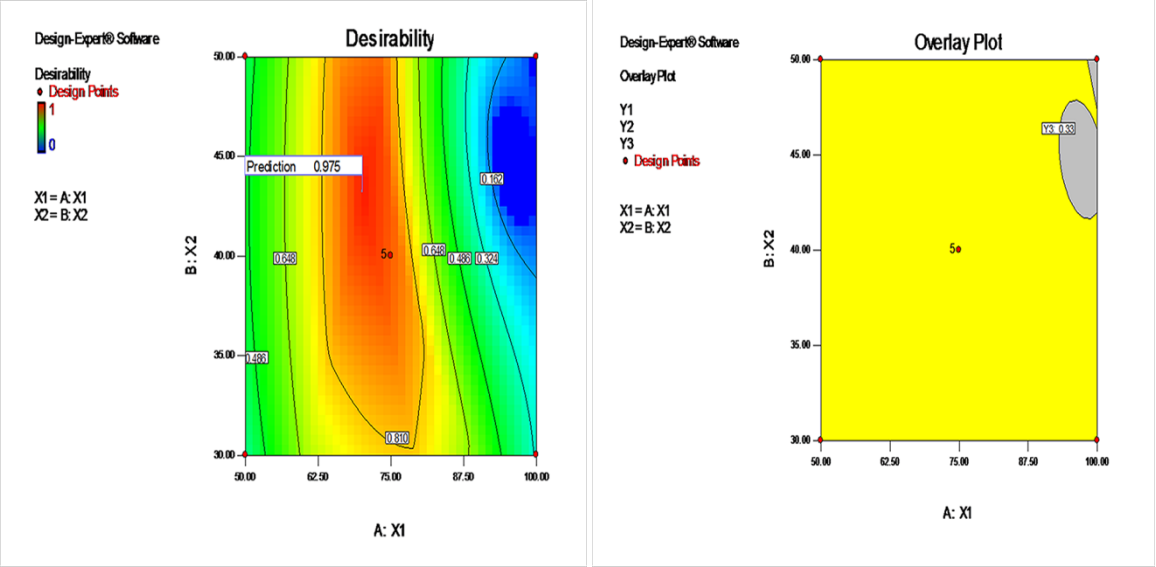

Figure 3. Desirability and overlay plot of the responses.

response Y1 were X_1 (amount of MCC used as diluent, p value <0.0001) and X_2 (amount of starch used as disintegrating agent, p value <0.0001). Significant factors affecting the response Y_2wereX_1 (p value<0.0001),X_2 (p value 0.0007) and quadric term X_1^2 (p value 0.0028). Response Y_3 was affected by three term, X_1 (p value <0.0001), X_2 (p value 0.0016), X_1X_2 (p value 0.0032) and X_1^2 (p value<0.0001).

In the 1st model (response Y_1), the value of R^2 and adjusted R^2 were 0.9712 and 0.9506 respectively. The value of R^2 was more significant indicating this model can predict disintegration time of tablets over a specific region of interest. There also existed a similarity between R^2 and adjusted R^2, indicted adequacy of the model. The Model F-value of 154.39 implied a significant model. In the 2nd and 3rd response model (Y2 and Y3), Model F-value of 130.51 and 103.25 respectively, indicated that these models also hold statistical significance. Table 4 listed statistical model summaries of all the models generated including the value of R^2, predicted R^2, adjusted R^2 and PRESS value.

3.3. Estimation of responses

Results of disintegration, hardness and friability were shown in Table 3 and all the results were found to be in accordance with the specifications prescribed in Indian Pharmacopoeia (IP) except run 3 and run 7 which failed to fulfill the IP specification of hardness greater than 5 kg/cm^2 and friability of less than 1%.

Fig.3a shows that disintegration time increases with increasing amount of MCC but at a low value of amount of starch added. Hardness of the tablet as in fig 3c, also increases with amount of MCC and higher hardness values are observed at higher amount of MCC and starch as well. This can be explained by the unique property of starch acting as both, a disintegrating and binding agent. Although in the formulations providone K30 is used as binder, a contribution of starch in the tablet hardness has been observed.In Fig 3e, friability showed a quadratic function with the two variables, indicating that a higher amount of MCC and starch is need for less friable formulations.

Additionally, weight variation and drug content of each run was determined and the results were listed in Table 6. which showed that variations of weights and drug content were within the prescribed limit of Indian Pharmacopoeia.

3.4. Optimization and Validation of Model

For optimization of the final formulation, the criteria was set to achieve a rapidly disintegrating formulation with sufficient hardness and less friability to withstand the wear during manufacture, packaging and shipping. The desirable range of disintegration time was considered to be between 90 to 120 seconds and hardness value above 6.5kg/cm^{2}with friability less than 0.5%. Considering all the desired criteria, a thorough search was conducted by the software which suggested one combination of all

Table7. Experimental value of responses and their predicted value with prediction error of final formulation

Run	Variables		Responses	Experimental value	Predicted value	Prediction error
Final formulation	X_1 (mg)	X_2(mg)	Y_1 (second)	100.16±4.24	102.82	-2.655%
	72.11	50	Y_2 (kg/cm^2)	6.44±0.748	6.499	-0.916%
			Y_3 (percent)	0.515	0.500	2.91%

the variables. The composition found to be optimum was 72.11mg of MCC with 50 mg of starch. The desirability of this composition was found to be 0.975 which was shown in the desirability graph in Fig 4a depicting regression ranges of for optimum formulation. The overlay plot in Fig 4b showed the area of operability.

To validate the accuracy and precision of the optimized model generated by the software, a final formulation run was prepared according to the optimized value of excipients and subjected to evaluation of responses. The responses obtained were compared to the predicted responses and percent of prediction error was calculated using the following formula

Prediction error = $\frac{experimentalvalue \ -prediction \ value}{experimentalvalue} \times 100$

A low percent of prediction error shown in table 7. indicates the high prognostic ability of the RSM method.

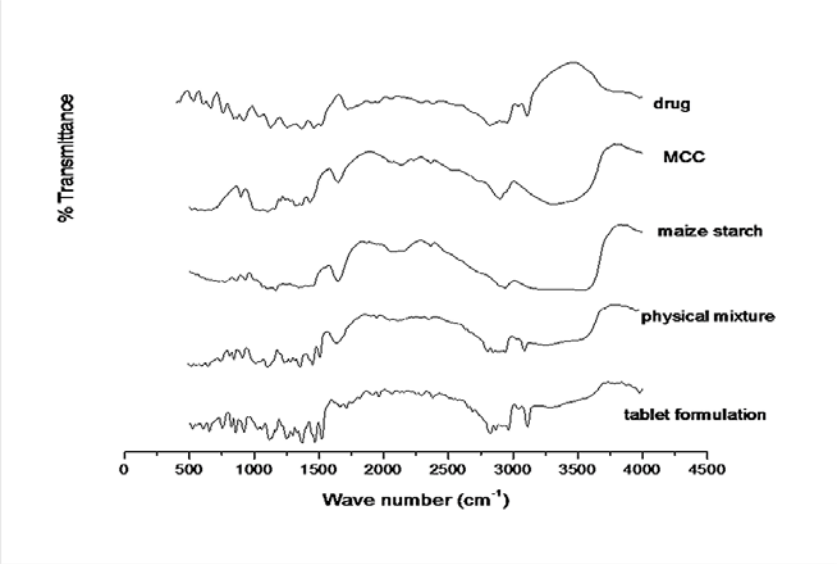

Figure 4. FTIR spectra of drug, MCC, starch, physical mixture and final tablet formulation.

3.5. Compatibility Study

3.5.1. FTIR Spectral Analysis

The FTIR spectra of tablet formulation of nimorazole with MCC and starch were compared with the standard spectrum of nimorazole in Fig5. IR spectrum of nimorazole

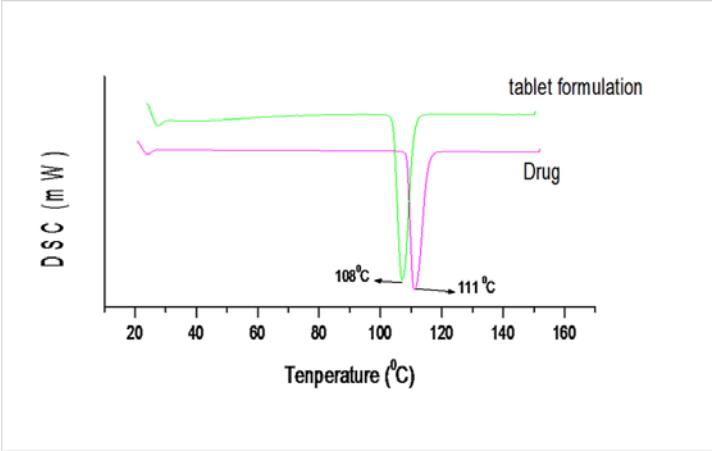

Figure 5. DSC thermogram of pure drug and final tablet formulation.

is characterized by the characteristic peaks for imidazole and morpholine nucleus. The characteristic peaks for morpholine was observed at 2962.66 cm^{-1} and 2819.93 cm^{-1} (C-$H_{aliphatic}$) along with sharp peaks at 1469.76 cm^{-1} (C-H), 1356.60 cm^{-1} (C-H bend) and 1118.71 cm^{-1} (C-N stretch). The CO stretch was found to be at 1253.73 cm^{-1}. The characteristic peaks for imidazole nucleus was observed with prominent peaks at 3109.25 cm^{-1} (C-H stretch) and 1365.50 cm^{-1} (C-N). The absorption of N-O asymmetric stretch of NO_2 was prominent at 1519.91 cm^{-1}. All the characteristics peaks were prominent in physical mixture and in tablet formulation as well, which indicated the drug's compatibility with excipients.

3.5.2. DSC Thermogram Analysis

DSC thermogram of pure drug corresponded to its melting point by a sharp endothermic peak as shown in Fig6. Pure nimorazole showed a sharp peak at 111°C and the tablet formulation showed a peak at 108^0C. These two peaks lie between the melting point ranges of pure nimorazole, hence, absence of major interaction between drug and excipients can be concluded.

3.6. Morphological study

Morphology of drug particles and granules were shown in Fig7 a, b and Fig7 c, d respectively. SEM images of drug particles showed smoother whereas the surface of the granules was rough.

3.7. In vitro dissolution study

For the conventional immediate release tablet, it is disintegrated in stomach and dissolution of drug molecule is expected to take place in the gastric fluid. The active substance in our formulation is weakly acidic in nature and is a highly water soluble compound. For that reason, dissolution medium was chosen as 0.1N HCl. Dissolution study was performed on the final formulation run and run 6 to compare the

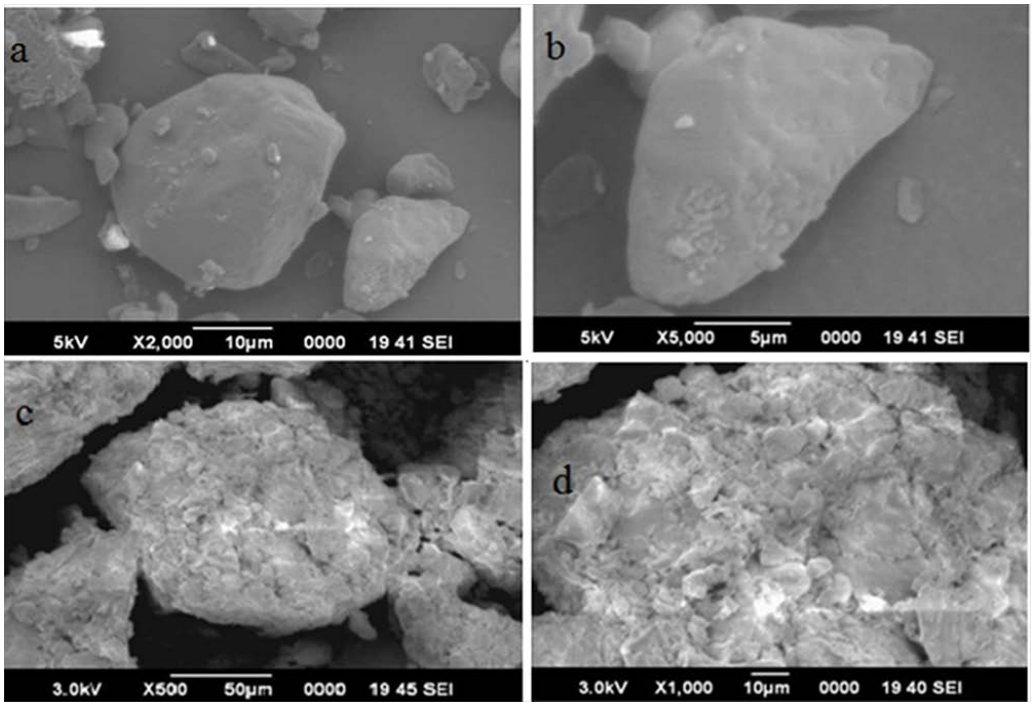

Figure 6. SEM images of drug particle (a, b) and granules (c, d).

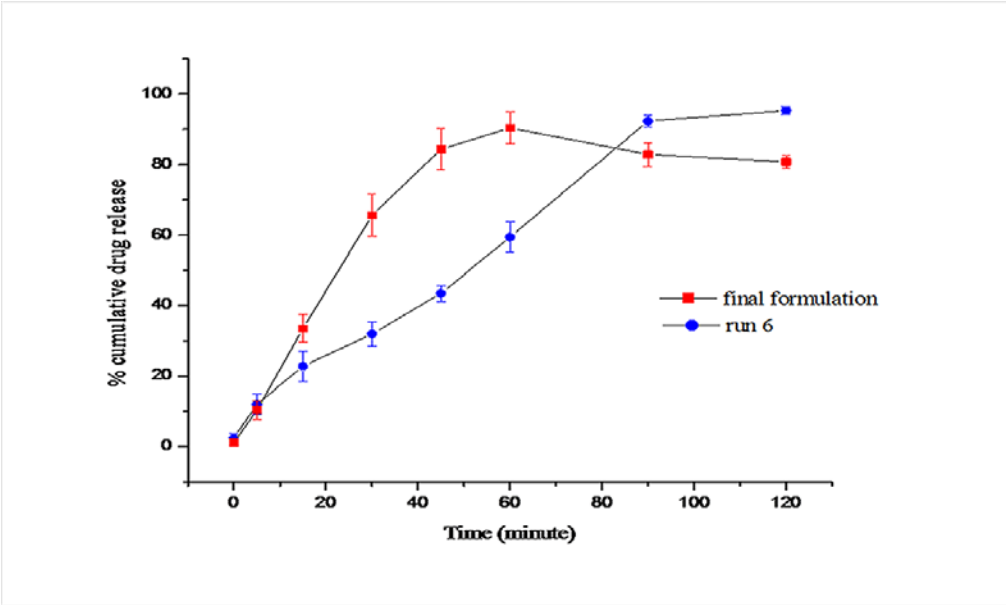

Fig. 7. Cumulative percent drug release from optimized final formulation of nimorazole immediate release tablet.

release rate and the %cumulative release graphs were shown in Fig 8. The release mechanism was determined which followed 1st order kinetics (R^2 value 0.973).

4. Conclusion

The results obtained from preformulation suggested wet granulation method was the most suitable tableting method for nimorazole. MCC as diluent and starch as binder showed suitable excipients property and can be successfully used to formulate tablets. A 70:50 MCC and starch was considered to be the best optimized ratio. This ratio was selected depending upon the desired range of response. FT-IR and DSC study confirmed absence of interaction between drug and excipients. In conclusion, the study has shown that statistical design can be successfully used to optimize tablet formulation of nimorazole.

Acknowledgements

Authors express their generous regards to the Central Instrumental Facility, BIT, Mesra for assistance in all instrumental analysis. Authors also acknowledge Centaur Pharmaceutical, Pune, India for providing the gift sample of nimorazole.

References

[1] http://www.drugs.com/international/nimorazole.html. Accessed on 10th April, 2014

[2] Roy RB, Laird SM, Heasman L. Treatment of trichomoniasis in the female: A comparison of metronidazole and nimorazole. *Brit. J . Vener. Dis* (1975) 51: 281- 286.

[3] Overgaard J, Hansen HS, Overgaard M, Bastholt L, Berthelsen A, Specht L, Lindelov B, Jorgensen K. A randomized double-blind phase III study of nimorazole as a hypoxic radiosensitizer of primary radiotherapy in supraglottic larynx and pharynx carcinoma. Results of the Danish Head and Neck Cancer Study (DAHANCA) Protocol 5-85. *Radiother. Oncol* (1998) 46: 135-46.

[4] Henk JM, Bishop K, Shepherd SF. Treatment of head and neck cancer with CHART and nimorazole: phase II study. *Radiother. Oncol* (2003) 66: 65-70.

[5] Banker GS, Anderson NR. Tablets. In: Lachman L, Lieberman HA, Kanig JL, eds. The Theory and Practice of Industrial Pharmacy. 3rd ed. Philadelphia, PA: Lea & Febiger; (1986) 293- 345.

[6] Agarwal R, Naveen Y. Pharmaceutical Processing – A Review on Wet Granulation Technology. *Int. J. Pharm. Front. Res* (2011) 1: 65-83.

[7] Azubuike PC, Okhamafe AO, Falodun A. Some Pharmacopoeial and Diluent-Binder Properties of α-Cellulose derived from Maize Cob in Selected Tablet Formulations. *J. Chem. Pharm. Res* (2011) 3: 481-88.

[8] Bas B, Boyac IH. Modeling and optimization I: Usability of response surface methodology. *J. Food Eng* (2007) 78: 836 - 845.

[9] Vincent G, Coteron A, Martinez M, Aracil Z. Application of the factorial design of experiments and response surface methodology to optimize biodiesel production. *IND. CROP. PROD* (1998) 8: 29-35.

[10] Nazzal S, Khan MA. Response surface methodology for the optimization of ubiquinone self-nanoemulsified drug delivery system. *AAPS Pharm. SciTech* (2002) 3(1): 1-9.

[11] The british pharmacopeia. Her Majesty's stationary office, London: 2004.

[12] Martin A, Swarbrick J, Cammarata A. Physical pharmacy. 3rd ed. Bombay: KM Varghese Company (1991) 314–46.

[13] Martin A, Bustamante P, Chun AHC, Physical Pharmacy, 4th Ed., Indian Reprint, B.I. Waverly Pvt.Ltd., New Delhi (1994) 444.

[14] Train D. Some aspects of the property of angle of repose of powders. *J Pharm Pharmacol* (1958) 10: 127T-134T.

[15] K Marshall. Compression and Consolidation of Powered Solid. In: Lachman L, Lieberman HA, editors. The theory and practice of industrial pharmacy. Special Indian edition (2009) 66-99.

[16] Deshmukh RK, Naik JB. Diclofenac Sodium-Loaded Eudragit® Microspheres: Optimization Using Statistical Experimental Design. *J. Pharm. Innov* (2013) 8: 276–87.

[17] Nayak AK, Pal D. Development of pH-sensitive tamarind seed polysaccharide–alginate composite beads for controlled diclofenac sodium delivery using response surface methodology. *Int. J. Bio. Macro* (2011) 49: 784 - 93.

[18] Al haushey L, Bolzinger MA, Bordes C, Gauvrit JY, Briancon S. Improvement of a bovine serum albumin microencapsulation process by screening desing. *Int. J. Pharm.* (2007) 344:16–25.

[19] De Lima JBC, Coelho LF, Contiero J. TheUse of Response Surface Methodology in Optimization of Lactic Acid Production: Focus on Medium Supplementation, Temperature and pH Control. *Food Technol. Biotechnol* (2010) 48(2): 175–81.

[20] Damodharan N, Manimaran V, Sravanthi B. Formulation development and evaluation of delayed release doxycycline tablets. *Int. J. pharm. Pharm. Sci* (2010) 2(1):116-19.

[21] Korsemeyer R, Gurny RNP. Mechanism of solute release from porous hydrophilic polymers. *Int. J. Pharm* (1983) 15:25–35.

[22] Costa P, Lobo JMS. Modeling and comparison of dissolution profile. *Eur. J. Pharm. Sci* (2001) 13(2):123-33.