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MODERN PHARMACEUTICS

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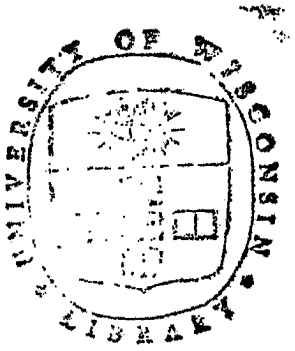

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Chapter 7

CHEMICAL KINETICS AND DRUG STABILITY

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I. INTRODUCTION

In any rational design and evaluation of dosage forms for drugs, the stability of the active component must be a major criterion in determining acceptance or rejection of trial formulations. There are several forms of instability which can lead to rejection of a drug product. First, there may be extensive chemical degradation of the active drug, leading to a substantial lowering of the quantity of the therapeutic agent in the dosage form. With the rapid advance of medicinal chemistry, drugs have become increasingly more potent and a number of them now have very narrow therapeutic ranges. Drugs like nitroprusside, digoxin, theophylline, and others need to be carefully titrated in individual patients so that serum levels are neither so high as to be potentially toxic nor so low as to be ineffective. In these cases, it is of paramount importance that the drug dosage form can reproducibly deliver the same amount of drug. Second, although chemical degradation of the active drug may not be extensive, a very toxic product may be formed in the decomposition process. Dearborn [1] described a number of 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

Mapharsen, and p-aminosalicylic acid to m-aminophenol in dosage forms give rise to potentially toxic agents which, when ingested, can cause undesirable effects. Third, with the development of analytical methodologies which allow for precise measurements of blood levels of drugs, we learn about the problem of bioavailability. (This topic has been extensively dealt with in Chapters 2 through 6.) Instability of a drug product can be exhibited by a decrease in its bioavailability, rather than by loss of drug or production of toxic degradation products. This reduction in bioavailability can lead to a substantial lowering in the therapeutic efficacy of the dosage form. This phenomenon can be brought about by physical and/or chemical changes of the diluents in the dosage form, independent of whatever changes the active drug may have undergone. A more detailed discussion of this phenomenon will be given later in Section II.B.3. 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, or 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, has to satisfy stability criteria chemically, physically, therapeutically, and toxicologically. 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. In the present chapter, stability problems and examples are discussed from the viewpoint of the research and development scientist. The presentation follows the following sequence: 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; and, finally, a discussion of the factors which can affect degradation rates, with an emphasis on stabilization techniques. It is not the intent of this chapter to document stability data for the various drugs. Readers are referred to a classic chapter on stability of drugs by Garrett [2] and a more recent compilation by Lintner [3] for this information.

II. MODES OF PHARMACEUTICAL DEGRADATION

Since most drugs are organic molecules, it is important to first recognize that most pharmaceutical degradations 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 type of reactions which are commonly encountered in drug product stability as opposed to those seen in classical organic chemistry. In the latter case, reactions are generally described for the purpose of synthesis; thus the conditions under which they are carried out are most likely to be quite drastic. Reactive agents, e.g., thionyl chloride or lithium aluminum hydride, are employed in relatively high concentrations (usually > 10%) and are treated at exaggerated conditions such as refluxing. Reactions are effected in relatively short periods of time (hours or days). In contrast, pharmaceutical reactions pertaining to drug product stability usually involve the active drug components in relatively dilute concentrations. For example, dexamethasone sodium phosphate, a synthetic adrenocortical steroid salt, is

present only to the extent of about 0.01% in its elixir, 0.4% in its injection, 0.1% in its cream, and 0.05% in its ophthalmic ointment. The decomposition of a drug is more likely to be mediated not through reaction with another active ingredient but through reaction with comparatively inert environmental chemicals or stimuli such as water, oxygen, or light. Reaction conditions are usually ambient and sometimes even at refrigerated temperatures. The durations for pharmaceutical reactions are in terms of months or years as opposed to hours or days in synthetic organic chemistry.

Students need to refocus their experiences on chemical reactions learned from organic chemistry classes. 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 degradation is concerned. On the other hand, hydrolysis, oxidation, and photolysis reactions constitute some of the most important modes of pharmaceutical degradation.

Appreciation of reactions of particular functional groups is important if we are to gain a broader view of drug degradation. It is difficult, and perhaps impossible, to remember degradative pathways of all commonly used drugs. By utilizing some functional group chemistry, it is possible to anticipate the potential mode(s) of degradation which the drug molecule will likely undergo. The following discussion, therefore, is mainly oriented, where possible, to describing drug degradative modes through indentification of the reactive functional groups in the drug molecule. The degradative routes are described, through the use of selected examples, as chemical, when new chemical entities are formed as a result of drug degradation, and as physical, when drug loss does not produce distinctly different chemical products.

A. Chemical Degradative Routes

1. Solvolysis

This type of reaction involves the decomposition of the active drug through reaction with the solvent present. In most instances the solvent is water; but in some cases the reaction may involve pharmaceutical cosolvents such as ethyl alcohol or polyethylene glycol. These solvents act as nucleophilic agents, and they attack electropositive centers in the drug molecule. The commonest solvolysis reactions encountered in drug instability are those involving "labile" carbonyl compounds such as esters, lactones, and lactams (Table 7.1).

Although all the functional groups cited are in principle subjected 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 very much faster than that of its linear analog. The half-life (the time needed for half the drug to decompose) of the β-lactam in potassium phenethicillin at 35°C and pH 1.5 is about 1 hr. A corresponding value for penicillin G is about 4 min [4]. By comparison, the half-life of propionamide at 0.18 molal H_2SO_4 and at 25°C is about 58 hr [5]. The extreme susceptibility of the penicillin group toward hydrolysis is due to the high degree of steric strain in the 4-membered β-lactam ring.

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