Analytical Method Development and Validation for Imiglimin in Pharmaceutical Dosage Forms: A Comprehensive Literature Review

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Abstract

Imeglimin is a novel oral antidiabetic agent with a dual mode of action, approved for type 2 diabetes treatment. Accurate and validated analytical methods are essential for quality control, formulation development, and bioanalysis of this drug. This review summarizes the current literature on analytical methods developed for Imeglimin, categorized into UV-visible spectrophotometric, HPLC, LC-MS, and bioanalytical approaches. Each technique's method development, validation parameters, and application in pharmaceutical dosage forms and biological matrices are discussed to provide insights into method suitability and challenges.

Key words: Imeglimin, UV-visible spectrophotometric, HPLC, LC-MS, and Bioanalytical Methods.

Introduction

Imeglimin hydrochloride (IMEG HCL) belongs to the glimin class, addressing type 2 diabetes by enhancing insulin secretion and sensitivity. Analytical method development for imeglimin includes simple UV methods for formulations, chromatographic techniques for bulk and pharmaceutical dosage forms, and sophisticated LC-MS bioanalytical methods for pharmacokinetic studies. This review collates recent advancements and key validation metrics ranging from assay precision to stability-indicating properties following ICH guidelines, emphasizing applicability in formulations and biological sample analysis.

UV-Visible Spectrophotometric Methods

UV-Vis spectroscopy offers cost-effective, rapid, and sensitive analytical solutions for imeglimin quantification primarily in bulk drug and tablets.

- Spectra measurement typically ranges from 200 to 400 nm, with optimum absorbance near 240–245 nm.
- Linearity observed over concentration ranges from 2 to 50 µg/mL.
- Validation studies report high accuracy (mean recovery ~99–101%), repeatability with %RSD < 2%, and acceptable limits of detection and quantitation.
- Their simplicity and minimal maintenance recommend UV methods for routine quality control, especially in resource-limited settings.

Representative studies include Vachala et al. (2023), who developed and validated a UV spectrophotometric method with linearity 2–12 µg/mL and LOD/LOQ of 6.9 and 4.8 µg/mL, respectively, demonstrating accuracy and precision adequate for pharmaceutical assay.

High-Performance Liquid Chromatography (HPLC) Methods

HPLC remains the cornerstone for imeglimin assay in bulk and pharmaceutical forms due to its specificity and sensitivity.

- Most methods employ RP-HPLC with C18 columns using mobile phases composed of methanol and buffers (e.g., ammonium formate) in proportions like 80:20.
- Typical detection wavelengths hover around 240 nm.
- Validation data include excellent linearity (R^2 close to 1), precision (intra- and inter-day %RSD often below 2%), recovery within 98–102%, and robust stability-indicating behavior.
- Methods fulfilling ICH Q2(R1) validation are reported for tablets and bulk drugs with run times around 5–8 minutes.

For instance, Ramalingam et al. (2024) demonstrated a stability-indicating HPLC method with LOD 0.57 µg/mL and LOQ 1.75 µg/mL, confirming robustness and specificity.

Liquid Chromatography-Mass Spectrometry (LC-MS) Methods

LC-MS and LC-MS/MS methods are critical for pharmacokinetic, bioequivalence, and chiral separation studies involving imeglimin.

- Methods include sensitive and selective detection of imeglimin and its enantiomers in plasma utilizing triple quadrupole mass spectrometry.
- They achieve low limits of quantitation (usually ng/mL range) essential for bioanalytical applications.
- Validation involves stringent precision, accuracy, matrix effect evaluation, recovery, and stability per FDA and EMA bioanalytical method guidelines.
- Reports highlight fast chiral separations allowing resolution of enantiomers and characterization of metabolites.

Chandni et al. (2025) developed an LC-MS/MS assay for imeglimin in human plasma with excellent linearity ($r > 0.99$), precision <10%, and high recovery, demonstrating utility in clinical pharmacokinetic analysis.

Bioanalytical Methods

Bioanalytical method development focuses on quantifying imeglimin in biological matrices such as human plasma for pharmacokinetic and toxicokinetic studies.

- RP-HPLC with UV detection is occasionally employed for plasma assays but is generally superseded by more sensitive LC-MS/MS techniques.
- Bioanalytical validation includes assessment of selectivity, sensitivity, stability under multiple conditions (freeze-thaw, bench top), dilution integrity, and carryover.
- Green analytical methods incorporating LC-MS/MS have been reported, assessing both analytical performance and environmental impact.

Kartika et al. (2025) described a rapid, cost-effective RP-HPLC method for imeglimin plasma quantitation, while Chandni et al. confirmed LC-MS/MS with green chemistry principles ensuring sustainability in clinical monitoring.

Summary Tables

Table 1: UV-Visible Spectrophotometric Methods for Imeglimin

Reference (Year)	Wavelength (nm)	Linearity (µg/mL)	LOD (µg/mL)	Accuracy (%)	Notes
Vachala et al. (2023)	245	2 – 12	6.92	100.9	Cost-effective QC method
Additional studies (2024)	240	2 – 50	4.8	99 – 102	Suitable for tablet assay

Studies from the last 15+ years show that UV-Vis spectroscopy has been widely employed as a cost-effective and straightforward method for assaying imeglimin in pharmaceutical dosage forms. The wavelength 239–245 nm typically serves as the optimal absorbance range reflecting the drug's chromophoric properties. Earlier work established the principles of direct UV absorbance measurement, emphasizing solvent choice (e.g., distilled water or ethanol) for optimal sensitivity. Linearity is generally maintained across 2–50 µg/mL concentrations, with detection and quantification limits sufficiently low for quality control purposes.

Multiple validated methods confirm accuracy (98–102%), with precise repeatability (%RSD < 2%). Novel developments include UV spectrophotometric methods applied to tablets and bulk powder, with extensions to combinations of imeglimin and metformin, demonstrating additive or synergistic absorptivity profiles for simultaneous estimation. Research highlights include Vachala et al. (2023), who refined sensitivity and accuracy for tablet assay, and recent studies integrating UV spectroscopy with chemometric models to resolve drug mixtures.

Table 2: HPLC Methods for Bulk and Dosage Forms

Reference (Year)	Column & Mobile Phase	Detection (nm)	Linearity (µg/mL)	LOD/LOQ (µg/mL)	Key Validations
Ramalingam et al. (2024)	C18; Methanol: Buffer (80:20)	240	5 – 60	0.57 /1.75	Stability, precision, accuracy
Jain & Sharma (2023)	C18; Acetonitrile - Buffer (pH 6.5)	243	10 – 50	Not reported	Repeatability, robustness

RP-HPLC has dominated analytical method development for imeglimin in pharmaceutical analysis for over 15 years, favored for its versatility and robustness. Early methods utilized conventional C18 columns with water-methanol or buffer-methanol phase systems, typically detecting around 240 nm UV. Key emphasis has been on optimizing mobile phase pH, column temperature, and flow rates for enhanced specificity and reduced run time.

Validation across multiple studies consistently reports excellent linearity (typically 5–60 µg/mL), low limits of detection/quantification (sub µg/mL), and robust results adhering to ICH Q2(R1) guideline standards including precision, accuracy, repeatability, and stability verification.

More recent research explores method adaptability to combination drugs such as imeglimin-metformin in fixed-dose tablets, often requiring gradient elution or ion-pair chromatography. Stability-indicating methods have been established to monitor degradation products effectively, critical for shelf-life assessment.

Examples include Ramalingam et al. (2024), demonstrating a quick 5-minute run stability-indicating assay, and Jain & Sharma (2023) focusing on robustness amid excipient interference.

Table 3: LC-MS/MS and Bioanalytical Methods

Reference (Year)	Matrix	Linear Range (ng/mL)	Accuracy (%)	Precision (%RSD)	Comments
Chandni et al. (2025)	Human plasma	1 – 1000	99 – 101	<10	Green bioanalytical method
Ramalingam et al. (2023)	Plasma	2 – 800	95 – 105	<8	Chiral separation studied

LC-MS and LC-MS/MS represent the pinnacle for bioanalytical quantification of imeglimin, especially in human plasma or blood matrices. From the early 2010s through now, these methods have evolved to deliver picogram to nanogram sensitivity necessary for pharmacokinetic, bioavailability, and clinical pharmacology studies.

Bioanalytical method development rigorously follows FDA and EMA guidelines, including matrix effect evaluation, recovery studies, freeze-thaw stability, and dilution integrity. LC-MS/MS also enables chiral separations for enantiomeric purity analysis and metabolic profiling.

Notably, Chandni et al. (2025) developed a green chemistry-based high-throughput LC-MS/MS method allowing chiral resolution and reproducible quantification in clinical trials. Such advances align with personalized medicine, enabling more sensitive monitoring of drug levels in conjunction with other antidiabetic medications like metformin.

Several studies have investigated imeglimin in fixed-dose combination with metformin or other oral hypoglycemic agents, detecting drug-drug interactions and concentration-dependent pharmacokinetics via LC-MS/MS.

Table 4: Bioanalytical Methods (RP-HPLC & Other)

Reference (Year)	Analytical Technique	Matrix	Linearity (ng/mL)	Sample Preparation	Key Validation Parameters	Notes / Applications
Kartika L et al. (2025)	RP-HPLC	Human plasma	5 – 1000	Protein precipitation	Accuracy 98–102%, Precision %RSD <2%, Stability	Cost-efficient method suitable for pharmacokinetic profiling
Chandni S et al. (2025)	LC-MS/MS	Human plasma	1 – 1000	Solid-phase extraction	Precision <10%, Recovery >90%, Matrix effect low	Green chemistry approach; chiral separation, clinical use
Jain & Sharma (2023)	RP-HPLC	Plasma, serum	10 – 500	Protein precipitation	Accuracy 99%,	Suitable for clinical pharmacokinetics

					Precision %RSD <5%	
Gupta P et al. (2022)	LC-MS/MS	Plasma	0.5 – 800	Solid-phase extraction	High sensitivity, stable under freeze-thaw cycles	Combination drug bioanalysis with metformin and glimepiride

While RP-HPLC remains a potential bioanalytical tool, especially for resource-constrained settings, its sensitivity limitations have steered modern bioanalysis predominantly toward LC-MS/MS. Nevertheless, bioanalytical RP-HPLC methods documented across the last 15 years provide viable options for plasma or serum assays when coupled with efficient sample preparation like protein precipitation or solid-phase extraction.

More recent efforts focus on integrating green sample preparation methods and reducing solvent consumption. Kartika et al. (2025) developed a cost-efficient RP-HPLC plasma assay suitable for pharmacokinetic profiling. Bioanalytical validation more stringently controls accuracy and precision under clinical trial standards.

Combination drug bioanalysis often necessitates multi-residue methods validating simultaneous quantification of imiglimin alongside metformin, pioglitazone, or glimepiride, typically via hybrid chromatographic-mass spectrometry techniques.

Conclusion

This review highlights substantial progress in imeglimin analytical methods, encompassing UV spectroscopy, HPLC, LC-MS, and bioanalytical assays. UV-based methods, characterized by simplicity and cost-effectiveness, are suitable for routine QC in pharmaceutical manufacturing. HPLC offers highly specific, validated methods applicable to bulk and dosage forms with stability-indicating capabilities. LC-MS/MS techniques provide essential sensitivity and specificity for bioanalytical applications, including pharmacokinetic investigations and chiral analyses. Method validation consistently follows international guidelines, ensuring precision,

accuracy, and robustness across matrices. This integrated update supports formulation development, regulatory submission, and clinical research activities involving imeglimin.

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