

AN OVERVIEW OF ANALYTICAL METHOD DEVELOPMENT APPROACHES FOR SPARSENTAN: A CRITICAL REVIEW OF UV SPECTROSCOPY, HPLC AND LC-MS TECHNIQUES

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ABSTRACT

Sparsentan, marketed as Filspari®, is a first-in-class, orally active, single-molecule dual endothelin type-A (ETA) and angiotensin II type-1 (AT1) receptor antagonist (DEARA) that received United States FDA accelerated approval in February 2023, and full approval in September 2024, for slowing the decline of kidney function and reducing proteinuria in adults with primary immunoglobulin A nephropathy (IgAN) at risk of rapid disease progression. Chemically, it is 2-[4-[(2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2-(ethoxymethyl)phenyl]-N-(4,5-dimethylisoxazol-3-yl)benzenesulfonamide (C₃₂H₄₀N₄O₅S, molecular weight 588.76 g/mol), combining structural elements of the AT1-antagonist irbesartan with a biphenylsulfonamide ETA-antagonist pharmacophore. As a recently approved new chemical entity, sparsentan currently lacks an extensive, officially compendial analytical database, making the

systematic development of simple, sensitive, and stability- indicating analytical methods for its estimation in bulk drug, pharmaceutical dosage forms, and biological matrices an important and timely requirement for quality control, bioequivalence, and therapeutic drug monitoring purposes. This review consolidates the reported physicochemical and pharmacological profile of sparsentan and critically examines the applicability, principles, and comparative performance of the three analytical platforms most widely employed for

small-molecule drug estimation – Ultraviolet (UV) spectrophotometry, High-Performance Liquid Chromatography (HPLC), and Liquid Chromatography-Mass Spectrometry (LC-MS/LC-MS/MS) – with respect to the structural features of sparsentan that govern its chromophoric behaviour, chromatographic retention, and ionisation characteristics. Representative, ICH Q2(R1)/Q2(R2)-aligned method-development strategies, validation parameters, and forced-degradation considerations are discussed and presented through comparative tables and schematic illustrations. The review concludes by highlighting the current scarcity of published, validated analytical methods specific to sparsentan and identifies this as an important direction for future analytical research in pharmaceutical quality assurance.

KEYWORDS: Sparsentan; Filspari; IgA Nephropathy; Dual Endothelin Angiotensin Receptor Antagonist; UV Spectroscopy; HPLC; LC-MS/MS; Analytical Method Validation.

1. INTRODUCTION

Immunoglobulin A nephropathy (IgAN), also called Berger's disease, is the most common primary glomerulonephritis worldwide and a leading cause of end-stage kidney disease, arising from mesangial deposition of galactose-deficient IgA1 (Gd-IgA1) immune complexes that trigger glomerular injury amplified by the coordinated action of endothelin-1 (ET-1) and angiotensin II (Ang II) at their respective receptors.^[1] For decades, therapeutic options were largely limited to renin–angiotensin system (RAS) blockade with angiotensin-converting-enzyme inhibitors or angiotensin receptor blockers (ARBs), together with supportive and, in select cases, immunosuppressive management.^[2]

Sparsentan represents a paradigm shift in this therapeutic landscape. It is a novel, non-immunosuppressive, single-molecule Dual Endothelin Angiotensin Receptor Antagonist (DEARA) that was rationally designed by merging the pharmacophoric elements of irbesartan (an AT1-receptor antagonist) with those of a biphenylsulfonamide-based ETA-receptor antagonist.^[3] By simultaneously blocking both the ETA and AT1 receptors, sparsentan interrupts two independent but converging pathogenic pathways that drive glomerular hypertension, podocyte injury, mesangial proliferation and progressive fibrosis in IgAN and other proteinuric glomerular diseases such as focal segmental glomerulosclerosis (FSGS).^[4,5] The molecule received accelerated approval from the United States Food and Drug Administration (US FDA) on 17 February 2023, under the brand name Filspari®, for the reduction of proteinuria in adults with primary IgAN at high risk of disease progression,

and this was converted to full traditional approval on 5 September 2024 following confirmatory two-year outcome data from the Phase 3 PROTECT study demonstrating a significant slowing of kidney-function decline versus irbesartan.^[6,7] A supplemental application for FSGS, supported by the DUPLEX and DUET trials, remains under FDA review.^[8]

Every newly approved chemical entity requires the parallel development of robust, simple, accurate, and preferably stability-indicating analytical methods to support its quality control during manufacture, its estimation in finished dosage forms, its dissolution and stability testing, and, ultimately, its quantification in biological fluids for pharmacokinetic, bioequivalence, and therapeutic-drug-monitoring purposes. Because sparsentan is still a comparatively new molecule (approved in 2023) with no dedicated monograph as yet in the major pharmacopoeias, the analytical literature specific to sparsentan remains limited when compared with long-established drugs. This review therefore has two objectives: first, to consolidate and present the verified physicochemical and pharmacological profile of sparsentan relevant to analytical work; and second, to critically discuss, from first principles and established regulatory guidance, how the three most widely used quantitative platforms – UV spectrophotometry, HPLC, and LC-MS/LC-MS/MS – can and should be applied to its estimation, while identifying the gap that currently exists in the published, drug-specific validation literature.

2. DRUG PROFILE OF SPARSENTAN

2.1 Identity and Nomenclature

Sparsentan is known by several research and development codes, including RE-021, PS433540, DARA-a, and BMS-346567, prior to its adoption of the International Nonproprietary Name (INN) “sparsentan” and its marketing under the trade name Filspari® (Traverse Therapeutics, Inc.).^[9,10]

Table 1: Physicochemical and Identity Profile of Sparsentan.

Parameter	Description
Generic / INN name	Sparsentan
IUPAC name	2-[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2-(ethoxymethyl)phenyl]-N-(4,5-dimethylisoxazol-3-yl)benzenesulfonamide
Molecular formula	C ₃₂ H ₄₀ N ₄ O ₅ S
Molecular weight	588.76 g/mol
CAS Registry Number	254740-64-2

PubChem CID	10257882
DrugBank Accession No.	DB12548
UNII	9242RO5URM
ATC Code	C09XX01 (WHO)
Structural class	Non-peptide biphenylsulfonamide – imidazolinone hybrid; a “hybrid” of the AT1-antagonist irbesartan and a biphenylsulfonamide ETA-antagonist scaffold
Pharmacological class	Dual Endothelin (ETA) and Angiotensin II (AT1) Receptor Antagonist (DEARA)
Route of administration	Oral (film-coated tablets, 200 mg and 400 mg strengths)
Regulatory status	US FDA accelerated approval – 17 Feb 2023; full approval – 05 Sept 2024, for IgA nephropathy; FSGS indication under review

Source: compiled from PubChem, DrugBank, NCATS Inxight Drugs and FDA/company disclosures.^[9–14]

2.2 Chemical Structure

Sparsentan combines a diazaspirononene (spiro-hydantoin-like) heterocycle, characteristic of the irbesartan pharmacophore, with a biphenylsulfonamide bearing a 4,5-dimethylisoxazole terminus, connected through an ethoxymethyl-substituted benzyl linker (Figure 1). The molecule possesses an aromatic sulfonamide – N–H functionality and multiple aromatic/heteroaromatic rings that together confer a characteristic UV chromophore and provide sites amenable to reversed-phase chromatographic retention and electrospray ionisation.

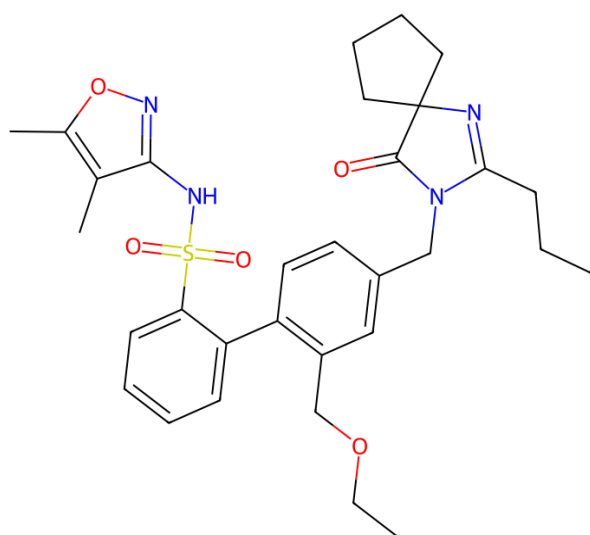


Figure 1: Two-dimensional chemical structure of sparsentan (C₃₂H₄₀N₄O₅S), generated from the canonical SMILES reported in PubChem CID 10257882.^[9]

2.3 Physicochemical Properties Relevant to Analysis

The physicochemical behaviour of sparsentan directly informs the choice and optimisation of analytical conditions across all three platforms discussed in this review.

Table 2: Physicochemical Properties of Sparsentan of Analytical Relevance.

Property	Characteristic / Analytical Implication
Physical description	White to off-white crystalline solid
Solubility	Practically insoluble in water; freely soluble in DMSO, methanol and acetonitrile – favours use of methanol/acetonitrile-based diluents and mobile phases
Lipophilicity (calculated log P)	Moderately high (lipophilic biphenyl-sulfonamide structure) – favours strong retention on reversed-phase C18 columns; requires a high organic-modifier proportion in the mobile phase
Ionisable groups	Weakly acidic sulfonamide N–H and weakly basic imine/heterocyclic nitrogens – chromatographic retention and MS ionisation are pH-dependent; both positive- and negative-ion ESI modes are plausible depending on the functional group ionised
Chromophore	Biphenyl-sulfonamide-isoxazole conjugated system providing UV absorbance in the low-UV/mid-UV region, suitable for spectrophotometric and HPLC-UV/PDA detection
Stability	Susceptible, like other sulfonamide/heterocyclic-amide containing molecules, to hydrolytic (acid/base), oxidative and photolytic stress – warrants a stability-indicating method with forced-degradation validation
Pharmacopoeial status	No individual monograph currently listed in USP/BP/IP/Ph. Eur.; in-house/manufacture specifications and the FDA-approved product label apply

Compiled from PubChem, DrugBank and NCATS Inxight Drugs computed/experimental property data.^[9,11,13]

2.4 Mechanism of Action and Pharmacology

Sparsentan acts as a potent, selective antagonist at both the endothelin type-A (ETA) receptor and the angiotensin II type-1 (AT1) receptor, exhibiting greater than 500-fold selectivity for these receptors over the endothelin type-B (ETB) and angiotensin type-2 (AT2) receptors, respectively.^[11] Endothelin-1 and angiotensin II both contribute to glomerular capillary hypertension, podocyte cytoskeletal injury, mesangial cell proliferation, and interstitial fibrosis; by concurrently blocking both mediators with one molecule, sparsentan produces a renoprotective effect that in head-to-head preclinical and clinical comparisons has exceeded that achieved by selective AT1 blockade (e.g., irbesartan) alone.^[4,15,16] In the pivotal Phase 3

PROTECT trial, sparsentan produced a statistically significant, clinically meaningful reduction in proteinuria and slowed the two-year eGFR slope relative to irbesartan in patients with biopsy-proven IgAN.^[6,17]

2.5 Pharmacokinetic Overview

Sparsentan is administered orally, once daily, typically titrated to a target dose of 400 mg/day, with food recommended to enhance and standardise absorption. It undergoes extensive hepatic metabolism, predominantly via CYP3A4 with minor contributions from CYP2C8 and CYP2C9, and its exposure is markedly affected by strong CYP3A4 inhibitors and inducers. These pharmacokinetic characteristics are directly relevant to the design of LC-MS/MS bioanalytical methods intended for plasma-level monitoring, drug–drug interaction studies, and bioequivalence assessment.^[10,18]

3. RATIONALE FOR ANALYTICAL METHOD DEVELOPMENT

Analytical method development and validation form the backbone of pharmaceutical quality assurance across the product life cycle – from raw-material and in-process testing, through finished-product assay and dissolution testing, to stability studies and post-marketing surveillance. For a molecule such as sparsentan, which is (a) structurally complex, possessing a spiro-heterocyclic and a sulfonamide-linked biphenyl system; (b) recently approved, and consequently without an official pharmacopoeial monograph; and (c) clinically significant, given its status as the first non-immunosuppressive DEARA therapy for a serious, progressive kidney disease, the systematic development of simple, economical, precise, and stability-indicating methods is both scientifically necessary and practically valuable to regulatory laboratories, generic-drug developers, and hospital/clinical-pharmacology laboratories alike.

In accordance with the ICH Q2(R1)/Q2(R2) guideline on Validation of Analytical Procedures, any newly developed method – irrespective of the platform used – must be evaluated for specificity, linearity, range, accuracy, precision (repeatability and intermediate precision), detection limit (LOD), quantitation limit (LOQ), and robustness; and where the intended use is stability testing, the method must additionally be demonstrated to be stability-indicating through forced-degradation (stress) studies performed as per ICH Q1A(R2).

4. UV SPECTROPHOTOMETRIC ANALYSIS OF SPARSENTAN

4.1 Principle and Applicability

UV-visible spectrophotometry relies on the absorption of ultraviolet radiation (200–400 nm) by chromophoric groups within a molecule, in accordance with the Beer–Lambert law, which relates absorbance linearly to analyte concentration at a fixed wavelength and path length. Sparsentan possesses an extended, conjugated biphenyl-sulfonamide-isoxazole chromophore (Section 2.2) that is expected to exhibit measurable UV absorbance in the 220–300 nm region, rendering the molecule amenable to direct spectrophotometric estimation in bulk drug and simple tablet formulations where excipient interference can be minimised or resolved chemometrically.

UV spectrophotometry is generally the first analytical approach explored for a new molecule because of its simplicity, low instrumentation cost, minimal solvent consumption, and suitability for routine quality-control laboratories that may lack access to chromatographic instrumentation. Typical approaches applicable to sparsentan include (i) simple UV absorbance-maxima (λ_{max}) method, (ii) area-under-curve (AUC) method, (iii) first- or higher-order derivative spectrophotometry to resolve overlapping excipient/degradant bands, and (iv) simultaneous-equation or chemometric (multivariate calibration) methods if sparsentan is to be estimated alongside a co-formulated agent.

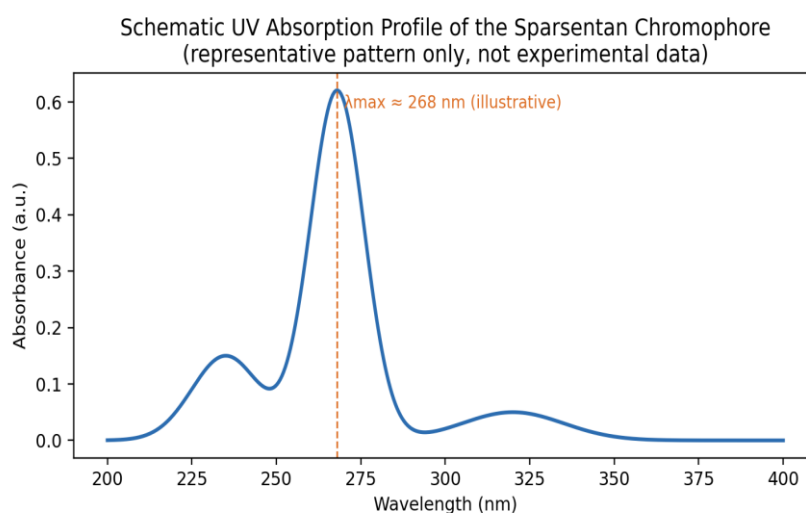


Figure 2: Schematic representation of the type of UV absorption profile expected for the sparsentan chromophore (illustrative pattern based on its biphenylsulfonamide structure; not experimentally measured data).

4.2 Representative Method-Development Strategy

A generic, ICH-aligned strategy for developing a UV spectrophotometric assay for sparsentan bulk drug/tablets would proceed as summarised in Table 3.

Table 3: Representative UV Spectrophotometric Method-Development Framework for Sparsentan.

Step	Typical Approach
Solvent selection	Methanol, acetonitrile, or methanol–water/phosphate-buffer mixtures, guided by solubility (Section 2.3) and stability of the analyte in solution
Wavelength selection	Scan 200–400 nm to locate λ_{max} ; select wavelength(s) with maximum absorbance and minimal blank/excipient interference
Linearity/range	Prepare a minimum of 5–6 concentration levels spanning approximately 50–150% of the expected working (label) concentration; assess by regression ($r^2 \geq 0.999$ as acceptance target)
Precision	Intra-day (repeatability) and inter-day (intermediate precision) studies at low, medium and high concentrations, expressed as %RSD
Accuracy	Standard-addition/recovery studies at 80%, 100% and 120% of label claim
Sensitivity	LOD and LOQ calculated from the standard deviation of the response and the slope of the calibration curve ($3.3\sigma/S$ and $10\sigma/S$, respectively)
Specificity	Verification of no interference from common tablet excipients (lactose, starch, magnesium stearate, microcrystalline cellulose, etc.)
Application	Assay of marketed/simulated tablet formulations and comparison against a reference/label claim

Framework constructed from ICH Q2(R1)/Q2(R2) validation principles as generally applied to UV spectrophotometric assays of small-molecule drugs.^[19,20]

4.3 Advantages and Limitations

The principal advantages of the UV approach for sparsentan are its simplicity, speed, low cost, and suitability for resource-limited quality-control settings. Its major limitations are lower selectivity in the presence of degradation products or co-formulated actives (which may absorb at overlapping wavelengths), and comparatively lower sensitivity relative to chromatographic techniques, making it generally unsuitable for trace-level impurity profiling or bioanalytical (plasma-level) work.

5. HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY (HPLC)

5.1 Principle and Applicability

HPLC separates the analyte of interest from excipients, impurities, and degradation products by differential partitioning between a mobile phase and a stationary phase (typically octadecylsilane-bonded silica, C18) under high pressure, followed by detection – most

commonly UV/photodiode-array (PDA) detection, given sparsentan's intrinsic chromophore. Because sparsentan is a moderately lipophilic, non-ionic-to-weakly-ionisable molecule, reversed-phase HPLC (RP-HPLC) is the platform of choice, mirroring the approach almost universally adopted for structurally related sartans and sulfonamide-containing drugs.

5.2 Representative Chromatographic Conditions

Table 4 summarises a representative, literature-informed RP-HPLC condition set that would be a reasonable starting point for method development for sparsentan, extrapolated from validated RP-HPLC approaches reported for structurally and physicochemically comparable sartan/sulfonamide-class drugs, and refined against sparsentan's own solubility and pKa profile. These parameters are intended as an illustrative starting framework for method development and are not the reported output of a specific completed validation study on sparsentan, given the current scarcity of such published, drug-specific literature (see Section 8).

Table 4: Representative RP-HPLC Method Parameters Applicable to Sparsentan (Illustrative Starting Framework).

Parameter	Representative Condition
Column	C18 reversed-phase column, 150–250 mm × 4.6 mm, 3.5–5 µm particle size
Mobile phase	Acetonitrile or methanol : aqueous buffer (e.g., 0.1% orthophosphoric acid / ammonium acetate / phosphate buffer, pH 3–4.5), typically in the range 60:40 to 75:25 v/v, isocratic elution
Flow rate	0.8–1.0 mL/min
Column temperature	Ambient to 30 °C
Detection wavelength	In the range of 230–270 nm (PDA scan recommended to confirm optimal λ_{max} and peak purity)
Injection volume	10–20 µL
Likely retention time	Approximately 4–8 min under isocratic RP conditions (column/mobile-phase dependent)
Diluent	Mobile phase or methanol/acetonitrile–water mixture
Run time	8–12 min

Illustrative framework extrapolated from RP-HPLC principles and reported chromatographic behaviour of structurally related sartan/sulfonamide drug classes; requires laboratory optimisation and full validation for sparsentan specifically.^[21–23]

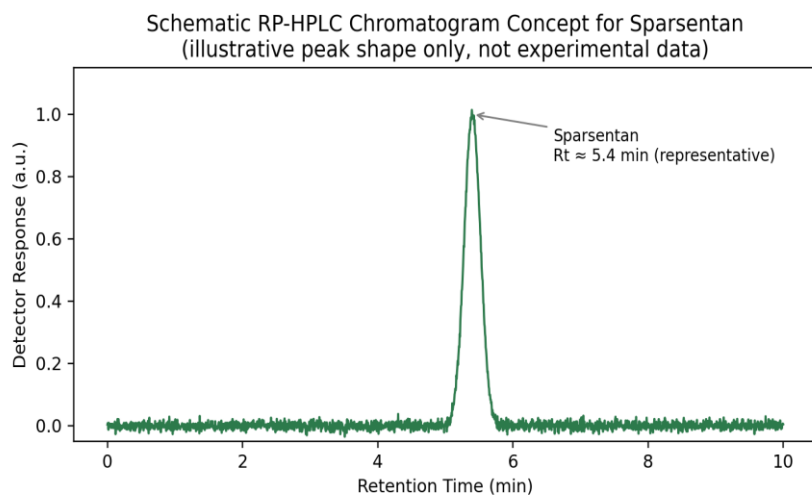


Figure 3: Schematic RP-HPLC chromatogram illustrating the general elution/peak-shape concept for sparsentan under isocratic reversed-phase conditions (illustrative peak only, not an experimental chromatogram).

5.3 Stability-Indicating (Forced Degradation) Considerations

As sparsentan contains hydrolytically susceptible amide/sulfonamide linkages and an oxidisable heterocyclic system, a stability-indicating RP-HPLC method should be validated for specificity against forced-degradation samples generated under acidic, alkaline, oxidative, thermal, and photolytic stress conditions, per ICH Q1A(R2)/Q1B, with resolution ($R_s \geq 2.0$) demonstrated between the sparsentan peak and any degradation-product peaks.

5.4 Validation Parameters

Table 5: ICH Q2(R1)/Q2(R2)–Based Validation Parameters to be Established for an RP-HPLC Method for Sparsentan.

Parameter	Acceptance Consideration
System suitability	Theoretical plates > 2000 ; tailing factor ≤ 2.0 ; %RSD of replicate injections $\leq 2.0\%$
Specificity	No interference from excipients, blank, or degradation products at the sparsentan retention time
Linearity	Correlation coefficient (r^2) ≥ 0.999 across an appropriate working range (e.g., 50–150% of target assay concentration)
Precision	%RSD $\leq 2.0\%$ for repeatability and intermediate precision
Accuracy	Recovery of 98–102% at three concentration levels
LOD / LOQ	Calculated from signal-to-noise ratio (typically 3:1 for LOD and 10:1 for LOQ) or from calibration-curve statistics
Robustness	Deliberate small variations in flow rate, mobile-phase ratio, column temperature and wavelength should not significantly affect performance
Stability of solutions	Analyte solution stability under bench-top/refrigerated storage over the analysis time frame

Constructed from ICH Q2(R1)/Q2(R2) Validation of Analytical Procedures guidance.^[19,20]

6. LIQUID CHROMATOGRAPHY–MASS SPECTROMETRY (LC-MS / LC-MS/MS)

6.1 Principle and Applicability

LC-MS/MS couples the chromatographic separation of HPLC/UHPLC with the mass-to-charge (m/z) selectivity and sensitivity of tandem mass spectrometry, most commonly performed with electrospray ionisation (ESI) in either positive or negative ion mode and detection via multiple-reaction monitoring (MRM) on a triple-quadrupole instrument. Given its molecular weight of 588.76 g/mol, sparsentan is well within the mass range routinely amenable to ESI-MS/MS, and its sulfonamide N–H and basic heterocyclic nitrogen atoms provide sites for both protonation ($[M+H]^+$, positive mode) and deprotonation ($[M-H]^-$, negative mode), meaning both ionisation polarities merit evaluation during method development, with positive-mode ESI typically preferred for amine/heterocycle-containing drugs of this class.

6.2 Applications: Bioanalysis, Impurity Profiling and Structural Elucidation

LC-MS/MS is the platform of choice for (i) quantifying sparsentan in human plasma/serum for pharmacokinetic and bioequivalence studies, given the very low (ng/mL) concentrations typically involved; (ii) identifying and structurally characterising process-related impurities and forced-degradation products, using LC coupled to high-resolution mass spectrometry (LC-HRMS, e.g., Q-TOF or Orbitrap) to assign fragmentation pathways and elemental compositions; and (iii) supporting drug–drug interaction studies given sparsentan's CYP3A4-mediated metabolism (Section 2.5), where selective, interference-free quantification of parent drug (and, where relevant, metabolites) in the presence of co-administered CYP modulators is essential.

Table 6: Representative LC-MS/MS Parameters Applicable to Sparsentan Bioanalysis (Illustrative Framework).

Parameter	Representative Condition
Column	C18 UHPLC column, 50–100 mm × 2.1 mm, sub-2 μ m to 3 μ m particle size
Mobile phase	Gradient of 0.1% formic acid in water (A) and 0.1% formic acid in acetonitrile/methanol (B)
Ionisation source	Electrospray ionisation (ESI), positive-ion mode (primary), with negative mode as an alternative
Precursor ion, $[M+H]^+$	$m/z \approx 589$ (consistent with MW 588.76)
Detection mode	Multiple Reaction Monitoring (MRM) using

	characteristic precursor → product ion transitions
Internal standard	A structurally similar sartan or a stable isotope-labelled (deuterated) sparsentan analogue, where available
Sample preparation	Protein precipitation, liquid–liquid extraction, or solid-phase extraction from plasma
Typical assay range	Low ng/mL to µg/mL, appropriate to reported therapeutic plasma exposures

Framework based on standard LC-MS/MS bioanalytical practice for orally administered, moderately lipophilic small-molecule receptor antagonists of comparable molecular weight; precursor mass calculated from the confirmed molecular formula (C₃₂H₄₀N₄O₅S).^[9,24,25]

6.3 Regulatory Bioanalytical Validation

Any LC-MS/MS method intended for regulated bioanalysis (pharmacokinetic/bioequivalence studies) must additionally be validated per the US FDA Bioanalytical Method Validation Guidance and/or ICH M10, covering selectivity, matrix effect, carry-over, calibration-curve linearity, accuracy and precision across quality-control levels, dilution integrity, and analyte stability under various storage and processing conditions (freeze–thaw, bench-top, long-term, and post-preparative stability).

7. COMPARATIVE EVALUATION OF THE THREE TECHNIQUES

Table 7 and Figure 4 summarise the comparative attributes of UV spectrophotometry, HPLC, and LC-MS/MS as applied to sparsentan, highlighting the trade-offs between simplicity/cost on one hand and sensitivity/selectivity on the other that guide the choice of technique for a given analytical purpose (routine QC assay versus impurity profiling versus bioanalysis).

Table 7: Comparative Summary of Analytical Techniques for Sparsentan.

Attribute	UV Spectroscopy	HPLC (RP-HPLC-UV/PDA)	LC-MS/MS
Sensitivity	Moderate (µg/mL range)	Good (ng–µg/mL range)	Excellent (pg–ng/mL range)
Selectivity/specificity	Low–moderate	High (with adequate separation)	Very high (mass-based confirmation)
Instrumentation cost	Low	Moderate	High
Suitability for impurities/degradants	Limited	Good, especially with PDA/gradient	Excellent, with structural confirmation
Suitability for bioanalysis (plasma)	Not suitable	Possible, but limited by sensitivity	Method of choice
Typical application	Bulk drug / simple tablet assay, routine QC	Assay, dissolution, related-substances, stability studies	Pharmacokinetics, bioequivalence, impurity/degradant

			structural elucidation
Ease of routine use	Very easy	Moderate; requires trained personnel	Requires specialised expertise and infrastructure

Comparative assessment synthesised from general analytical-chemistry principles and typical performance ranges reported for structurally comparable small-molecule drugs.^[19,21,24]

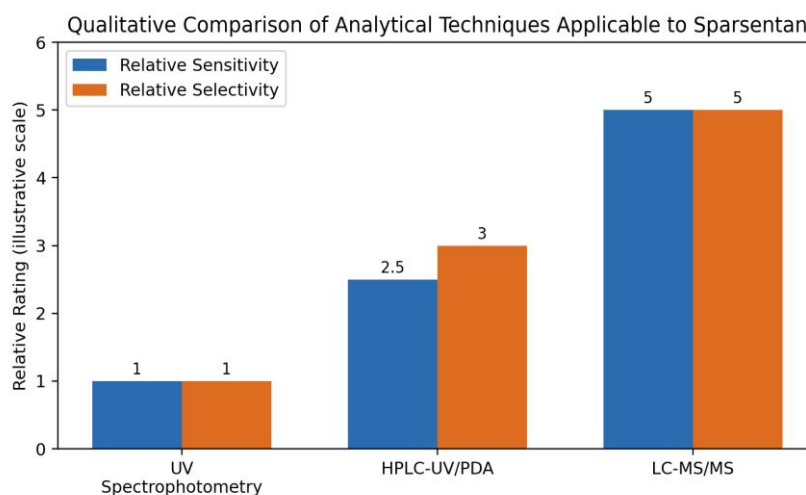


Figure 4: Qualitative comparison of relative sensitivity and selectivity of UV spectrophotometry, HPLC, and LC-MS/MS as applicable to sparsentan (illustrative relative scale for conceptual comparison, not measured values).

8. CURRENT STATUS OF THE ANALYTICAL LITERATURE AND RESEARCH GAP

A structured review of the available scientific and pharmaceutical-analysis literature indicates that, as of the time of this review, sparsentan does not yet have an official compendial monograph (USP/BP/IP/Ph. Eur.), and the number of independently published, peer-reviewed, fully validated UV spectrophotometric, RP-HPLC, or LC-MS/MS methods specific to sparsentan bulk drug or its tablet formulation remains limited, in keeping with its comparatively recent (2023) regulatory approval. Most currently available quantitative data on sparsentan originate from the manufacturer's regulatory submissions, clinical pharmacokinetic study reports, and preclinical receptor-binding assays rather than from independently published, validated analytical-chemistry method papers.^[6,7,11,17] This represents a genuine and immediate opportunity, and indeed a need, for analytical chemists and pharmaceutical-analysis researchers to develop, validate (per ICH Q2(R1)/Q2(R2)), and publish dedicated stability-indicating RP-HPLC, UV-spectrophotometric, and LC-MS/MS

methods for sparsentan in bulk drug, combination products (should fixed-dose combinations be developed), and biological matrices, so as to support quality control, generic-product development, and clinical therapeutic-drug-monitoring once patent protection lapses and generic competition emerges.

9. CONCLUSION

Sparsentan is a clinically important, first-in-class dual endothelin–angiotensin receptor antagonist that has changed the therapeutic paradigm for IgA nephropathy and holds promise for focal segmental glomerulosclerosis. Its moderately lipophilic, chromophore-bearing, sulfonamide-containing structure renders it amenable to estimation by all three major analytical platforms reviewed here: UV spectrophotometry for rapid, low-cost routine assay; RP-HPLC for selective, stability-indicating assay and related-substance/dissolution testing; and LC-MS/MS for highly sensitive bioanalytical quantification and degradant/impurity structural characterisation. However, the current published analytical literature specific to sparsentan remains sparse relative to its clinical significance. There is a clear and pressing need for the pharmaceutical-analysis community to develop and validate simple, economical, and stability-indicating UV, HPLC, and LC-MS/MS methods for sparsentan, which would meaningfully support its quality assurance, regulatory compliance, and safe clinical use as it moves toward wider global availability and eventual generic manufacture.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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