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FACTORS THAT IMPACT THE DEVELOPABILITY OF DRUG CANDIDATES: AN OVERVIEW

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1.1. ISSUES FACING THE PHARMACEUTICAL INDUSTRY

Drug discovery is a long, arduous, and expensive process. It was estimated that the total expenditure for research and development in the U.S. pharmaceutical industries

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was over $20 billion a year in the late 1990s, and this figure has been increasing. The average cost for every new drug (a new chemical entity, NCE) from research laboratory to patients is a staggering number: $400 to $650 million, and the whole process may take up to 14 years! Because of the high cost, there is tremendous pressure to maximize efficiency and minimize the time it takes to discover and bring a drug to the market. In order to do this, it is necessary to analyze the entire drug discovery and development process and identify steps where changes can be made to increase efficiency and save time. Analyzing the entire drug discovery and development process will help reveal where maximal improvements can be expected with some effort.

The entire endeavor of bringing a new drug from idea to market is generally divided into several stages: target/disease identification, hit identification/discovery, hit optimization, lead selection and further optimization, candidate identification, and clinical trials. Each stage has many aspects and components. A target is identified early in the discovery period, when there is sufficient evidence to validate the relationship between this target and a disease of interest. Tens of thousands of new compounds are then synthesized and screened against the target to identify a few compounds (hits) with the desired biological activity. Analogs of these selected compounds are then screened further for better activity and optimized in order to identify a small number of compounds for testing in pharmacological models. These efficacious compounds (leads) are further optimized for their biopharmaceutical properties, and the most drug-like compounds (drug candidate, only one or two) are then selected for further development. The drug discovery and development path, with emphasis on the discovery stages, is schematically illustrated in Figure 1.1.

![Figure 1.1](image-url)
Of those drug candidates with most drug-like properties, only about 40% make their way to evaluation in humans (Phase I clinical trial). Unfortunately, the historical average reveals an almost 90% overall attrition rate in clinical trials; in another words, only 1 compound makes it to market from among 10 compounds tested in humans. Results from another statistical analysis gave a similar success rates for NCEs for which an IND (investigational new drug) was filed during 1990–1992. This high attrition rate obviously does not produce the long-term success desired by both the pharmaceutical and health care industries.

In order to reduce the failure rate, it is necessary to analyze how and where failures occur. More than 10 years ago, Prentis et al. analyzed the cause of the high attrition rate based on data from seven UK-based pharmaceutical companies from 1964 to 1985. The results revealed that 39% of the failure was due to poor pharmacokinetic properties in humans; 29% was due to a lack of clinical efficacy; 21% was due to toxicity and adverse effects; and about 6% was caused by commercial limitations. Although not enough detailed information was available, it is believed that some of these causes are interrelated. For instance, toxicity or lack of efficacy can be caused by poor or undesired pharmacokinetic properties. With the understanding that most failure was not due to a lack of “biological activities” per se as defined by in vitro testing, there is a drive to incorporate the evaluation of the other major factors that may potentially precipitate developmental failures in the early drug discovery and candidate selection processes. This is intended to reduce the rate of late-stage failures, which is most costly. This point is further substantiated by the studies indicating that the major cost in drug discovery and development occurs at late stages. For example, in a $400 million total R&D cost, preclinical research costs probably account for only tens of million dollars, whereas clinical studies cost hundreds of millions of dollars (Figure 1.2).

![Total R & D Expenses](image)

**Figure 1.2.** Estimated annual expenses based on a hypothetical $400 million total R&D expense for the development of a NCE within a nine-year period (launch in 10th year). Data from Drews, J. and Ryser, S. (1997).
Another factor that is fueling the movement for early integration of multiple disciplines in the drug discovery and development processes is the rapid development of chemical and biological sciences. The past decade has seen tremendous advances in both areas. Advances in combinatorial chemistry, molecular and cellular biology, high-throughput screening, and genomic research have provided both great opportunities and challenges to the pharmaceutical industry. With the rapid development in biological sciences, current interests in therapeutic targets are more focused on rational targets such as receptors, enzymes, and hormones with well-characterized structures and functions. New technologies such as combinatorial chemistry, automation in high-throughput screening, and better instrumentation in bioanalysis have also significantly accelerated the lead identification and discovery process for a given target. With these new technologies, large pharmaceutical research organizations are capable of synthesizing and screening several thousand compounds or more in a year or two to find potential drug candidates. These efforts typically result in the discovery of many lead compounds or potential candidates for a target in the drug discovery process. Then there is the question of how to pick a winner and how to minimize failures. This requires a thorough evaluation of all the factors that are known to affect the developability of a NEC at the early stages. These factors may include efficacy, pharmacokinetics, pharmacodynamics, toxicology, and drug-drug interactions based on the metabolism and substrate properties of certain transporters and enzymes, as well as physicochemical properties, many of which are related to drug delivery issues. For this reason, a drug discovery and development program is more like a symphony (not just a cross-functional action) of multiple sciences including chemistry, biology, toxicology, clinical science, and pharmaceutical engineering.

Under the pressure to reduce the cost and shorten the time needed to bring an NCE to the market, many major pharmaceutical organizations have undergone rapid and drastic changes in the past decade, both in terms of organizational structures and fundamental approaches, in order to develop an integrated approach to drug discovery and development. A conference entitled “Opportunities for Integration of Pharmacokinetics, Pharmacodynamics, and Toxicokinetics in Rational Drug Development” was the landmark event in this fundamental change in the pharmaceutical industry. A brand new concept, “ensuring developability,” was introduced and well accepted, which employs criteria for drug development throughout the entire drug discovery and development processes. Under the guidance of such criteria, a drug discovery and development team will not only maximize the chance of success by selecting the best developable drug candidate, but will also play off the failures faster and more cheaply.

The paradigm shifts mostly involve the integration of research activities in functional areas such as pharmacokinetics and drug metabolism, pharmaceutical development, safety assessment, and process chemistry into drug discovery and development process in the very early stages of discovery. The inputs from these functional areas, as well as those from clinical, regulatory, commercial, and marketing groups in the early stages, help to minimize costly mistakes in late stages of development and have become more and more important to the success of the
drug discovery and development process. Developability is an overall evaluation of the drug-like properties of a NCE. Many of the recent changes in the pharmaceutical industry have been driven by the concept of ensuring developability. These changes, that is, the integration of multifunctional areas in drug discovery and development, ensure that the NCEs of interest will be successful in every step toward the final goal.

Below is a brief introduction to the factors that impact developability and a discussion on why the examination of drug delivery issues is very important in helping to ensure the developability of a drug candidate.

1.2. FACTORS THAT IMPACT DEVELOPABILITY

In most pharmaceutical companies, many efforts have been made to create a clear framework for selecting compound(s) with minimal ambiguity for further progression. Such a framework is not a simple list of the factors that impact the quality of a drug-like molecule. This framework, which is more often referred as “developability criteria,” is a comprehensive summary of the characteristics, properties, and qualities of the NCE(s) of interest, which normally consist of preferred profiles with a minimally acceptable range. The preferred profile describes the optimal goal for selection and further progression of a candidate, whereas the minimum range gives the acceptable properties for a compound that is not ideal but may succeed. Molecules that do not meet the criteria will not be considered further. Such criteria cover all the functional areas in drug development. Some of the major developability considerations are briefly described in the following subsections.

1.2.1. Commercial Goal

It does not need to be emphasized that we are in a business world. Generally speaking, a product needs to be profitable to be viable. Therefore, early inputs from commercial, marketing, and medical outcome professionals are very important for setting up a projective product profile, which profoundly affects the creation of the developability criteria for the intended therapeutics. In general, this portfolio documents the best possible properties of the product and the minimum acceptable ones that may succeed based on the studies of market desires. These studies should be based on the results of professional analyses of the medical care needs, potential market, and existing leading products for the same, similar, or related indications. The following aspects need to be well thought out and fully justified before the commencement of a project: (1) therapeutic strategy; (2) dose form and regimen; and (3) the best possible safety profile, such as the therapeutic window, potential drug interactions, and any other potentially adverse effects. Using the development of an anticancer agent as an example for therapeutic strategy selection, one may consider the choice of developing a chemotherapeutic (directly attacking the cancer cells) versus an antiangiogenic agent (depriving cancer cells of their nutrients), or combined or stand-alone therapy. In deciding the optimal dose form and regimen,
one may consider whether an oral or intravenous (iv) formulation, or both, should be developed, and whether the drug should be given once daily or in multiple doses. The results of such an analysis form the framework for developing the developability criteria and become the guideline in setting up the criterion for each desired property. For example, pharmacokinetic properties such as the half-life and oral bioavailability of a drug candidate will have a direct impact on developing a drug that is to be administered orally once a day.

1.2.2. The Chemistry Efforts

Medicinal chemistry is always the starting point and driver of drug discovery programs. In a large pharmaceutical R&D organization, early discovery of bioactive compounds (hits) can be carried out either by random, high-throughput screening of compound libraries, by rational design, or both. Medicinal chemists will then use the structural information of the pharmacophore thus identified to optimize the structures. Chemical tractability needs to be examined carefully at the very beginning when a new chemical series is identified. Functional modifications around the core structure are carefully analysed. After the examination of a small number of compounds, the initial exploratory structure–activity relationship (SAR) or quantitative SAR (QSAR) should be developed. Blackie et al. \(^{16}\) described how the establishment of exploratory SAR helped the discovery of a potent oral bioavailable phospholipase A\(_2\) inhibitor. In this example, numerous substructural changes were made, leading to the most active compounds; this is normally done in parallel with several different chemical series. For medicinal chemists, it is important that many different SARs are considered, developed, and integrated into their efforts at the same time, providing more opportunities to avoid undesirable properties unrelated to their intended biological activities. Such factors, again, may include potential P450 inhibition, permeability, selectivity, stability, solubility, etc.

Structural novelty of the compounds (i.e., can this product be patented?), complexity of synthetic routes, scalability (can the syntheses be scaled up in an industrial way?) and the cost of starting materials (cost of goods at the end of the game), and potential environmental and toxicity issues will all need to be closely examined at early stages of the drug discovery and development processes. It is never too early to put these thoughts into action.

1.2.3. Target Validation in Animal Models

Although drug discovery efforts almost always start with \textit{in vitro} testing, it is well recognized that promising results of such testing do not always translate into efficacy. There are numerous reasons for this to happen, some of which are well understood and others that are not. Therefore, target validation in animal models before clinical trials in humans is a critical step. Before a drug candidate is fully assessed for its safety and brought to a clinical test, demonstration of the efficacy of a biologically active compound (e.g., active in an enzyme binding assay) in
pharmacological models (in vivo, if available) is considered a milestone in the process of discovering a drug candidate. Many cases exemplify the challenges and importance of pharmacological models. For example, inhibitors of the integrin receptor αvβ3 have been shown to inhibit endothelial cell growth, which implies their potential as clinically useful antiangiogenic agents for cancer treatment. However, the proposed mechanism did not work in animal models, although compounds were found to be very active in vitro. What has been recognized is that the integrin receptor αvβ3 may not be the exclusive pathway on which cell growth depends. Its inhibition may induce a compensatory pathway for angiogenesis.

Ideally, an in vivo model should comprise all biochemical, cellular, and physiological complexities, as in a real-life system, which may predict the behavior of a potential drug candidate in human much more accurately than an in vitro system. In order to have a biological hypothesis tested in the system with validity, a compound has to be evaluated in many other regards. Knowing the pharmacokinetic parameters such as absorption, distribution, and metabolism in the animal species that is used in the pharmacological model is critical. Showing successful drug delivery in an animal model serves as an important milestone.

The pharmacokinetics/pharmacodynamics relationship, systemic and tissue levels of drug exposure, frequency of dosing following which the drug may demonstrate efficacy, and the strength of efficacy are very important factors that may affect further development of an NEC. They are all directly or indirectly related to drug delivery.

1.2.4. Pharmacokinetics and Drug Metabolism

Pharmacokinetics and drug metabolism are more often abbreviated as DMPK. The importance of DMPK in drug discovery and development practices is reflected in the statistics of the attrition rate. Most of the changes in the pharmaceutical industry during the past decade occurred in DMPK and related fields. The overall goal of DMPK in drug discovery and development is to predict the behavior of a drug candidate in humans. Nevertheless, the focus could be different at different stage of the process. Pharmacokinetics (PK) parameters in animal species that will be used in pharmacological (as noted briefly in the previous paragraph) and safety assessment models provide very important insights (systemic and tissue exposures) for those studies. The results of PK studies in several animal species generate the data for physiologically based models or allometric scaling to predict the basic pharmacokinetic behavior of a compound in humans. Assays using human tissues, cells, and genetically engineered cell lines provide a tremendous amount of information before the real clinical studies begin. Optimizing DMPK developability factors is immensely beneficial for finding the candidate with best potential for success.

The desirable (or undesirable) biological effects of a drug in vivo normally are directly related to its exposure. One of these factors, namely, the total systemic exposure, maximum concentration, or duration of the concentration above a certain
level, is usually used as a parameter that is correlated with the drug’s efficacy and adverse effects.\(^{23}\) The exposure at a given dose is governed by (1) the ability of the body to remove the drug as a xenobiotic and (2) the route by which the drug is delivered. Blood or plasma clearance is often used as a measure of the ability to eliminate a drug molecule from the systemic circulation. A low to moderate clearance molecule is desirable in most situations unless a fast-action, short-duration drug is needed.\(^{24}\)

A drug can be directly introduced into the systemic circulation by several methods. However, for convenience and many other reasons, oral dosage forms are preferred in many situations. Therefore, oral bioavailability of the compound is one of the very important developability criteria for oral drug delivery. Many factors affect the oral bioavailability of a drug. These factors will be discussed in detail in several chapters. In addition to clearance and bioavailability, other major pharmacokinetic parameters also should be evaluated.

Volume of distribution is a conceptual pharmacokinetic parameter that scales the extent of a drug distributed into the tissues. A well-known parameter, elimination half-life, can be derived from clearance and volume of distribution. It is a very important developability criterion that warrants the desired dose regimen. It should be noted here that half-life must be discussed in the context of a biologically relevant concentration. A purely mathematically derived half-life is sometimes biological irrelevant. Some more definitive explanations and comprehensive discussion of the major pharmacokinetic parameters and their biological relevance have been extensively reviewed.\(^{25,26}\) These parameters should be examined across several different preclinical species to predict the behavior in humans. The DMPK topics will be discussed in Chapters 5 and 6.

Inhibition and induction of drug-metabolizing enzymes,\(^{27,28}\) P-glycoprotein (P-gp) substrate property,\(^{29,30}\) plasma protein binding and binding kinetics,\(^{31,32}\) and metabolic stability in the microsomes or hepatocytes from different species including humans,\(^{33}\) as well as the metabolic pathway and the metabolite identified,\(^{34}\) are all very important developability measurements in the assessment of safety, potential drug-drug interaction, and predictability. These factors need to be optimized and carefully examined against developability criteria. Drug metabolism–related issues are outlined and discussed in Chapter 5. The impact of the transporter, including the efflux transporter in drug delivery and the models used to study and address the issues, will be discussed in Chapters 18, 2, and 3.

### 1.2.5. Preparation for Pharmaceutical Products

Before the early 1990s, the solid state, salt form, aqueous solubility, and dosing formulation for agents used in pharmacological, pharmacokinetic, and toxicological studies were not of major concern. However, an inappropriate salt version or solid form may cause potential drug delivery and stability problems (both physicochemically and chemically) during formulation and pharmaceutical engineering. It is now understood that the investigation of the physicochemical properties of an NCE against developability criteria should start early in the R&D processes.
Chapter 4 discusses the physicochemical properties that have a major impact on drug delivery.

Aqueous solubility is one of the most important physicochemical properties. It is believed that a drug has to be in solution to be absorbed.\textsuperscript{35} From the pharmaceutical development point of view, the solid state form is another important factor that affects solubility, the dissolution rate, and eventually developability. The solid state form is the determinant of, to some extent, physicochemical stability, intellectual property, and formulation scalability; this factor should be carefully examined and optimized. Change in crystallinerity from different chemical processes, in some cases, results in a big difference in bioavailability when the drug is delivered by a solid dosage formulation.

Many of these properties could change when the salt version and form change. The salt with the best solubility, dissolution rate (which therefore could result in the best bioavailability if given as a solid dose), stability, and other properties such as moisture absorption should be selected before a molecule enters full development.\textsuperscript{36} \textit{In situ} salt screening is a new technology used to select the right salt form for a drug candidate.\textsuperscript{37} For instance, the HCl salt\textsuperscript{38} was formerly almost the default version for a weak base; however, it has been shown in many cases not to be the best.\textsuperscript{39} Application of these screening processes in early drug development is one of the major steps in integrating pharmaceutical development into drug discovery and development.

Preclinical safety assessment (toxicology) is another functional area, which serves as a milestone in drug discovery and development. The NCEs have to be evaluated for their potential genetic toxicity, as well as for acute, short-term, and long-term toxicity. The results are crucial for further development of the compound. Although the principle and importance of toxicology will not be discussed in this book, many efforts in DMPK and pharmaceutics are made to assure drug delivery in the animal models used in toxicological studies. Metabolic profiles of a drug candidate in the species used in the toxicology studies should be compared with those from human tissues for major differences. The profiles are also examined for potential active/toxic metabolite(s). The factors that have an impact on drug delivery will be extensively discussed in the following chapters.

Process chemistry is a large functional area that can have major impacts on a drug’s developability, but it will not be covered in this book. Although the developability criteria in this area will not be discussed here, it is important to point out that quite often collaboration with process chemists is also required early on in order to find the right salt and solid state form.

1.2.6. Remarks on Developability Criteria

The concept of ensuring developability in drug discovery and development represents an integration of all functional areas that impact the efficiency, success rate, and timetable of a drug’s development. Coordination of these multifunctional, interlinked, parallel, ongoing scientific and technological research activities is a new challenge to the management of a drug discovery and development enterprise.
DELIVERY FACTORS THAT IMPACT THE DEVELOPABILITY OF DRUG CANDIDATES

Figure 1.3. A simplified illustration of the involvement, collaboration, and interrelationship of different functional areas in a preclinical research and development organization. The bullet points summarize the major developability factors examined at different stages.

Figure 1.3 is a simplified scheme of the interrelationship of major functional areas and their roles in drug discovery and development.

1.3. DRUG DELIVERY FACTORS THAT IMPACT DEVELOPABILITY

Delivery of a pharmaceutical agent to the systemic circulation, and consequently to the site of action to produce a desired pharmacological effect, is the ultimate goal of drug delivery. The developability of a drug candidate from a drug delivery perspective has become the core of developability criteria in drug development. As discussed in the previous subsections, many other factors in developability criteria are closely related to drug delivery; this holds true from the research laboratory to clinical trials and from early discovery to postmarket development. In order to accomplish this task, one has to overcome numerous barriers that hinder drug delivery.

In a biological system, multiple mechanisms exist to protect the system from exposure to almost any foreign substance while preserving nutrient uptake. The physiological arrangement and the chemical and biochemical barriers associated with the physiological structures form the first line of defense. Any drug, delivered by any route, will almost certainly encounter some of these barriers before reaching at the site of action. These barriers, as well as their physiological and biochemical
functions and their role in drug delivery, will be discussed in detail in Chapter 2. The special situations related to drug delivery to the central nervous system (CNS) is covered in Chapter 3.

How a drug molecule interacts with these barriers is very much determined by the properties of the molecule. These properties are the physicochemical and biochemical characteristics of the molecule. In Chapter 4, physicochemical properties and their implications for formulation and drug delivery will be extensively discussed.

Pharmacokinetics and pharmacodynamics provide a general approach by allowing mathematical modeling of the interaction of a drug molecule with the entire biological system to predict drug concentrations in the systemic circulation and therefore providing a prediction of pharmacological responses. Better understanding of the system will allow a pharmaceutical scientist to utilize and manipulate the system for the purpose of drug delivery. Chapter 5 discusses the basic principles and topics in pharmacokinetics and pharmacodynamics. Approaches in drug delivery based on an understanding of pharmacokinetic principles are essential in pharmaceutical development.

Developability in drug delivery is an overall assessment of all important factors. Take oral drug delivery as an example. Solubility is important because a drug molecule has to be dissolved to be absorbed. Some lipophilicity is essential for the molecule to cross cell membranes by diffusion. In order to finally reach the systemic circulation, the molecule has to survive various chemical and biochemical attacks in the gastrointestinal system and the liver. A flow chart describing sequentially the factors that can impact drug delivery is illustrated in Figure 1.4. The order

![Flow chart](image)

**Figure 1.4.** The evaluation steps of various factors that impact the oral bioavailability of a drug candidate.
in which these factors are listed could also be the order of logical thinking when one plans to tackle an oral drug delivery problem. It can also be a reference point for other routes of delivery.

It is believed that the permeability and metabolic stability of a drug molecule are two major factors in drug delivery or in the prediction of a drug’s absorption\textsuperscript{41} when the molecule is in solution. Permeability can be further detailed by passive diffusion and transporter-mediated process. Metabolism of a drug molecule in the liver and intestine can be evaluated by \textit{in vitro} experimental methods. In many cases, \textit{in vitro} metabolism (intrinsic clearance) can be used to predict \textit{in vivo} metabolic clearance.\textsuperscript{42} Drug metabolism–related issues are discussed in depth in Chapter 6. It is obvious that when efflux transporters such as P-gp are involved, the predictability of \textit{in vivo} clearance using metabolic intrinsic clearance becomes uncertain.\textsuperscript{43} A more in-depth understanding of drug transporters and their function in combination with our knowledge of drug metabolism will help predict oral absorption.\textsuperscript{44,45} Transporter-related drug deliver issues, as well as \textit{in vivo} and \textit{in vitro} models used to address these issues, are discussed in the following chapters.

Although not discussed in detail in this book, in addition to parenteral (e.g., iv infusion) drug delivery, many other routes of drug delivery are developed for convenience, safety, specific targeting, and delivery of special agents. Most of the physiological and biochemical issues discussed in oral and CNS delivery can be extrapolated to the situations in other drug delivery routes. Knowledge of the physiological and biological barriers for each specific delivery route will help medicinal chemists to design drug candidates with optimal drug delivery properties or at least to avoid obvious problems. Prodrug approaches, utilization of metabolic activation to target a specific organ, and taking advantages of a substrate of specific transporters or carriers are some invaluable examples in modern drug delivery. Many of these issues are discussed in various chapters.

The aim of this book is to provide a basic understanding of the major issues in drug delivery. More detailed examination of various topics can be found in the references cited.

REFERENCES

REFERENCES


