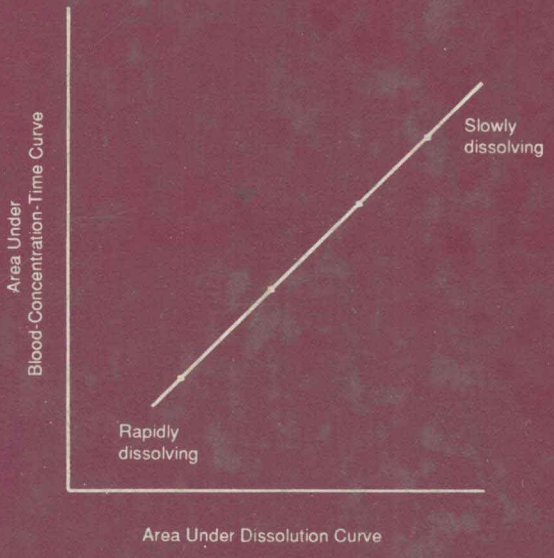
DRUGS AND THE PHARMACEUTICAL SCIENCES VOLUME 49

Pharmaceutical Dissolution Testing



Umesh V. Banakar

Pharmaceutical Dissolution Testing

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This work is dedicated to the fond memories of my late grandmother, Aaji. I am eternally indebted to her for three virtues—patience, perseverance, and positive thinking—which were communicated to me through her approach to life and life-style itself.

Foreword

The importance of dissolution rate on clinical performance of drugs and drug delivery systems has long been recognized. It is the overwhelmingly important property of dosage forms that contributes to the rate and extent of drug availability to the body and, as such, is deserving of the effort that has been put forth to develop dissolution systems that provide fundamental information on the dissolution process of many drugs and chemicals as well as meaningful in vitro dissolution system models that can be correlated with some index of in vivo performance.

Notwithstanding the considerable efforts expended in trying to understand fundamentals and application of dissolution, great deficiencies in our database still exist. Indeed, in the applied area of attempting to model in vivo with in vitro systems, it is not yet possible to routinely correlate in vitro dissolution rate data with biological performance of sustained-release systems, i.e., in vivo data. The reason for this is simply that we do not yet understand the many biological variables that can influence the dissolution rate of dosage forms and, as such, all in vitro models are unable to realistically duplicate biological conditions.

An appreciation of the historic development of oral in vitro dissolution apparati dramatizes our general lack of the biological variables involved in dissolution. Thus, when the Stohl-Gershberg disintegration apparatus was first introduced it was run in 500 mL of fluid, because it was believed that was the volume of the resting stomach. The 32 cycles per minute of tube movement was to simulate peristaltic motion of the stomach, and no allowance was made

for any form of mixing conditions. The resting stomach has closer to 30–50 mL of fluid in the fasted state and the motility pattern is divided into three separate phases of differing activity. The role of various biological solutes, in conjunction with the now-known mixing characteristics and motility pattern of the stomach, has not been fully explored. Indeed, the present official dissolution apparati bear no relationship to physiological conditions, and hence it is not possible to completely examine dissolution of drugs and drug delivery systems under simulated biological conditions nor to explore the influence of physiological conditions, e.g., pH, bile salts, enzymes, and glycoproteins, on the dissolution process.

Despite the importance of dissolution, the various publications in scientific journals and review articles, and the numerous committees formed within the Academy of Pharmaceutical Sciences and AAPS, there are surprisingly few comprehensive texts in the field and none that delineate problems in the area. The present text is badly needed and fills a void in the field. Dr. Banakar has provided a valuable service in the preparation of this text.

Joseph R. Robinson
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Preface

More than 100 years ago, Bernard S. Proctor recognized that "pill" dissolution was a necessary prerequisite for drug absorption. Nevertheless, it was not until 1930 that pharmaceutical scientists attempted to relate in vitro testing to in vivo availability. Parrot et al. have stated: "The release of a drug from the primary particle and its subsequent availability to the body is governed by the dissolution rate of the particle." There is little doubt that the determination of dissolution rates is an important tool in the design, fabrication, evaluation, and quality control of solid dosage forms.

Dissolution analysis of pharmaceutical solid dosage forms has emerged as the single most important test that, when carried out appropriately, will ensure the quality of the product. Interest in dissolution standards and their significance has been mounting steadily during the past decade. Knowledge of critical operating variables for a dissolution device is important to the pharmaceutical scientist interested in product development, quality control, and research applications. Since the recognition of the fact that the dissolution rate of a drug from its dosage form can often become the rate-limiting process in the physiological availability, interest has been focused on the development of a reliable in vitro dissolution test method that can positively characterize the in vivo dissolution rate-controlled absorption of drugs.

Dissolution tests are critical and they are difficult to carry out properly. There are a variety of critical factors that influence the dissolution behavior and subsequent bioavailability characteristics of a drug and drug product(s).

With the steady accumulation of data in this discipline over the past two decades, pharmaceutical dissolution technology has become an important area of study in pharmacy schools and a vital item in the armamentarium of technical know-how of a pharmaceutical scientist. Since dissolution is extremely important in pharmaceutical systems, particularly solid dosage forms, each chapter is devoted to a specific area in dissolution technology. Each area is discussed in sufficient depth with regard to historical background and development, theoretical and practical aspects, and current status. A wide variety of examples, citing references, along with rational guidelines for potential applications in practice are provided. It is the intention of this book to present a consolidated update of and comprehensive information on dissolution technology that is not otherwise currently available as a single source, and to promote better understanding and fuller appreciation of the phenomenon.

It is hoped that *Pharmaceutical Dissolution Testing* will serve as an invaluable guide to aid the pharmacy professional, in both academia and practice (industry or otherwise), in selecting and utilizing the available means in overcoming problems in design and development of better dosage forms. It is anticipated that the collective knowledge gained hereby will result in acquisition of expertise in the field of dissolution technology.

I wish to extend my gratitude and sincere appreciation to Ms. Barbara Lorimor for her excellent technical expertise in preparing the manuscript. I also wish to acknowledge Ms. Kathleen Gardon, editorial assistant, for meticulous proofing. I appreciate the contributions by the authors of Chapters 4, 6, 10, and 11. Special appreciation is extended to Sandra Beberman and Carol Mayhew of Marcel Dekker, Inc., for their expert assistance. I owe special thanks to Dr. Joseph R. Robinson for writing the foreword to this text and for his encouragement in bringing this project to fruition. Last but not the least, I am indebted to my wife, Suneeta, and to my parents for their unending love and support.

Umesh V. Banakar

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ONE

Introduction, Historical Highlights, and the Need for Dissolution Testing

INTRODUCTION

Dissolution is defined as the process by which a solid substance enters in the solvent to yield a solution. Stated simply, dissolution is the process by which a solid substance dissolves. Fundamentally, it is controlled by the affinity between the solid substance and the solvent.

Pharmaceutical solid dosage forms and solid-liquid dispersed dosage forms on administration undergo dissolution in biological media, followed by absorption of the drug entity into systemic circulation. In determining the dissolution rate of drugs from solid dosage forms under standardized conditions, one has to consider several physicochemical processes in addition to the processes involved in the dissolution of pure chemical substances. The physical characteristics of the dosage form, the wettability of the dosage unit, the penetration ability of the dissolution medium, the swelling process, the disintegration and deaggregation of the dosage form are a few of the factors that influence the dissolution characteristics of drugs. Wagner proposed the scheme depicted in Fig. 1.1 for the processes involved in the dissolution of solid dosage forms (1). This scheme was later modified to incorporate other factors that precede the dissolution process of solid dosage forms. Carstensen proposed a scheme incorporating the following sequence (2):

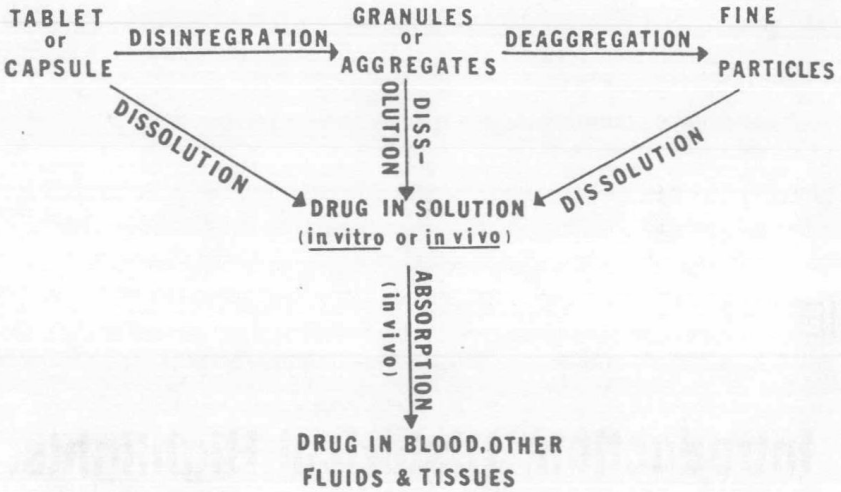

Fig. 1.1 Schematic illustration of dissolution process of solid dosage forms. (From Ref. 2.)

1. Initial mechanical lag
2. Wetting of the dosage form
3. Penetration of the dissolution medium into the dosage form
4. Disintegration
5. Deaggregation of the dosage form and dislodgment of the granules
6. Dissolution
7. Occlusion of some particles of the drug

It is apparent from Fig. 1.1 that the rate of dissolution of the drug can become the rate-limiting step before the drug appears in blood. However, when the dosage form is placed into the gastrointestinal tract in solid form, there are two possibilities for the rate-limiting step. The solid form must first dissolve and the drug in solution must then pass through the gastrointestinal membrane. Freely water-soluble drugs will tend to dissolve rapidly, making the passive diffusion of drug and/or the active transport of drug the rate-limiting step for absorption through the gastrointestinal membrane. Conversely, the rate of absorption of poorly soluble drugs will be limited by the rate of dissolution of the undissolved drug or disintegration of dosage form. Intermediate cases exist when the absorption rate is not clearly determined by one of the two steps but is affected by both of them. In such instances, neither of the steps is rate-limiting.

Dosage forms vary with regard to the rate at which they can present drug in solution to the gastrointestinal mucosa. Assuming that dissolution is rate-limiting, drugs administered orally in solution form (e.g., syrups, elixirs, and