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Optimization of directly compressible mixtures of microcrystalline cellulose and lactose granules for tablet formulation using a simplex lattice model

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ABSTRACT

Some directly compressible powders and granules can be combined to prepare tablets of optimum qualities. The aim of this research work was to formulate, optimize and characterize diclofenac sodium tablets using varying concentrations of microcrystalline cellulose (MCC) powder and lactose granules (DC excipients), and maize starch powder. Diclofenac tablets were prepared by direct compression using a simplex lattice (centroid) optimization design involving maximum, mid-point and minimum levels of MCC, lactose granules and maize starch. The powder mixtures were evaluated for micromeritic properties, which include bulk and tapped densities, Hausner's quotient, Carr's compressibility index, while the tablets were assessed for weight uniformity, crushing strength, friability, disintegration time and dissolution rate. The friability and crushing strength of the tablets batches were within the ranges of 0.3-1.7% and 1.4-8.4 KgF, respectively. Powder blends containing low MCC, low lactose granules and high starch levels and also, combinations comprising low MCC and mid-point lactose granules and starch concentrations showed the lowest disintegration times and the highest drug release. Special cubic and quadratic equations were derived for the prediction of diclofenac release and tablet disintegration time, respectively, using Design Expert 9. In conclusion, combinations of directly compressible excipients and disintegrant were effectively optimized for the formulation of diclofenac tablets.

Keywords: Optimization, diclofenac, compression.

INTRODUCTION

Direct compression (DC) is the process by which tablets are compressed directly from powder blends of the active ingredient, directly compressible excipients/ diluents, disintegrants and lubricants. Some advantages of direct compression include simplicity and economy of production, suitability for moisture and heat-sensitive drugs, less excipient requirement and sometimes, rapid disintegration. No pre-treatment of the powder blend is required. It involves compressing tablets directly from powder materials without modifying the physical nature of the material itself [1]. However, problems associated with direct compression include poor flow of materials, unblending, poor capacity of diluents, high lubricant requirement, poor uniformity and homogeneity in the distribution of colours. Mixtures of direct compression excipients can be used to obtain tablets of varying physical, chemical, mechanical and drug release characteristics.

Microcrystalline cellulose, as DC excipient, may trap insoluble drugs in its aggregates formed upon tablet disintegration and combinations with a soluble filler (e.g lactose) and a super disintegrant may facilitate drug release [2]. In this study, MCC was mixed with granulated lactose and maize starch (disintegrant) at different concentration ratios and tablets produced from this were characterized accordingly.

EXPERIMENTAL SECTION

Materials

Diclofenac sodium (Pauco, Nigeria), microcystalline cellulose (Qualikems Lab Chemicals, India), lactose (Evans Pharmaceutical Company, England), maize starch powder (BDH England), magnesium stearate (BDH, England).

Methods

Preparation of lactose granules

A 20 g quantity of maize starch was used to prepare starch mucilage by dispersing with 20 ml of boiled water. A 70 g quantity of lactose powder (monohydrate) was weighed out into a mortar and, the starch mucilage and the lactose powder were titrated in the mortar to form a wet mass. The wet mass was granulated manually by passing through a 1.7 mm sieve and drying in a hot air oven at 60 °C for 2 h. The dried granules were thereafter passed through a 1.00 mm sieve. The final lactose granules were stored in an air tight container.

Preparation of powder-granule mixture for diclofenac tablets

Simplex lattice design

A simplex lattice design [3] was adopted to optimize the formulation variables. In this design, three factors were evaluated by changing their concentrations simultaneously and keeping their total concentration constant. The simplex lattice design for a 3-component system is represented by an equilateral triangle in 2-dimensional space (Fig. 1). A total of eight batches were prepared. Seven batches (batches 1–7) were prepared, one at each vertex (A, B, C), one at the halfway point between vertices (AB, BC, AC), and one at the center point (ABC) using Table 1 as a guide for variations. Each vertex represents a formulation containing the maximum (1) amount of one component, with the other two components at a minimum (0) level. The midpoint (0.5) between two vertices represents a preparation containing the average of the minimum and maximum amounts of each of the two ingredients represented by the two vertices, while the third ingredient is maintained at its minimum. The center point (0.33) represents a formulation containing one third of each ingredient. This is a form of simplex centroid design. An eighth batch was also formulated, and this represented an interior point within the design space. The amount of microcrystalline cellulose (A, X_1, directly compressible excipient 1), lactose granules (B, X_2, directly compressible excipient 2) and maize starch (C, X_3, disintegrant) were selected as independent variables. The tablet disintegration time (DT), drug release at 30 min (Q_{30}) and drug release at 60 min (Q_{60}) were taken as responses for optimization. The responses were fitted into different models to generate equations and plots for the prediction of outcomes using Design Expert® 9 software.

Preparation of powder mixtures

Appropriate quantities of diclofenac sodium powder, microcrystalline cellulose (MCC), lactose granules, maize starch and magnesium stearate were weighed out (according to Table 2) and mixed together in a rotary mixer to produce 100 tablets per batch after compression.

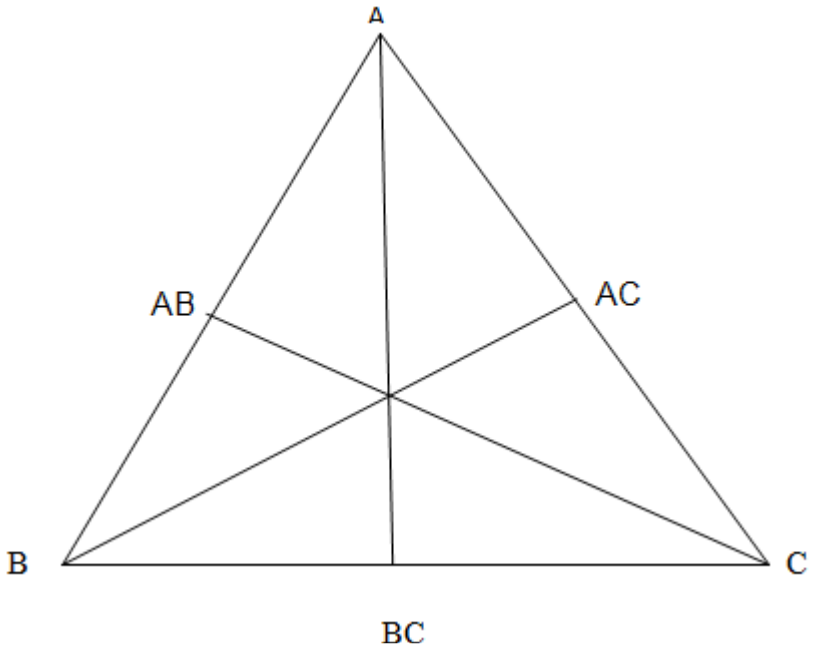

Fig. 1: An equilateral triangle representing simplex lattice design for 3 variables

Table 1: Transformed values and their equivalent excipient concentrations per tablet

Transformed values (%)	Transformed values	A (X_1)	B (X_2)	C (X_3)
		MCC (mg)	Lactose granules (mg)	Maize starch (mg)
0	0	100	62	5
50	0.5	140	102	45
100	1	180	142	85

- *Formulation at centre point of triangular simplex space (33.3%) contain 126.64, 88.64 and 31.64 mg as X_1, X_2 and X_3 respectively*

Evaluation of powder mixtures

Bulk and tapped density, Hausner's quotient, percentage compressibility index of the powder-granular mixtures

A 20 g amount of the sample mixture from each batch was weighed out and separately placed in a 100 ml graduated measuring cylinder. The volume occupied by the powder mixtures was noted and recorded as bulk volume (V_b). The bulk density was obtained from the bulk volume by dividing the weight of the samples by the bulk volume. The cylinder was tapped on a wooden platform by dropping the cylinder from a height of one centimeter at 2 seconds interval until there was no change in volume. This volume was recorded as the tapped volume, and tapped density was calculated by dividing weight of samples by tapped volume.

Hausner's quotient of the powder mixtures was calculated as the ratio of the tapped density to the bulk density [4]. This is expressed in Equation 1

$$\text{Hausner's quotient} = \frac{Tapped\ density}{Bulk\ density} \quad ----------1$$

The percentage compressibility was calculated as one hundred times the ratio of the difference between the tapped density and bulk density to the tapped density [5]. This is expressed in Equation 2

$$\text{Percentage compressibility} = 100\frac{(Tapped\ density - bulk\ density)}{Tapped\ density} \quad ----------2$$

Table 2: Formula for each diclofenac tablet batch

Ingredients	Batch 1 (mg)	Batch 2 (mg)	Batch 3 (mg)	Batch 4 (mg)	Batch 5 (mg)	Batch 6 (mg)	Batch 7 (mg)	Batch 8 (mg)
Diclofenac Sodium	50	50	50	50	50	50	50	50
Microcrystalline Cellulose	180	100	100	140	140	100	126.64	124
Lactose granules	62	142	62	102	62	102	88.64	110
Maize starch	5	5	85	5	45	45	31.64	13
Magnesium Stearate	3	3	3	3	3	3	3	3
Total weight per tablet	300	300	300	300	300	300	300	300

Tablet compression

The required weight of the powder mixture (300 mg) from the batches was filled into the die of Manesty F3 single punch tableting machine and compressed at 50 KgF. The tablets so formed were then subsequently evaluated.

Evaluation of tablets

Tablet dimensions and weight uniformity

The thickness and diameter of the tablets produced from the powder mixtures were determined using vernier calipers. The mean and standard deviation of twenty randomly selected tablets from each batch was calculated.

For uniformity of weight, twenty tablets were randomly selected from each batch. These tablets were weighed individually using an electronic weighing balance. The mean weight and deviation from mean, was calculated for each batch.

Crushing strength (hardness) and tensile strength

Monsato hardness tester (Monsato, USA) was used to determine the force required to diametrically break ten randomly selected tablets from each batch of the tablets. Mean hardness values (in KgF) and standard deviations were obtained.

The tensile strength of the tablets from each of the batches was calculated using Equation 3

$$T_s = \frac{2P}{\pi dt} \quad ----------3$$

T_s is tensile strength, P is crushing strength, d is diameter and t is thickness of the tablets

Friability
Ten tablets selected randomly from each batch of the tablets were de-dusted and weighed using electronic weighing balance. These tablets were introduced into a Roche friabilator and rotated for 4 min at 25 rpm, after which the tablets were de-dusted, re-weighed and the percentage friability calculated using Equation 4

$$Percent\ friability\ = \frac{Weight\ loss*100}{Initial\ weight} - - - - - - - 4$$

The Crushing Strength-Friability Ratio (CSFR) was calculated by dividing the crushing strength by the friability.

Disintegration Time
The disintegration times of six randomly selected tablets from each of the batches were evaluated in 500 ml of phosphate buffer pH 6.8 at 37 $\pm$ 1 °C using a disintegration apparatus (Erweka, Germany). The time for each tablet to completely disintegrate was noted. The mean value and standard deviation were calculated.

Assay of active ingredients
Ten tablets from each batch were weighed and the mean weight calculated. The tablets were crushed properly to powder form and the weight of the powder equivalent to the mean weight of the tablets (corresponding to one tablet) was collected and transferred into a 100 ml volumetric flask. This was shaken vigorously with phosphate buffer solution (pH 6.8). Thereafter, the content of the flask was made up to 100 ml mark with phosphate buffer pH 6.8. This was filtered and 1 ml of the filtrate was collected and diluted to 10 ml to form the test solution for assay. The absorbance values of the test solutions were taken in a UV/VIS spectrophotometer (Jenway 6405, England) at 263nm. Results were interpreted from a standard calibration curve.

Dissolution Time
The static magnetic stirrer apparatus was used for the dissolution test. A one litre beaker was filled with 900 ml of phosphate buffer pH 6.8 and maintained at 37 $\pm$ 1 °C. The apparatus was set at a rotating speed of 100 rpm. Each tablet from each batch was separately introduced into the medium and a five (5) ml sample was withdrawn after 10, 20, 30, 40, 50, and 60 min. Each withdrawn sample was replaced with an equal volume of the dissolution medium maintained at 37 °C. Each sample withdrawn was assayed by reading the absorbance of at 263nm using the UV/VIS spectrophotometer. The percentage of the drug released into the solution was calculated as a percentage of the absolute content.

Response surface contour plots and 3D response surface plots
The tablet disintegration time (DT), drug release at 30 min (Q30) and 60 min (Q60) were taken as responses and design expert 9 software was used to plot response surface contour plots and 3D response surface plots for each category of response.

Models and equations for response prediction
Based on results obtained, models and equations are suggested for prediction of response within the design space. Models are suggested based on the following conditions:

- In the sequential model sum of squares, the highest order polynomial where the additional terms are significant is selected.
- The model with the highest (or maximum) R-squared values (and its other derivatives) is selected.
- Model with a high f value and "prob > f" less than 0.05 is selected.

The equation is derived by multiple linear regression analysis and coefficients are obtained using established procedure [3].

RESULTS AND DISCUSSION

Flow properties of powders and weight uniformity of tablets
The batches generally showed moderate or fair flow qualities which is typical of most powders for direct compression. Furthermore, the % weight deviations from the mean weight were less than 5%, which indicated batch acceptability.

Crushing strength and friability of tablets
Batches 2 and 6 showed higher crushing strength with average values of 8.43 and 7.36 KgF, respectively (Table 3). These batches contain high (maximum) and moderate (mid-point) amounts of lactose granules, respectively. This

attribute of higher crushing strength may show the impact of degree of particle fragmentation during compression. The process of compression causes particle fragmentation, thereby revealing smaller lactose granules which are not covered by other ingredients and these 'clean and fresh' surfaces will bond differently and strongly.

Friability measures the resistance of tablets or granules to abrasion. The friability of the batches was within a range of 0.35 to 1.69%. The batches had friability values less than 1% except batches 5 (1.69%) and 8 (1.2%). The values suggested that the tablets can withstand the rigours of production and transportation. Batch 2 also had the highest CSFR ratio which showed that tablets prepared with high lactose granules possess high mechanical strength.

Disintegration Time

The disintegration time of the tablets was significantly reduced ($p < 0.05$) in the presence of elevated quantities of maize starch which functioned as disintegrant. The maize starch was able to overcome the cohesive forces keeping the particles together.

Table 3: Crushing strength, friability and CSFR of the diclofenac tablets

Batch	Crushing strength (KgF)	Friability (%)	CSFR
1	3.44	0.61	5.64
2	8.43	0.44	19.16
3	5.36	0.79	6.78
4	5.35	0.61	8.77
5	1.35	1.69	0.80
6	7.36	0.48	15.33
7	5.84	0.35	16.69
8	2.84	1.2	2.34

Batch 3 with high (maximum) concentration of maize starch disintegrated in approximately 20 s. However, high (maximum) amounts of microcrystalline cellulose and lactose granules resulted in tablets that disintegrated more slowly at 26.03 and 37.75 min, respectively.

Based on results obtained from design expert 9.0 software, the disintegration time can best be predicted using the following quadratic model in Equation 5:

$$DT = 26.47A + 36.88B + 0.50C - 69.47AB - 38.19AC - 72.47BC \quad \text{-----5}$$

Where DT is disintegration time, A is microcrystalline cellulose, B is lactose (granulated) and C is starch.

The response surface contour plot (Fig. 2) and 3D response surface plot (Fig. 3) show the disintegration times at different use levels and combinations of MCC, lactose granules and maize starch. The negative values of the coefficients of the mixture terms indicated that the mixtures resulted in reduction of the disintegration times. In the sequential model sum of squares, the quadratic model was selected as the highest order polynomial where the additional terms are significant.

After transformation to natural logarithm, disintegration time of the mixtures fitted the linear model and could be predicted using the following Equation 6, Figs. 4 and 5.

$$In\ DT = 3.16A + 2.80B - 1.50C \quad \text{----------6}$$

These results show that the maize starch have a reductive effect while MCC and lactose granules had an incremental effect on the disintegration times of the diclofenac tablets.

Dissolution time of diclofenac sodium tablets

From the results, the release profile of tablets containing low MCC and mid-point lactose granules and starch concentrations (batch 6) and also, combinations comprising low MCC, low lactose granules and high starch levels (batch 3) showed the highest drug release (Fig. 6). This may have been caused by the low disintegration times of these formulations. After 10 min of dissolution study, batches '6' and '3' released 76 and 73% of their diclofenac concentrations. However, low levels of drug release were observed in batches '1' and '2' containing high (maximum) concentrations of microcrystalline cellulose and lactose granules, respectively. The formulations showed sustained release profile.

Based on results obtained from design expert 9.0 software, percent drug release after 30 min (Q30) and 60 min (Q60) can best be predicted using the following special cubic mixture models (Equations 7 and 8)

$$Q30 = 14.55A + 14.65B + 93.75C + 66.56AB - 95.63AC + 140.27BC - 782.36ABC \text{ - - - -} 7$$

$$Q60 = 20.05A + 20.75B + 80.70C + 29.85AB - 9.95AC + 194.49BC - 989.70ABC \text{ - - - -} 8$$

In the sequential model sum of squares, the special cubic mixture model was selected as the highest order polynomial where the additional terms are significant. The equations clearly confirmed that increase in maize starch concentration significantly increased the values of Q30 and Q60 since a positive sign and high coefficient values were observed for term 'C'. Also, the combinations of MCC and lactose granules showed a positive effect on the value of Q30 and Q60. Therefore, mixtures of MCC and lactose granules improved the drug releasing capacity of each directly compressible excipient. However, drug releasing effect of maize starch (disintegrant) may be inhibited when combined with MCC ('AC' term has negative coefficients). The response surface contour plots and 3D response surface plots of tablet drug release after 30 min (Q30) and 60 min (Q60) are presented in Figs. 7-10. The plots show regions representing different levels of Q30 and Q60. This would allow a formulator to select combinations based on the biopharmaceutical and therapeutic goal of the formulation.

Table 4: Disintegration times, percentage drug release after 30 min (Q30) and 60 min (Q60)

Batch	DT (min)	Q30 (%)	Q60 (%)
1	26.03	14.51	19.93
2	37.75	14.76	21.07
3	0.28	93.73	80.65
4	17.38	31.57	28.80
5	3.74	30.18	47.71
6	1.03	89.28	99.39
7	3.19	24.68	28.57
8	6.67	25.32	23.60

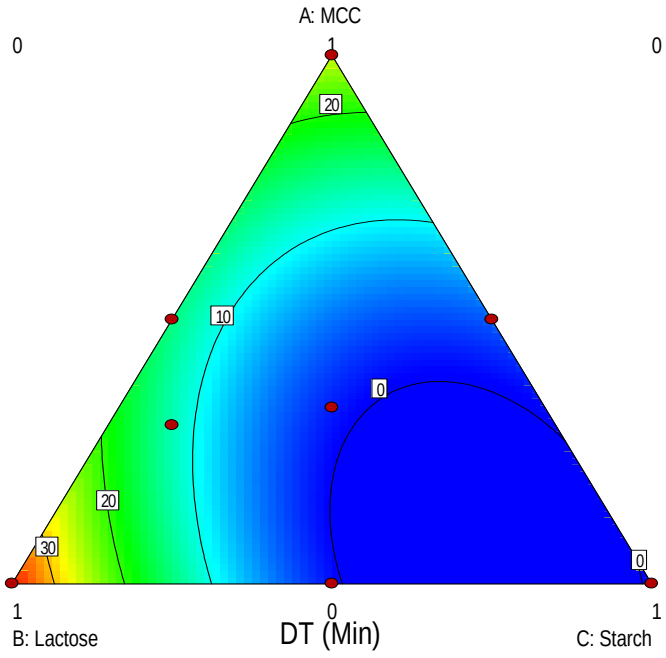

Fig. 2: Response surface contour plot of tablet disintegration time

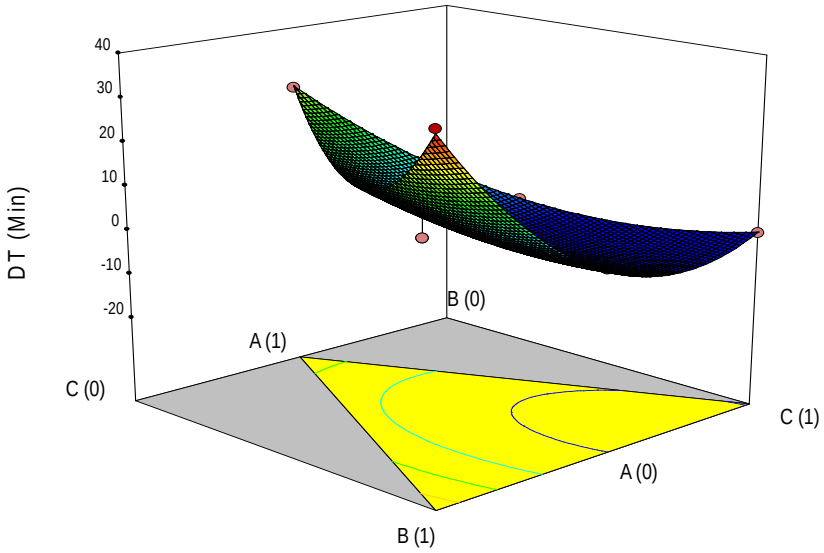

Fig. 3: 3D response surface plot of tablet disintegration time

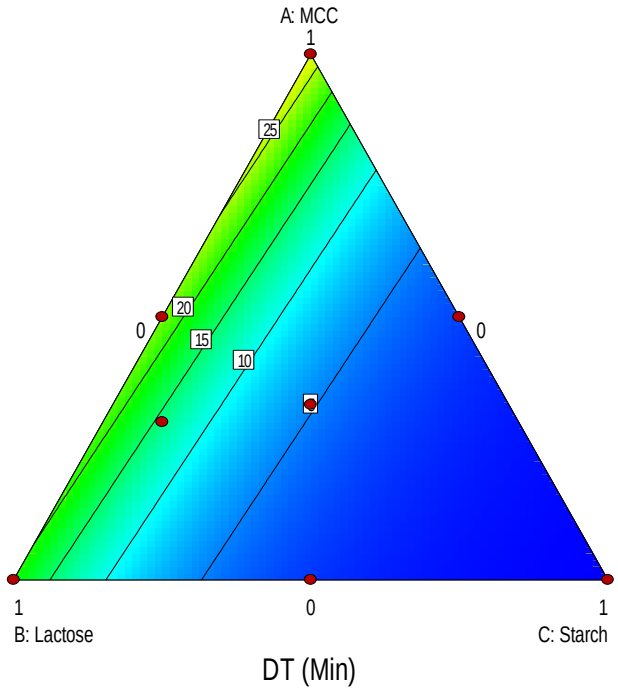

Fig. 4: Response surface contour plot of disintegration time after transformation to natural logarithm

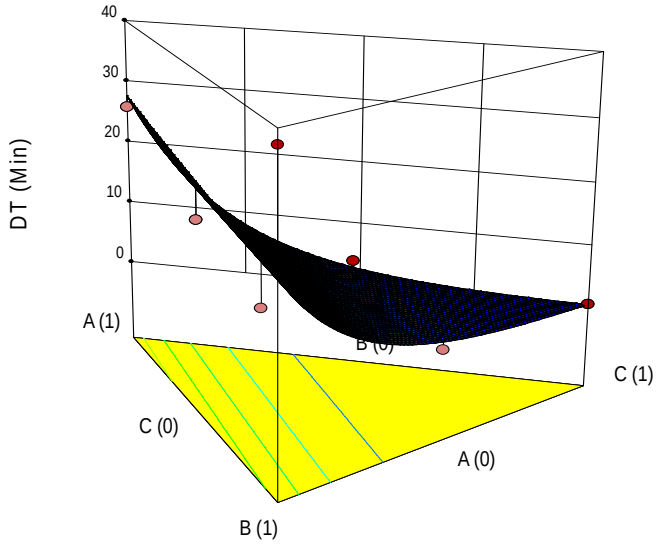

Fig. 5: 3D response surface plot of disintegration time after logarithmic transformation

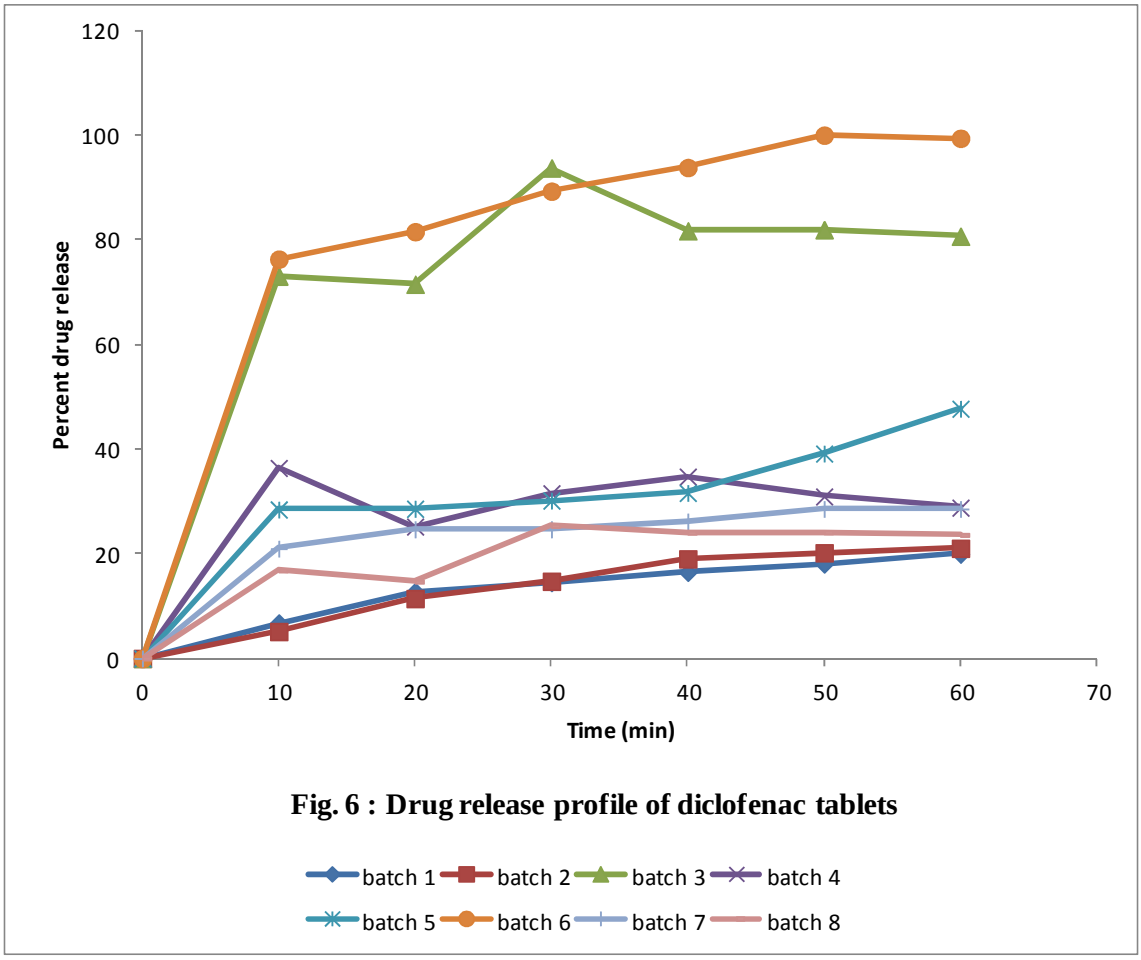

Fig. 6 : Drug release profile of diclofenac tablets

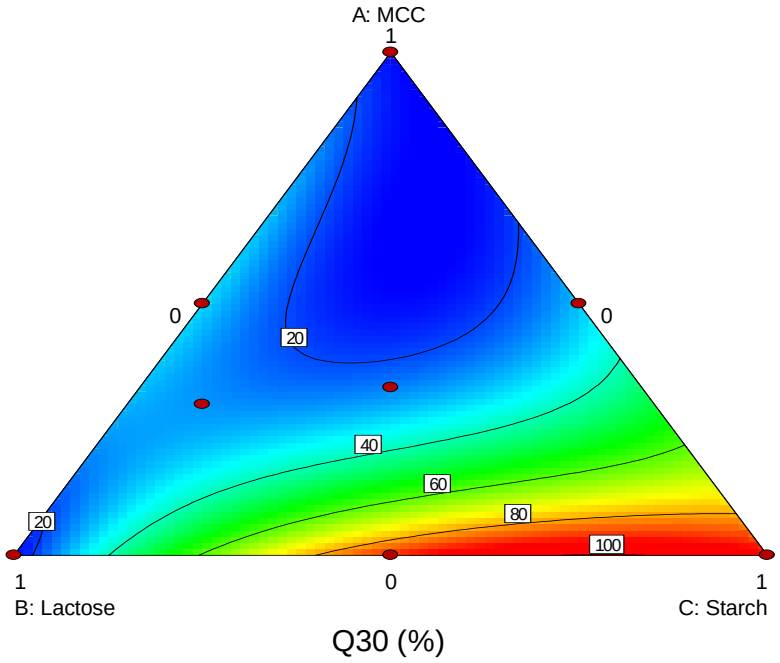

Fig. 7: Response surface contour plot of tablet drug release after 30 min (Q30)

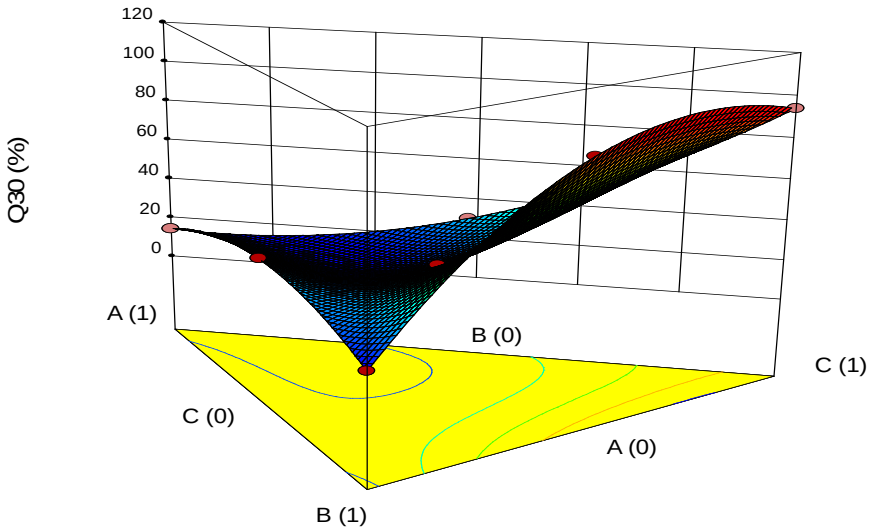

Fig. 8: 3D response surface plot of tablet drug release after 30 min (Q30)

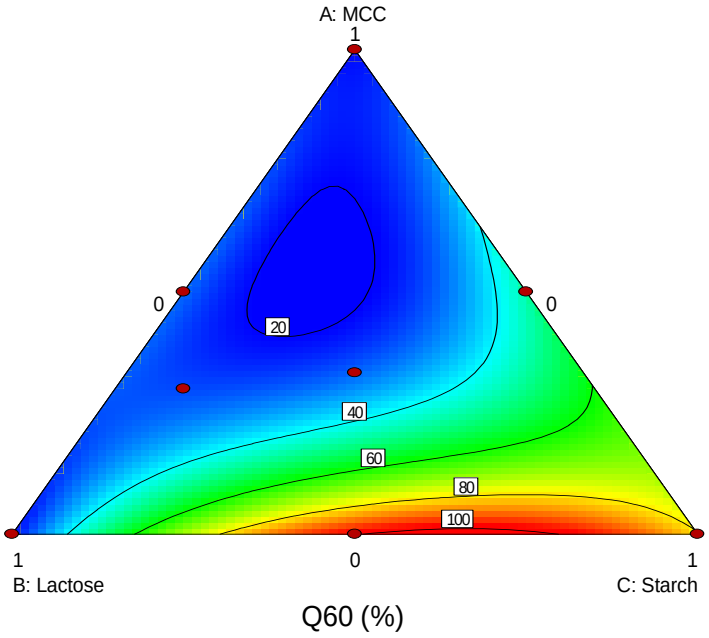

Fig. 9: Response surface contour plots of tablet drug release after 60 min (Q60)

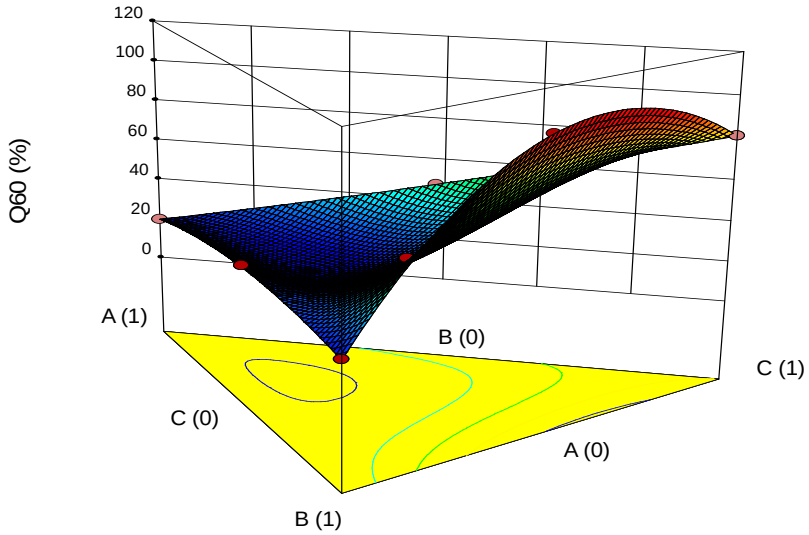

Fig. 10: 3D response surface plot of tablet drug release after 60 min (Q60)

CONCLUSION

Special cubic and quadratic equations were derived for the prediction of diclofenac release and tablet disintegration time, respectively, and response surface plots were generated using Design Expert 9 software. Combinations of directly compressible microcrystalline cellulose powders and lactose granules were used to effectively produce tablets that are physically and mechanically satisfactory, and have desirable diclofenac release profile. Therefore, combinations of microcrystalline cellulose, lactose granules and maize starch were effectively optimized for the formulation of diclofenac tablets.

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