



APPLICATION AND EVALUATION OF 3-COMPONENT MIXTURE OF DIRECTLY COMPRESSIBLE EXCIPIENTS IN TABLET FORMULATION USING AN OPTIMIZATION TECHNIQUE

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ABSTRACT

Different excipients can be mixed to achieve optimal outcomes in direct compression of tablets. The aim of this study is to formulate and evaluate hydrochlorothiazide tablets based on mixtures of directly compressible excipients using the simplex lattice optimization technique. Hydrochlorothiazide tablets were prepared by direct compression technique using a simplex lattice optimization design involving eight different formulations with varied amounts of microcrystalline cellulose (MCC), dextrose and lactose granules. The tablets were evaluated for weight uniformity, crushing strength, friability, disintegration time and dissolution rate. The friability values of the tablets were within the range of 0.2-0.5% while the crushing strengths were within the range of 7-12 KgF. Batches 2 and 8 containing MCC (26.5% w/w and 32.4% w/w, respectively), dextrose (37.5% w/w and 23.4% w/w, respectively) and lactose granules (26.5% w/w and 34.7% w/w, respectively) were selected as the optimized products on the basis of high dissolution (97.7% and 101.8% respectively, at 60 min) and least disintegration time of 13.8 min and 12.7 min, respectively. Equations and response surface plots were derived for the prediction of hydrochlorothiazide release, tablet disintegration time and friability using Design Expert® 10 software. Optimization has proven to be an effective tool in product development and can be used to achieve Quality by Design (QbD). Mixtures of the directly compressible excipients were effectively optimized for the formulation of hydrochlorothiazide tablets.

KEYWORDS: *Directly compressible, optimization, excipients, simplex lattice*

INTRODUCTION

Direct compression (DC) is the formation of tablet compacts from blends of active ingredient and excipients without a granulation step or other modifications of the physical nature of the powder blend [1]. This has the advantage of simplicity and economy, and serves to avoid the use of water, organic solvents and heat in the process of granulation. It involves far less steps than either roller compaction or wet granulation [2] and also has less excipients' requirement. Additionally, it may result in

rapid disintegration of the dosage form and is less likely to cause changes in dissolution profiles in the course of storage than tablets made by regular granulation [3]. In spite of these advantages, direct compression suffers from several challenges including poor flow of excipients, poor capacity of the excipients to accommodate the active pharmaceutical ingredient and poor uniformity of character. Direct compression is also more susceptible to segregation due to the differences in density between the ingredients [4]. This may lead to problems like weight

variation and content uniformity. Some of the directly compressible excipients also have poor reworkability. To reduce the problems associated with production of directly compressible tablets, careful optimization of the formulation process is needed. However, pharmaceutical optimization processes, are themselves saddled with trial and error due to absence of a clear relationship between formulation characteristics and process variables [5]. A system of optimization that consists only of changing the levels of one variable at a time while keeping others constant [6] cannot yield the desired results and would be simplistic and of limited predictability. Real optimization ought to take into consideration not only the relationship between the level of a variable and the response obtained, but also the effect of interaction between two or more variables. To avoid this problem, experimental design studies (EDS) are employed both in formulation and process optimization [7]. The simplex lattice is an experimental technique mostly used in analytical processing. It is a geometric figure that has one more point than the number of factors. It may be plotted in several contours or planes [8]. Optimization is a crucial part of the concept of Quality by Design (QbD).

Hydrochlorothiazide is a thiazide diuretic which has proved very important in the management of mild to moderate hypertension. It has been used in several experiments as a model drug for comparing directly compression excipients [9,10].

The aim of this study is to optimize, formulate and evaluate hydrochlorothiazide (HCTZ) tablets by direct compression using the simplex lattice design.

MATERIALS AND METHODS

Materials

Hydrochlorothiazide (Juhel, Nigeria), microcrystalline cellulose (Qualikems Lab Chemicals, India), lactose (Qualikems Lab Chemicals, India), dextrose (Qualikems Lab Chemicals, India). All other materials were used as procured from their manufacturers without further processing.

Methodology

Preparation of directly compressible lactose granules

A 20 g quantity of maize starch was used to prepare 40 %w/w starch mucilage by dispersing in boiled water. A 130 g of lactose powder (monohydrate) was weighed out into a mortar and, the starch mucilage and the lactose powder were titrated in a 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 hydrochlorothiazide tablet powder mixtures

The desired quantity of hydrochlorothiazide powder (25 mg per tablet) and appropriate quantities of microcrystalline cellulose (MCC), lactose granules, dextrose and maize starch (Table 1) were weighed out and mixed uniformly using the undulating method to achieve a uniform mix. The required quantity of magnesium stearate was weighed and mixed with the powder blend of each batch uniformly for the production of tablets after compression.

Optimization by Simplex Lattice design

A simplex lattice design [11] was utilized to optimize the formulation variables. In this design, three independent factors (DC excipients) were assessed by changing their concentrations simultaneously while keeping their total concentration constant. A simplex lattice design for a 3-component system is represented by an equilateral triangle in 2-dimensional space as represented in Fig. 1. A total of eight batches were prepared for the study. Seven batches (batches 1-7) were prepared, one at each vertex of the triangle (A, B, C), one at the halfway point between vertices (AB, BC, AC), and one at the centre point (ABC) using Table 1 and 2 as a guide for variations. Each vertex represents a formulation containing the maximum (1) amount of one component, with the other two at minimum (0) levels. 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 corresponding vertices, while the third ingredient is maintained at its minimum. The centre point (0.33) represents a formulation containing one third of each DC excipient. This is a form of simplex centroid design. An eight batch was also formulated, and this represented a chosen interior point within the design space. The amount of microcrystalline cellulose (A, X_1 , directly compressible excipient 1), dextrose (B, X_2 , directly compressible

excipient 2) and lactose granules (C, X_3 , directly compressible excipient 3) were selected as independent variables. Friability, disintegration time and drug released after 30 min (Q30) and 60 min (Q60) were taken as response for optimization. The responses were fitted into different models to generate equations and plots that best predict of outcomes using Design Expert® 10.

Table 1: Formula for hydrochlorothiazide tablets

Ingredients (mg)	Batches (mg)							
	H ₁	H ₂	H ₃	H ₄	H ₅	H ₆	H ₇	H ₈
Hydrochlorothiazide	25	25	25	25	25	25	25	25
Microcrystalline cellulose	200	106	106	153	153	106	137.3	129.5
Dextrose	56	150	56	103	56	103	87.3	93.6
Lactose Granules	106	106	200	106	153	153	137.3	138.9
Maize starch	10	10	10	10	10	10	10	10
Magnesium Stearate	3	3	3	3	3	3	3	3
Tablet total weight	400	400	400	400	400	400	400	400

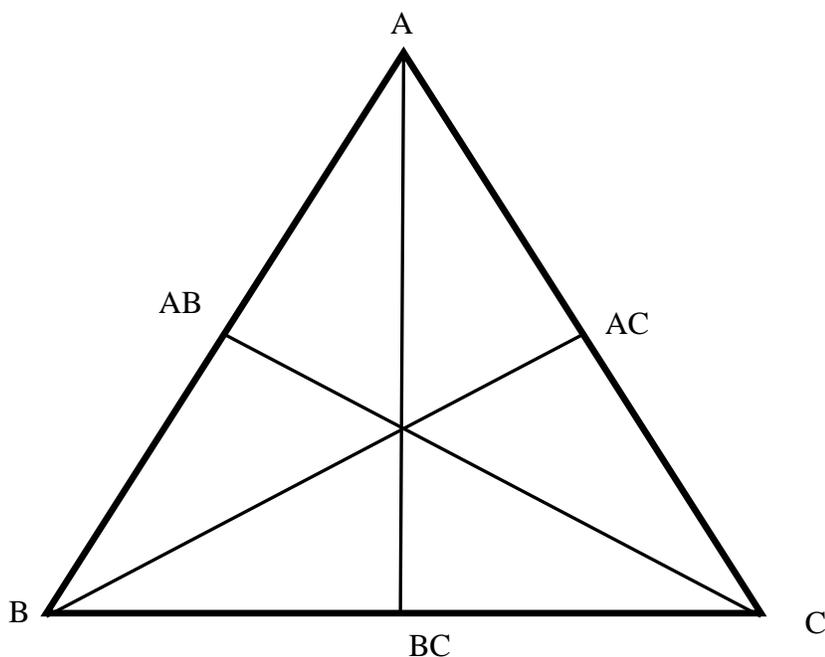


Fig. 1: Simplex Lattice Design for a 3-component system

Table 2: Transformed values and their equivalent excipient concentrations

Transformed values (100%)	Transformed values	X1 (A) MCC (mg)	X2 (B) Dextrose (mg)	X3 (C) Lactose granules (mg)
0	0	106	56	106
50	0.5	153	103	153
100	1	200	150	200

Tablet Compression

Uniform weights of the powder mixture (400 mg) from each batch was filled into the die cavity of Manesty F3 single punch tableting machine serially and compressed at 47 KgF. The tablets so formed were then subsequently evaluated.

Weight uniformity of tablets

The average tablet weight was determined by randomly selecting 20 tablets and weighing each individually using an electronic weighing balance (Mettler Toledo B204-S, Germany). The mean weight and standard deviations of each batch was determined. The percentage deviation of each tablet weight from the mean weight was also calculated and used to assess the quality of the batch.

Crushing strength (Hardness) of tablets

Ten tablets were taken randomly and individual hardness measured using Mosanto Hardness Tester (Mosanto, USA). The mean hardness values (in KgF) and \pm standard deviations of ten tablets of each formulation were obtained.

Friability

Ten tablets were taken randomly from each batch of the tablets and were de-dusted and weighed using an electronic weighing balance. The tablet samples were placed in a Roche Friabilator. After twenty five rotations for 4 min, loose dust was removed from the tablets as before. Finally, the tablets were re-weighed. The loss in weight is used to evaluate the ability of the tablets to withstand this type of wear. The percent friability was determined by using Equation 1;

$$\text{Friability} = \frac{\text{Initial weight} - \text{final weight}}{\text{Initial weight}} \times 100 \text{ --- Equation 1}$$

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

Disintegration time test

Six tablets from each batch were utilized for disintegration studies in 500 ml of phosphate buffer medium, (pH 7.4) at 37 °C using the Erweka disintegration apparatus. The disintegration time was taken to be the time the tablet completely broke down or no granule of any tablet was left on the mesh of the apparatus. The mean value and the 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 7.4). Thereafter, the content of the flask was made up to 100 ml mark with phosphate buffer (pH 7.4). This was filtered and 1 ml of the filtrate was collected and diluted to 25 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 271nm. Results were interpreted on a standard calibration curve.

Dissolution rate studies

In vitro drug release studies were undertaken using USP apparatus I (basket method). The investigation was performed with 900 ml of phosphate buffer, (pH

7.4) as dissolution medium at 37 °C for 60 min. In all experiments, 5 ml of sample was withdrawn from the medium containing suspended test tablets at 10 min interval and replaced with fresh medium to maintain sink condition. Samples were filtered and assayed in a spectrophotometer (Jenway 6405, England) at 271 nm.

Interpretation of response surface plots and response prediction

The tablet percentage friability, disintegration time (DT), drug release at 30 min (Q30) and 60 min (Q60) for each batch were taken as responses and Design Expert 10® was used to plot a response surface contour plot and 3D response surface plot for each category of response. Based on data obtained, models and equations are suggested for prediction of response within the design space. Models are suggested based on the following criteria: (a) In the sequential model sum of squares, the highest order polynomial where the additional terms are significant are selected, (b) The model with the highest (or maximum) R-squared values (and its derivatives) is selected (c) Model with high f value and “prob> f” that is less than 0.05 is selected. The equation is derived by multiple linear regression analysis and coefficients are obtained using established procedure [11].

RESULTS AND DISCUSSION

Weight uniformity of tablets

Table 3: Physicochemical and mechanical attributes of the tablets

S/ No	Parameters	H ₁	H ₂	H ₃	H ₄	H ₅	H ₆	H ₇	H ₈
1	Mean weight	399.15	395.15	400.00	397.25	398.55	398.10	398.10	397.90
2	Friability (%)	0.45	0.45	0.33	0.38	0.23	0.45	0.41	0.43
3	Average Crushing strength (KgF)	12.0	9.5	11.5	12.0	12.0	11.3	10.8	7.6
4	CSFR	26.49	20.93	34.74	31.66	53.10	25.11	26.15	17.72
5	Average disintegration time (min)	231.76±	13.76±	43.32±	78.43±	141.12±0	33.06±	117.16±0	12.66±
		0.00	0.00	0.00	0.11	.00	0.01	.00	0.01

Based on results obtained from Design expert® 10.0, the friability of the tablets can best be predicted using the following special cubic mixture model (Equation 2):

The percent weight deviations from the mean weight (Table 3) were less than 5%, which indicated batch acceptability. Weight uniformity, is an indication of the amounts of active pharmaceutical ingredient (API) in tablets, however, it is not a guarantee that the API is uniform in all tablets especially in formulations with low dose drugs. Furthermore, if the weights of tablets in a batch vary, there will be variations in disintegration and dissolution.

Friability test, crushing strength and crushing strength-friability ratio (CSFR)

Friability measures the resistance of tablets or granules to abrasion while crushing strength test shows the ability of tablets to withstand pressure or stress during handling, packaging and transportation. The friabilities of the batches were within the range (%) of 0.23 to 0.5 (Table 3). The values suggest that the tablets can withstand the rigours of production and transportation. Batch 2 (containing 26.5% w/w MCC, 37.5% w/w dextrose and 26.5% w/w lactose granules) and batch 8 (comprising 32.4% w/w MCC, 23.4% w/w dextrose and 34.7% w/w lactose granules) showed lower crushing strength with average values of 9.54 and 7.6 KgF, respectively, although the tablet batches generally had relatively high crushing strength. All the batches showed relatively high values of CSFR, which is an overall assessment of the physico-mechanical strength of the tablets.

$$\text{Friability} = 0.45A + 0.45B + 0.33C - 0.30AB - 0.66AC + 0.23BC + 2.16ABC \dots\dots 2$$

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 equation clearly showed that lactose granules had the least positive effect on the friability of the tablets while the combination of MCC, dextrose and lactose granules showed highest positive or incremental effect on the friability of the tablets. The higher incremental effect of the combinations of the three on friability could be due to dissimilarities in the physical characteristics of the DC excipients leading to a reducing resistance to abrasion. Generally the values of the coefficients are low since friability values are usually low. The response surface contour and 3D response surface plots (Fig. 2) showed the effects of these variables on the response. The equation and

plots can allow prediction of responses from different combinations of the variables.

In the contour plots (Fig. 2a), selecting excipient concentrations and combinations close to 0.25-marked contour lines (blue-coloured zone) would produce tablets with very low friability. This zone corresponds to formulations with minimal dextrose and average quantities of MCC and lactose granules. Excipient combinations around contour line marked 0.45 (within the orange-coloured zones) would produce tablets with higher friability values and this corresponds with higher amounts of dextrose. In the 3D response surface plot (Fig. 2b), the lower friability outcomes were shown to exist at the lower portion of the response plane whereas higher values are obtained at the elevated portions.

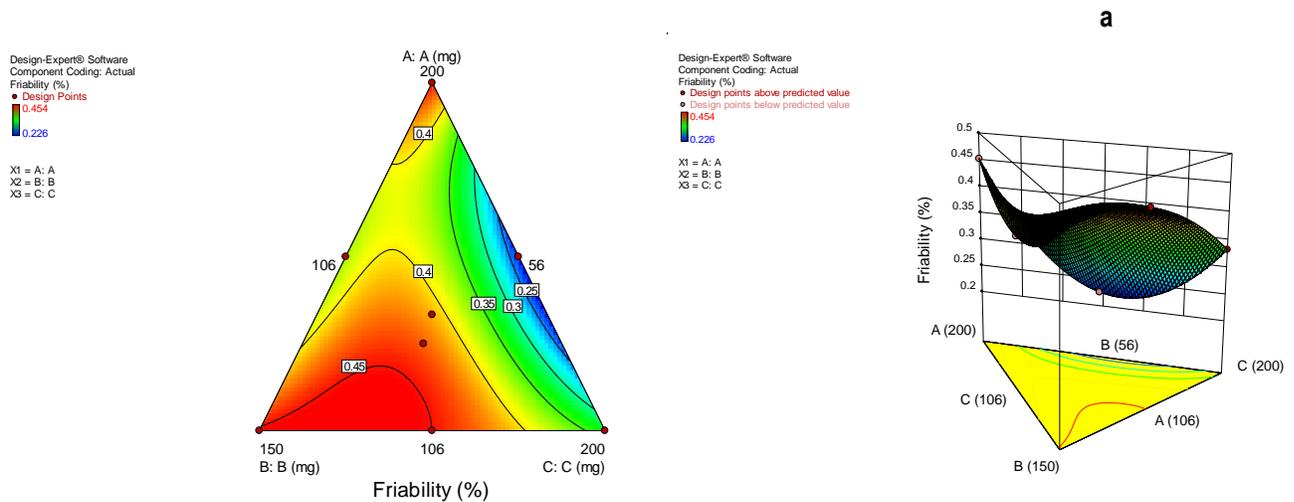


Fig. 2: Response surface contour (a) and 3D response surface plots (b) of percentage friability

Disintegration time of tablets

Batches 2 and 8 had the lowest disintegration time of approximately 14 min and 13 min, respectively (Table 3). This could be attributed to relative amounts of microcrystalline cellulose, dextrose and lactose granules used for batches 2 and 8. In these two formulations, the concentrations of MCC and lactose granules were equal or similar (creating a balance), while a relatively substantial quantity of dextrose was present.

Disintegration is the rate-limiting step for dissolution and batches with low disintegration time may show improved dissolution rate and consequently higher absorption and bioavailability.

A linear equation best describes the disintegration time (DT) of the tablet batches and this is presented as Equation 3:

$$DT = 218.69A - 5.61B + 45.34C \dots\dots\dots 3$$

The negative values of the coefficients of the B term indicated that the dextrose resulted in reduction of disintegration time. This is obvious considering the high aqueous solubility of dextrose which initiates tablet break-up. MCC contributes to increments in disintegration time more than lactose granules. This tendency towards increasing disintegration time of tablets produced by direct compression of mixed excipients has been reported earlier [12].

The relationship between the concentration of the DC excipients and disintegration time of the tablets is visually expressed in the response plots (Fig. 3). In the contour plot (Fig.3a), the zone at the base of the triangle (blue-coloured) corresponds to low disintegration time and this represents combinations with minimal MCC and maximal or moderate dextrose, whereas the combinations involving maximum amounts of MCC around the tip of the triangle (orange-coloured) would produce tablets with higher disintegration time. This was also expressed in the 3D response surface plot (Fig. 3b).

Dissolution time of hydrochlorothiazide

From the results, the release profile of tablets containing 26.5% w/w MCC, 37.5% w/w dextrose and 26.5% w/w lactose granules (batch 2) and also, combinations comprising 32.4% w/w MCC, 23.4% w/w dextrose and 34.7% w/w lactose granules (batch 8) showed the highest drug release (Fig. 4). In 30 min, batches 2 and 8 released 71.6% and 67.8% hydrochlorothiazide content of tablets, respectively, whereas in 60 min the same batches released 97.7% and 101.1% of their hydrochlorothiazide contents, respectively. Batches 2 and 8 with high percentage release will show high bioavailability when administered. The drug release was calculated using the absolute drug content of each tablet batch (average drug content from assay was 25 mg). The

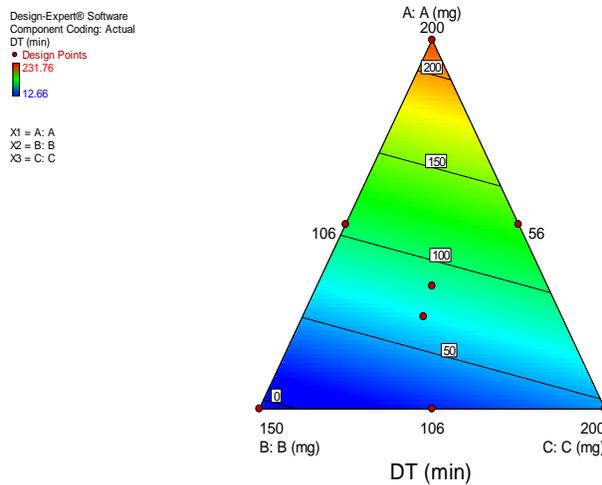
lowest percent drug release was observed in the two formulations where MCC had the highest concentrations compared to other DC excipients. This could be attributed to the increasing effect MCC has on the disintegration time of these systems.

Based on results obtained from design expert®, percent drug release after 30 min (Q30) and 60 min (Q60) can best be predicted using the following special cubic mixture models (Equations 4 and 5):

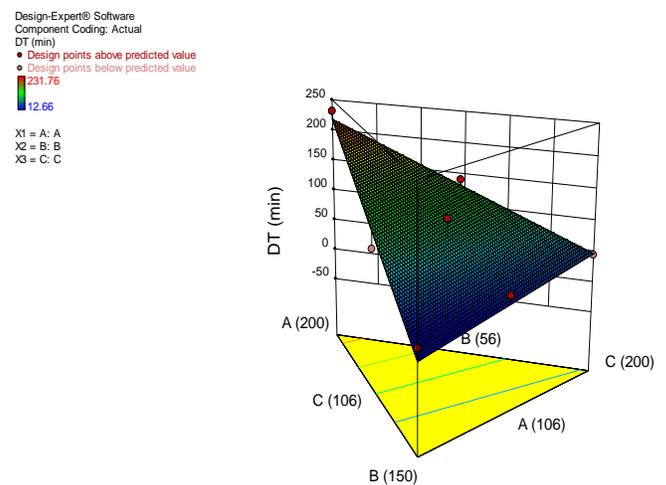
$$Q30 = 53.09A + 71.74B + 41.80C - 77.30AB - 36.12AC - 13.99BC + 529.76ABC \dots\dots 4$$

$$Q60 = 62.48A + 97.86B + 71.4C - 77.16AB - 47.89AC - 2.62BC + 802.69ABC \dots\dots\dots 5$$

In the sequential model sum of squares, the special cubic mixture model was selected as the highest order polynomial with significant additional terms. The very high positive coefficients of the ABC term in equations for Q30 and Q60 clearly show that the combination and interactions of the three DC excipients have a massive positive effect on the amount of drug released at these time points.



a



b

Fig. 3: Response surface contour (a) 3D response surface plots (b) of disintegration time

It was also observed from the equations that dextrose has a high impact on the overall increase in drug release which can still be attributed to its effect on disintegration.

In the contour plot for drug release after 30 min (Fig.5a), the zones around contour line marked 70 (orange portion) and the area between the contour line 70 and contour line marked 60 (yellow-coloured) represents zones where the response is highest while the higher portion of the plane in the 3D response surface (Fig. 5b) represents higher response. These correspond to areas with maximum concentrations of dextrose or relatively substantial quantities of the three. The 3D response surface resembles an

undulating plane with elevated zones signifying higher predicted responses when the DC excipients are mixed at the optimum proportions.

In the contour plot for drug release after 60 min (Fig 6a), the zone around the centre point (orange-coloured) which is higher than the contour line marked 90 represent higher drug release and this is observed in tablet batches 8 and 2, and possibly other batches that contains substantial quantities of the three DC excipients (close to one-third of the maximum transformed concentration of each excipient or with a high dextrose). These optimum zones are expressed as the most elevated parts of the plane in the 3D response surface (Fig. 6b)

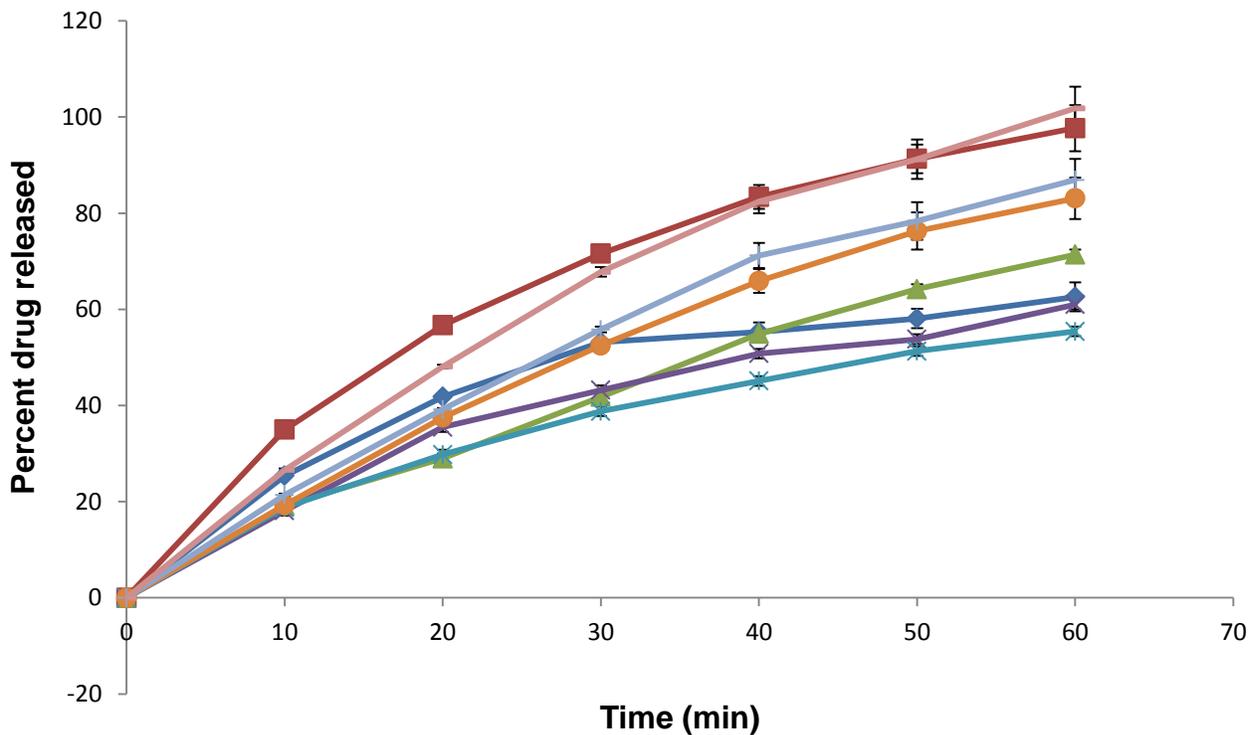


Fig. 4: Drug release profile of hydrochlorothiazide tablets

◆ H1 ■ H2 ▲ H3 ✕ H4 * H5 ● H6 □ H7 ■ H8

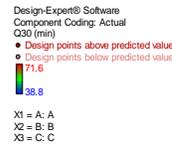
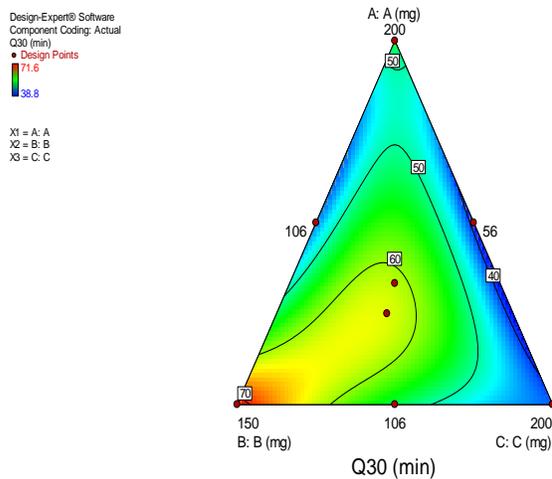


Fig.5: Response surface contour (a) and 3D response surface plots (b) of drug dissolution at Q30

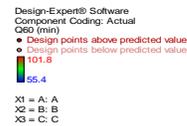
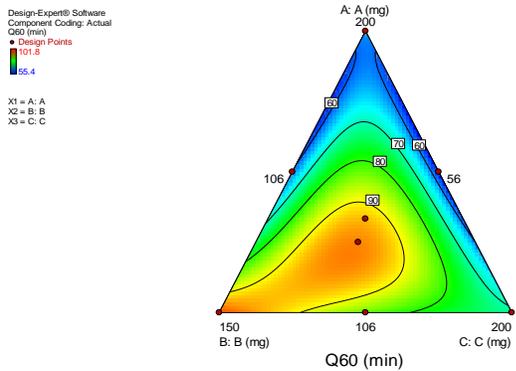


Fig. 6: Response surface contour (a) and 3D response surface plot (b) of drug dissolution at Q60

CONCLUSION

In conclusion, optimization is considered as an efficient and economical method to understand the relationship between independent and dependent variables. This makes it easier to achieve Quality by Design (QbD). Effects of three dependent variables (concentrations of microcrystalline cellulose, dextrose and lactose granules) on response variables were

observed by changing the amounts of the former in a simplex lattice design. Amongst the eight formulated batches, batches 2 and 8 (H_2 and H_8) were selected as the optimized products on the basis of desired outcome using parameters like dissolution, disintegration and friability. Batches 2 and 8 contain MCC (26.5% w/w and 32.4% w/w, respectively), dextrose (37.5% w/w and 23.4% w/w, respectively) and lactose granules (26.5% w/w and 34.7% w/w,

respectively) at appropriate quantities. These batches contain mixtures of the directly compressible excipients in amounts and combinations that produced hydrochlorothiazide tablets of desired qualities. Other optimized tablets can be prepared by choosing combinations of the excipients within the desired zone in the response surface plots or using the equations to achieve Quality by Design (QbD).

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