Original Research Article

Design and optimization of bilayered tablet of Hydrochlorothiazide using the Quality-by-Design approach

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Abstract

Aim: The aim of the present study is to develop an optimize bilayered tablet using Hydrochlorothiazide (HCTZ) as a model drug candidate using quality by design (QbD) approach. **Introduction and Method:**The bilayered tablet gives biphasic drug release through loading dose; prepared using croscarmellose sodium a superdisintegrant and maintenance dose using several viscosity grades of hydrophilic polymers. The fundamental principle of QbD is to demonstrate understanding and control of pharmaceutical processes so as to deliver high quality pharmaceutical products with wide opportunities for continuous improvement. Risk assessment was carried out and subsequently 2^2 factorial designs in duplicate was selected to carry out design of experimentation (DOE) for evaluating the interactions and effects of the design factors on critical quality attribute. The design space was obtained by applying DOE and multivariate analysis, so as to ensure desired disintegration time (DT) and drug release is achieved. Bilayered tablet were evaluated for hardness, thickness, friability, drug content uniformity and *in vitro* drug dissolution. **Result:** Optimized formulation obtained from the design space exhibits DT of around 70 s, while DR $T_{95\%}$ (time required to release 95% of the drug) was about 720 min. Kinetic studies of formulations revealed that erosion is the predominant mechanism for drug release. **Conclusion:** From the obtained results; it was concluded that independent variables have a significant effect over the dependent responses, which can be deduced from half normal plots, pareto charts and surface response graphs. The predicted values matched well with the experimental values and the result demonstrates the feasibility of the design model in the development and optimization of HCTZ bilayered tablet.

Key words: Bilayered tablets, Design of experiment, Design space, Quality-by-design, Surface response plot

INTRODUCTION

Controlled release dosage form is a term used to describe the dosage forms having drug release features based on the time, course and/or location and which are designed to accomplish therapeutic or convenience objectives which are not offered by conventional release dosage forms. However, controlled release dosage form does not provide a rapid onset of action of drug entity. Whereas immediate release drug delivery system is intended to disintegrate rapidly and exhibits instant drug release. However, it is also associated with fluctuations in drug plasma levels, which leads to reduction or loss in drug effectiveness or increased incidence of side-effects. Therefore, to compensate the dip in drug plasma concentration due to metabolism and excretion, it is necessary to administrate the dosage form several times per day. A relatively constant plasma level of a drug is often preferred to maintain the drug concentration within the therapeutic window. However, it is difficult to achieve, especially for once-daily dosage forms. Bilayered tablet is suitable for combination therapy, i.e., for sequential release of two different drugs, separate two incompatible substances and also for sustained release dosage form in which one layer is immediately released as a loading dose and second layer act as a maintenance dose.[1,2]

On the basis of these considerations, the bilayered tablet have been specially developed to provide two different release rates or biphasic release of a drug from a single dosage form in which one layer is formulated to obtain immediate release effect of the drug, with the aim of reaching a high plasma concentration in a short period of time while the second layer is designed as sustained released layer, which provides effective plasma concentration by a maintenance dose of drug for an extended

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period of time. The design of bilayered tablet dosage form holds many advantages over conventional dosage forms such as a reduction in frequency of drug administration, improved patient compliance, reduction in drug level fluctuation in blood and quantitative reduction in total drug usage when compared with conventional therapy.[3-6]

Hydrochlorothiazide (HCTZ) is a first line diuretic drug from the thiazide class and chemically it is 6-chloro-3, 4-dihydro-2H-1, 2, 4-benzothiadiazine-7-sulphonamide 1, 1-dioxide. It is a drug used in the management of hypertension. HCTZ belongs to biopharmaceutics classification system Class IV, thus this poorly soluble and poorly permeable compound leads to high intra- and inter-subject variability and lack of dose proportionality resulting in fluctuation of dosing with conventional dosage form. HCTZ has been reported to produce significant additive effects in mild to moderate hypertension with twice-daily dosing. Thus, there is a need for the development of bilayered tablet to deliver loading dose of the drug so as to achieve desired onset of action, to reduce the frequency of administration and to increase the efficacy of the drug by providing bimodal drug release pattern.[7-9]

The application of quality-by-design (QbD) approach for formulation development has provided an opportunity for a harmonized pharmaceutical quality system based on continuous quality improvement which can yield safer, more efficacious and quality product.[10] QbD implementation requires a thorough understanding of the relationship between the critical quality attributes (CQAs) and the clinical properties of the product, leading to successful product development with predefined quality attributes. The fundamental assumption underlying QbD is that if critical sources of variability can be understood then product performance can be controlled using the manufacturing process to mitigate variability in the material properties. Risk management is a "systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle". It is performed to identify material attributes and process parameters whose variability may influence these potential CQAs. The degree of risk can then be used to prioritize the activities for the process characterization.[11,12] From risk assessment study, high risk parameters will be considered for design of experimentation (DOE) using a suitable model from statistical software tools. By performing the experiments and analyzing data in the selected model; design space is obtained within which product quality can be assured as per the set acceptance criteria.

The present study aims at formulating bilayered tablets of HCTZ which comprises of immediate release layer with croscarmellose sodium; as superdisintegrants, formulated by direct compression techniques while the sustained release layer formulated using several viscosity grades of hydrophilic polymers, which is designed using wet-granulation techniques.

MATERIALS AND METHODS

Materials

HCTZ, croscarmellose sodium, HPMC K4M, HPMC K100M, microcrystalline cellulose (MCC) (pH 101 and pH 102), polyvinyl pyrrolidone (PVP) K30, sprays dried lactose and tartrazine were received as gift samples from Medley Pharmaceuticals (Mumbai, India). All other chemicals were of analytical grades.

Preparation of immediate released layer

HCTZ immediate release tablets were prepared using direct compression method.[13-15] The active ingredient, MCC, lactose and croscarmellose sodium were mixed geometrically. Magnesium stearate and talc were further added as a lubricant to the above dry mix and were mixed well. The colorant tartrazine was then mixed homogenously to get uniform blend without mottling. The whole blend was passed though mesh #40 and was subjected to compression using 8.00 mm flat faced punch on single stroke punching machine to form immediate released tablet.

Preparation of sustained released layer

HCTZ sustained release layer were prepared by wet granulation method.[16-18] The active ingredient, HPMC K4M, HPMC K100M, MCC PH 102 and spray-dried lactose were passed through mesh #40 and were mixed homogenously. PVP K30 (5%) was added as a binder to the above blend and was mixed to get a final coherent mass. Obtained coherent mass was passed through mesh #20 to get desired granules. The granules were primarily air dried and were finally dried at 50°C until a constant Loss on Drying (LOD) reaches 3-4% analyzed by moisture analyzer. The whole blend of dried granules was lubricated and homogenously mixed by magnesium stearate and talc.

Tablet compression

The bilayered tablet compression was made using 8.00 mm flat punch on a 12-station rotary tablet machine. In that, sustained release HCTZ granules were introduced first into the die cavity and a light pre-compression was imparted so that the layer gets uniformly distributed in the die cavity doesn't mix up with the other layer. Further, immediate release layer blend was added above the previously light pre-compressed sustained release layer and final compression was carried out with optimum compression force.[4,14,15]

Calculation of dose for bilayered tablet

The immediate release part of bilayered tablet was calculated using the following equation;[19-21]

$$D_{IR} = C_p \times V_d/F$$

Where Cp is target serum level, V_d is volume of distribution and F is bioavailability factor.

The total dose of HCTZ to deliver a once daily-sustained released formulation was calculated by the following equation using available pharmacokinetic data:

$$D_{SR} = D_{IR}(1 + 0.693 \times t/t_{1/2})$$

where D_{SR} is a total dose of drug for sustained released layer, D_{IR} is dose of the immediate release part; *t* is the time (hours) duration for which the sustained release of the drug is desired and $t_{1/2}$ is half-life of the drug.

Risk assessment of critical attributes

Risk assessment was carried out[22] and it was observed that both types as well as concentration of polymer and superdisintegrants were critical parameters for the formulation of HCTZ bilayered tablet as shown in [Table 1].

Experimental design

With thorough risk assessment of critical material and process attributes and from the results of preliminary batches of bilayered tablets, 2^2 full factorial design in replicate was selected with 8 experiments to carry out for applying DOE as shown in [Tables 2 and 3].[22,23] The independent variables for this study were concentration of superdisintegrants (X_1) and drug:polymers blend (X_2) whereas the dependent variables were disintegration time (DT) (Y_1) and $T_{100\%}$ (Y_2) of bilayered tablet.

Evaluation

Evaluation of granules flow properties

The prepared granules were evaluated for parameters such as bulk density, tap density, compressibility index, Hausner's ratio and angle of repose as per the pharmacopoeial specification.

Evaluation of tablet

Tablets were evaluated for hardness, weight variation, friability and drug content as per pharmacopoeial methods. A total of 20 tablets were triturated and an accurately weighed powder equivalent to 50 mg of HCTZ was dissolved in 10 ml of methanol in a volumetric flask, 70 ml of 6.8 pH phosphate buffer was added into the same volumetric flask and was allowed to sonicate for 10 min and the solution was filtered through 0.45 μm membrane filter (Millipore millex-HN, Nylon 0.45 μm), then the final volume was adjusted with 6.8 phosphate-buffered saline, i.e., up to 100 ml. The absorbance was measured in triplicate using ultraviolet (UV)-visible spectrophotometer at 272 nm after suitable dilution. All results were represented as a mean ± standard deviation (SD).

In vitro *dissolution study*

In vitro dissolution studies were carried out using USP dissolution test apparatus I (basket) at 100 rpm, 37 ± 0.5°C.[24,25] The dissolution medium was simulated gastric fluid (900 ml) adjusted to pH 1.2 with HCl for initial 2 h and later it replaced with pH 6.8 phosphate buffer (900 ml) and dissolution continued for another 10 h. At different time intervals, samples were withdrawn and filtered using 0.45 μm membrane filter (Millipore millex-HN, Nylon 0.45 μm) and was further analyzed by UV spectrophotometer at 272 nm. The release studies were conducted in triplicate for each batch and the mean values versus time with SD was plotted.

Characterization of the drug release profile

The rate and mechanism of release of HCTZ from prepared bilayered tablets were analyzed by fitting the dissolution data into following exponential equations.[9,26]

Zero order release equation:

$$Q = K_0 t$$

Where Q is the amount of drug released at time t and K_0 is the zero order release rate constant.

The first order equation:

$$\ln(100 - Q) = \ln 100 - K_1 t$$

Where, K_1 is the first order release rate constant.

The dissolution data was fitted to the Higuchi's equation:

$$Q = K_2 t_{1/2}$$

Where, K_2 is the diffusion rate constant.

The dissolution data was also fitted to the Korsmeyer-Peppas equation, which is often used to describe the drug release behavior from polymeric systems:

$$\text{Log}(Mt/M_\infty) = \log K + n \log t$$

Where Mt is the amount of drug released at time *t*, M_∞ is the amount of drug release after infinite time, K is a release rate constant and n is the diffusion exponent indicative of the mechanism of drug release.

Table 1: Risk assessment parameters to identify variables affecting product quality

Drug product CQAs	Type of superdisintegrants	Type of polymer	Drug:superdisintegrants ratio	Drug:polymer ratio	Ratio of different polymer blend	Compression force
Disintegration/dissolution	High	High	High	High	High	High
Drug release	High	High	High	High	High	High
Hardness	Medium	Medium	Medium	Medium	Medium	High

CQAs: Critical quality attributes

For matrix tablets, if the exponent $n < 0.5$, then the drug release mechanism is quasi-fickian diffusion (If $n = 0.5$ then fickian diffusion and if the value is $0.5 < n < 1$, then it is anomalous diffusion coupled with erosion. An exponent value of 1 is indicative of Case-II Transport or typical zero-order and $n > 1$ non-fickian super Case II). The diffusion exponent was based on Korsmeyer-Peppas equation.[9,26,27]

Table 2: Experimental design of HCTZ bilayered tablet as per 2^2 factorial designs

Formulation code	X_1 (concentration of superdisintegrants)	X_2 (drug:polymers blend ratio)
A-1	−1 (6)	−1 (38:15)
A-2	−1 (6)	−1 (38:15)
A-3	−1 (6)	1 (38:20)
A-4	−1 (6)	1 (38:20)
A-5	1 (10)	−1 (38:15)
A-6	1 (10)	−1 (38:15)
A-7	1 (10)	1 (38:20)
A-8	1 (10)	1 (38:20)

HCTZ: Hydrochlorothiazide

Table 3: Formulation design of HCTZ bilayered tablet as per design 2^2 layout

Ingredients (mg/tab)	A1	A2	A3	A4	A5	A6	A7	A8
Immediate released layer								
HCTZ	12	12	12	12	12	12	12	12
Croscarmellose sodium	6	6	6	6	10	10	10	10
MCC	43	43	43	43	41	41	41	41
Lactose	32	32	32	32	30	30	30	30
Tartrazine	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Talc	3	3	3	3	3	3	3	3
Magnesium stearate	3.8	3.8	3.8	3.8	3.8	3.8	3.8	3.8
Sustained released layer								
HCTZ	38	38	38	38	38	38	38	38
HPMC K4M	7.5	7.5	10	10	7.5	7.5	10	10
HPMC K4100M	7.5	7.5	10	10	7.5	7.5	10	10
MCC (pH 102)	56	56	54	54	56	56	54	54
Lactose	56	56	53	53	56	56	53	53
5% PVP K30	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Talc	5	5	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5	5	5
Total weight of tablet	275	275	275	275	275	275	275	275

HCTZ: Hydrochlorothiazide, HPMC: Hydroxypropyl methylcellulose, PVP: Polyvinyl pyrrolidone, MCC: Microcrystalline cellulose

RESULT AND DISCUSSION

Evaluation of granules

The granules for different formulations of bilayered tablet were evaluated for their physical properties. The bulk and tapped density for prepared granules ranged between 0.40-0.48 g/cm^3 and 0.44-0.54 g/cm^3 respectively as determined by the tap method, indicates good packing characteristics. The Carr's index and Hausner's ratio were ranged from 5.11-12.16% to 1.07-1.14% respectively indicating good flow property.[28] The flow properties of granules were further analyzed by determining the angle of repose and it ranged between 28.47° and 34.16° respectively. The value indicates a good flow property of granules with HPMC K4M and K100M.[28]

Physical properties of bilayered tablet

All the batches of bilayered tablets were produced under similar conditions to avoid processing variables. The drug content, weight variation, hardness, thickness and friability of all formulations were found within acceptable limits as per official specifications shown in [Table 4]. All batches passes standard weight variation (90-110%) and drug content uniformity (90-110%)[29] and the observed percentage friability of all batches were less than 1.0%. Values of the hardness test and percent friability indicates that the prepared bilayered tablet have good handling properties.[28-30]

DT

DT for all formulation was observed to be less than 2 min, whereas it decreased with an increase in the concentration of superdisintegrant.

In vitro dissolution study

The release profile of HCTZ bilayered tablets were analyzed by plotting the cumulative percentage drug release versus time as shown in [Figure 1]. *In vitro* study revealed initial burst release up to 30% from the immediate release layer of bilayered tablet; further study was carried out for 12 h to determine release profile of sustained release layer. Drug release from sustained release layer was mainly dependent on polymer concentration. T_{100}% was obtained in 9 h for

Table 4: Post compression parameters of bilayered tablet

Formulation code	Drug content (%)*	Weight variation (mg)**	Hardness (kg/cm^2)***	Thickness (mm)***	Friability (%)*
A1	97.52±2.32	174.61±1.80	8.78±0.056	4.08±0.025	0.532±0.071
A2	101.85±1.26	170.98±1.94	8.81±0.079	4.06±0.068	0.545±0.030
A3	96.15±2.10	171.24±1.26	8.70±0.012	4.08±0.051	0.493±0.060
A4	98.78±1.88	172.12±2.04	8.56±0.046	4.10±0.032	0.470±0.055
A5	103.05±1.49	178.06±2.10	8.50±0.015	4.11±0.025	0.552±0.051
A6	99.25±2.06	174.45±1.05	8.85±0.025	4.07±0.068	0.539±0.012
A7	95.48±1.70	175.26±1.45	8.50±0.134	4.11±0.028	0.501±0.025
A8	98.27±3.04	173.89±0.09	8.65±0.064	4.10±0.048	0.495±0.019

*n = 20, **n = 10, ***n = 6

formulation containing low level of polymer blend. Drug release was retarded up to 12 h with an increase in concentration of polymer blend of HPMC K4M and HPMC K 100M.

Drug release kinetics

The kinetics of drug release from bilayered sustained released tablets was determined based on equation obtained by *in vitro* dissolution data to various kinetics models and by the value of '*n*' i.e., release exponent. The *n* value is used to interpret the release mechanism. The kinetic data obtained for all formulations of bilayered tablets are shown in [Table 5]. According to the results of different kinetic models, the R^2 value of Korsmeyer-Peppas model was close to 1 and *n* value was found to be within 0.8530-0.9638. Hence, the release kinetics best fits to Korsmeyer-Peppas model and the mechanism of drug release was regarded as anomalous diffusion of drug from matrix.[9,27]

Statistical design and analysis

The 2^2 design in replicate mode with '8-runs' was used in the present study to evaluate the main effects of two independent variables selected as high risk parameters, which affects product quality from the risk assessment analysis study. The 2^2 design application considerably reduces the number of experiments that are required to evaluate the main effects.[23,31]

Effect on DT

Polynomial equation 1 depicts significant effects of X_1 and X_2 on DT. The negative value for the coefficient, X_1 in the equation 1 indicates decrease in the DT for immediate release layer of bilayered tablet with an increase in the concentration superdisintegrants. While the positive value of the coefficient of X_2 indicates an increase in the response of Y_1. The relationships between variables were further elicited using half-normal plots/ pareto charts as shown in [Figures 2 and 3]. In half-normal plot, large effects (absolute values) appear in the upper-right section of the plot, i.e., concentrations of superdisintegrants have more significant effect on DT as compared to polymer blend. In pareto chart, effects above the Bonferroni limit are almost certainly significant, i.e., X_1, while effects above the T-value limit are possibly significant, i.e., X_2. The two levels of independent variables indicate the linearity in surface response shown in [Figure 4]. This indicates, as the concentration of superdisintegrants increases the DT for immediate released layer decreases, the similar results were reported by Karwa and Kasture[19] This is because the increase in the concentration of superdisintegrants absorbs the more dissolution medium and disintegrates rapidly.

$$Y_1 = 68.63 - 7.63\ X_1 + 2.62\ X_2 + 0.38\ X_1X_2 \quad (1)$$

The calculated *F* value, *P* value and Student *t* value for response Y_1 and Y_2 as shown in [Tables 6 and 7] respectively for main response and individual terms of equation, indicates a significant effect of the two factors on the response Y_1 (DT) and Y_2 (DR T_{100}%).

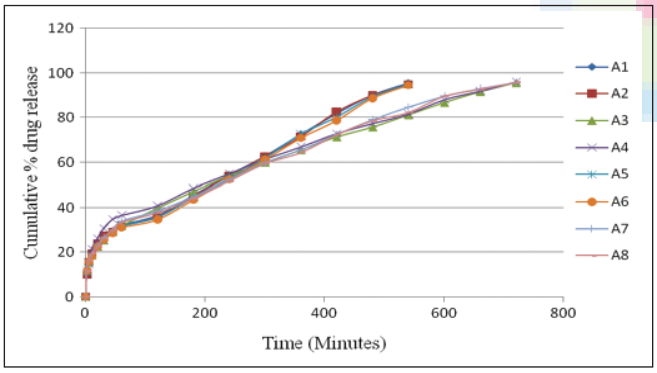

Figure 1: *In vitro* drug dissolution profile of bilayered tablet in 0.1N HCL and 6.8 pH phosphate-buffered saline medium

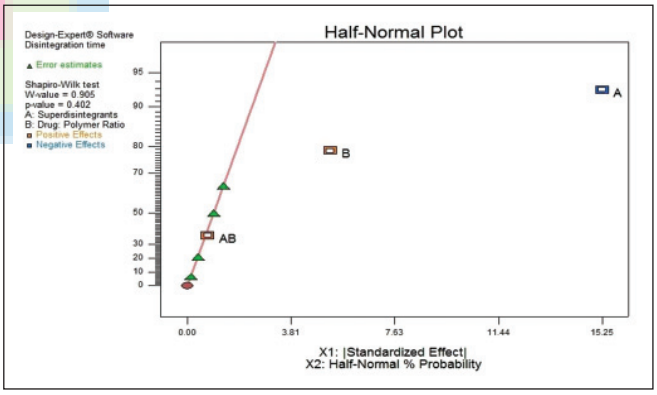

Figure 2: Half-normal plot of the formulation variables affecting on disintegration time

Table 5: Model fitting data of HCTZ sustained released tablet for drug release kinetics

Formulation code	*R*					*n*	*k*
	Zero order	First order	Matrix	Peppas	Hixon-crowel		
A1	0.946	0.971	0.960	0.985	0.965	0.8687	9.8701
A2	0.941	0.969	0.962	0.983	0.962	0.8530	10.1685
A3	0.993	0.996	0.958	0.999	0.997	0.8681	7.6802
A4	0.993	0.996	0.959	0.998	0.996	0.8570	7.8502
A5	0.950	0.974	0.959	0.985	0.969	0.8863	9.6194
A6	0.953	0.976	0.960	0.987	0.972	0.8837	9.7590
A7	0.991	0.995	0.952	0.998	0.996	0.9638	6.8808
A8	0.992	0.997	0.952	0.998	0.995	0.9589	6.9935

HCTZ: Hydrochlorothiazide

Effect on T_{100}% (time required for total drug release)

Polynomial equation 2 reveals significant effects of independent variables on response T_{100}%. In the case of response Y_2, the X_1 coefficient was negative while the X_2 was positive according to equation 2. Theoretically it means that, as the concentration of superdisintegrants increases the dissolution time decreases. While the drug:polymers blend (X_2) increases to high level (+1), T_{100}% increases up to 12 h as compared to low level of (−1), which was also observed in earlier preliminary batches of sustained released formulation and also reported by Atram[30] In half-normal plots for DR T_{100}%, it was confirmed that drug:polymers blend has a large effect as compared to concentration of superdisintegrants as shown in [Figure 5].

$$Y_2 = 645 - 15.0\ X_1 + 75.0\ X_2 \quad (2)$$

In pareto chart [Figure 6], effect above the Bonferroni limit, i.e., drug:polymer blend is certainly significant, while the effect below the T-value limit, concentration of superdisintegrants is possibly significant. The effect of two independent variables was found to be linear in surface response of DR T_{100}% [Figure 7]. Decrease in drug release was due to the matrix and integrity of matrix of hydrophilic polymer. The increased viscosity of layer controls the penetration of medium through gel layer and hence the drug diffusion and dissolution was controlled. As the concentration of hydrophilic polymer increases the strength and viscosity of the gel layer formed by polymer also increases and hence the matrix of tablet maintains their integrity for a long period of time depending on concentration of polymer and the ultimately drug release was sustained.

Establishing design space and control strategy

The design space within the QbD-approach represents the whole range of interactions between critical material and process parameters and their effects on CQAs that has been examined during process characterization studies to provide assurance on drug product quality.[22,23]

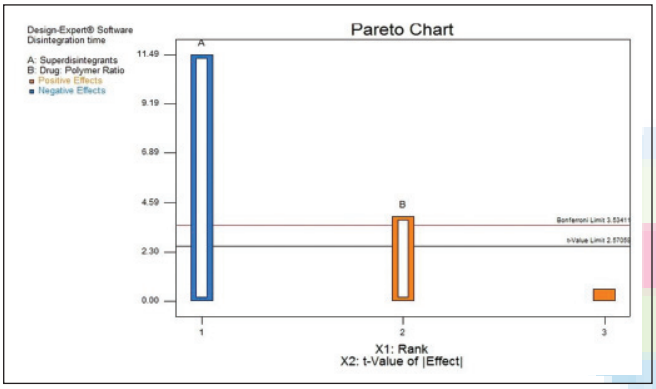

Figure 3: Pareto chart for the formulation variables affecting on disintegration time with Bonferroni limit

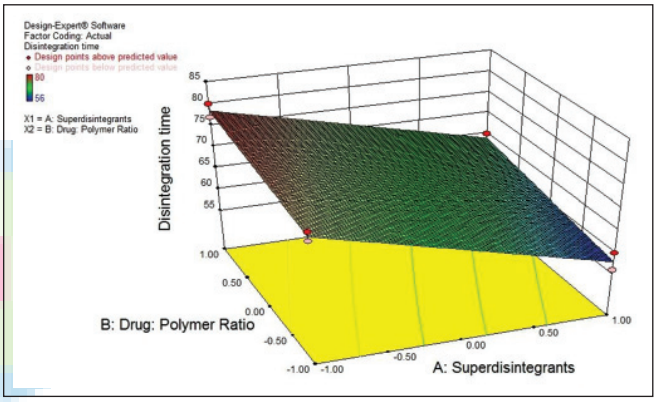

Figure 4: Surface response plot (3D) demonstrating influence of concentration of superdisintegrants and drug:total polymer ratio on the $T_{100\%}$

Table 6: Analysis of variance for DT

Source	Sum of squares	Degree of freedom	Mean square	*F* value	*P* > *F*	Comments
Model	521.38	3	173.79	42.13	0.0017	Significant
A-Superdisintegrants	465.13	1	465.13	112.76	0.0004	Significant
B-Drug:polymer ratio7	55.12	1	55.12	13.36	0.0217	Significant
AB	1.13	1	1.13	0.27	0.6291	Not significant
Pure error	16.5	4	4.12			
Core total	537.88	7				

DT: Disintegration-time

Table 7: Analysis of variance for time required for total drug release (T100%)

Source	Sum of squares	Degree of freedom	Mean square	*F* value	*P* > *F*	Comments
Model	46800	2	23400	65	0.0003	Significant
A-Superdisintegrants	1800	1	1800	5	0.0756	Significant
B-Drug:polymer ratio	45000	1	45000	125	<0.0001	Significant
Residual	1800	5	360			
Lack of fit	1800	1	1800			
Pure error	0	4	0			
Core total	48600	7				

During the process and formulation variable characterization study, the impact of the input parameters such as concentration of superdisintegrants and drug-to-total polymer ratio on DT of immediate released layer and time for total drug release ($T_{100\%}$) for sustained released layer were assessed. The criteria considered for responses of DT and $T_{100\%}$ for design space was less than 180 s and 720 min respectively. This study provide the knowledge space and ultimately design space from multidimensional combination of concentration of superdisintegrants and drug-to-total polymer ratio and thus gives the acceptable operating ranges. The variables ranked as high risk in the initial risk assessment and needed to be controlled in their acceptable ranges were included in the control strategy. The design space shown in [Figure 8], it also called as overlay plot. The shaded region with dark yellow color indicates the region of successful operating ranges.

Validation of optimized formulations

From the polynomial equations generated for each responses using Design Expert software (8.0.4) (by Stat-Ease Inc.), intensive grid and integrated search was performed over the experimental domain and three optimized formulations were selected (B1-B3). The composition of the checkpoints, the predicted and experimental values of all the response variables (DT and $T1_{00\%}$) and the percentage error in prognosis were as shown in [Table 8]. According to the statistical equivalence percentage standard error for experimental data and predicted values, it was demonstrating the validity of the applied model.

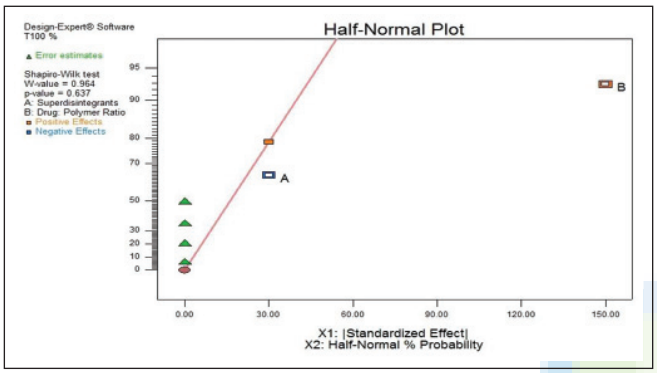

Figure 5: Half-normal plot of the formulation variables affecting on $T_{100\%}$

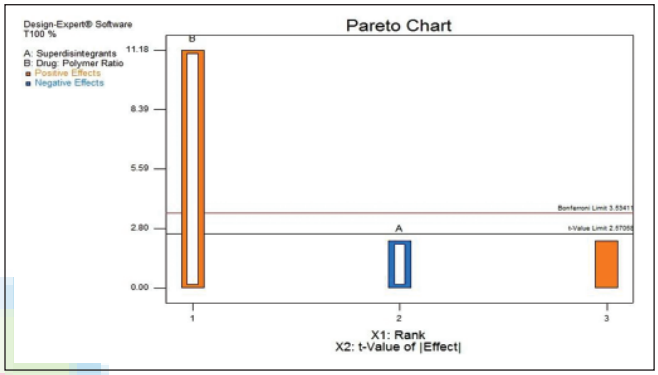

Figure 6: Pareto chart for the formulation variables affecting on $T_{100\%}$ with Bonferroni limit

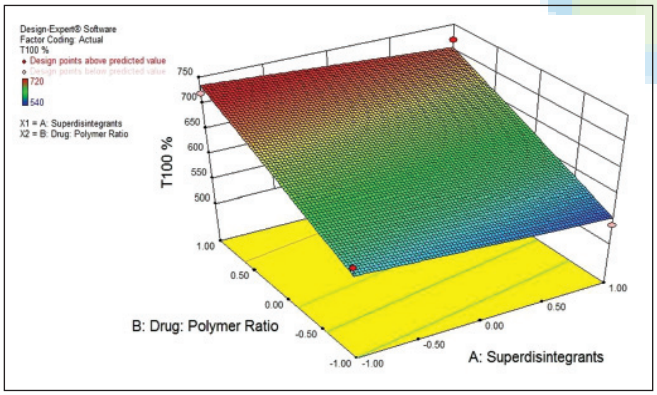

Figure 7: Surface response plot (3D) demonstrating influence of concentration of superdisintegrants and drug:total polymer ratio on the $T_{100\%}$

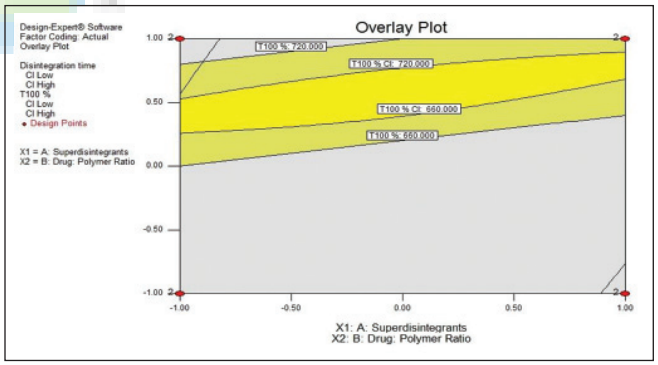

Figure 8: Design space (overlay plot) for bilayered tablet for validation of optimized formulations

Table 8: Comparison of experimental results with predicted responses of optimized formulations

Formulation code	Composition (mg/tab)		Response	Predicted value	Experimental value	Standard error
	X1	X2				
B1	8.45	19.45	Y1 (DT) (s)	69.08	70	−1.33179
			Y2 (T100%) (min)	701	710	−1.28388
B2	8.75	18.77	Y1 (DT) (s)	66.4	65	2.108434
			Y2 (T100%) (min)	679.33	660	2.845451
B3	7.45	19.25	Y1 (DT) (s)	71.99	70	2.764273
			Y2 (T100%) (min)	702.06	700	0.293422

DT: Disintegration-time, T100%: Time required for total drug release

CONCLUSION

This work has demonstrated the successful implementation of QbD approach, 2^2 factorial design, polynomial equations and surface response plot in optimizing formulation variables of HCTZ bilayered tablets. Risk assessment was carried out for various process and formulation variables for their effect on DT of immediate released layer and time required for total drug release ($T_{100\%}$) from the matrix of sustained release layer of bilayered tablets. High risk variables were selected for applying DOE. 2^2 factorial design was used, with concentration of superdisintegrants (X_1) and drug:total polymer ratio (X_2) as independent variables and DT (Y_1) and time required for drug release from matrix (Y_2) as responses. The bilayered tablets shows an initial burst release to achieve loading dose of the drug, followed by sustained release for 12 h, indicating a promising potential of the HCTZ bilayered tablet as an alternative to the conventional dosage form. The predicted and experimental values of all the response variables form validation batch according to design were correlated and the percentage error in prognosis was determined. These correlation plots demonstrated higher values of R^2, indicating excellent fitting of model. Here, implementing and using statistical tools renders robust formulation and also help in optimizing variables, this leads to structuring a sensitive yet well-controlled, formulation to deliver drug for biphasic drug delivery. It can be concluded that QbD principles and tools play an important role in facilitating a higher-level of process understanding and create opportunities for root-of-cause investigation and developing control strategies in the formulation and process development.

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