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Review Article

A REVIEW: FACTORS THAT IMPACT THE DEVELOPABILITY OF DRUG CANDIDATES

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ABSTRACT

Development of a new chemical entity (NCE) is main aim of branch of drug discovery. But development of a new chemical entity is not an easy task. During the development of new chemical entity a lot of numbers of factors has to be considered to make the process effective, less time consuming and profitable. Some developability criteria are used for the development of new chemical entity. There are many factors which have their major impact on the developability of a drug candidate. This review article includes major factors which have very important role in developability of a drug candidate. Major factors includes; Commercial Goal, The Chemistry Efforts, Target Validation in Animal Models, Pharmacokinetics and Drug Metabolism, Preparation for Pharmaceutical Products, Drug Delivery Factors.

Keywords: New chemical entity, Pharmacokinetics, Drug metabolism, Animal models, Pharmaceutical products, Developability criteria.

INTRODUCTION

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 was over $20 billion a year in the late 1990s,' and this figure has been increasing.[1] 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,[2,3] and the whole process may take up to 14 years![4] 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.[5] 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.

Factors That Impact Developability

Commercial Goal

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.

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. 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 may include potential P_{450} inhibition, permeability, selectivity, stability, solubility, etc. Structural novelty of the compounds, complexity of synthetic routes, scalability and the cost of starting materials, and potential environmental and toxicity issues will all need to be closely examined at early stages of the drug discovery and development processes.

Target Validation in Animal Models

Although the drug discovery efforts almost always start with *in vitro* testing. 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 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. 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 NCE. They are all directly or indirectly related to drug delivery.

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.[6] Most of the changes in the pharmaceutical industry during the past decade occurred in DMPK[7] 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 and safety assessment models provide very important insights for those studies. The results of PK studies in several animal species generate the data for physiologically based models or allometric scaling[8,9] to predict the basic pharmacokinetic behavior of a compound in humans. Optimizing DMPK developability factors is immensely beneficial for finding the candidate with best potential for success.[10] 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.[11] 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.[12] 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. 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.[13,14] These parameters should be examined across several different preclinical species to predict the behavior in humans.. Inhibition and induction of drug-metabolizing enzymes,[15,16] P-glycoprotein (P-gp) substrate property,[17,18] plasma protein binding and binding kinetics,[19,20] and metabolic stability in the microsomes or hepatocytes from different species including humans,[21] as well as the metabolic pathway and the metabolite identified,[22] 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.

Preparation for Pharmaceutical Products

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. Aqueous solubility is one of the most important physicochemical properties. It is believed that a drug has to be in solution to be absorbed[23] 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.[24] In situ salt screening is a new technology used to select the right salt form for a drug candidate.[25] 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. 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). Process chemistry is a large functional area that can have major impacts on a drug's developability,

Drug Delivery Factors

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 trails and from early discovery to post market 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, 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. 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 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. 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.[26] A more in-depth understanding of drug transporters and their function in combination with our knowledge of drug metabolism will help predict oral absorption[27,28] 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. 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.

CONCLUSION

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.

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