

CHAPTER 2

Biopharmaceutical and Pharmacokinetic Foundations of Modern Drug Delivery

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Abstract

The performance of any drug delivery system is ultimately governed by biopharmaceutical and pharmacokinetic processes that determine how a drug is liberated, absorbed, distributed, metabolized, and eliminated. This chapter establishes these foundational principles and connects them directly to the rational design of delivery systems. It begins with the core concepts of biopharmaceutics and the biopharmaceutical implications of the route of administration, then examines absorption pathways and the membrane transporters and efflux mechanisms that modulate drug uptake. Distribution and tissue targeting, metabolism and the first-pass effect, and elimination and clearance are each considered in terms of their consequences for formulation strategy. The determinants of bioavailability and bioequivalence are discussed alongside the critical roles of solubility, permeability, and dissolution, and these properties are organized through the Biopharmaceutics Classification System and the complementary Developability Classification System. The chapter then defines the principal pharmacokinetic parameters relevant to delivery design, relates them to pharmacodynamic response, and explores pharmacokinetic–pharmacodynamic relationships in controlled and targeted delivery. In vitro–in vivo correlation and physiologically based pharmacokinetic modeling are presented as quantitative tools that link formulation behaviour to clinical exposure and increasingly support regulatory decision-making. Finally, dose optimization within the therapeutic window is examined as the integrating objective of biopharmaceutical design. Throughout, the emphasis is on how advanced delivery systems exploit or overcome biopharmaceutical constraints, providing the mechanistic vocabulary and quantitative framework that underpin the carrier platforms, enabling technologies, and targeted strategies discussed in subsequent chapters of this volume.

Keywords: *biopharmaceutics, pharmacokinetics, bioavailability, BCS, PK–PD modeling*

2.0 Introduction

The therapeutic success of a drug delivery system is decided not at the moment of administration but throughout the body, by the processes that govern what the body does to the drug and what the drug does to the body. These processes are described, respectively, by pharmacokinetics and pharmacodynamics, and together with biopharmaceutics they constitute the scientific foundation on which rational delivery design rests [1,2]. Whereas Chapter 1 traced the historical evolution of

delivery technologies, this chapter establishes the quantitative principles that determine whether any such technology will perform as intended *in vivo*.

Biopharmaceutics concerns the relationship between the physicochemical properties of a drug and its dosage form on the one hand, and the rate and extent of absorption on the other. Pharmacokinetics quantifies the time course of absorption, distribution, metabolism, and elimination—collectively the ADME processes—while pharmacodynamics relates the resulting concentrations to therapeutic and toxic effects [2]. A delivery system can be understood as a device for manipulating these processes: a controlled-release matrix alters the rate of drug input, a targeted nanoparticle alters distribution, and a long-acting depot reshapes the entire temporal profile of exposure [1,3].

This chapter surveys these foundations in turn, beginning with the core concepts of biopharmaceutics and the influence of the route of administration, proceeding through each ADME process and the determinants of bioavailability, and concluding with the classification systems, pharmacokinetic–pharmacodynamic relationships, and modeling approaches that translate these principles into formulation strategy. The emphasis throughout is on how delivery systems exploit or overcome biopharmaceutical constraints, providing the mechanistic vocabulary used in the technical chapters that follow.

2.1 Basic Concepts of Biopharmaceutics in Drug Delivery

Biopharmaceutics is the study of how the physicochemical properties of a drug substance and the characteristics of its dosage form influence the rate and extent of drug absorption and, ultimately, therapeutic performance. The sequence of events following administration of a solid oral dosage form is conveniently summarized by the acronym LADME: liberation of the drug from its formulation, absorption across biological membranes, distribution to tissues, metabolism, and elimination [2]. For most solid dosage forms the drug must be released and then dissolved in physiological fluids before it can be absorbed, and dissolution is frequently the rate-limiting step for poorly soluble compounds [15].

The central premise of biopharmaceutics is that the formulation is not a passive vehicle but an active determinant of clinical outcome. Two products containing the same drug at the same dose may produce markedly different plasma profiles depending on excipients, particle size, polymorphic form, and release mechanism. This recognition underpins the entire discipline of pharmaceutical product design and the regulatory requirements for demonstrating that a given formulation delivers its drug reliably [3]. Figure 2.1 depicts the ADME continuum and its relationship to the pharmacodynamic effect that follows from drug reaching its site of action.

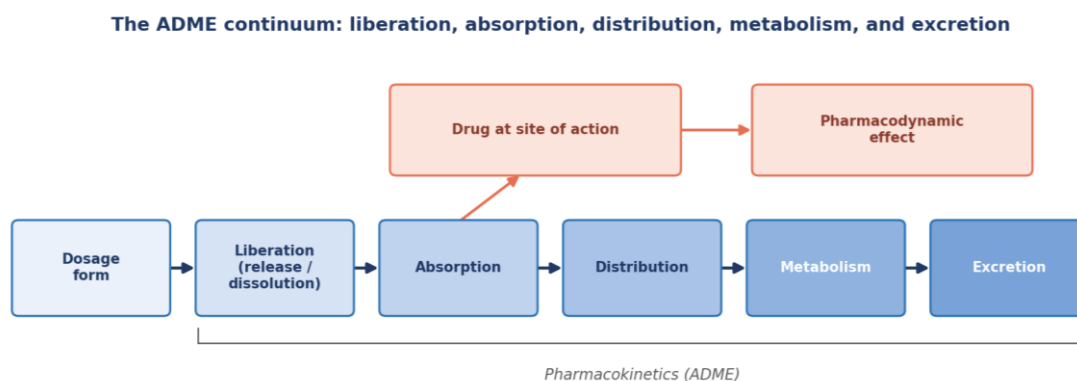


Figure 2.1. *The ADME continuum: liberation, absorption, distribution, metabolism, and excretion, and their relationship to pharmacodynamic effect.*

2.2 Routes of Administration and Their Biopharmaceutical Implications

The route of administration is among the most consequential decisions in delivery design because it dictates the barriers a drug must cross, the extent of presystemic loss, and the achievable rate and duration of exposure. The oral route remains dominant owing to its convenience, low cost, and patient acceptability, but it exposes the drug to gastrointestinal degradation, variable absorption, and first-pass metabolism, often resulting in low and variable bioavailability [5]. The intravenous route, by contrast, delivers the entire dose directly to the systemic circulation, giving complete bioavailability and precise control but requiring invasive administration.

Parenteral depot routes such as intramuscular and subcutaneous injection permit sustained release and are well suited to biologics and long-acting formulations, while non-invasive routes—transdermal, pulmonary, nasal, buccal, and ocular—offer the advantages of avoiding first-pass metabolism and improving adherence, at the cost of restricted dose capacity and route-specific barriers [3]. The choice of route is therefore a biopharmaceutical optimization in its own right, and many delivery technologies exist precisely to make an otherwise unsuitable route viable for a given drug. Table 2.1 compares the principal routes and their biopharmaceutical characteristics, themes developed in detail in Chapters 15 through 18.

Table 2.1. Principal routes of administration and their biopharmaceutical characteristics.

Route	Typical bioavailability	Key advantages	Key limitations
Oral	Variable (low–high)	Convenient, non-invasive, low cost	First-pass metabolism; GI degradation; variable absorption
Intravenous	Complete (100%)	Immediate, complete, titratable	Invasive; requires trained personnel
Intramuscular / subcutaneous	High; can be sustained	Suitable for biologics; depot formats possible	Injection-site reactions; limited volume
Transdermal	Low–moderate	Avoids first pass; steady delivery	Limited to potent, lipophilic, low-MW drugs
Pulmonary	Moderate–high	Rapid action; large absorptive area	Device-dependent; variable deposition
Buccal / sublingual / nasal	Moderate	Avoids first pass; rapid onset	Small area; clearance and washout

2.3 Absorption Pathways and Factors Influencing Drug Uptake

Absorption is the process by which a drug moves from its site of administration into the systemic circulation, and for most routes it requires passage across one or more epithelial barriers. The dominant mechanism for the majority of small-molecule drugs is passive

transcellular diffusion, driven by the concentration gradient and favoured by lipophilicity and an uncharged molecular species; the paracellular route, through tight junctions, accommodates small hydrophilic molecules, while carrier-mediated transport and endocytosis handle nutrients, peptides, and some drug substrates [6]. The relative contribution of these pathways depends on the physicochemical properties of the drug and the physiology of the absorbing surface.

Numerous factors modulate the rate and extent of absorption. Physicochemical determinants include solubility, dissolution rate, lipophilicity, ionization state, and molecular size, while physiological factors include gastrointestinal pH, transit time, surface area, blood flow, the presence of food, and the activity of metabolizing enzymes and transporters [5,13]. This variability is substantial between and within individuals and is amplified in special populations such as the very young, the elderly, and patients with gastrointestinal disease, complicating the prediction of in vivo performance [35]. A central goal of oral delivery technology is to render absorption more complete and more reproducible in the face of this variability [32].

These influences are not merely theoretical. Food can alter the bioavailability of a drug by severalfold, either enhancing the absorption of lipophilic compounds through stimulation of bile secretion and delayed gastric emptying or reducing it through binding and complexation, and food effects are a routine consideration in delivery design and product labelling [5]. Regional differences along the gastrointestinal tract—in pH, surface area, transit time, and the expression of transporters and enzymes—create opportunities for site-specific oral delivery, such as colon-targeted systems that exploit the distal gut environment [32]. Systematic efforts to map and predict this variability, including large collaborative reviews of gastrointestinal physiology, have improved the reliability with which oral absorption can be anticipated, although interindividual variability remains a fundamental constraint that delivery technology seeks to mitigate [5,35].

2.4 Drug Transporters and Efflux Mechanisms in Delivery

Membrane transporters are now recognized as major determinants of drug absorption, distribution, and elimination, and their consideration is integral to modern delivery design. Transporters fall broadly into two superfamilies: the ATP-binding cassette (ABC) transporters, which use energy to efflux substrates out of cells, and the solute carrier (SLC) transporters, which mediate the uptake of substrates into cells [7]. The interplay between uptake and efflux at the intestinal, hepatic, renal, and blood–brain interfaces shapes the net disposition of many drugs.

The most studied efflux transporter, P-glycoprotein, limits the intestinal absorption and central nervous system penetration of a broad range of substrates and contributes to multidrug resistance in tumours, while breast cancer resistance protein and the multidrug resistance-associated proteins extend this protective barrier function [7,8]. Uptake transporters such as the organic anion-transporting polypeptides and the organic anion and cation transporters govern hepatic and renal handling and are frequent sites of drug–drug interactions. For delivery, transporters present both an obstacle—efflux that must be overcome to achieve absorption or tissue penetration—and an opportunity, since transporter substrates and prodrugs can be designed to exploit uptake carriers for targeted delivery [6,8]. Table 2.2 summarizes the principal transporters relevant to delivery.

Table 2.2. Major drug transporters relevant to delivery design.

Transporter	Family	Direction	Representative role in delivery
P-glycoprotein (ABCB1)	ABC	Efflux	Limits intestinal and CNS uptake; multidrug resistance
BCRP (ABCG2)	ABC	Efflux	Restricts oral absorption; barrier at BBB and placenta
MRPs (ABCC)	ABC	Efflux	Cellular extrusion of drug conjugates
OATPs (SLCO)	SLC	Influx	Hepatic uptake of many drug substrates
OATs / OCTs (SLC22)	SLC	Influx	Renal and hepatic uptake; basis of interactions
PEPT1 (SLC15A1)	SLC	Influx	Intestinal peptide and prodrug absorption (targeting)

2.5 Drug Distribution and Tissue Targeting Considerations

Once in the systemic circulation, a drug distributes among plasma, interstitial fluid, and intracellular compartments according to its physicochemical properties, its binding to plasma proteins and tissues, and the perfusion and permeability of each organ. The apparent volume of distribution is the pharmacokinetic parameter that captures this behaviour, relating the amount of drug in the body to the measured plasma concentration; a large volume indicates extensive tissue distribution, whereas a small volume suggests confinement to the circulation [11]. Plasma protein binding modulates the free, pharmacologically active fraction and influences both distribution and clearance.

Distribution is central to the logic of targeted delivery, because the fundamental aim of targeting is to alter the natural biodistribution of a drug so that it accumulates preferentially at the site of action and is spared from healthy tissue [25,28]. Nanocarriers can profoundly change distribution by virtue of their size and surface properties, prolonging circulation, restricting access to certain compartments, and promoting accumulation in others, as discussed in Chapters 3 and 4 [26]. Understanding the physiological determinants of distribution is therefore a prerequisite for the rational design of any system intended to achieve site-specific delivery [28].

Several features of distribution have direct delivery consequences. Plasma protein binding can act as a circulating reservoir that prolongs apparent half-life but also limits the free drug available to act or to be cleared, and displacement interactions can carry clinical significance. Anatomical sanctuaries such as the central nervous system, protected by the blood–brain barrier, are inaccessible to most drugs and demand dedicated delivery strategies, as discussed in Chapter 17 [26]. The quantitative reality of nanocarrier distribution has been sharply illustrated by analyses showing that, historically, only a very small percentage of an injected nanoparticle dose reaches solid tumours, underscoring that favourable distribution cannot be assumed but must be deliberately engineered against the body's clearance and barrier systems [27,28].

2.6 Metabolism, First-Pass Effect, and Implications for Delivery Design

Metabolism converts drugs, usually into more polar and more readily excreted products, through phase I reactions such as oxidation, reduction, and hydrolysis—predominantly mediated by the cytochrome P450 enzymes—and phase II conjugation reactions such as glucuronidation and sulfation [9]. While metabolism is essential for the clearance of most drugs, it also poses a major obstacle to delivery when it occurs before the drug reaches the systemic circulation. The first-pass effect, whereby orally absorbed drug is metabolized in the gut wall and liver before entering the systemic circulation, can dramatically reduce oral bioavailability and is a primary motivation for alternative routes and delivery strategies [3,9].

Delivery technologies address metabolism in several ways. Routes that bypass the portal circulation—transdermal, buccal, nasal, pulmonary, and parenteral—avoid hepatic first-pass loss, while prodrug strategies can protect a drug from premature metabolism or exploit specific enzymes for site-selective activation [3]. Encapsulation within nanocarriers can also shield labile drugs from metabolic degradation. Conversely, metabolism can be harnessed deliberately, as in enzyme-responsive systems that release their payload in response to disease-associated enzymatic activity, a principle examined in Chapter 8. An understanding of a drug's metabolic fate is therefore indispensable to selecting both the route and the delivery system.

The clinical importance of metabolism is magnified by its variability. Polymorphisms in cytochrome P450 enzymes, notably CYP2D6 and CYP2C19, produce poor, intermediate, extensive, and ultrarapid metabolizer phenotypes that can change exposure severalfold for affected drugs, and this pharmacogenomic variability is an increasingly recognized driver of individualized therapy [9]. Metabolic activation is also exploited deliberately: prodrugs such as the antiviral valacyclovir and numerous ester prodrugs are designed to be converted to the active species after absorption, improving permeability or stability en route [3]. Delivery systems must therefore be designed with the metabolic context in mind, anticipating both the protective avoidance of unwanted metabolism and, where useful, the intentional harnessing of enzymatic conversion for activation or triggered release.

2.7 Elimination Pathways and Clearance-Related Challenges

Elimination removes drug from the body, principally through renal excretion and hepatic metabolism, with biliary, pulmonary, and other routes contributing for particular compounds. Clearance, the volume of plasma cleared of drug per unit time, is the pharmacokinetic parameter that quantifies the efficiency of elimination and, together with the volume of distribution, determines the elimination half-life [10]. Clearance is the parameter that governs the maintenance dose or infusion rate required to sustain a target steady-state concentration, making it central to the design of any system intended to maintain prolonged exposure.

Rapid clearance is a frequent challenge in delivery, particularly for biologics and nanocarriers. Small peptides and proteins are often cleared within minutes by renal filtration and proteolysis, and a major function of delivery technology is to extend their functional half-life through PEGylation, depot formulation, or carrier binding [3]. Nanoparticles face clearance by the mononuclear phagocyte system, which removes them from the circulation and limits their access to target tissues; stealth coatings are employed specifically to slow this process and prolong circulation [26]. Thus, just as with absorption, much of delivery science is concerned with deliberately modulating elimination to achieve a desired exposure profile.

For particulate and macromolecular systems, the physical basis of elimination introduces specific design rules. Renal filtration efficiently removes molecules and particles below a hydrodynamic diameter of roughly eight nanometres, so very small carriers are rapidly excreted while larger ones persist but become subject to phagocytic capture, creating a design

window between rapid renal loss and reticuloendothelial sequestration [26]. Strategies to extend functional half-life therefore aim to position a therapeutic within this window or to slow its recognition and clearance: PEGylation and albumin binding prolong the circulation of proteins, while sustained-release depots decouple the duration of effect from the intrinsic half-life of the drug entirely [3]. Clearance considerations thus permeate delivery design from the molecular to the device scale, shaping decisions about size, surface, and dosing.

2.8 Bioavailability and Bioequivalence in Formulation Development

Bioavailability denotes the rate and extent to which the active drug reaches the systemic circulation, and it is the integrating measure of the absorption and first-pass processes discussed above. Absolute bioavailability compares systemic exposure after extravascular administration with that after intravenous administration, by definition complete for the latter, while relative bioavailability compares two extravascular products. Exposure is quantified principally by the area under the plasma concentration–time curve, with the peak concentration and time to peak describing the rate of absorption [2]. Maximizing and stabilizing bioavailability is one of the central objectives of pharmaceutical and delivery design.

Bioequivalence is the demonstration that two products—typically a generic and a reference—produce sufficiently similar systemic exposure to be considered therapeutically interchangeable, judged by statistical comparison of exposure metrics within defined limits. The concept is fundamental to generic drug approval and to the assessment of formulation changes during development. Because in vivo bioequivalence studies are costly, regulatory frameworks permit biowaivers for certain drugs on the basis of in vitro dissolution and biopharmaceutical classification, linking the science of bioavailability directly to that of the classification systems described in Section 2.10 [4,17]. For advanced delivery systems, establishing bioavailability and comparability is frequently complicated by their structural complexity.

For advanced delivery systems, the assessment of bioavailability and comparability is considerably more complex than for conventional small molecules. The relevant exposure may be that of the encapsulated drug, the released drug, or the carrier itself, and conventional plasma metrics may not capture the parameter that drives efficacy, particularly for targeted systems whose benefit lies in altered tissue distribution rather than increased systemic exposure [25]. Demonstrating bioequivalence between complex products—so-called nanosimilars—poses distinctive analytical and regulatory challenges that conventional dissolution-based biowaivers were not designed to address, an issue revisited in Chapter 19 [26]. These complexities mean that the classical bioavailability framework, while foundational, must be thoughtfully extended when applied to the systems that are the subject of this volume.

2.9 Solubility, Permeability, and Dissolution as Critical Determinants

For orally administered drugs, two physicochemical properties dominate absorption: aqueous solubility, which limits how much drug can dissolve in gastrointestinal fluids, and membrane permeability, which limits how readily the dissolved drug crosses the intestinal epithelium. A large and growing proportion of contemporary drug candidates suffer from poor solubility, poor permeability, or both, reflecting the lipophilic, high-molecular-weight character of molecules emerging from modern discovery [12,13]. Dissolution, the rate at which solid drug enters solution, is the kinetic process that links solubility to absorption and is frequently rate-limiting for poorly soluble compounds [14,15].

Delivery science offers an extensive toolkit for addressing these limitations. Solubility and dissolution can be enhanced by particle-size reduction and nanosizing, amorphous solid dispersions, salt and cocrystal formation, lipid-based formulations, and complexation with agents such as cyclodextrins [12,16,33]. Permeability can be improved through prodrugs, permeation enhancers, and transporter-targeted designs [6]. These strategies, which recur throughout the volume, are the practical embodiment of biopharmaceutical principles, and the systematic relationship between solubility, permeability, and formulation strategy is captured by the classification systems considered next.

The practical importance of these determinants is reflected in the prominence of enabling formulation technologies in contemporary product development. Amorphous solid dispersions, in which a drug is molecularly dispersed in a polymer matrix to suppress crystallization, have become a mainstream solution for poorly soluble Class II compounds, while lipid-based and self-emulsifying systems present the drug in a pre-dissolved or readily dispersible form [12]. Nanocrystal technology, which reduces particle size to increase dissolution rate and apparent solubility, underlies several marketed long-acting and oral products [16]. The choice among these approaches is guided by the biopharmaceutical profile of the drug, illustrating how the abstract properties of solubility and permeability translate directly into concrete formulation decisions and, ultimately, into clinically and commercially viable products.

2.10 Biopharmaceutics and Developability Classification Systems (BCS and DCS)

The Biopharmaceutics Classification System (BCS) provides a rational framework for relating the in vitro properties of a drug to its in vivo absorption by categorizing compounds according to high or low solubility and high or low permeability into four classes [4]. Class I drugs, with high solubility and high permeability, are generally well absorbed and limited only by their release rate; Class II drugs are absorption-limited by dissolution; Class III drugs are limited by permeability; and Class IV drugs, low in both, present the greatest formulation challenge. The BCS has had profound regulatory impact, providing the scientific basis for biowaivers that exempt certain products from in vivo bioequivalence testing [4,17]. Figure 2.3 illustrates the four classes and their associated formulation strategies.

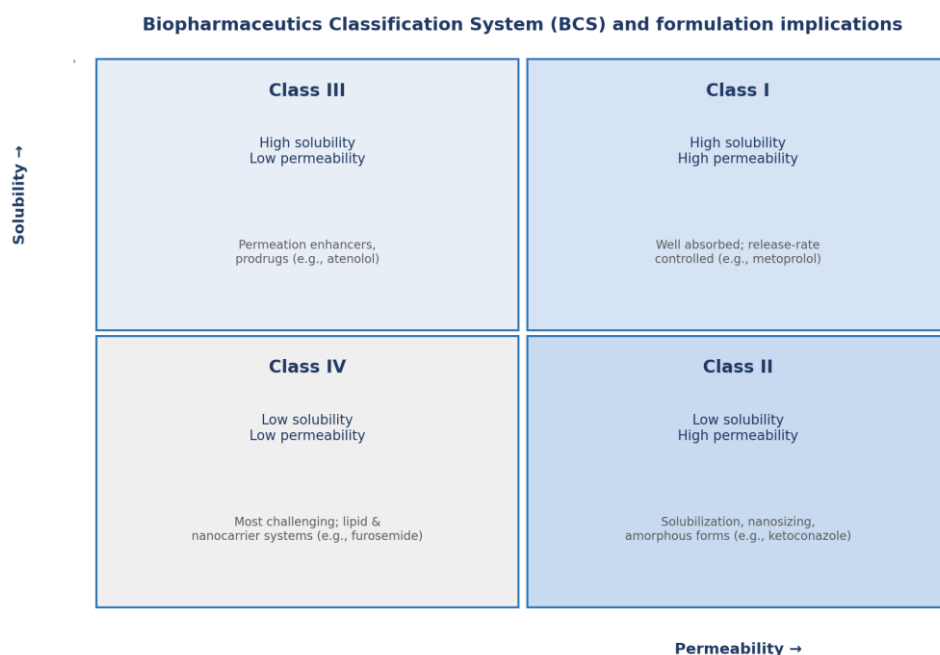


Figure 2.3. *The Biopharmaceutics Classification System: four classes defined by solubility and permeability, with representative formulation strategies.*

The Developability Classification System (DCS) refines the BCS for formulation development by recognizing that solubility limitations may be dissolution-rate-limited or solubility-limited, subdividing Class II accordingly and using more biorelevant solubility criteria to guide formulation choice [15]. The related Biopharmaceutics Drug Disposition Classification System extends the concept to predict the roles of metabolism and transporters in drug disposition, providing insight into clearance and interaction potential [16,18,19]. Together these frameworks translate the physicochemical determinants of Section 2.9 into actionable development strategy and are now embedded in both industrial practice and regulatory science.

2.11 Pharmacokinetic Parameters Relevant to Delivery Systems

A small set of pharmacokinetic parameters captures the essential behaviour of a drug in the body and provides the quantitative targets for delivery design. The peak plasma concentration and the time at which it occurs describe the magnitude and rapidity of exposure; the area under the concentration–time curve measures total exposure and underlies bioavailability and bioequivalence; the elimination half-life governs the dosing interval; the volume of distribution reflects tissue penetration; and clearance determines the dose rate needed to maintain a target concentration [2,10,11]. These parameters are interdependent, and a delivery system that modifies one frequently affects the others.

Controlled and long-acting delivery systems are designed explicitly to reshape these parameters. By slowing drug input, a controlled-release formulation lowers the peak concentration and extends the time above the minimum effective concentration, smoothing the plasma profile and reducing both toxicity and dosing frequency [30,31]. Figure 2.2 contrasts the plasma profiles of an immediate-release and a controlled-release product, illustrating how the same dose can produce very different exposure depending on the delivery system. Table 2.3 summarizes the key parameters and their relevance to design.

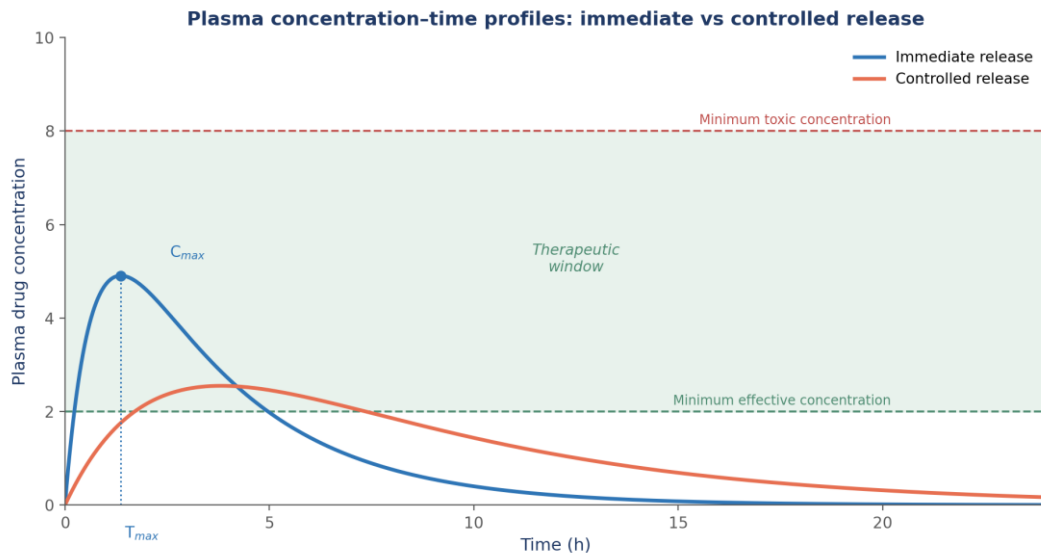


Figure 2.2. Plasma concentration–time profiles for immediate-release and controlled-release products, showing peak concentration, time to peak, and the therapeutic window.

Table 2.3. Key pharmacokinetic parameters and their relevance to delivery design.

Parameter	Definition	Relevance to delivery design
C_{max}	Peak plasma concentration	Governs concentration-dependent toxicity; lowered by controlled release
T_{max}	Time to peak concentration	Reflects absorption rate; modified by release rate
AUC	Area under the concentration–time curve	Measure of total exposure; basis of bioavailability and bioequivalence
$t_{1/2}$	Elimination half-life	Sets dosing interval; extended by long-acting systems
V_d	Apparent volume of distribution	Reflects tissue distribution; altered by targeting
CL	Clearance	Determines maintenance dose or rate at steady state
F	Bioavailability	Fraction reaching systemic circulation; central design goal

2.12 Pharmacodynamic Principles and Therapeutic Response

Pharmacodynamics describes the relationship between drug concentration and biological effect, completing the link from dose to therapeutic response. Most drug effects arise from interaction with a specific molecular target—a receptor, enzyme, ion channel, or transporter—and the resulting response typically follows a concentration–effect relationship that rises and then saturates, characterized by the maximum achievable effect and the concentration producing half-maximal effect. The therapeutic window, bounded by the minimum effective concentration and the concentration at which toxicity appears, defines the range of exposures that delivery systems aim to maintain [2].

The implications for delivery are direct. For drugs with a wide therapeutic window, maintaining concentrations within range is straightforward, but for those with a narrow window—many cytotoxic, cardiovascular, and central nervous system agents—precise control of exposure is essential, and the value of controlled and targeted delivery is correspondingly greater [28]. Some effects depend on peak concentration, others on sustained exposure or time above a threshold, and the optimal delivery strategy differs accordingly. Pharmacodynamic understanding therefore informs not only which drug to use but how its delivery should be engineered, motivating the integrated analysis considered next.

The form of the concentration–effect relationship has practical consequences for how delivery should be engineered. Some effects are reversible and track concentration closely, described by direct-response models, whereas others involve the synthesis or turnover of a mediator and lag behind concentration, requiring indirect-response models that capture the delayed and sometimes prolonged effect [2]. The distinction between concentration-dependent and time-dependent activity is well illustrated by antimicrobials, where some agents act best when delivered to achieve a high peak relative to the pathogen's sensitivity while others depend on the duration for which concentrations exceed a threshold. Such pharmacodynamic considerations determine whether a peaked or a sustained delivery profile is optimal, and they are a central input to the rational design of dosing regimens and delivery systems.

2.13 PK–PD Relationships in Controlled and Targeted Delivery

Pharmacokinetic–pharmacodynamic (PK–PD) modeling integrates the time course of drug concentration with the time course of effect, providing a unified description of how a dosing regimen produces a therapeutic outcome. Because the effect often lags behind the plasma concentration, link models introduce an effect compartment to account for the delay between exposure and response, while mechanism-based models incorporate the underlying physiology [2]. PK–PD analysis allows the prediction of how changes in formulation or delivery will translate into changes in clinical effect, and is increasingly central to both development and regulatory evaluation.

For controlled and targeted delivery, PK–PD relationships are decisive. A controlled-release system that maintains concentrations within the therapeutic window can improve efficacy and reduce toxicity relative to an immediate-release product delivering the same total dose, and PK–PD modeling quantifies this advantage [30]. In targeted delivery, the relevant concentration is that at the target site rather than in plasma, so conventional plasma-based PK–PD must be extended to account for altered biodistribution—a recognition that has reframed the evaluation of nanomedicines and informed the physiology-led design strategies discussed in later chapters [25,28]. Computational approaches, including machine learning, are increasingly applied to capture these complex relationships [34].

The discipline of model-informed drug development has elevated PK–PD analysis from a descriptive exercise to a predictive engine that guides dose selection, trial design, and labelling, and regulatory agencies increasingly expect a quantitative justification of dosing decisions [22]. For delivery systems, the principal methodological frontier is the incorporation of target-site pharmacokinetics: because the therapeutic action of a targeted carrier depends on local rather than systemic concentration, predictive models must couple whole-body disposition with tissue-level and even subcellular processes [28]. Advances in imaging, microsampling, and computational modeling—including machine-learning approaches—are

progressively making such target-site PK–PD analysis tractable, promising more rational optimization of the advanced delivery systems examined later in this volume [34].

2.14 In Vitro–In Vivo Correlation (IVIVC)

In vitro–in vivo correlation (IVIVC) establishes a predictive mathematical relationship between an in vitro property of a dosage form, usually drug dissolution, and a relevant in vivo response, usually plasma concentration or the amount of drug absorbed. A validated IVIVC is valuable because it allows in vitro dissolution testing to serve as a surrogate for in vivo performance, supporting formulation development, quality control, and regulatory biowaivers for certain post-approval changes [18]. IVIVCs are classified by their level of predictivity, from the point-to-point Level A correlation to the less informative Level B and Level C relationships [18,20].

IVIVC is most readily achieved for controlled- and modified-release products, where dissolution genuinely governs the rate of absorption, and is correspondingly difficult for immediate-release products of highly permeable drugs whose absorption is not dissolution-limited [18]. Establishing a robust correlation requires biorelevant dissolution methods that reproduce physiological conditions, and the endeavour is subject to well-recognized pitfalls when in vitro conditions fail to capture in vivo complexity [20]. For advanced delivery systems with intricate release mechanisms, IVIVC remains both especially valuable and especially challenging, and it is increasingly complemented by mechanistic modeling. Table 2.4 summarizes the levels of IVIVC.

Table 2.4. Levels of in vitro–in vivo correlation (IVIVC).

Level	Basis of correlation	Utility
Level A	Point-to-point: in vitro dissolution vs in vivo input	Highest; supports biowaivers and prediction
Level B	Statistical moment analysis (mean times)	Limited; uses all data but not point-to-point
Level C	Single dissolution point vs one PK parameter	Lowest; useful in early development
Multiple Level C	Several dissolution points vs PK parameters	Approaches Level A utility

2.15 Physiologically Based Pharmacokinetic (PBPK) Modeling and Simulation

Physiologically based pharmacokinetic (PBPK) modeling represents the body as a network of anatomically defined compartments connected by blood flow, each corresponding to an organ or tissue with its own volume, perfusion, and partitioning behaviour. By combining drug-specific physicochemical and biochemical parameters with system-specific physiological data, PBPK models simulate the time course of drug concentration in plasma and individual tissues from first principles [21,23]. This mechanistic foundation distinguishes PBPK from empirical compartmental modeling and allows extrapolation across doses, routes, populations, and species. Figure 2.4 illustrates the structure of a typical whole-body PBPK framework.

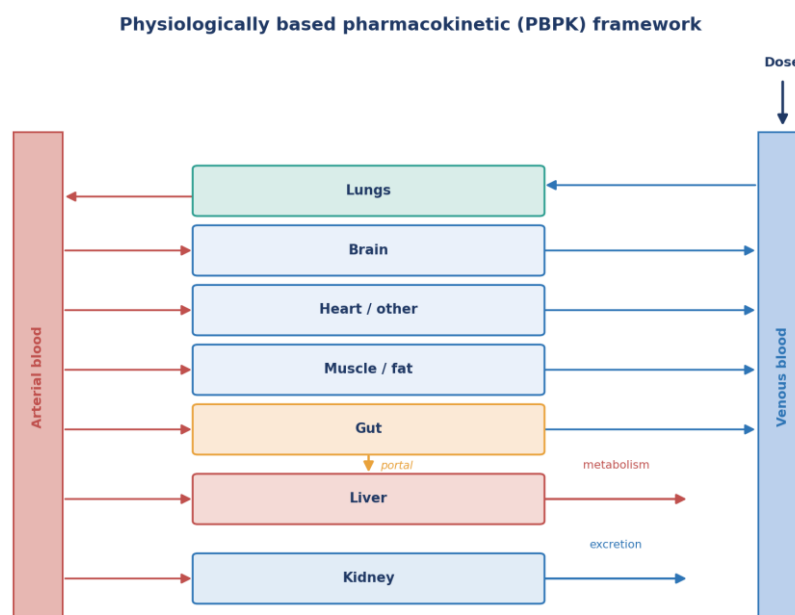


Figure 2.4. A whole-body physiologically based pharmacokinetic (PBPK) framework, in which organs are connected by arterial and venous blood flow, with hepatic metabolism and renal excretion as routes of elimination.

PBPK modeling has become a mainstream tool in drug development and regulatory science, applied to predict drug–drug interactions, to support dosing in special populations such as children and patients with organ impairment, and to inform first-in-human dose selection [22,24]. For delivery science it offers a route to predicting how formulation-dependent changes in absorption and distribution propagate to systemic and tissue exposure, and emerging models increasingly incorporate the behaviour of nanocarriers and the physiology of target tissues. As computational power and biological data continue to expand, PBPK and related quantitative systems approaches are expected to play a growing role in the rational design and regulatory evaluation of advanced delivery systems [24,34].

2.16 Dose Optimization and Therapeutic Window Management

Dose optimization is the integrating objective toward which the principles of this chapter converge: the selection of a dose and dosing regimen that maintains drug exposure within the therapeutic window for the required duration, maximizing efficacy while minimizing toxicity. This requires the joint consideration of the drug's pharmacokinetics, its concentration–effect relationship, the variability among patients, and the capabilities of the delivery system [2,28]. For drugs with a narrow therapeutic window, even modest variability in exposure can have serious clinical consequences, and the precision afforded by advanced delivery becomes especially valuable.

Delivery technology contributes to dose optimization in complementary ways. Controlled-release systems narrow the fluctuation between peak and trough, keeping exposure within the therapeutic window with fewer doses; targeted systems raise the concentration at the site of action relative to the rest of the body, effectively widening the therapeutic window; and responsive systems adjust release to physiological need, as in glucose-responsive insulin delivery [25,28,30]. Increasingly, dose individualization guided by pharmacokinetic monitoring, biomarkers, and computational models aligns the delivered dose

with the characteristics of the individual patient, linking the biopharmaceutical foundations of this chapter to the precision-medicine themes developed throughout the volume [34].

In practice, dose optimization is increasingly achieved through model-informed precision dosing, in which pharmacokinetic models are combined with individual patient data—drug concentrations from therapeutic drug monitoring, organ-function markers, genotype, and demographics—to recommend an individualized regimen [22,34]. This approach is well established for narrow-window agents such as aminoglycosides, certain immunosuppressants, and some anticoagulants, and it is expanding as point-of-care measurement and computational tools mature. When coupled with delivery systems capable of administering individualized doses or adjusting release in response to physiological signals, model-informed dosing represents a convergence of biopharmaceutical science, delivery technology, and digital health toward the goal of therapy precisely matched to the individual patient.

2.17 Conclusion

The biopharmaceutical and pharmacokinetic principles surveyed in this chapter constitute the quantitative foundation of drug delivery science. The fate of a drug—its liberation, absorption, distribution, metabolism, and elimination—is shaped at every stage by physicochemical properties, physiological barriers, transporters, and metabolizing enzymes, and the resulting exposure determines the pharmacodynamic response within the bounds of the therapeutic window [2,9,11]. Delivery systems succeed precisely to the extent that they manipulate these processes in a controlled and predictable manner, whether by reshaping the temporal profile of exposure, redirecting biodistribution, or protecting a fragile molecule from premature loss [1,3].

Frameworks such as the Biopharmaceutics and Developability Classification Systems, in vitro–in vivo correlation, and physiologically based pharmacokinetic modeling translate these principles into rational, predictive design and increasingly underpin regulatory decision-making [4,17,24]. As delivery systems grow more sophisticated and as therapy becomes more personalized, the integration of biopharmaceutical understanding with computational modeling and biomarker-guided dosing will be central to realizing their full potential. The chapters that follow build on this foundation, applying these principles to the specific carrier platforms, enabling technologies, advanced modalities, and site-specific strategies that define the frontiers of modern drug delivery.

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Citation: Dr. G. Santhiya, Muthukumaran Mylasalam, *Frontiers in Drug Delivery: Emerging Technologies and Therapeutic Innovations, Biopharmaceutical and Pharmacokinetic Foundations of Modern Drug Delivery*, Genome Publication. 2026; Pp1-16. https://doi.org/10.61096/978-81-998875-6-5_2
