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Original Article

QbD-Enhanced HPLC Method Development for Vildagliptin and Metformin HCl Formulations

Pankaj Sopan Hasabe[1,2], Kishor Vinayak Gaikwad[1], Venketa Satyanarayana Nandmuri[2], Akanksha Govind Kolekar[3], Kalyanraman Lakshmi Narayanan[2], Samadhan Prakash Pawar[1,3,*]

[1]Department of Chemistry, Rajarshi Chhatrapati Shahu College, Kolhapur, Maharashtra, INDIA.
[2]Research and Development, Integrated Product Development, Dr. Reddy's Laboratories Ltd., Bachupally, Hyderabad, Telangana, INDIA.
[3]Department of Chemistry, Fluorescence Spectroscopy Research Laboratory, Shivaji University, Kolhapur, Maharashtra, INDIA.

ABSTRACT

Objectives: This research employs the Quality by Design strategy to design an optimized High-Performance Liquid Chromatography method aimed at analyzing vildagliptin and metformin hydrochloride in pharmaceutical dosage forms. **Materials and Methods:** The mobile phases A and B comprised a buffer-acetonitrile mixture in ratios of 950:50 v/v and 600:400 v/v, respectively. Chromatographic separation was achieved using an YMC Triart C-18 column, with Vildagliptin detection conducted at 210 nm via UV absorbance. Various independent parameters were selected for investigation and risk assessment was employed to evaluate their impact on the analytical responses. **Results:** QbD prioritizes product understanding, risk management and process control to enhance quality assurance and regulatory tractability. Analytical Quality by Design principles ensure robust and flexible methods throughout the product lifecycle. **Conclusion:** This study developed a robust HPLC method for Vildagliptin using a Quality by Design (QbD) approach. Key factors like mobile phase composition and buffer pH were optimized through multivariate analysis. The resulting method, validated for accuracy, precision and robustness, outperformed traditional methods and is suitable for routine pharmaceutical analysis.

Keywords: HPLC method development, Metformin hydrochloride, Pharmaceutical dosage forms, Product understanding, Quality by Design, Risk management, Vildagliptin.

Correspondence:
Dr. Samadhan Prakash Pawar[1,2]
[1]Department of Chemistry, Rajarshi Chhatrapati Shahu College, Kolhapur-416003, Maharashtra, INDIA.
[2]Department of Chemistry, Fluorescence Spectroscopy Research Laboratory, Shivaji University, Kolhapur-416004, Maharashtra, INDIA.
Email: sampawar1987@gmail.com

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INTRODUCTION

The current research work aims to utilize the QbD procedure for developing and optimizing a high performance LC technique for vildagliptin and metformin hydrochloride in a pharmaceutical dosage form. QbD is a methodical method improvement strategy that kicks off with predetermined goals and stresses a comprehensive consideration of both the product and the process. This involves prioritizing knowledge of products and manufacturing procedure, quality risk assessment and process rheostat, all based on thorough scientific principles.[1] By employing QbD principles, the primary goal is to ensure a higher level of confidence regarding product eminence, gain regulatory flexibility and continuously improve the method throughout its lifecycle. To achieve this, the foundation of the QbD method lies in implementing established guidelines, such as ICH Q8 Pharmaceutical Development, ICH Q9 Quality Risk Management and ICH Q10 Pharmaceutical Quality System.[2-4] In context of pharmaceutical product development, analytical science plays a critical role leading to the concept of analytical QbD. A scientific and risk-based approach for developing analytical methods is analytical QbD. Its objective is to recognizing predetermined goals and effectively drive critical essential scheme having properties that are affected by method variables. The end outcome of this strategy is improved method performance as well as high resilience, robustness and adaptability for ongoing expansion.[5,6] The application of AQbD leads to the establishment of a well-known, appropriate and reliable technique that consistently conveys the projected results over the entire product life span, analogous to the method QbD.[7,8] To make sure the technique is effective and reliable throughout the product's lifespan, it is crucial to assess the robustness and ruggedness of HPLC methods early in the method development stage for QbD. This proactive approach prevents the need for extensive redevelopment, revalidation and retransfer of analytical methods in the case of adopting a weak or unreliable system.[9] The primary vision of AQbD is to recognize potential drawback strategy and provide a reliable, operational design environment or design space while adhering to relevant

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system suitability standards and maintaining unceasing life cycle supervision.

This literature investigation delves into previously reported QbD methodologies for High-Performance Liquid Chromatography (HPLC) methods,[10-13] providing inspiration for the present work aimed at developing and optimizing a QbD-driven HPLC strategy for vildagliptin and metformin hydrochloride in a pharmaceutical dosage form. By employing a systematic and scientific method development approach, the study endeavors to establish a reliable and high-quality analytical method for the intended purpose. An analytical method, being a systematic approach used for the qualitative and quantitative assessment of substance composition, holds paramount significance. Its accuracy and reliability are pivotal in various scientific disciplines, notably pharmaceuticals, environmental monitoring and materials science. This method facilitates the detection, identification and quantification of specific components within a sample, supporting quality control, research and regulatory compliance.[14] The selection of an appropriate analytical method is critical for ensuring data integrity, reproducibility and the generation of meaningful results, highlighting its indispensable role in scientific investigations and decision-making processes across diverse industries.[15] In the current pharmaceutical landscape, traditional quality testing of finished products has proven insufficient, highlighting the need for a more comprehensive approach focused on total quality assurance through in-process testing and analysis.

The Quality by Design (QbD) framework, now widely adopted by countries following the International Conference on Harmonization (ICH) guidelines, addresses this need. Specifically, the ICH Guidelines Q8 for pharmaceutical development, Q9 for quality risk management and Q10 for pharmaceutical quality systems provide a structured foundation for embedding quality into the product lifecycle. Additionally, components such as Quality Risk Management, the Pharmaceutical Quality System and Process Analytical Technology (PAT) are increasingly integrated into analytical method development, collectively recognized as Analytical Quality by Design (AQbD). This paper aims to review the progress made with QbD, explore regulatory perspectives, compare traditional methods with AQbD approaches and discuss the challenges related to its practical implementation.[16]

MATERIALS AND METHODS

Materials

Vildagliptin and Metformin Hydrochloride SR tablets were procured as gift sample, Dr. Reddy's Laboratories, IPDO and Hyderabad. The solvents employed were of HPLC grade and all other chemicals and reagents were of analytical grade.

Instrumentation and Standard solution

The Waters 2695 HPLC system, model number 2695 and manufactured by Waters Corporation employing UV VIS dual absorbance detector WATERS-2487 finds application. YMC Triart C18 (250*4.6) mM having 5.0 µM was used at 30°C column temperature, 5°C sampler temperature.

Conditions favorable for chromatography

The YMC Triart C-18 column (250 mM×4.6 mM) having 5.0 µM particle size.YMC triart is hybrid silica column gives high reproducibility and C18 column used for strong retention of Vildagliptin impurities. It was balanced with a MP (A) comprising of Buffer solution: Acetonitrile (950:50 v/v) was used. MP B comprising of Buffer solution: Acetonitrile (600:400 v/v) was employed. The MP dissolve 6.8 g of KH_2PO_4 in 2000 mL water, adjusted the pH 7.0 with 10% KOH solution. pH 7.0 was finalized because of pKa of Vildagliptin is 9.03 which is on basic side hence buffer KH_2PO_4 adopted . Acetonitrile used in mobile phase due to its low UV cutoff. The temperature of the column was set to ambient and 1 mL/min was the constant flow rate with gradient program (Time in min)/(% mobile phase-B): 0/0, 10/0, 25/20, 70/65, 70.1/0 and 80/0. A PDA detector operating at 210.0 nm was cut off to screen the effluents. With the aforementioned chromatographic surroundings, the parting and peak symmetry of analyte were satisfactory. MP and pH are two descriptors that were optimized for employing central composite design in the HPLC method for vildagliptin at three different levels.

Preparation of reference standard solution

50 mg of vildagliptin was precisely dissolved in 250 mL of methanol to create the 200 g/mL standard stock solution. To make the sub-stock, the stock solution was further diluted to 10 PPM. The 10-PPM solution was made by adding methanol to 5.0 mL of sub-stock solution to dilute it to 100 mL.

Selection of detection wavelength

10 g/mL was scanned between 198 and 210 nm and the detection wavelength was chosen to be the wavelength maxima at 210 nm.

RESULTS

Throughout the method, it was focused on optimization of different conditions like, pH of phosphate buffer, flow rate and column temperature were recognized to be CMPs. The resolution amid cyclic impurity and vildagliptin were identified as the CMAs. Response surface was chosen for DoE outcomes utilizing "Design-Expert" 13 software. A series of coefficients and their corresponding factorial levels made up a factorial model and a description of this model would be $Y=\beta0+\beta1X1+\beta2X2+\beta12X1X2+\beta11X2\ 1+\beta22X2\ 2+\ldots$ where βn is the coefficient concomitant with factor n and the alphabets, A, B, C…signify the factors in the generated model. Amalgamations of factors (like AB) show how the various components interact with one another.

The link between the variables was elicited using cubes, 3D plots, interactivity and desirability stratagem as portrayed in Figure 1 for cyclic impurity and vildagliptin, respectively. The charts here indicate that pH of buffer has more significant effect on cyclic impurity and vildagliptin and Positive (+ve) effect of pH of phosphate buffer (a) whereas the negative outcome (-ve) of flow rate (b) and temperature (c) specifies that lowering of the buffer's pH (A) surges the tenacity/resolution of cyclic impurity, whereas the rising flow rate (b) and temperature makes tenacity of cyclic impurity to increase. Plots for desirability and interaction verified the same for cyclic impurity and vildagliptinrespectively. In addition, the 3D plot displays the quadratic impact of pH on phosphate buffer solution on perseverance/resolution of cyclic impurity and vildagliptin (c) and (e) for the conditions of the used approach, the desirability stratagem and cubes projected resolution of 8 for cyclic impurity were optimal.

Statistical Analysis through analysis of ANOVA, Desirability and Overlay Plot

ANOVA analysis (Table 1) screening exemplary 'F-value' of 11.38 for response of cyclic impurity entails the archetypal was noteworthy. R2 values that were predicted and those that were changed diverged by less than 0.2 along with '*p*-value' 0.0077 that was below 0.05 hence the model was significant. It demonstrates a notable impact of pH of buffer on resolution cyclic impurity and vildagliptin. In order to surpass the resolution of 5 for cyclic impurity, the buffer's pH should be between 6.9 and 7.1. The method was highly sensitive to pH of the buffer for cyclic impurity.

Forced Degradation Study

To show how to effectively separate degradants, a study was done from Vildagliptin. Sections of the medicinal drug and the placebo were each subjected to various stressors in isolation. According to the test method specifications, stressed sample was introduced into the HPLC having PDA detector. All degradants crests were separated from Vildagliptin and its known impurities peaks in all the samples chromatograms. The chromatograms of the samples were looked at for ultimate purity of vildagliptin and using empowered software. Every sample of forced deterioration was meeting the acceptance criteria i.e purity angle was beneath purity threshold for Vildagliptin peak. In addition, there is nope purity flag observed in the purity results table for Vildagliptin. The stress conditions and respective consequences are summarized in Table 2. This demonstrates that degradants are not interfering with quantifying the Vildagliptin impurities in Vildagliptin and Metformin Hydrochloride SR tablets (50 mg/500 mg and 50 mg/1000 mg). Consequently, this approach is thought of as "Stability Indicating". Mass balance; mb (For Related substances) Mass balances of all the stressed testers were confirmed by scheming as follows:

$$Mb = \frac{(96 \text{ Assay of stressed sample} + \% \text{ impurities})}{\% \text{ Assay of unstressed sample}} \times 100$$

Percentage assay of stressed samples was calculated against working standard. Mass balance outcomes are summarized in Table 2.

Analytical Method Validation

An approved technique called method validation provides a strategy with a high level of assurance that the steps taken to ensure the analytical course is adequate for the method's anticipated use

Table 1: ANOVA analysis for selected factorial model-used for prediction and diagnostic plots (Partial sum of squares-Type-III).

Source	Sum of squares	Df	Mean square	F-value	*p*-value	Model type	R^2	Adjusted R^2	Predicted R^2
Model	10.43	9	1.16	11.38	0.0077	Significant	0.9534	0.8697	0.6658
A-buffer pH	5.44	1	5.44	53.47	0.0007				
B-flow rate	1.9	1	1.9	18.67	0.0076				
C-Temp	0.0313	1	0.0313	0.3069	0.6035				
AB	0.0225	1	0.0225	0.2209	0.6581				
AC	0.1225	1	0.1225	1.2	0.3227				
BC	0.49	1	0.49	4.81	0.0797				
A^2	2.41	1	2.41	23.69	0.0046				
B^2	0.0256	1	0.0256	0.2518	0.6371				
C^2	0.0256	1	0.0256	0.2518	0.6371				
Residual	0.5092	5	0.1018						
Lack of Fit	0.1825	3	0.0608	0.3724	0.7854				
Pure Error	0.3267	2	0.1633						
Cor Total	10.94	14							

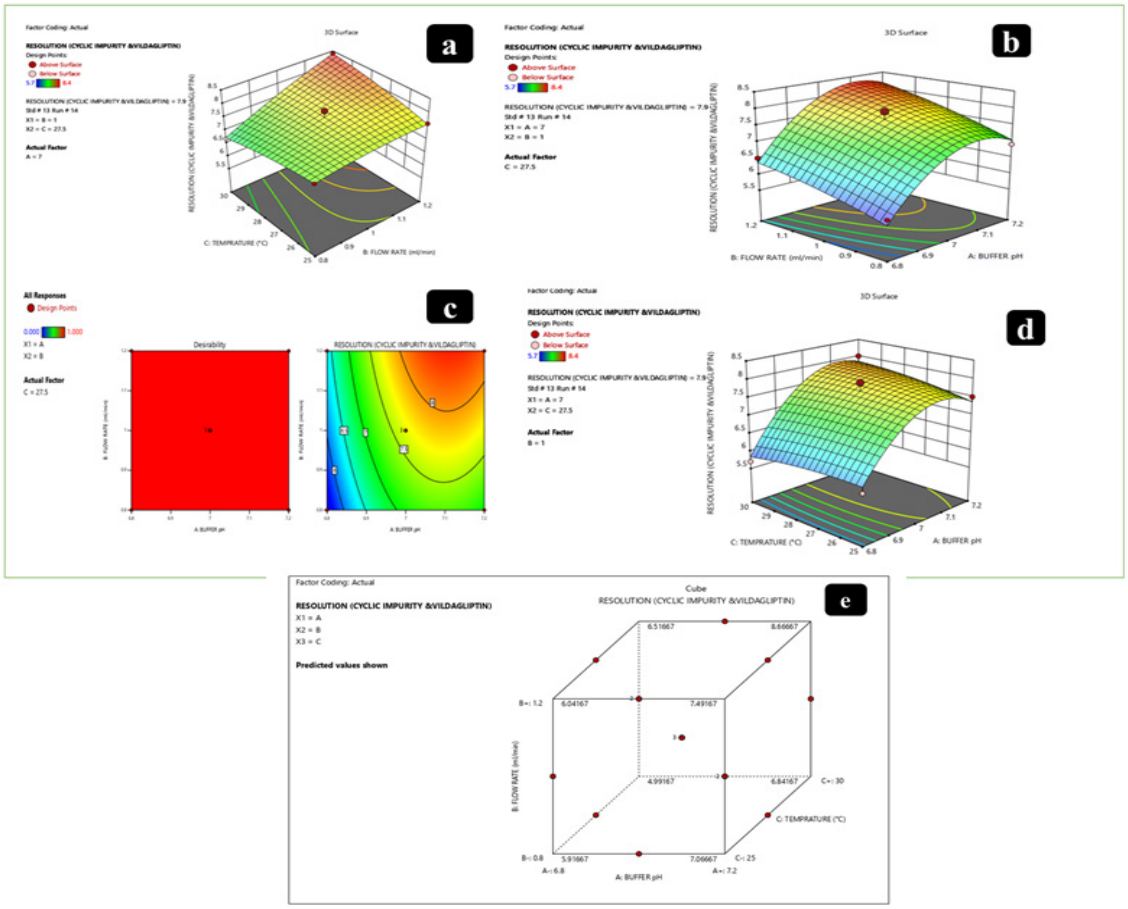

Figure 1: (a) 3d plots showing influence pH of phosphate buffer on resolution of cyclic impurity (b) 3D charts displaying impact pH of buffer and flow rate on resolution of cyclic impuritys and (c) The need for a resolution between cyclic impurity and vildagliptin. (d) Effect on resolution of cyclic impurity resulting from the interplay of buffer pH and temperature (e) Cube.

are suitable. The created HPLC estimation technique Vildagliptin and metformin Hydrochloride was authenticated following ICH Q2 (R1) guiding principle.[17]

System Suitability

The HPLC system received standard solution that had been prepared in accordance with the test method. Evaluation of the system suitability parameters and the outcomes are abridged in Table 3. The criteria for system appropriateness were within the acceptance limits.

Specificity

Placebo Interference

An investigation of placebo interference was directed. Analysis was achieved in duplicate with placebo, Placebo for vildagliptin, equal to the quantity used for test preparation according to the test procedure. Chromatograms of placebo solutions were not shown any interferenceat the retention period of Vildagliptin and its known impurities. This indicates that the placebo, Placebo for Vildagliptin utilized in the creation is not interfering in the related substances of Vildagliptin (Figure 2). The placebo interference results are summarized in Table 4.

Precision

For known impurities

The precision of the test procedure has to be assessed by investigating six test samples by spiking known impurities [Amide impurity (1.0%), cyclic impurity (1.0%) and Dimer impurity (0.5%)] into the test preparation and calculated % RSD of each of the impurity. The outcomes are summarized in Table 5. The precision results are within the acceptance limits.

For Vildagliptin

The precision of test process was performed by scrutinizing six placebo samples by quashing them with Vildagliptin (0.5%) and calculated % RSD of Vildagliptin. The outcomes are briefed in Table 5. The precision values are within the acceptance limits.

Table 2: The stress conditions and respective responses.

Stress condition	Drug product						
	Peak purity				% of net degradation	% assay	Mass balance
	Name	Purity Angle	Purity Threshold	Purity flag			
Unstressed test	Vildagliptin	0.120	0.321	No	0.04	102.1	NA
Stressed with 2 mL of 0.5N HCL solution for RT/10 min.	Vildagliptin	0.091	0.312	No	0.00	100.5	98.5
Stressed with 2 mL of 1N NaoH solution for RT/10 min.	Vildagliptin	0.161	0.325	No	23.81	80.73	102.4
Stressed with 2 mL of 3% hydrogen peroxide for RT/10 min	Vildagliptin	0.179	0.275	No	0.062	101.4	99.4
Stressed with heat at 60°C for 7 hr.	Vildagliptin	0.159	0.280	No	0.493	103.5	101.9
Stressed with 1 mL of water at 60°C for 30 min.	Vildagliptin	0.215	0.313	No	0.042	104.2	102.1
Stressed at (25°C/90%RH) for 7 days.	Vildagliptin	0.122	0.307	No	0.032	103.1	101.1
Stressed with photo light for 1.2 Million lux Hr.	Vildagliptin	0.089	0.270	No	0.040	104.2	102.1

Table 3: System suitability criteria with their observed and acceptance values.

Sl. No.	System suitability parameter	Observed value	Acceptance criteria
1	Peak tailing for vildagliptin in standard chromatogram.	1.0	NMT 2.0
2	Theoretical plate count for vildagliptin in standard chromatogram.	90223	NLT 15000
3	Relative standard deviation for vildagliptin on peak area in 3 replicate injection for standard.	2.7	NMT 10%

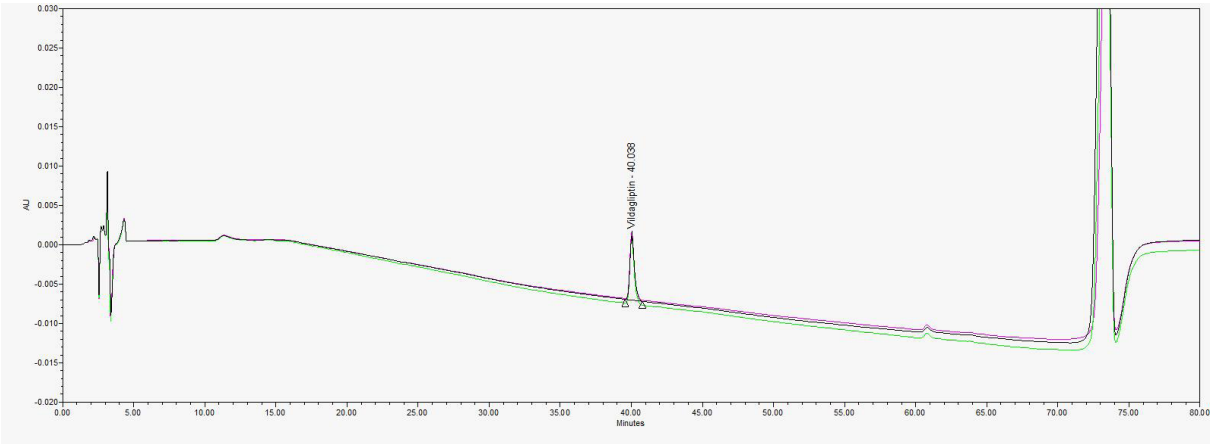

Figure 2: Placebo interference for vildagliptin.

Limit of Detection (LOD) and Limit of Quantitation (LOQ)

LOD and LOQ establishment (Signal to Noise Ratio Method)

A learning to establish the LOD and LOQ for amide impurity, cyclic impurity, dimer impurity and vildagliptin were piloted. Signal to noise proportion was employed to identify the LOD and LOQ. By locating the concentration that results in a signal to noise proportion greater than 3.0, the LOD was recognized. By locating the amount that produces a signal to noise ratio greater than 10.0, the LOQ was established. The LOD and LOQ consequences are concise in Table 6.

Precision at LOQ

For Known Impurities

Precision of known impurities at LOQ level was steered (Figure 3). Six test preparations were made by adding known contaminants to formulation preparation at a level just below the limit of quantification containing Vildagliptin at LOQ level and introduced into the HPLC. The % RSD was within the acceptance limits for known impurities.

For Vildagliptin

Precision of Vildagliptin at LOQ level was steered. Six test preparations were made ready by quashing vildagliptin at the level of about LOQ on placebo for vildagliptin and introduced into the HPLC. The precision at LOQ fallouts are abridged in Table 5. The % RSD was within the acceptance limits for Vildagliptin.

Table 4: Placebo interference for vildagliptin.

Sample	Preparation No.	Interference found at retention time of validation (Yes/No)
Placebo preparation	01	No
	02	No

Linearity

A graph was plotted between Vildagliptin and its impurities concentrations (LOQ to 150% of stability specification) versus peak areas and determined the correlation coefficient and bias at 100% response (Figure 4). The linearity results are summarized in Table 7. The correlation co-efficient was within the acceptance limits for Vildagliptin and its known impurities.

Ruggedness

Analyst to analyst, system-to-system, column to column and day-to-day variability

Six sample preparations and samples were the ruggedness of the test method was performed preparing Analyzed as described in test method an altered predictor by means of changed HPLC system and changed HPLC column on different days. The % RSD of individual impurity from six preparations and cumulative % RSD of 12 preparations (including 6 method precision preparations) were considered. The criteria for system appropriateness evaluated.

Robustness

Impact variation in column oven temperature

To ascertain the impact of temperature change in column ovens, research was done. Standard solution and spiked test solutions were equipped in accordance with the test procedure and shooted up into the HPLC system at 35°C and 25°C column oven temperatures (Actual temperature SI 30°C). The system suitability considerations were evaluated for their results were within the acceptance 1imits.

Table 5: Precision table of different impurity.

Name	% impurity						
	SPL-1	SPL-2	SPL-3	SPL-4	SPL-5	SPL-6	%RSD
Amide impurity	1.088	1.052	1.023	1.006	1.010	0.989	3.5
Cyclic impurity	1.115	1.116	1.113	1.107	1.106	1.105	0.5
Dimer impurity	0.529	0.525	0.513	0.513	0.512	0.513	1.4
Vildagliptin	0.522	0.535	0.534	0.533	0.537	0.528	1.1

Table 6: LOD and LOQ result.

Sl. No.	Name	Conc (ppm)		S/N	
		LOD	LOQ	LOD	LOQ
1.	Amide impurity	0.324	0.971	5.3	11.9
2.	Cyclic impurity	0.328	0.984	3.4	13.8
3.	Dimer impurity	0.327	0.982	3.5	11.9
4.	vildagliptin	0.320	1.005	3.3	10.7

Impact of disparity in flow rate

Learning on SEM undertaken to ascertain the impact of changing the MP flow rate. Standard solution and spiked test solutions were equipped as the test up into the HPLC system with a flow rate 0.8 mL/min to 1.2 mL/min (actual flow rate ST 1.0 mL/min). With both flow rates, the system suitability characteristics were evaluated as a test procedure. The results were within the acceptance limits.

Impact of variation in acetonitrile in MP-A

A SBM investigation carried out to ascertain the impact % change in acetonitrile concentration in MP composition. Standard solution and spiked test solution were made ready by injecting it into the HPLC system with Buffer: Acetonitrile (95:4.5 v/v) and Buffer: Acetonitrile (95:5.5 v/v) (actual composition SI 95:5), according to the test procedure. The system suitability considerations were assessed through the test protocol-using buffer: Acetonitrile both the MP compositions. The results were within the acceptance limits.

Impact of disparity in acetonitrile in MP-B

A research was performed to define the impact of disparity in acetonitrile concentration in MP composition. Standard solution and spiked test solutions were equipped in accordance with test protocol and introduced into the HPLC system with Buffer: Acetonitrile: 60:36 and Buffer: Acetonitrile: 60:44 (actual composition is Buffer: Acetonitrile: 60:40) The system suitability criteria's were served according to the defined procedure with both the MP compositions. The results were within the acceptance limits.

DISCUSSION

The development of an analytical Quality-by-Design (QbD) HPLC method for estimating vildagliptin in pharmaceutical formulations represents a significant advancement over traditional analytical approaches. The QbD framework facilitates a thorough understanding and control of the process variables, leading to a method that is not only more precise but also more robust and adaptable to various conditions.

The QbD approach begins with a systematic identification and optimization of Critical Quality Attributes (CQAs) that directly influence the method's performance. In this case, the mobile phase

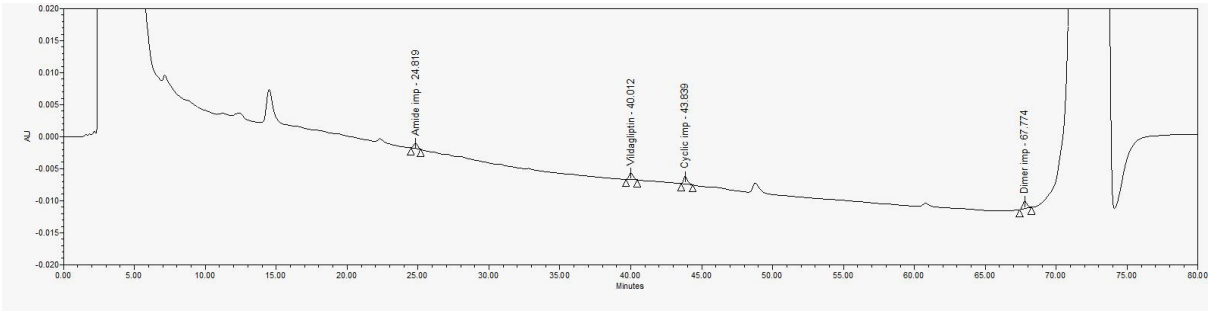

Figure 3: Known impurities at LOQ level.

Table 7: Linearity of detector response for amide, dimer, cyclic and vildagliptin impurities.

Sl. No.	Level%	Conc. (ppm)	Area	Conc. (ppm)	Area	Conc. (ppm)	Area	Conc. (ppm)	Area
		Amide Impurity		Dimer Impurity		Cyclic Impurity		Vildagliptin	
1	LOQ	1.2648	25,062	1.2785	27954	1.2811	25566	1.0052	15952
2	25%	5.0594	96,859	5.114	57345	5.1242	102041	2.5089	37249
3	50%	10.1188	1,91,159	10.228	117622	10.2485	203426	5.0178	75370
4	75%	15.1782	2,86,348	15.3421	175057	15.3727	306394	7.5268	113678
5	100%	20.2376	3,81,693	20.4561	238561	20.4969	407274	10.0357	150529
6	150%	30.3563	5,74,557	30.6841	352535	30.7454	612206	15.0535	224101
Correlation Coefficient			0.9999		0.9991		0.9999		0.9999
Intercept			715.8759		5582.8052		-102.7635		815.7593
Slope			18869.803		11258.0704		19905.6979		14872.799
Bias			0.19		2.34		-0.03		0.5

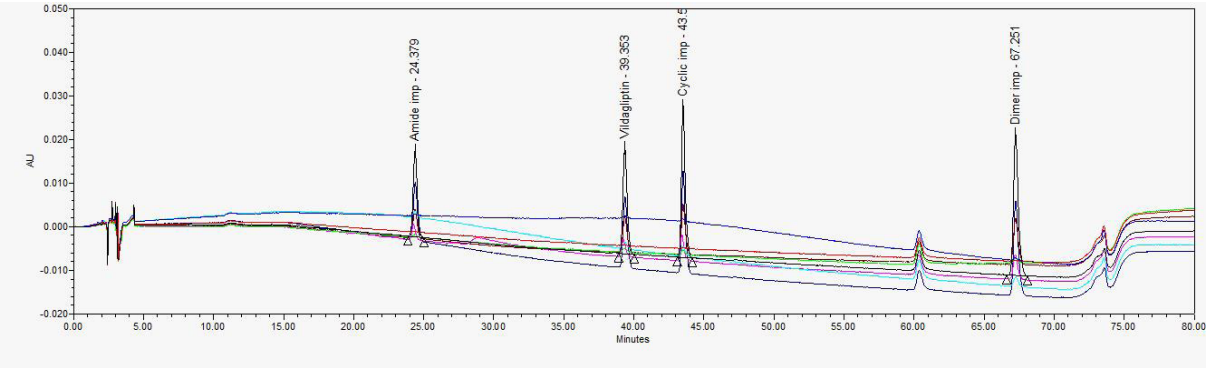

Figure 4: Vildagliptin and its impurities concentrations (LOQ to 150% of stability specification).

composition and buffer pH were identified as the most influential parameters affecting key analytical targets such as retention time, theoretical plates and peak asymmetry. By employing Design Expert Software and a central composite design, these parameters were fine-tuned to achieve optimal sensitivity and specificity.

Sensitivity is crucial in detecting and accurately quantifying vildagliptin, especially at low concentrations or in the presence of impurities. Traditional HPLC methods, which often use predetermined, fixed mobile phase compositions, may not be able to achieve this level of sensitivity, particularly if the method development does not involve a detailed assessment of the interaction between various factors. The QbD approach, however, allows for a more nuanced adjustment of the method, leading to enhanced detection limits and quantification that is more reliable.

Robustness is another critical aspect where the QbD-developed method shows superiority. By systematically varying key parameters such as mobile phase pH, flow rate and column temperature during method development, the robustness of the method was rigorously tested. This ensures that the method remains reliable and consistent even under slight variations in analytical conditions, which are inevitable in routine laboratory environments. Traditional methods, without such a thorough robustness study, might be more susceptible to variations, leading to inconsistencies in results.

Additionally, the robustness study also considered factors like column selection, instrument design and injection volume. By controlling these variables, the method demonstrates a high degree of adaptability, making it less prone to performance degradation when transferring between different laboratories or equipment. This adaptability is particularly important in the pharmaceutical industry, where methods must be validated and applied across different sites and under varying conditions.

The practical implications of using a QbD-based HPLC method are significant. For routine analysis, especially in a quality control setting, the method's robustness translates into fewer batch rejections and more reliable product quality assessments. The enhanced sensitivity and specificity ensure that even trace levels of impurities can be accurately detected, which is critical for ensuring the safety and efficacy of pharmaceutical products. Furthermore, the method's compliance with ICH guidelines, as evidenced by the statistical validation (F-value of 11.38 and *p*-value of 0.0077), underscores its readiness for regulatory acceptance, streamlining the approval process for pharmaceutical formulations containing vildagliptin.

When compared to traditional HPLC methods, the advantages of the QbD approach become evident. Traditional methods often lack the comprehensive optimization process inherent in QbD, which can lead to less precise and less reliable results. The fixed nature of traditional method parameters does not account for the inherent variability in analytical systems, leading to potential issues with reproducibility and robustness.

In contrast, the QbD-based method's adaptability to different conditions and its rigorous validation process provide a more reliable and effective approach for the estimation of vildagliptin. The ability to fine-tune the method during development ensures that it can be tailored to specific analytical needs, whether in research or quality control.

CONCLUSION

The article provided instructions on how to build an HPLC method utilizing the quality-by-design philosophy. The goals of this approach are made very clear by using the analytical target product sketch. The experimental design detailed investigating the key elements of HPLC technique like MP and pH, etc. To develop an HPLC method for vildagliptin, the analytical QbD concepts were applied. To recognize the finest accomplishing set up and the final design space, a multi-variant research on a number of critical course descriptors, comprising the grouping of two descriptors the MP composition and pH of the buffer at three diverse echelons was carried out. Using central composite design, their interrelationships were examined and optimized at different levels. Here, the factors persuading chromatographic parting as well as the effectiveness of the procedures are well acknowledged. This methodology bids practical acquaintance that facilitates the development of a chromatographic optimization that may be casted off in the forthcoming years. Every parameter that had

been verified had been found to meet the acceptance criteria. The validated scheme for determining Vildagliptin was shown to be linear, exact, precise, accurate, specific, robust and rugged. Thanks to the QbD approach for method designing, as there is a lesser risk of failure during method validation and transfer with a better grasp on the hidden details of different method variables. The automated QbD method development approach employing the Design Expert software has created a method that performs better and is more resilient in comparison to human method creation in a shorter amount of time. Statistics-based data analysis demonstrates the procedure's accuracy, robustness and dependability. This technology drives to be used for routine analysis and quality control in the medicinal industry going forward.

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AUTHORS CONTRIBUTIONS

Pankaj S. Hasabe: conceived, designed and performed the experiments and writing of original draft, Venketa S Nandmuri, Akanksha G. Kolekar and Kishor V. Gaikwad: analysis of data, Kalyanraman L. Narayanan and Samadhan P. Pawar: Supervision, conceptualization, reviewing and editing.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

QbD: Quality by design; **AQbD:** Analytical Quality by design; **LC:** Liquid chromatography; **HPLC:** High-Performance Liquid Chromatography; **UV:** Ultra Violet; **ICH:** International Conference on Harmonisation Metformin hydrochloride; **SR:** Sustained release; **MP-A:** Mobile Phase A; **MP-B:** Mobile Phase B**; PDA detector:** Photo Diode Array detector; **PPM:** Parts per million; **LOD:** Limit of detection; **LOQ:** Limit of quantitation; **RSD:** Relative standard deviation.

SUMMARY

The term "Quality by Design" (QbD) describes the attainment of a specific, predictable quality with intended and specified parameters. Due to its emphasis on risk assessment and management, the quality-by-design approach for method creation has the potential to provide a more robust/rugged method than the old or conventional approach. Understanding dependent variables, different factors and their interaction effects through a desired series of tests on the responses to be examined is a crucial part of QbD. The invention of a risk-based HPLC technique and its validation for vildagliptin and metformin hydrochloride in pharmaceutical dose form are described in the current study. With the use of the Design Expert 11.0 version, the primary composite design experimental design specifies the interactions between the mobile phase and pH at distinct levels. The responses to be monitored were retention time, theoretical plates and peak asymmetry. Here, the elements influencing chromatographic separation are more understood and the created HPLC method's capacity to fulfill its intended functions is more confidently acknowledged. A deeper comprehension of method variables with varying degrees was achieved by the application of the QbD technique to analytical method development.

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