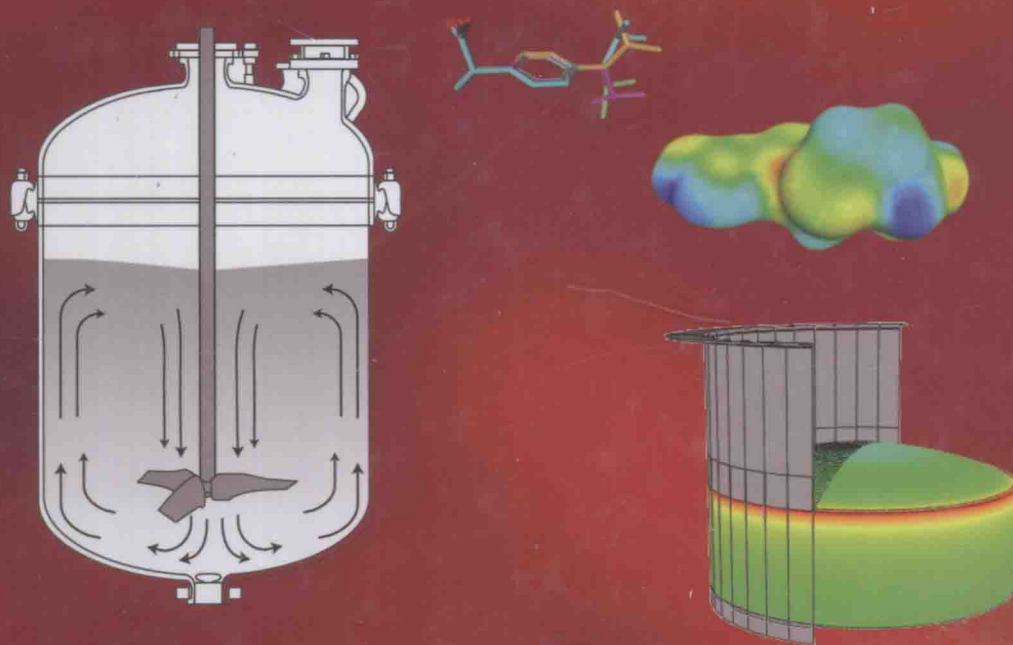


Edited by
David J. van Ende

CHEMICAL ENGINEERING IN THE PHARMACEUTICAL INDUSTRY

R&D to Manufacturing



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DAVID J. AM ENDE



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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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CONVERSION TABLE

Quantity	Equivalent Values
Length	$1 \text{ m} = 100 \text{ cm} = 1000 \text{ mm} = 10^6 \mu\text{m} = 10^{10} \text{ \AA}$ $= 39.37 \text{ in} = 3.2808 \text{ ft} = 1.0936 \text{ yards}$ $= 0.0006214 \text{ mile}$ $1 \text{ ft} = 12 \text{ in} = 0.3048 \text{ m} = 1/3 \text{ yard} = 30.48 \text{ cm}$
Area	$1 \text{ m}^2 = 10.76 \text{ ft}^2 = 1550 \text{ in}^2 = 10,000 \text{ cm}^2$ $1 \text{ in}^2 = 6.4516 \text{ cm}^2 = 645.16 \text{ mm}^2 = 0.00694 \text{ ft}^2$ $1 \text{ ft}^2 = 929.03 \text{ cm}^2 = 0.092903 \text{ m}^2$
Volume	$1 \text{ m}^3 = 1000 \text{ L} = 10^6 \text{ cm}^3 (\text{mL}) = 1000 \text{ dm}^3$ $= 35.3145 \text{ ft}^3 = 220.83 \text{ imperial gallons}$ $= 264.17 \text{ gal (U.S.)}$ $1 \text{ ft}^3 = 1728 \text{ in}^3 = 7.4805 \text{ U.S. gallons}$ $= 0.028317 \text{ m}^3 = 28.317 \text{ L}$ $1 \text{ gal (U.S.)} = 3.785 \text{ L} = 0.1337 \text{ ft}^3 = 231 \text{ in}^3$
Mass	$1 \text{ kg} = 1000 \text{ g} = 0.001 \text{ metric ton (MT)}$ $= 2.20462 \text{ lb}_m = 35.27392 \text{ oz}$ $1 \text{ lb}_m = 16 \text{ oz} = 453.593 \text{ g} = 0.453593 \text{ kg}$ $1 \text{ MT} = 1000 \text{ kg} = 2204.6 \text{ lb}_m$
Pressure	$1 \text{ atm} = 1.01325 \text{ bar} = 1.01325 \times 10^5 \text{ N/m}^2 (\text{Pa})$ $= 0.101325 \text{ MPa}$ $= 101.325 \text{ kPa} = 1.01325 \times 10^6 \text{ dynes/cm}^2$ $= 760 \text{ mmHg @ } 0^\circ\text{C (Torr)}$ $= 10.333 \text{ m H}_2\text{O @ } 4^\circ\text{C}$ $= 14.696 \text{ lb}_f/\text{in}^2 (\text{psi}) = 33.9 \text{ ft H}_2\text{O @ } 4^\circ\text{C}$ $= 2116 \text{ lb}_f/\text{ft}^2$ $= 29.921 \text{ in Hg @ } 0^\circ\text{C}$
Temperature	$^\circ\text{C} = \frac{5}{9} (^\circ\text{F} - 32)$ $^\circ\text{F} = (9/5^\circ\text{C}) + 32$ $\text{K} = ^\circ\text{C} + 273.15 = \frac{5}{9}^\circ\text{R}$ $^\circ\text{R} = ^\circ\text{F} + 459.67$
Density	$1 \text{ g/cm}^3 = \text{kg/L} = 62.4 \text{ lb}_m/\text{ft}^3$ $1 \text{ lb}_m/\text{ft}^3 = 16.0185 \text{ kg/m}^3 = 0.01602 \text{ g/cm}^3$

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

(Continued)

Quantity	Equivalent Values	Quantity	Equivalent Values
Thermal conductivity	$1 \text{ Btu}/(\text{h}\cdot\text{ft}\cdot^{\circ}\text{F}) = 1.7307 \text{ W}/(\text{m}\cdot\text{K})$ $= 0.00413 \text{ cal}/(\text{s}\cdot\text{cm}\cdot\text{K})$ $1 \text{ W}/(\text{m}\cdot\text{K}) = 0.5779 \text{ Btu}/(\text{h}\cdot\text{ft}\cdot^{\circ}\text{F})$ $= 0.85984 \text{ kcal}/(\text{h}\cdot\text{m}\cdot^{\circ}\text{C})$	Diffusivity	$1 \text{ m}^2/\text{s} = 10.76 \text{ ft}^2/\text{s} = 38749 \text{ ft}^2/\text{h}$ $1 \text{ ft}^2/\text{s} = 929.03 \text{ cm}^2/\text{s} = 0.092903 \text{ m}^2/\text{s}$
Throughput (continuous @ 365 days/year)	$1 \text{ year} = 365 \text{ days} = 8760 \text{ h} = 5.256 \times 10^5 \text{ min}$ $1 \text{ kg}/\text{h} = 16.67 \text{ g}/\text{min} = 24 \text{ kg}/\text{day}$ $= 8760 \text{ kg}/\text{year} = 8.76 \text{ MT}/\text{year}$ $10 \text{ MT}/\text{year} = 10,000 \text{ kg}/\text{year} = 27.4 \text{ kg}/\text{day}$ $= 1.14 \text{ kg}/\text{h} = 19.03 \text{ g}/\text{min}$ $1 \text{ Billion tablets}/\text{year} = 2.74 \times 10^6 \text{ tablets}/\text{day}$ $= 114,155 \text{ tablets}/\text{h} = 31.7 \text{ tablets}/\text{s}$ $10 \text{ MT API}/\text{year} = 10,000 \text{ kg API}/\text{year}$ $\text{formulated as a } 10 \text{ mg dose API}/\text{tablet}$ $= 1.0 \text{ Billion tablets}/\text{year}$	Viscosity	$1 \text{ centipose (cp)} = 0.01 \text{ poise} = 0.01 \text{ g}/(\text{cm}\cdot\text{s})$ $= 0.001 \text{ N}\cdot\text{s}/\text{m}^2 \text{ (Pa}\cdot\text{s)}$ $= 3.6 \text{ kg}/(\text{m}\cdot\text{h}) = 0.001 \text{ kg}/(\text{m}\cdot\text{s})$ $= 2.419 \text{ lb}_m/(\text{ft}\cdot\text{h})$ $1 \text{ centistoke (cs)} = 1 \times 10^{-6} \text{ m}^2/\text{s} = 0.01 \text{ stoke}$ $= 0.0036 \text{ m}^2/\text{h} = 0.0388 \text{ ft}^2/\text{h}$
		Gas constant R	$8.31451 \text{ J}/(\text{mol}\cdot\text{K}) = 1.987 \text{ cal}/(\text{mol}\cdot\text{K})$ $= 1.987 \text{ Btu}/(\text{lb}\cdot\text{mol}\cdot^{\circ}\text{R})$ $0.0820578 \text{ L}\cdot\text{atm}/(\text{mol}\cdot\text{K}) = 82.057 \text{ atm}\cdot\text{cm}^3/(\text{mol}\cdot\text{K})$ $= 10.73 \text{ psi}\cdot\text{ft}^3/(\text{lb}\cdot\text{mol}\cdot^{\circ}\text{R})$
		Gravitational force	$g = 9.8066 \text{ m}/\text{s}^2 = 32.174 \text{ ft}/\text{s}^2$

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PART I

INTRODUCTION

