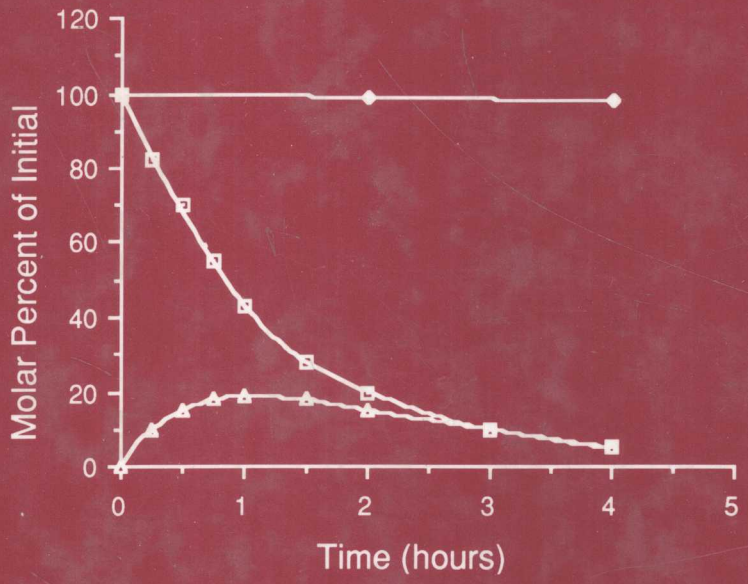
DRUGS AND THE PHARMACEUTICAL SCIENCES VOLUME 43

Drug Stability

Principles and Practices



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Drug Stability

Principles and Practices

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Drug Stability

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A Series of Textbooks and Monographs

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To Dorothy Dolfini

for her inspiration, support, and love

Preface

I have been engaged in one or another phase of stability testing or theory for most of my professional life. Beyond the purely organizational subdivisions of stability and its association with the science of kinetics there exist fascinating aspects of the subject from a work point of view.

A stability problem is never simple. It is, as Dr. E. G. Garrett of the University of Florida says, never a "Saturday afternoon experiment." No two problems are alike. Once a drug substance is manipulated into a dosage form, it interacts with the excipients in an individual manner that always presents challenge, variety, and constant search for knowledge. At the time a product is ready for new drug application (NDA), there is a storehouse of unique knowledge, which frequently leads to one or more publications. The dissemination of this knowledge was not always a timely or smooth process. It was not until the last decade that companies in general began to look kindly on publication efforts by their applied scientists. Fortunately, stability efforts now find their way to the journals where they can be shared for a better general understanding of common stability problems.

This book is written primarily with the stability scientist in mind. Although over 500 references are cited, it is not merely a reference text. The references were selected to illustrate the examples of the principles that I have presented, not to serve as an exhaustive bibliography.

Because the book also presents the underlying theory of stability testing, there is a fair amount of mathematical machinery brought into play, but this should not discourage the mathematically uninitiated. The chapters, especially the later ones, all have very applied aspects and can be read by skipping the math. The reason for employing the

mathematics, the modeling, and the mechanistic aspects is to provide a well-rounded publication which will serve as a reference model for models and mechanistics of stability theory. Colleagues in this field may wish to use the book as a text for courses in stability.

I owe special thanks to Dr. Charles Kumkumian of the United States Food and Drug Administration, Professor Christopher Rhodes of the University of Rhode Island, Dr. Rohit Kothari and Ms. Dorothy Dolfini of Marion Labs, Dr. Robert Cohn and Dr. D. Wadke of Bristol-Squibb, Corp., Dr. G. K. Mooney of Lederle Labs, and Drs. Paul Turi, Bert Brown, and Claire Bosco of Sandoz for valuable technical assistance, information, and encouragement.

Finally, I owe special thanks to the scientists who will read this text and enjoy it.

Jens T. Carstensen

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References

An important document in stability testing of pharmaceuticals is the FDA Guideline (which first appeared in 1984, with an updated edition in 1987). This document will be referred to frequently (and it will always be the 1987 edition which is called upon).

There will also be commentary by the author. The opinions and commentary are those of the author, not necessarily those of the Food and Drug Administration (FDA). (They often, hopefully, conform quite well with the FDA's opinion, except on certain points where the author disagrees with the Guidelines.)

First of all the author cannot speak for the FDA. Second, the opinion of the FDA is a somewhat undefined term, since the FDA houses many scientists and, therefore, many opinions. So to speak of the FDA's opinion on a matter is only applicable after the fact, namely whether they accept or reject a certain concept in a new drug application (NDA). Third, the Guidelines are subject to revision from time to time, and commentary that is made today may not apply in a year's time. We now give an overview of what led up to the policies of today.

1. HISTORICAL BACKGROUND

Historically there has always been evidence of concern on the part of the pharmaceutical practitioner and the pharmacist that the drug in the developing or dispensed dosage form be stable. Early incompatibilities (e.g., aspirin and magnesium stearate) were quite obvious from the odor (acetic acid) of the tablets. Quantitization was another matter, since in the first half of this century quantitative assays to detect such problems relied on some color reaction and a colorimeter (not necessarily wavelength specific) for quantitation. (Spectrophotometers, for all practical purposes, were not easily accessible until the late 1940s.)

The introduction of the spectrophotometer on a commercial scale was a giant step forward, yet, since many chromophores are common in both parent and decomposition product, specificity was still lacking. In the 1950s and 1960s such specificity was supplied in a semiquantative manner by thin-layer chromatography (TLC), since quite good separations could usually be achieved by this method. Attempts at quantitating TLC were many, but they never really gained a foothold. Instead, high-precision liquid chromatography (HPLC) proved to be the sensor of small amounts of impurity and decomposition product.

There is no doubt that products produced prior to 1950 often were quite unstable, yet assays (nonspecific) would not reveal such instabilities. Solutions (e.g., of procaine hydrochloride) would darken, yet the titrimetric assay would not detect the hydrolysis of the ester group. On the other hand, some of the products at the time (e.g., the sulfonamides) were remarkably stable. Others were not. The best assay for specificity in those years were biological or microbiological assays (vitamin D, penicillins, and, later, tetracyclines). The substances known to be unstable were penicillins, aspirin, and some of the vitamins (vitamin A, thiamine hydrochloride, and ascorbic acid, for instance).

To improve the stability of such compounds, it was desirable to "speed up" the decomposition by some means of stress, and the custom in those days was to consider five weeks at 42°C as equivalent to two years at room temperature. This test had its roots in an article which appeared in Drug and Cosmetic Industry in 1948, espousing (correctly) that five weeks storage of vitamin A at 42°C brought about the same amount of decomposition as vitamin A stored for two years at room temperature. What was forgotten was that this only applies to substances with the same activation energy as vitamin A, and hence general adherence should not be expected. E. R. Garett (1955) was greatly instrumental in the general understanding of the possibilities and limitations of accelerated testing.

For NDAs in the early years, stability reporting was meager, at times nonexisting, and it was not until the 1960s that there were