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IMPLEMENTATION OF QUALITY BY DESIGN STUDY ON ANALYTICAL METHOD DEVELOPMENT AND VALIDATION OF TENELIGLIPTINE HYDROBROMIDE

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ABSTRACT

Quality by Design (QbD) is a philosophy that refines the level of knowledge associated with a product that uses process understanding to deliver a product with the desired critical quality attributes. The variables are studied using the design expert software version 10. The objective of this study was to develop an integrated multivariate QbD approach to develop and quantify the constituent concentrations of teneligliptin hydrobromide (TNG) drug in its pure and formulated forms. To facilitate studies investigating the determination of TNG in pure drug and its pharmaceutical formulations, a HPLC method was developed and validated for the determination of TNG. The method fulfilled validation criteria and was shown to be sensitive, with limits of detection (LOD) and quantitation (LOQ) of 0.956 ug/ml and 0.171 ug/ml, respectively. The percentage standard deviation for repeatability, intraday and interday precision was observed is 1.83,1.08 and 1.64. The calibration graph was linear in the range of 10 -50 ul/ml at 247nm. The proposed method can be used for routine analysis in quality control laboratories for its bulk and formulated product and this is the first reported HPLC method for the assay of TNG.

Keywords *– QbD, Validation, HPLC, Teneligliptin hydrobromide*

1. INTRODUCTION

The need of validation of an analytical or bioanalytical method is encountered by analysts in the pharmaceutical industry on an almost daily basis, as adequately validated methods are a necessity for approvable regulatory filings.[1,2]

Quality by Design is defined as "a systematic approach to development that begins with predefined objectives and emphasized product and process understanding and process control, based on sound science and quality risk management. The analytical quality by design for a drug and related substances is describe by the concept of ICH Q-8 to Q-11 guidelines which include Pharmaceutical Development, Quality Risk Management, and Pharmaceutical Quality system. The Box– Behnken design, surface response methodologies, and central composite design are mostly used for QbD. The robustness and ruggedness should be verified early in the method development stage of HPLC. For the method development the sequence generally recommended is[3-7]

a. Understanding of the purpose of study.

b. Perform risk assessments to screen out factors that may have an influence on the analytical method.

c. Characterization studies for quantification and minimizing its effect on precision, accuracy, and linearity.

For the recognition of ATP, selection of method is requiring which include type of analytical technique, and specifications of the product, target analytes (product and impurities) ATP for analytical procedures comprises of [8-12]

a. selection of target analytes (API and impurities).

b. conglomeration of analytical techniques like HPTLC, HPLC, GC, ion chromatography, and chiral HPLC.

c. choice of method requirements.

The basic principle behind operating HPLC is the separation of sample into the constituent's parts because of difference in the affinities of deferent molecule for the mobile phase and stationary phase used in the separation.

1.1 Implementation of QbD [13-17]

a. Defining method intent

As the process emphases on the product development and process understanding and control the goals of the method development must be clearly defined, the goal of the analytical method is to separate and quantify the main compound.

b. Performing experimental design.

It is necessary to consider systematic experimental design for obtaining profound method understanding and optimization. It forms a database which helps for method understanding, optimization and selection.

c. Evaluation of experimental results and selection of final method conditions.

The method is evaluated using the three tired approach. At first the condition should be evaluated for peak symmetry, peak fronting, and peak tailing.

d. Performing risk assessment with robustness and ruggedness evaluation.

This method is for method verification and finalization and evaluation of method ruggedness and robustness to be carried out.

2. MATERIALS AND METHODS

A pharmaceutical grade TNG as a dry powder was kindly supplied as a gift sample by Wockhardt limited, Aurangabad. Solvents methanol and water were of HPLC grade and purchased from Loba Pvt. Ltd. Mumbai. India. The tablet formulation was purchased from local market containing 20mg of the drug which is used for the analysis. UV spectrophotometer of Shimadzu Corporation, Japan and HPLC was from Analytical technological ltd binary gradient system. UV-3000-M detector was used with P-3000-M Reciprocating. Column used was grace C18(250mm × 4.6ID,Particle size 5micron) and Injection volume 20ul was used .In addition, Adventure Pro AVG264C (0.0001 gm to 260 gm) digital balance, Systonic S901 digital Ph meter and Toshcon ultrasonic Cleaner Sonicator of Toshniwal Instruments Mfg. Pvt. Ltd, India were used for analysis.

2.1 Preparation of working stock solution

1ml of standard stock solution (100 ug/ml) of teneligliptin was transferred in10ml of volumetric flask. The volume was made up to mark with mobile phase. This mixture contained 10ug/ml. The solution was further diluted with the mobile phase to get the concentration of (10ug/ml-50ug/ml) for the studies of various parameters.

2.2 Preparation of sample solution

Ten tablets of (ziten, Glenmark pharmaceuticals) each contain 20mg of teneligliptin were weighted. Accurately weighted 10mg of tablet equivalent to 93mg was transferred into a 10ml of volumetric flask containing 5 ml of methanol and sonicated. The volume was made up to the mark with methanol which gives the concentration of 1000ug/ml.

2.3 Box Behnken Designs of DOE

The three variables and the three factors randomized response surface determined with the Box-behnken design. To study the impact of these factors 17 trial runs were taken. In this design 3 factors were evaluated, each at 3 levels, and experimental trials were performed at all 3 possible combinations. The flow rates (X1), pH (X2), mobile phase concentration (X3) were selected as independent variables and retention time (RT) and Tailing factor were selected as dependent variables. The resulting data were fitted into Design Expert 10 software and analyzed statistically using analysis of variance (ANOVA). The data were also subjected to 3-D response surface methodology to determine the influence of flow rate, pH, mobile phase composition on dependent variables. The probable trial runs using 3^3Box-Behnkendesigns.

2.4 Validation of chromatographic method

From the designed expert the selected developed combination of the method was validated according to the ICH guidelines using following parameters.

2.5 Linearity and range

Linearity of the method was checked by analyzing standard solutions containing different concentration of teneligliptin of 10ug/ml,20ug/ml,30ug/ml,40ug/ml and 50ug/ml respectively. Prepared in mobile phase. Calibration graph were plotted using peak areas of standard drugs Vs concentration. Results were subjected to the regression analysis.

2.6 Precision

The precision of the method was checked by carrying out repeatability, intraday and interday precision. To check the repeatability of the method, standard solution of concentration 10ug/ml of TNG was injected 6 times and %RSD was calculated. Intraday and interday precision was carried out by analyzing 10ug/ml of sample on the same day and different days.

2.7 Accuracy

Recovery studies was carried out by addition of standard drug to pre-analysed sample solution of 20 ug/ml TNG at the three different level 50,100 and 150% to check the accuracy of the method. The resulting solutions were analyzed and % recovery was calculated. The result of the accuracy study was assessed based on the percentage of standard TNG and recovered from the formulation.

2.8 LOD and LOQ

The limit of detection and limit of quantification of TNG were calculated using the below mentioned equation.

LOD = $3.3 \times \sigma/S$

LOQ = $10 \times \sigma/S$

Where, σ= Standard deviation of the response,

S = Slope of the calibration curve

2.9 Robustness

Robustness of the method was checked on the basis of slight alteration in the organic phase,(78 ± 3), flow rate (0.9±0.1),and pH (3±0.2).The chromatogram responses such as peak area and the retention time were recorded and calculated .

2.10 System suitability test

System suitability tests were performed to confirm that the instrument was in appropriate condition for the analysis to perform. Six replicates of the standard solution were injected, and chromatogram was recorded to confirm the suitability of the chromatograph.

2.11 Analysis of marketed formulation

From the marketed formulation dilutions are prepared as described earlier in the sample preparation. The desired concentration 30ug/ml was prepared.20 ul of sample was injected in HPLC system and chromatogram was recorded. Based on the peak area of analysis, percentage assay of formulation was calculated.

3. RESULTS AND DISCUSSION

UV spectra of the drug were taken in UV-spectrometer and 247 nm was selected as detected wavelength as the drug shows good absorbance for the detection.

According to the Box Behnken model the summery of three variables ware taken, and the layout of actual design shows the significant variable results. The ANOVA result for retention time of TNG shows model F-value implies the model is significant. There is only a 0.73% chance that an F-value this large could occur due to noise. Values of P is less than 0.0500 indicate model terms are significant. Area of TNG shows the model F-value of is significant. There is only a 0.24% chance that an F-value this large could occur due to noise. Values of Prob > F less than 0.0500 indicate model terms are significant. In this case B, AC, BC are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. Theoretical plate of TNG shows The Model F-value implies the model is significant. There is only a 0.14% chance that an F-value this large could occur due to noise. Values of Prob > F less than 0.0500 indicate model terms are significant. In this case A, AC, BC, A^2, B^2, C^2 are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. The Model F-value for asymmetric factor 7.99 implies the model is significant. There is only a 0.60% chance that an F-value this large could occur due to noise. Values of Prob –F is less than 0.0500 indicate model terms are significant. In this case A, C, A2, B2, C2 are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. All the parameters of system suitability were observed within the acceptable limits as per the ICH guidelines for TNG hence system is suitable for the further validation. From the obtained data, calibration graph were plotted using peak areas of standard drug vs concentration for establishing linearity The TNG was found to be linear in the concentration range 10 -50 ul/ml. Result of precision studies expressed in % RSD according to ICH guidelines acceptable limit (< 2) which indicates good repeatability and low variability in inter-day. The values of LOD were found to be 0.956 ug/ml for TNG. and the calculated LOQ values were found to be 0.171 ug/ml. The standard and marketed formulation ware prepared and analyzed by the proposed optimized HPLC method which was successfully used for the quantitative determination of TNG in tablet formulation (20mg per tablet). The experimental value was found to be 99.769%. Therefore, the optimized developed method can be successfully applied for the quantitative analysis of TNG in tablet formulation.

Table 1: Layout of actual design of DOE of TNG

		Factor 1	Factor 2	Factor 3	Response1	Response2	Response 3	Response4
std	Run	C.M.P (%)	Flow rate (ml/min)	pH	RT (min)	Area	TP	AF
1	1	70	0.8	4.5	3.803	914845	413	2.96
11	2	80	0.8	6	4.043	667585	1201	2.55
13	3	80	0.9	4.5	3.504	816646	516	3.6
09	4	80	0.8	3	4.361	847820	7497	1
17	5	80	0.9	4.5	3.504	816646	516	3.6
03	6	70	1	4.5	4.653	823456	2453	3.48
05	7	70	0.9	3	4.664	898105	7859	1.01
16	8	80	0.9	4.5	3.504	816646	516	3.6
14	9	80	0.9	4.5	3.504	816646	516	3.6
07	10	70	0.9	6	4.177	844563	2736	2.38
15	11	80	0.9	4.5	3.504	816646	516	3.6
06	12	90	0.9	3	3.253	826306	6369	1.06
10	13	80	1	3	3.244	710384	5370	1.05
02	14	90	0.8	4.5	3.678	805643	4281	0.97
12	15	80	1	6	3.281	557645	2131	2.46
08	16	90	0.9	6	3.438	533653	2635	1.41
04	17	90	1	4.5	2.986	888665	1240	0.89

Table 2: ANOVA for Response surface linear model for different variables

Source	F-value	P-Value	F-value	P-Value	F-value	P-Value	F-value	P-Value	
	Retention Time		Surface Area		Asymmetric factor		Theoretical plates		
Model	6.2726	0.00725	3.3353	0.0451	7.9932	0.006	12.862	0.001	significance
A-pH	0.3394	0.57010	1.9259	0.9965	10.110	0.0154	11.217	0.012	
B-Flow Rate	2.9581	0.10910	5.3096	0.0439	0.0738	0.7936	2.389	0.163	
CM. P Conc	15.5201	0.00169	2.1749	0.1710	13.964	0.0072			
AB			12.3589	0.0055	0.3323	0.5823	0.2383	0.640	
AC			0.16870	0.6899	0.9605	0.3596	9.9190	0.016	
BC			9.5189	0.99240	0.0180	0.8967	6.7513	0.035	
A2			3.3353	0.0451	12.947	0.0087	83.917	3.801	
B2			1.9259	0.9965	5.833	0.0464	0.0719	0.796	
C2			5.3096	0.0439	23.239	0.00191	0.0005	0.981	
Residual			2.1749	0.1710			12.860	0.001	
Lack of Fit			12.3589	0.0055					
Pure Error			0.16870	0.6899					
Core total									

Table 3: Calibration curve of TNG

Sr. No	Conc ug/ml	Peak area (±SD)*	%RSD
1	10	62.27 ± 0.363	1.165
2	20	263.01 ± 1.088	0.765
3	30	276.29 ± 1.862	0.865
4	40	362.87 ± 2.181	0.822
5	50	462.12 ± 3.441	0.845

*(n=6) number of determinations

Table 4: Summer of validation and asst. parameters

Parameters (units)	TNG
Linearity range (µg/ml)	10 -50 ul/ml
LOD (µg/ml)	0.956 ug/ml
LOQ (µg/ml)	0.171 ug/ml.
Recovery (%)	99.89
Precision (%RSD)	
Interday (n=3)	1.08
Intraday (n=3)	1.64
Robustness	Robust
Retention Time (min.)	0.342
Theoretical Plates	7587.40
Tailing Factor (asymmetry factor	1.095

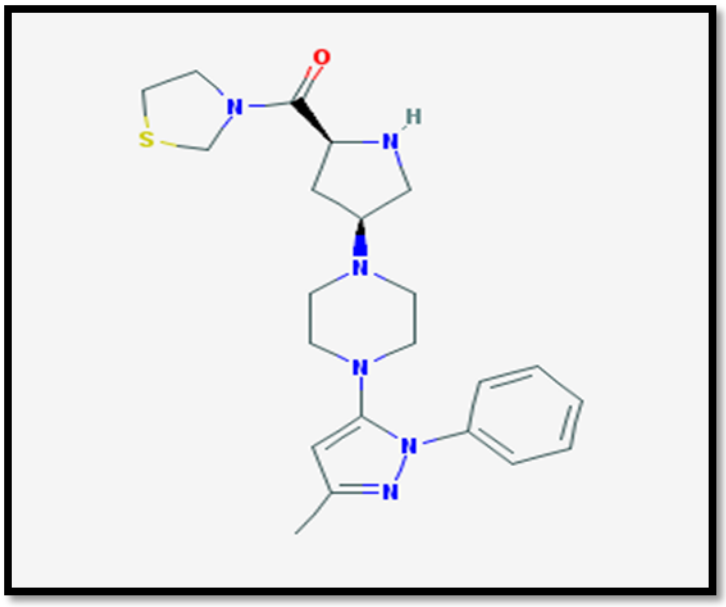

Fig 1: Structure of teneligliptin (TNG)

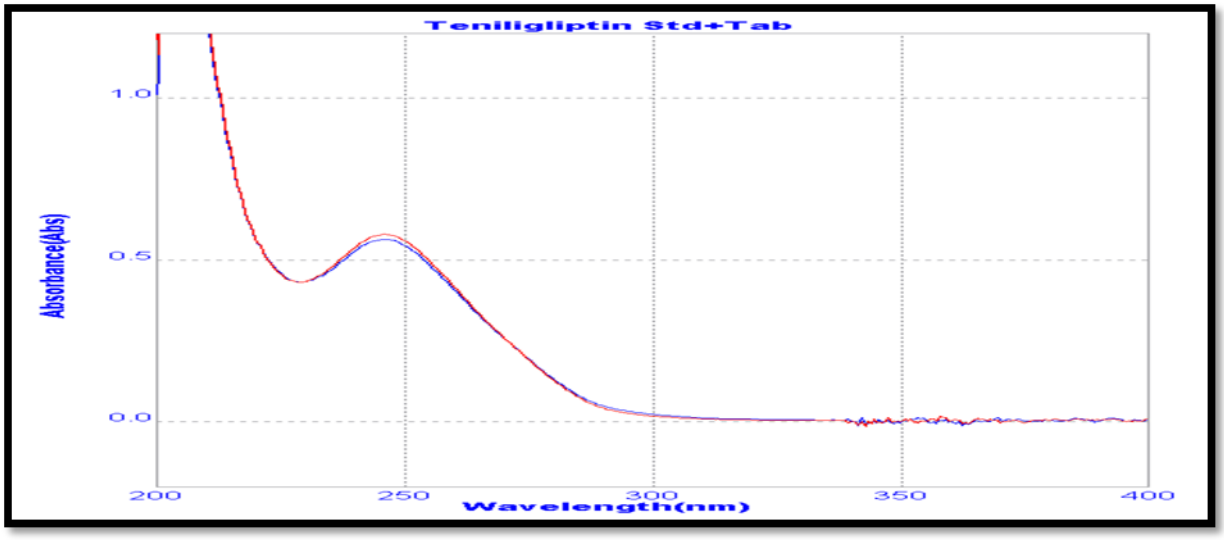

Fig 2: Overlay spectra for teneligliptin standard and reference

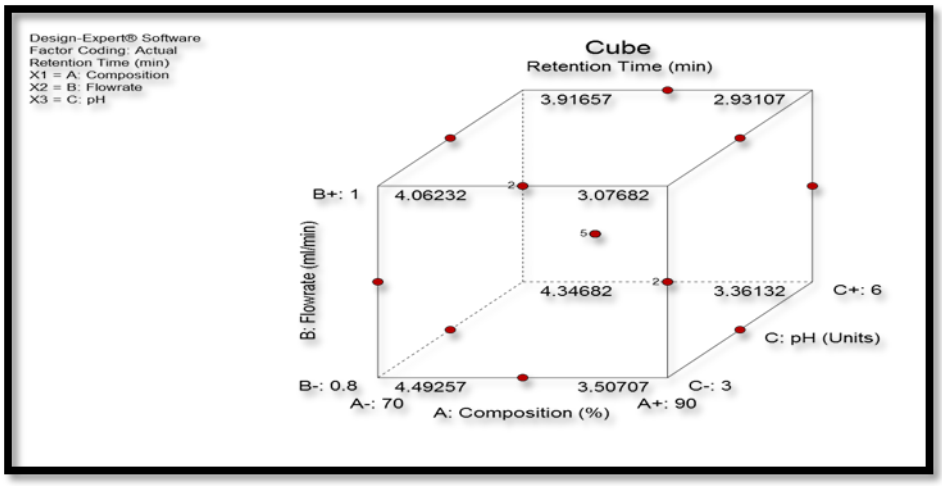

Fig 3: Box-Behnken cube plot for retention time

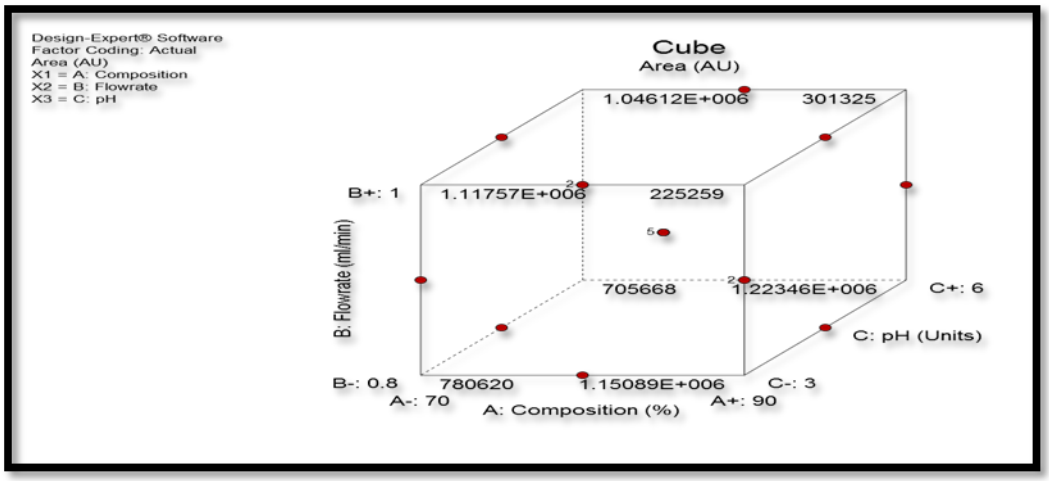

Fig 4: Box-Behnken cube plot for area

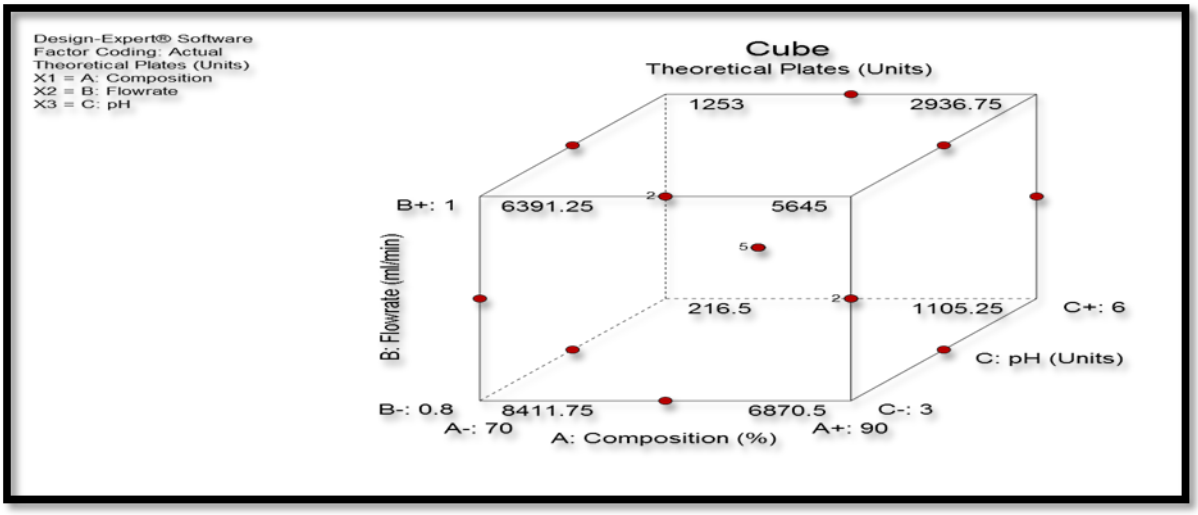

Fig 5: Box-Behnken cube plot for theoretical plates

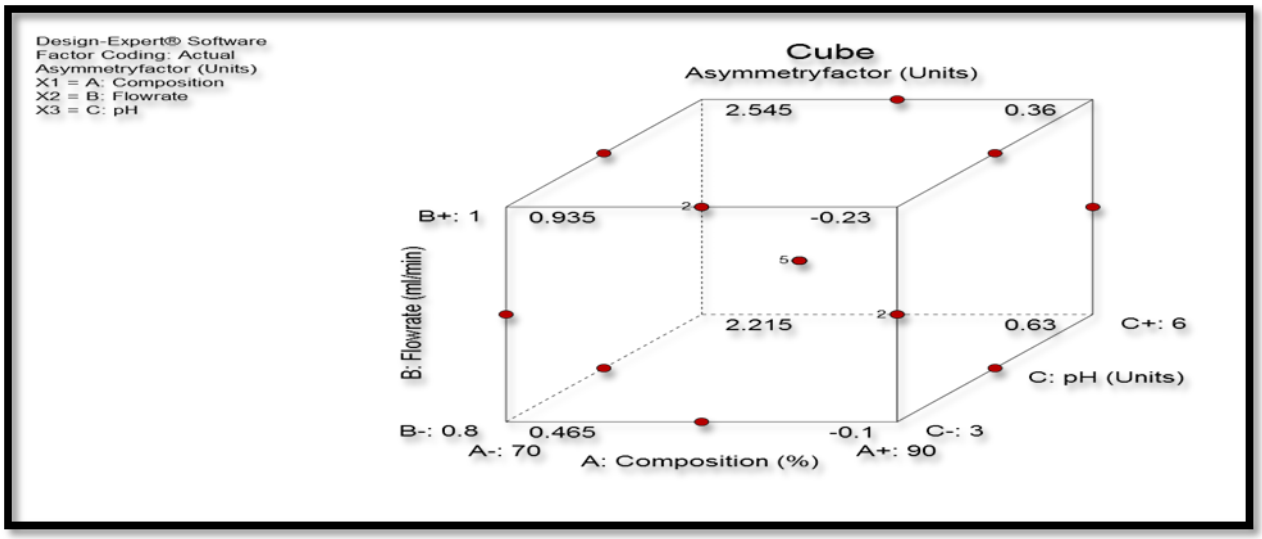

Fig 6: Box-Behnken cube plot for asymmetric factor

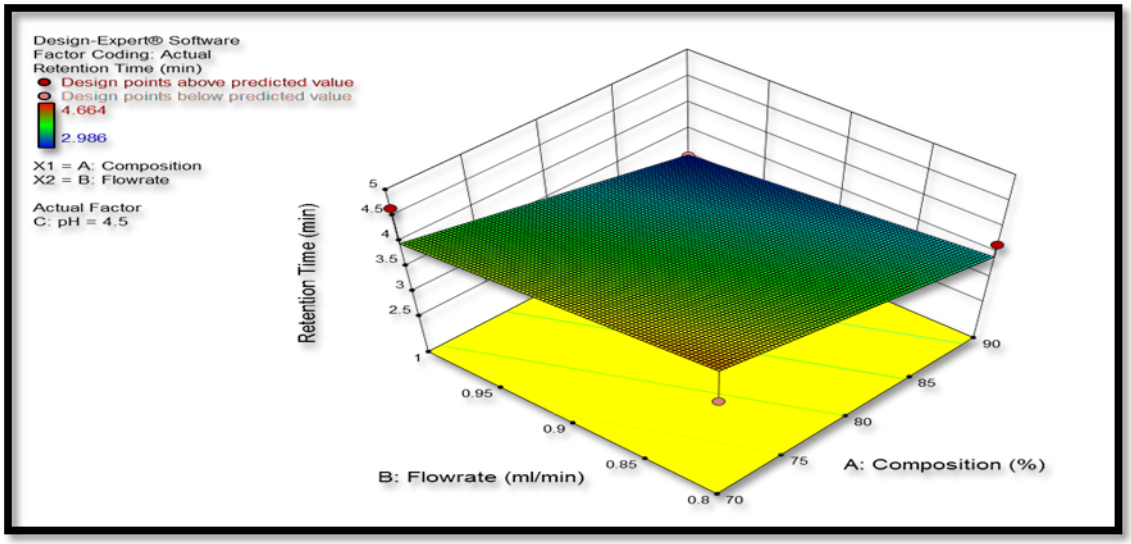

Fig 7: Model 3D graph of R1 retention time

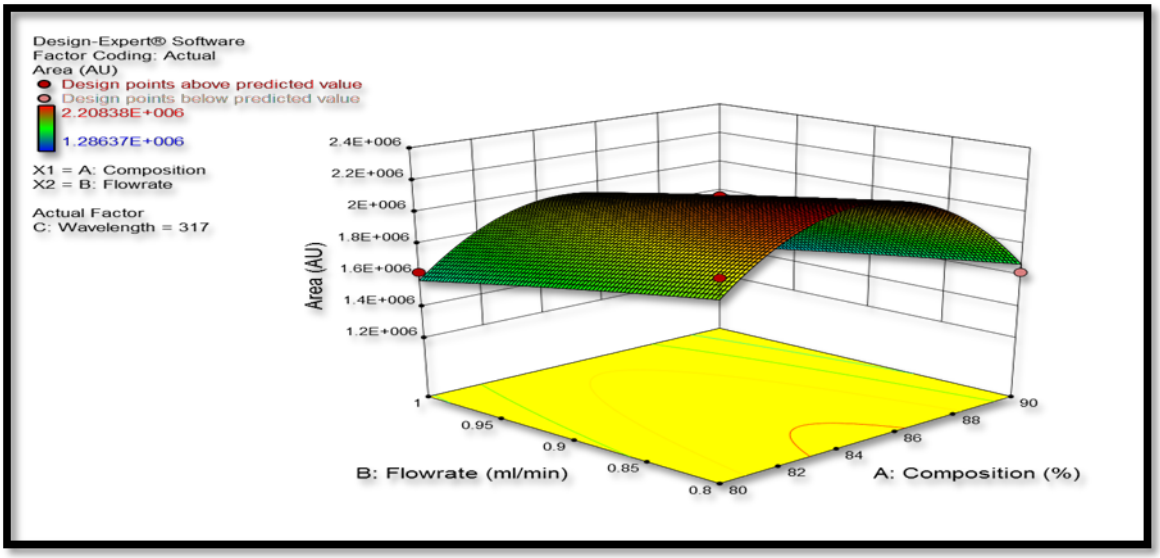

Fig 8: Model 3D graph of R2 area

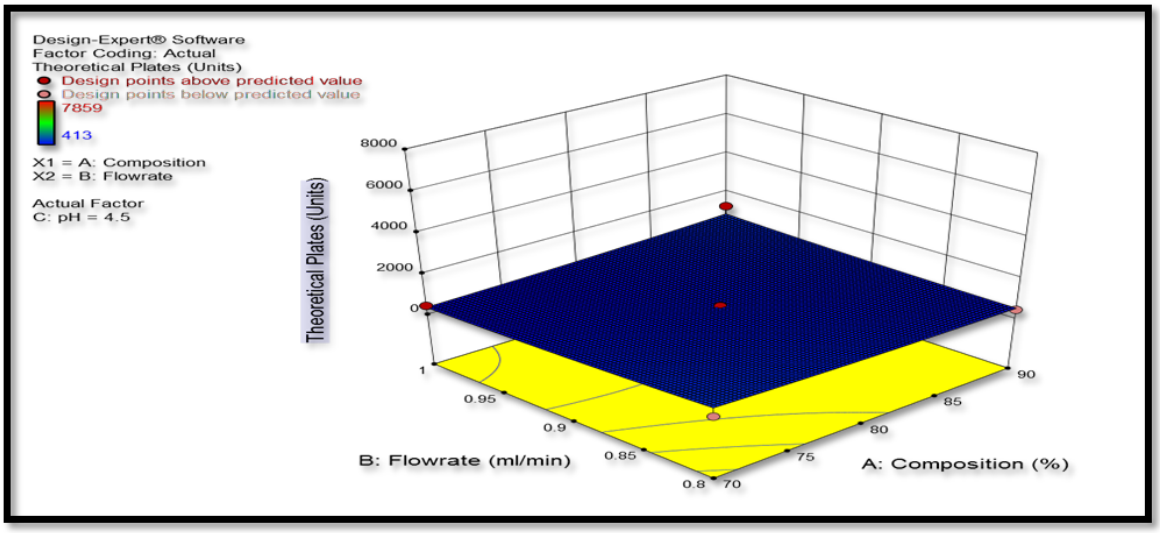

Fig 9: Model 3D graph of R3 theoretical plates

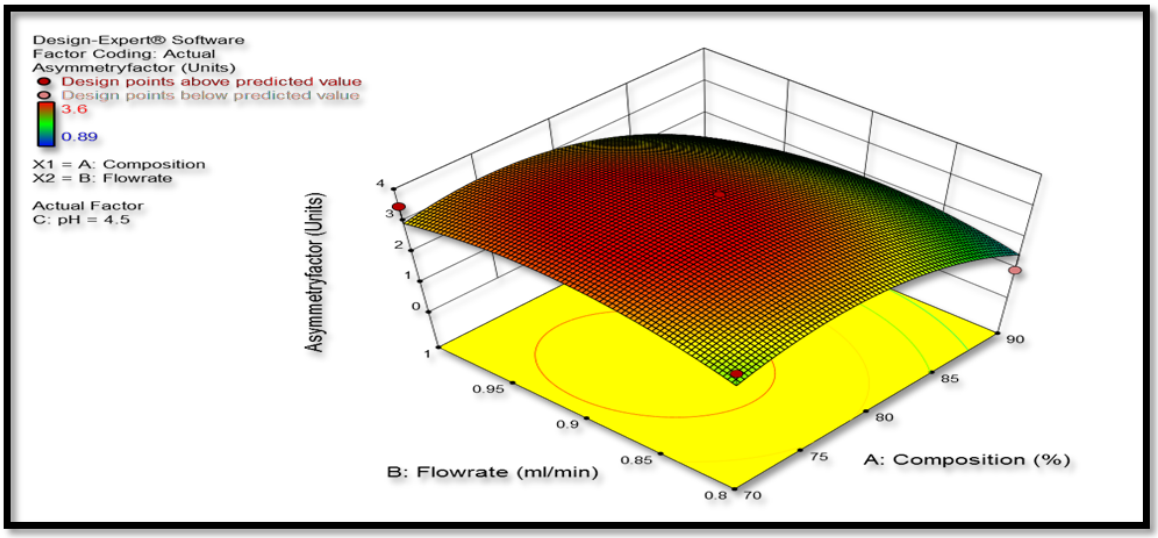

Fig 10: 3D plot of asymmetry factor

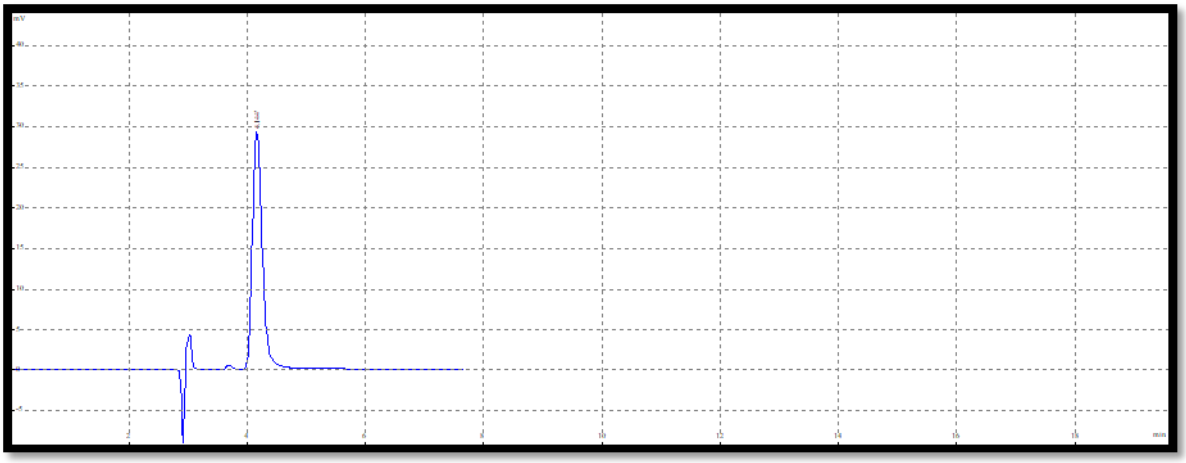

Fig. 11: HPLC chromatogram of TNG at fixed chromatographic condition

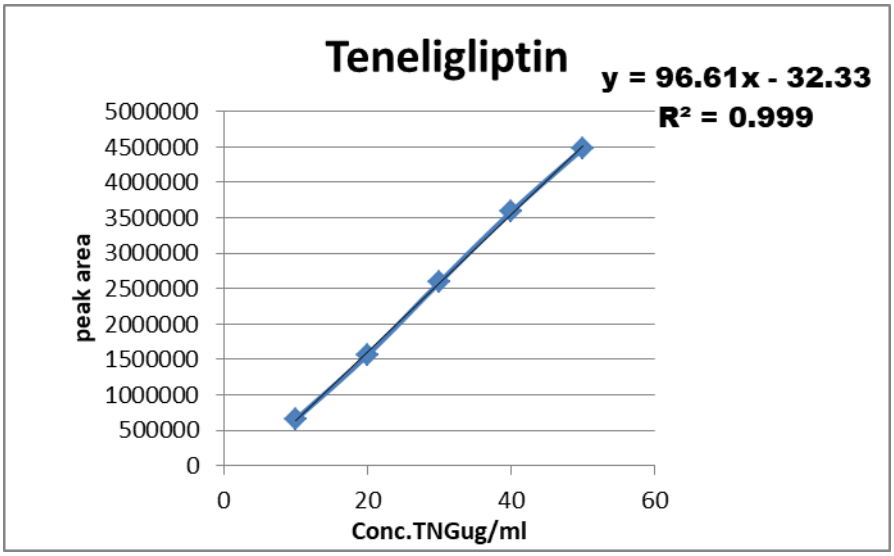

Fig. 12: calibration curve of TNG (10-50ul/ml) at 247 nm

CONCLUSION

The implementation of quality by design technique aims to encourage debate about quality in the complete development of the drug in a systematic matter. The article forced on the ideas, research, practice about the quality determination of TNG. First the method goals are clarified based on the process understanding. The experimental design describes the scouting of key HPLC method components including pH, mobile phase, wavelength, theoretical plates, asymmetric factor, and retention time. The preliminary optimized conditions are obtained by studying the interrelationship for each combination. So better understanding of the factors influences the chromatographic separation. This approach ensures the better design of the product with the fewer problems in development, relies more on the process, mitigation and understanding of the risk. The validated method is specific, linear, precise, accurate, robust and rugged. and can be applied for the formulation determination.

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