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Analytical Qbd-Driven Development and Validation of Stability-Indicating Rp-Hplc Method for Related Substances in Octreotide Acetate Depot Formulations

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KEYWORDS:

Octreotide Acetate, RP-HPLC, Validation, Method Development, Analytical Quality by Design.

ABSTRACT:

This study aimed to develop and validate a precise, selective, and robust reverse phase high performance liquid chromatographic method for the determination of octreotide acetate and its related substances in pharmaceutical dosage forms using an analytical quality by design approach. A systematic experimental design was applied to optimize critical chromatographic variables, ensuring consistent separation and reliable performance. The optimized method achieved clear resolution of octreotide acetate from its process- and degradation-related impurities within a single analytical run. Validation demonstrated excellent linearity over the studied concentration range, high accuracy with recoveries within acceptable limits, and satisfactory precision. Statistical evaluation confirmed the significance and reliability of the optimized method. The developed method proved suitable for accurate quantification of octreotide acetate and multiple related substances in dosage forms. Overall, the analytical quality by design strategy enhanced method understanding, robustness, and regulatory acceptability, making the method efficient and reliable for routine quality control analysis in pharmaceutical laboratories.

INTRODUCTION:

Octreotide acetate is a synthetic somatostatin analog used to treat acromegaly and neuroendocrine tumors, including carcinoid and vasoactive intestinal peptide (VIP)-secreting tumors. It works by inhibiting excessive growth hormone secretion, thereby managing symptoms and disease progression. The drug is available in a long-acting injectable formulation, which is both costly and clinically important.[1]

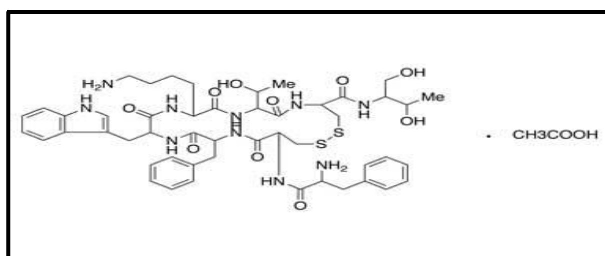

Fig. 1: Chemical Structure of Octreotide Acetate

Despite its therapeutic relevance, no validated analytical method has been reported for the estimation of related substances in octreotide acetate formulations. Impurities and degradation products can compromise drug quality, safety, and efficacy, making their detection essential for regulatory compliance.[2]

To address this gap, an Analytical Quality by Design (AQbD)-based RP-HPLC method was developed and validated as per ICH Q2(R1) and Q14 guidelines. AQbD ensures method robustness, accuracy, and regulatory flexibility, and minimizes the chances of post-approval changes and regulatory rejections. The developed method can be effectively applied for quality control of octreotide acetate in pharmaceutical formulations.

Journal of Chemical Health Risks
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JCHR (2026) 16(2), 2749-2758 | ISSN:2251-6727

MATERIALS AND METHODS:

Chemicals and Reagents

Octreotide Acetate was obtained from Marathwada Mitra Mandal's College of Pharmacy, Pune. HPLC-grade methanol, acetonitrile, and water were used throughout the study, along with AR-grade trifluoroacetic acid, sodium acetate, glacial acetic acid, and GC-grade DMSO. All other chemicals of analytical or HPLC grade were sourced from Merck and Supelco, Mumbai. A pilot-scale injectable depot formulation was prepared in-house at the same institution.

Chromatographic Conditions

Analyses were performed using gradient elution on a Lichrospher C18 column (250 × 4.6 mm, 5 µm). The mobile phase included:

- **Phase A**: 0.02 % trifluoroacetic acid in water
- **Phase B**: 1:1 (v/v) acetonitrile and methanol

The flow rate was 1.0 mL/min, with a column temperature of 40°C. Samples (10 µL) were injected and detected at 220 nm using a PDA detector. Total runtime was 90 minutes, and Octreotide Acetate eluted around 45 minutes.[5]

Diluent Preparation

Two diluents were employed during the preparation of solutions: Diluent-1 consisted of dimethyl sulfoxide (DMSO), and Diluent-2 was a 0.1 M sodium acetate buffer.[6]

Preparation of Impurity Stock

To prepare the impurity stock, 5.0 mg of each known impurity (six total) was weighed and dissolved in DMSO to make 100 ppm solutions. For the identification solution, 5.0 mg of Octreotide Acetate was combined with 1.0 mL impurity stock, 4.0 mL Diluent-1, and diluted to volume with Diluent-2, followed by thorough mixing.[7-9]

Preparation of Sample Solution

Approximately 250 mg of the pooled sample was weighed and placed in a 20 mL volumetric flask. About 10 mL of Diluent-1 was added, and the mixture was allowed to stand for 5 minutes at room temperature before vortexing. The volume was then brought up to 20 mL with Diluent-2 and vortexed again. The solution was filtered through a 0.45 µm PVDF filter before HPLC injection.[11]

Method Validation Approach

The method was validated following ICH guidelines, evaluating parameters such as specificity, linearity, accuracy, precision, robustness, and stability. Analytical-grade reagents and high-purity water were used to ensure the method reliably detects both known and unknown impurities in Octreotide Acetate under varied conditions.[12]

Preparation of Analytical Solutions

All necessary solutions were prepared as per validated protocols. Blank solution, placebo, system suitability, and impurity identification solutions were prepared according to the standard operating procedure. Two spiked stock solutions were prepared: Stock A contained Acetyl-Lys5-Octreotide and Acetyl-Phe1-Octreotide in water, and Stock B contained four specified impurities in anhydrous DMSO. Spiked sample solution was prepared by combining pooled sample with Diluent-1, followed by the addition of both stock solutions, and then diluted to volume with Diluent-2. The solution was vortexed and centrifuged at 10,000 RPM for 5 minutes prior to injection.[13]

System Suitability Assessment

Prior to each phase of the validation process, the system suitability of the chromatographic setup was thoroughly assessed. This involved performing six consecutive injections of the standard solution into the chromatographic system.[14-17]

Sample Sequence and Chromatographic Conditions

The sample injection sequence included triplicate injections of the blank solution, followed by single injections of placebo, system suitability, and impurity identification solutions. Spiked and as-is sample solutions were then injected, and the sequence was bracketed with system suitability and impurity identification standards. Chromatographic analysis was carried out using a validated HPLC system under the described variable and control conditions. In case of failure to meet acceptance criteria, the variable parameter range was adjusted accordingly.[18]

Acceptance Criteria

The acceptance limits for system suitability were predefined to guarantee reliable analysis. Specifically, the USP tailing factor or asymmetry for the Octreotide peak, as determined by the system software, was required to be no greater than 2.0. Additionally, the

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JCHR (2026) 16(2), 2749-2758 | ISSN:2251-6727

theoretical plate count for the Octreotide peak was expected to be at least 5000, indicating sufficient column efficiency.[19]

Stability of Analytical Solutions

Solution stability was evaluated to determine the duration for which the analytical solutions remained accurate and reliable when stored under various conditions. Solutions were divided into three sets and stored ~25°C, 2–8°C, and in a sample cooler (10°C). Initial injections were conducted using freshly prepared solutions. Subsequent injections were performed at defined intervals up to 220 hours. The sequence included as-is and spiked sample solutions under each storage condition, along with bracketing system suitability and impurity standards. Acceptance criteria included no new impurity peaks above LOQ and minimal deviation in impurity levels from the initial values, based on impurity concentration thresholds.[20-22]

RESULTS:

Preliminary Method Development

Initial method development involved testing various columns, temperatures, pH values, and mobile phase compositions. Optimal separation was achieved using Mobile Phase-A (1.0 mL trifluoroacetic acid in 5000 mL water) and Mobile Phase-B (a 50:50 v/v mix of acetonitrile and methanol) at a flow rate of 1.0 mL/min with the column temperature maintained at 40°C. Detection was set at 220 nm, and the total run time was 90 minutes, yielding satisfactory system suitability results.

Risk Assessment

A risk assessment was performed using ICH Q9 guidelines and Failure Mode and Effects Analysis (FMEA) to identify critical method variables. Flow rate, column temperature, and the proportion of acetonitrile in Mobile Phase B were found to be key factors influencing resolution, USP tailing, and efficiency, based on their high Risk Priority Numbers (RPNs).

Central Composite Design

A Central Composite Design (CCD) matrix comprising 17 experiments was used to optimize the chromatographic system. The design included a three-level factorial setup with central points. Analysis of variance (ANOVA) confirmed the model's significance for all measured responses, with acceptable probability values ($p < 0.05$), adjusted R^2, and adequate precision, indicating a reliable optimization.

Table I: Chromatographic factors and level for Central Composite Design

Independent Factors	Low level (-1)	Medium level (0)	High level (+1)
X1: Flow Rate	0.9	1.0	1.1
X2: Column Oven Temperature	35	40	45
X3: Mob.Phase-B Ratio (% Acetonitrile)	45	50	55

Table II: Central Composite Design optimization layout

Run	Factor 1	Factor 2	Factor 3	Response 1	Response 2
	A:Flow	B:Temp	C:Mob.Phase-B Ratio	USP Tailing	USP Plate Count
	mL/min	ºC	mL		
1	1	45	45	1.1	112636
2	1.1	40	55	1.2	121587
3	1.1	40	45	1.1	118920
4	0.9	35	50	1.2	123515
5	1.1	45	50	1.4	142384

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(2), 2749-2758 | ISSN:2251-6727

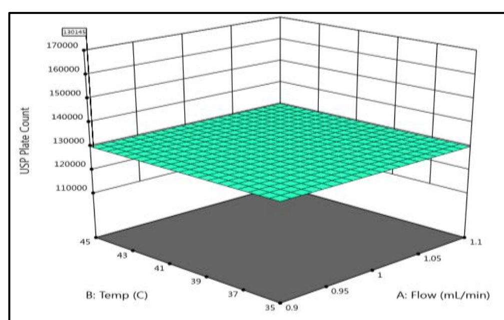
6	1	40	50	1.1	124583
7	1	35	45	1.3	116793
8	1	45	55	1.2	145934
9	0.9	40	55	1.1	124376
10	1	40	50	1.2	139534
11	1	40	50	1.4	142954
12	0.9	45	50	1.1	123543
13	1	40	50	1	168456
14	1	35	55	1.1	111863
15	1.1	35	50	1.1	138974
16	0.9	40	45	1.1	128564
17	1	40	50	1.1	127845

Table III: ANOVA results for each CAAs

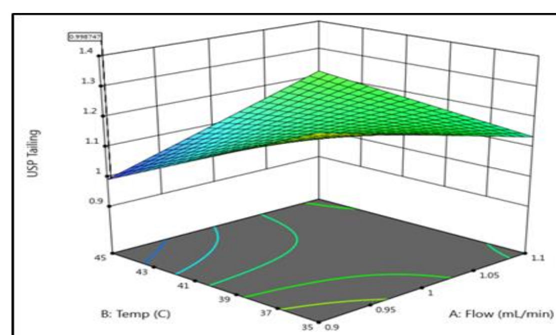
ANOVA Parameters	**Y1: USP Tailing**	**Y2: USP Theoretical Plates**
R- square	0.4275	0.2329
Adjusted R-square	0.0840	0.0559
F- Value	1.24	1.32
P- Value	0.3615	0.3114
C.V. %	9.16	10.84

Identification of Optimum Method Conditions

The effect of CMPs on the USP tailing factor and theoretical plates of octreotide acetate was analyzed using 3D surface plots. These plots showed that increasing flow rate and column oven temperature reduced the USP tailing factor, while the number of theoretical plates remained largely unaffected by these changes. Numerical optimization aimed to achieve desirability close to one, setting the theoretical plates within an acceptable range and targeting a USP tailing factor of not less than 1.5. Based on these analyses, the optimized chromatographic conditions were established: Mobile Phase-A (1.0 mL trifluoroacetic acid in 5000 mL water), Mobile Phase-B (acetonitrile:methanol 50:50 v/v), flow rate of 1.0 mL/min, column temperature at 40°C, and detection wavelength at 220 nm. Graphical optimization helped define the Method Operable Design Region, confirming method robustness and eliminating the need for revalidation within this range.



(A)



(B)

Fig. 2: 3D plots (A) Effect of Temp. and Flow rate of mobile phase on USP Tailing of Octreotide Acetate. (B) Effect of Temp. and Flow rate of mobile phase on USP Plate Count of Octreotide Acetate

Journal of Chemical Health Risks

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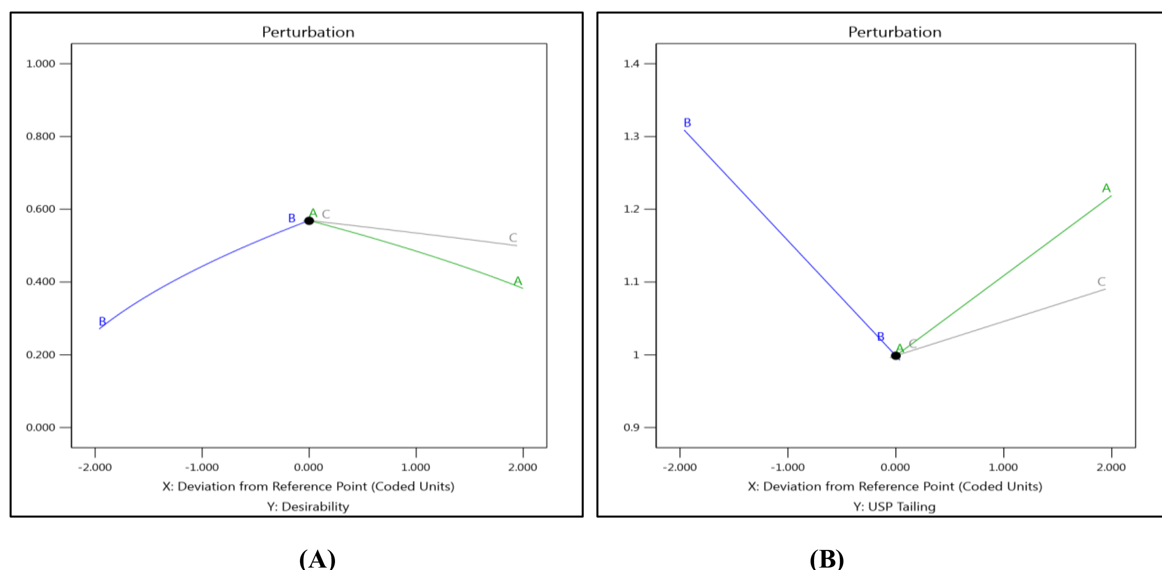

(A) **(B)**

Fig. 3: Perturbation plot showing (A) the effect of independent factor on USP Tailing of Octreotide Acetate. (B) the effect of independent factor on USP Plate Count of Octreotide Acetate

Analytical Method Validation

System Suitability

The results consistently met acceptance criteria across system suitability, specificity, precision, linearity, accuracy, robustness, and stability assessments. For example, the USP tailing factor ranged between 1.1 and 1.6, and plate counts exceeded 90,000 under various conditions, confirming method reliability (Table 4).

Table IV: System suitability parameter of the optimized chromatogram

Sr. No.	Parameters	Octreotide Acetate	
		USP Tailing Factor	USP Plate Count
1.	System Suitability	1.6	91658
2.	Specificity	1.6	91658
3.	System Precision	1.6	91658
4.	Method Precision	1.6	94840
5.	Intermediate Precision	1.2	111424
6.	LOD/LOQ Verification & LOQ Precision	1.6	91658
7.	Linearity	1.6	91658
8.	Accuracy	1.2	111424
9.	Solution Stability	1.6	94840
10.	**Robustness Conditions**		
10.1	+10 % Flow Rate	1.2	112636
10.2	-10 % Flow Rate	1.2	111587
10.3	+5 °C Column Oven Temperature	1.1	118920
10.4	-5 °C Column Oven Temperature	1.1	123515
10.5	+3 nm Wavelength (223 nm)	1.6	91580
10.6	-3 nm Wavelength (217 nm)	1.6	91630

Specificity

Specificity was confirmed by analyzing blank, placebo, standard, impurities, and spiked samples to ensure no interference at the analyte or impurity retention times. All peaks were well resolved, and purity analysis showed that the purity angle was below the threshold, indicating the method's capability to distinguish octreotide acetate from related substances.

Precision

Precision was assessed through six replicate injections of both unspiked and impurity-spiked samples at

Journal of Chemical Health Risks

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JCHR (2026) 16(2), 2749-2758 | ISSN:2251-6727

specified concentrations. System, method, and intermediate precision were evaluated, with % RSD values for Octreotide and its impurities remaining within acceptable limits below 5 % for system precision and 10 % for method precision indicating consistent performance.

LOD) and LOQ

Sensitivity was confirmed by determining LOD and LOQ based on USP signal-to-noise ratios. The LOD had a minimum S/N ratio of 3, and LOQ had a minimum of 10 for both octreotide and impurities, fulfilling the sensitivity requirements of the method.

Linearity

The linearity was performed for concentrations ranging from Octreotide acetate (0.2 to 3.75 µg/mL), Acetyl-Lys^5-Octreotide (0.15 to 7.75 µg/mL), Acetyl-Phe^1-Octreotide (0.15 to 7.25 µg/mL), Glycolyl-Threoninyl Octreotide (0.15 to 10.25 µg/mL), Diglycolyl-Threoninyl Octreotide (0.15 to 5 µg/mL), Glycolyl-Lysyl Octreotide (0.2 to 7.50 µg/mL) and Glycolyl-Phenylalanyl Octreotide (0.2 to 7.50 µg/mL). Linearity was tested across a broad concentration range for octreotide acetate and its impurities. The calibration curves exhibited strong linearity with correlation coefficients (R) above 0.99. Intercepts were within ±10 % of the expected response, confirming accurate quantitation over the tested range.

Accuracy

The method's accuracy was validated via recovery studies at LOQ, 50 %, 100 %, and 150 % of target concentrations. Recoveries ranged from 90 % to 120 %, with % RSD values under 10 %, confirming reliable quantification of Octreotide and its related substances in the formulation.

Table V: Results of Accuracy

Impurity Name	Sample No.	Amount Added (%)	Amount Found (%)	Net Amount Recovered (%)	% Recovery	Mean % Recovery	% RSD
Acetyl-Lys5-Octreotide	**LOQ**	0.03	0.23	0.03	100.0	98.5 %	3.0 %
	50 %	0.51	0.69	0.51	100.0		
	100 %	1.01	1.13	0.95	94.1		
	150 %	1.54	1.73	1.54	100.0		
Acetyl-Phe1-Octreotide	**LOQ**	0.03	0.24	0.03	100.0	97.9 %	1.7 %
	50 %	0.50	0.67	0.49	98.0		
	100 %	1.02	1.13	0.98	96.1		
	150 %	1.51	1.61	1.47	97.4		
Glycolyl-Threoninyl Octreotide	**LOQ**	0.03	0.24	0.03	100.0	98.8 %	1.5 %
	50 %	0.50	0.67	0.49	98.0		
	100 %	1.02	1.13	0.99	97.1		
	150 %	1.50	1.61	1.50	100.0		
Diglycolyl-Threoninyl Octreotide	**LOQ**	0.03	0.24	0.03	100.0	96.7 %	3.2 %
	50 %	0.50	0.67	0.47	94.0		
	100 %	1.02	1.13	0.96	94.1		
	150 %	1.49	1.61	1.47	98.7		
Glycolyl-Lysyl Octreotide	**LOQ**	0.04	0.24	0.04	100.0	96.5 %	3.5 %
	50 %	0.50	0.67	0.46	92.0		

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JCHR (2026) 16(2), 2749-2758 | ISSN:2251-6727

	100 %	1.03	1.13	0.99	96.1		
	150 %	1.52	1.61	1.49	98.0		
Glycolyl-Phenylalanyl Octreotide	**LOQ**	0.04	0.24	0.038	95.0	95.0 %	2.3 %
	50 %	0.50	0.67	0.46	92.0		
	100 %	1.01	1.13	0.98	97.0		
	150 %	1.51	1.61	1.45	96.0		
Octreotide	**LOQ**	0.04	0.04	NA	100.0	100.0 %	0.0 %
	50 %	0.25	0.25	NA	100.0		
	100 %	0.50	0.50	NA	100.0		
	150 %	0.75	0.75	NA	100.0		

Robustness

Robustness testing involved deliberate variation of flow rate (±10 %), column temperature (±5 °C), and detection wavelength (±3 nm). Under all these variations, system suitability and sample results remained within acceptance criteria, confirming the method's robustness to small operational changes.

Solution Stability

This was evaluated by storing standard, sample, and spiked solutions at RT (~25 °C) and refrigerated conditions (~2–8 °C) for up to 220 hours. The solutions remained stable throughout the period, with system suitability parameters and sample results within specifications.

Analytical Range

The validated analytical range covered concentrations for octreotide acetate and its impurities, spanning from as low as 0.03 % to over 2 % of the analyte concentration, ensuring the method's applicability for quantifying both major and trace impurities.

Table VI: Analytical Range

Impurity Name	Range (%)
Acetyl-Lys^5-octreotide	0.03 % to 1.55 %
Acetyl-Phel.-octreotide	0.03 % to 1.45 %
Glycolyl-Threoninyl Octreotide	0.03 % to 2.05 %
Diglycolyl-Threoninyl Octreotide	0.03 % to 1.00 %
Glycolyl-Lysyl Octreotide	0.04 % to 1.50 %
Glycolyl-Phenylalanyl Octreotide	0.04 % to 1.50 %
Octreotide	0.04 % to 0.75 %

Forced Degradation Study

Forced degradation studies following ICH guidelines subjected the drug to stress conditions including acid/base hydrolysis, oxidation, heat, and light exposure. These studies confirmed the method's ability to separate degradation products from the parent compound. Peak purity analysis via PDA detector verified that analyte peaks were free from co-eluting impurities, with mass balance between 95 % and 105 %, indicating the method's stability-indicating capability.

Table VII: Forced Degradation Data

Nature of stress	Condition	% Assay	% RS	Mass Balance	Purity angle	Purity threshold
Unstressed	NA	99.9 %	2.4 %	NA	0.165	0.348

Journal of Chemical Health Risks

www.jchr.org

JCHR (2026) 16(2), 2749-2758 | ISSN:2251-6727

Acid	1.0 mL of methanolic 0.5 N HCL at 60 °C for 5 min.	92.4 %	6.2 %	96.4 %	0.482	0.739
Base	1.0 mL of methanolic 0.5 N NaOH at 60 °C for 1 min.	89.8	8.5 %	96.1 %	0.072	0.143
Peroxide	1.0 mL of methanolic 1 % H_2O_2 solution at 60 °C for 2 min.	91.6 %	6.8 %	96.2 %	0.284	1.652
Acylation	1.0 mL of glacial acetic acid at 80 °C for 5 min.	98.6 %	4.1 %	99.4 %	1.905	2.945
Hydrolytic	1.0 mL of water at 60 °C for 30 min.	99.1 %	2.1 %	98.6 %	0.541	0.693
Thermal	Heat at 60 °C for 12 hrs.	98.8 %	3.3 %	98.8 %	0.182	0.939
Photolytic	Exposed to 1.2 million lux hours and an integrated near ultra violet energy of not less than 200 watt hours per square meter.	98.9 %	3.5 %	99.1 %	1.843	2.349

DISCUSSION:

The study successfully demonstrates the development of a robust and reliable reverse phase high performance liquid chromatographic method for the determination of octreotide acetate and its related substances using an Analytical Quality by Design approach. Systematic evaluation of chromatographic variables enabled effective separation of the drug from closely related impurities, which is critical for peptide-based formulations. Risk assessment identified flow rate, column temperature, and organic phase composition as critical method parameters influencing peak symmetry and efficiency. Optimization using a Central Composite Design provided a well-defined Method Operable Design Region, ensuring consistent performance and minimizing the risk of method failure during routine use. Method validation confirmed adequate specificity, precision, accuracy, linearity, sensitivity, and robustness in accordance with regulatory guidelines. The method also demonstrated stability-indicating capability through forced degradation studies, with clear separation of degradation products and acceptable mass balance. Although the method involves a relatively long run time, it offers reliable impurity profiling and high regulatory confidence. Overall, the AQbD-based strategy enhanced method understanding, robustness, and suitability for routine quality control and stability studies of octreotide acetate in dosage forms.

CONCLUSION:

The RP-HPLC method developed for Octreotide Acetate using the AQbD framework exhibited strong performance in all validation criteria, confirming its precision, accuracy, robustness, and reliability. Design of Experiments (DoE) facilitated effective optimization of critical parameters, ensuring consistency and reproducibility. Stability-indicating potential was verified through forced degradation studies, which confirmed clear separation of degradation products. This optimized method provides a reliable, cost-efficient tool for routine quality testing and regulatory submissions.

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Journal of Chemical Health Risks
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CONFLICT OF INTEREST:

The authors declare that there is no conflict of interest regarding the publication of this work.

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