CHAPTER 1

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Drug Delivery: An Evolving Concept

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CHAPTER OBJECTIVES

Upon completing this chapter, the reader should be able to

- Recognize the factors impacting drug discovery and development in pharmaceutical industry.
- Understand the evolution of drug delivery concept.

CHAPTER OUTLINE

INTRODUCTION

Drugs play a vital role in the current era of contemporary medicine. The total revenue generated from the global pharmaceuticals, biotechnology, and life sciences industry is more than $1.1 trillion in 2011, with a compounded annual growth rate of 6.7% between 2007 and 2011. Among specific segments, pharmaceuticals and biotechnology markets account for $798 and $289 billion in revenues. Interestingly, the Americas region accounts for 46% of total revenues, representing the largest share of the global market. The large market size permits pharmaceutical and biotechnology industries to invest profoundly in research and development.

Despite escalating research and development budgets, drug development is slow, with a limited number of new drugs introduced, whereas a large number of drugs are going off patent protection. The real cost of developing a new drug is considered to be greater than $800 million. Such high cost is due to the fact that many drug candidates are dropped from the preliminary screening portfolio because of their unfavorable physiochemical and biochemical properties. Drug absorption is often limited by the presence of physiological (epithelial tight junctions), biochemical (efflux transporters and enzymatic degradation), and chemical (size, lipophilicity, molecular weight, charge, etc.) barriers. Another major factor in designing and developing new drugs is the difficulty of active molecules to reach their desired and intended targets.

FACTORS IN DRUG DEVELOPMENT

Attributing to the high cost of development process, pharmaceutical companies try to create a framework in which the lead molecules with minimal ambiguity proceed further. This framework involves the study of characteristics, properties, and qualities of the lead molecules and setting of acceptable ranges for further progression of the candidate. This framework is often termed as the "developability or druggability criteria" [1]. A range of acceptable characteristics allows for molecules with properties that may not be ideal but have a high probability of success to progress. The setting of druggability and developability criteria also depends on multiple factors of commercialization and scientific feasibility, described further below.

COMMERCIAL GOALS

Because the pharmaceutical industry is a commercial entity, the lead molecule being developed as a drug needs to be profitable. Therefore, the critical and minimum acceptable properties making up the developability criteria are based on what the market desires. This process involves input from commercial, marketing, and medical professionals on Medicare needs, potential market, and existing leading products for an indication. No drug can be commercially viable if it does not meet the criteria for optimum

therapeutic efficacy, good safety profile (sufficient therapeutic window), and minimal adverse effects. These factors should be the part of the developability criteria. If an agent already exists in the market with these properties, a new lead molecule may still be profitable if a large enough market exists and if the new molecule either improves the efficacy and/or the ease of delivery with a simpler therapeutic regimen.

CHEMICAL LIMITATIONS

Medicinal chemists led the early discovery of bioactive compounds during research and development. This initial process is carried out by random, high-throughput screening of compound libraries, by rational design, or both. The structures identified from these methods are then further modified and optimized. After the development of a small set of related lead molecules, the initial exploratory structure–activity relationship is developed that allows for further structural changes and for selecting the most active compound. The detailed structural analysis at this stage involves more factors, such as potential stability, solubility, interaction with metabolic enzymes, and permeability, to be included in the developability criteria. Commercial aspects also may be involved, such as the novelty/patentability of the structure, scalability and the cost of industrial-scale synthesis, and the potential environmental safety issues related to production.

IN VITRO AND *IN VIVO* EFFICACY STUDIES

Initially, *in vitro* testing is carried out to narrow down the number of lead molecules based on their efficacy. Although it is a good technique for initial screening, such testing does not always result in good *in vivo* efficacy. Hence, studying the drugs in an *in vivo* animal model is essential before it is introduced into human clinical trials. For a drug to be safe and efficient in humans, it needs to be tested in an appropriate animal model that represents complex human physiology and the epidemiology of the disease. Although a molecule may be efficient *in vitro* working in a particular mechanism, it may not work in humans because of the presence of a compensatory mechanism. Thus, an *in vivo* model that has all the biochemical, cellular, and physiological complexities of human systems can truly predict the actual efficacy of the drug candidate. Another important use of *in vitro* and *in vivo* testing is the calculation of pharmacokinetic parameters that may eventually be the critical factor that decides the overall success of a compound.

PHARMACOKINETICS AND DRUG METABOLISM

Drug metabolism and pharmacokinetics (DMPK) estimations are a very critical part of the drug development process and a main reason for high attrition rates [2]. The main goal of DMPK studies is to predict the absorption, distribution, metabolism, and excretion of the drug candidate in humans. The dose and dosing frequency, calculated as a part of the process, provide the optimum efficacy. DMPK studies are carried out in multiple animal models. However, allometric scaling and overall animal pharmacokinetics and metabolism data are applied to predict human parameters [3, 4]. A combination of *in vitro* and *in vivo* studies determines the important mechanistic parameters that regulate the pharmacokinetic profile of a drug. The lead compound with an optimized DMPK profile usually provides the highest probability of success.

Major pharmacokinetic drug parameters such as systemic bioavailability, maximum concentration achieved, time to achieve maximum concentration, and duration for which concentration is above minimum effective level are usually well correlated with the drug's efficacy and adverse effects [5]. The overall levels achieved are decided by multiple factors, such as site of administration, complexity of the dosage form, and rate at which the systemic circulation eliminates the active drug (total body clearance). Unless a rapidly acting drug is needed that has a short duration of action, usually a compound with low to moderate clearance is preferred [6].

Because oral dosing is the most common and convenient way to administer most drugs, the pharmacokinetic profile after oral dosing, including bioavailability, is a very important criterion. Additional pharmacokinetic parameters such as volume of distribution and elimination half-life are also important, and all these pharmacokinetic parameters should be calculated in different species. These results in combination with *in vitro* testing may be able to project human pharmacokinetics. Other major factors that control bioavailability and in turn the efficacy are interactions with drug-metabolizing enzymes [7, 8], efflux transporters [9, 10], and plasma proteins [11].

FINAL FORMULATION CHARACTERISTICS

Pharmacokinetic and pharmacodynamic studies should be carried out with a finished product. The crystalline state, salt form, and the presence of formulation excipients can lead to potential drug delivery and stability issues. These physiochemical properties and their eventual effects on drug delivery and pharmacokinetics should thus be a part of the drug developmental process. Aqueous solubility is one of the major drug delivery criteria, especially for orally administered drugs, because it is only the dose in the solution that can undergo the absorption process [1]. Indirectly, the crystal state of the drug is also an important factor that eventually affects both solubility and dissolution rates. The crystal state can also often determine the stability and the patentability of a molecule and hence is a critical developmental criterion. Similarly, the salt form of the molecule can also play a critical role in deciding the best solubility, dissolution rate, stability, and overall bioavailability [12].

Toxicological analysis is very important to the drug discovery and development process. The new molecules need to be tested for toxicities in both acute and chronic dosing because toxicological concerns are key factors in determining the developability of a drug and are a major cause of attrition. The factors essential for success of DMPK studies are also required for the toxicological studies, such as the selection of the appropriate animal models and suitable delivery systems and routes. Pharmacological and toxicological profiles should be studied for the active drug as well as its metabolites.

Although a single molecule in its native form may not be able to fulfill all the criteria of developability, the use of appropriate drug delivery techniques can often overcome these shortcomings. Selection of drug delivery technologies right from the early stages can lead to a more efficient and cost-effective drug development process.

DRUG DELIVERY

Since the evolution of the drug delivery concept in the 1970s, the field has advanced into an array of novel technologies that provide alternate routes of administration and/or sustained/controlled release for both novel and established pharmaceuticals. Pharmaceutical scientists increasingly depend on novel delivery technologies for successful product

development and performance. Drug delivery can be defined as the method or process of administering a pharmaceutical compound to achieve a therapeutic effect in humans or animals. This process may involve utilization of several approaches, formulations, technologies, and systems to facilitate drug at the target site.

Drug delivery is a concept heavily integrated with dosage form and route of administration. The active drug needs to enter the target cells to exert its therapeutic effect. During this process, however, a number of hurdles need to be overcome. The first step in this process involves dissolution of the active agent in aqueous media (**Figure 1-1**, step A). As previously mentioned, one of the major concerns with newly developed as well as many of the existing drugs is their poor aqueous solubility. It is estimated that up to 90% of novel drug development candidates potentially display poor aqueous solubility and are classified as class II or class IV compounds based on the Biopharmaceutics Classification System [13]. Several of these compounds have solubilities in the range of 1–10 μg/mL. Such low solubility often poses significant challenges for pharmaceutical formulators and scientists to develop dosage forms that allow sufficient absorption and improved bioavailability. A drug delivery scientist can enhance the solubility of hydrophobic drugs by fabrication of nanoparticles and nanomicelles and prodrug strategies. For example, the solubility and stability of macromolecules such as proteins can be enhanced by PEGylation and microencapsulation approaches while retaining their bioactivity.

The second step in this process is to facilitate the availability of drug at the target site (Figure 1-1, step B). Once a compound is in solution, it may be delivered throughout the body. Often, the drug is required only at the physiological site of action, and hence this extensive biodistribution may cause toxicity and unwanted side effects. Active targeting strategies, therefore, direct the drug to act only at the intended target site, thereby minimizing side effects.

The last step in this process is drug uptake by cells (Figure 1-1, step C). This step plays a very crucial role in gene delivery, which can only be successful when genes are delivered at the target site and effectively enter the target cells for expression. For most therapeutics, the ultimate bioactivity is achieved only after the active molecules are taken up by cells. Each of these steps is associated with challenges at every stage.

The drug delivery technology landscape is greatly competitive and rapidly progressing. New classes of pharmaceuticals and biologics (peptides, proteins, RNA, and DNA-based therapeutics) are stimulating the rapid advancement in drug delivery technology. These new drugs typically cannot be efficiently delivered by conventional means. Controlled and sustained delivery technologies are warranted to improve drug efficacy and reduce side effects. In addition to these technologies, targetability and localized delivery would drive any system to advance from bench to bedside. Most often, delivery devices and drugs are tightly coupled. Biotech and pharmaceutical companies all over the world are currently engaged in increasing the value their combinations of drugs and delivery devices and/or systems can gain in the marketplace. Because drug development can be a very long process, advanced development and technology portfolio plans must be related to current market requirements and value propositions over a decade or more into the future.

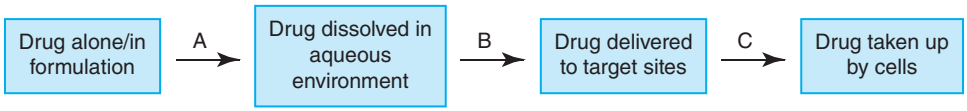

FIGURE 1-1 Fate of a drug in the body.

REVIEW QUESTIONS

1. No drug can be commercially viable unless it meets the minimum criteria of
   a. Optimum therapeutic efficacy
   b. Good safety profile (sufficient therapeutic window)
   c. Minimal adverse effects
   d. All of the above
2. The main goal of DMPK studies is to predict the _____ of the drug candidate in humans.
   a. Absorption
   b. Distribution
   c. Metabolism
   d. Excretion
   e. All of the above
3. The overall levels achieved by a drug in the body are *not* decided by which of the following factors?
   a. Site of administration
   b. Color of the formulation
   c. Complexity of the formulation
   d. Total body clearance
4. The salt form of the molecule can play a critical role in deciding the _____ of the drug.
   a. Solubility
   b. Dissolution rate
   c. Stability
   d. Bioavailability
   e. All of the above
5. Which of the following is the most common and convenient dosage form for most drugs?
   a. Intravenous
   b. Oral
   c. Topical
   d. Nasal spray
6. An ideal *in vivo* model should have all the _____ complexities of human systems.
   a. Biochemical
   b. Cellular
   c. Physiological
   d. Psychological
   e. a, b, and c
   f. All of the above

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