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Spectrophotometric Determination of Chlorpheniramine Maleate in its Pharmaceutical Dosage form using Quality by Design Approach

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ABSTRACT:

A UV Spectrophotometric method was developed by applying Quality by Design (QbD) approach for the determination of Chlorpheniramine Maleate in its pharmaceutical dosage form. In this research work, three critical method variables which are solvent, scanning speed and sampling interval were assessed by applying Design of Experiment (DoE) approach and was also optimized. Two wavelengths which are 261 nm and 245 nm was selected using water, 0.1 N HCl and 0.1 N NaOH as solvents (later HCL was selected as final solvent). Linearity was observed at concentration of 10µg/ml – 50µg/ml. The correlation coefficients for Chlorpheniramine maleate at both wavelengths is 0.9995 and 0.999. The results of method validation were in the acceptable range as per ICH guidelines.

KEY WORDS: Chlorpheniramine Maleate, UV spectrophotometry, Quality by design, Validation parameters, Pharmaceutical formulation.

INTRODUCTION [1], [2], [3], [4]

Chlorpheniramine Maleate is chemically 1-(N, N-Dimethylamino)-3-(p-chlorophenyl)-3-(alpha-pyridyl) propane maleate (Fig. No.1). CPM is a first-generation alkyl amine antihistamine.

Mechanism- Chlorpheniramine binds to the histamine H1 receptor. It blocks the action of endogenous histamine, which subsequently leads to temporary relief of the negative symptoms brought on by histamine.

Uses- CPM is effectively used to treat common cold, conjunctivitis and acute allergic symptoms like rhinitis and urticaria, sneezing, rhinorrhea and itching of eyes, nose, throat and pruritus, atopic dermatitis, contact dermatitis and insect bites.

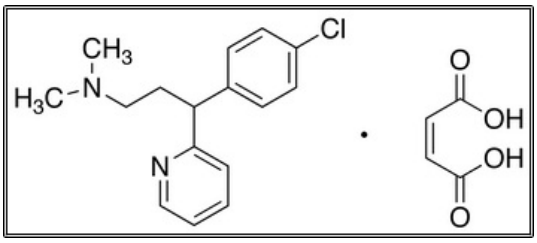


Figure 1: Chemical structure of Chlorpheniramine Maleate

The ultraviolet-visible (UV-VIS) absorption spectrophotometry is a widely used technique for measurement of molecules with chromophoric groups, part of the molecule with unsaturated and covalent group, resulting in characteristic absorption in the UV (or visible) region. It is reliable, fast and easy to use.

Quality By Design (QbD) - The concept of Quality by Design (QbD) was first developed by Dr. Joseph M Juran in various publications, he called that quality could be planned. ICH Q8 guidelines were mentioned the concept of QbD, which state that "Quality should be built into the product by design but quality cannot be tested in the product".

Quality by Design (QbD) is a systematic approach for the development of pharmaceutical products and processes beginning with the predefined objectives and primarily emphasizes on product and process understanding based on the principles of sound science and quality risk management.

In the analytical and scientific research area the QbD is applied mainly in the Design of Experiments (DoE). This should be used to determine the impact of various factors and their interaction. Since its introduction by ICH and USFDA through series of guidance from Q8-Q10. QbD application is a mandatory requirement for the development of pharmaceutical products. QbD principle when applies to the development of analytical method is called as "AQbD". Analogue to process QbD. Analytical QbD helps in development of a robust and cost effective analytical method which is applicable throughout the lifecycle of the product, to facilitate the regulatory flexibility in analytical method.

The present study describes the development and validation of novel, alternative and simplified analytical method for the quantification of antihistamine drug Chlorpheniramine Maleate that meets the requirements of the International Conference on Harmonization, which shows the practicality, reliability, safety and low cost of using this method routinely in pharmaceutical industry.

Elements of QbD: [5],[6]

Quality target product profile- According to ICH Q8 (R2), QTTP is "Prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product".

Select appropriate analytical technique- Selection of appropriate analytical technique are done with reference which are defined in the ATP and should satisfy the required method validation parameters as required by regulatory requirement.

For eg: Specificity may not be included in ATP, but the analytical technique should satisfy the specificity.

Method performance criteria- Analytical method performance characteristic are defined to meet the need of analytical target profile .According to USP & ICH guidelines there are many validation parameters for separations, which are considered as method performance characteristics.

Method performance are of 2 types - a) Systematic (bias)

b) Inherent random (variance) component.

Among these parameter accuracy & precision are quite commonly considered as method performance characteristic to quantify the substance.

Critical quality attributes- According to ICH Q8 guideline defines as a physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range or distribution to ensure the desired product quality.

Quality risk assessments- According to ICH Q9 guideline "It is the systematic process for the assessment, control, communication and review of risks to the quality across the product lifecycle." It can be carried out in three steps risk identification, risk analysis and risk evaluation.

Design of experiment (doe) & design space- It is defined as, "Multidimensional combination and interaction of input variables that have been demonstrated to assure the quality."

Control strategy- A control strategy is designed to ensure that a product of required quality will be produced consistently. Data generated during development and verification of method forms the basis of the control strategy. A risk factor has identified and controlled.

Continuous improvement- Products of desired quality are obtained and the potential areas of continual improvement are identified by the use of a process performance and product quality monitoring system. The continuous monitoring allows an analyst to detect, identify & address any abnormal or out of trend performance of analytical method.

Benefits of analytical QbD: [7]

1. Increased understanding and control.
2. Flexibility in analysis of API, impurities in dosage forms, stability samples, and metabolites in biological sample.

3. Reduction in variability in analytical attributes for improving the method robustness.
4. To keep the values of analytical attributes within the pharmacopoeial monographs and away from Out Of Specification (OOS) limits.
5. Smooth process of method transfer to the production level.
6. No requirement of re-validation within method operable design region.

MATERIAL AND METHOD:

I. Instrument: UV- Visible spectrophotometer

(Double beam) having matched quartz cells of light path 1 cm of Shimadzu 1800 Model with UV probe – 2.42 Version of software.

II. Apparatus: Electronic analytical weighing balance (REPTECH)

III. Glassware: Volumetric flask (Borosilicate), Pipettes, etc.

IV. Reagents and chemicals: Chlorpheniramine Maleate, Methanol (RANKEM)

V. Preparation of standard and working solution:

Procedure for preparation of CM (DRUG) Standard stock solution (1000µg/ml)

10mg of CM (drug) was weighed and transferred to a 10ml volumetric flask and 5ml of HCL is added to dissolved the solution and finally volume is made up to mark with HCL.

Procedure for preparation of CM (DRUG) working stock solution (100µg/ml)

Aliquot of 1.0 ml from above solution was pipette out into 10 ml of volumetric flask and volume is made up to mark with HCL. Further this solution was used to prepare the required dilutions of concentration ranging from 10-50µg/ml.

Analysis of tablets

Finely ground and powdered tablet equivalent to 5 mg of Chlorpheniramine Maleate was transferred into 50 ml volumetric flask and volume is adjusted to HCL up to the mark. Filtered the solution using Whatmann filter paper and further the dilution is carried out to obtained the concentration of 30µg/ml. Drug content in the above solution was determined using the calibration curves of standard Chlorpheniramine Maleate.

VI Method Validation : [8],[9],[10]

According to ICH Q2 (R1) Guideline the method was validated.

Linearity

The solution were prepared by pipetting 1, 2, 3, 4, 5 ml from working stock solution into 10ml volumetric flask and the volume was adjusted to mark with HCl to produce 10-50 µg/ml respectively. The absorbance of solutions was measured at 261 nm and 245 nm. Calibration curve was generated by taking the absorbance verses concentration.

Accuracy

The accuracy of the method was determined by calculating recovery of CM by the standard addition method. Reference standard solution of each drug was added to samples at three different concentrations level (80,100 and 120%). At each level, samples were prepared in triplicate and the mean percentage recoveries and % RSD value was calculated.

Precision

Repeatability

Aliquots of 3 ml of working standard solution of CM (100µg/ml) were transferred to 10ml volumetric flask and volume was adjusted to HCl to get concentration of 30µg/ml. The absorbance of solution was measured spectrophotometry six times to calculate % RSD.

Intraday and Inter day

Aliquots of 2, 3, 4 ml of working standard solution of CM (100µg/ml) were transferred to 10ml volumetric flask and volume was adjusted to methanol to get concentration of 20, 30 and 40 µg/ml. The absorbance of solution was measured by spectrophotometry three times and % RSD was calculated. For intraday, the analysis was carried out at different intervals on the same day and for inter day, the analysis was carried on different days.

Limit of detection (LOD)

The LOD is estimated from the set of 5 calibration curves used to determine method linearity. The LOD may be calculated as,

LOD = 3.3 × (S.D./Slope)

Where, SD = Standard deviation of the Y- intercepts of the 5 calibration curves.

Slope = Mean of the 5 calibration curves.

Limit of Quantitation (LOQ)

The LOD is estimated from the set of 5 calibration curves used to determine method linearity. The LOD may be calculated as,

LOQ = 10 × (S.D./Slope)

Where, SD = Standard deviation of the Y- intercepts of the 5calibration curves.

Slope = Mean of the 5 calibration curves.

RESULTS AND DISCUSSION:

The present work describes UV Spectrophotometric method with QbD approach for analysis of Chlorpheniramine Maleate in tablets. Chlorpheniramine Maleate was soluble in water, 0.1N HCl and 0.1N NaOH. Standard Chlorpheniramine Maleate solution showed absorption maximum at 261 & 245 nm respectively in water, 0.1N HCl and 0.1N NaOH & was selected as the detection wavelength.

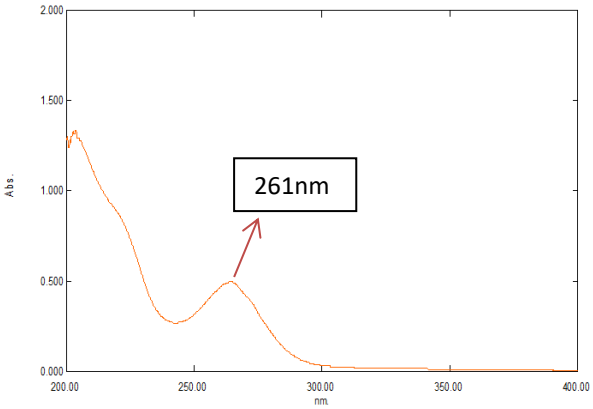


Figure 2 Absorption Maxima in 0.1n HCL

CCD experiment was performed based on 27 randomized experimental runs on UV spectrophotometer to observe the effect of CMV on CAA. CCD (central composite design) model was utilized for experimental investigation and the obtained result was studied through ANOVA, parameter estimates and prediction profiler.

Analysis of the obtained results suggest Quadratic model for wavelength 261 nm and 245 nm. Analysis of ANOVA p value ($p< 0.05$) and satisfactory value of r2 ($r2> 0.9$) indicates the adequacy of the selected mathematical model for obtaining optimum values of CAAs. Minimum interaction among both the CMVs was observed for CAA, as the factor lines were not intersecting each other. Satisfactory p- value found in ANOVA & predicted residual sum of square (PRESS) value suggest that the model is well fitted and optimized.

The prediction expression for adopted model are in the following polynomial equation form:

Quadratic Polynomial Equation at 261nm:

= 0.57 + 0.25 A + 0.009022 B - 0.007317 C + 0.013 AB - 0.011 AC + 0.012 BC – 0.12 A2 - 0.010 B2 – 0.004828 C2

Quadratic Polynomial Equation at 246.6 nm:

= 0.26 + 0.11 A + 0.002017 B - 0.001306 C + 0.002625 AB - 0.002192 AC + 0.002525 BC -

0.083 A2 - 0.002572 B2 - 0.007389 C2

A = Solvent B = Scanning speed C = Sampling interval

Table no: 1 Response 1- 261 nm

ANOVA for Response Surface Quadratic model						
Analysis of variance table [Partial sum of squares - Type III]						
	Sum of		Mean	F	p-value	
Source	Squares	df	Square	Value	Prob > F	
Model	0.096	9	0.011	2173.97	< 0.0001	significant
A-solvent	0.026	1	0.026	5236.66	< 0.0001	
B-sample speed	2.801E-006	1	2.801E-006	0.57	0.4606	
C-sample interval	1.227E-006	1	1.227E-006	0.25	0.6236	
AB	6.453E-006	1	6.453E-006	1.31	0.2676	
AC	1.021E-006	1	1.021E-006	0.21	0.6543	
BC	5.333E-008	1	5.333E-008	0.011	0.9182	
A2	0.070	1	0.070	14325.94	< 0.0001	
B2	9.335E-007	1	9.335E-007	0.19	0.6684	
C2	2.987E-006	1	2.987E-006	0.61	0.4463	
Residual	8.352E-005	17	4.913E-006			
Cor Total	0.096	26				

Table no: 1 Response 1- 245 nm

ANOVA for Response Surface Quadratic model						
Analysis of variance table [Partial sum of squares - Type III]						
	Sum of		Mean	F	p-value	
Source	Squares	df	Square	Value	Prob > F	
Model	0.17	9	0.019	408.94	< 0.0001	significant
A-solvent	0.027	1	0.027	574.07	< 0.0001	
B-sample speed	1.578E-004	1	1.578E-004	3.38	0.0837	
C-sample interval	1.076E-004	1	1.076E-004	2.30	0.1477	
AB	2.539E-004	1	2.539E-004	5.43	0.0324	
AC	1.606E-004	1	1.606E-004	3.43	0.0813	
BC	1.197E-004	1	1.197E-004	2.56	0.1280	
A2	0.14	1	0.14	3086.64	< 0.0001	
B2	3.536E-005	1	3.536E-005	0.76	0.3966	
C2	8.868E-005	1	8.868E-005	1.90	0.1863	
Residual	7.949E-004	17	4.676E-005			
Cor Total	0.17	26				

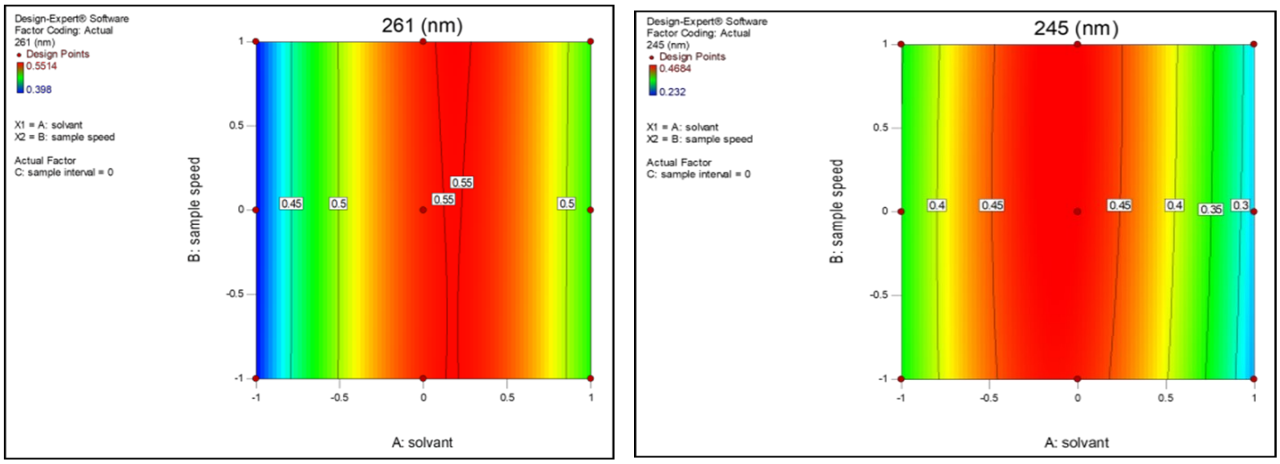


Figure 3: 2-D contour plot at 261 nm and 245 nm

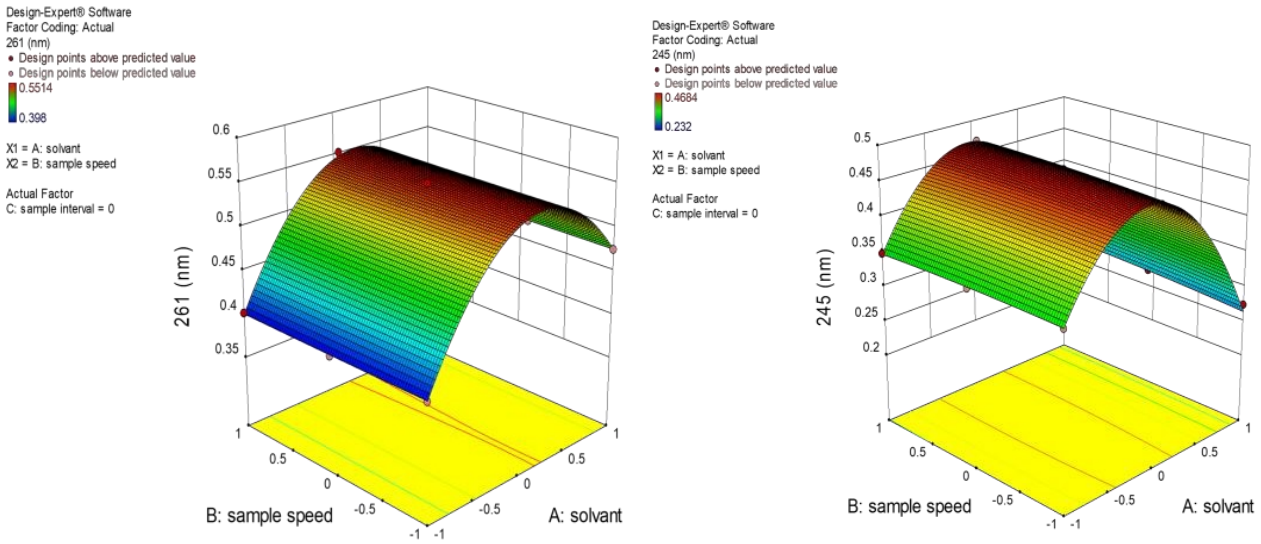
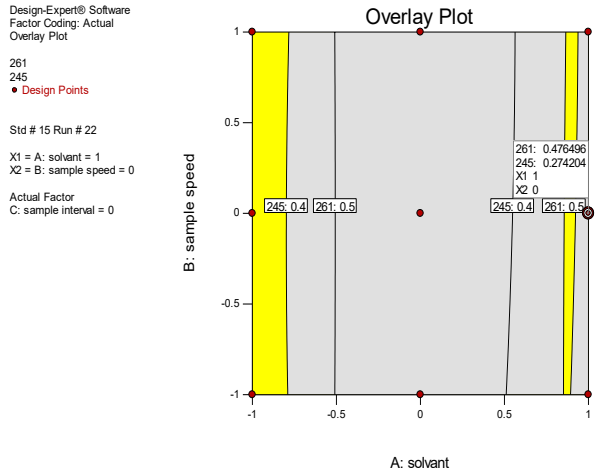


Fig no 4: 3-D contour plot at 261 nm and 245 nm

The 3-D Surface profiler & 2-D Contour analysis was carried out for interpretation as well as for optimization purpose. The contours obtained for optimized condition were proceed to further study with selected value for both CMVs. A curvilinear increase in response was observed at low level of scanning speed and there is no significant effect of sampling interval.



Optimization of Response

The optimized response for the factors X1 and X2 was obtained from the software Design Expert which is shown in figure below. In figure, the yellow region represents the optimized region as shown below.

Figure 3: Overlay Plot at 261 nm and 245 nm

Method validation:

Table 1: Linearity study of CM (n=5)

Sr No.	Conc. (µg/ml)	Absorbance at 261 nm	Absorbance at 245 nm
1	10	0.21892 ±0.000608	**0.22398 ±0.001827**
2	20	0.45332 ±0.001206	**0.37792 ±0.001211**
3	30	0.67286 ±0.001652	**0.51670 ±0.002665**
4	40	0.89952 ±0.000265	**0.65608 ±0.002066**
5	**50**	**1.15312 ±0.0009**	**0.78944 ±0.002494**

Table 2: Determination of Accuracy of CM

Level	Amount of drug taken (µg/ml)	Amount of Standard drug added (µg/ml)	Total Amt. (µg/ ml)	% Recovery		Standard deviation		%RSD	
				245 nm	261 nm	245 nm	261 nm	245 nm	261 nm
80%	20	16	36	95.36	96.54	0.00030	0.00043	0.082	**0.076**
100%	20	20	40	97.69	102.23	0.00042	0.00065	0.079	**0.149**
120%	**20**	**24**	**44**	**101.34**	**103.48**	**0.00032**	**0.00046**	**0.066**	**0.112**

Table 3: Repeatability data of CM (n=6)

Wavelength	Mean ± SD	%RSD
261 nm	0.682783±0.000504	0.073765
245 nm	0.5179±0.000358	0.069081

Table 4: Intraday Precision of CM

Concentration	At 261 nm		At 245 nm	
(µg/ml)	Mean ± SD (n=3)	%RSD	Mean ± SD (n=3)	%RSD
20	0.454833±0.000351	0.07715	0.376533±0.000306	0.081079
30	0.672133±0.000252	0.037427	0.5146±0.000458	0.08912
40	0.899467±0.000208	0.023145	0.655467±0.000404	0.061617

Table 5: Interday Precision of CM

Concentration (µg/ml)	At 261 nm		At 245 nm	
	Mean ± SD (n=3)	%RSD	Mean ± SD (n=3)	%RSD
20	0.456467±0.00040415	0.088454	0.375767±0.00035119	0.093376
30	0.672467±0.00035119	0.052198	0.514967±0.00032146	0.062406
40	0.899233±0.00023094	0.025686	0.6567±0.00052915	0.080528

Table 6: Analysis of tablet formulation

Formulation	Label claim mg/Tablet	Amount obtained mg/Tablet	% CM ± S.D.
ALLERMIN	4 mg	3.962	**99.56 ± 0.002218**
CADISTIN	4 mg	3.981	**98.73 ± 0.002346**
HISTA-12	**8 mg**	**7.976**	**99.12 ± 0.002145**

Table 7: Summary of Method Validation Parameters

Parameters	Observed Value	
Wavelength (nm)	261 nm	**245nm**
Linearity Range (µg/ml)	10-50 µg/ml	**10-50 µg/ml**
Regression equation	y = 0.0231x - 0.0129	**y = 0.0142x + 0.0858**
Correlation coefficient (R^2)	0.9995	**0.9996**
Precision (% RSD)		
Repeatability	0.073765	**0.069081**
Intra-day	0.07715-0.023145	**0.081079-0.061617**
Inter-day	0.088454-0.025686	**0.093376-0.080528**
Accuracy (% Recovery ± SD)		
80%	95.36 ± 0.00030	**96.54 ± 0.00043**
100%	97.69 ± 0.00042	**102.23 ± 0.00065**
120%	101.34 ± 0.00032	**103.48 ± 0.00046**
LOD (µg/ml) (n=5)	0.1527	**0.1436**
LOQ (µg/ml) (n=5)	**0.8235**	**0.7659**

CONCLUSION:

By employing the Analytical QbD Approach, robust UV spectrophotometric method was developed for the determination of Chlorpheniramine maleate in its pharmaceutical dosage form. CCD was performed on UV spectrophotometer to observe the effect of CMVs on CAAs. The three CMVs: Solvent, Scanning speed and Sampling interval was optimized to obtain a quality analytical method. The values obtained from method validationwereinthe range as per the ICH guideline. And so this QbD based analytical method can be employed for the estimation of Chlorpheniramine maleate in its pharmaceutical dosage form.

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