Remington's Pharmaceutical Sciences

Eighteenth Edition

DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.

Entered according to Act of Congress, in the year 1885 by Joseph P Remington,
in the Office of the Librarian of Congress, at Washington DC

Copyright 1889, 1894, 1905, 1907, 1917, by Joseph P Remington

Copyright 1926, 1936, by Joseph P Remington Estate

Copyright 1948, 1951, by The Philadelphia College of Pharmacy and Science

Copyright © 1956, 1960, 1965, 1970, 1975, 1980, 1985, 1990, by The Philadelphia College of Pharmacy and Science

All Rights Reserved

Library of Congress Catalog Card No. 60-53334

ISBN 0-912734-04-3

The use of structural formulas from USAN and the USP Dictionary of Drug Names is by permission of The USP Convention. The Convention is not responsible for any inaccuracy contained herein.

NOTICE—This text is not intended to represent, nor shall it be interpreted to be, the equivalent of or a substitute for the official United States Pharmacopeia (USP) and/or the National Formulary (NF). In the event of any difference or discrepancy between the current official USP or NF standards of strength, quality, purity, packaging and labeling for drugs and representations of them herein, the context and effect of the official compendia shall prevail.

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

DOCKET ALARM Find authenticated court documents without watermarks at docketalarm.com.

Table of Contents

Part 1 Orientation

1 Scope 3
2 Evolution of Pharmacy 8
3 Ethics 20
4 The Practice of Community Pharmacy 28
5 Opportunities for Pharmacists in the Pharmaceutical Industry 33
6 Pharmacists in Government 38
7 Drug Information 49
8 Research 60

Part 2 Pharmaceutics

9 Metrology and Calculation 69
10 Statistics 104
11 Computer Science 138
12 Calculus 145
13 Molecular Structure, Properties and States of Matter 158
14 Complex Formation 182
15 Thermodynamics 197
16 Solutions and Phase Equilibria 207
17 Ionic Solutions and Electrolytic Equilibria 228
18 Reaction Kinetics 247
19 Disperse Systems 257
20 Rheology 310

Part 3 Pharmaceutical Chemistry

21 Inorganic Pharmaceutical Chemistry 329
22 Organic Pharmaceutical Chemistry 356
23 Natural Products 380
24 Drug Nomenclature—United States Adopted Names 412
25 Structure-Activity Relationship and Drug Design 422

Part 4 Testing and Analysis

26 Analysis of Medicinals 435
27 Biological Testing 464
28 Clinical Analysis 495
29 Chromatography 529
30 Instrumental Methods of Analysis 555
31 Dissolution 589

Part 5 Radioisotopes in Pharmacy and Medicine

32 Fundamentals of Radioisotopes 605
33 Medical Applications of Radioisotopes 624

Part 6 Pharmaceutical and Medicinal Agents

34 Diseases: Manifestations and Pathophysiology 655
35 Drug Absorption, Action and Disposition 697
36 Basic Pharmacokinetics 725
37 Clinical Pharmacokinetics 746
38 Topical Drugs 757
39 Gastrointestinal Drugs 774
40 Blood, Fluids, Electrolytes and Hematologic Drugs 800
41 Cardiovascular Drugs 831
42 Respiratory Drugs 860
43 Sympathomimetic Drugs 870
44 Cholinomimetic Drugs 889
45 Adrenergic and Adrenergic Neuron Blocking Drugs 898
46 Antimuscarinic and Antispasmodic Drugs 907
47 Skeletal Muscle Relaxants 916
48 Diuretic Drugs 929
49 Uterine and Antimigraine Drugs 943
50 Hormones 948
51 Vitamins and Other Nutrients 1002
52 Enzymes 1035
53 General Anesthetics 1039
54 Local Anesthetics 1048
55 Sedatives and Hypnotics 1057
56 Antiepileptics 1072
57 Psychopharmacologic Agents 1082
58 Analgesics and Antipyretics 1097
59 Histamine and Antihistamines 1123
60 Central Nervous System Stimulants 1132
61 Antineoplastic and Immunosuppressive Drugs 1138
62 Antimicrobial Drugs 1160
63 Parasiticides 1242
64 Pesticides 1249
65 Diagnostic Drugs 1272
66 Pharmaceutical Necessities 1286
67 Adverse Drug Reactions 1300
68 Pharmacogenetics 1344
69 Pharmacological Aspects of Drug Abuse 1349
70 Introduction of New Drugs 1365

Part 7 Biological Products

71 Principles of Immunology 1379
72 Immunizing Agents and Diagnostic Skin Antigens 1389
73 Allergenic Extracts 1405
74 Biotechnology and Drugs 1416

Part 8 Pharmaceutical Preparations and Their Manufacture

75 Preformulation 1435
76 Bioavailability and Bioequivalency Testing 1451
77 Separation 1459
78 Sterilization 1470
79 Tonicity, Osmoticity, Osmolality and Osmolarity 1481
80 Plastic Packaging Materials 1499
81 Stability of Pharmaceutical Products 1504
82 Quality Assurance and Control 1513
83 Solutions, Emulsions, Suspensions and Extractives 1519
84 Parenteral Preparations 1545
85 Intravenous Admixtures 1570
86 Ophthalmic Preparations 1581
87 Medicated Applications 1596
88 Powders 1615
89 Oral Solid Dosage Forms 1633
90 Coating of Pharmaceutical Dosage Forms 1666
91 Sustained-Release Drug Delivery Systems 1676
92 Aerosols 1694

Part 9 Pharmaceutical Practice

93 Ambulatory Patient Care 1715
94 Institutional Patient Care 1737
95 Long-Term Care Facilities 1758
96 The Pharmacist and Public Health 1773

DOCKET ALARM Find authenticated court documents without watermarks at docketalarm.com.

97 The Patient: Behavioral Determinants 1788
98 Patient Communication 1796
99 Drug Education 1803
100 Patient Compliance 1813
101 The Prescription 1828
102 Drug Interactions 1842
103 Clinical Drug Literature 1859
104 Health Accessories 1864
105 Surgical Supplies 1895
106 Poison Control 1905
107 Laws Governing Pharmacy 1914
108 Community Pharmacy Economics and Management 1940
109 Dental Services 1957

Index

Alphabetic Index 1967

DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.

CHAPTER 75

Preformulation

Louis J Ravin, PhD
Department of Pharmaceutics
Research & Development
Smith Kline & French Laboratories
King of Prussia, PA 19406

Galen W Radebaugh, PhD
Director of Pharmaceutics
Parke-Davis Pharmaceutical Research Division
Warner-Lambert Co
Morris Plains, NJ 07950

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.

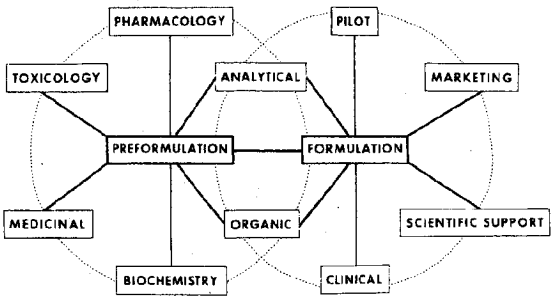

Fig 75-1. The wheels of product development.

DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.