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SUZETRIGINE: STUDY, ESTIMATION AND DEVELOPMENT OF ANALYTICAL METHODS BY GAS CHROMATOGRAPHY — A REVIEW

***D. Sravanthi, D. Haritha, E. Sailaja, K. Tharun Kumar, N. Pujitha**

Department of Pharmaceutical Analysis, Browns College of Pharmacy, Telangana, India.

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***Corresponding Author: D. Sravanthi**

Department of Pharmaceutical Analysis, Browns College of Pharmacy, Telangana, India.

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ABSTRACT
GC is well suited to the intact molecule suzetrigine has a molecular weight of 473.4, two amide groups one a primary carboxamide and four stereocentres, so it has low volatility and is prone to thermal degradation and on-column adsorption. GC nevertheless has firm roles in suzetrigine quality control, residual solvents in the API, volatile process impurities and reagents, and potentially mutagenic low-molecular-weight impurities. A derivatisation-based GC-MS strategy for the parent drug, intended for forensic or toxicological screening, is outlined along with its ICH Q2(R2) validation plan.

KEYWORDS: suzetrigine; VX-548; NaV1.8; gas chromatography; GC-MS; headspace GC; residual solvents; derivatisation; method validation; ICH.

1. INTRODUCTION

Suzetrigine is the first oral, selective inhibitor approved for acute pain, cleared by the US FDA in January 2025 under the brand name Journavx is expressed in peripheral dorsal root ganglion sensory neurons, so blocking it interrupts pain signals before they reach the spinal cord and brain. It offers a non-opioid alternative after surgery and is being studied in neuropathic conditions such as lumbosacral radiculopathy.

A new drug creates immediate demand for analytical methods: assay and impurity profiling of the API and tablets, bioanalysis for pharmacokinetics, and screening in forensic and anti-doping laboratories. Generic development (ANDA filings) further requires stability-indicating and impurity methods; reference standards and impurity standards are already sold for exactly these purposes.[1]

2. Drug profile

Suzetrigine is a fluorinated pyridine-carboxamide built on a tetrahydrofuran (oxolane) core, with five fluorine atoms from a CF3 group and a difluorophenyl ring. Its properties point to liquid-phase analysis and away from direct GC.

Physicochemical properties of suzetrigine and their analytical relevance

Property	Value	Analytical relevance
IUPAC name	4-[[(2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)oxolane-2-carbonyl]amino]pyridine-2-carboxamide	Two amide groups (secondary + primary) → H-bonding, low volatility
CAS / UNII	2649467-58-1 /	Identity

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Property	Value	Analytical relevance
	LOG73M21H5	
Formula / MW	C21H20F5N3O4 / 473.39 g/mol	High for underivatised GC; [M+H]+ 474 in ESI
Stereochemistry	4 defined stereocentres, absolute	Enantiomer and diastereomer impurities need chiral methods
logP	about 3	Good retention in reversed-phase LC; extractable into organic solvents
Solubility	DMSO 95 mg/mL; ethanol 4 mg/mL; water insoluble	Organic diluents for sample prep; suits liquid-liquid extraction
UV	Detected at 250 nm in reported HPLC methods	UV assay feasible
Fluorine content	5 F atoms	Electron-capture or halogen-selective response possible in GC

Pharmacology. Suzetrigine inhibits human NaV1.8 with an IC50 of about 0.68 nM and is at least 31,000-fold selective over other NaV subtypes. It binds the second voltage-sensing domain (VSD2) and stabilises the closed state of the channel.[2]

Dosing and pharmacokinetics. The approved regimen is 100 mg first, then 50 mg every 12 hours, supplied as 50 mg film-coated tablets. Median Tmax is 3 h for suzetrigine and 8–10 h for its metabolite, and food has no effect on exposure [.Reported half-lives are about 24 h for the parent and 33 h for the metabolite.

Metabolism. CYP3A converts suzetrigine to M6-SUZ, a major active metabolite about 3.7-fold less potent at NaV1.8. Strong CYP3A inhibitors are contraindicated, and suzetrigine itself induces CYP3A.[10] Any bioanalytical method, GC or LC, should therefore resolve and ideally quantify M6-SUZ alongside the parent.

Why GC is absent. The intact molecule is large and polar for GC, and its primary carboxamide hydrogen-bonds strongly to active sites in the inlet and column. At the 280–320 °C needed to elute a compound of this size, amide dehydration to the nitrile and cleavage at the oxolane–carbonyl bond are plausible. LC-MS/MS also already delivers low-ng/mL sensitivity without derivatisation, leaving little incentive to develop a GC assay for bioanalysis.

3. Where GC is still needed. The same API that is assayed by LC must be tested for residual solvents and volatile impurities, which is GC territory by pharmacopoeial convention. A screening laboratory that relies on GC-MS libraries also needs to know whether, and in what form, suzetrigine will appear. Sections 5 and 6 address these two needs.

4. GC principles and suitability for suzetrigine

GC separates compounds that can be vaporised without decomposition, by partitioning between an inert carrier gas and a liquid stationary phase coated in a capillary column. Retention depends on vapour pressure and on interaction with the phase, so analytes must be volatile and thermally stable at the operating temperature.

Core components and the choices that matter here

- **Carrier gas** — helium or hydrogen at 1–2 mL/min constant flow; nitrogen for headspace residual-solvent work.
- **Inlet** — split/splitless for liquid injection; static headspace (HS-GC) for solvents; programmed-temperature vaporisation (PTV) or cold on-column reduces thermal stress on labile analytes.
- **Column** — 5% phenyl-methylpolysiloxane (DB-5ms, HP-5MS) for derivatised drugs; 6% cyanopropylphenyl (DB-624, ZB-624) for residual solvents; polyethylene glycol (WAX) for polar volatiles.
- **Detector** — FID for general quantitation; ECD responds well to polyfluorinated compounds; MS (EI, or NCI for fluorinated species) for identity and trace levels; MS/MS for complex matrices.

GC suitability checklist for intact suzetrigine:

Criterion	Suzetrigine	Verdict
Molecular weight < about 500	473	Borderline
No free –NH2, –OH, –COOH	Primary amide –CONH2 and secondary amide –NH–	Fails without derivatisation
Thermal stability at 300 °C	Not reported; amide dehydration plausible	Must be shown experimentally
Volatility	Low (polar, H-bonding)	Needs derivatisation or high-temperature column

Criterion	Suzetrigine	Verdict
Detector response	5 F atoms; aromatic rings	Good for ECD, NCI-MS and EI-MS

5. GC applications in suzetrigine quality control

GC's established role for suzetrigine is in API and tablet quality control, not in assaying the active itself. Three applications follow.

5.1 Residual solvents (ICH Q3C, USP <467>)

Static headspace GC-FID is the standard for Class 2 and 3 solvents left from synthesis and crystallisation. A typical set-up uses a DB-624 or Elite-624 column (30 m × 0.32–0.53 mm, 1.8–3 µm), helium or nitrogen carrier, and FID at about 250°C; one recent validated method covers 19 common solvents this way.[15] Because suzetrigine is water-insoluble, the API is best dissolved in DMSO, DMF or DMAc in the headspace vial.[3]

Suggested starting conditions for HS-GC-FID residual solvents

Parameter	Setting
Column	DB-624, 30 m × 0.53 mm × 3.0 µm
Oven	40 °C (10 min) → 10 °C/min → 240 °C (5 min)
Headspace	Vial 80–90 °C, 30–45 min equilibration
Diluent	DMSO or DMAc, 100–200 mg API in 5 mL
Detector	FID, 250–260 °C
System suitability	Resolution ≥ 1.5 for the critical solvent pair (e.g. acetonitrile / dichloromethane)

5.2 Volatile and semi-volatile process impurities

Several catalogued suzetrigine impurities are small enough for GC, either directly or after silylation or methylation. Examples include 2-(3,4-difluoro-2-methoxyphenyl)acetic acid (MW 202.2) and the oxolane-2-carboxylic acid fragment (MW 336.3).[13] Carboxylic acids need methylation (TMS-diazomethane) or silylation (BSTFA + 1% TMCS) before GC-FID or GC-MS.[4]

5.3 Potentially mutagenic impurities (ICH M7)

Acyl chlorides and small alkylating reagents used in amide coupling are typical ICH M7 concerns. The acid chloride intermediate (MW 372.7)[13] is too reactive to inject directly. It is usually quenched with methanol to form the stable methyl ester, then quantified by GC-MS in SIM mode at ppm levels relative to the API. Any sulfonate esters or alkyl halides in the route would likewise be controlled by GC-MS.[5]

6. Proposed GC-MS method development for suzetrigine

The strategy below is a proposal derived from the molecule's structure and standard GC practice; it has not been published or experimentally verified. Its most realistic use is qualitative or semi-quantitative screening in forensic and toxicology laboratories that run GC-MS libraries, with LC-MS/MS kept for confirmation.

1. **Test the underivatised drug first.** Inject 10–50 µg/mL in ethyl acetate on a DB-5ms column via PTV or a deactivated splitless liner. Record peak shape, recovery against a reference and any degradation peaks (for example, the nitrile from amide dehydration). This decides whether derivatisation is needed.
2. **Derivatise the amide hydrogens.** Silylate with MSTFA or BSTFA + 1% TMCS (60–70 °C, 30 min), or use MTBSTFA for more stable TBDMS derivatives. Optimise reagent excess, time and temperature by design of experiments, and confirm that a single derivative (mono- vs di-TMS) dominates.
3. **Select column and oven programme.** Start with a 30 m × 0.25 mm × 0.25 µm 5%-phenyl phase; a 15 m column or a high-temperature phase shortens residence time for this late eluter.
4. **Choose the detector.** EI-MS full scan (m/z 50–650) to build a library spectrum and identify diagnostic ions; then SIM for quantitation. NCI-MS with methane, or ECD, can exploit the five fluorine atoms for higher sensitivity.
5. **Pick an internal standard.** Ideally deuterated suzetrigine; otherwise a structurally similar, derivatisable fluorinated amide that elutes nearby.
6. **Develop sample preparation.** For blood or urine: basified liquid-liquid extraction (ethyl acetate or MTBE) or mixed-mode SPE, dry under nitrogen, then derivatise. For tablets: dissolve in acetonitrile, filter, dry an aliquot, derivatise.
7. **Include the metabolite.** Run M6-SUZ through the same steps where a standard is available, since it is a major circulating species.
8. **Confirm stability-indicating power.** Analyse acid, base, oxidative, thermal and photolytic stress samples and show that degradants and impurities do not co-elute with the derivative.[6]

Suggested starting conditions for GC-MS of derivatised suzetrigine

Parameter	Setting
Column	HP-5MS UI or DB-5ms, 30 m × 0.25 mm × 0.25 µm
Carrier	Helium, 1.2 mL/min constant flow
Inlet	Splitless (1 min) or PTV, 260–280 °C, ultra-inert liner
Oven	100 °C (1 min) → 20 °C/min → 300 °C (5–8 min)
Transfer line / source	290 °C / 230 °C
Ionisation	EI 70 eV; NCI (methane) as an option
Acquisition	Full scan m/z 50–650 for identification; SIM on 3 ions for quantitation
Injection	1 µL of derivatised extract

7. Method validation (ICH Q2(R2); ICH M10 for bioanalysis)

A GC method for suzetrigine or its impurities is validated against the same characteristics as any chromatographic procedure; the targets below are typical acceptance criteria, to be fixed in the validation protocol.[7]

Validation parameters and typical acceptance criteria

Characteristic	How it is tested	Typical acceptance
Specificity	Blank, placebo, known impurities, stressed samples; MS spectral confirmation	No interference at analyte RT; peak purity confirmed
Linearity and range	≥ 5 levels (e.g. LOQ–150% of limit for solvents; 80–120% for assay)	r ≥ 0.99 (impurities), ≥ 0.999 (assay)
Accuracy	Spiked recovery at 3 levels, triplicate	80–120% at trace level; 98–102% for assay
Precision	Repeatability (n = 6) and intermediate precision (day, analyst, column)	RSD ≤ 10–15% trace; ≤ 2% assay
LOD / LOQ	Signal-to-noise 3:1 and 10:1, or SD of response / slope	LOQ ≤ reporting threshold or ICH Q3C/M7 limit
Robustness	Flow ±10%, oven ramp ±2 °C/min, inlet ±10 °C, derivatisation time	System suitability still met
Solution and derivative stability	Re-inject over 24–48 h at bench and autosampler temperature	Change ≤ 2% (assay) or ≤ 10% (trace)
Derivatisation yield (GC-MS only)	Compare derivative response across reagent excess and time	Plateau reached; single dominant derivative
Matrix effect and recovery (bioanalysis)	Post-extraction spike vs neat; pre- vs post-extraction spike	Consistent across 6 matrix lots; CV ≤ 15%

For biological samples, ICH M10 additionally requires calibration-curve, QC-sample and incurred-sample reanalysis criteria (± 15%, ± 20% at LLOQ). As a benchmark, the published UHPLC-MS/MS method reached 1 ng/mL with a single protein-precipitation step[1]; a GC-MS method would need to approach this to be useful for pharmacokinetics.

8. GC versus LC, challenges and outlook

For the intact drug, LC wins on every practical count; GC wins only where the analyte is volatile.

Table 7: Comparison of GC and LC for suzetrigine.[8,9,10]

Aspect	GC / GC-MS	HPLC / LC-MS/MS
Sample preparation for suzetrigine	Extraction + drying + derivatisation	Dilution or protein precipitation
Thermal risk	Amide degradation possible	None
Sensitivity (parent)	Unknown; NCI/ECD could be high	Proven 1 ng/mL in plasma
Chiral purity	Not practical for this molecule	Validated chiral HPLC exists
Residual solvents and volatiles	Method of choice (HS-GC-FID)	Unsuitable
Library-based screening	Large EI libraries; suzetrigine spectrum not yet in them	HRMS libraries growing
Cost per run	Lower gas and solvent cost	Higher solvent and instrument cost

challenges

- Thermal stability of suzetrigine and M6-SUZ in a hot GC inlet has not been reported.
- No EI mass spectrum of suzetrigine or its derivatives is in public libraries, so GC-MS screens may miss it.
- The synthetic route, and hence the definitive residual-solvent and mutagenic-impurity list, is proprietary.
- Deuterated internal standards and M6-SUZ reference material are not yet widely available.

Future work. Priorities are a thermal-stability study and an EI library spectrum of underivatised and silylated suzetrigine; a validated HS-GC method for its residual solvents; GC-MS/MS for M7 impurities; and green-chemistry scoring (AGREE, BAGI) of any new method, as the chiral HPLC study did.

9. CONCLUSION

Suzetrigine is currently estimated almost entirely by liquid chromatography, from UV assay and chiral HPLC to UHPLC-MS/MS and LC-HRMS, because its size, polarity and amide groups make direct Gc is practical. GC remains essential for residual solvents and volatile or mutagenic impurities in the API, and a silylation-based GC-MS method is a credible, still-unpublished route for screening laboratories. Developing and validating such methods against ICH Q2(R2) is an open opportunity for research.

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