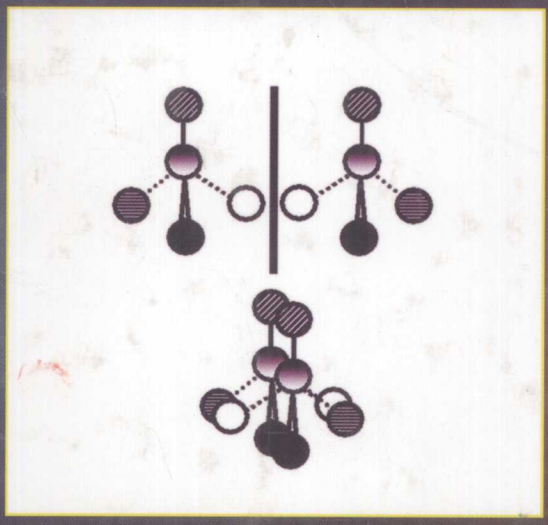
Chirality in Drug Design and Development



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CHIRALITY IN DRUG DESIGN AND DEVELOPMENT

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Foreword

The importance of stereochemistry in drug research and development as well as pharmacotherapy is well acknowledged. This is mainly due to a collective understanding of scientists involved in the area in the 1980s and 1990s. The main emphasis of the activities was on the potential therapeutic benefits of these new findings. Additionally, the industry was also exploring the intellectual properties involved. The potential benefit of developing stereochemically pure drugs from available racemates occupied many minds. This was thought to have two main advantages: first, the stereochemically pure drug was intuitively presumed to be superior to the racemate, particularly when beneficial effects were mainly attributable to one of the enantiomers; second, the development of the single enantiomer was to provide an opportunity to expand market exclusivity. In both instances, it was thought that the availability of the vast amount of data already generated from the use of racemate would facilitate the development of the enantiomer. In this context, the use of "bridging" data was an essential part of all discussions. The interest in the development of stereochemically pure drugs and the belief that they may provide safer and more efficacious alternatives to racemates resulted in the introduction of guidance by many regulatory agencies. In some of these guidance documents, sponsors of racemic drugs were required to provide convincing data as to why the racemate and not the enantiomer was being developed. This clearly reflected the belief of the time that the single enantiomer was intuitively superior to the racemate, a notion that, with a few exceptions, has not been supported with many robust clinical data. While the belief of superiority of single enantiomers was the motive behind a great deal of activity, the potential complication involved in stereochemically pure drugs was, for some time, a deterrent in choosing chiral molecules for development of new medicinal products. The term "stereophobia" has been used to reflect the feeling of the time.[1] Now that the dust has settled, we can say that the single enantiomer does not necessarily provide a better alternative to the racemate. Indeed,

except for a few examples, the effort put into development of single enantiomers to switch from racemic drugs has been found to be fruitless for many reasons including lack of clinically significant therapeutic advantages and overestimation of the value of the bridging data. Thus, the interest in developing single enantiomers of racemic drugs has subsided over the years. It follows that the opportunity to generate robust clinical data comparing enantiomers with racemate no longer exists since new chiral molecules are likely to be developed as stereochemically pure drugs.

Whether the emergence of regulatory guidance and the resultant stereophobia prevented development of useful racemic drugs is hard to discern. Nevertheless, presently the stereochemical considerations in drug action and disposition are well recognized in all steps of research and development. In addition, the emergence of more sophisticated chiral separation and synthesis techniques has helped to eliminate the stereophobia of the 1980s and 1990s.

Stereochemistry of the molecule must be carefully considered in all fields of pharmaceutical sciences ranging from discovery to the bedside. An understanding of the role of chirality in the properties of the molecule of interest is undoubtedly a main key to the rational process of developing as well as clinical use of chiral drugs. Keeping in mind the issue of "racemate versus single enantiomer" during various steps of drug discovery and development may save money and time.

Physicochemical properties of a racemate may be drastically different from the enantiomers depending on the nature of the former.[2] Chirality may also influence drug delivery because a single enantiomer or a non-racemic blend may have improved solubility, dissolution, and stability (see Chapter 1). In addition, many available pharmaceutical excipients (e.g., cellulose and its derivatives) either naturally occur as single enantiomers or are derivatives of the latter chiral molecules. These stereochemically pure molecules may interact with other chiral molecules (i.e., the active ingredient) and form stereoisomers. The latter will have physicochemical properties different from the original chiral molecule (see Chapter 2). For example, the presence of heptakis(2,6-di-O-ethyl)-beta-cyclodextrin results in stereoselective dissolution of tiaprofenic acid.[3] While this stereoselective release did not result in stereoselective bioavailability, it highlights the potential implication of the effect of chirality on physicochemical properties of drugs.

Similar to the solid dosage forms containing chiral excipients, biological membranes may provide chiral environments (see Chapter 3). Most drugs cross the gastrointestinal membrane through simple passive diffusion; thus, no stereoselectivity in the process is expected. It appears,

however, that stratum corneum possesses chiral discrimination properties. Indeed, in vitro data indicate significant stereoselectivity in skin penetration of ketoprofen and propranolol. In addition, preferential transport and bioavailability of racemic drugs has been achieved by administration of prodrugs (see Chapter 4). Although the therapeutic significance of these findings is not established, the available data point to their potential application.

The two main sources of stereoselectivity in drug disposition are the circulatory proteins and enzymes in both the gastrointestinal tract and the liver. Both binding of drugs to proteins and metabolism by various isozymes are, therefore, often stereoselective. Many examples of stereoselective systemic clearance and presystemic metabolism exist (see Chapters 6 and 7). For a few classes of drugs, metabolism may include chiral inversion (see Chapter 8). This, if unidirectional, adds to the overall stereoselectivity in disposition of drugs. Bidirectional bioinversion (see Chapter 8), on the other hand, similar to chemical racemization (thalidomide, see Chapter 5), may diminish stereoselectivity.

Enantiomers may interact with one another at both pharmacokinetic and pharmacodynamic levels.[4] One of the earlier and more interesting examples of such interactions was that of propoxyphene enantiomers.[5] The analgesic activity of propoxyphene is due mainly to the *d* enantiomer. However, at least in the rat, the racemate is more potent than an equimolar dose of *d*-propoxyphene due to a reduced clearance of the latter caused by the presence of *l* enantiomer in the racemate.

Use of stereospecific data in determination of bioequivalence between products of the same racemic drug has been the topic of many discussions (see Chapter 9). The issue, however, is mainly focused on relatively older drugs for which the approval of the brand product has been based on nonstereospecific data. More recent new drug applications, however, either deal with single enantiomers or contain stereospecific data. In the former case (single enantiomers), and in the absence of chiral conversion, stereospecific approaches become nonissues. However, if the approval of the brand name is based on stereospecific data, stereochemistry in bioequivalence should be considered. The regulatory agencies in various countries have provided guidance in developing safer and efficacious products of streochemically pure drugs or racemates (see Chapter 10).

Stereochemical aspects of drug action have been known for many decades. It is, however, only within the last couple of decades that emphasis has been placed on stereochemistry of drug disposition. The area that still needs far more attention is the effect of chirality on the physicochemical properties of drugs. Nevertheless, the present state of knowledge of the area

should assist us to provide better therapeutic interpretations and develop better drugs.

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Preface

The stereoisomeric composition of drug substances has become a critical issue in the development, approval, and clinical use of drugs. Over the past three decades, stereoselectivity in drug action and disposition has become a well-recognized consideration in clinical pharmacology and product development of chiral drugs. Although the initial focus of many investigations in this field was on implications of stereoselectivity for pharmacologic action and, later on, the pharmacokinetics of chiral drugs, more recently other aspects of chirality such as physicochemical properties and formulation issues have also been explored. Additionally, after much debate, the regulatory agencies have provided guidelines for the development and characterization of chiral drugs. However, the information currently available on many relevant issues of chirality, including the recent developments, though extensive, is still fragmented into various disciplines, making meaningful dissemination of knowledge difficult. This is especially important because today more than 50% of marketed drugs are chiral. Therefore, we took a multidisciplinary approach to create this volume so that it may be used as a reference book for the research community and pharmaceutical industries interested in this area or as an educational tool for medical and health-related practitioners.

The choice of developing a drug as a racemate or an individual enantiomer must be based on a sound and critical evaluation of chiral characteristics with respect to their pharmacodynamic, pharmacokinetic, and toxicological considerations. This book entails the relevant topics in chiral drug product development, including an overview of crystal structure and physical properties of chiral drugs, the interaction of chiral drugs with chiral excipients in formulation, pharmaceutical considerations in transdermal delivery, stereoselective drug delivery through a prodrug approach, pharmacokinetics and dynamics, and regulatory issues of chiral drugs with regard to product development. Recent developments in these areas such as the use of nonconventional ratios of isomers are also discussed.

This book serves as a comprehensive review of chirality with respect to biopharmaceutic, pharmacologic, pharmacokinetic, bioequivalence, and regulatory issues. Experts from academia, industry, and/or regulatory agencies have written all chapters of the book. Each chapter presents a detailed discussion of the implications of chirality in various interdisciplinary areas of drug development and integrates the knowledge from various applied areas. The last chapter presents a concise discussion of the "enantiomer versus racemate" debate and provides some regulatory perspectives and guidance on drug product development of chiral molecules. Further, a thorough and thoughtful foreword, from Dr. Fakhreddin (Mo) Jamali, a pioneering researcher in this area, sets the tone for this volume.

This book is targeted toward pharmaceutical scientists in academia and industry, pharmacologists, pharmacokineticists, toxicologists, and graduate students in various research-intensive programs who are dealing with any aspect of drug development for chiral drugs. It may also be adopted as a resource supplement in a graduate-level course.

We gratefully acknowledge our thanks to Dr. Fakhreddin Jamali, Dr. Philip Breen, and Dr. E. Kim Fifer for their helpful suggestions and editorial assistance. We also thank our families for their inspiration, support, and forbearance, which made this undertaking a pleasure.

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Chirality in Drug Design and Development

Contents

1

Effects of Crystal Structure and Physical Properties on the Release of Chiral Drugs

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1. INTRODUCTION

Chiral drugs are a subgroup of drug substances that contain one or more chiral centers. More than one-half of marketed drugs are chiral [1]. It is well established that the opposite enantiomer of a chiral drug often differs significantly in its pharmacological [2], toxicological [3], pharmacodynamic, and pharmacokinetic [4,5] properties. Therefore from the points of view of safety and efficacy, the pure enantiomer is preferred over the racemate in many marketed dosage forms. However, the chiral drug is often synthesized in the racemic form, and it is frequently costly to resolve the racemic mixture into the pure enantiomers. Currently, then, most chiral drugs, including some "blockbuster" drugs, such as fluoxetine hydrochloride (Prozac®) and omeprazole (Losec®), are still marketed as racemates. However, the recent trend is toward marketing more single-enantiomer drugs [6]. In addition, a "racemic switch," which involves the development of a pure enantiomer of a drug that is already marketed as a racemate, is actively pursued by many companies to improve its therapeutic efficacy and to extend patent protection [7]. The decision whether to market the racemate or the enantiomer of a chiral drug is mainly based on pharmacology, toxicology,

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and economics. From a pharmaceutical perspective, the physical properties of both the racemate and the enantiomer should be characterized in detail in order to develop a safe, efficacious, and reliable formulation, no matter whether the racemate or the enantiomer is chosen as the marketed form. Furthermore, the chirality of a drug will also influence the efficiency of delivery, which has not been well recognized in the pharmaceutical field. Many physical properties of a crystalline solid, such as density, solubility, dissolution behavior, stability, and mechanical properties, are governed by the crystal structure [8]. Knowledge of the relationship between the crystal structure and the physical properties, and their influence on drug release, may therefore provide a fundamental understanding of the property–delivery relationship. This chapter provides an overview of the physical characterization of chiral drugs with an emphasis on the influence of physical properties on the rate of drug release.

2. ENANTIOMERS, RACEMIC SPECIES (OR RACEMATES), AND DIASTEREOMERS

Molecular *chirality* is a concept that was derived historically from the distinction between the configurational isomers of asymmetric molecules, which was discovered by Pasteur and reported in 1894 [9]. Configurational isomers are compounds with the same molecular formula and the same substituent groups but with different configurations. The asymmetric center in configurational isomers is called the *chiral* center [10]. Configurational isomers, which are a subset of stereoisomers and also termed optical or chiral isomers, may be classified as enantiomers, racemic species (or racemates), and diastereomers. *Enantiomers* are pairs of configurational isomers that are mirror images of each other and yet are not superimposable. Each enantiomer is *homochiral*, meaning that all the molecules have exactly the same configuration. *Diastereomers* are pairs of compounds that contain more than one chiral center, not all of which are superimposable. Enantiomers behave differently only in a chiral medium, such as when exposed to polarized light or when participating in a chemical reaction catalyzed by a chiral catalyst, particularly an enzyme in the body. Diastereomers generally exhibit different physical properties, even in an achiral environment. An equimolar mixture of opposite enantiomers is termed a *racemic species* or *racemate*, and is *heterochiral*, meaning that the molecules have different chiralities. The word *racemate* has at least two different interpretations. Chemists reserve the term racemate for a racemic compound, discussed in Sec. 4, whereas pharmaceutical scientists generalize the term racemate, as in