1

An Introduction to Biopharmaceutics

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1.1 Introduction

The aim of this chapter is to introduce biopharmaceutics and to define some key terms used within biopharmaceutics. It will also briefly introduce where biopharmaceutics sits in the drug development process.

1.2 History of Biopharmaceutics

The term **biopharmaceutics** was introduced in the 1960s by Levy [1]. The word originates from the combination of bio- from the Greek meaning relating to living organisms or tissue and pharmaceutics defined as the science of pharmaceutical formulations; in this case the living organism is the person (or animal being treated). In modern parlance, the term biopharmaceutics encompasses the science associated with the physical/chemical properties of the drug product (including all components therein) and the interactions of this product with parameters linked to the route of administration that affect the rate and extent of drug uptake or presence at the site for local action. It combines knowledge of materials science; physiology; anatomy and physical sciences.

In more simple terms it is everything that controls the availability of the drug: that is how the drug exits the dosage form and travels to the systemic circulation (for systemically

Biopharmaceutics: From Fundamentals to Industrial Practice, First Edition. Edited by Hannah Batchelor.

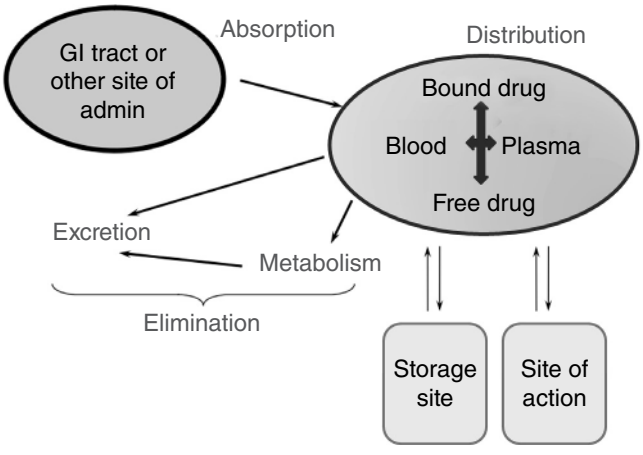

Figure 1.1 *Schematic of the fate of drugs once administered orally; biopharmaceutics relates to the absorption aspect of this image.*

acting drugs) or to the local site of action for locally acting agents. It provides a link between the formulation and the clinical performance of a drug; a mechanistic understanding of biopharmaceutics ensures that the formulation is optimised in terms of exposure. This is shown schematically in Figure 1.1 where biopharmaceutics is focussed on absorption.

The term biopharmaceutics can cause confusion; particularly with the advent of biopharmaceutical drug products. There is evidence in confusion in terminology back in the 1970s where efforts were made to standardise the terminology used [2]; these efforts defined biopharmaceutics in several ways according to the experts at the time of publication. The most widely used definition is, 'The study of the influence of formulation on the therapeutic activity of a drug product. Alternatively, it may be defined as a study of the relationship of the physical and chemical properties of the drug and its dosage form to the biological effects observed following the administration of the drug in its various dosage forms' [3].

An analysis of new drug approvals in 2019 (US, EU and Japan) showed that oral products represented the majority of approvals (50%) with tablets and capsules as the dominant oral dosage forms [4]. Thus biopharmaceutics has tended to focus on oral more than alternative routes of administration.

Historically biopharmaceutics was part of **clinical pharmacology** and **pharmaceutical chemistry**, only becoming its own scientific discipline in the 1970s. In scientific terms, the MeSH definition (MeSH [Medical Subject Headings] is the United States National Library of Medicine controlled vocabulary thesaurus used for indexing articles for PubMed) of biopharmaceutics (introduced in 1970) is, 'The study of the physical and chemical properties of a drug and its dosage form as related to the onset, duration and intensity of its action'. The MeSH term 'biopharmaceutics' being introduced in the 1970s provides an

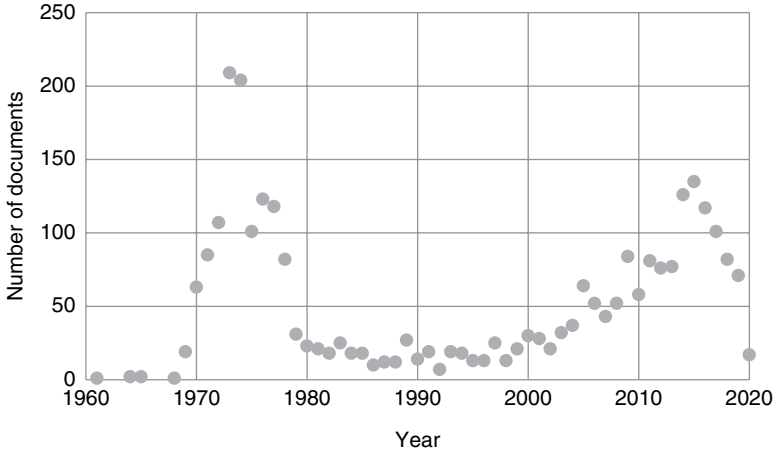

Figure 1.2 *Frequency of biopharmaceutics as a MESH terms in publications versus time. Source: Data from Pubmed.gov, November 2020.*

insight into the history of the topic; the scientific discipline existed long before but was previously listed in scientific data based under a bigger heading of pharmacology as:

- Chemistry, Pharmaceutical (1966–1969)
- Drug Compounding (1966–1969)
- Drugs (1966–1969)
- Pharmacology (1966–1969)

A search in PubMed of 'Biopharmaceutics' [Mesh] conducted in November 2020 resulted in 2725 retrieved documents with a peak in the early 1970s as the science of biopharmaceutics developed. There has also been a general trend of increased use of the term biopharmaceutics since the year 2000. This is shown in Figure 1.2.

There have been a number of key events in the history of biopharmaceutics and these are highlighted in Figure 1.3.

1.3 Key Concepts and Definitions Used Within Biopharmaceutics

There is a strong link between biopharmaceutics and **pharmacokinetics**. Pharmacokinetics measures the concentration of drug at a site in the body versus time. Understanding the biopharmaceutics will influence the pharmacokinetic profile observed. In particular, biopharmaceutics has a focus on the absorption phase of a drug as this is the phase where the dosage form design has influence over the pharmacokinetic profile. The metabolism and subsequent elimination and excretion are driven by the drug properties rather than those of the formulation used to administer the drug.

Pharmacokinetic studies provide information on drug concentrations (typically in plasma or blood) versus time; these studies can be used to demonstrate safety and efficacy of a drug as well as compare the relative performance of alternative dosage forms (for further

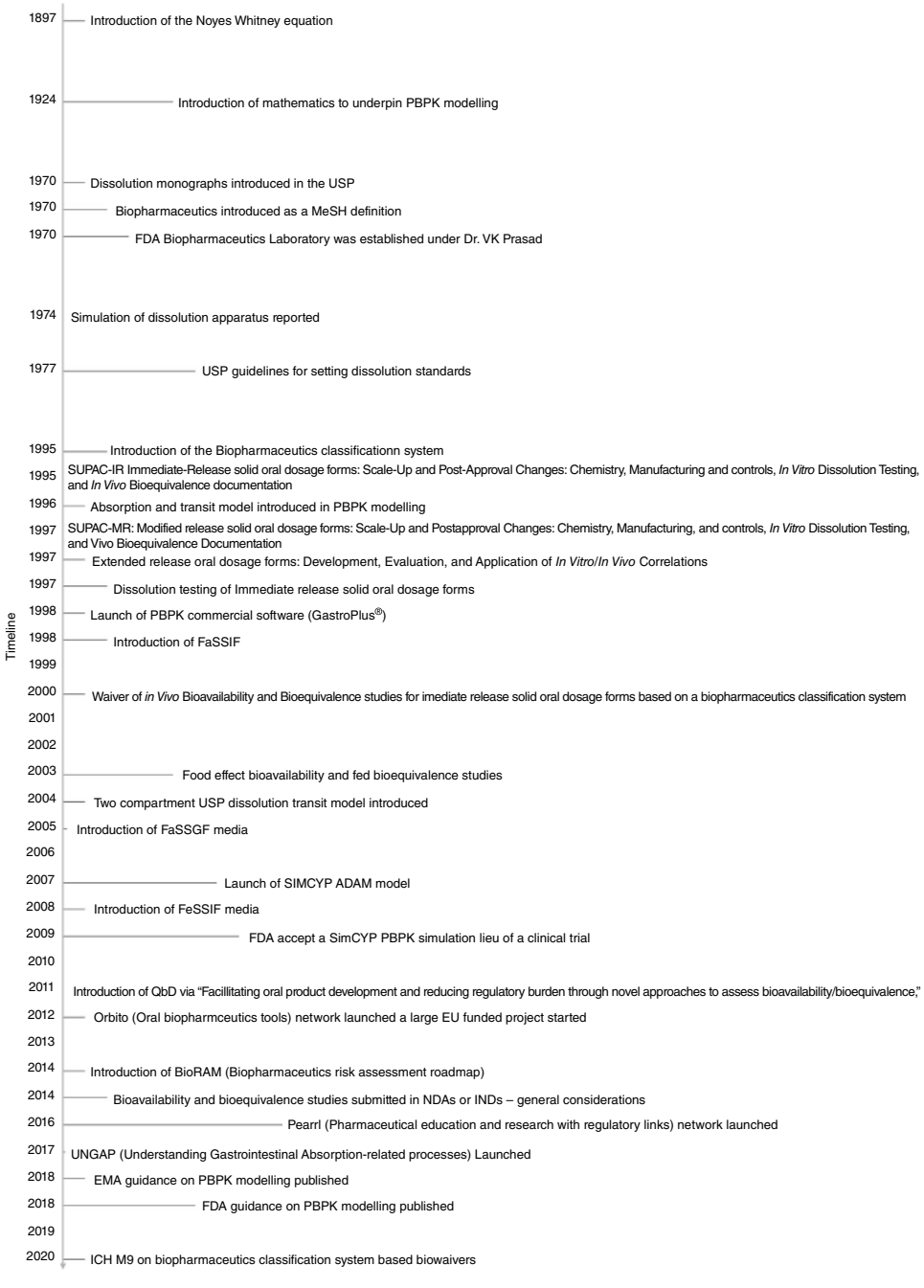

Figure 1.3 *Overview of the biopharmaceutics timeline of key events.*

details see Chapter 2). This performance can be by design, for example, to develop a sustained release product to alter dosing frequency. Generation of statistically similar pharmacokinetic profiles for alternative drug products provides reassurance that these medicines can be interchanged with limited effects on clinical efficacy. These statistically similar pharmacokinetic profiles show **bioequivalence** between drug products, this bioequivalence is discussed more in the chapter on regulatory biopharmaceutics (Chapter 10). This is of great importance for generic medicine development to ensure that medicines can be interchanged with not clinical impact to the patient.

Pharmacokinetic data can be analysed to demonstrate what fraction of the drug administered orally was measured within the system; this fraction is termed the **bioavailable dose**. It is recognised that not all drug administered will reach the site of measurement as some will be lost due to: localised degradation; failure to permeate membranes to reach the site of measurement; metabolism between site of absorption and site of measurement. Calculation of the **bioavailability** of a drug is important in dosage form design as it will influence the dose to be administered as well as the likelihood of reaching the target concentration at the site of measurement (and site of action). This can also be termed the **bioperformance** of a product.

The processes that influence the bioavailable dose are key to the science of biopharmaceutics. There is emphasis on the fraction of drug absorbed as this relates to the inherent drug properties and how they link with the dosage form as well as the site where absorption occurs. Formulation scientists can design dosage forms for a range of sites for administration and understanding how the **fraction absorbed** varies by site of administration is important for systemically acting drugs. **Absorption** can be complex and is not a single-step process; there are often several membranes or other barriers that lie between the site of administration and the site of measurement (or action) for a drug. The **permeability** (Chapter 5) of the drug across each of these barriers will dictate the fraction that can traverse the membrane. Measuring the fraction absorbed at each membrane is not possible and often there is a single point for administration and a single point for measurement which can complicate accurate determination of the fraction absorbed. This is exemplified in oral absorption of drugs. Drugs will enter the gastro-intestinal system where some of the drug will be solubilised and will traverse the intestinal membrane; however, there may be some metabolism at the intestinal wall meaning that not all the drug absorbed reaches the systemic circulation. Furthermore, the portal vein drains from the intestine directly into the liver where further metabolism is likely to occur again reducing the quantity of drug present in the systemic circulation. The site of measurement; typically a blood or plasma sample taken peripherally will only show the drug that successfully traversed the intestinal wall AND was not metabolised within the liver; therefore this is lower than the actual fraction of drug absorbed.

First pass metabolism is the term used to describe the fraction of drug lost between entering the portal vein directly from the intestine and existing the liver. This describes the fraction of drug lost during the first pass through the liver, prior to reaching the sampling site.

The oral route is the most common route of drug administration and as such much of this book will focus on oral biopharmaceutics; however there are chapters on alternative routes of administration (Chapter 14: Inhaled Biopharmaceutics; Chapter 15: Biopharmaceutics of Injectable Formulations and Chapter 16: Topical Bioavailability).

A key factor that influences the absorption of drug from the gastro-intestinal tract is the **solubility** (Chapter 4) of the drug within the intestinal fluids. The intestinal fluids are complex, affected by food and many other factors associated with ethnicity, disease and gender

(Chapter 13: Special Populations). Understanding the composition of intestinal fluids and replication of this for *in vitro* models is of huge interest to those working within biopharmaceutics. Due to the transit time within the intestinal tract, it is not just the solubility that is important but the rate of drug **dissolution** (Chapter 6) within the fluids present that will influence the rate and extent of drug absorption.

The **biopharmaceutics classification system (BCS)** (Chapter 9), introduced in 1995 by Gordon Amidon [5], sought to classify drugs based on their dissolution and permeability as these factors are fundamental in controlling the rate and extent of oral absorption. This system is still in use in regulatory science and has been extended to also look at the developability of drugs [6]. The BCS can also justify a **biowaiver**; this is a situation where the *in vitro* solubility and permeability data can negate the need for a clinical study to demonstrate bioequivalence, resulting in a large cost saving for those involved in development.

The major emphasis of research in biopharmaceutics is the development of *in vitro* and *in silico* model that predict how a drug will be absorbed *in vivo*. Thus the use of **biorelevant** models that replicate the physiology, anatomy and local environment within the gastro-intestinal tract (or other site of administration) are important. In particular, the use of **physiologically based pharmacokinetic (PBPK)** models (Chapter 12) that not only replicate the body but also provide indications on the population-based variability in drug absorption.

1.4 The Role of Biopharmaceutics in Drug Development

Drug development is a complex process that involves many scientists, a lot of money and at least 10 years. The process starts with target identification where chemicals are manufactured to 'fit' the receptor of interest and they are typically ranked by potency for that receptor. At this stage, there is little biopharmaceutics input. The next step is to evaluate the lead chemicals using **preclinical** models; this can be cell lines or animal models to determine whether the chemical is as potent *in vivo*. At this stage, some biopharmaceutics input is crucial as the drug may need to be formulated for administration to the animal model and may even be administered orally so the fraction absorbed can be measured. This often relates to the 'drugability' of the lead candidates; defined as the technical evaluation of whether a compound will be a commercially successful drug. Drugability here relates to the likelihood for sufficient and non-variable pharmacokinetic exposure.

Success in preclinical models will trigger **clinical evaluation** in humans. There are three phases of clinical trial prior to launch of a product: **phase 1** will measure safety and efficacy of a compound in healthy volunteers where possible; at this stage the bioavailable dose will be assessed. **Phase 2** studies explore the safety and efficacy of the drug in patients with the disease of interest. The product used for phases 1 and 2 is often different to the final commercial product as the dose is still to be defined. Thus there may be differences in the bioavailable fraction of each formulation administered that needs to be accounted for when interpreting the data and determining the dose. The term **bridging** is used to describe how any differences between formulations used in preclinical and clinical testing are managed during the clinical testing. **Phase 3** studies evaluate the efficacy and safety in a large patient population. Where possible the final commercial formulation will be used in phase 3 studies as these are **pivotal** to underpinning the evidence to justify the introduction of a

new product. Biopharmaceutics is integral to the phases of clinical testing as predictive models to understand absorption and consequences of bridging are critical to the success of the interpretation of clinical data.

In parallel to the clinical evaluation (phase 1, 2 and 3 studies) work will be ongoing to ensure that the **chemistry manufacturing and controls (CMC)** activities are on track. These CMC activities ensure that the product and manufacturing process meet the stringent regulatory requirements ensuring that a safe and high-quality product is available to the patient population. Any changes to the product or manufacturing process need to be understood, particularly if there are likely to be consequences to the patient; thus biorelevant predictive tests are of value in de-risking the development process. In addition to biorelevant tests, often **discriminatory dissolution testing** is required; this is a method that links to clinical data and shows where changes in the product (as a result of composition or manufacturing changes) are likely to have an effect on the clinical performance. These discriminatory dissolution tests are generated by links to *in vivo* clinical data; either using an ***in vitro in vivo* relationship (IVIVR)** or using the principles of **quality by design (QbD)**.

Regulatory approval of new products is essential. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (**ICH**) brings together the regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of drug registration. ICH guidelines include information on biopharmaceutics that are essential for the approval of medicines. Two guidelines are focussed on biopharmaceutics specifically: ICH M9 Biopharmaceutics classification system based biowaivers and M13 Bioequivalence for Immediate release solid oral dosage forms. Within the US the major regulatory agency is the **FDA** (Food and Drug Administration); the FDA have a Biopharmaceutics council within the centre for drug evaluation and research. This office is responsible for the generation, implementation and review of biopharmaceutics-related guidance, policies and practices. There are several biopharmaceutics specific FDA regulatory guidance papers issues that are critical to the approval of new drugs. Similar to the USA there are many global regulatory bodies where biopharmaceutics guidance has been issued including the **EMA (European Medicines Agency)** and the **Japanese Food and Drug Administration**. Recently the ICH M9 guidance has sought to align these where possible for the BCS classification.

Biopharmaceutics interfaces with several other scientific disciplines, this book aims to provide a background to biopharmaceutics and to showcase how knowledge can be applied to the efficient development of drug products. The level of detail in terms of biopharmaceutics knowledge of a drug and a drug product will increase during the drug development process. This is shown schematically in Figure 1.4.

Biopharmaceutics is an important scientific discipline, particularly for those developing new drugs. An understanding of biopharmaceutics aids in the design of appropriate drug candidates (Chapter 7) as well as optimised drug products (Chapter 8) to ensure that the drug is well absorbed from the site of administration. Clinical testing of drugs, from phase 1 to phase 4 clinical trials is expensive and time-consuming. Biopharmaceutics tests and knowledge are critical to de-risk changes in the clinical performance as a result of minor changes in the product and process used to manufacture the drug product used within these clinical trials. There is a strong relationship between biopharmaceutics and regulatory science during the development of drug products.

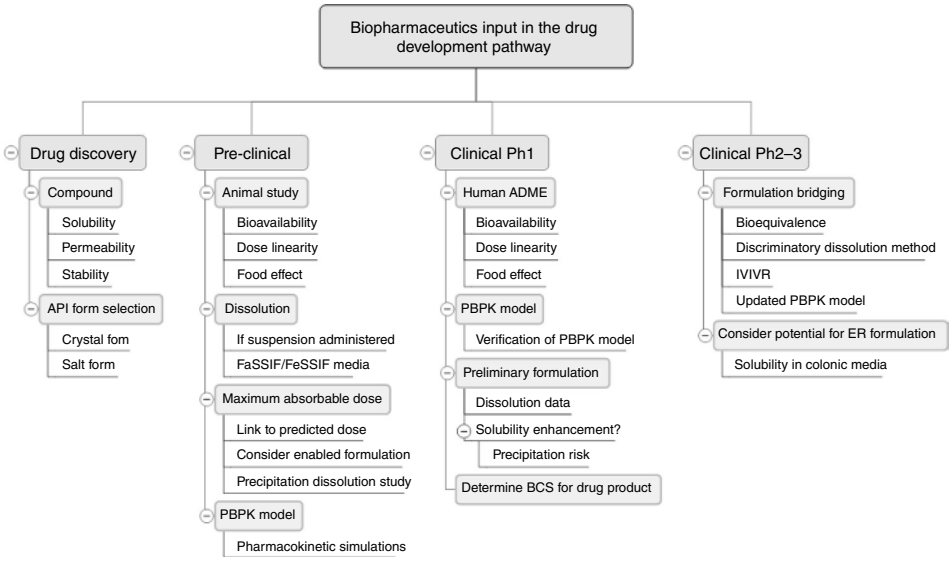

Figure 1.4 *Overview of biopharmaceutics input in the drug development pathway.*

1.5 Conclusions

Biopharmaceutics is a relatively new science that brings together knowledge on anatomy and physiology to understand the biological environment where drugs are absorbed with materials science to appreciate the drug and excipient related effects on these processes. This book brings together the knowledge required to better understand biopharmaceutics and to apply this knowledge in the development of drug products.

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