Remington's Pharmaceutical Sciences

Eighteenth Edition

Library of Congress Catalog Card No. 60-53334

ISBN 0-912734-04-3

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Printed in the United States of America by the Mack Printing Company, Easton, Pennsylvania

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CHAPTER 75

Preformulation

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The attention presently being given to multisource pharmaceutical products regarding their equivalency places much emphasis on the formulation of these products. In some instances, the bioavailability of a drug formulation represents a quality parameter of enormous proportion. It is a matter of record that with certain drugs, depending on the formulation, the rate at which the drug substance becomes available can vary significantly from very high to none at all. As a result, the effectiveness of these formulations will range dramatically from that expected to no effect. Unfortunately, most examples are less dramatic and fall somewhere in between. The difference in the bioavailability of these drug products is less readily discernible, but nonetheless real. This has led to a great deal of confusion and information which, though understood by the scientist, is unclear and jumbled to the practitioner. That information which is available also has been interpreted differently by different individuals or groups, depending very often on the motivation, viewpoint and attitude of the interpreter.

Drug products indeed do vary in their bioavailability characteristics and this variation, in most instances, is related directly to formulation considerations. To optimize the performance of drug products, it is necessary to have a complete understanding of the physical-chemical properties of drug substances prior to formulating them into drug products. The development of an optimum formulation is not an easy task, and many factors readily influence formulation properties. Drug substances rarely are administered as chemical entities, but almost always are given in some kind of formulation. These may vary from a simple solution to a very complex drug delivery system. The complexity usually is not intentional, but rather is determined by the properties that are expected from or built into the dosage form and by the resulting composition that is required to achieve these qualities.

The high degree of uniformity, physiological availability and therapeutic quality expected of modern medicinal products usually are the results of considerable effort and expertise on the part of the formulating pharmacist. These qualities are attained by careful selection and control of the quality of the various ingredients employed, appropriate manufacturing according to well-defined processes and, most importantly, adequate consideration of the many variables that may influence the composition, stability and utility of the product. In dealing with the formulation of new products it has become necessary to apply the best research methods and tools in order to develop, produce and control the potent, stable and effective dosage forms which make up our modern medical armamentarium.

The pharmaceutical formulator has need for specialized areas of science in order to acquire scientific information about the drug substance which is necessary to develop an optimum dosage form. The pharmaceutical industry is in an era in which one can no longer rely on past experience to formulate. A thorough understanding of the physical and chemical properties as well as the pharmacokinetic and biopharmaceutical behavior of each drug substance being developed is necessary. In short, as much information as possible must be acquired about the drug substance very early in its development. This requires an interdisciplinary approach at the preformulation stage of development. Fig 75-1 schematically indicates that the development of any drug product requires a multidisciplinary approach, involving basic science, during the preformulation stage followed by applied science during the development stage.

This chapter will discuss the physical-chemical evaluation that takes place during the preformulation stage of development. In addition, consideration will be given to some specialized formulation ingredients that may require discretion in their selection.

Preformulation may be described as a stage of development during which the physical pharmacist characterizes the physical-chemical properties of the drug substance in question which are considered important in the formulation of a stable, effective and safe dosage form. Such parameters as crystal size and shape, pH-solubility profile, pH-stability profile, polymorphism, partitioning effect, drug permeability and dissolution behavior are evaluated. During this evaluation possible interactions with various inert ingredients intended for use in the final dosage form also are considered. The data obtained from this evaluation are integrated with data obtained from the preliminary pharmacologic and biochemical studies and provide the formulating pharmacist with information that permits selection of the optimum dosage form containing the most desirable inert ingredients for use in its development.

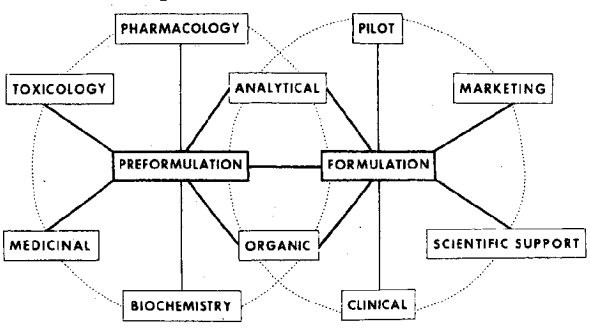

Fig 75-1. The wheels of product development.

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