

SECOND EDITION

Chemical Stability of Pharmaceuticals

A HANDBOOK FOR PHARMACISTS

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A Handbook for Pharmacists

Second Edition

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Chemical Stability of Pharmaceuticals

To the memory of Lloyd Kennon

Preface

Pharmaceutics instruction in the pharmacy curriculum provides pharmacists with (among other kinds of knowledge) a sound theoretical basis for understanding chemical kinetics and its uses in studying drug stability. This is a research application of kinetics in pharmacy, and it is entirely appropriate that the pharmacist be aware of the methods used (primarily in the pharmaceutical industry) to assess and control drug and dosage form stability. There is, however, another area of pharmacy in which a knowledge of kinetics can be usefully applied: this is the area of professional practice. Teachers of pharmaceutics have not been highly successful, it seems to us, in developing this application. The purpose of this book is to assist the pharmacist in applying kinetic methods and data to stability problems in professional practice.

The way from theory to practice is not always easy or obvious. Part One of this book treats the calculations, approximations, and estimates that are useful in practical situations. Part Two is a collection of selected drug-stability data from the literature. Although it is clearly not encyclopedic, this collection makes readily accessible to the pharmacist much of the information necessary to make pharmaceutical decisions about drug stability. It has been interesting to learn, in the several years since the first edition appeared, that research pharmacists in the pharmaceutical industry also have found the book useful, primarily because of the data presented in the stability monographs.

In this second edition the principal changes are a thorough revision of the chapter on oxidation, addi-

tion of a new chapter on solid-state stability, and a tripling of the number of stability monographs. Significant changes were also made in the treatment of industrial stability-testing requirements and protocols, and for this we acknowledge the assistance of Pradip K. Banerjee.

The monographs have been contributed by graduate students and faculty members in the pharmaceuticals areas of the University of Kansas, the University of Michigan, and the University of Wisconsin. The affiliation of each author is given, although in most instances the author will have left the institution to take a position elsewhere; should a reader wish to correspond with a monograph author, this can be done by addressing one of us at the appropriate school.

All monograph figures have been redrawn, most of them from published data, and all sources are cited. For the record, K.A.C. was responsible for Chapters 1, 3, and 4, G.L.A. for Chapters 2 and 7, and V.J.S. for Chapters 5 and 6. The camera-ready copy was prepared by the very able Linda Frei.

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of Pharmaceuticals**

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PART ONE

PRINCIPLES

CHAPTER 1

Introduction

A. STABILITY PREDICTION BY THE PHARMACIST

When a drug dosage form is altered (e.g., by dissolution, pulverization, or addition to other materials) or the environment of the drug is modified by changes in storage conditions, the stability of the drug may be affected. Although the pharmacist's formal education includes consideration of the basic chemical kinetics necessary to understand these pharmaceutical problems, their actual solution may be prevented by other factors. One of these factors is the inaccessibility of data on the drugs or dosage forms of interest. Another is the lack of "feel" for kinetic data in general and, in particular, the inability to make approximations when the necessary data are unavailable. This book addresses both of these problems. Since there are many detailed and more exact treatments of chemical kinetics (see later references), in this book we emphasize simple approximating expressions and qualitative insights. This we do without apology, since any person working with chemical kinetics always has approximate and qualitative ideas in mind as a rough guide to estimate or predict the results.

Part One deals with drug principles. Chapter 2 starts the main body of the text; shelf-life calculations are described in which kinetic equations are applied to pharmaceutical problems in approximating forms. With their few justifiable assumptions, these calculations are practical and valuable aids in pharmaceutical practice. A good understanding of Chapter 2 is essential to the use of this book, so numerical examples are included that will help in developing a

facility in making the necessary calculations. Chapter 3 introduces, at an elementary level, some fundamental concepts and techniques useful in understanding kinetic data. Chapters 4 and 5 are qualitative accounts of some of the most important drug degradation reactions, and Chapter 6 describes solid state stability. Chapter 7 describes governmental regulations, stability protocols, and decision-making processes used in establishing expiration dates for commercial products; this material is hence not directly needed by the practitioner, but will be helpful in providing a background for appreciating the significance of an expiration date.

Part Two contains information on individual drugs. Each signed stability monograph presents the essential kinetic information that will be found useful in making stability predictions and shelf-life calculations. The monographs are not comprehensive reviews of the kinetics and mechanisms of drug decomposition; rather, they are brief presentations of selected data and stability observations that will be helpful to the pharmacist. The writers of these monographs have attempted more than simple collection of data from the literature. They have also evaluated and organized the data to make them more accessible for effective use by the pharmacist.

One way to assist the user of a collection like this is to adopt a common format for the monographs. This has been done, and the stability-monograph format is as follows:

DRUG NAME

General

Names

Structure

Forms available

Physical properties

Stability summary

Drug Kinetics

Reactions and rate equations

pH-Rate profile

Activation energy

Other data

Formulations and Combinations

Degradation reactions

Stabilization methods

References

All of the data in the monographs bear on the problems of drug stability. For example, the physical properties listed are limited to those that may have such utility. Information on commercially available dosage forms and brand names is easily found in other reference sources. The first section of each monograph includes a stability summary, which is essentially an abstract of the monograph, and which will quickly provide the reader with a qualitative picture of the drug's stability. The following sections give the data, selected for reliability and utility. References are cited for all data. Although in many cases only a small fraction of available papers on a drug have been cited, the reader interested in obtaining a more complete survey should have little difficulty by beginning a search of the literature with the references given here. Of course, not all stability problems can be solved by reference to published accounts; reliable kinetic data on formulations, in particular, are often lacking. Yet, as these monographs reveal, it is remarkable how much useful stability information is available in the literature.

B. OTHER SOURCES OF INFORMATION

The literature of physical chemistry includes many treatments of chemical kinetics in textbooks of physical chemistry. Physical organic chemistry texts also devote much attention to kinetics, which, it should be noted, is a powerful means for studying reaction mechanisms.

The pharmaceutical literature provides many discussions of drug stability and drug kinetics. Some of these are chapters in textbooks, and others are review articles. They are excellent introductions to the fundamentals of the subject, and some of them should constitute a portion of the education of the pharmacist. Others are directed more specifically to the experimental study of drug stability, which is usually carried out within the pharmaceutical industry. For reasons described earlier, most literature sources are less pertinent and useful to the professional needs of the pharmacy practitioner (hence the present book); but many serious students and practicing pharmacists will find them stimulating and informative. Some