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Implementation of quality by design approach to method development and validation of daclatasvir on UV spectroscopy

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Abstract

The application of QbD in analytical method development focused on the building quality into the method Quality is the heart of pharmaceutical industry. Daclatasvir an antiviral agent was estimated by uv spectrophotometric method followed by methanol used as solvent. The spectrum shows the maximum peak amplitude at 317 nm. graph shows linear in the range of 05-30 µg/ml. The graphical optimization done with the help of Design Expert software version 10. Three factor with three level randomized response surface designs on a Box-Behnken design were used with 17 trial impact on the one key response variables. Optimized responses were selected validation. Validation was done according to International Conference on Harmonization. Good co-relation between responses and concentration was found as value of regression coefficient R^2 is 0.999. The accuracy of the method was ranged in between 98.75-99.79 was in acceptable range. The percentage RSD values for method precision for all the methods were within the limit of ≤ 2. From the data it was concluded that the methods developed have scope to be applied for quantitative estimation of Daclatasvir.

Keywords: QbD, method development, validation, daclatasvir

Introduction

Quality is the heart of pharmaceutical industry. The analytical method development and validation plays key role in pharmaceutical industry. QbD methods builts quality within the process.It eliminates quality testing at the end of the process [1, 2]. It defines quality targets by identifying critical quality attributes. The concept has been introduced in pharmaceutical industries in 2004 for 21st century through cGMPs. QbD helps to implement Q8 and Q9.QbD principles are supported by International Conference on harmonization (ICH) guidelines. 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 [3, 4]. Daclatasvir is used in therapy for the treatment of hepatitis C genotype 1, 3, or 4 infections. Daclatasvir stops HCV viral RNA replication and protein translation by directly inhibiting HCV protein NS5A [5, 6].

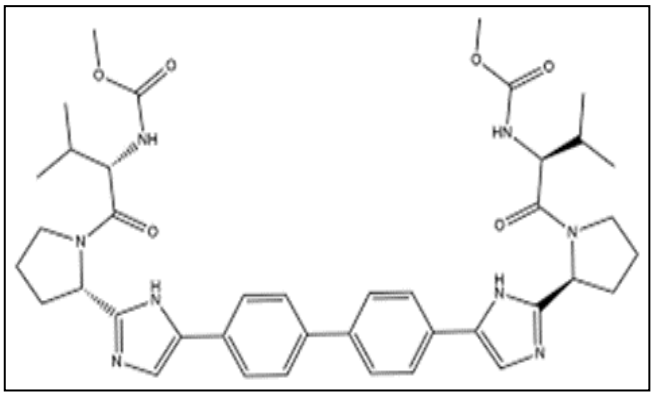

Fig 1: Structure of daclatasvir

Materials and methods

Daclatasvir dihydrochloride (DCR) pure drug was received as gift sample from Cipla pvt limited, Pune, Maharashtra, India Tablet with 20 mg strength was purchased from local market under commercial available brand name Hepcdac manufactured by Cipla pvt. UV-Spectroscopic method used having model UV-2012(UV Probe) with PDA detector and UV-VIS analyst software.

Result and Discussion

UV Spectroscopy has been widely used as a instrument for quantitave and qualitative analysis and quality control. This is a simple, precise technique and has various advantages

Preparation of standard stock solution

Stock solution of Daclatasvir was prepared by accurately weighing 10mg of active drug standard. It was then transferred to a 10ml of volumetric flask containing 5 ml of methanol. The solution was sonicated for few minutes. The solution again diluted up to the mark with methanol to get concentration up to 1000µg/ml.

Selection of wavelength

Standard stock solution of DCR was further diluted to get the drug concentration of 10 µg/ml. The solution was scanned in UV region (200-400nm) and spectrum was recorded. The peak maxima of DCR was found at 317nm.

Preparation of sample solution

Twenty tablets are powdered and weighted accurately. A portion of powder (72.16mg) equivalent to 10mg of DCR was transferred to 10ml of volumetric flask containing 5 ml of methanol and sonicated. The further volume was made up with methanol and filtered through whatman filter paper

no.1.From the resulting sample solution 1 ml was diluted to 10ml in volumetric flask to get the final concentration of 10 µg/ml.

Implementation of QbD

Three factor three level randomized response surface designs with a Box-Behnken design were used with 17 trial runs to study the impact of three factors on the one key response variables. In this design 3 factors were evaluated, each at 1 levels, and experimental trials were performed at all possible combinations. The composition (X1), pH (X2), Wave length (X3) were selected as independent variables and Peak amplitude (RT) was selected as dependent variables. The resulting data were fitted into Design Expert 10 software and analysed statistically using analysis of variance (ANOVA). The data were also subjected to 3-D response surface methodology to determine the influence of wavelength, pH, Mobile phase composition on dependent variables.

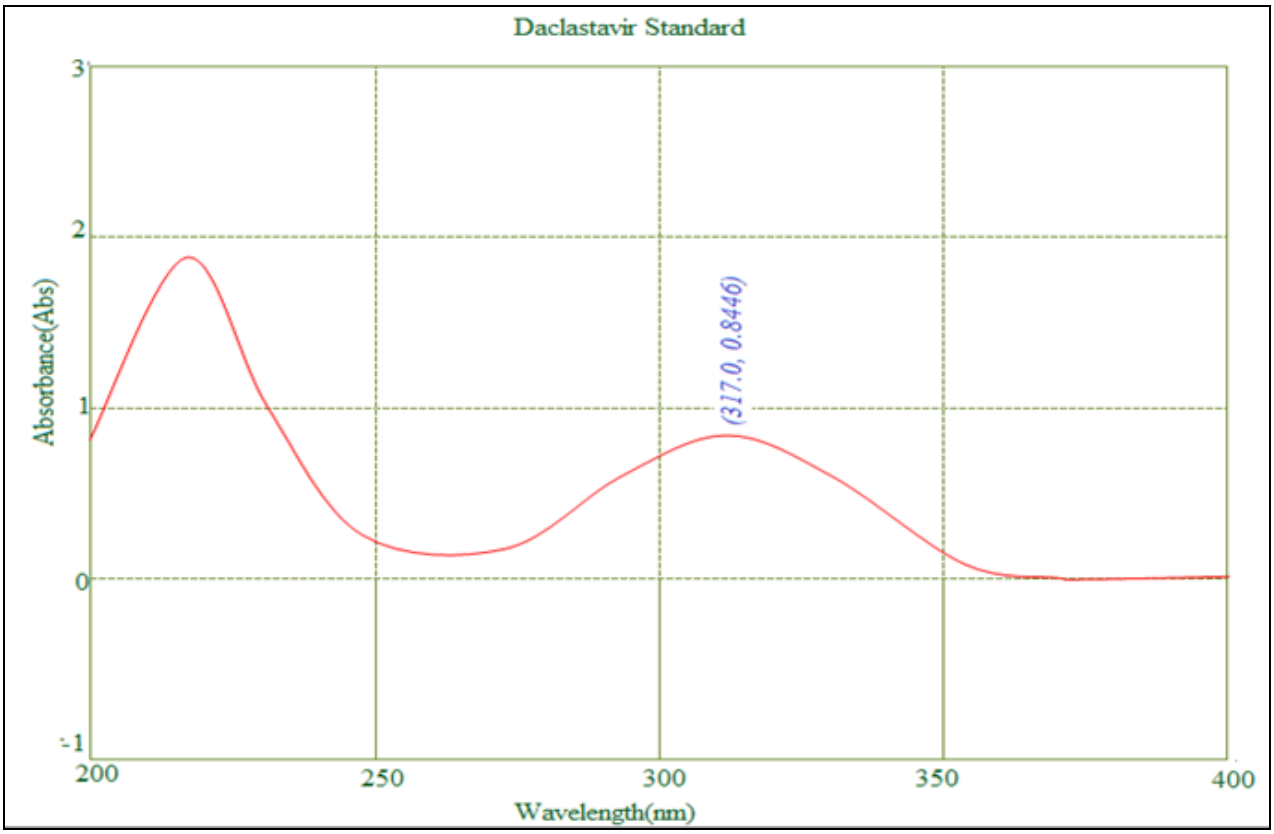

Fig 2: Spectrum of standard DCR with solvent

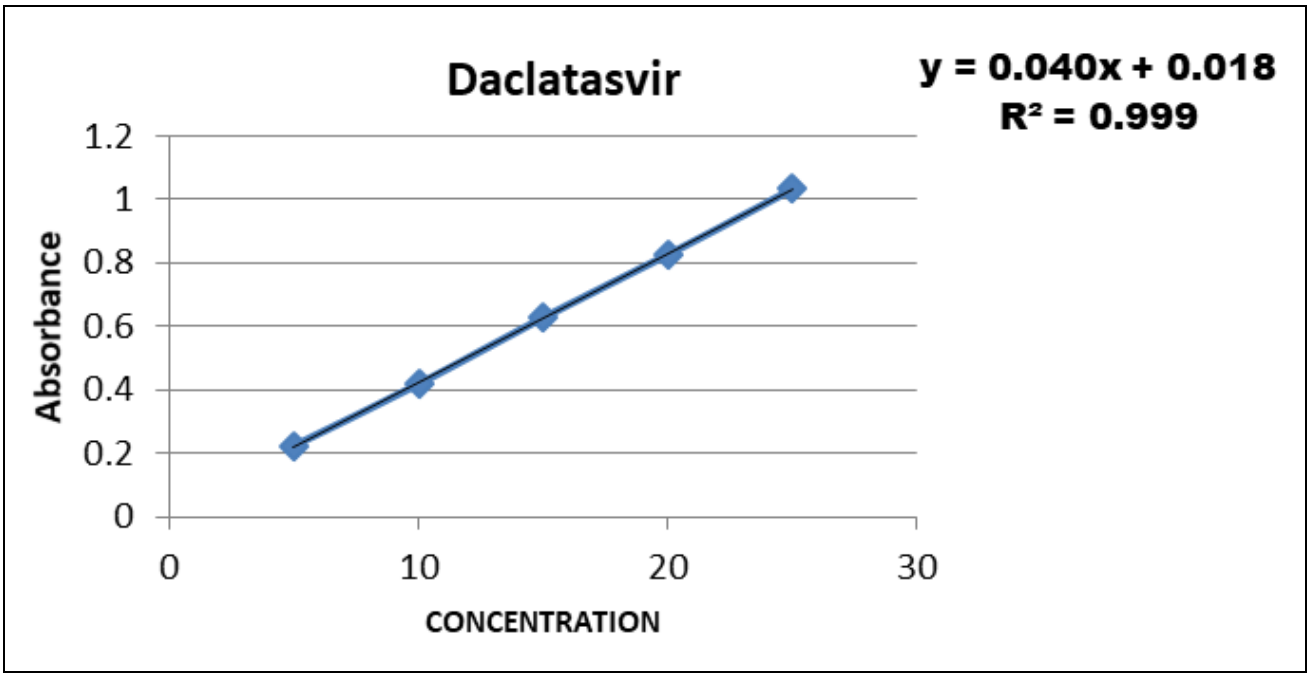

Fig 3: Calibration curve of DCR at 317 nm

ANOVA for Response Surface Linear model of peak amplitude

Table 1: ANOVA for peak amplitude of DCR

Source	Sum of Squares	Df	Mean Square	F-value	p-value	
Model	3.70	3	1.23	6.71	0.0056	Significant
A-C.M.P	0.2790	1	0.2790	1.52	0.2396	
B-Wavelength	3.39	1	3.39	18.47	0.0009	
C-pH	0.0255	1	0.0255	0.1390	0.7153	
Residual	2.39	13	0.1837			
Lack of Fit	0.6771	9	0.0752	0.1759	0.9855	not significant
Pure Error	1.71	4	0.4277			
Cor Total	6.09	16				

Table 2: Layout of actual design of DOE

		Factor 1	Factor 2	Factor 3	Response 1
Std	Run	A:C.M.P	B:Wavelength	C:Ph	Peak Amplitude
9	1	80	269	2.5	0.463
1	2	90	325	3.25	0.625
2	3	95	317	3	0.814
11	4	80	290	4	1.690
5	5	80	318	2.5	0.342
6	6	90	365	2.5	0.789
13	7	80	304	3	0.845
17	8	80	248	3	1.684
15	9	85	320	3.25	1.665
16	10	80	248	3.25	1.582
14	11	75	319	3.25	1.659
7	12	80	354	4	1.645
8	13	90	249	4	1.658
10	14	85	319	2.5	0.867
3	15	75	370	3.25	1.588
4	16	85	264	3.25	1.657
12	17	90	269	3.5	1.798

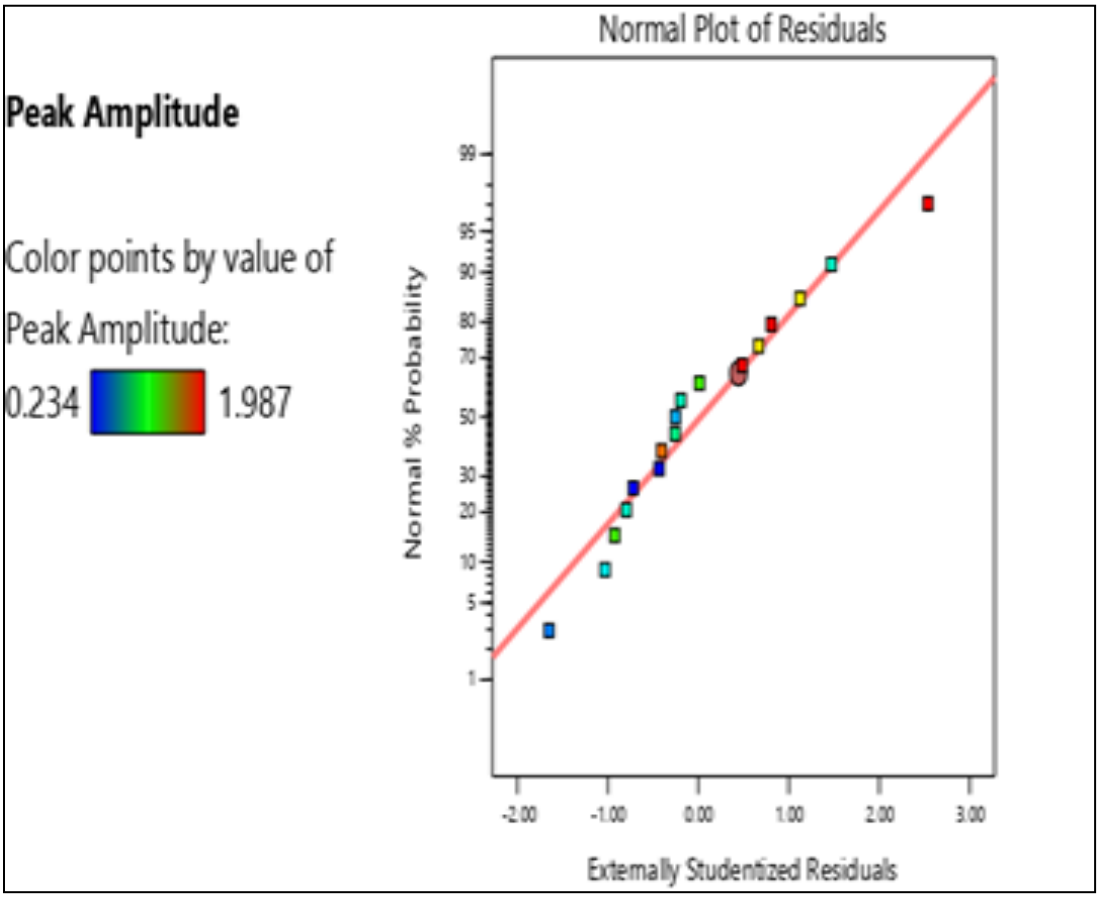

Fig 4: Predicted v/s actual plot of peak

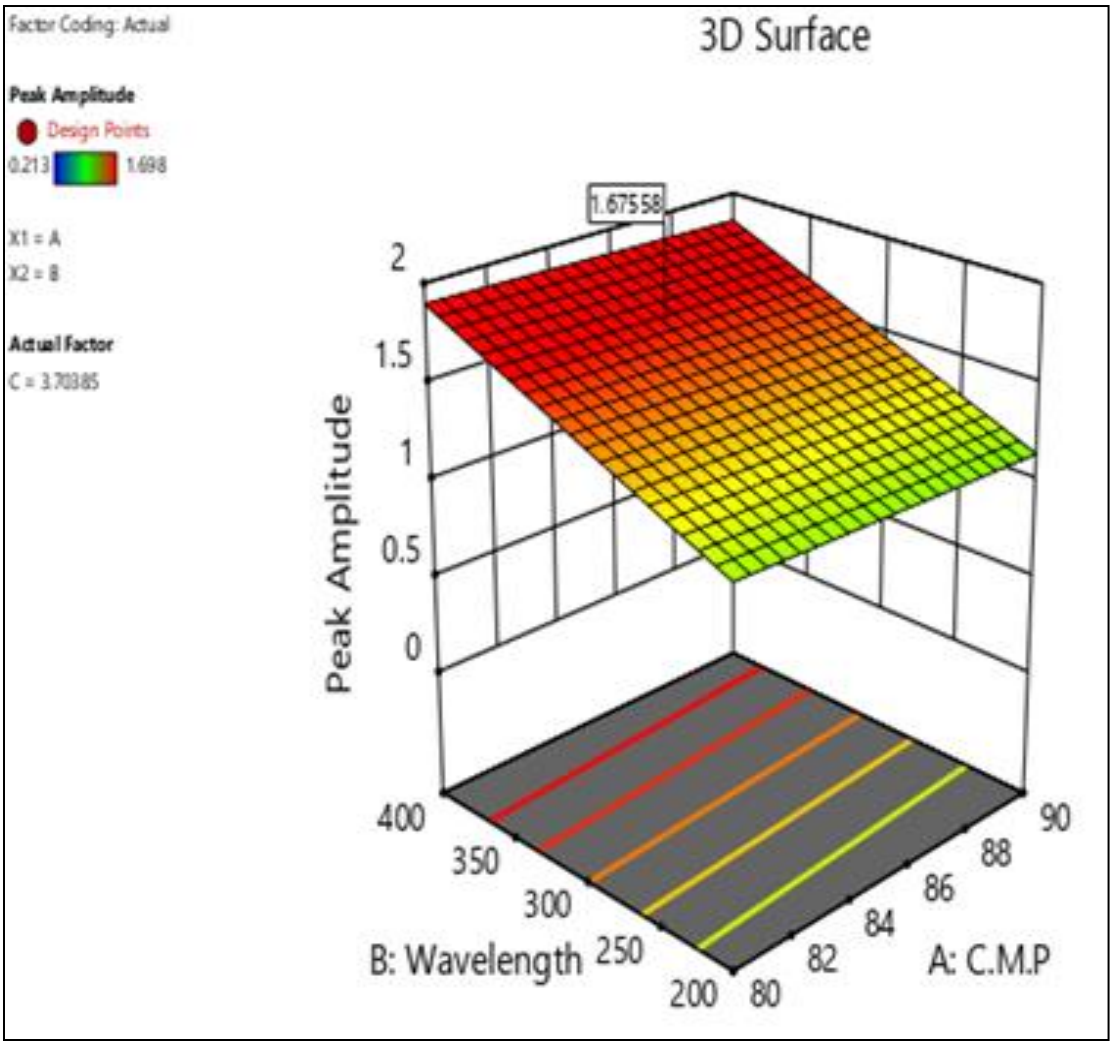

Fig 5: Model 3D graph of peak amplitude

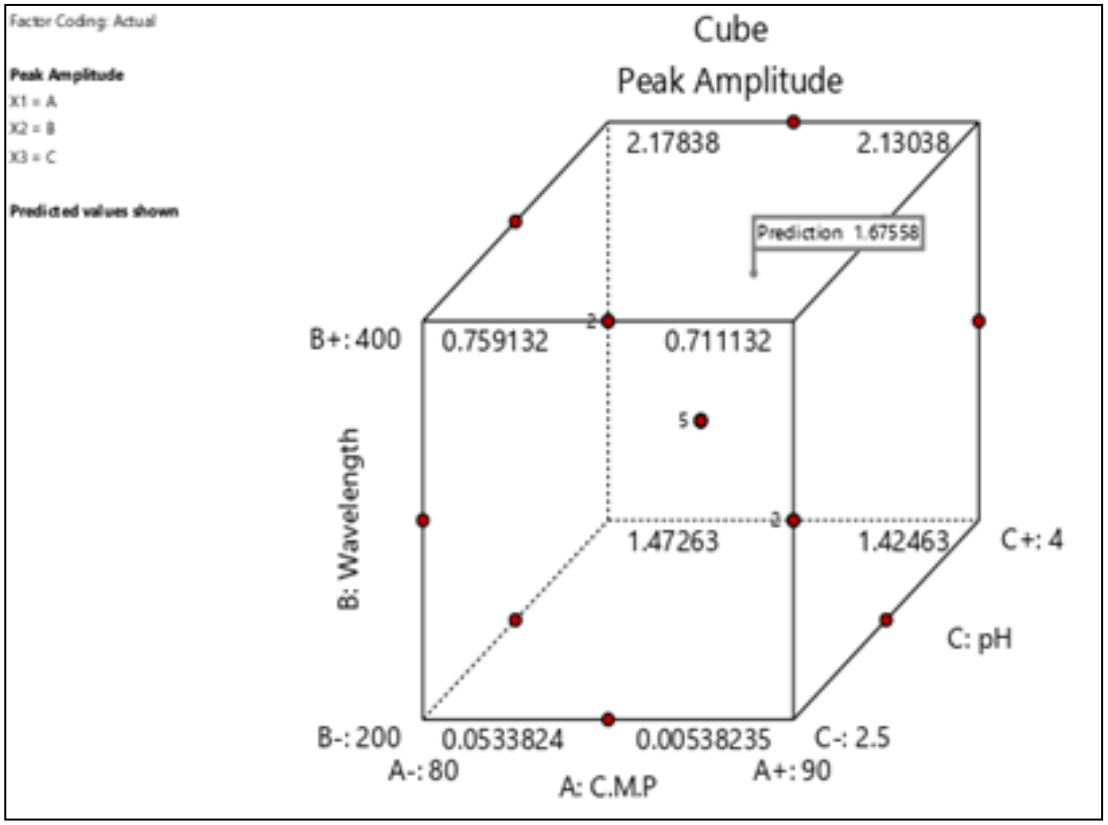

Fig 6: Cube plot for peak amplitude

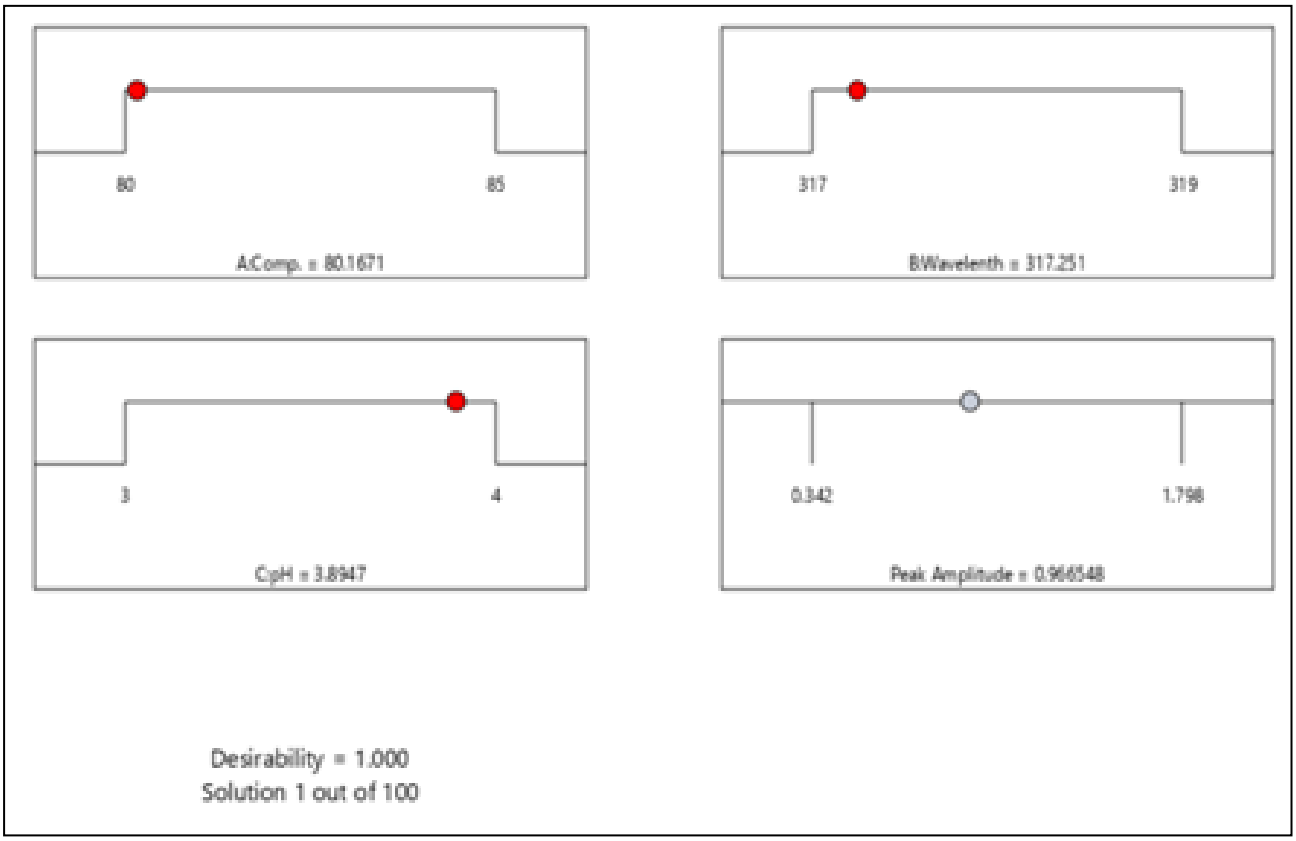

Fig 7: Desirability of responses

Graphical Optimisation: Developed Method Operable Design Region The graphical optimization done by with the help of Design Expert software provided the base to define the design space

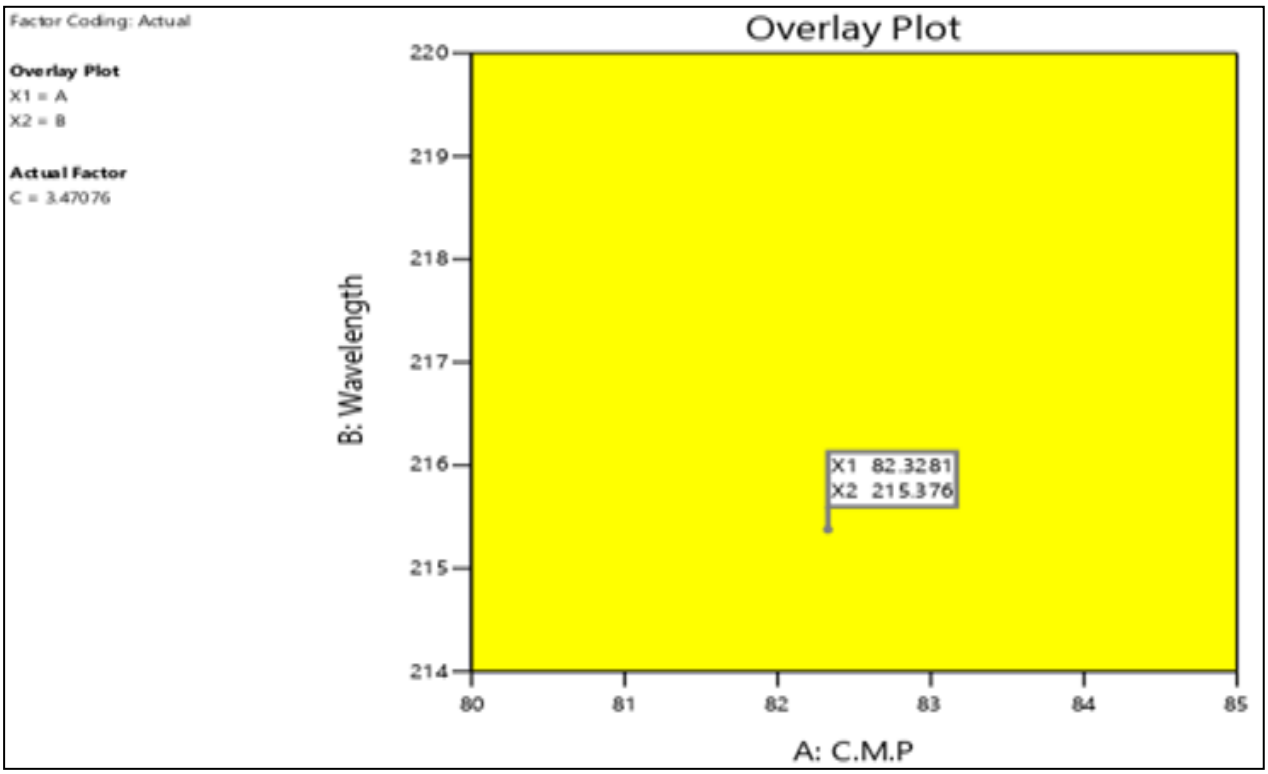

Fig 8: Overlay plot of responses against composition vs wavelength

This plot elaborates that the optimized values of both independent variables in the required target range of composition & wavelength lie within the yellow region which is the useful optimum region where the design space can be determined.

Post Analysis

Table 3: Point Prediction

Factor	Name	Level	Low Level	High Level	Std. Dev.	Coding
A	C.M.P	83.61	80.00	90.00	0.342	Actual
B	Wavelength	234.12	234.00	400.00	1.234	Actual
C	pH	3.75	2.50	4.00	0.450	Actual
	Peak Amplitude	0.228	0.231		1.500	

Analytical method validation

Linearity and range

Graph of DCR was found to be linear in the concentration range of 10-50 µg/ml. The correlation coefficient was found 0.997

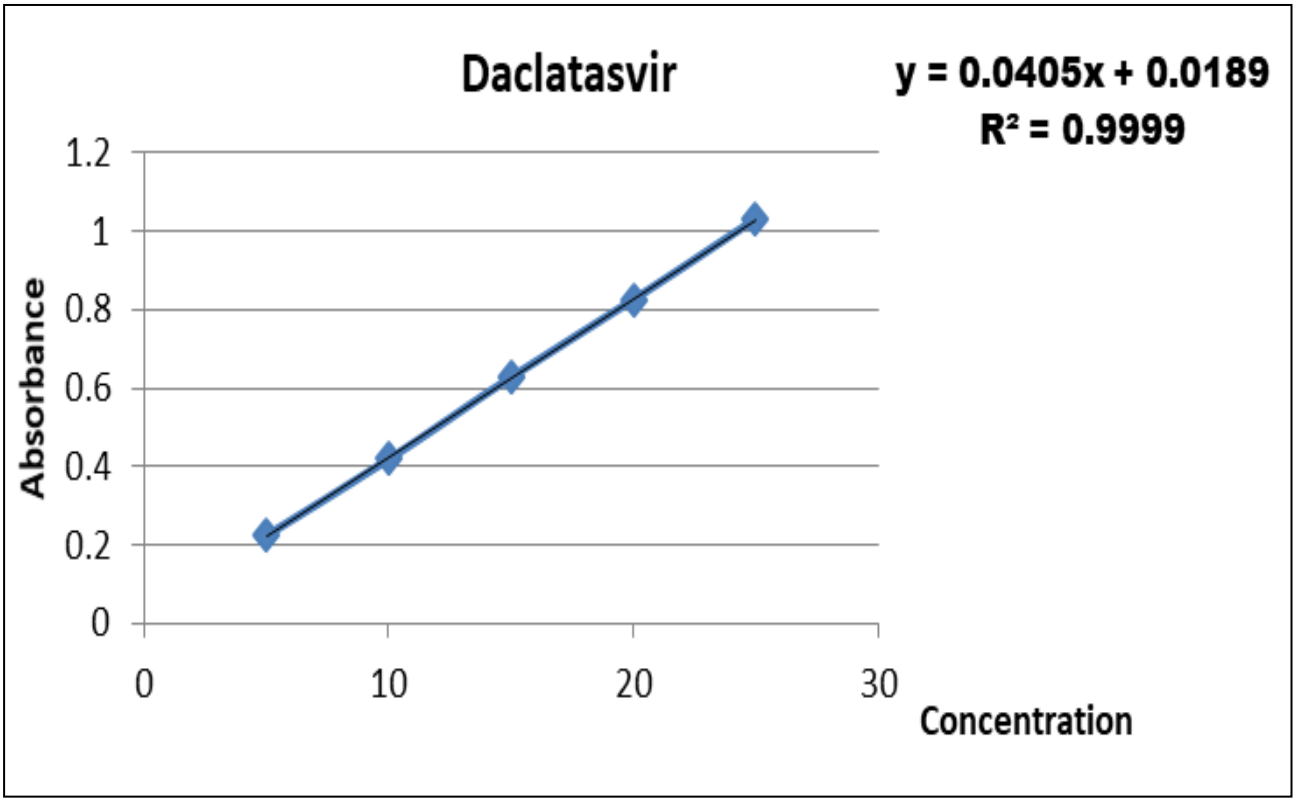

Fig 9: Calibration curve of DCR at 317 nm

Accuracy

Table 4: Result of recovery studies

Accuracy (% Recovery)						
Recovery level	**Initial amt. of formulation(µg/ml)**	**Std added (µg/ml)**	**Recovered (µg/ml)**	**% Recovered**	**Mean**	**R.S.D**
80%	10	5	7.60	98.75	99.07	0.45
80%		5	7.55	99.37		
100%		5	9.63	99.30	98.75	0.91
100%		5	9.60	98.00		
120%		5	11.34	99.33	99.79	0.27
120%		5	11.44	99.66		

Precision

Table 5: Results of intraday precision study

Sr.no.	Conc. (µg/ml)	Absorbance			Mean	S.D.	%R.S.D.
		Morning	Afternoon	Evening			
1.	2	0.125	0.127	0.128	0.127	0.0015	1.205
2.	4	0.225	0.223	0.226	0.224	0.0022	0.679
3.	6	0.329	0.329	0.33	0.329	0.0019	0.175
4.	8	0.447	0.445	0.448	0.446	0.0018	0.341
5.	10	0.549	0.551	0.548	0.550	0.0016	0.278
6.	12	0.662	0.661	0.659	0.660	0.0021	0.231
Average					0.471	0.0018	0.903

Table 6: The Result of Interlay Precision Study

Sr. no.	Conc. (µg/ml)	Absorbance			Mean	S.D.	% R.S.D.
		Day 1	Day 2	Day 3			
1.	2	0.090	0.095	0.097	0.189	0.0015	0.809
2.	4	0.145	0.147	0.151	0.231	0.0015	0.662
3.	6	0.171	0.182	0.188	0.332	0.0025	0.758
4.	8	0.220	0.231	0.238	0.450	0.0025	0.559
5.	10	0.236	0.242	0.250	0.554	0.0043	0.786
6.	12	0.242	0.244	0.248	0.663	0.0045	0.691
Average					0.178	0.0026	0.989

LOD and LOQ

The value of LOD was found to be 0.519 µg/ml and LOQ was found to be 1.781 µg/ml respectively.

Conclusions

The research work concluded that the implementation of quality by design approach to method development of uv-spectroscopy made the entire process systematic, rational, and ingrained with robustness within the process.

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