Review Article

Principles and Strategies of ADME Profiling in Drug Development

Rashmi Parihar[1], Sumit Kumar Dubey[2*]

[1]Department of Microbiology, Govt. E. Raghavendra Rao Post Graduate Science College, Bilaspur, Chhattisgarh, 495006, India.

[2] D.L.S. P.G. College, Bilaspur, Chhattisgarh, 495006, India.

***Corresponding author's E-mail:** sumitdubeybiotech@gmail.com

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ABSTRACT

ADME profiling is a vital part of assessing drug candidates' pharmacokinetics early in drug discovery. It evaluates how a drug behaves in a biological system and forecasts its efficacy, safety, and clinical potential. Historically, several promising therapies failed in clinical trials mainly due to poor ADME properties, emphasizing the importance of thorough ADME evaluation. The main challenge is the complexity of biological interactions and the variability in drug responses among species and individuals, which reduces the accuracy of traditional *in vitro* and *in vivo* models. Recent progress includes advances in in vitro techniques (such as Caco-2, liver microsomes, and hepatocytes), in vivo approaches (such as rodent studies and mass balance experiments), and computational methods (including QSAR and PBPK modelling), enabling more precise and rapid profiling. These advances enable earlier detection of potential issues and support rational drug design. Additionally, integrating AI and biologics is pushing forward precision medicine field. Despite this progress, challenges persist (such as poor correlation between models and human physiology), limits of static cell-based models, ethical issues related to animal testing, and the need for large along with validated datasets for computational models. Looking ahead, the adoption of multi-organ-on-chip systems, artificial intelligence and personalized pharmacogenomics promises to enhance predictive power, lower costs and reduce the use of animals. These evolving tools mark a paradigm shift in drug development, empowering development of safer, more effective therapies with higher success rates.

Keywords: ADME profiling, pharmacokinetics, drug discovery, in silico modeling, personalized medicine.

INTRODUCTION

A drug is a chemical substance designed to diagnose, treat, prevent, or mitigate diseases by interacting with biological systems to produce therapeutic effects[1]. The evolution of clinical trials reflects a long journey of methodological advancement, beginning with early documented experiments such as the legume diet trials in biblical times[2]. A key milestone was James Lind's 1747 scurvy trial, often regarded as an early form of a controlled study[2]. In the 20th century, the UK's Medical Research Council (MRC) made significant contributions, notably the 1943–44 patulin trial, recognized as the first double-blind controlled trial conducted for the common cold[2,3,4]. This was followed by the landmark 1946 streptomycin trial for pulmonary tuberculosis, which established rigorous standards for trial design and systematic data collection[6].

In India, the foundation of modern clinical research was laid with the establishment of the Indian Research Fund Association (IRFA) in 1911, which later became the Indian Council of Medical Research (ICMR)[7]. Over decades, ICMR expanded its infrastructure by creating specialized research units and national centers for major diseases (e.g., Plague Laboratory, Bombay)[2]. Ethical oversight advanced with the formation of the Central Ethical Committee in 1996, which issued the first comprehensive Ethical Guidelines for Biomedical Research in 2000[7], revised in 2006[8]. Regulatory frameworks also matured, with Schedule Y of the Drugs and Cosmetics Act being revised in 1988 to mandate Phase III trials[9]. However, this revision initially limited global trial participation due to phase lag restrictions. The 2005 revision of Schedule Y introduced flexible, Good Clinical Practice (GCP)-compliant norms, allowing India to engage in concurrent global Phase II-III trials. Today, clinical trials emphasize efficacy, patient safety and ethical integrity. Additionally, continuous regulatory adaptations are needed to meet evolving scientific and societal demands.

The global pharmaceutical market was valued at approximately $1.5 trillion in 2023[10] and is propelled by biologics and personalized therapies. According to the India Brand Equity Foundation[11] the Indian pharmaceutical industry ranks third globally by volume and fourteenth in terms of value. The domestic pharmaceutical market is projected to reach an estimated value of US$ 130 billion by the year 2030. Clinical trials are providing robust evidence of a drug's safety and efficacy, ensuring regulatory compliance, minimizing patient risks, and advancing medical knowledge. The drug discovery process begins with target identification, which involves pinpointing biological targets, such as proteins or genes, linked to a specific disease[12]. High-throughput screening tests thousands of compounds to identify hits with therapeutic potential, which undergo hit-to-lead optimization to refine potency, selectivity, and safety[13]. Lead compounds are further optimized through medicinal chemistry to enhance pharmacokinetic properties, followed by preclinical testing in in vitro and in vivo models[14]. ADME (Absorption, Distribution, Metabolism, and Excretion) profiling is a fundamental aspect of this phase[15]. It systematically evaluates the pharmacokinetic (PK) behavior of drug candidates in biological systems, assessing how a drug is

absorbed into the bloodstream, distributed throughout the body, metabolized into active or inactive forms, and eventually eliminated[15]. Hence, these ADME properties are crucial for predicting *in vivo* efficacy, optimising bioavailability, reducing toxicity, and increasing the likelihood of clinical success.

Afterwards, successful drug candidates progress to clinical trials. Kandi & Vadakedath[16] mentioned that four phases of clinical trials are conducted in structured phases to assess a drug's safety and efficacy. Phase 0 uses micro-doses (1/100th of therapeutic levels) to study basic pharmacokinetics in humans. Phase I, involving fewer than 50 healthy volunteers, focuses on safety, maximum tolerated dose (MTD), and pharmacodynamics. It includes Phase Ia (Single Ascending Dose) and Phase Ib (Multiple Ascending Dose). Phase II (encompasses 5–100 patients) assesses efficacy and determines the optimal dosage. Phase IIa determines the dosing regimen, while Phase IIb evaluates the dose-response relationship and compares it with placebos. Phase III involves 300 to 3,000^{+} patients in multicenter trials to confirm therapeutic efficacy and safety, supporting regulatory submissions such as NDAs. Phase IV monitors long-term safety and potential drug interactions after approval. Each phase plays a critical role in ensuring the drug's effectiveness and public safety.

1. RESEARCH METHODOLOGY

A structured PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) review was used to assess principles and strategies of ADME profiling in drug development.

Search Strategy and Data Sources

A comprehensive systematic literature search was conducted to evaluate the principles and strategies of ADME profiling in drug development, using databases viz., SpringerLink, ScienceDirect, and Google Scholar to retrieve relevant content. The search was limited to English-language articles published over the past ten years to reflect the current state and technological progress.

Screening and Selection

The screening was conducted in accordance with PRISMA guidelines to ensure transparency and reproducibility (Fig 1). The selection process was conducted through the following stages:

- Identification: A total of 397 records were initially identified through database searching.
- Screening: Duplicate records were removed. The remaining titles and abstracts were screened for relevance to principles and strategies of ADME profiling in drug development.
- Inclusion criteria: We have used pre-defined inclusion criteria focused on the principles and strategies of ADME profiling in drug development. Specifically, articles were included if they: (1) addressed core principles of ADME or specific ADME assays; (2) investigated drug metabolism, absorption, or pharmacokinetics; and (3) utilized *in vitro*, *in situ*, *in vivo*, or *in silico* tools for precise ADME characterization and drug screening. To ensure the review reflected contemporary technological advancements, eligibility was restricted to peer-reviewed papers published in last decade.
- Exclusion criteria: Articles were excluded if they did not meet inclusion criteria.

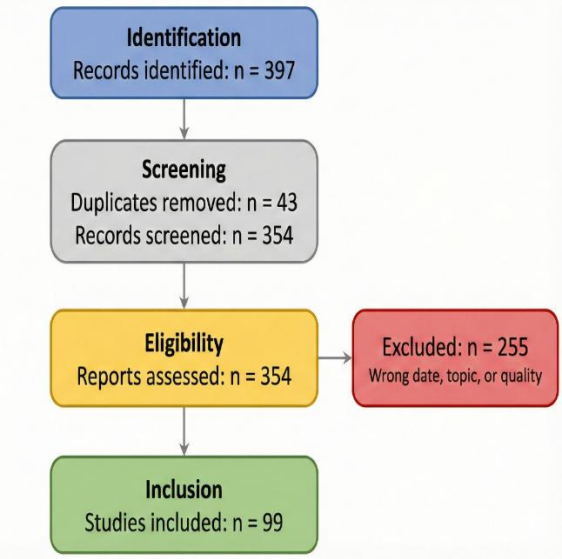

Figure 1: PRISMA-based Screening and Selection chart

2. RESULTS AND DISCUSSION

A total of 397 records were initially identified. After removing 43 duplicates, 354 records were screened based on title and abstract. Upon full-text assessment, 255 articles were excluded because they fell outside the 2020–2026 publication window, did not meet the specific domain criteria, lacked quality content, study design, outcome measures, or addressed principles and strategies of ADME profiling in drug development. Consequently, 99 research articles were selected for the present review. The comprehensive account of ADME profiling in drug development is systematically summarized and discussed.

Problem and Context

Drug discovery and development are complex, time-consuming, and exceedingly costly ventures with notably high failure rates[17]. It is estimated that approximately one in every five thousand synthesized compounds successfully progresses through the entire development process and ultimately qualifies for regulatory approval[18]. Additionally, clinical trials often require investments of billions of dollars and can render late-stage failures financially devastating[19]. Historically, a substantial proportion of these failures exceeds 50% during the preclinical and early clinical stages[17]. It is not primarily due to a lack of therapeutic efficacy, but is predominantly caused by undesirable PK or safety profiles[20]. In particular, deficiencies in ADME properties are identified as the principal causes of clinical attrition.

Inadequate absorption may result in insufficient bioavailability. Thereby, it requires impractical dosing regimens. In many cases, the unfavorable distribution could lead to toxicity in non-target organs or insufficient drug concentrations at the intended site of action[21]. Additionally, unpredictable metabolism or excretion may cause harmful accumulation or adverse drug-drug interactions (DDIs)[22]. The inherent difficulty in accurately predicting and managing these ADME properties during the optimization stage has historically impeded the efficiency of the pharmaceutical industry. Consequently, contemporary drug development has increasingly prioritized early ADME profiling, which combines both predictive and experimental data prior to preclinical testing, in order to minimize risk and ensure that only candidates with optimal PK and exposure-response (ER) characteristics advance further[23]. This ultimately protects patient safety and safeguards investment capital.

Overview of ADME Profiling

The ADME profiling process is critical in drug delivery, as it ensures that a drug's journey through the body maximizes therapeutic efficacy[24]. Absorption determines how effectively a drug enters the bloodstream and is influenced by administration routes, such as oral (exhibit variable bioavailability) or intravenous (offer 100% bioavailability)[25]. Distribution monitors the dispersal of the drug to target tissues, ensuring therapeutic concentrations at the site of action (Liang et al., 2024). Metabolism, primarily occurring in the liver, transforms drugs into active or inactive metabolites, thereby affecting efficacy and duration of action[25]. Excretion, primarily through the kidneys, removes drugs from the body to prevent toxicity from accumulation of toxic metabolites[26]. ADME studies identify compounds with optimal bioavailability and thereby mitigating risks of inefficacy or toxicity. They inform formulation strategies, such as designing tablets for specific gut pH to enhance solubility, and predict drug-drug interactions, including CYP450 inhibition, to prevent adverse effects during co-administration[27]. ADME guarantees that pharmaceuticals maintain safety and efficacy across various populations by assessing pharmacokinetic parameters such as half-life and clearance, thus it minimize probability of clinical trial failures.

Advanced ADME tools, including AI-driven prediction models[28] and 3D cell-based assays[29] accelerate selection of drug candidates, reduce costs, and enhance precision in personalized medicine. For instance, pharmacogenetic testing of genes like CYP2D6 allows for tailored dosing strategies for drugs such as codeine, where poor metabolizers encounter inefficacy and ultra-rapid metabolizers face toxicity risks[30]. In India, ADME-driven approaches support the development of affordable generics[31], while globally, they streamline the drug development pipeline, addressing the 90% failure rate of clinical candidates by early elimination of compounds with poor ADME profiles[32]. Researchers can optimize dosage forms (e.g., tablets, injections, or topical preparations) to balance efficacy, safety, and patient compliance by integrating ADME parameters with biopharmaceutics[33], and thereby ensuring that drugs meet therapeutic objectives and market demands.

Core Principles and Parameters of ADME

ADME profiling encompasses the comprehensive evaluation of Absorption, Distribution, Metabolism, and Excretion of a test drug to assess its pharmacokinetic behavior in biological systems. It optimizes bioavailability, predicts efficacy, and minimizes toxicity to enhance clinical success.

a. Absorption

Absorption is the process through which a drug reaches systemic circulation from the site of administration. It is governed by parameters such as solubility (which affects the dissolution rate), permeability (indicating the drug's ability to cross biological membranes, such as the intestinal epithelium) and bioavailability (F), which denotes the fraction of an administered dose that reaches the circulation intact[34]. Peak plasma concentration (C_{max}) and the time to reach it (T_{max}) further characterize absorption kinetics[35]. Mechanistically, absorption can occur via passive diffusion, facilitated diffusion, active transport, or endocytosis[36]. Drug absorption hinges on three main pillars, viz., the drug's physicochemical properties (e.g., solubility, pKa, molecular size), formulation factors (like dosage form, excipients, and particle size), and physiological elements (such as Gastrointestinal pH, gastric emptying, blood flow and first-pass metabolism)[37]. These interconnected aspects dictate a drug's ultimate bioavailability and therapeutic impact. PK compartment models are mathematical constructs used to describe and predict the time course of drug concentrations in the body during absorption[38]. They simplify the complex physiological processes of drug distribution, metabolism, and elimination by conceptualizing the body as one or more interconnected compartments.

i. One-Compartment Model

The one-compartment model represents the body as a single, homogenous unit where drug distribution is considered instantaneous and uniform throughout all tissues and fluids[39]. Drug absorption and elimination are assumed to occur directly from this single compartment. This model is most appropriate for drugs that distribute very rapidly and extensively, such that their distribution phase is negligible compared to their elimination half-life[40]. It is ideal when plasma concentration changes primarily reflect drug elimination, as the drug quickly equilibrates between the blood and all body tissues. For instance, drugs like ethanol (alcohol) in many clinical contexts or highly water-soluble antibiotics such as gentamicin (under specific dosing scenarios) often fit a one-compartment model due to their swift distribution relative to their removal from the body[41]. This model proves helpful for initial dose calculations, predicting steady-state concentrations, and

interpreting drug levels for agents where elimination is the dominant pharmacokinetic process.

ii. Two-Compartment Model

The two-compartment model offers a more nuanced representation, dividing the body into a central compartment and a peripheral compartment[39]. The central compartment encompasses highly perfused organs and blood, where drug equilibration is rapid while peripheral compartment comprises less perfused tissues, such as muscle, fat, and skin, where drug distribution occurs more slowly[42]. Typically, drug administration and elimination occur in the central compartment, with transfer between the central and peripheral compartments. This model is employed when a drug exhibits a discernible distribution phase followed by a distinct, slower elimination phase. It is suitable for drugs that distribute at different rates into various tissues, leading to an initial rapid decline in plasma concentration (reflects distribution into peripheral tissues) followed by a slower, more gradual decline (reflects elimination from the central compartment)[43]. Many lipophilic drugs, such as digoxin, which slowly accumulates in muscle and other tissues after initial distribution in the blood, or sedatives like midazolam, frequently exhibit two-compartment kinetics[43,44]. This model is widely used for drugs where understanding the initial rapid distribution is crucial, particularly after intravenous bolus administration, as it provides a more accurate prediction of drug concentrations over time for agents with distinct distribution and elimination phases.

iii. Multi-Compartment Model

The multi-compartment model incorporates three or more distinct compartments to represent various tissue groups, each with differing perfusion rates and drug affinities[39,45]. It provides the most physiologically detailed representation of drug distribution. These models are also inherently the most complex. This model is utilized for drugs that exhibit very intricate and prolonged distribution patterns, especially when simpler models fail to describe the observed drug concentration-time profile accurately[46]. It is applicable when a drug distributes into multiple distinct tissue compartments at significantly different rates or undergoes substantial re-distribution among these compartments over time. For example, thiopental is ultra-short-acting barbiturate drug that rapidly enter brain, then redistribute to muscle, and subsequently diffuse slowly into fat[47], it requires multi-compartment model to capture its complexity disposition. Similarly, drugs that exhibit significant and prolonged accumulation in specific deep tissue compartments may also require this model. While providing highly detailed pharmacokinetic characterization, particularly for predicting tissue-specific drug concentrations or optimizing very complex dosing regimens for drugs with intricate distribution characteristics, the inherent complexity of multi-compartment models often limits their routine clinical use.

b. Distribution

Distribution involves the reversible transfer of the drug from the bloodstream to tissues and organs. A vital determinants of drug distribution include the Volume of distribution (V_d), which indicates how much of the drug is distributed from the blood into tissues[48]. Furthermore, plasma protein binding (PPB) influences the amount of free, active drug in the blood[49]. Later, the tissue affinity (e.g., fat solubility and membrane permeability) influences how the drug interacts with body tissues. Drug metabolism involves the biotransformation of both endogenous compounds and externally administered drugs. During this process, most drugs undergo chemical modifications that reduce or eliminate their pharmacological activity, facilitating their excretion from the body. These metabolic reactions are broadly categorized into two phases, viz., Phase I, which typically introduces or exposes functional groups through oxidation, reduction, or hydrolysis, and Phase II, which involves conjugation reactions that increase water solubility[50]. The characterizing drug-metabolizing enzymes are crucial, as they help identify potentially toxic metabolites and predict variations in drug response. A thorough grasp of metabolic pathways is essential not only for ensuring drug safety but also for guiding rational drug design and development. Drug distribution, a key pharmacokinetic phase, is governed by several factors, including tissue blood flow and the tissue-to-blood partition coefficient, which dictate organ uptake. Apparent V_d, protein binding, lipid solubility, molecular size, and ionization state significantly impact how drugs permeate membranes[49].

c. Metabolism

Drug metabolism transforms drugs into active or inactive metabolites, primarily in the liver, converting lipophilic compounds into hydrophilic ones for excretion[51]. Gut, kidneys and lungs also contribute to this process. This process typically involves two phases, viz., in Phase I, the drug molecule undergoes chemical reactions (e.g., oxidation, reduction, and hydrolysis) that either introduce new polar functional groups i.e., -OH, -NH2, and -SH, or expose existing ones that were previously "hidden" or less accessible within the molecule[52]. For instance, most drugs are lipophilic (fat-soluble) and can easily cross cell membranes. However, to be excreted from the body, they need to become more hydrophilic (water-soluble). Phase I reactions act as a "first step" to make the drug more polar by adding or revealing these functional groups[53]. They further stated that these newly introduced or exposed groups then serve as attachment points for Phase II reactions, in which larger, highly water-soluble molecules are conjugated to the drug, further aiding its elimination. In Phase II, these groups undergo conjugation with endogenous substances. This process makes the drug more water-soluble for more straightforward elimination via urine or bile. Various types of enzymes that participate in metabolism are listed in **Table 1**.

Table 1: Enzyme types involved in Metabolism[54-56]

Enzyme Type	Characteristics	Reactions	Examples
Microsomal	Inducible (activity can be increased by certain drugs/substances), primarily found in the endoplasmic reticulum.	Mixed-function oxidation (Phase I), Glucuronidation (Phase II), Hydrolysis, and Reduction	Cytochrome P450 (CYP450) enzymes (e.g., CYP3A4, CYP2D6), NADPH-cytochrome P450 reductase, and UDP-Glucuronosyltransferases (UGTs)
Non-Microsomal	Non-inducible, found in cytoplasm and mitochondria.	All conjugations except glucuronidation (Phase II), Oxidation, Reduction, and Hydrolysis	Alcohol Dehydrogenase, Aldehyde Dehydrogenase, Monoamine Oxidase (MAO), N-Acetyltransferases (NATs), Sulfotransferases (SULTs), and Glutathione S-Transferases (GSTs)

Table 2: Excretory Organs and Routes of Drug Elimination[60-63]

Excretory Organ	Mechanism of Excretion	Characteristics	Drugs and Metabolites Elimination
Kidneys	• **Glomerular Filtration:** Filtration of unbound drugs from plasma. • **Tubular Secretion:** Active transport of drugs (acids/bases) from blood into tubule lumen. • **Tubular Reabsorption:** Passive or active reabsorption of lipophilic/unionized drugs back into circulation from filtrate.	The primary route for elimination of water-soluble drugs and their polar metabolites. Renal clearance is heavily influenced by glomerular filtration rate (GFR), active tubular transport mechanisms (e.g., OATs, OCTs), and urine pH (affecting reabsorption of weak acids/bases). Impaired renal function significantly impacts dosing.	Penicillins, Aminoglycosides (e.g., Gentamicin), Digoxin, Lithium, Metformin, and many polar metabolites including glucuronides, sulfates
Liver (Biliary Excretion)	Active transport of drugs and metabolites from hepatocytes into bile canaliculi. Bile then enters the small intestine.	Significant for large, highly polar, and often conjugated molecules (e.g., glucuronides). It sometime can lead to enterohepatic recirculation, where drugs excreted in bile are reabsorbed in the intestine, prolonging their half-life. Important for lipophilic drugs undergoing extensive metabolism.	Morphine (as glucuronide), Indomethacin, Steroid hormones, some oral contraceptives, certain antibiotics (e.g., Rifampicin and Erythromycin) and Digoxin.
Lungs (Pulmonary Excretion)	Passive diffusion of volatile and gaseous substances from blood into alveolar air, and then exhaled.	Primary route for volatile general anesthetics and alcohols. Efficiency depends on blood/gas partition coefficient, respiratory rate, and pulmonary blood flow. Metabolites are generally not exhaled.	Volatile general anesthetics (e.g., Halothane and Isoflurane), Ethanol and Paraldehyde.
Skin	Diffusion from blood into sweat glands.	Minor route, but can be relevant for certain drugs and forensic analysis. Excretion is often limited by drug concentration in plasma and sweat volume.	Some heavy metals (e.g., Arsenic), Alcohol, Amphetamines, Cocaine, tricyclic antidepressants (e.g., Amitriptyline) and Phenytoin.
Hair	Incorporation into growing hair follicles from blood and sweat/sebum.	Not a significant route for rapid drug elimination, but useful for long-term drug exposure monitoring in forensics due to drug binding to melanin and keratin and hair's slow growth.	Illicit drugs (e.g., Cocaine, Opioids, Cannabinoids), Amphetamines and certain antidepressants.
Saliva	Passive diffusion of unionized, unbound drug from plasma into saliva.	Generally, a minor route of elimination. Saliva drug levels can sometimes correlate with unbound plasma concentrations, making it a non-invasive sample for therapeutic drug monitoring for some agents.	Lithium, Phenytoin, Theophylline and Caffeine
Tears	Passive diffusion from plasma into lacrimal fluid.	Very minor, but drugs can be detected in tears. Relevance is usually limited to ocular drug delivery or specific research.	Often related to drugs with systemic effects on lacrimal glands.
Milk (Lactation)	Passive diffusion of drugs from maternal plasma into breast milk.	Highly significant in pharmacology due to potential drug exposure to the nursing infant. Factors include maternal plasma concentration, protein binding, lipid solubility, molecular weight, pKa (ion trapping in slightly acidic milk).	Ethanol, Nicotine, Caffeine, some antibiotics (e.g., Penicillins and Cephalosporins) and certain sedatives

d. Excretion

Excretion is the final step, involving the irreversible removal of the drug and its metabolites, predominantly through the kidneys. Renal clearance (CLR), which encompasses glomerular filtration, tubular secretion, and reabsorption, plays a crucial role[57]. Total body clearance (CL_{total}) represents the sum of all excretion routes, determining the duration and intensity of the drug's action. Augmented renal clearance (ARC) in critically ill patients can lead to subtherapeutic drug concentrations, particularly for medications that are renally cleared, such as antibiotics[58]. Furthermore, this leads to treatment failure, increased mortality, and the development of antimicrobial resistance. To mitigate subtherapeutic drug concentrations in patients with augmented renal clearance, strategies include Therapeutic Drug Monitoring (TDM) for drugs with narrow windows, enabling real-time dose adjustments. More frequent dosing, or prolonged and continuous infusions for time-dependent drugs, is essential using higher doses[59]. Regular 24-hour creatinine clearance monitoring and vigilant assessment of clinical response are also essential. A comprehensive summary of excretory organs and their routes of drug elimination is shown in Table 2.

ADME Assay

ADME assays are laboratory evaluations that are used to assess the absorption, distribution, metabolism, and excretion characteristics of drug candidates. A pharmaceutical researcher forecasts the pharmacokinetic behaviour of a drug within the human body, identifies potential risks such as toxicity or drug interactions, and selects more promising compounds for subsequent development by examining these properties[64]. A general context of ADME assays and their interpretation is mentioned in Table 3.

Drug metabolic reactions are categorized into two main classes: phase I, phase II and Phase III reactions (Table 4).

Table 3: ADME Assays and their Interpretation[65-71]

ADME Component	Standard Assay Method	Parameter Measured	Significance
Absorption	Caco-2 Permeability Assay	P_{app} (Apparent Permeability)	Predictor of passive and active intestinal absorption. Determines eligibility for oral dosing.
	PAMPA (Parallel Artificial Membrane Permeability)	P_{eff} (Effective Permeability)	High-throughput assessment of passive permeability. Rapid filter for poor lipophilicity.
Distribution	Plasma Protein Binding (PPB)	f_u (Fraction Unbound)	Determines the concentration of free drug available to reach the target and be eliminated, influencing the volume of distribution (Vss).
Metabolism	Hepatic Microsomal Stability	Intrinsic Clearance (CL_{int})	Rate of metabolism by CYP450 enzymes; helps estimate hepatic clearance CL_H.
	CYP Inhibition (e.g., Cocktail Assay)	area under the curve (AUC), maximum plasma concentration (C_{max}), and half-life ($t_{1/2}$)	Risk assessment for Drug-Drug Interactions (DDI) as it identifies identify risks associated with the use of comedication.
Excretion	Hepatocyte Uptake and Efflux	CL_{int} (Uptake)	Determines clearance contributions via non-CYP metabolism and active transport (e.g., OATPs and BCRP).

Table 4: Drug Metabolism: Phase I and Phase II Metabolic Pathways[52]

Feature	Phase I (Functionalization)	Phase II (Conjugation)	Phase III (Elimination/Transport)
Nature of Process	Non-synthetic: modifying the existing structure.	Synthetic: adding an endogenous molecule.	Post-synthetic: active transport and efflux.
Role	To introduce or unmask polar functional groups (e.g., -OH, -NH_2, -SH).	To increase water solubility and further decrease pharmacological activity.	To pump metabolites out of the cell into the blood, bile or urine for final removal.
Reactions	Oxidation, Reduction and Hydrolysis.	Glucuronidation, Sulfation and Glutathione conjugation.	Active efflux via ATP-binding cassette (ABC) transporters.
Enzymes or Proteins involved	Cytochrome P450 (CYP450), FMOs and esterases.	UDP-glucuronyl transferases (UGTs), NATs and GSTs.	P-glycoprotein (P-gp) and Multidrug Resistance Proteins (MRPs).
Reaction Outcome	Product is often chemically reactive or a polar metabolite.	Product is a highly polar, water-soluble, and usually inactive conjugate.	No chemical change; the metabolite is physically relocated across membranes.
Significance	Can activate prodrugs or create toxic intermediates.	Critical for detoxification and neutralizing Phase I intermediates.	Essential for preventing the accumulation of toxic metabolites within cells.

Several *in vitro*, *in situ*, *in vivo* and *in silico* tools are employed for precise ADME characterization, which have arisen with advancements in analytical, cellular, and computational technologies (Table 5).

Table 5: *In vitro*, *in situ*, *in vivo* and *in silico* tools for precise ADME characterization

Category	Technique	Description	Advantages	Limitations	References
***In Vitro* Techniques**	Caco-2 Cell Permeability Assay	Mimics human intestinal epithelial barrier to assess absorption.	High predictability of intestinal absorption.	Does not account for first-pass metabolism.	72
	Microsomal Stability Assay	Measures Phase I metabolism using liver microsomes.	Rapid screen for metabolic stability.	Lacks Phase II metabolism; non-physiological conditions.	73
	Plasma Protein Binding (PPB) Assays (e.g., ultrafiltration, equilibrium dialysis)	Assesses free vs. bound drug fraction in plasma.	Provides insight into drug availability.	Cannot replicate dynamic in vivo binding changes.	74
	Hepatocyte Incubations	Evaluates both Phase I and II metabolic enzymes in hepatocytes.	Physiologically relevant.	Limited culture lifespan; inter-donor variability.	75
***In Vivo* Studies**	Animal Models	Uses rodents, dogs, or non-human primates for full PK profiling.	Integrates all ADME processes.	Ethical concerns; interspecies extrapolation challenges.	76
	Mass Balance Studies	Tracks metabolic and excretory routes using radiolabeled drugs.	Comprehensive tracking of drug fate.	High cost and regulatory restrictions on radioactive materials.	77
***In Silico* Approaches**	QSAR (Quantitative Structure–Activity Relationship) Models	Predicts ADME properties based on molecular descriptors.	Rapid and cost-effective early screening.	It depends on the training data and lack precision.	78
	Physiologically Based Pharmacokinetic (PBPK) Modeling	Simulates drug kinetics across organs using physiological parameters.	Integrates diverse in vitro/ in vivo data for human prediction.	Requires extensive input data and model validation.	79
	Molecular Docking	Predicts transporter/enzyme interactions.	Useful for early-stage interaction studies.	Static models may not reflect conformational dynamics.	80

Initial Compound Screening is fundamentally divided into two complementary approaches designed to discover and refine drug candidates, viz., Structure-Based Screening (SBS) and Ligand-Based Screening (LBS)[17,81]. Initial compound screening strategies and available techniques are mentioned briefly in Table 6.

Pharmacokinetics

Pharmacokinetics involves studying how drugs are absorbed, distributed, metabolized, and eliminated in the human body. It is often summarized by the acronym ADME. A clear understanding of bioavailability, volume of distribution, half-life, and total clearance is essential for rational drug design and effective dosing strategies (Table 7).

ADME Integration with Regulatory Frameworks

ADME profiling is central to the Biopharmaceutics Classification System (BCS) and IVIVC models used by regulatory agencies, e.g., FDA and EMA, to classify drug candidates and justify waivers for bioequivalence studies[90]. BCS Class I drugs (high solubility and high permeability) are typically fast-tracked, whereas Classes III and IV demand extensive profiling. Modern ADME approaches offer several key advantages that enhance the efficiency and ethics of drug development. One significant benefit is the early identification and elimination of compounds with poor drug-like properties, and thereby it helps to avoid costly preclinical or clinical stages[91]. These approaches also support rational lead optimization, enabling medicinal chemists to modify molecular structures based on predictive ADME data to enhance bioavailability, reduce toxicity, and improve overall drug performance[92]. Importantly, modern methods emphasize ethical compliance by reducing reliance on animal testing through the use of advanced *in vitro* and *in silico* models[93]. Furthermore, the application of PBPK modeling is gaining regulatory acceptance, offering robust tools for simulating human pharmacokinetics and aiding in dosage predictions and drug–drug interaction assessments[94]. Collectively,

these advantages contribute to faster, safer, and more cost-effective drug development pipelines.

Limitations and Challenges

Moreover, ADME profiling faces certain limitations and challenges that impact its predictive accuracy and applicability. The correlation between in vitro and in vivo studies (IVIVC) can be weak, particularly for sophisticated formulations, leading to discrepancies in predicting real-world drug behavior[95]. Static models, such as Caco-2 cell assays, often fail to capture dynamic biological cues, including gut microbiota and bile flow, which limits their physiological relevance[96]. Interspecies variability further complicates extrapolation from animal models to humans, as differences in metabolism and physiology introduce uncertainty[97]. Transporter and enzyme polymorphisms, such as CYP450 variants, introduce complexity, making predictions of human metabolism less reliable, especially across diverse populations[98,99]. Additionally, Multifaceted biologics like monoclonal antibodies (mAbs) require specialized ADME models[100], which are still in development and not yet fully optimized. Current challenges of ADME and possible mitigation strategies are enlisted in Table 8.

Table 6: Initial Compound Screening Strategies and Available Techniques

Screening Strategy	Basis of Strategy application	Available Techniques	Primary Objective	Immediate Outcome	References
Structure-Based Screening	Utilizes the known protein structure of the target.	Molecular Docking, Molecular Dynamic Simulations, Fragment-Based Approaches.	Virtually assess receptor–ligand interactions across a large compound set.	Identification of Potential Hits (New scaffolds).	82, 83, 84,17
Ligand-Based Screening	Relies on confirmed active compounds or known probes (ligands).	Pharmacophore Modeling, Scaffold Hopping, Structural Similarity Searches.	Optimize known hits in the drug discovery process.	Valuable insights for Lead Optimization and development.	85, 86,87, 17

Table 7: Pharmacokinetic Parameters and their Translational Significance

PK Parameter	Definition	Direct Clinical Relevance	Decision Impact	References
Bioavailability (F)	Fraction of administered dose reaching systemic circulation.	Determines required oral dose strength versus IV dose.	Go/No-Go for oral formulation development.	88, 89
Volume of Distribution (V_{ss})	Theoretical volume required to account for the total drug in the body.	Indicator of tissue penetration and drug sequestration.	Influences loading dose and potential for accumulation.	
Half-Life ($t_{1/2}$)	Time required for plasma drug concentration to be reduced by half.	Determines dosing interval and steady-state time.	Critical for once-a-day vs. twice-a-day dosing schedules.	
Total Clearance (CL)	Rate of irreversible drug removal from the systemic circulation.	Defines the maintenance dose rate.	Primary determinant of drug exposure and steady-state concentration.	

Table 8: ADME Challenges and Current Mitigation Strategies

ADME Challenge	Impact on Drug Development	Mitigation Strategy	Emerging Technologies	References
Poor Oral Permeability	Low bioavailability, high dose required, high inter-patient variability.	Prodrug design, nanocrystal formulations, and efflux pump inhibition.	Lipid-based drug delivery systems (LBDDS), advanced co-crystals.	101
Cytochrome P450 Inhibition (DDI Risk)	Increased toxicity or reduced efficacy of co-administered drugs.	Scaffold modification to reduce binding affinity, PBPK modeling for risk quantification.	Human liver microphysiological systems (micro-livers).	102
Hepatotoxicity Risk	Severe safety signal, common cause of late-stage failure.	Early screening using plated primary human hepatocytes to assess reactive metabolite formation.	3D bioprinted liver models, high-content imaging endpoints.	103
Low Solubility	Limited dissolution rate and poor absorption kinetics.	Salt formation, particle size reduction (micronization/nanosuspension), amorphous solid dispersions (ASDs).	Microfluidic platforms for controlled nanoparticle formation.	104

Future Perspectives

The emerging technologies are poised to transform ADME profiling by addressing its current limitations and enhancing predictive accuracy in the drug development process. Organs-on-chips, microfluidic devices that replicate the physiological environment of human organs, such as the gut or liver, enable integrated and dynamic ADME testing. For instance, a gut-on-a-chip model can simulate intestinal absorption under realistic conditions, incorporating factors such as mucus layers and peristalsis[93], thereby offering a more accurate prediction of oral drug bioavailability than static Caco-2 assays.

Similarly, liver-on-chip and kidney-on-chip systems can mimic hepatic metabolism, providing insights into drug clearance and metabolite formation[105]. AI and machine learning advance multi-parametric predictions of ADME properties, leveraging vast datasets to improve accuracy through iterative learning[105].

For example, AI models trained on molecular descriptors can predict CYP450-mediated metabolism with up to 90% accuracy[106], thereby streamlining the selection of compounds. High-throughput screening, powered by automated systems, enables the rapid testing of thousands of compounds, significantly accelerating the drug discovery process. Technologies such as automated liquid handling systems can process 100000 compounds daily[107]. Integration with genomics, especially pharmacogenomics, improves personalized ADME predictions by customizing drug responses based on individual genetic profiles. For example, pharmacogenomic testing of the SLCO1B1 gene can forecast statin uptake in the liver, guiding personalized dosing to prevent myopathy risks[108].

Researchers use machine learning models and genomic data to predict differences in warfarin metabolism caused by *CYP2C9* polymorphisms as it helps to optimize anticoagulant treatment[109]. Silica-based computer-aided methods for discovering and assessing the pharmacological potential of new lead compounds have been extensively studied[110]. Modern pharmacological strategies rely on *in vitro* models, such as PAMPA and hepatic microsomal assays, to predict human absorption, metabolic clearance, and potential drug-drug interactions[113,114,115].

Systematic and scientifically evaluated integration these ADME parameters with nanotoxicology assessments[111] is essential for optimizing therapeutic drug monitoring and refining adaptive Phase II clinical trial designs for precision medicine[112, 116]. These advancements, such as organs-on-chips mimicking human physiology, AI-driven predictions, high-throughput automation, and pharmacogenomic personalization, address limitations like weak *in vitro–in vivo* correlations and interspecies variability, thereby significantly improving the accuracy and efficiency of ADME profiling in drug development.

CONCLUSION

The pharmacokinetic evaluation of ADME helps to establish the scientific foundation for identifying drug candidates that are not only effective but also safe and bioavailable. A clear idea about how a drug behaves in the body, is crucial for minimizing adverse effects, optimizing therapeutic outcomes, and ensuring regulatory compliance. Historically, ADME profiling relied heavily on in vivo animal models and simplistic in vitro assays. While informative, these traditional approaches often fail to accurately replicate human physiology. As the pharmaceutical industry shifts towards more complex molecules (such as biologics, gene therapies, and personalized medicines), there is a growing demand for advanced ADME tools. Innovations, i.e., 3D cell culture systems, organ-on-a-chip platforms, and AI-driven predictive models have transformed the landscape of preclinical drug evaluation.

These tools provide more human-relevant data and allow for early-stage screening, thereby reducing late-stage clinical failures. However, significant challenges remain. One major limitation is the biological relevance of many *in vitro* systems, which may not fully capture the complexity of human metabolism or variability across populations. Additionally, the scalability and cost-effectiveness of advanced models, particularly those involving stem cell-derived organoids or microfluidic devices, present practical hurdles for widespread adoption. Integration of these tools into regulatory frameworks also requires standardization and validation. Looking forward, a multidisciplinary approach that blends empirical data with in silico modeling holds immense promise. By incorporating machine learning, population-level genomics, and real-world data, ADME profiling can evolve into a more predictive and personalized science. Addressing current limitations will be crucial to unlocking the full potential of modern ADME technologies, ultimately accelerating the development of safer and more effective therapeutics tailored to individual patient needs.

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