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DRUG DELIVERY APPROACHES

PERSPECTIVES FROM PHARMACOKINETICS AND PHARMACODYNAMICS

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Preface

Drug delivery aims to enable appropriate drug absorption based on the physical and chemical properties, expected dose, and route of administration. For new chemical entities, drug delivery is initially expedient and adapts the dosage form of the active compound to the stage of development based on feedback from the iterative understanding of the pharmacokinetics (PK), pharmacodynamics (PD), and potential sources of variability of the candidate drug. In actual practice, the final formulation is often based at most on the determination of a dose response. Models combining physical and pharmacokinetic properties of a drug candidate with dissolution, in vivo studies, and known transporter and biomarkers have been shown to predict the time course of events successfully in vivo. To improve delivery of older chemical entities, whether controlled release, modified release, temporally or site-controlled delivery, development of a target pharmacokinetic profile to optimize efficacy for duration and/or to reduce adverse events is the starting and ending point for designing a dosage form.

This book discusses the options for drug delivery within the available routes of administration to achieve the target profiles and approaches as defined by these models. It is intended for use by graduate students and novice and skilled practitioners, who are developing either new or re-purposed drugs. In particular, this book should prove useful to pharmaceutical scientists and engineers, including formulators, pharmacokineticists, clinical pharmacologists, and those interested in the interaction of these disciplines.

This book begins with an appreciation of modeling of drug absorption and physiological effects and the use of pharmacokinetic and physiologically based models and follows with an introduction to physiological-based pharmacokinetics (PBPK). For the most common route of delivery, oral administration, there are chapters dealing with both PBPK and the multiplicity of options for oral drug delivery dosage forms. Endpoints that may substitute for measures of delivery or efficacy and rigorous skin permeation testing are discussed as targets for topical drug delivery and may have both development and regulatory applications. In the case of systemic transdermal delivery, understanding the pharmacokinetics of the formulation and the drug is essential to guide formulation from earliest conception throughout development. Separate chapters discuss the biological and delivery approaches to pulmonary and mucosal delivery. For emergency care settings, the relationship between parenteral infusion profiles and PK/PD is the key topic discussed. The book concludes with some more recent trends with chapters discussing virtual experiments to elucidate mechanisms and approaches to drug delivery and personalized medicine.

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1
Introduction: Utility of Mathematical Models in Drug Development and Delivery

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1.1 Introduction

Models, particularly mathematical models, have been widely used to understand different aspects of human lives for a long period of time. Mathematical models not only can help explain observations, but also aid in predicting outcomes of experiments. Models are frequently used in our daily lives. As an example, consider the following equation as a model:

$$\text{Distance} = \text{Speed} \times \text{Time}$$

Knowing the relationship between distance, speed, and time, we use the model to predict the time to reach our destination on a trip. Furthermore, we plan our daily lives by predicting the time it takes for a trip or a simple question of whether we will be on time for a meeting. For this well-established model, instead of performing the experiment of driving from point A to B to know how long it may take, we can have a good estimate of the time by knowing the distance of the destination is from us and how fast we expect to travel. Models can simplify our

experiments or even alleviate them. The powerful ability of models to predict outcomes of unknown experiments makes them an essential part of a wide range of modern industries, from aviation to auto to computer and financial entities. New airplane designs are tested less than a handful times in the air before large-scale production starts and they are in regular use. New car crash tests are performed in computer simulations before an actual prototype is crash-tested a few times. Models help advance product development at a faster rate and a fraction of the cost associated with actual experiments. It is not surprising that the use of mathematical models has gained widespread attention within the pharmaceutical industry and with regulators. With drug development being a lengthy and enormously expensive process, mathematical models have the potential of optimizing a therapeutic regimen, decreasing costs, and shortening the timelines significantly.

In this chapter, we describe a few mathematical models and their utility in drug development and provide examples of the use of these models in predicting clinical study outcomes or indicating possible causes of the observations, thereby helping researchers focus on areas that have the most impact on the development path of a drug. Within physiologically- based pharmacokinetic (PBPK) in regulatory submissions, only a small fraction, quoted as 6% of PBPK models, focused on drug delivery [1], whether it be food effects or issues in drug absorption. In some exceptional cases, the verification of the PBPK model was sufficient to avoid bioequivalence studies. In this chapter, we focus mostly on models of the drug delivery itself to design or select the target delivery profile or the dosage form itself. Other chapters throughout this book will provide more detailed descriptions of the principles of

developing mathematical models in the drug-development process and for the different routes of drug delivery.

1.2 Use of Mathematical Models in Drug Development

The relationship between dose and effect of a remedy must have been known to ancient healers, who often used mixtures of different herbs and other organic material at certain proportions to combat diseases. Despite significant changes to pharmacological intervention aimed at mitigation of symptoms and curing various diseases, drug-development goals today are strikingly similar: find the dose of a compound that provides the maximum desired effect while avoiding unwanted side effects. This central question of what dose (amount, frequency) is a major reason for late-phase, confirmatory clinical development programs [2]. In early stages of the modern pharmaceutical industry, the focus was on establishing a dose–response relationship. With advances in analytical chemistry to allow measurement of drug concentrations in blood, plasma, urine, or other body fluids, the focus has shifted to elucidating a concentration–response, or in broader form, dose–concentration–response relationships. This shift is logical as the larger observed variability in and the complexity of a dose–response relationship is reduced when investigating the concentration–response. Furthermore, concentration measurements offer the possibility to follow the temporal changes of drug concentrations, thereby providing a tool to understand the time course of the pharmacological effect of a compound. Mathematical models that could describe the time course of drug concentrations were first proposed in late 1930s [3,4]. However, due to the complexity of models required and the lack of computers, only models solved by analytical

solutions could be developed. The perceived complex underlying mathematics resulted in the utility of mathematical models not being appreciated by the medical community. Introduction of physiologically related parameters such as clearance during 1970s made it easier for the medical community to understand and appreciate these models by relating them to the biology of the disease and the pharmacology of the treatment [5]. Furthermore, academic centers contributed to the advancement of general concepts of using mathematical models to describe the time course of drug concentrations in the body (pharmacokinetics, PK) and its effects (pharmacodynamics, PD) [6–8].

Mathematical models have two main functions: describing observations and predicting untested scenarios using simulations. Thus, models are modified when new experimental data becomes available. that are not consistent with the original model. The process of model development involves building simple models based on limited available data. This simple model is then used to guide the design of future studies. Once a new study is performed, the generated data are compared to the simulations by the model to test its validity. If the new data agree with the predictions of the model, the experimental data can be added to the data pool and re-estimate the model parameters using a larger data set. On the other hand, if the model was unable to predict the new data, the underlying assumptions or the model may be modified to include new insights gained through the new experiment. This cycle of learning and testing is an essential part of the model development process and is routinely used in drug development [9,10]. Early development programs of a new drug can be more efficient by developing and enhancing the relevant models, allowing for more accurate and reliable design and prediction of clinical studies.

1.3 Noncompartmental Analysis

Although generally not considered as mathematical modeling, noncompartmental analysis (NCA) of a drug's plasma concentration data over time adds substantial understanding of its PK properties and is therefore briefly described here.

NCA refers to estimating various PK parameters of a compound through simple analysis of its concentration–time profiles at a biological fluid (most commonly plasma), where drug concentrations have been measured. Although the same principles are used when other body fluids, e.g. blood or saliva, are used, in this chapter we will refer to plasma drug levels, the most widely used sample collection medium. Figure 1.1 shows the concentration–time profile of losmapimod, a p38 mitogen-activated protein kinase inhibitor, after intravenous (i.v.) and oral (p.o.) administrations [11]. Since the entire administered dose of the drug is available to the body after an i.v. dose, the bioavailability equals 100% or 1 after an i.v. administration. After a p.o. administration, part of the drug may not reach the systemic circulation due to various reasons: it may degrade in the intestinal tract; it may not be fully absorbed; or drug molecules may be metabolized by enzymes in the gut wall or liver before reaching the circulation. Therefore, the bioavailability of the drug may vary from 0 (not at all bioavailable) to 1 (fully bioavailable). Losmapimod in Figure 1.1 has a bioavailability of 0.62.

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