Part 1

Introduction

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1.1 Molecular biopharmaceutics

The goal of the present book is to describe aspects of molecular biopharmaceutics related to drug characterisation, drug delivery and dosage form evaluation of small active pharmaceutical ingredients.

Although molecular biopharmaceutics is a complex and developing academic scientific area, it is relevant to both industrial preformulation, formulation and preclinical scientists as well as chemical assessors within regulatory affairs. This book is primarily aimed at biopharmaceutical scholars and scientists within academia. However, we believe that employees in industrial pharmaceutical development as well as chemical assessors in pharmaceutical regulatory affairs may find the book valuable.

1.2 Important definitions and terms

Bioavailability is defined in this book as the rate and extent to which an active substance or moiety is absorbed from the pharmaceutical dosage form, and becomes available at its site of action (Food and Drug Administration (FDA), 2000; European Medicines Agency (EMEA), 2001).

Leads are defined as a series of structurally related chemical compounds that have shown interesting pharmacological activity and from which drug candidates may be selected. *Drug candidates* are defined as pharmacologically active compounds undergoing evaluation of their potential as future drug substances. *Drug substances* are defined as active ingredients within a dosage form. A drug candidate/substrate is together named as an *active pharmaceutical ingredient (API)*. A drug substance is,

however, first accepted as such when it is registered within a dosage form in a single country such as Japan, or in regions such as Europe or USA, according to respective national Japanese, central European or US regulations. Thus a drug substance is the API within a drug product which is registered as a specific dosage form. The final dosage form is defined as the *drug product*. The European and US regulations are administered by the EMEA and by the FDA respectively.

1.3 Experimental methods within molecular biopharmaceutics

Molecular biopharmaceutics encompasses the field of characterising, describing, evaluating, optimising and predicting bioavailability, and methods applied in this field are described in the book.

Experimental methods applied within molecular biopharmaceutics were initially taken primarily from physical chemistry and physiology but related to aspects of interest for studying steps of importance for bioavailability, namely drug absorption, distribution, metabolism and elimination (ADME). Thus, physicochemical and physiological phenomena, for example acid/base properties, solubility, partition, stability and permeability within physiologically relevant environments, and of relevance for ADME, are studied. Biochemical and molecular biology methods have also been employed over recent years to study ADME phenomena such as absorptive, metabolic, distributive and eliminative pathways as well as expression of endogenous enzymes and transporters of relevance to ADME. Thus, modern molecular biopharmaceutical science is interdisciplinary and methods applied in the field are also applied and relevant to industrial preclinical and (pre)formulation drug development. Regulatory authorities are focused on requiring not only experimental documentation based on physicochemical methods, such as dissolution and permeability studies, but also documentation based on biochemical and molecular biology methods. An example is studies of drug interactions with enzymes and membrane transporters (FDA, 2006; EMEA, 2008).

1.4 Classification of drug substances

Drug substances may be classified according to pharmacological or chemical properties or to routes of administration. Examples are the classifications ‘antidepressive’, ‘steroid’ or ‘ocular’ drug substances. However,

drug substances may also be characterised by their biopharmaceutical properties, for example based on physicochemical parameters of importance for ADME such as those described by Lipinski's rule of five (Chapter 2.4) or by the Biopharmaceutics Classification System (BCS). Recently, classification of drug substances, in the Biopharmaceutical Drug Disposition Classification System (BDDCS), has also been based on biochemical pathways such as metabolism and elimination pathways, as well as on substrate properties in relation to absorptive and/or exsorptive membrane transporters (Chapter 4.2).

These classification systems thus organise drug substances into categories with related properties, in contrast to the *European Pharmacopoeia* (Ph Eur, 2009) and the *US Pharmacopoeia* (USP, 2009) which simply organise drug substances by alphabetical order.

1.5 The book chapters

This book is divided into three main Parts – Parts 2, 3 and 4. In Part 2, methods of importance for physicochemical characterisation of drug substances and candidates are described. Chapter 2.1 focuses on how acid/base, solubility, lipophilicity and solid state properties of (pro)drug candidates and substances may be characterised. Chapters 2.2 and 2.3 respectively examine mechanisms and kinetics of drug decomposition. In Chapter 2.4, examples of chemical approaches to improving bioavailability are described and Chapter 2.5 presents examples of how physicochemical methods may be applied in industrial preformulation.

Part 3 concerns how membrane transport is studied. The first Chapter, 3.1, describes the structure and function of absorptive barriers. This is followed by Chapter 3.2, which examines the kinetics of passive diffusion-driven flux and permeability; next, Chapter 3.3 discusses the kinetics of carrier-mediated flux and permeability. Classification of human transporters is described in Chapter 3.4 and absorptive and efflux transporters are respectively described in Chapters 3.5 and 3.6. The last chapter, 3.7, gives examples of how transport studies are used in preclinical evaluation.

Part 4 presents ways in which bioavailability may be described and predicted from various molecular biopharmaceutical studies. Chapter 4.1 concerns how *in vitro* dissolution is studied and how it may be applied to predict bioavailability. Chapter 4.2 describes how BCS and BDDCS may be applied in the industrial pharmaceutical development process to predict bioavailability, and examines molecular biopharmaceutical methods of importance in this process. Part 4 ends with Chapter 4.3, which

describes and reviews how biosimulation of drug absorption may be applied in predicting bioavailability.

Enjoy!

References

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