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Expert Opinion Article

A QbD-Guided RP-HPLC Method for Estimation of Repotrectinib: Design, Optimization, and Validation

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Abstract
Background: Repotrectinib ($C_{18}H_{18}FN_5O_2$) represents an advanced macrocyclic inhibitor targeting tyrosine kinases, specifically approved for managing ROS1-driven non-small cell lung cancer (NSCLC). The molecule's intricate design and scarcity of established quantification techniques highlight the demand for a dependable, verified analytical procedure. **Objective**: The goal was to create and confirm an uncomplicated, durable, and economical reverse-phase high-performance liquid chromatography (RP-HPLC) protocol for assessing repotrectinib levels, guided by a Quality by Design (QbD) strategy in line with ICH standards.**Methods:** Optimization involved a QbD methodology focusing on key factors like mobile phase makeup and acidity level, analyzed via a central composite experimental layout to examine primary, combined, and squared influences. The refined setup incorporated a Phenomenex Kinetex XB-C18 stationary phase (150 mm length × 4.6 mm diameter, 5 µm particles), eluent of 0.1% trifluoroacetic acid mixed with acetonitrile (60:40 volume ratio), elution speed of 0.9 mL per minute, UV detection at 280 nm wavelength, and sample introduction of 10 µL. Assessments covered selectivity, linear range (40–60 µg/mL), recovery rates, repeatability, detection threshold (LOD), quantification threshold (LOQ), durability, and degradation under forced conditions.**Results:** Strong linear correlation was observed (R^2 exceeding 0.999), with recovery values between 99.94% and 100.16%. Repeatability tests indicated relative standard deviation (%RSD) under 2%. Detection limit stood at 2.00 µg/mL, and quantification limit at 6.06 µg/mL. The protocol proved stable against slight purposeful adjustments and clearly resolved repotrectinib from breakdown fragments in stress tests. **Conclusion**: This QbD-based RP-HPLC protocol offers simplicity, reliability, precision, and durability, ideal for standard evaluations of repotrectinib in raw materials and formulated products.

Keywords: Repotrectinib, Quality by Design (QbD), RP-HPLC, Method Development, Validation, Non-Small Cell Lung Cancer (NSCLC), Analytical Method, Forced Degradation, Tyrosine Kinase Inhibitor (TKI)

Introduction

Repotrectinib ($C_{18}H_{18}FN_5O_2$) (Fig 1) serves as an innovative azamacrocycle-based therapeutic for cancer, acting as a tyrosine kinase blocker. Its main application lies in addressing advanced or spreading ROS1-linked non-small cell lung cancer (NSCLC). [1–3] The compound exhibits strong inhibition against ROS1, as well as TRKA through TRKC and ALK enzymes, serving both as a tumor-suppressing compound and a blocker of receptor-linked tyrosine kinases (EC 2.7.10.1). From a chemical perspective, it falls into categories like azamacrocycles, ether rings, pyrazolopyrimidine scaffolds, amide linkages, and fluorinated benzene rings. [4–6] Mutations in ROS1 play a key role in NSCLC progression, accounting for 50–60% of resistance cases to crizotinib via the G2032R shift in the solvent-front area .[6–8]

The drug's constrained macrocycle conformation allows precise engagement with such front-region alterations while blocking access to common resistance points, surpassing predecessors like crizotinib, lorlatinib, taletrectinib, and entrectinib that face known resistance issues. [9–11]. To date, no instances of resistance to repotrectinib have surfaced.

Figure 1 represents the chemical structure of RTC

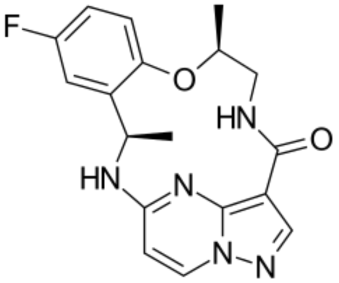


Figure 1. Chemical structure of Repotrectinib

The Quality by Design (QbD) principle, introduced by quality pioneer Joseph M. Juran, promotes a methodical, evidence-led strategy for improving manufacturing and output standards. First applied in fields such as vehicle production, it was integrated into pharmaceutical practices by the U.S. FDA via the "Pharmaceutical cGMPs for the 21st Century" program. [5,12–14] Per ICH definitions, QbD entails a forward-looking, hazard-focused creation process that stresses clear goals, deep insight into operations, and effective oversight. Within drug testing, reverse-phase HPLC stands out for its adaptability and exactness. Under QbD principles, verifying the sturdiness and consistency of such HPLC techniques is essential for sustained efficacy over a product's duration.[15–18] Known commercially as Augtyro, repotrectinib gained U.S. FDA clearance in November 2023 and Chinese NMPA endorsement in May 2024 for ROS1-positive NSCLC management. .[19,20] As a precision medicine, it disrupts vital tyrosine kinases fueling tumor expansion and metastasis. Yet, its elaborate architecture and susceptibility to instability complicate precise measurement in dosage forms. [21–23] Presently, a single LC-MS procedure exists for bioanalysis of repotrectinib, with few other options documented. This research fills that void by crafting an accessible, exact, dependable, budget-friendly, and consistent RP-HPLC technique for repotrectinib measurement via QbD, confirmed against ICH criteria.

EXPERIMENTALS

Materials and Solvents

The reference standard for Repotrectinib was obtained from BLD Pharmatech India Pvt. Ltd., located in Hyderabad, India. Acetonitrile came from Thermo Fisher Scientific India Pvt. Ltd. in Mumbai, India; ortho-phosphoric acid from Merck Life Sciences Pvt. Ltd.; and disodium hydrogen phosphate from Thomas Baker (Chemicals) Pvt. Ltd.

Elution Parameters

Elution utilized an isocratic blend of 20 mm sodium hydroxide buffer (adjusted to pH 8.0) and acetonitrile (50:50 volume basis). The eluent underwent filtration through a 0.45 µm Pall Nylon 6,6 filter (47 mm) and sonic degassing for 30 minutes with a Labman Scientific Pvt. Ltd. apparatus. Monitoring occurred at 222 nm, with 10 µL sample volumes. Protocol confirmation adhered to ICH analytical validation norms.

Protocol Refinement via QbD

Establishing Method Goals

QbD, as a structured risk-oriented system, demands explicit aims for technique creation to uphold scientific depth, operational awareness, and regulatory alignment in drug quality assurance.

Study Layout

A deliberate study framework was adopted to refine the RP-HPLC setup, methodically probing essential elements like eluent formulation and pH balance. This built an extensive elution records system to steer refinements and adaptations, including handling shifts in contaminants or stationary phase sourcing.

Response Surface Modeling

A central composite arrangement (two factors at three levels) was applied to probe primary, interactive, and nonlinear impacts of variables on release profiles. Leveraging Design Expert® (Version 10.0 from Stat-Ease Inc., Minneapolis, MN), a quadratic model was fitted:

$$Y = \beta_0 + \beta_1 A + \beta_2 B + \beta_{12}(AB) + \beta_{11}(A^2) + \beta_{22}(B^2)$$

In this equation, Y denotes the outcome metric, β_0 the baseline, β_1–β_{22} the derived coefficients from trial data, and A/B the scaled factors (elution speed and eluent mix). Outcomes tracked encompassed elution duration, signal intensity, and shape uniformity, drawn from initial explorations.

Refinement and Finalization of Setup

Setup refinement proceeded via a multi-stage review emphasizing shape balance, elution timing, and trailing. Elution variables were tuned as needed, with ideal parameters derived through Design Expert analysis.

Hazard Evaluation, Durability, and Consistency

Durability and consistency were gauged using a hazard-oriented tactic per ICH Q8/Q9, employing cause-effect mapping to scan risks in settings like varied sites, operators, devices, solvents, or slight tweaks. This secured long-term technique dependability.

Technique Oversight Plan

An oversight plan was formulated from the study records to set performance benchmarks, mitigating risks and affirming sturdiness across scenarios via durability/consistency probes.

Technique Confirmation

Selectivity and Discrimination

Discrimination was verified by overlaying elution profiles of repotrectinib reference and eluent blank, confirming no blank overlap at the target elution point.

Linear Range

Proportionality was tested across 40–60 µg/mL, showing direct linkage between amount and signal output.

Recovery Assessment

Recovery was gauged with spike trials at 80%, 100%, and 120% nominal levels, run thrice via addition of reference to pre-tested samples, then processed per the RP-HPLC setup.

Repeatability

Repeatability encompassed same-day (intra) and cross-day (inter) runs, with three levels each in triplicate; %RSD quantified variability, and inter-day checks spanned separate sessions.

Detection Threshold (LOD)

The minimal detectable level was derived as LOD = 3.3 (σ / slope), where σ is peak variability standard deviation and slope from the standard curve.

Quantification Threshold (LOQ)

The minimal reliable level was LOQ = 10 (σ / slope), ensuring suitable repeatability and recovery.

Discrimination

Reference (50 μg/mL) and blank runs identified peaks by timing; criterion: no blank disruption at target.

RESULTS AND DISCUSSION

Eluent Refinement

The eluent blend was settled post a series of tests, detailed in a results overview. These probes methodically tested (Table 1 & 2) mixes for superior elution traits in repotrectinib assessment.

Table 1.Method Development for Repotrectinib HPLC

Trial No.	Mobile Phase	Ratio	Diluent	Column	Wavelength (nm)	Flow rate (ml/min)
1	Buffer A:ACN	50-50	50% Buffer A: 50% ACN	Agilent Poroshell EC-120 C18 (150 x 4.6 mm, 4μ)	250	1
2	Buffer A:ACN	60-40	50% Buffer A: 50% ACN	Agilent Poroshell EC-120 C18 (150 x 4.6 mm, 4μ)	222	1
3	Buffer B:ACN	60-40	50% Buffer A: 50% ACN	Agilent Poroshell EC-120 C18 (150 x 4.6 mm, 4μ)	222	1
4	Buffer C:ACN	60-40	50% Buffer A: 50% ACN	Agilent Poroshell EC-120 C18 (150 x 4.6 mm, 4μ)	222	1
5	Buffer C:ACN	60-40	50% Buffer A: 50% ACN	Agilent Zorbax Bonus RP (250 x 4.6 mm, 5μ)	222	1
6	Buffer C:ACN	50-50	50% Buffer A: 50% ACN	Agilent Zorbax Bonus RP (250 x 4.6 mm, 5μ)	222	1

NOTE:

Buffer A- 20 mm Disodium Hydrogen Phosphate Buffer pH 8.0
Buffer B- 20 mm Disodium Hydrogen Phosphate Buffer pH 3.5
Buffer C-15 mm Disodium Hydrogen Phosphate Buffer pH 8.0
ACN- Acetonitrile

Trial 6

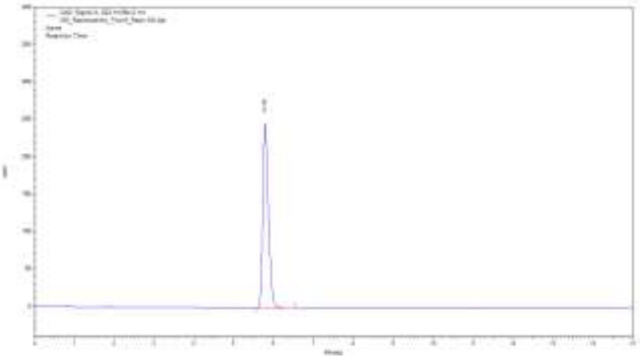


Figure 2.Chromatogram of Trial 6- Buffer C:ACN (50:50)

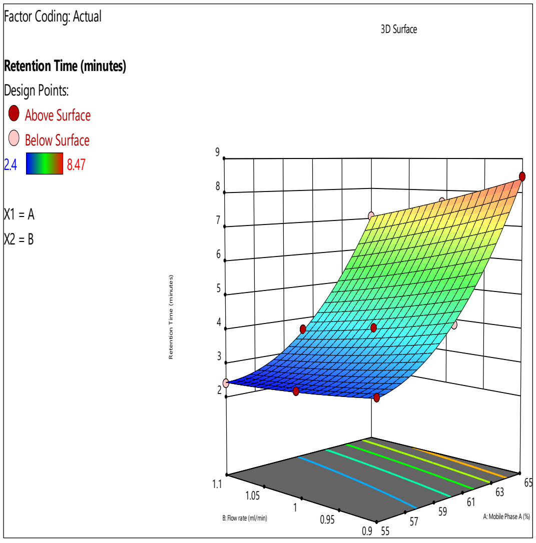


Figure 3.3D Surface Plot of Retention Time

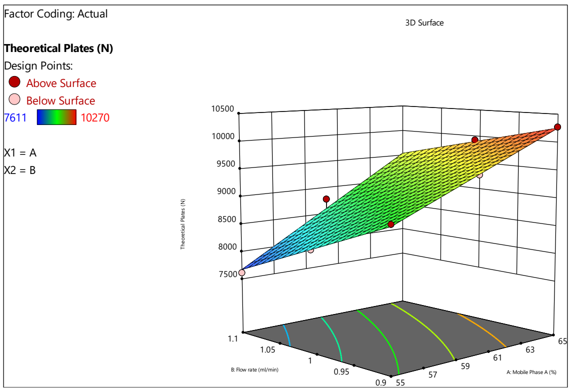


Figure 4.3D Surface Plot of Theoretical Plate

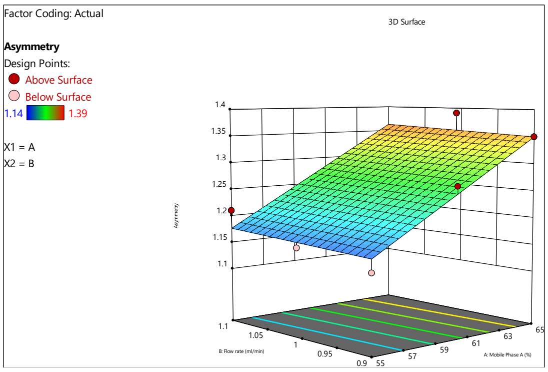


Figure 5.3D Surface Plot of Peak Symmetry

Table 2. Final Chromatographic conditions

Parameter	Condition
HPLC Instrument	Agilent 1260 Infinity II
Column	Phenomenex Kinetex XB-C18 (150 mm x 4.60 mm,5µm)
Wavelength	280 nm
Mobile Phase	Mobile Phase A – 0.1% Trifluroacetic acid-60 % Mobile Phase B – Acetonitrile- 40%
Diluent	0.1% TFA: Acetonitrile (50:50) v/v
Run time	15 minutes
Injection Volume	10 micro liters
Flow Rate	0.9 ml/min
Column oven Temperature	32°C (± 2°C allowed by Robustness)

Results and Discussion

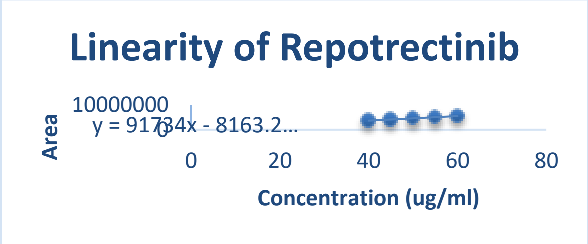
Analytical method validation

Linear Range

RP-HPLC proportionality was proven via standard curves from tablet-derived repotrectinib dilutions (40–60 µg/mL). Five runs per level plotted signal against amount; curves and fit metrics in an overview table 3 illustrated robust amount-signal alignment.

Table 3. Linearity data for Repotrectinib

Repotrectinib		
% Level	**Conc (ug/ml)**	**Area**
80	40	3671643
90	45	4104540
100	50	4589538
110	55	5019598
120	60	5507475



Accuracy

Recovery trials were carried out in triplicate using the standard addition method at 80%, 100%, and 120% to assess the method's level of accuracy.(Table 4) The pre-analyzed samples were mixed with known quantities of standard PCM and PDH, and then they were run through the suggested HPLC procedure. Table 4 displays the tablet solution's good recoveries and compliance with method validation requirements [25, 26].

Table 4. Accuracy for Repotrectinib

Std wt. (mg)	% Purity	Std Stock Conc. (ug/ml)	Working Std Area
5	99	495	4585767

Sample ID	Reps	Spiked Conc. (ng/ml)	Area	Amount Recovered (ug/ml)	% Recovery	AVG	STDEV	% RSD
80%	Rep 1	39.60	3671643	39.63	100.08	100.03	0.052689	0.05
	Rep 2	39.60	3667787	39.59	99.98			
	Rep 3	39.60	3669475	39.61	100.02			
100%	Rep 1	49.50	4589538	49.54	100.08	100.00	0.074602	0.07
	Rep 2	49.50	4584574	49.49	99.97			
	Rep 3	49.50	4582978	49.47	99.94			
120%	Rep 1	59.40	5507475	59.45	100.08	100.12	0.036479	0.04
	Rep 2	59.40	5509774	59.47	100.12			
	Rep 3	59.40	5511475	59.49	100.16			

Same-Day and Cross-Day Repeatability

RP-HPLC consistency was probed (Table 5) via same-day and cross-day evaluations, tracking signal variability for repotrectinib across intervals. %RSD computation met the <2% benchmark for assured steadiness.

Table 5 Intra and Inter day Precision

Repotrectinib						
Condition	**Sample ID**	**RT**	**Area**	**TP**	**Asymmetry**	**Peak Purity**
Morning	WS	5.25	4589538	8693	1.23	1.00
Evening	WS	5.25	4561227	8519	1.21	1.00
AVG		5.25	4575383			
STDEV		0.0000	20018.9001			
% RSD		0.00	0.44			
Day 2	WS	5.25	4536181	8322	1.24	1.00
AVG		5.25	4562315			
STDEV		0.0000	26695.1440			
% RSD		0.00	0.59			

Detection and Quantitation Thresholds

Repotrectinib DT/QT via noise-signal tactic per harmonized directives. DT (minimal discernible) at 2.00 µg/mL (noise-signal = 3); QT (minimal precise/true) at 6.06 µg/mL (=10). Yields affirm trace-level discernment/gauging.

Discernment

Discernment gauged via eluent blank vs. repotrectinib traces under matched conditions. (Figures 3, 4, and 5) Excipient-free analyte zone, sans delay overlaps in traces, affirms complex-matrix distinction.

Resilience

Resilience via targeted subtle shifts in wave, velocity, eluent makeup, oven heat. Tabulated (Table no 6) yields kept benchmarks; affirms shift tolerance sans yield drop, routine-ready.

Table 6: Robustness study - Change in Column Oven temperature

Variation in Column temperature						
Condition	**Sample ID**	**RT**	**Area**	**TP**	**Asymmetry**	**Peak Purity**
28C	WS	5.25	4578999	8723	1.21	1.00
30C	WS	5.25	4589538	8693	1.23	1.00
32C	WS	5.25	4581487	8591	1.24	1.00
AVG		5.25	4583341			
STDEV		0.0000	5508.7698			
% RSD		0.00	0.12			

Forced Degradation:

Below (Table 7) is the data on the forced degradation of Repotrectinib:

Table 7: Forced Degradation data for Repotrectinib

Sample ID	Condition	% Purity of STD	Area	% Assay	% Deg
Control WS	Control	99	5056848	100	-
Acid Sample	1 ml Std + 1 ml 0.1 M HCl for 10 min at RT	-	4999721	97.88	2.12
Base Sample	1 ml Std + 1 ml 0.1 M NaOH for 10 min at RT	-	4849395	94.94	5.06
Peroxide Sample	1 ml Std + 1 ml 3% H2O2 for 10 min at RT	-	5190319	101.61	-1.61
Dry Heat Sample	5 mg at 50C for 5 hours	-	5369170	99.27	0.73
UV Sample	5 mg at 254 nm for 5 hours	-	4751398	94.88	5.12

Conclusion

This investigation effectively crafted and verified an accessible, exact, and sturdy RP-HPLC technique for repotrectinib measurement, a cutting-edge kinase blocker for ROS1 NSCLC therapy. Through QbD, core elements like eluent blend, acidity, and speed were methodically tuned. Refined parameters featured a Phenomenex Kinetex XB-C18 phase (150 × 4.6 mm, 5 µm) with 0.1% TFA-acetonitrile (60:40 v/v) eluent, 0.9 mL/min flow, and 280 nm sensing. ICH-aligned checks showed superior proportionality ($R^2 > 0.999$, 40–60 µg/mL), recovery (99.94–100.16%), and repeatability (%RSD < 2%). Sensitivity shone with 2.00 µg/mL LOD and 6.06 µg/mL LOQ, plus resilience in stress and breakdown resolution. This QbD RP-HPLC suits daily checks, shelf-life monitoring, and norm adherence for repotrectinib raw and dosed forms.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this research work.

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