HANDBOOK OF
Pharmaceutical Manufacturing Formulations

Uncompressed Solid Products

VOLUME 2

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Dedication

Dedicated to the memory of
Takeru Higuchi

Preface to the Series

No industry in the world is more highly regulated than the pharmaceutical industry because of potential threat to a patient's life from the use of pharmaceutical products. The cost of taking a new chemical entity (amortized over the cost of all molecules racing) to final regulatory approval is a staggering $800 million, making the pharmaceutical industry one of the most research-intensive industries in the world. In the year 2004, it is anticipated that the industry will spend about $20 billion on research and development. The generic market of drugs as the new entities come off patent is one of the fastest growing segments of the pharmaceutical industry, with every major multinational company having a significant presence in this field.

Whereas many stages of new drug development are inherently constrained with time, the formulation of drugs into desirable dosage forms remains an area where expediency can be practiced with appropriate knowledge by those who have mastered the skills of pharmaceutical formulations. The *Handbook of Pharmaceutical Manufacturing Formulations* is the first major attempt to consolidate the available knowledge about formulations in a comprehensive, and by nature a rather voluminous, presentation.

The book is divided into six volumes, based strictly on the type of formulation science involved in the development of these dosage forms: sterile products, compressed solids, uncompressed solids, liquid products, semisolid products, and OTC products. The separation of OTC products, even though they may easily fall into one of the other five categories, is made to comply with the industry norms of separate research divisions for OTC products. Sterile products require skills related to sterilization of product, and of less importance is the bioavailability issue, which is an inherent problem of compressed dosage forms. These types of considerations have led to the classification of products into these six categories.

Each volume includes a description of regulatory filing techniques for the formulations described. Also included are the current regulatory guidelines on CGMP compliance specific to the dosage form. Advice is offered on how to scale up the production batches.

It is expected that formulation scientists will use this information to benchmark their internal development protocols and cut the race to file short by adopting formulae that have survived the test of time. Many of us who have worked in the pharmaceutical industry suffer from a close paradigm when it comes to selecting formulations — "not invented here" perhaps reigns in the mind of many seasoned formulations scientists subconsciously when they prefer to choose only a certain platform for development. It is expected that with the quick review of possibilities available to formulate made available in this book, scientists will benefit from the experience of others.

For the teachers of formulation sciences, this series offers a wealth of information. Whether it is a selection of a preservative system or the choice of a disintegrant, the series offers a wide choice to study and rationalize.

Many have assisted me in the development of this work that has taken years to compile, and I thank scores of my graduate students and colleagues for their help. A work of this size cannot be produced without errors, although I hope that these errors do not distract the reader from the utility of the book. I would sincerely appreciate if readers point out these mistakes for corrections in future editions.

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Preface to the Volume

Uncompressed solid products formulations comprise aggregates of powders, such as powders for topical application, for use as insufflations, and for extemporaneous suspensions, as well as hard gelatin capsules or any other form wherein the final form is not compressed. The rationale for this clear demarcation of formulations based on their state of aggregation is important to understand. Whereas compressed solid products require formulation components to render them compressible while allowing free flow into compression cavities, such considerations are of lesser importance for uncompressed solid products. (The flow requirement nevertheless stays because the powders must be forced into capsule shells or poured into bottles or other packaging forms.) Uncompressed solid products on the other hand offer their own set of formulation problems related to segregation of powders due to static charges, environmental contamination during the filling process, and inevitable problems in wetting and dissolution, thus leading to possible bioavailability problems *in vivo*. In the series of steps that determine the ultimate dissolution of the product, however, uncompressed solid products are one critical step ahead of compressed solid products — disintegration. The formulator is advised to read Chapter 4 of this volume, which discusses guidelines on the waiver of bioavailability requirements. Substantial development costs can be reduced when a drug undergoes fast dissolution, and these considerations must therefore be part of any new formulation effort. The reader is also referred to Volume 1 of this series where current and proposed bioavailability guidelines are provided.

Chapter 1 addresses the fundamental issues of good manufacturing practices (GMPs). The chapter provides access addresses to all major guidelines around the world and also highlights the U.S. Food and Drug Administration (FDA) guidelines. A discussion of the most recent changes in the philosophy of establishing the GMP guidelines based on risk assessment is addressed in this chapter as well.

Chapter 2 presents a more recent discussion of how the U.S. FDA inspectors are supposed to conduct inspections; this topic is of continuous importance to all drug manufacturers. Although it is included in this volume, the guidelines apply to all dosage forms.

Chapter 3 discusses the topic of bioequivalence and bioavailability of solid products. Although this is discussed more thoroughly in Volume 1, the emphasis in Chapter 3 is placed on the guidelines to request a waiver of bioavailability/bioequivalence testing; this is something of great importance to both the innovator and the generic drug manufacturer.

Chapter 4 highlights the manufacturing aspects of uncompressed drugs as well as various topics of general and specific interest.

Part II provides formulations for more than 400 pharmaceutical products. Included in part are not only the currently approved products, but also several innovative products such as small proteins, instantly liquefiable powders, and nanoparticles. Formulators are strongly urged to review the methodologies described here to serve as a reference point for their own formulations. Some combination products or dosage forms are described that are not currently approved by the FDA (i.e., not included in the *Orange Book*), and they may be in the development phase or in experimental phases. As is always the case, it is the responsibility of the manufacturer to ensure that the formulations used in the production do not violate any intellectual property or proprietary practice laws. The most effective means of establishing this is through a study of the *Orange Book*, which lists the exclusivities and unexpired patents. The patent numbers provided in the *Orange Book* should then be searched for collateral patents, the FDA Freedom of Information (FOI) database, and other literature to ensure that the intellectual or proprietary property rights are not violated.

Whereas coating solutions are not as important, as in the case of compressed solids, nevertheless, some capsules are coated and the granules that are filled in capsules for sustained or timed release are coated, utilizing nonpareil sugar beads most often. The coating solutions are described here, but the reader is further referred to Volume 1 for a detailed description of coating solutions that can be easily adapted to the product intended for formulation into a sustained release profile. Whereas some forms of powders are meant to be sterile, the sterility considerations are discussed in Volume 6.

The subject of powder technology is vast, with applications in many fields. The serious reader is referred to the journal *Advanced Powder Technology* (http://www.vsppub.com/journals/jn-AdvPowTec.html). Such advances as inhalation insulin in a powder form and the new science of nanoparticles opens a new phase of pharmaceutical research and development. Nanotechnology describes the ability to create new materials from building blocks the size of an atom cluster. Nanomaterials are powders and materials optimized at the nanoscale

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