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ADME IN PHARMACOKINETICS:

A Comprehensive Review of Absorption, Distribution, Metabolism, and Excretion in Drug Development and Clinical Practice

Review Article

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Abstract : Pharmacokinetics describes the time-course of drug concentrations in the body, encompassing four interrelated processes collectively termed ADME: Absorption, Distribution, Metabolism, and Excretion. A thorough understanding of ADME is indispensable in all stages of drug development, from early discovery screening to clinical dose optimisation. This review provides a comprehensive, evidence-based examination of each ADME component, including the mechanistic determinants of absorption (physicochemical drug properties, gastrointestinal physiology, first-pass effect, and bioavailability), the biophysical principles governing distribution (volume of distribution, plasma protein binding, and tissue-specific barriers), the enzymatic and metabolic pathways of biotransformation (Phase I and Phase II reactions, cytochrome P450 enzymes, pharmacogenomics, and drug–drug interactions), and the renal and extra-renal mechanisms of excretion (glomerular filtration, active tubular secretion, biliary excretion, and enterohepatic recirculation). Key pharmacokinetic parameters—clearance, half-life, area under the curve, and bioavailability—are defined and contextualised within their clinical applications. The review also addresses contemporary advances, including in silico predictive modelling, physiologically based pharmacokinetic (PBPK) simulations, machine learning applications in ADME prediction, and the pharmacokinetic challenges unique to next-generation therapeutic modalities such as monoclonal antibodies, oligonucleotides, and gene therapy vectors. Collectively, this review underscores the central role of ADME principles in rational drug design, individualised patient care, and the future of precision medicine.

Keywords: ADME; pharmacokinetics; absorption; distribution; metabolism; excretion; bioavailability; cytochrome P450; pharmacogenomics; PBPK modelling; drug development.

I. INTRODUCTION

Pharmacokinetics is the quantitative scientific discipline concerned with what the body does to a drug after administration. In contrast to pharmacodynamics—which addresses what the drug does to the body—pharmacokinetics characterises the time-dependent behaviour of a drug in biological systems. The acronym ADME (Absorption, Distribution, Metabolism, and Excretion) encapsulates the four fundamental processes through which the body handles any exogenous chemical entity, and mastery of these processes is fundamental to the safe and effective use of medicines [1].

The relevance of ADME extends well beyond academic pharmacology. In clinical practice, understanding these processes allows physicians and pharmacists to design rational dosing regimens, predict drug–drug and drug–disease interactions, and adjust doses in patients with renal or hepatic impairment. In drug discovery, the failure to achieve acceptable pharmacokinetic profiles was historically one of the leading causes of late-stage attrition in pharmaceutical development [6]. Early integration of ADME screening into the drug discovery workflow has therefore become a cornerstone of modern rational drug discovery programmes [6].

Since the early 2000s, the emergence of computational methods, high-throughput in vitro assays, and physiologically based pharmacokinetic (PBPK) modelling has dramatically transformed the speed and accuracy with which ADME properties can be predicted and optimised [8]. More recently, machine learning and artificial intelligence have been applied to predict ADME-related drug-likeness from molecular descriptors, further accelerating the identification of viable drug candidates [4]. Concurrently, the rapid growth of novel therapeutic modalities—including biologics, oligonucleotides, and cell-based therapies—has necessitated a fundamental re-examination and expansion of classical ADME frameworks [3,7].

The current review consolidates contemporary understanding of each ADME process, integrates key pharmacokinetic parameters that link these processes to clinical outcomes, and highlights frontier developments in ADME science. The aim is to serve as both a thorough reference for pharmacology students and clinicians, and an up-to-date resource for researchers working at the interface of drug discovery, pharmacokinetics, and personalised medicine [2,9,10].

II. NEED FOR THE STUDY

Despite ADME being a foundational pillar of pharmacology, a substantial gap persists between the depth of mechanistic knowledge generated in research settings and its consistent translation into routine clinical and early-discovery decision-making. Pharmacokinetic shortcomings have historically accounted for a large share of drug-development attrition, and inadequate appreciation of ADME determinants at the bedside continues to contribute to preventable adverse drug reactions, sub-therapeutic dosing, and avoidable drug–drug interactions. There is therefore a clear need for an integrated, up-to-date synthesis that links each ADME process to the pharmacokinetic parameters and clinical decisions it governs.

Furthermore, the ADME field is evolving rapidly. The maturation of in silico prediction, physiologically based pharmacokinetic (PBPK) modelling, and machine-learning approaches, together with the emergence of biologics, oligonucleotides, and gene-therapy vectors whose disposition departs markedly from classical small-molecule behaviour, has outpaced the scope of many existing reviews. A consolidated resource is needed that not only revisits the classical ADME framework but also critically examines these contemporary advances and their adaptation to next-generation modalities.

This review addresses that need by bringing together the mechanistic, parametric, computational, and clinical dimensions of ADME within a single, coherent, evidence-based account. In doing so, it aims to support rational drug design, individualised patient care, and the ongoing transition toward precision medicine, while serving as an accessible reference for students, clinicians, and researchers alike.

Table 1. Overview of the Four ADME Processes: Primary Sites, Key Parameters, and Clinical Relevance

ADME Process	Primary Site	Key Parameters	Clinical Relevance
Absorption	GI tract / skin / lungs	Bioavailability (F), Cmax, Tmax, ka	Determines onset and intensity of drug effect
Distribution	Plasma, tissues, organs	Volume of Distribution (Vd), protein binding	Governs drug concentration at target site
Metabolism	Liver (primary), intestine, lung	Clearance (CL), half-life (t½), CYP enzymes	Controls duration of drug action; produces metabolites
Excretion	Kidney (primary), bile, lungs	Renal clearance, GFR, tubular secretion	Terminates drug action; important in renal disease

III. ABSORPTION

3.1 Definition and General Principles

Absorption refers to the movement of a drug from its site of administration into the systemic circulation. Except for intravenous (IV) administration—where the drug is introduced directly into the bloodstream and bioavailability is by definition 100%—all other routes require an absorption phase before the drug reaches the plasma in meaningful concentrations [10]. The efficiency of this process is captured by the pharmacokinetic parameter bioavailability (F), defined as the fraction of the administered dose that reaches the systemic circulation in unchanged (active) form [9].

The rate and extent of absorption collectively determine the concentration–time profile in the plasma, including the peak plasma concentration (Cmax), the time to peak concentration (Tmax), and the area under the concentration–time curve (AUC). These parameters, in turn, govern the onset, intensity, and duration of pharmacological effect—a relationship that makes absorption optimisation one of the earliest priorities in drug formulation [2].

3.2 Routes of Administration and Bioavailability

The route of administration profoundly influences the rate, extent, and pattern of drug absorption. Oral administration is the most common route and the most subject to physicochemical and physiological barriers. Intravenous administration guarantees complete bioavailability and is the gold standard reference for bioavailability calculations. Sublingual, transdermal, and inhalation routes offer alternatives that bypass the gastrointestinal tract and, in many cases, circumvent hepatic first-pass metabolism [10]. The principal routes of administration and their characteristic bioavailability profiles are summarised in Table 2.

Table 2. Routes of Administration: Bioavailability, Onset, and Key Characteristics

Route of Administration	**Bioavailability**	**Onset**	**First-Pass Effect**	**Typical Uses**
Intravenous (IV)	100%	Immediate	None	Emergency, precise dosing
Oral (PO)	Variable (5–100%)	Slow (30–90 min)	Significant	Most drugs, chronic use
Sublingual (SL)	High (~70–100%)	Rapid (~2–5 min)	Bypassed	Nitroglycerin, buprenorphine
Transdermal	Low–moderate	Very slow (hours)	Bypassed	Nicotine, fentanyl, hormones
Inhalation	Moderate–high	Rapid	Minimal	Bronchodilators, anaesthetics
Subcutaneous / IM	75–100%	Moderate	Minimal	Vaccines, insulin, biologics

3.3 Physicochemical Determinants of Oral Absorption

For a drug administered orally to reach systemic circulation, it must dissolve in gastrointestinal (GI) fluids, traverse the intestinal epithelium, and survive the passage through the portal circulation without complete metabolic degradation. Several physicochemical properties are critical determinants of this process [6]:

Lipophilicity, expressed as the logarithm of the partition coefficient (logP), reflects the affinity of a molecule for lipid membranes relative to water. Moderately lipophilic molecules (logP 0–3) tend to exhibit the best oral absorption, as they are soluble enough in the aqueous GI environment yet sufficiently membrane-permeable to traverse the epithelial barrier [4]. Highly lipophilic compounds may suffer from poor aqueous solubility despite good membrane permeability, resulting in dissolution-limited absorption.

Ionisation state is a crucial determinant of membrane permeability. Unionised forms of a drug are considerably more membrane-permeable than ionised forms. The Henderson–Hasselbalch relationship governs the proportion of ionised to un-ionised drug at a given pH. In the acidic environment of the stomach (pH 1–3), weak acids (e.g., aspirin, pKa 3.5) are predominantly un-ionised and thus more readily absorbed, while weak bases are largely ionised and absorbed preferentially in the more alkaline small intestine (pH 5.5–7.5) [10].

Molecular weight and size affect membrane permeability through paracellular and transcellular pathways. Small molecules (MW <500 Da) pass more readily through tight junctions and membrane channels [6]. Lipinski's Rule of Five—molecular weight ≤500 Da, logP ≤5, hydrogen bond donors ≤5, and hydrogen bond acceptors ≤10—has been widely adopted as a heuristic for predicting oral drug-likeness and acceptable absorption, though modern ADME prediction tools extend beyond these simple rules [4].

3.4 Gastrointestinal Physiological Factors

Beyond molecular properties, GI physiology significantly influences absorption. Gastric emptying rate determines how quickly a drug reaches the small intestine—the primary site of absorption for most orally administered drugs. Food slows

gastric emptying and may alter drug absorption through direct binding (e.g., tetracyclines chelating calcium in dairy products), pH modification, or changes in splanchnic blood flow [10].

Intestinal motility affects transit time and therefore the duration of drug–membrane contact. Conditions such as diarrhoea shorten transit time, potentially reducing absorption, while constipation may extend exposure but may also increase degradation or bacterial metabolism [9]. The large surface area of the small intestine (~200 m²), mediated by villi and microvilli (the 'brush border'), provides an expansive site for passive and active drug uptake.

Active transport mechanisms include influx transporters such as the organic anion transporting polypeptides (OATPs) and efflux transporters such as P-glycoprotein (P-gp, MDR1). P-gp is expressed on the apical surface of enterocytes and actively pumps drug molecules back into the intestinal lumen, thereby limiting the oral bioavailability of numerous substrates including digoxin, cyclosporine, and many anticancer agents [5].

3.5 First-Pass Metabolism and Pre-Systemic Elimination

A major determinant of oral bioavailability is the first-pass effect—the pre-systemic metabolic elimination of a drug as it passes through the gut wall and liver before reaching the systemic circulation. Drugs absorbed from the small intestine enter the portal circulation and pass through the liver, where hepatic enzymes (predominantly CYP3A4) may substantially reduce the amount of intact drug that finally reaches the systemic venous circulation [10].

Classic examples include nitroglycerin, which is so extensively metabolised during first passage through the liver that oral administration yields negligible systemic bioavailability, necessitating sublingual or transdermal delivery. Similarly, morphine undergoes approximately 40% first-pass glucuronidation, and lidocaine's extreme first-pass metabolism renders the oral route clinically useless for antiarrhythmic purposes [9]. Prodrugs such as enalapril are intentionally designed to exploit hepatic first-pass activation, with the inactive prodrug being converted to the active form (enalaprilat) during this initial passage [10].

The extraction ratio (E) quantifies the extent of hepatic first-pass removal and is defined as the fraction of drug removed from the portal blood in a single pass through the liver. Drugs with a high extraction ratio ($E > 0.7$) are highly susceptible to first-pass effects and inter-individual variability in bioavailability, which is clinically important for dose individualisation [1].

IV. DISTRIBUTION

4.1 Definition and Conceptual Framework

After entering the systemic circulation, a drug distributes from the plasma into interstitial and intracellular fluids, as well as specialised compartments such as the central nervous system, synovial fluid, or adipose tissue. Distribution is not uniform; its extent and pattern depend on the physicochemical properties of the drug, regional blood flow, tissue composition, and various biological barriers [9]. The practical outcome of distribution is that only a fraction of the total drug in the body may reside in the plasma at any given time—the remainder being sequestered in tissues.

4.2 Volume of Distribution

The volume of distribution (Vd) is the most widely used pharmacokinetic parameter to characterise drug distribution. It represents the hypothetical volume of fluid that would be required to contain all of the drug in the body at the observed plasma concentration, and is calculated as:

$$Vd = Dose / Cp0$$

where Cp0 is the initial plasma concentration immediately after an IV bolus dose. While Vd is a mathematical construct with no direct anatomical correlate, it provides powerful clinical insights. A low Vd (~3–5 L) indicates that the drug is largely confined to the plasma compartment (e.g., large hydrophilic molecules, highly protein-bound drugs such as heparin). A moderate Vd (~12–20 L) suggests extracellular fluid distribution. A large Vd (>40 L) indicates extensive tissue sequestration, often in muscle, fat, or other organs—as seen with chloroquine (Vd >500 L), amiodarone (Vd ~60 L/kg), and digoxin (Vd ~7 L/kg) [1,10].

4.3 Plasma Protein Binding

Once in the bloodstream, many drugs reversibly bind to plasma proteins, principally albumin (for acidic and neutral drugs) and alpha-1-acid glycoprotein (for basic drugs). Only the free (unbound) fraction of a drug can cross cell membranes,

exert pharmacological effects, be metabolised, or be renally filtered [9]. The bound fraction acts as a circulating reservoir that maintains the equilibrium between bound and free drug as the free fraction is eliminated or distributed.

Clinically important consequences of plasma protein binding include: (1) drug–drug interactions arising from competitive displacement (e.g., sulfonamides displacing warfarin from albumin, transiently increasing free warfarin and haemorrhage risk); (2) altered pharmacokinetics in hypoalbuminaemia (e.g., hepatic cirrhosis, nephrotic syndrome, malnutrition) where the free fraction of highly bound drugs is elevated; and (3) reduced renal filtration of highly protein-bound drugs [1].

4.4 Tissue Distribution and Sequestration

Regional blood flow is a primary determinant of distribution rate. Highly perfused organs—the brain, heart, kidneys, and liver—equilibrate rapidly with plasma, while poorly perfused tissues such as adipose, bone, and cartilage equilibrate slowly. Lipophilic drugs tend to accumulate in fat depots, prolonging their elimination half-life (e.g., amiodarone, diazepam). This accumulation can result in a protracted duration of action that persists after drug discontinuation [10].

Redistribution is a clinically significant pharmacokinetic phenomenon wherein a drug initially distributes to highly perfused tissues (such as the brain) then gradually redistributes to peripheral compartments (such as muscle and fat). This mechanism underlies the short duration of action of thiopental used for anaesthetic induction: the drug rapidly enters the brain to produce unconsciousness, but the effect terminates within minutes as the drug redistributes to muscle and then fat, lowering brain concentrations below the threshold for anaesthesia [9].

4.5 Specialised Biological Barriers

Several anatomical barriers exert selective control over drug distribution into specific compartments. The blood–brain barrier (BBB), formed by tight junctions between cerebral capillary endothelial cells reinforced by astrocytic end-feet and pericytes, is highly restrictive. Only lipophilic, un-ionised, low-molecular-weight compounds, or substrates of specific uptake transporters (e.g., levodopa via the large neutral amino acid transporter) can effectively penetrate the CNS. This barrier is critical in neurological pharmacotherapy but also represents an obstacle in the treatment of CNS infections and tumours [10].

The placental barrier permits the passive diffusion of lipophilic, un-ionised, low-molecular-weight drugs into the foetal circulation, which has significant implications for prescribing during pregnancy. Many drugs including alcohol, thalidomide, and numerous anticonvulsants and antimicrobials can produce teratogenic effects via this route [9]. The blood–testis barrier similarly restricts entry to the seminiferous tubules, and the blood–aqueous humor barrier limits drug penetration into the anterior chamber of the eye.

V. METABOLISM (BIOTRANSFORMATION)

5.1 Objectives and Primary Sites

Drug metabolism, also termed biotransformation, refers to the enzymatic modification of a drug molecule to produce chemically distinct compounds (metabolites). The principal purpose of metabolism is to convert lipophilic drugs into more polar, water-soluble metabolites that are more readily excreted via the kidneys or bile. Without biotransformation, many lipophilic drugs would be reabsorbed across the renal tubules after glomerular filtration, persisting indefinitely in the body [10].

The liver is the predominant site of drug metabolism, owing to its high content of metabolic enzymes, its unique dual blood supply, and its strategic anatomical position in the portal circulation [9]. Other metabolically active sites include the intestinal epithelium (which contributes substantially to first-pass metabolism for orally administered drugs), the lungs, the kidneys, the skin, and the plasma (for drugs susceptible to esterase-mediated hydrolysis). Metabolism may either inactivate a drug (the most common outcome), activate a prodrug to its active form, or generate reactive toxic intermediates [10].

5.2 Phase I Metabolism

Phase I reactions introduce or unmask a polar functional group (–OH, –NH2, –SH, –COOH) on the drug molecule, typically via oxidation, reduction, or hydrolysis. These reactions increase polarity modestly and frequently yield pharmacologically active or reactive metabolites [6].

The cytochrome P450 (CYP) enzyme superfamily is responsible for the oxidative metabolism of the majority of clinically used drugs. CYP enzymes are haemoprotein monooxygenases localised primarily in the endoplasmic reticulum of

hepatocytes. The most clinically important isoforms are CYP3A4 (responsible for the metabolism of approximately 50% of all drugs), CYP2D6, CYP2C9, CYP2C19, and CYP1A2 [10]. Non-CYP Phase I enzymes include monoamine oxidase (MAO), flavin-containing monooxygenases (FMO), xanthine oxidase, esterases, and amidases.

Enzyme induction—the increase in CYP enzyme expression in response to certain drugs or environmental chemicals—can markedly reduce plasma concentrations of co-administered drugs metabolised by the same isoform. Classic inducers include rifampicin (CYP3A4, CYP2C9), carbamazepine, phenytoin, and phenobarbitone. Conversely, enzyme inhibition elevates co-administered drug levels, potentially causing toxicity. Notable inhibitors include azole antifungals (CYP3A4), quinidine (CYP2D6), and fluoxetine (CYP2D6) [10].

5.3 Phase II Metabolism

Phase II reactions involve the conjugation of a Phase I metabolite (or, less commonly, the parent drug itself) with an endogenous polar molecule, yielding a highly water-soluble, typically pharmacologically inactive product that is rapidly excreted. Principal Phase II reactions include glucuronidation (mediated by UDP-glucuronosyltransferases, UGTs), sulfation (sulfotransferases, SULTs), acetylation (N-acetyltransferases, NATs), glutathione conjugation (glutathione S-transferases, GSTs), and methylation [6,10].

Glucuronidation is the most abundant Phase II reaction and is catalysed by UGT enzymes in the liver, intestine, and kidney. Morphine undergoes glucuronidation to morphine-3-glucuronide (inactive) and morphine-6-glucuronide (active and more potent than morphine), illustrating that Phase II reactions do not always lead to inactivation. Acetaminophen (paracetamol) metabolism exemplifies the clinical importance of Phase II reactions: at therapeutic doses, it is primarily glucuronidated and sulfated to harmless metabolites, but overdose saturates these pathways, channelling more drug through CYP2E1 to the reactive metabolite NAPQI (N-acetyl-p-benzoquinone imine), which depletes hepatic glutathione and causes hepatocellular necrosis [9,10].

5.4 Pharmacogenomics and Metabolic Variability

Genetic polymorphisms in drug-metabolising enzymes are a major source of inter-individual variability in drug response. Based on their genotype, patients can be classified as poor metabolisers (PM), intermediate metabolisers (IM), extensive metabolisers (EM, the most common phenotype), or ultra-rapid metabolisers (UM) for specific CYP isoforms [2].

CYP2D6 polymorphism is among the most clinically consequential. Poor metabolisers (approximately 5–10% of Caucasians) may accumulate high plasma concentrations of CYP2D6 substrates such as codeine (which is ineffective in PMs as it cannot be converted to morphine) or tricyclic antidepressants (risking toxicity). Ultra-rapid metabolisers, conversely, may convert codeine to morphine so rapidly as to cause respiratory depression at standard doses. CYP2C19 polymorphism affects the antiplatelet efficacy of clopidogrel, which requires CYP2C19-mediated activation; poor metabolisers have reduced platelet inhibition and poorer cardiovascular outcomes [2,8].

Table 3. Phase I and Phase II Metabolic Reactions: Enzymes and Representative Drug Substrates

Phase	Reaction Type	Enzymes Involved	Example Drug
Phase I	Oxidation	CYP3A4, CYP2D6, CYP2C9	Midazolam, codeine, warfarin
Phase I	Reduction	Ketoreductases, aldehyde reductases	Haloperidol, warfarin
Phase I	Hydrolysis	Esterases, amidases, peptidases	Aspirin, enalapril (prodrug)
Phase II	Glucuronidation	UDP-glucuronosyltransferases (UGT)	Morphine, acetaminophen
Phase II	Sulfation	Sulfotransferases (SULT)	Paracetamol, estrogens
Phase II	Acetylation	N-acetyltransferases (NAT)	Isoniazid, hydralazine
Phase II	Glutathione conjugation	Glutathione S-transferases (GST)	Acetaminophen (toxic metabolite)
Phase II	Methylation	Methyltransferases (COMT, TPMT)	Catecholamines, 6-mercaptopurine

VI. EXCRETION

6.1 Overview and Primary Pathways

Excretion is the irreversible elimination of drug and/or its metabolites from the body. While metabolism transforms drug molecules to facilitate excretion, excretion itself refers to their physical removal from the organism. The kidney is the primary excretory organ for most drugs and their metabolites, though the biliary system (faeces), lungs, sweat, saliva, and breast milk also contribute to total body clearance to varying degrees [9].

6.2 Renal Excretion

Renal excretion is the net result of three simultaneous processes occurring in the nephron: glomerular filtration, active tubular secretion, and passive tubular reabsorption. The balance among these processes determines the renal clearance of a drug [10].

Glomerular filtration is the passive, non-selective filtration of free (unbound) drug through the glomerular capillary wall into the Bowman's capsule. The glomerular filtration rate (GFR, approximately 125 mL/min in healthy adults) sets the upper limit for filtration-based renal clearance. Only the unbound fraction of drug is filtered; highly protein-bound drugs (e.g., furosemide, warfarin) are therefore largely excluded from the filtrate despite reaching the kidney [1,9].

Active tubular secretion involves the energy-dependent transport of drug molecules from the peritubular capillaries into the tubular lumen. This process is mediated by organic anion transporters (OATs) and organic cation transporters (OCTs) on the basolateral membrane, and P-glycoprotein and multidrug resistance proteins (MRPs) on the apical membrane. Tubular secretion is a saturable, high-capacity process capable of clearing protein-bound as well as free drug, making it an important route for drugs such as penicillin, methotrexate, and probenecid [1].

Tubular reabsorption counteracts filtration and secretion by returning drug molecules from the tubular lumen back into the bloodstream. This process is largely passive and favours un-ionised, lipophilic molecules. Manipulation of urine pH can exploit this principle clinically: alkalinisation of urine (e.g., with sodium bicarbonate) traps weak acids (such as salicylate and phenobarbital) in their ionised form, reducing reabsorption and enhancing excretion—a manoeuvre used in the management of salicylate overdose [10].

6.3 Biliary and Faecal Excretion

Drugs and metabolites with a molecular weight above approximately 300–500 Da (variable by species) may be actively secreted from hepatocytes into the bile and subsequently excreted into the small intestine. If not reabsorbed, these compounds pass through the gastrointestinal tract and are eliminated in the faeces. This pathway is particularly relevant for lipophilic drugs, large conjugated metabolites (glucuronides), and drugs that undergo minimal renal excretion [5].

Enterohepatic recirculation occurs when a biliary-excreted glucuronide or sulfate conjugate is hydrolysed in the intestine by bacterial beta-glucuronidase or sulfatases, releasing the parent drug (or an active metabolite), which is then reabsorbed into the portal circulation. This cycle prolongs the half-life and duration of action of drugs such as ethinyl oestradiol, digitoxin, chloramphenicol, and rifampicin. Disruption of intestinal flora by broad-spectrum antibiotics can terminate this cycle, potentially reducing the efficacy of oral contraceptives [9].

6.4 Pulmonary and Other Minor Routes of Excretion

Volatile compounds and gases are excreted by the lungs via simple diffusion across the alveolar–capillary membrane. This route is clinically exploited in the use of exhaled breath analysis to estimate blood alcohol concentration (breathalyser testing). Similarly, volatile anaesthetic agents such as isoflurane and sevoflurane are both administered and largely eliminated via pulmonary exhalation [10].

Sweat and saliva contain trace amounts of certain drugs and metabolites (e.g., amphetamines, lithium, some antimicrobials), but these routes are of minimal quantitative importance for drug elimination in most clinical situations. Secretion into breast milk, however, carries significant clinical relevance. Lipophilic, un-ionised, low-protein-bound drugs—including opioids, benzodiazepines, and certain antiretrovirals—can reach concentrations in milk sufficient to cause pharmacological effects in breastfed infants, necessitating careful prescribing decisions in lactating mothers [9,10].

Table 4. Pathways of Drug Excretion: Mechanisms, Key Factors, and Clinical Notes

Excretion Pathway	Mechanism	Key Factors	Clinical Notes
Renal (glomerular filtration)	Passive filtration of free drug	GFR, protein binding	Major route for hydrophilic drugs
Renal (tubular secretion)	Active transport (OAT, OCT transporters)	Transporter saturation, drug interactions	Metformin, penicillin
Renal (tubular reabsorption)	Passive / active	Urine pH, lipophilicity	Alkalinisation increases salicylate excretion
Biliary / Faecal	Active transport into bile; enterohepatic recirculation	Molecular weight (>300 Da)	Rifampicin, digitoxin
Pulmonary	Diffusion across alveolar membranes	Volatility, lipophilicity	Volatile anaesthetics, ethanol
Salivary / Mammary / Other	Passive diffusion	Drug pKa, plasma protein binding	Drug transfer to infants via breast milk

VII. KEY PHARMACOKINETIC PARAMETERS

7.1 Clearance

Clearance (CL) is arguably the most important pharmacokinetic parameter because it directly determines the steady-state plasma concentration (Css) achieved during a given dosing rate. It is defined as the volume of plasma completely cleared of drug per unit time, typically expressed in L/h or mL/min:

$$CL = Dose / AUC$$

Total body clearance is the sum of renal clearance (CLrenal), hepatic clearance (CLhepatic), and clearance via all other routes. Hepatic clearance depends on hepatic blood flow (Q), the fraction of drug unbound in plasma (fu), and intrinsic metabolic clearance (CLint) according to the well-stirred (venous equilibration) hepatic model: CLhepatic = Q × fu × CLint / (Q + fu × CLint). This relationship implies that drugs with high extraction ratios are highly sensitive to changes in hepatic blood flow, whereas drugs with low extraction ratios are primarily sensitive to changes in protein binding and intrinsic clearance [1,2].

7.2 Volume of Distribution and Half-Life

As described in the Distribution section, Vd characterises the apparent extent of drug distribution throughout the body. The elimination half-life (t½)—the time required for plasma drug concentration to decrease by 50%—is a function of both Vd and CL:

$$t½ = 0.693 \times Vd / CL$$

This relationship reveals that half-life is not an independent parameter but is determined by the interplay of distribution and clearance. A drug may have a long half-life due to large Vd (extensive tissue binding) or due to slow clearance (reduced enzyme activity or renal failure), or both. Clinically, approximately five half-lives are required to reach steady-state plasma concentrations upon multiple dosing, and approximately five half-lives are required to eliminate ~97% of the drug after discontinuation [1,9].

7.3 Bioavailability and AUC

Bioavailability (F) is a composite parameter reflecting the fraction of the administered dose that reaches the systemic circulation unchanged, integrating the effects of incomplete dissolution, mucosal barriers, intestinal metabolism, and hepatic first-pass extraction. It is measured by comparing the AUC after extravascular administration to the AUC following IV administration of the same dose:

$$F = AUC(extravascular) / AUC(IV) \times 100\%$$

The AUC itself is a measure of total drug exposure—the integral of the concentration–time curve over all time—and is directly proportional to the dose and inversely proportional to clearance (AUC = Dose / CL). AUC is used in bioequivalence studies (comparing generic to reference formulations), in therapeutic drug monitoring, and in pharmacokinetic–pharmacodynamic (PK/PD) modelling [2,9].

Table 5. Summary of Key Pharmacokinetic Parameters: Definitions, Formulae, and Clinical Applications

Parameter	Definition	Formula / Units	Clinical Application
Bioavailability (F)	Fraction of dose reaching systemic circulation unchanged	F = AUC(oral)/AUC(IV) × 100 (%)	Determines appropriate dose route
Volume of Distribution (Vd)	Theoretical volume drug distributes into	Vd = Dose / Cp0 (L or L/kg)	Predicts tissue penetration
Half-life (t½)	Time for plasma concentration to decrease by 50%	t½ = 0.693 × Vd / CL (hours)	Guides dosing interval
Clearance (CL)	Volume of plasma cleared of drug per unit time	CL = Dose / AUC (L/h)	Determines maintenance dose
Cmax	Peak plasma concentration	Measured directly (mg/L)	Relates to efficacy and toxicity
Tmax	Time to reach Cmax	Measured directly (hours)	Reflects absorption rate
AUC	Area under the plasma concentration–time curve	Trapezoidal method (mg·h/L)	Measure of total drug exposure

VIII. IN SILICO PREDICTION OF ADME PROPERTIES

8.1 Rationale and Evolution

The traditional reliance on animal models and in vitro assays for ADME characterisation is time-consuming, expensive, and raises ethical concerns regarding animal use. In silico (computational) approaches to ADME prediction emerged in the late 1990s and early 2000s as a means of rapidly screening large compound libraries at the earliest stages of drug discovery, prior to chemical synthesis or biological testing [8].

Early computational models focused on simple physicochemical property calculations (molecular weight, logP, pKa, polar surface area) and structural alerts for metabolic liability (e.g., Michael acceptors, epoxide-forming moieties). The landmark Lipinski Rule of Five (1997) exemplified this approach by identifying empirical thresholds associated with acceptable oral bioavailability, drawing on the observation that poor permeability or solubility is more likely when certain limits are exceeded [6]. Although the Rule of Five does not apply to biopharmaceuticals, it remains widely used as a first-pass filter for oral small-molecule candidates [4].

8.2 PBPK Modelling

Physiologically Based Pharmacokinetic (PBPK) models represent a more sophisticated tier of computational ADME prediction. These models integrate detailed physiological parameters (organ volumes, blood flow rates, tissue composition, enzyme expression levels) with drug-specific physicochemical and biochemical data to simulate the full concentration–time profile of a drug in multiple body compartments simultaneously [5].

PBPK modelling has become a pivotal regulatory science tool, with the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) increasingly accepting PBPK simulations to support drug approval applications, particularly for drug interaction predictions, dose extrapolation to special populations (paediatric, geriatric, hepatic and renal impairment), and food effect evaluations. Software platforms such as Simcyp (Certara), GastroPlus (Simulations Plus), and PK-Sim (Open Systems Pharmacology Suite) are widely used in both industry and academia [5,8].

8.3 Machine Learning and AI in ADME Prediction

The application of machine learning (ML) and deep learning algorithms to ADME prediction has expanded substantially in recent years, driven by the availability of large public pharmacokinetic datasets and advances in molecular representation techniques. Multi-task deep learning models, graph neural networks, and transformer-based molecular foundation models have demonstrated superior predictive performance for ADME properties—including Caco-2 permeability, plasma protein binding, metabolic stability, and renal clearance—compared to traditional quantitative structure–activity relationship (QSAR) methods [4].

A particularly notable innovation is the integration of ADME pharmacokinetics into drug-likeness prediction within multi-task learning frameworks. By co-training on ADME endpoints and pharmacological activity data simultaneously, these models enrich the molecular representations used for drug-likeness scoring, yielding more accurate and holistic assessments of a compound's clinical potential [4]. Such approaches are expected to significantly accelerate early drug discovery by enabling virtual screening of billions of compounds with high confidence in ADME outcomes [8].

IX. ADME AS PART OF RATIONAL DRUG DISCOVERY

9.1 Historical Perspective and the Attrition Problem

Prior to the systematic integration of ADME testing into drug discovery pipelines, pharmacokinetic failure was responsible for nearly 40% of drug attrition in clinical development during the 1990s. This represented an enormous economic burden, as late-stage clinical failures are disproportionately costly relative to the expenditure required to identify and correct PK liabilities during preclinical development [6].

The recognition that many clinical failures were predictable from early-stage in vitro and in silico ADME data catalysed a paradigm shift: ADME screening was moved earlier in the discovery process ('front-loading'), and multidisciplinary DMPK (Drug Metabolism and Pharmacokinetics) teams became integral participants in lead identification and optimisation programmes. By the mid-2000s, this strategic shift had substantially reduced pharmacokinetic-related clinical attrition [6].

9.2 ADME Screening Strategies

Contemporary drug discovery employs a tiered approach to ADME characterisation. At the earliest stages (lead identification), high-throughput in vitro screens assess aqueous solubility, chemical stability, membrane permeability (using artificial membrane assays or Caco-2 cell monolayers), and metabolic stability (using liver microsomes or hepatocytes). Compounds with gross ADME liabilities are deprioritised before significant synthetic resources are invested [6].

As promising leads are identified, more detailed ADME profiling is undertaken: cytochrome P450 inhibition and induction assays identify interaction risks, plasma and microsomal binding studies determine the free fraction, and reactive metabolite screens (using trapping agents such as glutathione and potassium cyanide) identify potential electrophilic intermediates associated with idiosyncratic toxicity [8].

In vivo pharmacokinetic studies in rodents and non-rodent species (typically rat, dog, or non-human primate) provide integrated pharmacokinetic data including oral bioavailability, systemic clearance, Vd, and half-life. Allometric scaling—the extrapolation of animal PK data to humans using body weight-based power functions—is used to estimate human pharmacokinetic parameters for dose prediction [2]. However, species differences in CYP isoform activities, plasma protein binding, and transporter expression limit the accuracy of simple allometric extrapolation, and PBPK-assisted species scaling is increasingly preferred [5].

9.3 The Role of Drug Transporters

An expanding area of ADME science is the role of drug transporters in governing the absorption, distribution, and excretion of drugs. Transporters are membrane proteins that facilitate the movement of drugs across biological membranes via energy-dependent or facilitated mechanisms, either importing drugs into cells (uptake transporters) or expelling them (efflux transporters). Key transporters include P-glycoprotein (P-gp/ABCB1), breast cancer resistance protein (BCRP/ABCG2), organic anion transporting polypeptides (OATPs), organic anion transporters (OATs), and organic cation transporters (OCTs) [3,5].

The US FDA and the International Transporter Consortium (ITC) now recommend routine assessment of transporter-mediated drug interactions during drug development. Clinically significant examples include the interaction between rifampicin (an inducer of P-gp and OATPs) and digoxin (a P-gp substrate), which reduces digoxin plasma concentrations and potentially therapeutic efficacy, and the interaction between ciclosporin and atorvastatin, where OATP1B1 inhibition elevates atorvastatin exposure and statin-related myopathy risk [5].

X. ADME CONSIDERATIONS FOR NEXT-GENERATION THERAPEUTIC MODALITIES

10.1 The Expanding Therapeutic Landscape

Classical pharmacokinetic theory was developed primarily to describe the behaviour of small-molecule drugs—compounds of low molecular weight, defined chemical structure, and largely understood metabolic pathways. The past two decades have witnessed an exponential expansion of the therapeutic armamentarium to include large-molecule biopharmaceuticals: monoclonal antibodies (mAbs), antibody–drug conjugates (ADCs), oligonucleotide therapies (antisense oligonucleotides and siRNAs), gene therapy vectors, and cell-based therapies including CAR-T cells [3,7]. These modalities differ so fundamentally in their physicochemical properties, mechanisms of action, and pharmacokinetic behaviour from small molecules that classical ADME frameworks require substantial adaptation [3].

10.2 Monoclonal Antibodies and Biologics

Monoclonal antibodies are large glycoproteins (~150 kDa) that cannot be absorbed orally due to their size and susceptibility to gastrointestinal proteolysis. They are administered parenterally (intravenously or subcutaneously) and distribute primarily in the plasma and extracellular fluid, yielding relatively low volumes of distribution (~3–8 L). Unlike small molecules, mAbs are not metabolised by cytochrome P450 enzymes but are instead catabolised by proteolytic degradation in lysosomes throughout the body. Their characteristically long half-lives (10–21 days) are conferred by the neonatal Fc receptor (FcRn), which recycles IgG antibodies from endosomes back into the circulation, protecting them from lysosomal degradation [3,7].

Drug–drug interactions for mAbs are mediated not through CYP enzymes but through indirect mechanisms, such as cytokine-mediated modulation of CYP expression (disease–drug interactions), or competition for FcRn-mediated recycling. The pharmacokinetics of mAbs are further complicated by target-mediated drug disposition (TMDD), wherein binding to the pharmacological target (which may be expressed at varying levels across patients and tissues) constitutes a saturable elimination pathway that contributes to non-linear pharmacokinetics at low doses [3].

10.3 Oligonucleotide Therapies

Antisense oligonucleotides (ASOs) and small interfering RNAs (siRNAs) are short synthetic nucleic acid strands designed to selectively modulate gene expression. Their pharmacokinetics differ markedly from both small molecules and antibodies. Unmodified oligonucleotides are rapidly degraded by plasma and tissue nucleases, necessitating chemical backbone modifications (e.g., phosphorothioate substitutions, 2′-O-methoxyethyl modifications) to improve metabolic stability [7]. After subcutaneous or intravenous administration, ASOs distribute rapidly and extensively to tissues—particularly the liver and kidneys—resulting in very large volumes of distribution. Elimination occurs primarily through slow exonucleolytic metabolism in tissues rather than by renal or biliary excretion [3,7].

10.4 Summary of ADME Challenges Across Modalities

Table 6. ADME Challenges and Adaptations for Next-Generation Therapeutic Modalities

Modality	ADME Challenge	Adaptation Required
Small molecules	Rapid CYP metabolism; renal clearance	Standard ADME screening; Lipinski's Rule of Five
Monoclonal antibodies (mAbs)	No CYP metabolism; proteolytic degradation; very long t½ (weeks)	FcRn-mediated recycling; unique distribution kinetics
Oligonucleotides (ASO/siRNA)	Rapid plasma nuclease degradation; poor cellular uptake	Chemical modifications (e.g., phosphorothioate); delivery vehicles
Gene therapy / viral vectors	Immune clearance; tissue tropism	Vector engineering; immune suppression strategies
Cell therapies (CAR-T)	Complex trafficking; engraftment variability	In vivo tracking; novel PK/PD frameworks
Nanoparticles / Drug conjugates	Variable release kinetics; RES uptake	Surface modifications; PEGylation; targeted delivery

XI. CLINICAL APPLICATIONS OF ADME PRINCIPLES

11.1 Individualised Dosing and Therapeutic Drug Monitoring

The translation of ADME principles into clinical practice begins with dosage form selection and dosing regimen design. The dosing interval is governed by the half-life, and the maintenance dose is calculated from the target steady-state concentration, bioavailability, and clearance. For drugs with narrow therapeutic indices—such as digoxin, lithium, phenytoin, vancomycin, and aminoglycosides—therapeutic drug monitoring (TDM) is employed to measure trough or peak plasma concentrations and guide dose adjustments, using population pharmacokinetic models and Bayesian forecasting to individualise dosing [1,2].

11.2 Drug Interactions

Drug–drug interactions (DDIs) mediated via ADME mechanisms constitute a major source of preventable adverse drug events. Pharmacokinetic DDIs arise most commonly through inhibition or induction of CYP enzymes, inhibition or induction of drug transporters, alterations in plasma protein binding, and changes in renal blood flow or tubular transport. Clinically important interaction pairs include: fluconazole + warfarin (CYP2C9 inhibition, elevated warfarin levels), rifampicin + oral contraceptives (CYP3A4 induction, reduced contraceptive levels), probenecid + penicillin (OAT inhibition, prolonged penicillin levels), and clarithromycin + simvastatin (CYP3A4 inhibition, increased statin levels and myopathy risk) [6,10].

11.3 Special Populations

ADME parameters are substantially altered in certain patient populations. In renal impairment, drugs primarily renally eliminated accumulate; dose reductions or extended dosing intervals are required, and the Cockcroft-Gault or CKD-EPI equations are used to estimate GFR for dose adjustment. In hepatic impairment, reduced hepatic blood flow, decreased CYP enzyme expression, and reduced albumin synthesis collectively impair the metabolism, clearance, and protein binding of many drugs, necessitating careful dose reductions [1,10].

Elderly patients typically exhibit reduced GFR, decreased hepatic blood flow and enzyme activity, altered body composition (increased fat, decreased lean mass and total body water), and reduced plasma albumin, resulting in altered pharmacokinetics that may predispose to drug accumulation and toxicity. Paediatric patients—particularly neonates and infants—have immature enzyme systems, differing body compartment sizes, and evolving renal function, all of which significantly alter ADME and require age-specific dosing guidance [2,9].

XII. MODERN TOOLS AND TECHNOLOGIES IN ADME RESEARCH

Table 7. Modern Tools and Technologies Used in ADME Research and Drug Development

Tool / Approach	Purpose	Example Tools
In silico (computational)	Predict logP, pKa, solubility, CYP binding	SwissADME, ADMET Predictor, MOE
In vitro (cell-based)	Screen metabolic stability, permeability	Caco-2 cells, S9 fractions, hepatocytes
In vivo (animal models)	PK profiling, allometric scaling	Rat, mouse, dog models; cassette dosing
PBPK modelling	Predict human PK from physiological data	Simcyp, GastroPlus, PK-Sim
Machine learning (AI)	ADME prediction from molecular descriptors	Multi-task deep learning, graph neural networks
Microfluidics / organ-on-chip	Mimic human gut/liver for ADME testing	Emulate Technologies, CN Bio

The landscape of ADME research continues to evolve rapidly. Organ-on-chip microfluidic systems that recapitulate the cellular microenvironment of the human intestine, liver, and kidney are being developed to replace animal models and improve the human relevance of ADME data. These platforms allow the culture of primary human cells under physiologically relevant flow conditions, better approximating in vivo drug absorption and metabolism [5]. Advances in

mass spectrometry—including LC-MS/MS and high-resolution mass spectrometry—have dramatically improved the sensitivity and throughput of bioanalytical methods for measuring drug and metabolite concentrations in biological matrices, enabling detailed metabolite identification and quantification even at sub-nanomolar concentrations [8].

The integration of multi-omics data (genomics, transcriptomics, proteomics, metabolomics) with pharmacokinetic modelling is emerging as a powerful approach for predicting inter-individual variability in drug response and identifying patient sub-populations likely to benefit from specific therapies or at risk of adverse events. Coupled with electronic health records and real-world evidence, these data streams are helping bridge the gap between population-level ADME knowledge and truly individualised medicine [4].

XIII. FUTURE DIRECTIONS AND EMERGING CONCEPTS

ADME science is at a pivotal juncture, driven by convergent advances in technology, computation, and biology. Several key trends are likely to define the next decade of progress in pharmacokinetics and drug development [3,4,5]:

Artificial intelligence and machine learning will assume an increasingly central role in ADME prediction and optimisation. Foundation models trained on large molecular datasets are beginning to capture complex structure–property relationships at unprecedented scale, enabling accurate in silico prediction of multiple ADME endpoints simultaneously and guiding the design of new chemical entities with built-in favourable pharmacokinetic profiles [4].

PBPK modelling will be further integrated into regulatory decision-making, particularly for drugs targeting special populations and for conducting virtual clinical trials—in silico simulations of clinical pharmacology studies—that complement or even partially replace traditional clinical studies, thereby accelerating development timelines and reducing patient burden [5,8].

Precision pharmacokinetics—the systematic application of pharmacogenomics, proteomics, and real-time biomarker data to individualise dosing—is expected to move from academic research into routine clinical practice, supported by advances in point-of-care diagnostic platforms and digital health technologies [2].

New delivery modalities (lipid nanoparticles, exosome-based carriers, pH-responsive polymeric systems) are being developed to overcome classical ADME barriers—particularly poor oral bioavailability of biologics and targeted CNS delivery—and will require new theoretical frameworks to characterise their pharmacokinetic behaviour [5].

Finally, the development of ADME tools specific to next-generation modalities—including methods for quantifying oligonucleotide distribution to target tissues, tracking CAR-T cell trafficking and expansion in vivo, and characterising the pharmacokinetics of gene therapy vectors—represents an important frontier for the field [3,7].

XIV. CONCLUSION

ADME—the quartet of Absorption, Distribution, Metabolism, and Excretion—represents the foundational framework through which modern pharmacology understands and predicts the temporal behaviour of drugs within the human body. As this review has demonstrated, each of the four processes is governed by a rich interplay of physicochemical, physiological, genetic, and environmental determinants that collectively shape the plasma concentration–time profile and, ultimately, the clinical efficacy and safety of a drug [1,9].

From the perspective of drug discovery, ADME optimisation has transformed from an afterthought into an early-stage priority. The integration of high-throughput in vitro screens, computational PBPK modelling, and AI-driven prediction tools has dramatically reduced pharmacokinetic-related attrition in clinical development and accelerated the delivery of effective new medicines [4,6,8]. In clinical medicine, ADME principles underpin individualised dosing, therapeutic drug monitoring, the rational management of drug–drug interactions, and the adaptation of dosing regimens to special populations [1,2].

The emergence of next-generation therapeutic modalities—biologics, oligonucleotides, gene therapies—has expanded and challenged classical ADME frameworks, demanding new experimental approaches, novel analytical methods, and revised theoretical models [3,7]. This evolution, alongside the growing availability of multi-omics data and real-world evidence, positions pharmacokinetics at the heart of the transition toward precision medicine.

In summary, ADME in pharmacokinetics is not merely an academic discipline but a critical, dynamic science with direct implications for drug development timelines, regulatory decision-making, and patient outcomes. Continued investment in

ADME science—through technology development, mechanistic understanding, and clinical translation—will remain essential to the delivery of safe, effective, and personalised pharmacotherapy [5,9,10].

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