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}%).

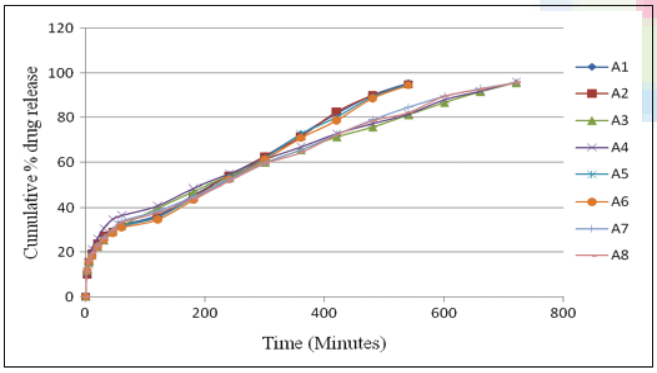

Figure 1: *In vitro* drug dissolution profile of bilayered tablet in 0.1N HCL and 6.8 pH phosphate-buffered saline medium

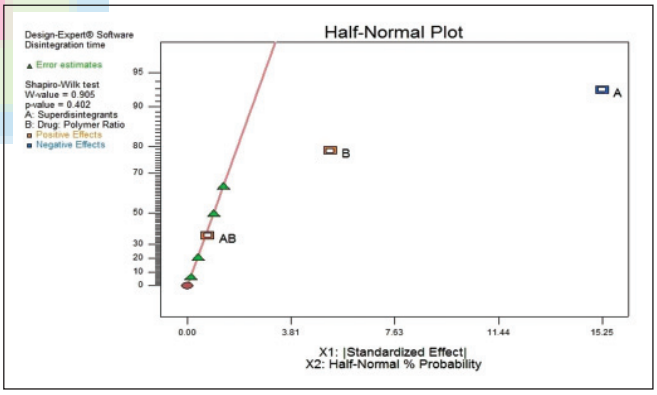

Figure 2: Half-normal plot of the formulation variables affecting on disintegration time

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]

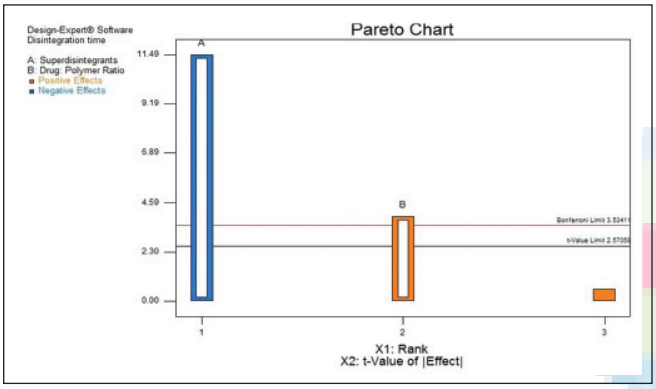

Figure 3: Pareto chart for the formulation variables affecting on disintegration time with Bonferroni limit

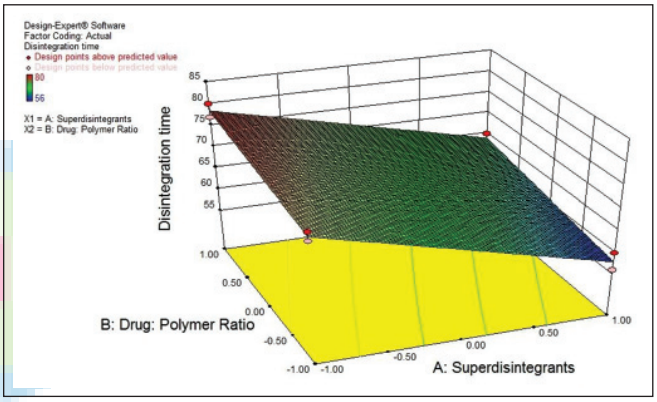

Figure 4: Surface response plot (3D) demonstrating influence of concentration of superdisintegrants and drug:total polymer ratio on the $T_{100\%}$

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.

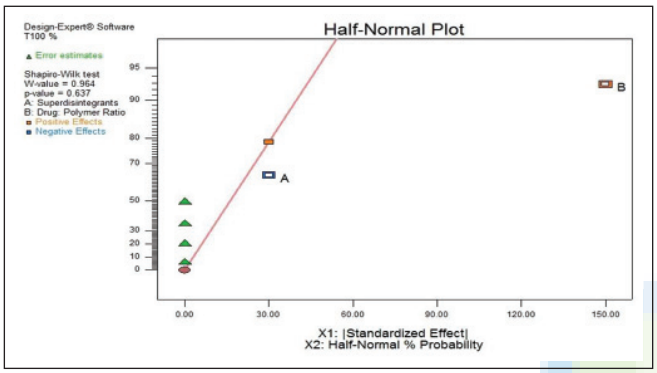

Figure 5: Half-normal plot of the formulation variables affecting on $T_{100\%}$

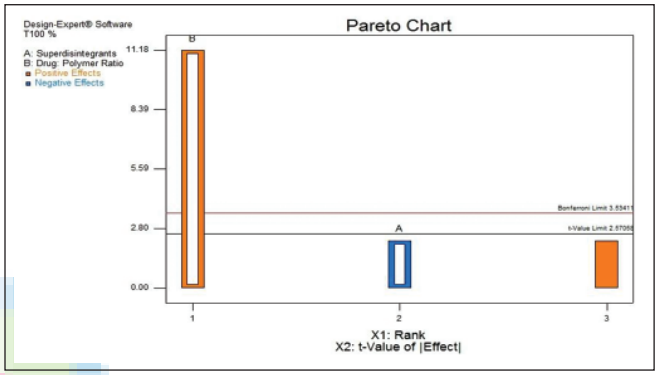

Figure 6: Pareto chart for the formulation variables affecting on $T_{100\%}$ with Bonferroni limit

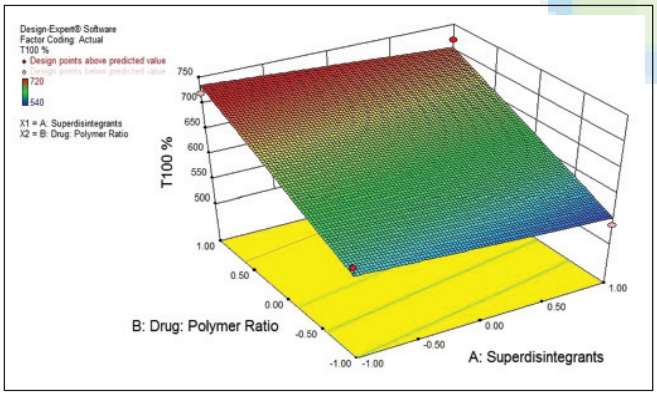

Figure 7: Surface response plot (3D) demonstrating influence of concentration of superdisintegrants and drug:total polymer ratio on the $T_{100\%}$

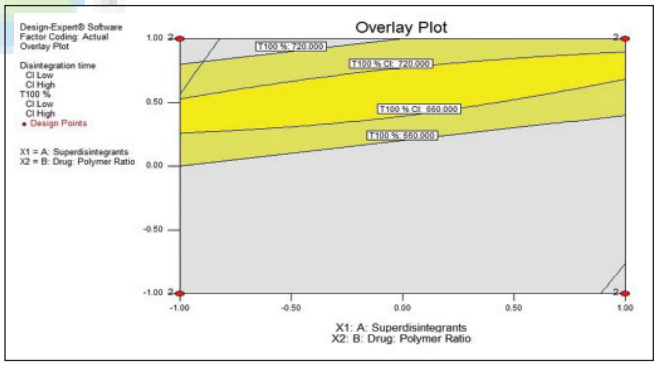

Figure 8: Design space (overlay plot) for bilayered tablet for validation of optimized formulations

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.

REFERENCES

1. Aulton ME. Aulton's Pharmaceutics: The Design and Manufacture of Medicines. 2nd ed. London Churchill Livingstone; 2002. p. 397-441.
2. Sanghavi S, Polara M, Patel J, Shah N. Bilayer tablets — A review on state of art. Res J Pharm Dosage Forms Tech 2012;04:160-6.
3. Despande RD, Gowda DV. Bilayer tablets-An emerging trend: A review. Int J Pharm Sci 2011;2:2534-44.
4. Remya PN, Damodharan N. Formulation and evaluation of bilayered tablets of Ibuprofen and methocarbamol. Int J PharmTech Res 2010;2:1250-5.
5. Karthikeyan D, Karthikeyan M. Effect of different viscosity grades of HPMC on drug Release profile. J Pharm Res 2008;1:23-8.
6. Enayatifard R, Saeedi M, Akbari J, Tabatabaee YH. Effect of hydroxypropyl methylcellulose and ethyl cellulose content on release profile and kinetics of diltiazem HCl from matrices. Trop J Pharm Res 2009;8:425-32.
7. Phillips SJ, Whisnant JP. Hypertension and stroke. In: Laragh JH, Brenner BM, editors. Hypertension: Pathophysiology, Diagnosis, and Management. 2nd ed. New York: Raven Press; 1995. p. 465-78.
8. Florey K. Analytical Profiles of Drug Substances. 1st ed. Vol. 10. Philadelphia: Academic Press, An Imprint of Elsevier; 2005. p. 405-43.
9. Brazel CS, Peppas NA. Mechanisms of solute and drug transport in relaxing, swellable, hydrophilic glassy polymers. Polymer 1999;40:3383-98.
10. ICH Q8: Pharmaceutical Development. Fed Reg 2006;71: 07-16. Available from: http://www.ich.org/LOB/media/MEDIA4986.pdf. Accessed on 17-02-2013.
11. ICH Q9: Quality Risk Management. Fed Reg 2006;71:32105-6. Available from: http://www.ich.org/LOB/media/MEDIA1957.pdf. Accessed on 17-02-2013.
12. Wu H, Tawakkul M, White M, Khan MA. Quality-by-design (QbD): An integrated multivariate approach for the component quantification in powder blends. Int J Pharm 2009;372:39-48.
13. Vaithiyalingam SR, Sayeed VA. Critical factors in manufacturing multi-layer tablets — Assessing material attributes, in-process controls, manufacturing process and product performance. Int J Pharm 2010;398:9-13.
14. Patel M, Sockan GN, Mani T. Challenges in the formulation of bilayered tablets: A review. Int J Pharma Res Dev 2010;2:30-42.
15. Shiyani B, Gattani S, Surana S. Formulation and evaluation of bi-layer tablet of metoclopramide hydrochloride and ibuprofen. AAPS PharmSciTech 2008;9:818-27.
16. Rao NG, Yadav A. Formulation and evaluation of zero order release glipizide bilayer matrix tablets using natural and synthetic polymers. Int J Curr Pharm Res 2010;2:34-42.
17. Podczeck F, Al-Muti E. The tensile strength of bilayered tablets made from different grades of microcrystalline cellulose. Eur J Pharm Sci 2010;41:483-8.
18. Ghimire M, Hodges LA, Band J, O'Mahony B, McInnes FJ, Mullen AB, *et al*. *In-vitro* and *in-vivo* erosion profiles of hydroxypropylmethylcellulose (HPMC) matrix tablets. J Control Release 2010;147:70-5.
19. Karwa P, Kasture PV. Formulation and *in vitro* evaluation of bilayer tablets of zolpidem tartrate for biphasic drug release. Int J PharmTech Res 2011;3:1919-29.
20. Reddy S, Panakanti P, Kandagalta R, Rao YM. Formulation and release characteristics of bilayer matrix tablet containing glimepride immediate release component and metformine hydrochloride as sustained release component. Int J Pharm Sci Nanotechnol 2010;3:851-9.
21. Patel RN, Bharadia PD. Formulation and evaluation of dual component tablets of metoprolol tartrate. Int J Pharm Chem Sci 2012;1:514-22.
22. Shivhare M, Graham MC. Practical considerations for DoE implementation in quality by design. Bioprocess 2010;6:22-30.
23. Shirsat AE, Deshkar S, Shirolkar S, Gatade V, Bhalerao A. Formulation and optimization of budesonide microspheres for site specific delivery by using 3^2 factorial designs. Acta Pharm Sci 2011;53:269-81.
24. Hapse SA, Wagh VS, Kadaskar PT, Dokhe MD, Shirsath AS. Spectrophotometric estimation and validation of hydrochlorothiazide in tablet dosage forms by using different solvents. Scholars Research Library, Der Pharmacia Lettre 2012;4:10-4.
25. Chaudhary AB, Patel RK, Chaudhary SA, Gadhvi KV. Estimation of valsartan and hydrochlorothiazide in pharmaceutical dosage forms by absorption ratio method. Int J Appl Biol Pharm Technol 2010;1:455-64.
26. Tativaka R, Subhakar M, Kumar AP. Development and *in vitro* dissolution studies of bilayer tablet of metoprolol succinate and hydrochlorothiazide. Int Res J Pharm Appl Sci 2012;2:5-15.
27. Brahmankar DM, Jaiswal SB. Biopharmaceutics and Pharmacokinetics — A Treatise. 2nd ed. Delhi: Vallabh Prakashan; 2009. p. 431-3.
28. US Pharmacopoeia-34, National formulary-29. Vol. 1, 2. Rockville: The United states Pharmacopoial Convention; 2011. p. 278-85, 403-4, 1240-3.

29. The Indian Pharmacopoeia. 4th ed. Vol. 2. Delhi: The Controller of Publication, Ministry of Health and Family Wealth Fare, Govt. of India; 1996. p. A82-5.
30. Atram SC. Formulation of bilayer tablet containing metoprolol succinate and amlodipine besylate as a model drug for antihypertensive therapy. J Pharm Res 2009;2:1335-47.
31. Kikuchi S, Takayama K. Multivariate statistical approach to optimizing sustained-release tablet formulations containing diltiazem hydrochloride as a model highly water-soluble drug. Int J Pharm 2010;386:149-55.

How to cite this article: Dholariya YN, Bansod YB, Vora RM, Mittal SS, Shirsat AE, Bhingare CL. Design and optimization of bilayered tablet of Hydrochlorothiazide using the Quality-by-Design approach. Int J Pharma Investig 2014;4:93-101.
Source of Support: R & D Department, Medley Pharmaceuticals Ltd., Andheri (E), Mumbai-400093. **Conflict of Interest:** No.