1
Introduction: The Why and How of Drug Bioavailability Research

Han van de Waterbeemd and Bernard Testa

Abbreviations

ADME	Absorption, distribution, metabolism, and excretion
EMEA	European Agency for the Evaluation of Medicinal Products
FDA	Food and Drug Administration (USA)
NCE	New chemical entity
PD	Pharmacodynamic(s)
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
R&D	Research and development

Symbols

AUC	Area under the plasma concentration versus time curve
CL	Total plasma clearance
C_{max}	Maximum plasma concentration in blood
F	Fraction of administered dose that reaches the general circulation
M	Amount of drug that reaches the general circulation
t_{max}	Time to reach C_{max}

1.1
Defining Bioavailability

1.1.1
The Biological Context

Before presenting and explaining the content of this book, it is necessary to ponder the concept of bioavailability, more accurately termed oral bioavailability.

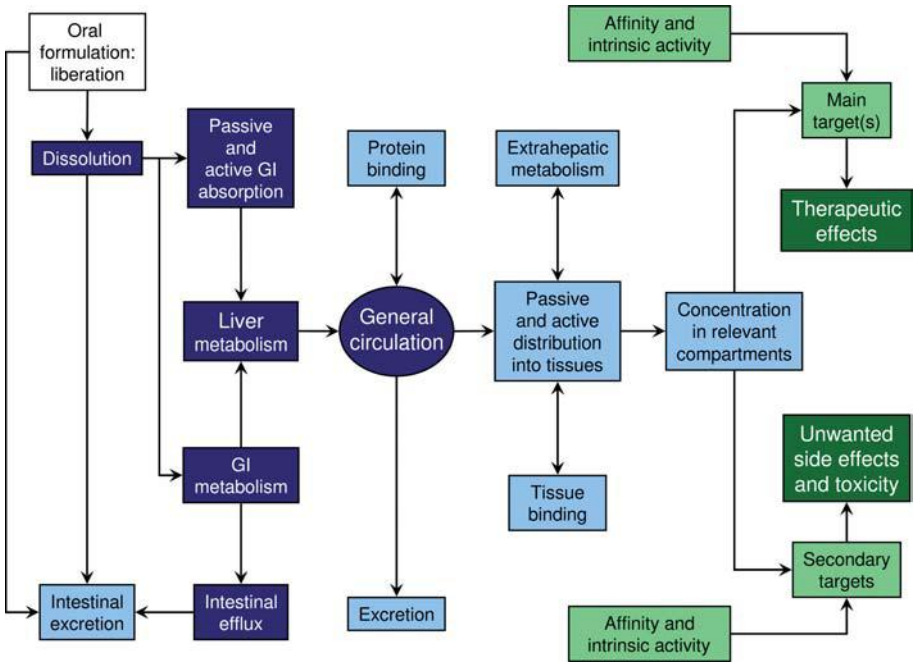

Figure 1.1 A schematic presentation of the fate of a drug in the body following oral administration. Pharmacokinetic processes are in blue, with the components of oral bioavailability in dark blue. Pharmacodynamic processes are in green, with the clinical effects in dark green.

As commonly defined, bioavailability implies the extent and rate at which a drug becomes available in the general circulation [1, 2].

After oral administration, a drug has to overcome a number of hurdles before reaching its sites of action. As schematized in Figure 1.1, a drug must

(a) be liberated from its pharmaceutical form (often a tablet);
(b) be dissolved in the gastrointestinal fluid;
(c) escape metabolism by the intestinal flora;
(d) be absorbed through the intestinal wall by passive and/or active (via transporters) permeation;
(e) escape metabolism in the gut wall;
(f) escape excretion in the intestine lumen by efflux transporters (mainly P-gp);
(g) escape metabolism in the blood while being transported to the liver via the portal vein;
(h) escape metabolism in the liver before reaching the general circulation from which it will be cleared by equilibration in tissues, excretion (mainly urinary), and metabolism (hepatic and extrahepatic).

For clarity, the obstacles a drug must overcome to reach the general circulation are shown in dark blue in Figure 1.1, while other pharmacokinetic (PK) processes are

in light blue. Pharmacodynamic (PD) processes are in green, with clinical effects in dark green.

1.1.2 A Pharmacokinetic Overview

In pharmacokinetic terms [3], bioavailability is described by two parameters, namely, the fraction of the administered dose (F) that reaches the general circulation (see Equations 1.1–1.3) and the rate of this transfer. When the drug is administered by the intravascular route, $F = 1$. When an extravascular route is used, for instance and most often the oral route, $F \leq 1$ due to the mechanisms of loss listed above. These mechanisms, particularly limited absorption (obstacles b, d, and f above) and metabolism (obstacles c, e, g, and h above), are called first-pass effects.

The fraction F of the administered dose that reaches the general circulation is calculated as (Equation 1.1)

$$F = \frac{M}{\text{dose}}, \tag{1.1}$$

where M, the amount of drug that reaches the general circulation, is obtained from Equation 1.2:

$$M = \text{CL} \cdot \text{AUC}. \tag{1.2}$$

In Equation 1.2, CL is the total plasma clearance, namely, the fraction of the volume of distribution cleared per unit of time, and is expressed in volume/time. AUC is the area under the concentration versus time curve and is expressed in (concentration)·(time). In other words (Equation 1.3),

$$F = \frac{\text{CL} \cdot \text{AUC}}{\text{dose}}. \tag{1.3}$$

As far as the rate component of bioavailability is concerned, it is estimated by two parameters, C_{max} and t_{max}. The maximum plasma concentration (C_{max}) is related to (a) total plasma clearance; (b) the fraction of dose that reaches the general circulation without being metabolized; (c) the rate of absorption; and (d) the rates of distribution and elimination . The time to reach C_{max} (t_{max}) depends on (a) the rate of absorption and (b) the rates of distribution and elimination.

After oral administration, bioavailability may be estimated by comparison with either the intravascular route, yielding the absolute bioavailability, or another pharmaceutical form of the drug by the same route, yielding the relative bioavailability.

1.1.3 Specific Issues

In a number of special cases, the above definitions of bioavailability are not directly applicable and singularly complicate the issue [4]. Thus, drugs having active metabolites present a special definitional challenge, particularly prodrugs (i.e., when most or all of the wanted effects are due to an active metabolite). Here, monitoring the

prodrug levels in the general circulation appears pointless due to presystemic metabolic activation. Monitoring the plasma levels of the active metabolite may be more informative, but again there are exceptions such as recent prodrugs designed to undergo *in situ* activation (see Part Five).

Another special case is that of racemic drugs in which all or most of the activity is due to one of the two enantiomers. In such a case, a stereospecific analytic method must be used to monitor the active enantiomer (known as the eutomer).

The thorniest issue with the definition of bioavailability is encapsulated in the question, "Bioavailability at the site of action?" Interestingly, both the Food and Drug Administration (FDA) in the United States and the European Agency for the Evaluation of Medicinal Products (EMEA) define bioavailability in almost identical terms, namely, "the rate and extent to which the active substance or active moiety is absorbed from a pharmaceutical form and becomes available at the *site of action* (italics ours)" [5, 6]. However, both agencies go on to recognize (but here their wordings differ) that in practice the bioavailability of oral medicines can be assessed by monitoring concentrations in the general circulation.

In other words, there are two determinants of a drug's therapeutic efficacy, namely, its intrinsic activity at a target and its bioavailability at the site of action. But given the frequent difficulty of defining that site of action (should it be defined at the organ, tissue, or cellular level?) and the frequent difficulty or impossibility (if only for ethical reasons) of measuring a drug's level at the site of action, the useful definition of bioavailability is indeed based on plasma concentrations. This is certainly the definition clinical pharmacologists work with, and it is the only meaningful definition for drug researchers engaged in drug discovery and development.

Why are bioavailability studies important to drug discovery? There are several good reasons to aim for highest feasible bioavailability in any oral drug project. Poor bioavailability in humans (<30%) results in erratic PK, making a compound difficult to dose to patients. High bioavailability is desired to stave off toxic effects because lesser amounts need to be administered, which also keeps the cost of drugs down.

How is bioavailability studied in drug discovery? Bioavailability is typically assessed *in vivo* in rats during the discovery phase. More advanced compounds (closer to be picked as clinical candidates) will also be studied in the dog and sometimes monkey. If rat and dog give similar results, the average can be used as a first estimate for bioavailability in man. If there is a large difference between the two species, it is better to understand the causes before deciding which of the two species best models humans. *In silico* predictions of oral absorption and bioavailability can help make a better decision and are indeed increasingly used in guiding projects to take the best candidates to the clinic.

1.2 Presentation and Layout of the Book

A few decades ago, pharmacokinetics, drug metabolism, and toxicology of selected clinical candidates were studied mainly during preclinical and clinical develop-

ment. In those days, the mission of medicinal chemistry was to discover and supply very potent compounds, with less attention to their behavior in the body. However, the R&D paradigm in the pharmaceutical industry has undergone dramatic changes since the 1970s and particularly since the mid-1990s, and is now better subdivided into drug discovery and development. A huge number of new chemical entities (NCEs) afforded by combinatorial chemistry and parallel synthesis are screened by high-throughput biological assays. These assays routinely include absorption, distribution, metabolism, and excretion (ADME properties) and ADME-related physicochemical properties (ionization, solubility, partitioning, and permeation).

As schematized in Figure 1.1, solubility, membrane permeation (passive and transporter-mediated), and metabolism are the main factors contributing to oral bioavailability, and hence are of special interest to drug researchers. Such are the focus and the audience of this book, whose first edition, published in 2003, met with considerable success and was reprinted four times [7]. However, progress in recent years has been so fast that the present edition became necessary and is fully updated in structure and content.

This book is organized into five parts according to the processes underlying oral bioavailability and the methodologies and technologies available to researchers. Thus and quite logically, Part One is dedicated to the physicochemical aspects of drug dissolution and solubility, with chapters presenting the industrial and clinical contexts and the prediction of aqueous solubility.

Part Two covers the physicochemical and biological methodologies to assess membrane permeability and oral absorption. Here, the reader begins with physicochemical principles and high-throughput technologies, and moves up the scale of biological complexity toward cell cultures, animal studies, and clinical investigations. As major determinants of bioavailability, transporters and metabolism deserve special attention (Part Three). Here again, biological background is covered explicitly, and so are specific technologies.

Part Four is dedicated to *in silico* tools, which have gained an irreplaceable significance in virtual experimentation by allowing medicinal chemists to predict physicochemical and ADMET properties of projected and existing molecules. Successive chapters present statistical tools, molecular properties, absorption, metabolism, and bioavailability predictions. The book ends with Part Five in which relevant issues in drug development are covered, namely, the biopharmaceutical classification system, prodrug strategy to improve bioavailability, modern biopharmaceutical strategies, and nanotechnologies.

With its logical structure and large number of chapters, this book aims at informing by providing data and examples, and instructing by presenting a conceptual and logical framework. As such, it presents an informative and didactic value even greater than that of the sum of its individual chapters. We do hope that the book will remain useful for many years and thank our contributors for their dedication and enthusiasm.

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