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Quality by Design Approach for an Orally Disintegrating Tablet Analytical Method Validation

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ABSTRACT

Quality by Design (QbD) is well established in the pharmaceutical industry for pharmaceutical development and manufacturing processes. The knowledge obtained during development may support the establishment of a design space and determines suitable process controls. This same QbD principle has been applied to the development of analytical methods and is termed "Analytical Quality by Design" (AQbD). Analogous to process QbD, the outcome of AQbD is well understood, fit for purpose, and robust method that consistently delivers the intended performance throughout its life cycle. The present work is aimed to develop an AQbD approach to analytical method development and validation based of Tadalafil and its impurities by the NP-HPLC method. The other objective of this work is to establish an in-depth understanding of the method and build in the quality during the method development to ensure optimum method performance over the lifetime of the product.

Keywords: Analytical Quality by Design (AQbD), Quality by Design (QbD), Robustness, Analytical Method Validation.

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INTRODUCTION

Tadalafil is a potent and selective inhibitor of phosphodiesterase type 5 (PDE5), the enzyme responsible for the degradation of cyclic guanosine monophosphate (cGMP). [1] Pulmonary arterial hypertension is associated with the impaired release of nitric oxide by the vascular endothelium and consequent reduction of cGMP concentrations within the pulmonary vascular smooth muscle. PDE5 is the predominant phosphodiesterase in the pulmonary vasculature. [1] Inhibition of PDE5 by tadalafil increases the concentrations of cGMP resulting in relaxation of the pulmonary vascular smooth muscle cell and vasodilation of the pulmonary vascular bed. [1] The chemical name of tadalafil is (6R-trans)-6-(1,3-

benzodioxol-5-yl)-2,3,6,7,12,12 a-hexahydro-2-methyl-pyrazino [1',2':1,6] pyrido [3,4-b] indole-1,4-dione. [1]

It is official in the European Pharmacopoeia where its purity testing is accomplished by using high-performance liquid chromatography (HPLC) with UV-detection on a Chiralpack AD-H column (250 × 4.6 mm, 5µ particle size) in isocratic mode with an eluent consisting of hexane and 2-propanol (50:50) and a flow rate of 0.75 mL/min. The monograph points out that the impurity A is a specified impurity, have a specific test method for A, B, and C, while impurities B, C, D, E, F, G and I are unspecified impurities (see Table 1).

Over the past decades, orally disintegrating tablets (ODTs) have gained considerable attention as a preferred alternative to conventional tablets and capsules due to better patient compliance. [2] ODTs are solid dosage forms containing active ingredients which disintegrate rapidly through the buccal mucosa. It is desirable in the treatment of a number of diseases. They are also advantageous for administrations of medicaments to patients who are travelling or have little access to water are similarly affected or patients who have difficulties swallowing other dosage forms.

The aim of our study was to apply Quality by Design (QbD) [3-4] principles to build in a more scientific and risk-based multi-factorial approach to the development and validation of a new HPLC method for tadalafil impurities and degradation products in the ODT formulation using knowledge acquired from analytical method which is described in European Pharmacopeia for tadalafil drug substance.

QbD is a concept first outlined by well-known quality expert Joseph M. Juran in various publications, most notably Juran on Quality by Design. [5] While QbD principles have been used to advance product and process quality in every industry, and particularly the automotive industry, they have most recently been adopted by the U.S. Food and Drug Administration (FDA) [6-9] as a vehicle for the transformation of how drugs are discovered, developed, and commercially manufactured. Since first initiated by the FDA in its "Pharmaceutical cGMPs for the twenty-first century", QbD has become an important concept for the pharmaceutical industry that is further defined in the International Conference on Harmonisation (ICH) guidance on pharmaceutical development. [10]

QbD [11-14] is well established in the pharmaceutical industry for manufacturing processes (ICH Q8 for pharmaceutical development and ICH Q11 for development and manufacture of drug substances). QbD is "a systematic approach to development that begins with predefined objectives and emphasizes understanding and control, based on sound science and quality risk management". The outcome of using QbD concepts is a well-understood product and process that consistently delivers its intended performance. The knowledge obtained during development may support the establishment of a design space and determines suitable process controls. This same QbD principle has been applied to the development of analytical methods and is termed "Analytical Quality by Design" (AQbD). Analogous to process QbD, the outcome of AQbD is well understood, fit for purpose, and robust method that consistently delivers the intended performance throughout its lifecycle. It is a current trend among pharmaceutical industry to implement AQbD in method development process as a part of risk management, pharmaceutical development, and pharmaceutical quality system (ICH Q10). Workflow of AQbD has been illustrated in Figure 1. [15]

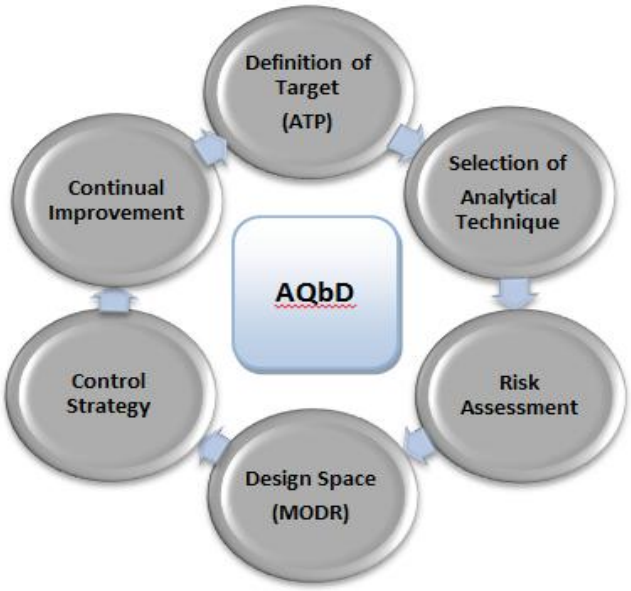

Fig. 1: Workflow of AQbD

Just as QbD requires a target product profile, drug developers also need an Analytical Target Profile (ATP). Definition of ATP means the determination of what to measure and where/when to measure it. ATP is the prospective summary of measurement requirements that ensure that the method is 'fit for purpose'. [16] ATP includes accuracy, precision, and validation parameters, and focuses on method understanding (e.g., multivariate relationships, mechanistic understanding). Examination of potential variables is performed in this definition phase, prior to experiments. This helps to focus on specific variables and their ranges. The potential variables that can impact method quality can be identified using an Ishikawa (fishbone) diagram (Figure 2). [17]

Statistical Design of Experiment (DoE) methods are extensively applied in process design to help process engineers understand the effects of possible multidimensional combinations and interactions of various parameters on final drug quality. [18] Application of a DoE strategy provides a scientific understanding of the effects of multiple process parameters and raw material attributes on product Critical Quality Attributes (CQAs) and leads to establishment of a "design space" and manufacturing control strategy.

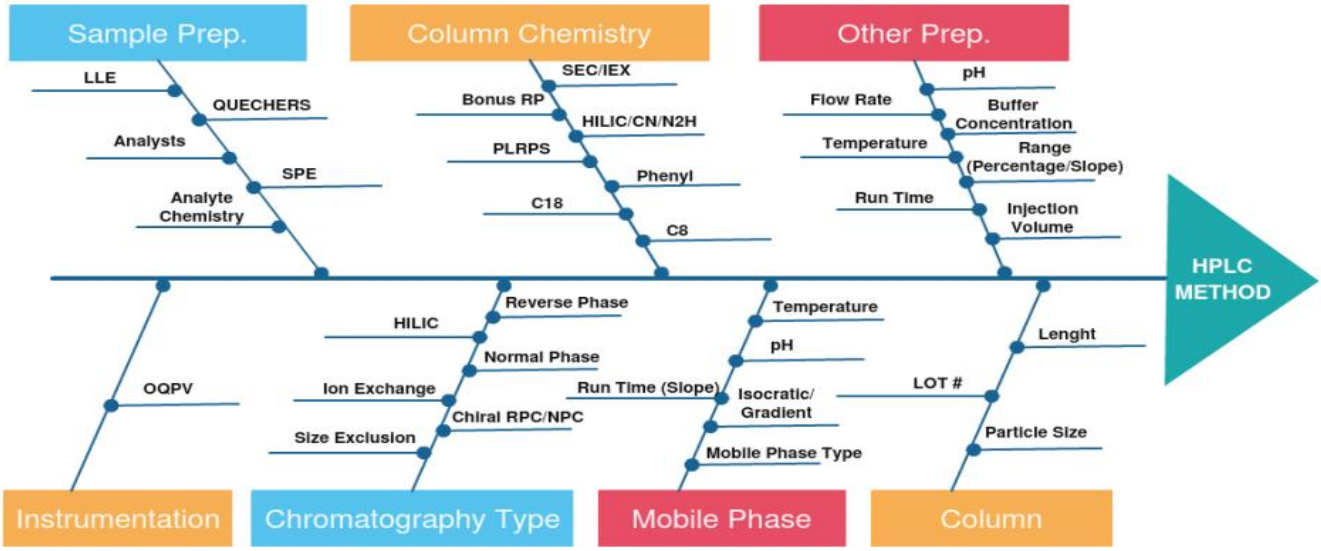

Fig. 2: The Ishikawa or Fishbone diagram to identify potential variables in HPLC method development

CQA is 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. CQAs are generally associated with the drug substance, excipients, intermediates (in-process materials), and drug product. [11] This interpretation of CQA is most applicable to in-process and finished product specification limits, which suggests that these limits must be critical given that they were designed to ensure product quality. During the early stages of process development and design, other quality attributes may be measured that, over the course of development, do not end up as either in-process or finished product test in the commercial process. [19] These test results may show little variation and present little to no risk to product quality. [19] In other cases, while process duration or yield is measured, they are not related to the product quality and are, therefore, not CQAs. [19] However, even when defined as critical, not all CQAs have equal impact on safety and effectiveness. [19]

In statistics, a Central Composite Design (CCD) is an experimental design, useful in response surface methodology, for building a second order (quadratic) model for the response variable without needing to use a complete three-level factorial experiment. [20] After the designed experiment is performed, linear regression is used, sometimes iteratively, to obtain results. Coded variables are often used when constructing this design. A central composite design is the most commonly used response surface design experiment. Central composite designs are a factorial or fractional factorial design with center points, augmented with a group of axial points (also called star points) that help to estimate curvature. A central composite design can be used to efficiently estimate first and second order terms. [21] Model a response variable with curvature by adding a center and axial points to a previously done factorial design. [21] Selection of analytical technique is one of the other important steps in AQbD workflow. Definition of the technique and method performance criteria should be performed a case by case in a scientific manner.

Risk Management tools like FMEA and hazards analysis used for process understanding can also be used for analytical development. For instance "What's the hazard in using the selected chromatography column vs another" can be the question. Analytical method design space is a science and risk-based and multivariate approach to evaluate effects of various method input variables on method performance. Method performance criteria can be considered as response factors. Analytical design space can be conducted together with method validation. [16] It may be determined by a first principles approach, a non-mechanistic, empirical approach, risk analysis, and other approaches. Analytical method design space can be named as Method Operable Design Region (MODR). Analytical methods are a key part of a robust control strategy. Process controls and specifications that have good analytical methods go a long way towards assuring product and process performance and product quality.

Continual Improvement: For analytical methods includes the continual monitoring of method performance, flexibility for movement with the design space (MODR), and the need to maintain models. It requires efficient change management so that analytical method developers can: track and trend method performance; respond to trends before they become problems; and verify that method changes are effective. [15] Summary of AQbD elements and examples has been presented in Table 2. [22]

High-performance liquid chromatography (HPLC) [23-24] is a type of column chromatography used frequently in analytical chemistry and biochemistry. NP-HPLC is one of the choices for the sample analysis. It consists of a polar stationary phase and a non-aqueous, moderately non-polar mobile phase. The quality of HPLC methods

has become increasingly important in AQbD environment. [25]

Development of HPLC methods, for active pharmaceutical ingredients and their impurities in drug substances and drug products, following AQbD concepts have been extensively reported in the literature. The tadalafil impurities are based on the pharmacopeial method and they are presented in Table 1.

Table 1: Structures of tadalafil and its impurities [26]

Name	Chemical Formula
Tadalafil	(6R,12aR)-6-(1,3-benzodioxol-5-yl)-2-methyl-2,3,6,7,12,12a-hexahydropyrazino [1′,2′:1,6]-pyrido[3,4-b]indole-1,4-dione
Impurity A	(6R,12aS)-6-(1,3-benzodioxol-5-yl)-2-methyl-2,3,6,7,12,12a-hexahydropyrazino [1′,2′:1,6]-pyrido[3,4-b]indole-1,4-dione
Impurity B	(6S,12aS)-6-(1,3-benzodioxol-5-yl)-2-methyl-2,3,6,7,12,12a-hexahydropyrazino [1′,2′:1,6]-pyrido[3,4-b]indole-1,4-dione
Impurity C	(6S,12aR)-6-(1,3-benzodioxol-5-yl)-2-methyl-2,3,6,7,12,12a-hexahydropyrazino [1′,2′:1,6]-pyrido[3,4-b]indole-1,4-dione
Impurity D	(6bR)-12-(1,3-benzodioxol-5-yl)-12a-hydroxy-8-methyl-6a,6b,8,9,12,12a-hexahydropyrazino[1′,2′:1,2]-pyrrolo[3,4-c]quinolone-6,7,10(5H)-trione
Impurity E	(6R,12aR,12bR)-6-(1,3-benzodioxol-5-yl)-6ahydroxy-2-methyl-2,3,6a,7,12a,12b-hexahydropyrazino[1′,2′:1,5]pyrrolo[3,4-b] quinolone-1,4,12(6H)-trione
Impurity F	(8a′R)-6′-(1,3-benzodioxol-5-yl)-2′methyl-2′,3′8′,8a′-tetrahydro-6′H-spiro[3,1-benzoxazine-4-7′-pyrrolo[1,2-a]pyrazine]-1′2,4′(1H)-trione
Impurity G	(12bR)-6-(1,3-benzodioxol-5-yl)-12-hydroxy-2-methyl-2,3,6,12b-tetrahydropyrazine [1′,2′:1,5]pyrrolo-[3,4-b]quinolone-1,4-dione
Impurity H	(6R,14aR)-6-(1,3-benzodioxol-5-yl)-2-methyl-2,3,14,14a-tetrahydropyrazino[1,2-d][1,4]benzodiazonine-1,4,7,13-(6H,8H)-tetrone
Impurity I	(8a′R)-6′-(1,3-benzodioxol-5-yl)-2′-methyl-2′,3′8′,8a′-tetrahydro-6′H-spiro[indole-3,7′-pyrrolo[1,2-a]pyrazine]-1′,2,4′(1H)-trione

Table 2: AQbD elements and examples [22]

AQbD Terminology	Examples
Analytical Target Profile	Accurate quantitation of API without interferences from degradants
Quality Target Method Profile (QTMP)	pKa, Log P, Solubility
Critical Method Parameters (CMP)	Flow rate, temperature, pH
Critical Method Attributes (CMA)	Resolution, peak tailing, peak capacity

MATERIAL AND METHODS

Materials

Solutions were prepared using Acetonitrile, n-Hexane, and 2-Propanol from Merck (Darmstadt, Germany) and all chemicals were analytical grade. Water used was purified by a Milli-Q Academic water purification system (Millipore, Eschborn, Germany). Tadalafil working standard, tadalafil impurity A, tadalafil impurity B and tadalafil impurity C working standards were obtained from Mylan Lab. (Kadubesanahalli, Bangalore, India). An Agilent 1200 Series HPLC (Agilent Technologies, Santa Clara, CA) system consisting of a high-pressure pump with an online degasser, an autosampler, a column oven, and a variable wavelength detector was used for all experiments. A diode array detector from Agilent was used for determining spectral peak purity. Chiralpak AD-H column (GL Science, Torrance, CA) of 4.6 mm x 250 mm dimensions and 5µm particle size was used in optimization of the in-house method. All chromatographic experiments were performed in the gradient mode. The eluent was prepared by mixing n-hexane and 2-propanol at the ratio 62:38 respectively. The eluent was filtered through 0.22µm membrane filter. The diluent was prepared by mixing acetonitrile, n-hexane, and 2-propanol at the ratio 20:40:40 respectively. The flow rate was set to 1.0 ml/min and the injection volume was 20µL. The temperature in the column oven was at 30°C. The UV detection was carried out at 222 nm and the UV spectra were taken in the range of 200–400 nm. Instrument control and data acquisition were performed using Waters' Empower 2 Chromatography Data System. Statistical analysis was calculated using the Design-Expert® statistical software (Stat-Ease, Inc., Minneapolis, USA).A standard solution containing tadalafil (Mylan, Bangalore, India) was prepared with diluent. This standard solution was used in all screening and optimization experiments.A sample solution of tadalafil ODT tablets (Sanovel, Istanbul, Turkey) was prepared with diluent. The sample solution was filtered through a 0.45µm teflon filter and the resulting clear solution was used for the HPLC determination.

Methods

Our innovative development strategy follows QbD principles of method validation. The primary goal of developing an HPLC method is generally to separate the API from impurities (resolution Rs > 2.0) that may impact the quality of the pharmaceutical formulation. Other factors, such as mobile phase flow and column temperature are also considered. Crucial for the Quality-by-Design approach is to create a visual "Design Space", in which the method is robust. In an early risk assessment, the critical parameters should be identified. As the result of the risk assessment, the three parameters gradient ratio, column temperature, and flow were optimized – after choosing the best stationary phase – due to their strong known influential effect on selectivity.

The optimized HPLC method was validated following the ICH Q2 (R1), ICH Q3A (R2), ICH Q3B (R2), guidelines for quantitation of impurities.

RESULTS AND DISCUSSION

The experimental variables included mobile phase flow from 0.8 to 1.2 mL/min. and column temperature from 25 to 35°C. The software generated test plan included 13 unique combinations of mobile phase flow/column temperature. The standard solutions, consisting of diluent and tadalafil were injected at each condition.

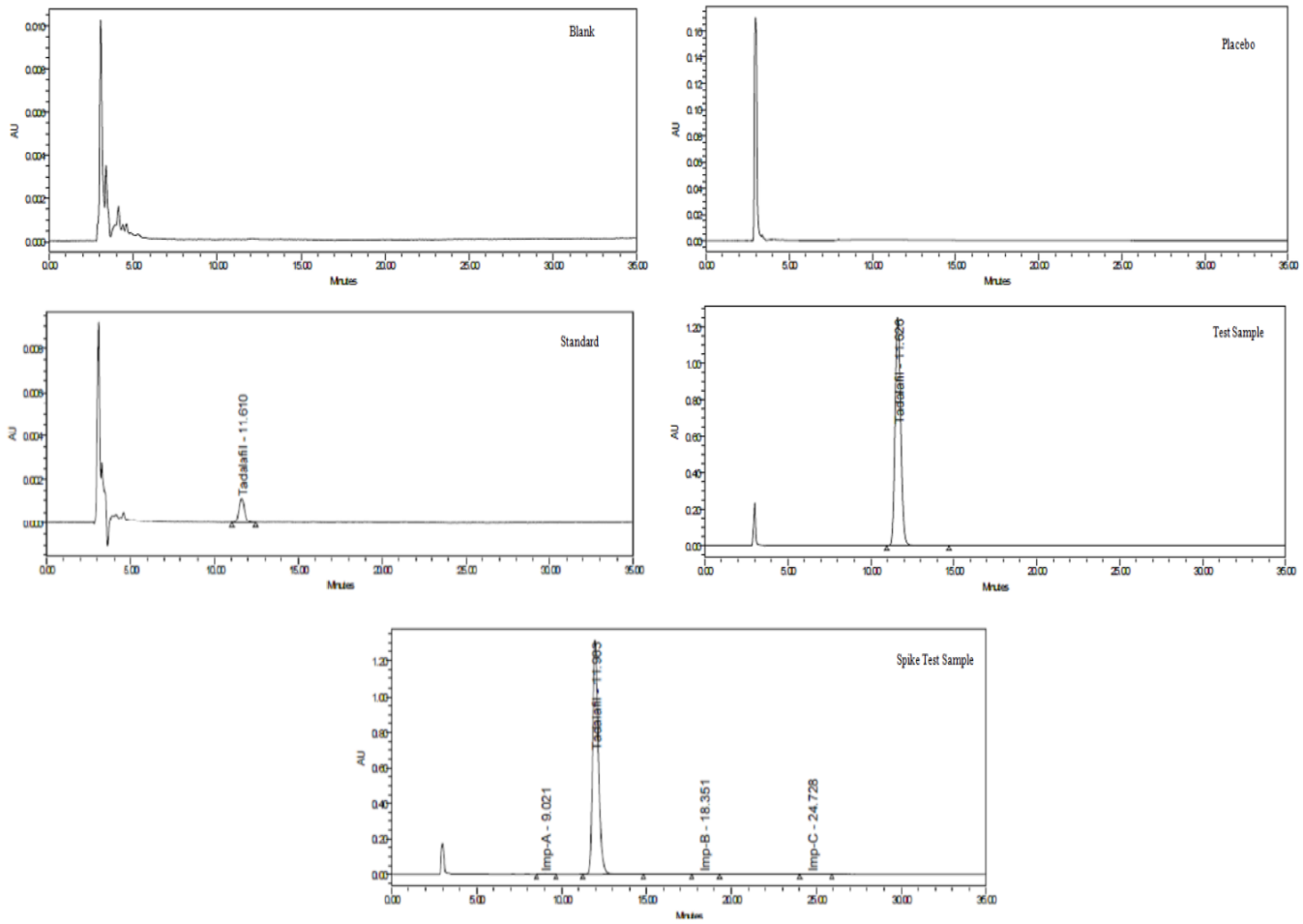

Fig. 3: Chromatograms of tadalafil and its impurities.

The Empower results were then transferred to the Design Expert® 8.0 software for modeling purpose, and the optimum conditions were obtained that would yield minimum retention time and maximum resolution between the consecutive peaks and minimum relative standard deviation for six replicate injections of standard solution. The software parameters set optimum conditions and mobile phase flow at 1.0 mL/min. and column oven temperature of 30.0°C. The results showed that it was feasible to run the optimized HPLC method using AD-H column for tadalafil and its impurities. Attempts to use mobile phase ratio of 50:50 (v:v) at flow rate 0.75 mL/min. was not successful since placebo solution gave a peak at the same retention time with impurity A and impurity C. Attempts to use mobile phase ratio of 65:35 (v:v) at a flow rate 0.75 mL/min. was not successful since placebo solution gave a peak at the same retention time with impurity B. Adjusting of mobile phase ratio as 62:38 (v:v) at a flow rate 0.75 mL/min. gave suitable peaks which the resolution between impurity A and tadalafil is higher than 2.0. The flow rate adjusted to 1.0 mL/min. to reduce the analysis time which resolution between impurity A and tadalafil is 2.5. AD-H column was then used to validate the method. Chromatograms are presented in Figure 3.

Robustness parameter and acceptance criteria are shown in Table 3. CCD was applied to method parameters presented in Table 4. The effect of this changes on system suitability parameters and test results were reviewed by the perspective of design space and statistical data. DoE was performed as randomly. Chromatographic factors and response variables for experimental design are presented in Table 5.

Table 3: Robustness parameter and acceptance criteria

Parameter	Experiments	Acceptance Criteria
Robustness	Mobile phase flow and column temperature	The difference of results between original analytical method and DoE should not be more than 0.03%. Changes in retention times will be observed and reported. All statistical models which are used for mathematical predictions and design space should be significant ($p<0.05$), lack of fits should be unsignificant ($p>0.05$), R^2 and Adeq precision which is used for evaluation of the adequacy of the model should be sufficient (>0.50 and >4 respectively).

Table 4: Method parameters

Software	Design Expert® 8.0
Method Parameters	Column Temperature (°C): 30 Flow Rate (mL/min.): 1.0

Table 5: Chromatographic factors and response variables for experimental design

Chromatographic Factors	Experiments	
	Low	High
Flow rate	0.75 mL / min.	1.2 mL / min.
Mobile phase ratio (n-Hexane:2-Propanol)	50:50 (v:v)	62:38 (v:v)
Column temperature	25°C	35°C
Runtime	35 min.	40 min.
Response	Goal	
USP Resolution	Maximize (< 2.0)	
Standard RSD (%)	≤ 5.0	

Run	Chromatographic Factors		
	A: Flow Rate	B: Column Temperature	Design Points
1	1.0	30	Center
2	1.2	30	Star
3	1.0	25	Star
4	1.1	34	Factorial
5	1.0	30	Center
6	1.0	30	Center
7	1.1	26	Factorial
8	0.9	26	Factorial
9	1.0	35	Star
10	1.0	30	Center
11	0.8	30	Star
12	0.9	34	Factorial
13	1.0	30	Center

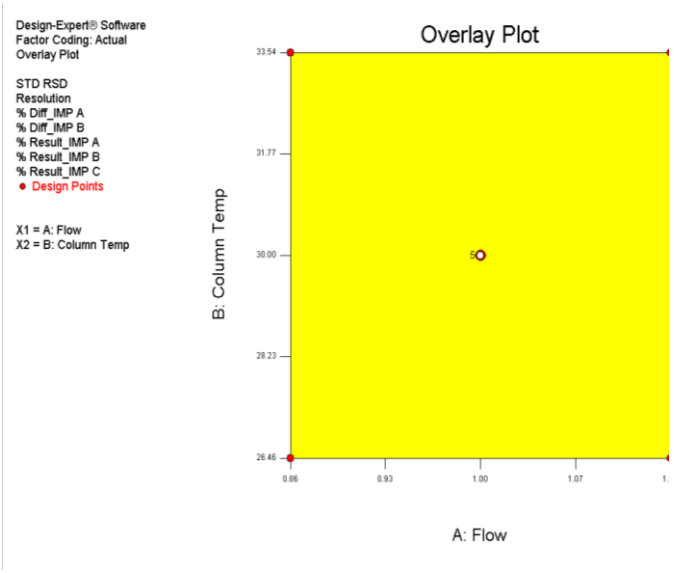

Fig. 4: Design space overlay plot

Results are presented in Table 6-7-8. Design space overlay plot is presented in Figure 4. Yellow area in Figure 4 is created the design space which is constituted of specification limits.

Table 6: Results of DoE

Run	Chromatographic Factors		Responses			Acceptance Criteria								
						Retention Time			Difference (%)			Results (%)		
	A Flow Rate	B Column Temperature	Design Points	RSD	Resolution	Impurity A	Impurity B	Impurity C	Impurity A	Impurity B	Impurity C	Impurity A	Impurity B	Impurity C
1	1.0	30	Center	2.6	5.1	9.12	18.09	25.84	0.00	0.00	0.00	0.173	0.105	0.094
2	1.2	30	Star	5.2	4.8	7.56	15.0	21.39	-0.01	0.00	0.01	0.160	0.105	0.099
3	1.0	25	Star	1.5	5.1	9.45	19.2.	28.77	-0.01	0.00	-0.02	0.167	0.103	0.075
4	1.1	34	Factorial	2.5	4.9	8.07	15.66	21.59	-0.01	0.00	0.00	0.160	0.101	0.094
5	1.0	30	Center	3.0	5.1	9.11	18.04	25.87	-0.01	-0.01	-0.01	0.160	0.099	0.080
6	1.0	30	Center	2.5	5.1	9.11	18.02	25.83	-0.01	-0.01	-0.01	0.160	0.097	0.081
7	1.1	26	Factorial	2.4	5.0	8.49	17.15	25.56	-0.02	-0.01	-0.01	0.150	0.094	0.087
8	0.9	26	Factorial	1.8	5.3	10.4	21.00	31.28	0.01	0.01	0.01	0.180	0.111	0.103
9	1.0	35	Star	1.4	5.1	8.8	16.97	23.29	0.01	0.01	0.02	0.178	0.117	0.116
10	1.0	30	Center	1.7	5.2	9.0	17.92	25.88	0.00	0.01	0.01	0.175	0.112	0.099
11	0.8	30	Star	2.0	5.5	11.36	22.45	32.44	0.00	0.00	0.01	0.174	0.109	0.100
12	0.9	34	Factorial	0.4	5.2	9.79	18.98	26.38	0.00	0.00	0.01	0.168	0.107	0.108
13	1.0	30	Center	1.4	5.1	9.0	17.81	25.69	-0.01	0.00	0.00	0.160	0.102	0.093

- System suitability criteria were met at each of the nominal and varied conditions.
- All results of retention time and % differences were within the limits that set in the analytical method protocol. Since variability is low, a statistical model was not applied and not included into DoE.
- It is reported that statistical models for the response to RSD, resolution, and results (%) are significant, errors are insignificant, R^2 and Adeq precision results are adequated. Thus these models and mathematical equations of prediction are used for optimization and formation of design space.
- From the models used in the DoE, Impurity C % results value is affected by column temperature, the flow rate was found to be the most effective parameter in other models. The reduction of flow rate was observed to affect the Impurity A and B (%) conclusion and the RSD and resolutions values of the system suitability parameters in the positive direction.
- Optimization limits are determined by analytical method protocol. All system suitability criteria (RSD, resolution) are met the acceptance criteria which in developed statistical of design space.
- The differences between original method and % result values of modified method are should be less than 0.03.
- Therefore the validated analytical method is stable within this design space.

The HPLC method for tadalafil impurity A, B and C was successfully optimized using QbD approach. Key quality attributes of the method are the constant retention times for standard and sample, robustness, and implementation of using significant and relevant system suitability. The optimized method was successfully validated. The method has been routinely

used for the determination of tadalafil impurity A, B, and C.

The understanding of the method was a major concern when developing an analytical method and even more so when dealing with impurities from complex matrices. In the presented case study, an AQbD approach was applied in order to optimize a method.

Table 7: Mathematical equations developed by statistically for significant models

		Equation of Predictions
Standard	RSD	+2.46582-65.77753*Flow rate Model p value 0.0279 Lack-of-fit p value 0.3867 R-Squared 0.8 Adeq Precision 8.136 6.348
Impurity A	Resolution	+6.73285-1.40533*Flow rate Model p value 0.0001 Lack-of-fit p value 0.2165 R-Squared 0.9 Adeq Precision 19.522
	Result	+0.20325-0.051088*Flow rate Model p value 0.0487 Lack-of-fit p value 0.6041 R-Squared 0.5 Adeq Precision 5.839
Impurity B	Result	+0.41096-0.42753*Flow rate Model p value 0.0493 Lack-of-fit p value 0.6476 R-Squared 0.7 Adeq Precision 5.717
Impurity C	Result	+0.048077+2.47426*10^{-3}*Column Temperature Model p value 0.0484 Lack-of-fit p value 0.3886 R-Squared 0.5 Adeq Precision 5.613

*The significant level of mathematical equations of prediction was created based on the real values by using factors determined according to the p-value. According to ANOVA table, p-value <0.05 factors are effective on results. R-Squared and Adeq Precision values are representative parameters of compatibility of theoretical and experimental results. The r-squared value should be more than 0.5 and Adeq Precision value should be more than 4 to use the model in optimization and DoE.

Table 8: Optimization limits identified for design space

	Optimisation Limits
RSD (%)	≤ 5.0
Result (%)	80-120

Commercialized software proposing an AQbD compliant HPLC method development is a critical requirement to harmonize the strategies and to arouse the interest of the scientific community about the improvement of these strategies. In this paper, the software dedicated to an AQbD compliant HPLC method development was used to develop a method for the analysis of tadalafil impurity A, B, and C. During the method development, some innovative improvements were made. One of them is the identification of the selectivity zone allowing easy and fast peak tracking and identification. It also allows the use of the resolution as the response within this selectivity zone because the elution order did not drastically change and selectivity was almost maintained. Therefore, the resolution followed a continuous variation without salient points allowing its accurate modeling by multiple linear regressions. Finally, the quality was built in the method development and the error propagation gave an estimation of the method robustness. Assurance of quality is thus achieved by simultaneously predicting qualitative and robustness CQAs.

A systematic and practical approach was utilized to develop an efficient and robust HPLC method to quantify the identified tadalafil impurity A, B, and C. The application of AQbD resulted in a methodology that was simple in implementation, chromatographically efficient and did not require gradient elution to separate the structurally similar tadalafil impurity A, B, and C. Multivariate regression analysis was successfully employed to effectively screen the main effects of factors that significantly affected the resolution and tailing of the impurity peaks. Two factors that were determined to significantly affect the peaks were then analyzed to determine their interactions and quadratic effects with the least number of runs as possible using a Design Expert® in conjunction with response surface methodology. A desirability function was applied to determine the optimum conditions that could accurately quantify tadalafil impurity A, B, and C.

An innovative AQbD approach for the development of a fast and reliable HPLC method has been presented in this article. A design space – a volume in which the method is robust – is defined and visualized. The method was fully validated in compliance with ICH guidelines and a robustness study was performed by varying a design space.

The AQbD approach on this method development and validation phases provided better understanding and more robust method in less time compared to traditional method development.

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