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RECENTLY APPROVED ANTIDIABETIC DRUGS BY FDA AND METABOLITE CHARACTERIZATION STUDIES USING LC/MS: A COMPREHENSIVE REVIEW

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ABSTRACT
Type 2 diabetes mellitus (T2DM) represents a significant global health burden, with over 38 million Americans currently affected. The FDA has approved nearly 60 antidiabetic agents, with continuous expansion of therapeutic options including glucagon-like peptide-1 receptor agonists (GLP-1 RAs), sodium-glucose cotransporter-2 inhibitors (SGLT2i), and novel co-agonists. This review synthesizes recent FDA approvals in antidiabetic therapeutics (2023-2025), with particular emphasis on GLP-1 RAs, SGLT2 inhibitors, and emerging combination therapies. Additionally, this paper comprehensively discusses the role of liquid chromatography-mass spectrometry (LC/MS) in metabolite identification and characterization studies, including FDA compliance protocols and method validation guidelines. The review highlights key regulatory considerations, including GLP status, bioanalytical method validation parameters, and metabolite profiling strategies relevant to drug development. This work synthesizes current literature, regulatory guidance, and clinical data to provide a comprehensive understanding of modern antidiabetic drug development and metabolite assessment methodologies.

Keywords: Antidiabetic drugs; Type 2 diabetes mellitus; FDA drug approvals; GLP-1 receptor agonists; SGLT2 inhibitors; Dual and triple incretin agonists; Drug metabolism; Metabolite identification; LC–MS/MS

1. INTRODUCTION

The prevalence of type 2 diabetes mellitus has reached epidemic proportions globally, with approximately 537 million adults affected worldwide. In the United States alone, the Centers for Disease Control and Prevention reports that more than 38 million Americans have diabetes, with 90-95% classified as type 2. The escalating healthcare burden necessitates continuous innovation in pharmacological interventions, leading to the FDA approval of multiple new antidiabetic agents over the past three years [1][2].

The therapeutic landscape for T2DM has evolved substantially from the initial monotherapy approach with metformin. Contemporary treatment paradigms emphasize combination regimens targeting multiple pathophysiological mechanisms, including defective insulin secretion, impaired glucose utilization, and hepatic glucose overproduction [3]. The recent approval of novel drug classes, particularly GLP-1 receptor agonists and SGLT2 inhibitors, has

revolutionized diabetes management with the added benefit of cardiovascular and renal protective effects [2].

Beyond clinical efficacy, the characterization of drug metabolites has become increasingly critical in the drug development pipeline. The FDA requires comprehensive metabolite profiling for new drug applications, necessitating robust analytical methodologies. Liquid chromatography coupled with mass spectrometry (LC/MS) has emerged as the gold standard for metabolite identification, quantification, and characterization due to its superior selectivity, sensitivity, and specificity [3].

This comprehensive review examines: (1) recently FDA-approved antidiabetic medications (2023-2025), (2) their mechanisms of action and clinical efficacy, (3) combination therapies currently in clinical use, and (4) the role of LC/MS in metabolite characterization studies including regulatory compliance and method validation standards [4][5][6].

2. RECENTLY FDA-APPROVED ANTIDIABETIC DRUGS (2023-2025)

2.1 Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RAs)

GLP-1 receptor agonists represent one of the most significant therapeutic advances in diabetes management. These incretin mimetics activate GLP-1 receptors on pancreatic beta cells, promoting glucose-dependent insulin secretion while simultaneously suppressing glucagon secretion [7].

2.1.1 Semaglutide (Ozempic) - Expanded Indications

While semaglutide was previously approved for T2DM management, the FDA expanded its approved indications on January 28, 2025, to reduce the risk of kidney disease worsening, kidney failure (end-stage renal disease), and cardiovascular death in adults with type 2 diabetes and chronic kidney disease [1][2]. The Phase 3 FLOW trial demonstrated that once-weekly semaglutide 1 mg resulted in significant reduction in kidney disease-related events compared to placebo. This approval represents a paradigm shift in addressing the secondary complications of diabetes, particularly diabetic nephropathy [8].

2.1.2 Generic GLP-1 RAs: Liraglutide and Exenatide

The FDA approved the first generic GLP-1 receptor agonist exenatide (Byetta) on November 11, 2024, through Amneal Pharmaceuticals, followed by generic liraglutide (Victoza) approval in December 2024. These approvals are particularly significant as they represent the first generic options in this drug class, potentially improving patient accessibility and reducing medication costs. Liraglutide is administered once-daily as a subcutaneous injection at doses ranging from 0.6-1.8 mg, while exenatide is administered twice-daily[2][9].

2.1.3 Injectable and Oral Formulations

Currently, the FDA-approved injectable GLP-1 receptor agonists include dulaglutide (Trulicity), exenatide (Byetta and Bydureon extended-release), liraglutide (Victoza), lixisenatide (Adlyxin), and semaglutide (Ozempic)[1]. All of these agents have demonstrated efficacy in reducing hemoglobin A1c (HbA1c) levels and promoting weight loss, with semaglutide showing the most substantial weight reduction among the class[10].

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2.2 Sodium-Glucose Cotransporter-2 Inhibitors (SGLT2i)

SGLT2 inhibitors represent a unique class of antidiabetic agents that improve glycemic control through a renal mechanism. These agents inhibit the sodium-glucose linked transporter-2 protein in the proximal convoluted tubule of the kidney, reducing glucose reabsorption and promoting urinary glucose excretion [2][3].

2.2.1 Bexagliflozin (Brenzavvy) - Recent FDA Approval

Bexagliflozin, approved by the FDA in January 2023 as TheracosBio's Brenzavvy, represents the most recent addition to the SGLT2 inhibitor class. Developed through a comprehensive clinical program involving 23 trials with over 5,000 adults, Phase 3 studies demonstrated significant reductions in HbA1c and fasting blood glucose levels within 24 weeks of treatment [4]. Bexagliflozin is administered as an oral tablet, typically at doses of 20 mg once daily [11].

2.2.2 Established SGLT2 Inhibitors

Five SGLT2 inhibitors currently hold FDA approval for type 2 diabetes management: canagliflozin (Invokana), dapagliflozin (Farxiga), empagliflozin (Jardiance), ertugliflozin (Steglatro), and bexagliflozin (Brenzavvy) [2]. Beyond glycemic control, canagliflozin, dapagliflozin, and empagliflozin have received additional FDA approvals for cardiovascular and renal indications, including heart failure reduction and chronic kidney disease protection [2] [12].

2.2.3 Mechanism and Clinical Advantages

SGLT2 inhibitors reduce HbA1c by approximately 0.5-1.5% as monotherapy and provide additional cardiovascular and renal benefits. The mechanism involves increased urinary glucose excretion, promotion of natriuresis (sodium excretion), and improvement of insulin sensitivity [3]. These agents are particularly beneficial in patients with chronic kidney disease, heart failure, and diabetic nephropathy [13].

2.3 Dual and Triple Combination Therapies

2.3.1 GIP-GLP-1 Receptor Co-Agonists: Tirzepatide (Mounjaro)

Tirzepatide represents a significant breakthrough as the first-in-class GIP-GLP-1 receptor co-agonist, approved for T2DM management under the brand name Mounjaro. By simultaneously activating both glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptors, tirzepatide achieves superior glycemic control and weight reduction compared to single-action GLP-1 receptor agonists [2] [14].

The FDA has granted additional approvals for tirzepatide beyond diabetes management, including weight loss indication (Zepbound) and obstructive sleep apnea treatment in 2024, with pending applications for heart failure with preserved ejection fraction expected in 2025[15].

2.3.2 Combination Regimens

As of 2025, the FDA has approved 23 unique antihyperglycemic drug combinations. Notable recent triple-combination therapies include [2][3]:

- Metformin + Saxagliptin + Dapagliflozin (approved 2019)
- Metformin + Linagliptin + Empagliflozin (approved 2020)
- Insulin Degludec + Liraglutide (Xultophy)

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- Insulin Glargine + Lixisenatide (Soliqua)
- Sidapvia: Dapagliflozin + Sitagliptin (approved 2024) [4]

These combination regimens address the progressive nature of T2DM, allowing comprehensive management of multiple pathophysiological defects through single-pill therapy, thereby improving medication adherence and patient outcomes [16].

2.4 Cell Therapy: Lantidra (Donislecel)

In a landmark development for type 1 diabetes management, the FDA approved Lantidra (Donislecel) in 2024, representing the first-ever cell therapy for severe hypoglycemia-prone type 1 diabetes. This therapy involves transplantation of beta cells from deceased donors into the hepatic portal vein, enabling endogenous insulin production and potentially eliminating the need for insulin injections or pump therapy [4]. This approval represents a paradigm shift from traditional pharmaceutical approaches to regenerative medicine.

3. METABOLITE CHARACTERIZATION: FDA GUIDELINES AND REGULATORY FRAMEWORK

3.1 Role of Metabolite Studies in Drug Development

Metabolite characterization represents a critical component of the preclinical and clinical drug development pipeline. The FDA mandates comprehensive metabolite profiling through its "Metabolite in Safety Testing" (MIST) guidance, which requires identification and characterization of metabolites representing ≥10% of the administered dose or ≥25% of total plasma radioactivity in humans [1][3].

Metabolite studies serve multiple critical functions [1][3]:

1. Assessment of drug safety and efficacy
2. Identification of potentially toxic metabolites
3. Evaluation of individual metabolizer phenotypes (poor, intermediate, extensive metabolizers)
4. Elucidation of drug-drug interaction potential
5. Support for regulatory submissions to FDA and international regulatory agencies
6. Establishment of metabolic pathways and biotransformation mechanisms

3.2 GLP Compliance Status for Metabolite Studies

A critical distinction exists regarding Good Laboratory Practice (GLP) compliance requirements for metabolite studies [3]. GLP compliance is NOT required for in vitro drug metabolism studies, including metabolite characterization experiments. However, in vitro metabolite characterization studies are conducted according to standard operating procedures (SOPs) developed based on FDA GLP regulations (21 CFR Part 58) to ensure rigorous record-keeping, data integrity, and reproducibility [3].

For in vivo studies and human metabolite studies conducted as part of clinical trials, GLP compliance is not applicable. However, studies conducted to support regulatory submissions must adhere to Good Clinical Practice (GCP) standards and demonstrate compliance with ICH guidelines [1][3].

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3.3 FDA Guidance Documents for LC/MS Method Validation

The FDA has issued comprehensive guidance documents for bioanalytical method validation using LC-MS/MS, particularly relevant to antidiabetic drug development [1][3]. Key regulatory guidance includes:

- FDA Guidance for Industry: Bioanalytical Method Validation (2018)
- ICH M10 Bioanalytical Method Validation and Study Sample Analysis Guidance (2019)
- FDA MIST Guidance for Metabolite Studies (2008)
- FDA Guidance on Drug Metabolism and Drug Interaction Studies (2017)

These guidance documents establish specific acceptance criteria for:

- Calibration curve performance (linearity, range, accuracy)
- Assay selectivity and specificity
- Accuracy and precision parameters
- Matrix effects assessment
- Stability testing protocols [1][3]

4. LIQUID CHROMATOGRAPHY-MASS SPECTROMETRY (LC/MS) IN METABOLITE CHARACTERIZATION

4.1 Principles and Instrumentation

Liquid chromatography-mass spectrometry combines the chromatographic separation capabilities of high-performance liquid chromatography (HPLC) with the selective detection and structural information provided by mass spectrometry [1][3]. The analytical system comprises four major components [1]:

1. Liquid chromatography system (pump, injector, column)
2. Ionization source (Electrospray Ionization - ESI or Atmospheric Pressure Chemical Ionization - APCI)
3. Mass analyzer (Time-of-Flight - TOF, Quadrupole, Ion Trap)
4. Detector and data acquisition system

For metabolite characterization, high-resolution LC/MS systems utilizing Time-of-Flight or Orbitrap mass analyzers provide accurate mass measurements enabling formula determination of metabolites [1][3].

4.2 Metabolite Detection and Identification Strategies

4.2.1 Multiple Reaction Monitoring (MRM)

Multiple Reaction Monitoring (MRM) or Selected Reaction Monitoring (SRM) represents a highly specific detection mode for targeted metabolite quantification. In MRM mode, the mass spectrometer monitors specific precursor ion → product ion transitions, providing exceptional selectivity while reducing matrix interference [1] [17].

4.2.2 Full Scan and High-Resolution MS

For metabolite discovery and characterization, full-scan mass spectrometry combined with high-resolution detection enables [1] [3]:

- Accurate mass determination (mass error <5 ppm)
- Formula determination through isotope pattern analysis

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- Fragment ion characterization
- Identification of minor metabolites (<10% of administered dose)

4.2.3 Metabolite Interference Resolution

A critical challenge in LC-MS metabolite studies involves resolving interference from glucuronide conjugate metabolites. Studies have demonstrated that glucuronide conjugates elute earlier than parent compounds due to increased polarity, potentially interfering with compound detection [1][3]. Enzymatic hydrolysis using beta-glucuronidase enables confirmation of glucuronide metabolite identity [18].

4.3 Sample Preparation Techniques

4.3.1 Protein Precipitation

Protein precipitation remains the simplest sample preparation approach, typically utilizing organic solvents (acetonitrile, methanol) to precipitate plasma proteins while allowing analyte and metabolite recovery [1][3]. This technique is particularly suitable for compounds with moderate hydrophobicity [19].

4.3.2 Solid-Phase Extraction (SPE)

Solid-phase extraction provides superior selectivity and analyte concentration compared to protein precipitation. SPE utilizes various sorbent materials (C18, C8, ion-exchange) to selectively retain analytes while permitting elution of interfering matrix components [1][3].

4.3.3 Liquid-Liquid Extraction (LLE)

Liquid-liquid extraction employs immiscible organic-aqueous phase partitioning to isolate analytes from biological matrices. This technique provides excellent selectivity, particularly for lipophilic compounds and metabolites [3].

4.4 Method Validation Parameters (ICH M10 Compliance)

4.4.1 Selectivity and Specificity

Method selectivity ensures the analytical procedure distinguishes the analyte and metabolites from other components in the biological matrix. Selectivity assessment requires analysis of blank matrices (drug-free plasma) from multiple sources to confirm absence of interfering peaks at retention times of target analytes [1][3].

4.4.2 Accuracy and Precision

Accuracy (% bias) and precision (% coefficient of variation) must demonstrate recovery within ±20% and ±25% for lower limits of quantification respectively. These parameters are assessed through analysis of quality control (QC) samples at three concentration levels (low, medium, high) [1][20].

4.4.3 Calibration Curve Requirements

Linear calibration curves spanning the analytical range with a minimum of 6 concentration levels (excluding zero) must be established. The correlation coefficient (r) must exceed 0.99, with back-calculated concentrations demonstrating ±20% accuracy [1][3].

4.4.4 Matrix Effects Assessment

Endogenous plasma components may suppress or enhance ionization, requiring quantitative assessment of matrix effects. Post-column and post-extraction infusion methods are employed

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to evaluate ionization suppression/enhancement at LC retention times of target analytes [1][21].

5. PRACTICAL APPLICATION: METABOLITE CHARACTERIZATION PROTOCOL FOR ANTIDIABETIC DRUGS

Table 1: LC/MS Method Validation Parameters and Acceptance Criteria per ICH M10 Guidance

Parameter	Specification	Acceptance Criteria	Reference
Selectivity	Blank plasma from 6+ donors	No interference at retention times	ICH M10[1]
Linearity	6-8 calibration levels	$r^2 \geq 0.99$	ICH M10[1]
Accuracy	Low, Medium, High QC samples	±20% recovery at all levels	ICH M10[1]
Precision (Intra-assay)	Replicate analysis n=3	CV ≤15%, ≤20% at LLOQ	ICH M10[1]
Precision (Inter-assay)	Analysis on 3 separate days	CV ≤15%, ≤20% at LLOQ	ICH M10[1]
Sensitivity (LLOQ)	Signal-to-noise ratio ≥3	≤20% deviation from nominal	ICH M10[1]
Sensitivity (ULOQ)	Signal-to-noise ratio ≥10	≤20% deviation from nominal	ICH M10[1]
Matrix Effects	Comparison of slopes (±25%)	Post-extraction infusion analysis	ICH M10[1]
Stability	4°C, -20°C, -70°C, 3 cycles	≤15% variation from reference	ICH M10[1]

6. CLINICAL SIGNIFICANCE OF METABOLITE STUDIES IN ANTIDIABETIC DRUG DEVELOPMENT

The comprehensive characterization of metabolites for recently approved antidiabetic agents provides critical safety and efficacy data. For GLP-1 receptor agonists such as semaglutide and tirzepatide, metabolite studies have identified minimal hepatic metabolism with primary metabolite formation through enzymatic dipeptidyl peptidase-4 (DPP-4) cleavage [1][2].

For SGLT2 inhibitors including empagliflozin and dapagliflozin, hepatic glucuronidation represents the primary metabolic pathway, with minimal oxidative metabolism. The characterization of glucuronide metabolites proves particularly significant for understanding elimination pathways and potential renal recirculation [2][3].

These metabolite data support [1] [22] [3]:

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- Minimal potential for drug-drug interactions through cytochrome P450 inhibition/induction
- Identification of pharmacologically active metabolites requiring quantification
- Establishment of metabolic phenotype effects (poor vs. extensive metabolizers)
- Support for dosing recommendations in special populations (renal/hepatic impairment)

7. REGULATORY PATHWAYS AND COMPLIANCE CONSIDERATIONS

7.1 Investigational New Drug (IND) Application Requirements

For new antidiabetic entities, comprehensive metabolite characterization studies must be included within IND applications submitted to the FDA. These submissions require [1][3]:

- In vitro metabolism studies in hepatic microsomes and recombinant human enzymes
- Human MIST studies in early clinical trials (Phase 1)
- Pharmacokinetic/Pharmacodynamic modeling incorporating metabolite data
- Proposed identification and quantification strategies for circulating metabolites [1][3]

7.2 New Drug Application (NDA) Requirements

For NDA submissions, the FDA requires [1] [2] [3]:

- Metabolite characterization data from clinical populations
- Comparative metabolite profiles across special populations (elderly, renal/hepatic impairment)
- Stability indicating assay methods for quantification of drug and metabolites
- Clinical pharmacology data including population pharmacokinetics incorporating metabolite data

8. EMERGING TECHNOLOGIES AND FUTURE DIRECTIONS

8.1 High-Resolution Mass Spectrometry (HRMS)

Advances in high-resolution mass spectrometry enable accurate mass determination with <5 ppm mass error, facilitating metabolite structure elucidation without reference standards. Orbitrap and Time-of-Flight analyzers provide sufficient resolution for formula determination from accurate mass measurements [1][3].

8.2 Liquid Chromatography Combined with Nuclear Magnetic Resonance (LC-NMR)

Hyphenated LC-NMR techniques enable on-line structural characterization of metabolites, providing functional group information complementary to MS fragmentation patterns [1].

8.3 In Silico Metabolite Prediction

Computational approaches utilizing machine learning and artificial intelligence enable prediction of metabolite structures prior to experimental confirmation, reducing time and cost of metabolite characterization studies [3].

9. CONCLUSION

Recent FDA approvals in antidiabetic therapeutics represent significant advances in diabetes management, with GLP-1 receptor agonists, SGLT2 inhibitors, and novel combination therapies providing multiple mechanisms for glycemic control. The expanded approval of semaglutide for diabetic nephropathy and emergence of tirzepatide as a GIP-GLP-1 co-agonist demonstrate the evolving landscape of antidiabetic drug development. Comprehensive metabolite characterization utilizing LC/MS remains essential for FDA regulatory compliance,

drug safety assessment, and understanding mechanisms of action. Adherence to ICH M10 guidelines and FDA MIST guidance ensures generation of high-quality, regulatory-compliant metabolite data. The integration of high-resolution mass spectrometry and emerging analytical technologies continues to advance metabolite characterization capabilities, supporting efficient and comprehensive evaluation of novel antidiabetic agents. Future directions in antidiabetic drug development will likely focus on personalized medicine approaches incorporating metabolic phenotype assessment, development of agents targeting additional pathophysiological mechanisms (e.g., glucokinase activators, G-protein coupled receptor agonists), and further exploration of combination therapies optimizing glycemic control while providing cardiovascular and renal protection.

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