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Spectrophotometric Determination of Dapoxetine 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 Dapoxetine its pharmaceutical tablet dosage form. Developed originally as a selective serotonin reuptake inhibitor. Dapoxetine is used as an antidepressant 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. The method optimization was performed using a factorial design 33. Two wavelengths which are 251 nm and 291 nm was selected using water, 0.1 N HCl and Methanol as solvents (later Methanol was selected as final solvent). Linearity was observed at concentration of 10µg/ml-50µg/ml. The correlation coefficients for Dapoxetine at both wavelengths are 0.999 and 0.9994 the results of method validation were in the acceptable range as per ICH guidelines.

KEY WORDS: Dapoxetine, UV spectrophotometry, Quality by design, Validation, Pharmaceutical formulation.

INTRODUCTION

Initially developed as an selective serotonin reuptake inhibitor.Dapoxetine - chemically ((S)-N,N-Dimethyl-3-(naphthalen-1-yloxy)-1-phenylpropan-1-amine)
Dapoxetine, a new antidepressant, has been found to be safe and effective for the treatment of premature ejaculation.

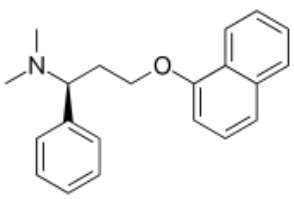

Figure 1. Chemical structure of the Dapoxetine

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.

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. 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. 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.

ELEMENTS OF QbD:

1) Quality target product profile- It is a summary of quality characteristics of drug product to ensure a desired quality, talk about safety and efficacy.

2) 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.

3) 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.

4) Critical quality attributes - CQA are a systemic aspect of a manufacturing control strategy and should be identified in stage 1 of Process Validation.

5) Quality risk assessments-"It is the fundamental process for the assessment, control, communication and review of risks to the quality of medical product across the product lifecycle."

6) Design of experiment (Doe) & design space- Design space is defined as, "Multidimensional combination and interaction of input variables that have been demonstrated to give assurance of quality."

7) Control strategy- A control strategy is designed to ensure that a required quality of product will be produced consistently. Data generated during method development the basis of the control strategy.

8) Continues improvement- The continuous monitoring allows an analyst to detect, identify & address any abnormal or out of trend performance of analytical method. The role of analytical method in control strategy is critical, & it begins from raw material testing to stability testing.

MATERIALS AND METHODS

Raw materials, reagents and equipment

For the corresponding steps to the development of the method and its validation, it was used as raw material the Intas pharmaceuticals ltd. The **reagents** were as follows: methanol, water and hydrochloric acid it was used **Instrumentation-**UV-Visible spectrophotometer: An UV-Visible spectrophotometer Shimadzu (UV-1800) with 1cm matched quartz cells was used for the spectral and absorbance measurements. And Digital balance: A REPTECH-RA123 digital Weighing balance was used for weighing purpose. Calibrated glassware was used for all parameters.

Preparation of standard and sample solution

Procedure for preparation of dapoxetine standard stock solution (1000µg/ml)

10mg of Dapoxetine was weighed and transferred to a 10ml volumetric flask and 5ml of methanol is added to dissolved the solution and finally volume is made up to mark with methanol.

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

Aliquot of 2.5 ml from above solution was pipette out into 25 ml of volumetric flask and volume is made up to mark with methanol to give a solution containing 25µg/ml.

Preparation of dapoxetine sample solution

Further from working solution 1ml-5ml was pipette out into 10 ml of volumetric flask and volume is made up to mark with methanol to give a solution containing 10-50µg/ml.

Analysis of tablets

Finely ground and powdered tablet equivalent to 5 mg of Dapoxetine was transferred into 50 ml volumetric flask and volume is adjusted to methanol up to the mark 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 Dapoxetine.

Validation of the analytical method developed

Linearity

The solution were prepared by pipetting 1,2,3,4,and 5 ml from working stock solution into 10ml volumetric flask and the volume was adjusted to mark with methanol to produce 10-50µg/ml respectively. The absorbance of solutions was measured at 291 nm and 251nm. Calibration

curve was generated by taking the absorbance verses concentration.

Accuracy

The accuracy of the method was determined by calculating recovery of dapoxetine 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 dapoxetine (100µg/ml) were transferred to 10ml volumetric flask and volume was adjusted to methanol to get concentration of 30µg/ml. The absorbance of solution was measured six times and calculate %RSD.

Intraday and Interday

Aliquots of 2,3 and 4 ml of working standard solution of dapoxetine (100µg/ml) were transferred to 10ml volumetric flask and volume was adjusted to methanol to get concentration of 20, 30 and 40µg/ml. The absorbance of solution was measured 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 = the standard deviation of Y- intercept of the calibration curves.

Slope = Mean slope of the 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 slope of the calibration curves.

RESULTS AND DISCUSSION

The experimental work describes UV Spectrophotometric method with QbD approach for analysis of dapoxetine in tablets. Dapoxetine was soluble in methanol. Standard Dapoxetine solution show absorption maximum at 251 &291 nm respectively in methanol & were selected as the detection wavelength.

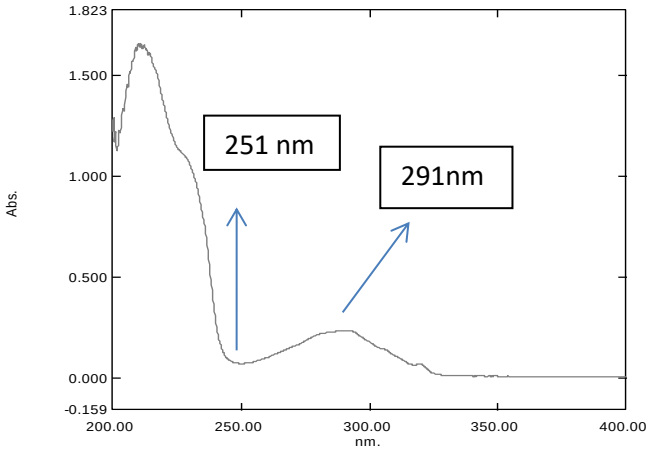

Figure 2 Typical UV spectra of Dapoxetine

CCD (central composite design) model was utilized for experimental investigation and the obtained result was studied through ANOVA. Analysis of the obtained results suggest Quadratic model for wavelength 291nm and linear model for wavelength 251nm. Analysis of ANOVA p value ($p< 0.05$) and satisfactory value of r2 ($r2> 0.9$) indicates the adequacy of the selected mathematical model. Satisfactory p- value found in ANOVA & predicted residual sum of square value suggest that the model is well fitted.

Quadratic Polynomial Equation at 291 nm

$= 0.49 + 0.11\ A + 2.222\ B + 1.550\ C – 9.667\ AB - 1.750\ AC - 1.300\ BC + 0.010A^2 + 4.811\ B^2 – 4.722\ C^2$

Quadratic Polynomial Equation at 251 nm

$= 0.13 + 0.11\ A – 2.611B – 2.161\ C + 3.033\ AB + 3.192\ AC + 1.917\ BC + 0.015\ A^2 – 6.267\ B^2 + 1.717C^2$

= Solvent B = Scanning speed C = Sampling interval

Table no: 1 Response 1- 291nm

Analysis of variance table [Partial sum of squares - Type III]						
	Sum of		Mean	F	p-value	
Source	Squares	df	Square	Value	Prob > F	
Model	0.20	9	0.022	818.67	< 0.0001	significant
A-solvent	0.20	1	0.20	7292.47	< 0.0001	
B-scanning speed	8.889E-005	1	8.889E-005	3.26	0.0889	
C-sampling interval	4.324E-005	1	4.324E-005	1.58	0.2252	
AB	1.121E-003	1	1.121E-003	41.07	< 0.0001	
AC	3.675E-005	1	3.675E-005	1.35	0.2620	
BC	2.028E-005	1	2.028E-005	0.74	0.4008	
A^2	6.114E-004	1	6.114E-004	22.39	0.0002	
B^2	1.389E-004	1	1.389E-004	5.09	0.0376	
C^2	1.338E-006	1	1.338E-006	0.049	0.8274	
Residual	4.641E-004	17	2.730E-005			
Cor Total	0.20	26				

Table no 2: Response 2- 251nm

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	2.171E-003	9	2.412E-004	3.65	0.0104	significant
A-solvent	1.227E-004	1	1.227E-004	1.86	0.1905	
B-scanning speed	6.728E-005	1	6.728E-005	1.02	0.3269	
C-sampling interval	8.407E-005	1	8.407E-005	1.27	0.2748	
AB	1.104E-004	1	1.104E-004	1.67	0.2132	
AC	1.222E-004	1	1.222E-004	1.85	0.1914	
BC	4.408E-007	1	4.408E-007	6.678E-003	0.9358	
A^2	1.411E-003	1	1.411E-003	21.37	0.0002	
B^2	2.356E-004	1	2.356E-004	3.57	0.0760	
C^2	1.768E-005	1	1.768E-005	0.27	0.6115	
Residual	1.122E-003	17	6.602E-005			
Cor Total	3.293E-003	26				

The 3-D Surface profiler & 2-D Contour analysis was carried out for interpretation as well as for optimization purpose Figure 3. The contour obtained (figure) for optimized condition were proceeded 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 responses

The optimized response for factor X1 and X2 was found from the Design Expert 10.0.1. and is shown in figure 4. The yellow region in figure is optimized region as shown below in that figure.

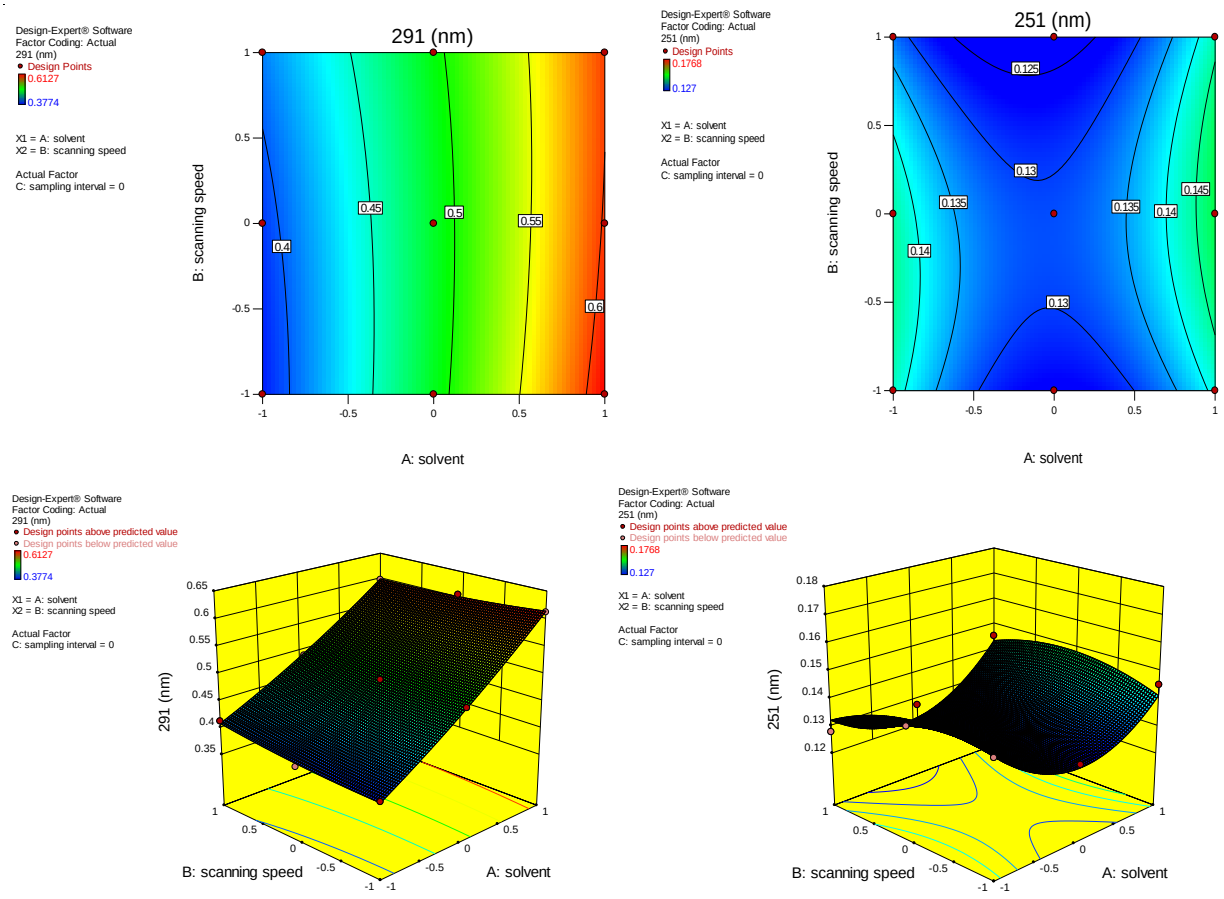

Figure 3. 3-D Surface profiler & 2-D Contour plots

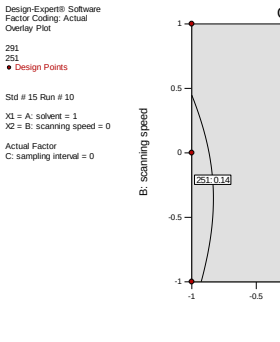

Figure 4 Overlay Plot

Table no 3: Linearity study of dapoxetine (n=5)

Sr No.	Conc. (µg/ml)	Absorbance at 291 nm	Absorbance at 251 nm
1.	10	0.2355 ± 0.0010	0.2164 ± 0.0012
2.	20	0.36660 ± 0.0008	0.3469 ± 0.0008
3.	30	0.4923 ± 0.0009	0.4738 ± 0.0003
4.	40	0.6396 ± 0.0003	0.6214 ± 0.0009
5.	50	0.7690 ± 0.0006	0.7364 ± 0.0005

Table no 4: Determination of accuracy of dapoxetine

Level	Amt of drug taken (µg/ml)	Amt of Std. drug added (µg/ml)	Total amt. (µg/ml)	% Recovery		Standard deviation		%RSD	
				291 nm	251 nm	291 nm	251 nm	291 nm	251 nm
80%	20	16	36	96.549	96.291	0.00030	0.00063	0.0830	0.0772
100%	20	20	40	98.225	101.231	0.00042	0.00075	0.0810	0.1636
120%	20	24	44	102.345	103.482	0.00032	0.00075	0.0469	0.1181

Table no 5: Repeatability data of dapoxetine (n=6)

Wavelength	Mean ± SD
291 nm	0.4963 ± 0.000241
251nm	0.4781 ± 0.000780

Table no 6: Intraday precision of dapoxetine

Concentration (µg/ml)	At 291 nm		At 251 nm	
	Mean ± SD (n=3)	%RSD	Mean ± SD (n=3)	%RSD
20	0.3664 ±0.0004	0.11029	0.3488 ± 0.0011	0.3306
30	0.4963 ± 0.0008	0.16577	0.4723 ± 0.0008	0.1825
40	0.6324 ± 0.0008	0.13814	0.6289 ± 0.0009	0.1442

Table no 7: Interday Precision of dapoxetine

Concentration (µg/ml)	At 291 nm		At 251 nm	
	Mean ± SD (n=3)	%RSD	Mean ± SD (n=3)	%RSD
20	0.3625 ± 0.0015	0.42996	0.3442 ± 0.0011	0.33524
30	0.4919 ± 0.0008	0.17288	0.4731 ± 0.0018	0.38063
40	0.6337 ± 0.0010	0.16892	0.6325 ± 0.0012	0.19775

Table no 8: Analysis of tablet formulation

Formulation	Label claim mg/Tablet	Amount obtained mg/Tablet	%dapoxetine ± S.D.
STAY TAL	60 mg	59.982	99.48 ± 0.000624
DURAJECT	60 mg	59.995	99.23 ± 0.000593

Table no 8: Summary of method validation parameters

Parameters	Observed Value	
Wavelength (nm)	291 nm	251nm
Linearity Range (µg/ml)	10-50	10-50
Regression equation	y = 0.0134x + 0.0986	y = 0.0131x + 0.0846
Correlation coefficient (R2)	0.9994	0.999
Precision (% RSD)		
Repeatability	0.6529	0.1639
Intra-day	0.1102-0.1381	0.4299-0.1689
Inter-day	0.3306-0.1442	0.3352-0.1977
Accuracy (% Recovery ± SD)		
80%		
100%	96.549-0.00030	96.291-0.00063
120%	98.225-0.00042	101.231-0.0005
	102.345-0.00032	103.82-0.00075
LOD (µg/ml) (n=5)	0.1899	0.1987
LOQ (µg/ml) (n=5)	0.5575	0.6022

CONCLUSION:

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

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