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Semisolid Products

VOLUME 4

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Dedication

*Dedicated to the memory of
John G. Wagner*

Preface to the Series

No industry in the world is more highly regulated than the pharmaceutical industry because of potential threats to patients' lives 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 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 in which 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 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 over-the-counter (OTC) products. The separation of OTC products, 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 current good manufacturing practice (CGMP) compliance specific to the dosage form and advice is offered on how to scale up the production batches.

It is expected that the formulation scientist would use this information to benchmark internal development protocols and to 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 closed paradigm when it comes to selecting formulations; "not invented here" perhaps subconsciously reigns in the minds of many seasoned formulations scientists when they prefer to choose only a certain platform for development. It is expected that with a 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, which has taken years to compile, and I am thankful to scores of my graduate students and colleagues for their help. A work of this size cannot be produced without errors, though I hope these errors do not distract the reader from the utility of the book. I would sincerely appreciate readers pointing out these mistakes to me for corrections in future editions.

Sarfraz K. Niazi, Ph.D.
Deerfield, Illinois

Preface to the Volume

The semisolid drugs category is comprised of ointments, creams, gels, suppositories, and special topical dosage forms. The formulations of semisolid drugs share many common attributes of consistency, presentation, preservation requirement, and the route of administration, mainly topical. As a result, grouping them together for the purpose of defining common formulation practices and problems is justified. The topical dosage forms present unique opportunities to design novel drug delivery systems such as patches and other transdermal systems. Some of these are described in the volume, but the reader is referred to specific patents issued, wherein greater details are readily obtainable. In selecting the formulations, I have tried to provide representative techniques and technologies involved in the preparation of semisolid products; for example, I have included a significant number of what is called "base" formulation, a formulation that can easily carry a drug, depending on the proportion involved. Obviously, considerations such as incompatibility of the drug with the ingredients is of pivotal importance; these base formulations of stable emulsions provide a good starting point in the development of new products or even when a different topical consistency is desired. I have also made an effort to highlight those formulations that are currently approved in the United States and provide them as they appear in the *Physicians Desk Reference*, where possible. Obviously, where the formulations are straightforward, I have chosen to only give the composition or mere identification of ingredients to conserve space for those formulations that need more elaborate description.

The regulatory agencies impose certain specific requirements on the formulation and efficacy determination of drugs contained in these formulations. For example, the CGMP factors, scale-up and postapproval changes, and dermatological testing for irritation or photosensitivity are some of the specified elements.

In this volume, we present over 350 formulations and, in keeping with the tradition in other volumes, a chapter on formulation-related matters. In the regulatory section, we offer a difficult area of compliance, changes to approved new drug applications (NDAs) and abbreviated new drug applications (ANDAs), particularly with reference to semisolid drugs. The stability considerations, particularly the evolving guidelines of the International Conference on Harmonization (ICH), are detailed in this volume, with particular reference to stability-testing requirements in postapproval stages. Unique to this category is the dermal testing of products, including photosensitivity testing requirements that are still evolving. It is noteworthy that

much of the regulatory discussion presented here is drawn from the requirements of the U.S. Food and Drug Administration (FDA) and the harmonized guidelines with the ICH listings. Although it is likely that some of the requirements and recommendations made here might change, it is unlikely that the basic thrust in establishing these guidelines will change. As always, the applicants are highly encouraged to communicate with the FDA on the changes made to these guidelines and especially for any significant changes made to compliance requirements. The Web site of the FDA, <http://www.fda.gov>, is very comprehensive and continuously evolving; pay special attention to the withdrawal and finalization of guidelines provided. Of particular importance is the listing of new and withdrawn guidelines (<http://www.fda.gov/cder/guidance/New-Revised-Withdrawn.PDF>), which should be reviewed periodically.

Chapter 1 provides details on how to handle changes made to approved NDAs or ANDAs; this is a significant topic for continued compliance with the CGMP requirements but, unfortunately, the one that is most easily misunderstood or misconstrued. For example, at what level of change should the FDA be informed, either before making a change or after? What happens if a change is made inadvertently and later discovered; how to report this change? Years of experience teaches me that a manufacturer can never be too careful in avoiding a 483 issuance when it comes to changes made to NDAs or ANDAs. The situation gets extremely complex when there are multiple dosage forms, for which the requirements may be different.

Chapter 2 gets into details of changes made pursuant to discussion in Chapter 1 when it comes to semisolid drugs. A more detailed description of level of changes is described here, and advice is provided on when to conduct a regulatory review.

Chapter 3 continues the themes developed in the first two chapters and applies to changes made to equipment. This is a topic of special interest to the FDA because in the processing of semisolid products, the equipment plays a pivotal role. The mixing of drugs within the base media is highly affected by the process and mechanism of mixing used. Also, because of the nature of product manufactured, often the cleaning and validation of equipment become serious issues.

Chapter 4 is a comprehensive review of the present thinking of the regulatory authorities on how the stability studies should be designed and conducted and how the data should be interpreted; the induction of ICH guidelines and an attempt to streamline the requirements of testing new drug products have resulted in much dispute when it comes to global marketing of products. Should the stability testing be done at all

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