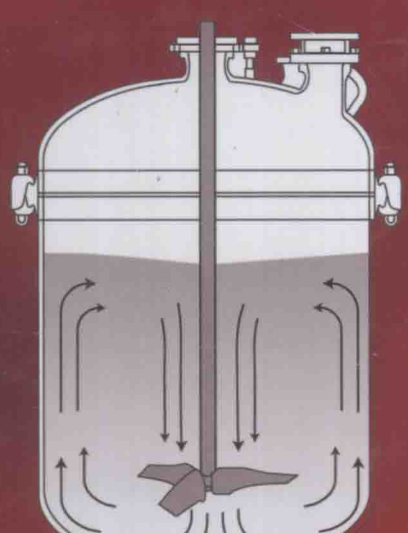
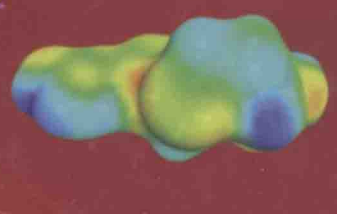
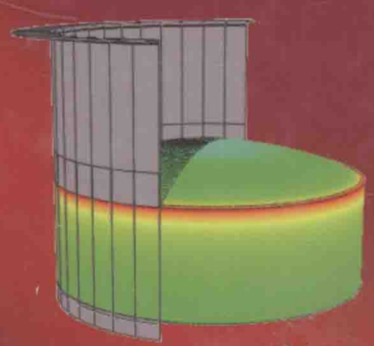
Edited by
David J. am Ende

CHEMICAL ENGINEERING IN THE PHARMACEUTICAL INDUSTRY

R&D to Manufacturing



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WILEY
A JOHN WILEY & SONS, INC., PUBLICATION

Published by John Wiley & Sons, Inc., Hoboken, New Jersey
Published simultaneously in Canada

Library of Congress Cataloging-in-Publication Data:

Chemical engineering in the pharmaceutical industry : R&D to manufacturing / edited by David J. am Ende.
p. cm.
Includes index.
ISBN 978-0-470-42669-2 (cloth)
1. Pharmaceutical technology. 2. Biochemical engineering. 3. Chemical engineering. I. Ende, David J. am.
RS192.C525 2010
615'.19–dc22

2010013146

Printed in Singapore

10 9 8 7 6 5 4 3 2 1

CHEMICAL ENGINEERING IN THE PHARMACEUTICAL INDUSTRY

PREFACE

Chemical Engineering in the Pharmaceutical Industry is unique in many ways to what is traditionally taught in schools of chemical engineering. This book is therefore intended to cover many important concepts and applications of chemical engineering science that are particularly important to the Pharmaceutical Industry. There have been several excellent books written recently on the subjects of process chemistry in the pharmaceutical industry and separately on formulation development, but relatively little has been published specifically with a focus on chemical engineering.

The intention of the book is to highlight the importance and value of chemical engineering to the development and commercialization of pharmaceuticals covering active pharmaceutical ingredient (API) and drug product (DP) as well as analytical methods. It should serve as a resource for practicing chemical engineers as well as for chemists, analysts, technologists, and operations and management team members—all those who partner to bring pharmaceuticals successfully to market. The latter will benefit through an exposure to the mathematical and predictive approach and the broader capabilities of chemical engineers and also by the illustration of chemical engineering science as applied specifically to pharmaceutical problems. This book emphasizes both the need for scientific integration of chemical engineers with synthetic organic chemists within process R&D and the importance of the interface between R&D engineers and manufacturing engineers. The importance of analytical chemists and other scientific disciplines necessary to deliver pharmaceuticals to the market place is also emphasized with chapters dedicated to selected topics.

Although specific workflows for engineers in R&D depend on each company's specific organization, in general it is clear that, as part of a multidisciplinary team in R&D, chemical engineering practitioners offer value in many ways including API and DP process design, scale-up assessment from laboratory to plant, process modeling, process understanding, and general process development that ultimately reduces cost and ensures safe, robust, and environmentally friendly processes are transferred to manufacturing. How effective the teams leverage each of the various skill sets (i.e., via resource allocation) to arrive at an optimal process depends in part on the roles and responsibilities as determined within each organization and company. In general, it is clear that with increased cost pressures facing the pharmaceutical industry, including R&D and manufacturing, opportunities to leverage the field of chemical engineering science continue to increase. Indeed I have observed a significant increase in chemical engineering emphasis in API process development within Pfizer over the 15 years since I joined the company and especially in the past 5 years.

This book is divided into four main parts:

(1) Introduction
(2) Active Pharmaceutical Ingredient (API)
(3) Analytical Methods and Applied Statistics
(4) Drug Product (DP)

The introductory chapters span roles and opportunities for chemical engineering in small-molecule API, biologicals, drug products, as well as environmental sustainability and quality by design (QbD) concepts. The Active Pharmaceutical Ingredient part consists of 23 chapters covering chemical engineering principles applied to pharmaceutical specific unit operations (reaction engineering, crystallization, chromatography, filtration, drying, etc.) as well as pilot plant and scale-up manufacturing assessment chapters, including process safety. Process modeling promises to have significant payback as more *in silico* screening enables process design to be performed with fewer resources (for selection process conditions/optimization, solubility, distillation, and extraction design, etc.). Several chapters are devoted to process modeling with emphasis on several of the software tools currently available. The section on drug product includes formulation chapters as well as chapters highlighting unit operations specific to drug product (wet granulation, dry granulation, extrusion, controlled release, and lyophilization). In addition, process modeling within drug product chapter describes the various modeling approaches used to understand and predict performance of powder blending, mixing, tablet presses, tablet coating, and so on. The Analytical Methods and Applied Statistics part describes important topics on chemometrics, statistics, and analytical methods applied toward chemical engineering problems (e.g., material balance, kinetics, design of experiments, or quality by design for analytical methods).

The contributors were encouraged to provide worked out examples—so in most chapters a quantitative example is offered to illustrate key concepts and problem-solving approaches. In this way, the chapters will serve to help others solve similar problems.

There are many people to thank who made this work possible. First, I would like to thank all the contributors of this book. I also would like to thank my colleagues at Pfizer for writing many of the chapters and for my management (past and present) who encouraged and made this effort possible and who continue to encourage the role of chemical engineering in chemical R&D and pharmaceutical sciences.

Special thanks to my family (Mary, Nathan, Noah, and Brianna) for their support during the preparation of this book. Special thanks to Mary, not only for contributing two chapters to this book but also for her assistance in all phases of the project including the cover art. Finally, a special thanks to my parents for their encouragement to pursue chemical engineering in 1983 and their support through my attendance at the University of Iowa and Purdue University.

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Chemical R&D
Pfizer, Inc.
Groton, CT
January 2010

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CONVERSION TABLE

Quantity	Equivalent Values
Length	1 m = 100 cm = 1000 mm = 10^6 μm = 10^{10} Å = 39.37 in = 3.2808 ft = 1.0936 yards = 0.0006214 mile 1 ft = 12 in = 0.3048 m = 1/3 yard = 30.48 cm
Area	1 m^2 = 10.76 ft^2 = 1550 in^2 = 10,000 cm^2 1 in^2 = 6.4516 cm^2 = 645.16 mm^2 = 0.00694 ft^2 1 ft^2 = 929.03 cm^2 = 0.092903 m^2
Volume	1 m^3 = 1000 L = 10^6 cm^3 (mL) = 1000 dm^3 = 35.3145 ft^3 = 220.83 imperial gallons = 264.17 gal (U.S.) 1 ft^3 = 1728 in^3 = 7.4805 U.S. gallons = 0.028317 m^3 = 28.317 L 1 gal (U.S.) = 3.785 L = 0.1337 ft^3 = 231 in^3
Mass	1 kg = 1000 g = 0.001 metric ton (MT) = 2.20462 lb_m = 35.27392 oz 1 lb_m = 16 oz = 453.593 g = 0.453593 kg 1 MT = 1000 kg = 2204.6 lb_m
Pressure	1 atm = 1.01325 bar = 1.01325 × 10^5 N/m^2 (Pa) = 0.101325 MPa = 101.325 kPa = 1.01325 × 10^6 dynes/cm^2 = 760 mmHg @ 0 °C (Torr) = 10.333 m H_2O @ 4 °C = 14.696 lb_f/in^2 (psi) = 33.9 ft H_2O @ 4 °C = 2116 lb_f/ft^2 = 29.921 in Hg @ 0 °C
Temperature	$°C = \frac{5}{9}(°F-32)$ $°F = (9/5°C) + 32$ $K = °C + 273.15 = \frac{5}{9}°R$ $°R = °F + 459.67$
Density	1 g/cm^3 = kg/L = 62.4 lb_m/ft^3 1 lb_m/ft^3 = 16.0185 kg/m^3 = 0.01602 g/cm^3

Quantity	Equivalent Values
Force	1 N = 1 kg-m/s^2 = 10^5 dynes = 10^5 g-cm/s^2 = 0.22481 lb_f 1 lb_f = 32.174 lb_m ft/s^2 = 4.4482 N = 4.4482 × 10^5 dynes
Energy	Based on conventional thermochemical definitions of calorie and Btu, 1 J = 1 N m = 0.23901 cal = 10^7 ergs = 10^7 dyne cm 1 J = 2.778 × 10^{-7} kW-h = 0.7376 ft-lb_f = 0.00094845 Btu 1 cal = 4.184 J (exact) 1 Btu = 1054.35 J = 1.054 kJ = 251.9958 cal = 0.2930 W-h = 10.406 L-atm 1 kW-h = 3.6 MJ *Note*: The international steam table (IT) convention defines $(calorie)_{IT}$ = 4.1868 J and $(Btu)_{IT}$ = 1055.056 J.
Heat generation	1 Btu/lb_m-h = 0.64612 W/kg
Heat transfer coefficient	1 W/(m^2 K) = 0.1761 Btu/(h-ft^2 °F) 1 Btu/(h-ft^2 °F) = 5.678 W/(m^2 K) = 4.886 kcal/(h-m^2 °C)
Latent heat	1 Btu/lb_m = 2.326 kJ/kg 1 J/g = 0.23901 cal/g
Power	1 W = 1 J/s = 1 kg-m^2/s^3 = 1 Nm/s = 0.23901 cal/s = 0.7376 ft-lb_f/s = 0.0009486 Btu/s = 3.414 Btu/h = 0.001341 hp
Power/volume	1 W/L = kW/m^3 = 0.03798 hp/ft^3 = 96.67 Btu/h-ft^3 = 12.9235 Btu/h-gal
Specific heat	1 kJ/(kg-K) = J/(g-K) = 0.2389 kcal/(kg °C) = 0.2389 Btu/(lb_m °F) 1 Btu/(lb_m °F) = 1 cal/(g °C)

(*Continued*)

Quantity	Equivalent Values
Thermal conductivity	1 Btu/(h-ft °F) = 1.7307 W/(m-K) = 0.00413 cal/(s cm-K) 1 W/(m-K) = 0.5779 Btu/(h-ft °F) = 0.85984 kcal/(h-m °C)
Throughput (continuous @ 365 days/year)	1 year = 365 days = 8760 h = 5.256×10^5 min 1 kg/h = 16.67 g/min = 24 kg/day = 8760 kg/year = 8.76 MT/year 10 MT/year = 10,000 kg/year = 27.4 kg/day = 1.14 kg/h = 19.03 g/min 1 Billion tablets/year = 2.74×10^6 tablets/day = 114,155 tablets/h = 31.7 tablets/s 10 MT API/year = 10,000 kg API/year formulated as a 10 mg dose API/tablet = 1.0 Billion tablets/year

Quantity	Equivalent Values
Diffusivity	1 m^2/s = 10.76 ft^2/s = 38749 ft^2/h 1 ft^2/s = 929.03 cm^2/s = 0.092903 m^2/s
Viscosity	1 centipose (cp) = 0.01 poise = 0.01g/(cm-s) = 0.001 N-s/m^2 (Pa-s) = 3.6 kg/(m-h) = 0.001 kg/(m-s) = 2.419 lb_m/(ft-h) 1 centistoke (cs) = 1×10^{-6} m^2/s = 0.01 stoke = 0.0036 m^2/h = 0.0388 ft^2/h
Gas constant R	8.31451 J/(mol-K) = 1.987 cal/(mol-K) = 1.987 Btu/(lb-mol °R) 0.0820578 L-atm/(mol-K) = 82.057 atm-cm^3/(mol-K) = 10.73 psi-ft^3/(lb-mol °R)
Gravitational force	$g = 9.8066$ m/s^2 = 32.174 ft/s^2

CONTENTS

PART I

INTRODUCTION