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Pharmacokinetics In the Era of Precision Medicine: From Molecular Mechanisms to Artificial Intelligence

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ABSTRACT

Pharmacokinetics (PK) has evolved from classical compartmental descriptions of drug movement to a multidimensional science integrating molecular biology, physiology, and computational modelling. The traditional ADME framework—absorption, distribution, metabolism, and excretion—remains foundational, yet contemporary insights highlight the complexity introduced by transporter–enzyme interactions, physicochemical determinants, lymphatic uptake, and disease-specific physiological alterations. Advances in genomic profiling and transporter phenotyping have reshaped our understanding of inter-individual variability in drug exposure, enabling the transition toward precision dosing. The emergence of biologics, monoclonal antibodies, bio-specifics, PROTACs, and gene- or protein-targeting modalities has challenged conventional PK paradigms, necessitating new models that account for FcRn recycling, target-mediated drug disposition (TMDD), and immunogenicity. In parallel, quantitative systems pharmacology (QSP), physiologically based pharmacokinetic (PBPK) modelling, and machine learning frameworks—including Neural Ordinary Differential Equations (Neural ODEs)—have become central tools for predicting drug disposition, optimizing study design, and supporting regulatory decision-making. This review synthesizes foundational ADME principles with emerging molecular mechanisms and artificial intelligence–driven modelling strategies. By bridging classical theory with modern computational and precision-medicine approaches, it provides a comprehensive and integrated perspective on the future of pharmacokinetics in drug development and personalized therapeutics.

I. Introduction: The Kinetic Basis of Therapeutics

Pharmacokinetics (PK), derived from the Greek *pharmakon* (drug) and *kinetikos* (movement), is fundamentally the study of thetime course of drug absorption, distribution, metabolism, and excretion—collectively determining systemic exposure and, ultimately, therapeutic response. Traditionally, PK has been interpreted through classical compartmental models and empirical relationships derived from plasma concentration–time profiles. However, contemporary drug development demands a more mechanistic understanding of how chemical structure, biological systems, and patient-specific variables shape drug disposition. Advances in transporter biology, enzyme phenotyping, physiologically based modelling, and systems pharmacology have revealed additional layers of regulation that significantly influence clinical outcomes.

ADME: The Pillars of Pharmacokinetics

Pharmacokinetics revolves around four fundamental processes—**Absorption, Distribution, Metabolism, and Excretion (ADME)** (Figure 1)—which collectively determine the fate of any drug or xenobiotic in the body. These processes not only define how much of a drug reaches its target but also how long it remains active, influencing both efficacy and safety.

Absorption: The journey begins when a drug enters the body. Factors such as route of administration, solubility, formulation, and first-pass metabolism determine how efficiently the drug reaches systemic circulation.

Distribution: Once absorbed, the drug disperses through body compartments. Plasma protein binding, tissue perfusion, and organ-specific barriers influence where and how much drug reaches its site of action.

Metabolism: The body modifies the drug—typically via liver enzymes—to facilitate elimination. These biochemical transformations can produce active, inactive, or toxic metabolites, highlighting the importance of enzyme variability

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and pharmacogenomics.

Excretion: Finally, the drug and its metabolites are cleared from the body through renal, hepatic, pulmonary, or other routes. Excretion kinetics, combined with metabolism, ultimately dictate the duration of drug action and the need for dosage adjustments.

Understanding these four pillars (fig.1) forms the foundation for designing safe, effective, and personalized drug therapies, as well as for interpreting pharmacokinetic parameters and models.

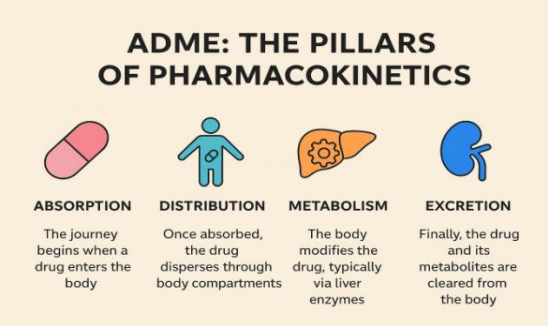

Fig.1: ADME – The Pillars Of PK

As drug development has expanded, so has the recognition that ADME processes are influenced by numerous molecular and physiological factors. Absorption involves not only passive diffusion but a complex interplay of membrane transporters, metabolic enzymes, formulation characteristics, and lymphatic mechanisms. Distribution depends on organ perfusion, tissue composition, protein binding dynamics, and restrictive barriers such as the blood–brain barrier. Metabolism is driven by genetically variable and inducible enzyme systems—most notably cytochrome P450 isoforms—while excretion is influenced by renal function, biliary transporters, and disease states.

Simultaneously, the rise of biologics, bispecific antibodies, antibody–drug conjugates, and PROTACs has challenged traditional PK paradigms. Their disposition is shaped by FcRn-mediated recycling, target-mediated drug disposition (TMDD), immunogenicity, molecular size, and intracellular degradation pathways—dynamics that differ markedly from small-molecule behaviour. Advanced computational approaches—including physiologically based pharmacokinetic (PBPK) models and emerging machine-learning frameworks such as Neural Ordinary Differential Equations (Neural ODEs)—are increasingly central to predicting drug disposition, informing dose selection, and guiding regulatory decisions.

This review integrates foundational ADME principles with modern molecular, physiological, and computational insights to provide a comprehensive and contemporary understanding of drug disposition. By bridging classical concepts with emerging technologies, it equips researchers, clinicians, and pharmacometricians with a robust framework for optimizing drug therapy in an era of rapidly evolving therapeutic modalities.

II. Physicochemical and Molecular Determinants of Absorption

Absorption describes the transfer of a drug from its site of administration to the systemic circulation. While the route of administration (oral, intravenous, subcutaneous, etc.) dictates the initial barrier, the efficiency of absorption is governed by the physicochemical properties of the drug and the physiological characteristics of the absorption site and pharmaceutical dosage form (image 2.1) (Table 2.1, 2.2 and 2.3)

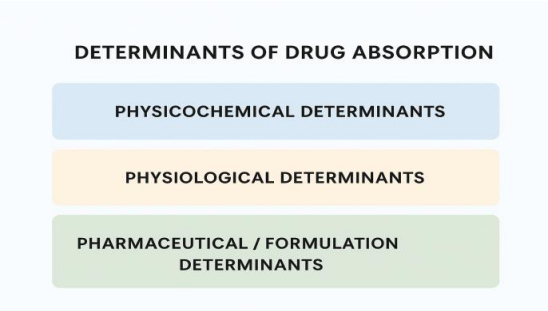

Image 2.1: Illustration of different Determinants of Drug Absorption

TABLE 2.1: Physicochemical Determinants of Drug Absorption

Determinant	Description / Impact on Absorption
Molecular Size	Smaller drug molecules diffuse more readily across membranes.
Lipid Solubility	Higher lipid solubility enhances passive diffusion through lipid bilayers.

International Journal of Pharmaceutical research and Applications
Volume 11, Issue 1, Jan - Feb 2026, pp:118-131 www.ijprajournal.com ISSN: 2456-4494

Ionization (pKa–pH Relationship)	Non-ionized forms are better absorbed; weak acids absorb in low pH, weak bases in high pH.
Drug Stability in GI Tract	Acid-labile or enzyme-sensitive drugs degrade before absorption (e.g., insulin, penicillin G).
Solubility & Dissolution Rate	Poorly soluble drugs have a slowand incomplete absorption.
Polymorphism / Crystal Form	Amorphous forms dissolve faster than crystalline forms.

TABLE 2.2: Physiological Determinants of Drug Absorption

Determinant	Description / Impact on Absorption
GI pH	Determines drug ionization and chemical stability at different GI segments.
Gastric Emptying Rate	Faster emptying accelerates absorption; delayed emptying slows onset.
Intestinal Surface Area	The villi & microvilli provide a large surface area, increasing absorption efficiency.
Blood Flow at Absorptive Site	High perfusion improves the rate of drug absorption.
First-Pass Metabolism	Metabolism in intestine & liver before reaching systemic circulation reduces bioavailability.
GI Motility	Increased motility reduces drug contact time; decreased motility enhances absorption.
Presence of Bile Salts	Enhances absorption of lipophilic drugs by emulsification.

TABLE 2.3: Pharmaceutical & Formulation Determinants

Determinant	Description / Impact on Absorption
Dosage Form	Liquids > suspensions > capsules > tablets for absorption speed.
Particle Size / Micronization	Smaller particles dissolve faster and are absorbed more efficiently.
Excipients	Surfactants, disintegrants, polymers modify dissolution, stability, and permeability.
Coatings (Enteric / Film)	Enteric coating prevents degradation in the stomach and alters the release site.
Controlled / Sustained-Release Systems	Modify the rate and duration of absorption.
Drug–Food Interactions	Food may enhance (lipophilic drugs) or reduce absorption (chelation with tetracyclines).
Drug–Drug Interactions	Antacids, P-gp inducers/inhibitors, enzyme modulators alter absorption kinetics.
pH Modifiers in Formulation	Adjust local pH to improve dissolution of weak acids/bases.

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2.1. Theoretical Foundations of Membrane Transport

The majority of drugs cross biological membranes via passive diffusion, a process described by Fick's First Law:

$$J \propto \frac{d\varphi}{dx} \quad \text{or} \quad J = -D\frac{d\varphi}{dx}$$

- **J** = Diffusion flux (amount diffusing per unit area per unit time)
- **D** = Diffusion coefficient (depends on temperature & molecular size)
- **dQ/dx** = Concentration gradient
- **Negative sign** = Movement from high → low concentration

This equation highlights why the small intestine, with its vast surface area provided by villi and microvilli, is the primary site of absorption for orally administered drugs. However, this model assumes a passive barrier. Modern biopharmaceutics recognizes the intestinal epithelium as a selective gatekeeper, heavily populated by transporter proteins that can facilitate or impede drug entry.

2.2. The Transporter-Enzyme Interplay

The "Interplay Hypothesis" suggests that the oral bioavailability (F) of a drug is not determined by transporters or enzymes in isolation, but by their concerted action. This is particularly relevant for the bioavailability of dual substrates of CYP3A4 and P-glycoprotein (P-gp), such as cyclosporine and tacrolimus.

2.2.1. Efflux Transporters (ABC Superfamily)

P-glycoprotein (P-gp), encoded by the *ABCB1* gene, is an ATP-dependent efflux pump located on the apical membrane of enterocytes. It actively extrudes xenobiotics back into the intestinal lumen, effectively reducing the net absorption.

- **Kinetic Impact:** By cycling the drug repeatedly between the enterocyte and the gut lumen, P-gp extends the residence time of the drug within the cell. This prolonged exposure increases the probability of metabolism by intracellular enzymes like CYP3A4, thereby reducing the fraction of drug that reaches the portal circulation intact.
- **Breast Cancer Resistance Protein (BCRP):** Encoded by *ABCG2*, BCRP also localizes to the apical membrane and limits the absorption of sulfasalazine, rosuvastatin, and topotecan. Recent FDA guidelines emphasize the necessity of screening new chemical entities (NCEs) for BCRP inhibition to predict drug-drug interactions (DDIs).

2.2.2. Uptake Transporters (SLC Superfamily)

Conversely, Solute Carrier (SLC) transporters facilitate the entry of hydrophilic or charged molecules that cannot traverse the lipid bilayer passively.

- **OATP Family:** Organic Anion Transporting Polypeptides (e.g., OATP1B1, OATP2B1) are crucial for the absorption of statins, fexofenadine, and fruit juice components (e.g., naringin). Inhibition of intestinal OATPs by grapefruit juice can paradoxically *decrease* the bioavailability of substrates like fexofenadine, contrasting with the typical CYP3A4-inhibition effect which increases bioavailability.
- **PEPT1:** The peptide transporter PEPT1 (SLC15A1) mediates the uptake of di- and tripeptides. Prodrug strategies, such as valacyclovir (valine ester of acyclovir), exploit this transporter to achieve superior oral bioavailability compared to the parent drug.

(Locationand description ofdifferent transporters and their clinical impact is illustrated in table 2.4)

TABLE 2.4: Transporter-Mediated Drug Interactions

Transporter	Location	Substrate	Inhibitor	Clinical Impact
P-gp (MDR1)	Intestine, BBB, Kidney, Liver	Digoxin, Dabigatran	Amiodarone, Verapamil	Increased systemic exposure (Digoxin toxicity).
BCRP	Intestine, Liver	Rosuvastatin, Sulfasalazine	Curcumin, Elacestrant	Increased statin exposure (myopathy risk).
OATP1B1	Liver (Uptake)	Simvastatin, Atorvastatin	Cyclosporine, Rifampin (acute)	Reduced hepatic uptake to Increased plasma levels.

International Journal of Pharmaceutical research and Applications
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OAT1/3	Kidney (Uptake)	Methotrexate, Furosemide	Probenecid, NSAIDs	Reduced renal clearance to MTX toxicity.

2.3. Lymphatic Transport: The alternative Pathway

For highly lipophilic drugs (LogP >5, long-chain triglycerides solubility > 50mg/mL) and macromolecules, the portal vein is not the primary route of entry. Instead, these agents are incorporated into chylomicrons and enter the lymphatic capillaries (lacteals).

- **Mechanism:** Unlike blood capillaries, which have a continuous basement membrane and tight junctions, lymphatic capillaries possess large inter-endothelial openings (button-like junctions) that allow the entry of particles up to 100nm in diameter.
- **Clinical Relevance for Biologics**: Following subcutaneous (SC) administration monoclonal antibodies (mAbs) are too large (>150 kDa) to enter blood capillaries directly. They are primarily absorbed via the lymphatic system, draining into regional lymph nodes before reaching the systemic circulation via the thoracic duct. This mechanism explains the delayed T_{max}(often 2–8 days) observed with SC biologics compared to small molecules.
- **Therapeutic Implications:** Lymphatic transport exposes the drug to high concentrations of immune cells in the lymph nodes. While this is advantageous for vaccines and immunotherapies, it poses a risk for immunogenicity (anti-drug antibody formation). Furthermore, the saturation of FcRn recycling mechanisms within the lymph node can lead to non-linear bioavailability at high doses.

III. Distribution: Compartments and Barriers

Distribution refers to the reversible transfer of drug between the systemic circulation and peripheral tissues. The extent of distribution is quantified by the apparent Volume of Distribution (V_d), a proportionality constant relating the total amount of drug in the body (A) to the plasma concentration (C_p):

$$V_d = \frac{\text{Amount of drug in body}}{\text{Plasma concentration}}$$

3.1. Physiological Determinants of Distribution

Distribution is rarely uniform. It is driven by organ blood flow (perfusion-limited distribution) and membrane permeability (permeability-limited distribution).

- **Perfusion-Limited:** For small lipophilic drugs (e.g., propofol, lidocaine), membranes offer no resistance. Distribution is determined solely by how much blood an organ receives. Highly perfused organs (heart, brain, liver, kidneys) equilibrate rapidly (the "vessel-rich group"), while poorlyperfused tissues (muscle, fat) equilibrate slowly. This redistribution phenomenon explains the short duration of action of thiopental anaesthesia: the drug doesn't leave the body; it simply moves from the brain to the muscle.

- **Permeability-Limited:** For polar molecules or those facing tight barriers (e.g., the Blood-Brain Barrier), the membrane itself is the rate-limiting step. P-glycoprotein at the BBB actively pumps substrates (e.g., loperamide) out of the CNS, effectively restricting their distribution volume to the plasma and peripheral tissues.

Factors affecting drug distribution and acting as barriers are illustrated in table 3.1

TABLE 3.1: Special Distribution Barriers

Factor	Description
Plasma Protein Binding	Albumin binds acidic drugs; α1-acid glycoprotein binds basic drugs. Only *unbound drug* is pharmacologically active.
Tissue Binding	Digoxin selectively binds cardiac tissue; tetracycline binds bone; chloroquine accumulates in melanin-rich tissues.

International Journal of Pharmaceutical research and Applications
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Drug Reservoir Effect	Highly bound drugs remain longer in the body → prolonged half-life and delayed clearance.

3.2. Protein Binding Dynamics

Drugs in plasma exist in equilibrium between unbound (free) and protein-bound states. The "Free Drug Hypothesis" posits that only the unbound fraction (f_u) is capable of crossing membranes to exert pharmacological effects or be eliminated.

- **Binding Proteins:** Albumin (HSA) binds primarily acidic and neutral drugs (e.g., warfarin, phenytoin), while \alpha$_1$-acid glycoprotein (AAG) binds basic drugs (e.g., lidocaine, propranolol). AAG acts as an acute-phase reactant; its concentration rises during inflammation/stress, potentially decreasing the free fraction of basic drugs.
- **Displacement Interactions:**Historically, displacement of highly bound drugs (e.g., warfarin displaced by phenylbutazone) was feared as a major cause of toxicity. However, modern kinetic theory clarifies that for drugs with low hepatic extraction (restrictive clearance), displacement increases f_u but simultaneously increases clearance. This leads to a new steady state where total drug concentration decreases, but the absolute concentration of free drugs remains unchanged. Thus, clinical toxicity from displacement alone is rare, unless the drug has a high extraction ratio and is given IV, or has an extremely narrow therapeutic index.

3.3. Volume of Distribution in Disease States

Pathological changes can dramatically alter V_d, necessitating dose adjustments.

- **Obesity:** Adipose tissue acts as a reservoir for lipophilic drugs (e.g., benzodiazepines), significantly increasing their V_d and elimination half-life. Dosing based on Total Body Weight (TBW) can lead to toxicity, while Ideal Body Weight (IBW) may result in sub-therapeutic levels. Specialized scalars like Lean Body Weight (LBW) or Adjusted Body Weight (ABW) are often required.
- **Fluid Shifts:** In conditions like sepsis, heart failure, or cirrhosis, the expansion of extracellular fluid (edema/ascites) increases the V_d of hydrophilic drugs (e.g., aminoglycosides,beta-lactams). This necessitates larger loading doses to achieve effective peak concentrations.

Conditions impacting volume of distribution are illustrated in Table 3.2.

TABLE 3.2: Conditions affecting Volume of distribution:

Condition	Mechanism	Impact
Hypoalbuminemia	↓ binding of acidic drugs	↑ free drug → risk of toxicity
Increased α1-AGP	↑ binding of basic drugs (e.g., propranolol)	↓ free drug → reduced effect
Obesity	↑ fat stores for lipophilic drugs	↑ Vd → prolonged half-life
Dehydration	↓ extracellular fluid	Hydrophilic drugs → ↓ Vd
Edema/Ascites	↑ extracellular fluid	Aminoglycosides → ↑ Vd

IV. Advanced Concepts in Metabolism

Metabolism (biotransformation) is the enzymatic conversion of drugs (Different enzymes involved in metabolism and possible interaction with other molecules are illustrated in table 4.1) into more polar compounds to facilitate excretion. While the liver is the primary metabolic organ - Metabolizing with the help of various liver enzymes (As shown in table), the intestine, kidneys, lungs, and plasma (esterases) also contribute.

International Journal of Pharmaceutical research and Applications
Volume 11, Issue 1, Jan - Feb 2026, pp:118-131 www.ijprajournal.com ISSN: 2456-4494

TABLE 4.1: Major CYP450 Enzymes and Clinical Interactions

Enzyme	Substrates (Examples)	Inhibitors (Strong)	Inducers (Strong)	Clinical Note
CYP3A4	Atorvastatin, Midazolam, Tacrolimus	Ketoconazole, Ritonavir, Grapefruit Juice	Rifampin, Carbamazepine, St. John's Wort	Metabolizes ~50% of all drugs. Highly susceptible to DDIs.
CYP2D6	Codeine, Metoprolol, Fluoxetine	Paroxetine, Fluoxetine, Quinidine	*None clinically significant*	Polymorphic (UM/PM). Critical for prodrug activation (e.g., Codeine \to Morphine).
CYP2C9	Warfarin, Phenytoin	Fluconazole, Amiodarone	Rifampin	Inhibition carries high risk of bleeding (warfarin) or toxicity (phenytoin).
CYP2C19	Clopidogrel, Omeprazole	Omeprazole (competitive), Fluconazole	Rifampin	PMs have poor outcome with Clopidogrel (stent thrombosis risk).
CYP1A2	Clozapine, Theophylline, Caffeine	Ciprofloxacin, Fluvoxamine	Tobacco Smoke, Omeprazole	Smoking cessation can acutely increase drug levels, risking toxicity.

4.1. Stereoselective Metabolism

Many drugs exist as racemic mixtures of enantiomers (chiral molecules). Biological systems, being chiral themselves, interact differently with each isomer.

- **Warfarin:** Administered as a racemate, S-warfarin is 3–5 times more potent than R-warfarin. However, S-warfarin is metabolized almost exclusively by CYP2C9, while R-warfarin is metabolized by CYP1A2 and CYP3A4. Consequently, a drug that inhibits CYP2C9 (e.g., fluconazole) will cause a much more profound increase in INR than a drug that inhibits CYP3A4, as it specifically potentiates the potent enantiomer.
- **Chiral Inversion:** Ibuprofen undergoes a unique, unidirectional metabolic inversion from the inactive R-enantiomer to the active S-enantiomer *in vivo*. This process is mediated by acyl-CoA thioesterases. Because the rate of inversion varies between individuals, measuring total plasma ibuprofen concentrations may not accurately reflect therapeutic activity.

4.2. Chrono-pharmacokinetics

Physiological processes, including enzyme activity and blood flow, exhibit circadian rhythms regulated by CLOCK genes.

- **Mechanism:** The expression of CYP enzymes, transporters, and renal blood flow oscillates over a 24-hour cycle. For example, CYP3A4 activity may be higher during the day than at night.
- **Clinical Relevance:** This has led to the concept of chronotherapy. Administering antihypertensives at night may better control the "morning surge" in blood pressure. Similarly, chemotherapeutic toxicity can be minimized by timing doses to coincide with troughs in normal tissue cell division or peaks in detoxification enzyme activity.

4.3. Hepatic Clearance Models

To predict how physiological changes (e.g., reduced blood flow in heart failure) affect hepatic clearance (CL_H), pharmacokineticists employ specific hepatic models relating blood flow (Q), fraction unbound (f_u), and intrinsic clearance (CL_{int}).

- **Well-Stirred Model:** This is the most common model. It assumes the liver is a well-mixed compartment where the concentration of drug in the hepatic vein equals the concentration inside the liver.
  - *High Extraction Ratio (E > 0.7):* If $f_u.CL_{int} >> Q_h$, then $CL_H \approx Q_h$. Clearance is limited by blood flow (e.g., propranolol, lidocaine).

International Journal of Pharmaceutical research and Applications
Volume 11, Issue 1, Jan - Feb 2026, pp:118-131 www.ijprajournal.com ISSN: 2456-4494

- *Low Extraction Ratio (E < 0.3):* If Q >> f_u. CL_{int}, then $CL_H \approx f_u$. CL_{int}Clearance is limited by enzyme capacity and protein binding (e.g., warfarin, phenytoin).

- **Parallel-Tube Model:** This model assumes the liver consists of a series of parallel tubes where drug concentration decreases exponentially along the length of the sinusoid. While mathematically distinct, both models often yield similar predictions in clinical scenarios, though the Parallel-Tube model is theoretically superior for high-extraction drugs.

V. Excretion and Renal Dosing Adjustments

Excretion involves the removal of intact drug or metabolites from the body. The kidney is the principal organ of excretion, utilizing three distinct mechanisms: Glomerular Filtration, Active Tubular Secretion, and Tubular Reabsorption.

5.1. Estimation of Renal Function

Accurate estimation of Glomerular Filtration Rate (GFR) is critical for dosing renally cleared drugs.

- **Cockcroft-Gault Equation (C-G):** Developed in 1976, this formula estimates Creatinine Clearance (CrCl) based on serum creatinine, age, weight, and sex.

  $$\text{Male: } CrCl(mL/min) = \frac{(140-age).\ weight\ (Kg)}{72.SCr}$$

  (Multiply by 0.85 for females). Despite its age, C-G remains widely used in drug labelling. However, it relies on weight, which can lead to overestimation of GFR in obese patients if Total Body Weight is used. Using Ideal Body Weight (IBW) or Adjusted Body Weight is recommended in obesity.

- **MDRD and CKD-EPI:** These newer equations estimate GFR (eGFR) normalized to Body Surface Area (1.73 m^2). While CKD-EPI is more accurate for staging chronic kidney disease (CKD), using normalized eGFR for drug dosing in patients with extremes of body size (very large or very small) can be dangerous. For dosing, eGFR should be "de-normalized" to the patient's actual BSA.

5.2. The Giusti-Hayton Method

When a patient has renal impairment, maintenance doses must be reduced to prevent accumulation. The Giusti-Hayton method is a standard approach for calculating the dose adjustment factor (G) based on the fraction of drug excreted unchanged in the urine (f_e) and the ratio of the patient's renal function to normal renal function.

Step 1: Calculate the Ratio of Renal Function (Q)
(Assume CrCl normal≈120 mL/min)

Step 2: Calculate the Giusti-Hayton Factor (G)
This factor G represents the fraction of the normal dose required by the patient.

Step 3: Adjust the Regimen

- **Dose Reduction:**
  Dose patient = $Dose_{normal}$x G (Keep interval constant).
- **Interval Extension:**
  $Interval_{patient}$ = $Interval_{normal}$/G (Keep dose constant).

This method is robust for drugs with linear kinetics and is widely used for antibiotics like gentamicin and vancomycin.

VI. Mathematical Modelling: From Compartments to Neural Networks

6.1. Compartmental Analysis

Compartmental modelling simplifies the body into kinetically homogeneous "tanks."

6.1.1. One-Compartment Model

The simplest model assumes rapid, instantaneous distribution.

- **IV Bolus:** The concentration decays mono-exponentially. Where C_0 = Dose/V_d and k_{el} = CL/V_d.
- **Oral Absorption (First-Order):** When input is extravascular, the curve is described by the Bateman function: This equation describes the initial rise (dominated by absorption rate constant k_a) and the subsequent fall (dominated by elimination rate constant k_{el}).

6.1.2. Two-Compartment Model

Most drugs distribute slowly into tissues, requiring a Central Compartment (V_1, blood/vessel-rich group) and a Peripheral Compartment (V_2, muscle/fat). The plasma concentration curve exhibits two distinct phases: a rapid distribution phase (alpha) and a slower elimination phase (beta).

- **Integrated Equation:** Here, alpha and beta are hybrid rate constants derived from the

International Journal of Pharmaceutical research and Applications
Volume 11, Issue 1, Jan - Feb 2026, pp:118-131 www.ijprajournal.com ISSN: 2456-4494

micro-constants (k_{12}, k_{21}, k_{10}). The alpha phase represents distribution, while the beta phase represents terminal elimination.

- **Relationships:** This model is essential for drugs like lidocaine or vancomycin where early sampling can misrepresent elimination kinetics.

6.2. Non-Linear Pharmacokinetics (Michaelis-Menten)

Linear PK assumes that Clearance is constant. However, enzymes and transporters are saturable. When drug concentration exceeds the K_m of the system, kinetics become non-linear (dose-dependent).

- **Derivation:** Based on enzyme kinetics, the rate of elimination (v) is:
  - **First-Order Region (C = K_m):** v $\approx V_{max}/K_m$x C. Clearance is constant (CL = V_{max}/K_m).
  - **Zero-Order Region (C >> K_m):** v $\approx V_{max}$. The enzyme is working at maximum capacity. Rate of elimination is constant, independent of concentration.
- **Phenytoin:** A classic example. Small dose increases can lead to disproportionate toxicity because the enzymes are near saturation ($K_m \approx 4$ mg/L, therapeutic range 10-20 mg/L). Dosing requires non-linear tools like the Ludden plot or Orbit graph.

6.3. Target-Mediated Drug Disposition (TMDD)

For high-affinity biologics (mAbs), the interaction with the pharmacological target acts as a significant clearance pathway. This is "Target-Mediated Drug Disposition."

- **Mechanism:** The drug binds its target (Receptor, R) to form a complex (RC), which is internalized and degraded.
- **Kinetic Signature:** At low doses, the target acts as a high-capacity "sink," causing rapid elimination. As the dose increases, targets become saturated, and linear, non-specific clearance mechanisms take over. This results in a characteristic "knee" or "bend" in the semi-log concentration-time profile.

6.4. Physiologically Based Pharmacokinetic (PBPK) Modelling

Unlike compartmental models which fit data to empirical boxes, PBPK models are "bottom-up" simulations. They mathematically reconstruct the body using organ volumes, blood flows, and tissue partition coefficients (K_p)k

- **Workflow:**
  1. **Drug Data:** Intrinsic clearance (CL_{int}), Permeability (P_{eff}), Solubility.
  2. **System Data:** Anatomy and physiology of the population (e.g., paediatric liver volume).
  3. **Simulation:** Differential equations describe mass balance for each organ.
- **Application:** PBPK is now the regulatory standard for predicting drug-drug interactions (DDIs) and scaling doses for paediatrics and pregnancy when clinical trials are unethical or impossible.

6.5. The Frontier: Neural ODEs and AI

The integration of Machine Learning (ML) with pharmacometrics is creating "Neural Ordinary Differential Equations" (NODEs). Traditional models require the modeler to specify the equations (e.g., "one compartment"). NODEs use neural networks to *learn* the underlying differential equations directly from the data.

- **Implication:** This allows for the modelling of complex, unknown biological dynamics ("black box" components) while retaining the interpretability of known physiology ("grey box" modelling). NODEs are proving superior in handling sparse data and predicting complex disease progression alongside PK profiles

VII. Pharmacokinetics of Biologics and Novel Modalities

The PK of large molecules differs fundamentally from small molecules. They are defined by their size, structural complexity, and interaction withthe immune system.

7.1. Monoclonal Antibodies (mAbs)

7.1.1. FcRn-Mediated Recycling

IgG antibodies have an extraordinarily long half-life (~21 days) compared to other proteins (Comparison of ADME parameters of monoclonal antibodies to small molecule drugs are illustrated in table 6.1). This is due to the Neonatal Fc Receptor (FcRn).

- **Mechanism:** Fluid-phase endocytosis takes IgG into endothelial cells. The endosome acidifies (pH 6.0), causing the Fc region of

International Journal of Pharmaceutical research and Applications
Volume 11, Issue 1, Jan - Feb 2026, pp:118-131 www.ijprajournal.com ISSN: 2456-4494

IgG to bind tightly to FcRn. Unbound proteins are trafficked to the lysosome for degradation. The FcRn-IgG complex is recycled back to the cell surface. At physiological pH (7.4) of the plasma, the affinity drops, and IgG is released back into circulation.

- **Engineering:** Modifications that increase binding affinity to FcRn at acidic pH (e.g., the "YTE" mutation) can extend half-life to months, as seen with ravulizumab.

Monoclonal antibodies provide better features such as longer half-life. Comparison of small drug molecules compared to monoclonal antibodies is shown in the below table:

Feature	Small Molecules (< 1 kDa)	Monoclonal Antibodies (> 150 kDa)
Route	Oral, IV, etc.	Parenteral (IV, SC, IM)
Absorption	Passive diffusion, Transporters	Lymphatic uptake (SC/IM)
Distribution	Wide (V_d often > TBW), intracellular	Limited to Plasma/ECF (V_d≈3-7 L)
Metabolism	Hepatic (CYP450), Phase II	Proteolysis, Lysosomal degradation
Elimination	Renal, Biliary	Target-mediated, FcRn recycling (No renal elimination.)
Half-life	Minutes to Hours	Days to Weeks (14-21 days typical)
Linearity	Usually linear (except at saturation)	Often Non-linear (TMDD) at low doses

7.1.2. Immunogenicity

Biologics can induce Anti-Drug Antibodies (ADAs). ADAs can form immune complexes that accelerate clearance (clearing ADAs) or neutralize efficacy (neutralizing ADAs). This creates time-dependent PK changes, often observed as a sudden drop in trough concentrations during chronic therapy.

7.2. Bispecific Antibodies (BsAbs)

BsAbs are engineered to bind two distinct antigens (e.g., T-cell engagers binding CD3 and a tumour antigen).

- **PK Challenges:** Smaller formats like BiTEs (e.g., blinatumomab, ~55 kDa) lack an FC region. They cannot bind FcRn and are below the renal filtration threshold (~60 kDa), resulting in elimination half-lives of hours. This necessitates continuous IV infusion. Larger, IgG-like BsAbs retain FcRn recycling but often suffer from stability issues and aggregation-prone physiochemistry, leading to faster non-specific clearance than standard mAbs.

7.3. Antibody-Drug Conjugates (ADCs)

ADCs consist of a mAb linked to a cytotoxic payload. Their PK is complex, requiring the tracking of three species:

1. **Conjugated Antibody (ADC):** Drives efficacy.
2. **Total Antibody:** (ADC + Naked mAb).
3. **Free Payload:** Released via linker instability or catabolism. This small molecule fraction drives systemic toxicity (e.g., neutropenia) and must be rigorously monitored. Deconjugation rates depend on linker chemistry (cleavable vs. non-cleavable).

7.4. Proteolysis-Targeting Chimeras (PROTACs)

PROTACs are bifunctional small molecules that recruit an E3 ubiquitin ligase to a target protein to induce degradation.

- **The "Hook Effect":** PROTAC kinetics are unique. Efficacy does not increase monotonically with concentration. At very high concentrations, the PROTAC saturates both the target and the E3 ligase separately, preventing the formation of the necessary ternary complex. This results in a bell-shaped dose-response curve, requiring precise PK/PD modelling to avoid overdosing.
- **ADME Issues:** PROTACs often violate Lipinski's Rule of 5 (High MW > 800 Da, high polar surface area). They frequently suffer from poor solubility and permeability, challenging oral formulation strategies.

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VIII. Pharmacokinetics in Special Populations

8.1. Paediatrics: The Ontogeny Factor

Children are not simply small adults. Enzyme systems mature at different rates (ontogeny).

- **CYP3A7 to CYP3A4 Switch:** Foetuses express CYP3A7. Immediately after birth, CYP3A7 expression declines, and CYP3A4 expression surges.
- **Glucuronidation:** UGT enzymes mature slowly. The inability of neonates to glucuronidate chloramphenicol leads to accumulation and "Gray Baby Syndrome".
- **Scaling:** Simple weight-based scaling often fails in neonates. PBPK models incorporating ontogeny functions are now essential for predicting paediatric doses.

8.2. Pregnancy

Pregnancy induces profound physiological changes:

- **Plasma Volume Expansion:** Increases V_d for hydrophilic drugs, diluting concentrations.
- **Enzyme Induction:** CYP3A4 and CYP2D6 activity increases (up to 50%), necessitating higher doses of drugs like metoprolol or protease inhibitors to maintain efficacy.
- **Renal Filtration:** GFR increases by ~50%, increasing the clearance of renally eliminated drugs (e.g., lithium, ampicillin).

IX. Conclusion:

Pharmacokinetics has transformed from a support discipline to a driver of precision medicine. The integration of high-resolution analytics (VAMS micro sampling), genomic data (PGx), and computational power (PBPK, NODEs) is enabling the creation of "Digital Twins"—virtual representations of individual patients that can predict drug response with unprecedented accuracy.

As we look to 2030, the challenges lie in modelling the intracellular kinetics of gene therapies, the immunokinetic of viral vectors, and the complex tumour penetration of next-generation ADCs. The mathematical and mechanistic frameworks detailed in this review provide the essential toolkit for scientists and clinicians to navigate this landscape, ensuring that the promise of these novel therapies translates into safe and effective treatments for patient

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