

Modern Pharmaceutics

Third Edition, Revised and Expanded

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Marcel Dekker, Inc.

New York • Basel • Hong Kong

Library of Congress Cataloging-in-Publication Data

Modern pharmaceuticals / edited by Gilbert S. Banker, Christopher T.

Rhodes.—3rd ed., rev. and expanded.

p. cm.—(Drugs and the pharmaceutical sciences ; v. 72)

Includes bibliographical references and index.

ISBN 0-8247-9371-4 (alk. paper)

1. Drugs—Dosage forms. 2. Biopharmaceutics.

3. Pharmacokinetics. 4. Pharmaceutical industry—Quality control.

I. Banker, Gilbert S. II. Rhodes, Christopher T. III. Series.

RS200.M63 1995

615'.1—dc20

95-33238

CIP

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Marcel Dekker, Inc.

270 Madison Avenue, New York, New York 10016

Current printing (last digit)

10 9 8 7 6 5 4 3 2 1

PRINTED IN THE UNITED STATES OF AMERICA

Chemical Kinetics and Drug Stability

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I. INTRODUCTION

In the rational design and evaluation of dosage forms for drugs, the stability of the active components must be a major criterion in determining their suitability. Several forms of instability can lead to the rejection of a drug product. First, there may be chemical degradation of the active drug, leading to a substantial lowering of the quantity of the therapeutic agent in the dosage form. Many drugs (e.g., digoxin and theophylline) have narrow therapeutic indices, and they need to be carefully titrated in individual patients so that serum levels are neither so high that they are potentially toxic, nor so low that they are ineffective. For these drugs, it is of paramount importance that the dosage form reproducibly deliver the same amount of drug.

Second, although chemical degradation of the active drug may not be extensive, a toxic product may be formed in the decomposition process. Dearborn [1] described several examples in which the products of degradation are significantly more toxic than the original therapeutic agent. Thus, the conversions of tetracycline to epianhydrotetracycline, arsphenamine to oxophenarsine, and *p*-aminosalicylic acid to *m*-aminophenol in dosage forms give rise to potentially toxic agents that, when ingested, can cause undesirable effects. Recently, Nord et al. [2] reported that the antimalarial chloroquine can produce toxic reactions that are attributable to the photochemical degradation of the substance. Phototoxicity has also been reported to occur following administration of chlordiazepoxide and nitrazepam [3]. Another example of an adverse reaction caused by a degradation product was provided by Neftel et al. [4], who showed that infusion of degraded penicillin G led to sensitization of lymphocytes and formation of antipenicilloyl antibodies.

Third, instability of a drug product can lead to a decrease in its bioavailability, rather than to loss of drug or to formation of toxic degradation products. This reduction in bioavailability can result in a substantial lowering in the therapeutic efficacy of the dosage form. This phenomenon can be caused by physical or chemical changes in the excipients in the dosage form,

independent of whatever changes the active drug may have undergone. A more detailed discussion of this subject is given in Sec. II.B.

Fourth, there may be substantial changes in the physical appearance of the dosage form. Examples of these physical changes include mottling of tablets, creaming of emulsions, and caking of suspensions. Although the therapeutic efficacy of the dosage form may be unaffected by these changes, the patient will most likely lose confidence in the drug product, which then has to be rejected.

A drug product, therefore, must satisfy stability criteria chemically, toxicologically, therapeutically, and physically. Basic principles in pharmaceutical kinetics can often be applied to anticipate and quantify the undesirable changes so that they can be circumvented by stabilization techniques. Some chemical compounds, called prodrugs [5,6], are designed to undergo chemical or enzymatic conversion in vivo to pharmacologically active drugs. Prodrugs are employed to solve one or several problems presented by active drugs (e.g., short biological half-life, poor dissolution, bitter taste, inability to penetrate through the blood-brain barrier, and others). They are pharmacologically inactive as such, but are converted back in vivo to their parent (active) compounds. Naturally, the rate and extent of this conversion (which are governed by the same laws of kinetics that will be described in this chapter) are the primary determinants of the therapeutic efficacy of these agents.

In the present chapter, stability problems and chemical kinetics are introduced and surveyed. The sequence employed is as follows: first, an overview of the potential routes of degradation that drug molecules can undergo; then, a discussion of the mathematics used to quantify drug degradation; a delineation of the factors that can affect degradation rates, with an emphasis on stabilization techniques; and, finally, a description of stability-testing protocols employed in the pharmaceutical industry. It is not the intent of this chapter to document stability data of various individual drugs. Readers are referred to the compilations of stability data [7] and to literature on specific drugs [e.g., Ref. 8 and earlier volumes] for this kind of information.

II. ROUTES BY WHICH PHARMACEUTICALS DEGRADE

Since most drugs are organic molecules, it is important to recognize that many pharmaceutical degradation pathways are, in principle, similar to reactions described for organic compounds in standard organic chemistry textbooks. On the other hand, it is also important to realize that different emphases are placed on the types of reactions that are commonly encountered in the drug product stability area, as opposed to those seen in classic organic chemistry. In the latter, reactions are generally described as tools for use by the synthetic chemist; thus, the conditions under which they are carried out are likely to be somewhat drastic. Reactive agents (e.g., thionyl chloride or lithium aluminum hydride) are employed in relatively high concentrations (often > 10%) and are treated using exaggerated conditions, such as refluxing or heating in a pressure bomb. Reactions are effected in relatively short time periods (hours or days). In contrast, reactions occurring in pharmaceuticals often involve the active drug components in relatively low concentrations. For example, dexamethasone sodium phosphate, a synthetic adrenocorticoid steroid salt, is present only to the extent of about 0.4% in its injection, 0.1% in its topical cream or ophthalmic solution, and 0.05% in its ophthalmic ointment. The decomposition of a drug is likely to be mediated not by reaction with another active ingredient, but by reaction with water, oxygen, or light. Reaction conditions of interest are usually ambient or subambient. Reactions in pharmaceuticals ordinarily occur over months or years, as opposed to the hours or days required for completion of reactions in synthetic organic chemistry.

Reactions such as the Diels-Alder reaction and aldol condensations, which are important in synthetic and mechanistic organic chemistry, are of only minor importance when drug degra-

dation is being considered. Students need to refocus their attention on reactions such as hydrolysis, oxidation, photolysis, racemization, and decarboxylation, the routes by which most pharmaceuticals degrade.

A cognizance of reactions of particular functional groups is important if one is to gain a broad view of drug degradation. It is a difficult task to recall degradative pathways of all commonly used drugs. Yet, through the application of functional group chemistry, it is possible to anticipate the potential mode(s) of degradation that drug molecules will likely undergo. In the following discussion, therefore, degradative routes are demonstrated by calling attention to the reactive functional groups present in drug molecules. The degradative routes are described, through the use of selected examples, as *chemical* when new chemical entities are formed as a result of drug decomposition, and as *physical* when drug loss does not produce distinctly different chemical products.

A. Chemical Degradative Routes

Solvolysis

In this type of reaction, the active drug undergoes decomposition following reaction with the solvent present. Usually, the solvent is water; but sometimes the reaction may involve pharmaceutical cosolvents, such as ethyl alcohol or polyethylene glycol. These solvents can act as nucleophiles, attacking the electropositive centers in drug molecules. The most common solvolysis reactions encountered in pharmaceuticals are those involving "labile" carbonyl compounds, such as esters, lactones, and lactams (Table 1).

Although all the functional groups cited are, in principle, subject to solvolysis, the rates at which they undergo this reaction may be vastly different. For example, the rate of hydrolysis of a β -lactam ring (a cyclized amide) is much greater than that of its linear analog. The half-life (the time needed for half the drug to decompose) of the β -lactam in potassium penethicillin at 35°C and pH 1.5 is about 1 hr. The corresponding half-life for penicillin G is about 4 min [9]. In contrast, the half-life for hydrolysis of the simple amide propionamide in 0.18 molal H_2SO_4 at 25°C is about 58 hr [10]. It has been suggested that the antibacterial activity of β -lactam antibiotics arises from a combination of their chemical reactivity and their molecular recognition by target enzymes. One aspect of their chemical reactivity is their acylating power and, although penicillins are not very good acylating agents, they are more reactive than simple, unsubstituted amides [11]. Unactivated or "normal" amides undergo nonenzymatic hydrolysis slowly, except under the most extreme conditions of pH and temperature, because the N—C(O) linkage is inherently stable, yet when the amine function is a good leaving group (and particularly if it has a pK_a greater than 4.5), amides can be susceptible to hydrolysis at ordinary temperatures. [For a recent review on this subject see Ref. 12.] Acyl-transfer reactions in peptides, including the transfer to water (hydrolysis), are of fundamental importance in biological systems in which the reactions proceed at normal temperatures, and enzymes serve as catalysts.

The most frequently encountered hydrolysis reaction in drug instability is that of the ester, but certain esters can be stable for many years when properly formulated. Substituents can have a dramatic effect on reaction rates. For example, the *tert*-butyl ester of acetic acid is about 120 times more stable than the methyl ester, which, in turn, is approximately 60 times more stable than the vinyl analog [13]. Structure–reactivity relationships are dealt with in the discipline of physical organic chemistry. Substituent groups may exert electronic (inductive and resonance), steric, or hydrogen-bonding effects that can drastically affect the stability of compounds. Interested students are referred to a recent review by Hansch and Taft [14], and to the classic reference text written by Hammett [15].

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