

The Theory and Practice of Industrial Pharmacy

LEON LACHMAN, Ph.D.

Lachman Consultant Services, Inc.

Garden City, New York

HERBERT A. LIEBERMAN, Ph.D.

H. H. Lieberman Associates, Inc.

Consultant Services

Livingston, New Jersey

JOSEPH L. KANIG, Ph.D.

Kanig Consulting and Research Associates, Inc.

Ridgefield, Connecticut

THIRD EDITION

INDIAN EDITION

VARGHESE PUBLISHING HOUSE

Hind Rajasthan Building

Dadar Bombay 400 014

1987

AstraZeneca Exhibit 2134 p. 1

Lea & Febiger
600 Washington Square
Philadelphia, PA 19106-4198
U.S.A.
(215) 922-1330

Library of Congress Cataloging in Publication Data
Main entry under title:

The Theory and practice of industrial pharmacy.

Includes bibliographies and index.

1. Pharmacy. 2. Drug trade. I. Lachman, Leon,
1929— II. Lieberman, Herbert A., 1920—
III. Kanig, Joseph L., 1921— [DNLM: 1. Drug
Industry.

QV 704 T396]

RSI92.L33 1985 615'.19 84-27806

ISBN 0-8121-0977-5

First Edition, 1970

Second Edition, 1976

Copyright © 1986 by Lea & Febiger. Copyright under the
International Copyright Union. All Rights Reserved. This book is
protected by copyright. No part of it may be reproduced in any
manner or by any means without written permission from the
publisher.

FIRST INDIAN REPRINT, 1987

SECOND INDIAN REPRINT, 1989

THIRD INDIAN REPRINT, 1990

FOURTH INDIAN REPRINT, 1991

Reprinted in India by special arrangement with LEA & FEBIGER
Philadelphia U S A.

Indian Edition published by

Varghese Publishing House, Hind Rajasthan Building, Dadar,
Bombay 400 014.

Reprinted in India by special arrangement with LEA & FEBIGER Philadelphia U S A.

Contents

Section I. Principles of Pharmaceutical Processing

1. Mixing 3
EDWARD G. RIPPPIE
2. Milling 21
EUGENE L. PARROT
3. Drying 47
ALBERT S. RANKELL, HERBERT A. LIEBERMAN, ROBERT F. SCHIFFMANN
4. Compression and Consolidation of Powdered Solids 66
KEITH MARSHALL
5. Basic Chemical Principles Related to Emulsion and Suspension Dosage Forms ✓ 100
STANLEY L. HEM, JOSEPH R. FELDKAMP, JOE L. WHITE
6. Pharmaceutical Rheology 123
JOHN H. WOOD
7. Clarification and Filtration ✓ 146
S. CHRAI

Section II. Pharmaceutical Dosage Form Design

8. Preformulation 171
EUGENE F. FIESE, TIMOTHY A. HAGEN
9. Biopharmaceutics 197
K.C. KWAN, M.R. DOBRINSKA, J.D. ROGERS, A.E. TILL, K.C. YEH
10. Statistical Applications in the Pharmaceutical Sciences 243
SANFORD BOLTON

Section III. Pharmaceutical Dosage Forms

11. Tablets 293
GILBERT S. BANKER, NEIL R. ANDERSON
12. Tablet Coating 346
JAMES A. SEITZ, SHASHI P. MEHTA, JAMES L. YEAGER

- 13. Capsules 374
 - Part One Hard Capsules 374
VAN B. HOSTETLER
 - Part Two Soft Gelatin Capsules 398
J.P. STANLEY
 - Part Three Microencapsulation 412
J.A. BAKAN
- 14. Sustained Release Dosage Forms 430
NICHOLAS G. LORDI
- 15. Liquids 457
J.C. BOYLAN
- 16. Pharmaceutical Suspensions 479
NAGIN K. PATEL, LLOYD KENNON*, R. SAUL LEVINSON
- 17. Emulsions 502
MARTIN M. RIEGER
- 18. Semisolids 534
BERNARD IDSON, JACK LAZARUS*
- 19. Suppositories 564
LARRY J. COBEN, HERBERT A. LIEBERMAN
- 20. Pharmaceutical Aerosols 589
JOHN J. SCIARRA, ANTHONY J. CUTIE
- 21. Sterilization 619
KENNETH E. AVIS, MICHAEL J. AKERS
- 22. Sterile Products 639
KENNETH E. AVIS

Section IV. Product Processing, Packaging, Evaluation, and Regulations

- 23. Pilot Plant Scale-Up Techniques 681
SAMUEL HARDER, GLENN VAN BUSKIRK
 - 24. Packaging Materials Science 711
CARLO P. CROCE, ARTHUR FISCHER, RALPH H. THOMAS
 - 25. Production Management 733
J.V. BATTISTA
 - 26. Kinetic Principles and Stability Testing 760
LEON LACHMAN, PATRICK DELUCA, MICHAEL J. AKERS
 - 27. Quality Control and Assurance 804
LEON LACHMAN, SAMIR A. HANNA, KARL LIN
 - 28. Drug Regulatory Affairs 856
WILLIAM R. PENDERGAST, RAYMOND D. MCMURRAY*
- INDEX 883

*Deceased.

Sustained Release Dosage Forms

NICHOLAS G. LORDI

With many drugs, the basic goal of therapy is to achieve a steady-state blood or tissue level that is therapeutically effective and nontoxic for an extended period of time. The design of proper dosage regimens is an important element in accomplishing this goal. A basic objective in dosage form design is to optimize the delivery of medication so as to achieve a measure of control of the therapeutic effect in the face of uncertain fluctuations in the *in vivo* environment in which drug release takes place. This is usually accomplished by maximizing drug availability, *i.e.*, by attempting to attain a maximum rate and extent of drug absorption; however, control of drug action through formulation also implies controlling bioavailability to reduce drug absorption rates. In this chapter, approaches to the formulation of drug delivery systems, based on the deliberate control of drug availability, are considered with emphasis on peroral dosage forms.

The Sustained Release Concept

Sustained release, sustained action, prolonged action, controlled release, extended action, timed release, depot, and repository dosage forms are terms used to identify drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. In the case of injectable dosage forms, this period may vary from days to months. In the case of orally administered forms, however, this period is measured in hours and critically depends on the residence time of the dosage form in the gastrointestinal (GI) tract. The term "controlled release" has become associated with those systems from which therapeutic agents may be automatically delivered at predefined rates over a long period of time. Products of this type have

been formulated for oral, injectable, and topical use, and include inserts for placement in body cavities as well.¹

The pharmaceutical industry provides a variety of dosage forms and dosage levels of particular drugs, thus enabling the physician to control the onset and duration of drug therapy by altering the dose and/or mode of administration. In some instances, control of drug therapy can be achieved by taking advantage of beneficial drug interactions that affect drug disposition and elimination, *e.g.*, the action of probenecid, which inhibits the excretion of penicillin, thus prolonging its blood level. Mixtures of drugs might be utilized to potentiate, synergize, or antagonize given drug actions. Alternately, drug mixtures might be formulated in which the rate and/or extent of drug absorption is modified. Sustained release dosage form design embodies this approach to the control of drug action, *i.e.*, through a process of either drug modification or dosage form modification, the absorption process, and subsequently drug action, can be controlled.

Physicians can achieve several desirable therapeutic advantages by prescribing sustained release forms. Since the frequency of drug administration is reduced, patient compliance can be improved, and drug administration can be made more convenient as well. The blood level oscillation characteristic of multiple dosing of conventional dosage forms is reduced, because a more even blood level is maintained. A less obvious advantage, implicit in the design of sustained release forms, is that the total amount of drug administered can be reduced, thus maximizing availability with a minimum dose. In addition, better control of drug absorption can be attained, since the high blood level peaks that may be observed after administration of a dose of a high-availability drug can be reduced by formulation in an extended action form. The safety margin of

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.