CHEMICAL ENGINEERING IN THE PHARMACEUTICAL INDUSTRY
CHEMICAL ENGINEERING IN THE PHARMACEUTICAL INDUSTRY

Drug Product Design, Development, and Modeling

Second Edition

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Pharmaceutical research and development is unique to traditional chemical engineering curricula, which has focused intensively on the chemical industry. This book is intended to be used as a professional reference and as a textbook reference for undergraduate or graduate studies in engineering and pharmaceutical sciences. Many of the experimental methods related to drug product design and process development are learned on the job. This book is intended to provide many of those important concepts that R&D engineers and manufacturing engineers should know and be familiar in those roles. Formulation design and process development of drug products will be treated from the engineer’s perspective and span from solid to semisolid and lyophilized drug products and sterilization. Technology transfer and scale-up of batch processes will be exemplified experimentally and computationally, including in silico process modeling tools that streamline experimental screening approaches. The emerging field of continuous drug product manufacturing will also be discussed by skilled professionals. Although continuous manufacturing is in the mainstream for chemical engineers, it is unique in the pharmaceutical industry with regard to the range of scales and the complex economics associated with transforming existing batch plant capacity. Basic analytics for quantitation of drug product quality attributes, such as potency, purity, content uniformity, and dissolution, will be addressed with consideration of the applied statistics, process analytical technology (PAT), and process control. In addition, contemporary methods of data analysis will be introduced, and these concepts extended into quality by design strategies for regulatory filings. Advances in the drug product pharmaceutical R&D are now being strongly supported by precompetitive consortia. Finally, technical chapters on commonly used software tools with examples are an important part of this book.

This book deals with the elements of chemical engineering science unique to drug product development and commercialization specifically related to the successful formulation design and process development of the active pharmaceutical ingredient (API) into the desired dosage form. It emphasizes the need for scientific integration of chemical engineering and pharmaceutical sciences during R&D, as well as with manufacturing engineers, analytical chemists, and other scientific disciplines necessary to deliver pharmaceuticals to the market place. As part of a multidisciplinary team in R&D, engineering contributes to process design, process understanding, and process development, which ultimately enables improvements in quality, reduces cost, and ensures safe, robust processes are transferred to manufacturing. As cost and time pressures increase, engineers play an important role in leveraging process modeling tools that can help focus the experimental work more rapidly with techniques to ensure the desired formulation and manufacturing process will scale as planned — so as to avoid surprises on scale-up. This book covers the basic chemical engineering theories with its emphasis toward providing experimental methods, analysis, and contemporary process modeling methods in chemical engineering. This book provides guidance on analytical methods for engineers in R&D as well as manufacturing. In addition, emphasis is given on experimental techniques and considerations necessary to address scale-up issues and approach general process design-related challenges to pharmaceutical process R&D. As a professional reference it is intended to be part “text” book and part “how-to” book and includes many worked examples related to problem solving via experimental and modeling methods. The book is organized to provide a foundational introduction on challenges and opportunities for chemical engineers in this industry in Part I. In Part II, chemistry and engineering activities
I am grateful to all the contributing authors for making this book possible. I would also like to thank my supervisors and leadership team for their long-standing support of the important role chemical engineers play at Pfizer. A special note of gratitude to Lyndra Therapeutics for making my next career endeavor an inspiring one. Thank you to my graduate advisor, Professor Nicholas Peppas, for all of your amazing support in my academic development and opportunity to pursue chemical engineering in the pharmaceutical field.

I would also like to state a special note of gratitude to my ever-supportive family (David, Nathan, Noah, and Brianna) for encouraging me to pursue this opportunity to serve as editor. It is a pleasure to work with my strongest advocate in my career and life, who is also the best chemical engineer I know – my husband David. Finally, I am ever grateful to my family (James, Donna, Tami, Kevin, Jaime, Miles, and Michele) for their unwavering belief in me to pursue degrees in chemical engineering at the University of Iowa (BS 1988) and Purdue University (PhD 1993).

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# UNIT CONVERSIONS

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<th>Equivalent Values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Length</strong></td>
<td></td>
</tr>
<tr>
<td>1 m</td>
<td>100 cm = 1000 mm = 10^6 μm = 10^{10} Å</td>
</tr>
<tr>
<td>1 m</td>
<td>39.37 in = 3.2808 ft = 1.0936 yards = 0.0006214 mile</td>
</tr>
<tr>
<td>1 ft</td>
<td>12 in = 0.3048 m = 1/3 yard = 30.48 cm</td>
</tr>
<tr>
<td><strong>Area</strong></td>
<td></td>
</tr>
<tr>
<td>1 m²</td>
<td>10.76 ft² = 1550 in² = 10 000 cm²</td>
</tr>
<tr>
<td>1 in²</td>
<td>6.4516 cm² = 645.16 mm² = 0.00694 ft²</td>
</tr>
<tr>
<td>1 ft²</td>
<td>929.03 cm² = 0.092903 m²</td>
</tr>
<tr>
<td>Example:</td>
<td>cross-sectional area of ¼&quot; ID tube: ( \frac{\pi d^2}{4} ) = \frac{\pi 0.25^2}{4} = 0.0491 in² = 0.3167 cm²</td>
</tr>
<tr>
<td><strong>Volume</strong></td>
<td></td>
</tr>
<tr>
<td>1 m³</td>
<td>1000 L = 10^6 cm³ (ml) = 1000 dm³</td>
</tr>
<tr>
<td>1 m³</td>
<td>35.3145 ft³ = 220.83 imperial gallons = 264.17 gal (U)</td>
</tr>
<tr>
<td>1 ft³</td>
<td>1728 in³ = 7.4805 gal (US) = 0.028317 m³ = 28.317 L</td>
</tr>
<tr>
<td>1 gal (US)</td>
<td>3.785 L = 0.1337 ft³ = 231 in³ = 4 quart = 8 pints</td>
</tr>
<tr>
<td>1 L</td>
<td>0.264 gal = 1.0567 quart = 2.113 pint = 4.2267 cup = 202.88 teaspoon (US) = 0.035 31 ft³ = 61.02 in³</td>
</tr>
<tr>
<td><strong>Mass</strong></td>
<td></td>
</tr>
<tr>
<td>1 kg</td>
<td>1000 g = 0.001 metric ton (MT) = 2.20462 lbm = 35.273 oz</td>
</tr>
<tr>
<td>1 lbm</td>
<td>16 oz = 453.593 g = 0.453593 kg</td>
</tr>
<tr>
<td>1 ton (metric)</td>
<td>1000 kg = 2204.6 lbm</td>
</tr>
<tr>
<td><strong>Pressure</strong></td>
<td></td>
</tr>
<tr>
<td>1 atm</td>
<td>1.01325 bar = 1.01325 × 10^5 \frac{N}{m^2} (Pa) = 0.101325 MPa</td>
</tr>
<tr>
<td></td>
<td>= 101.325 kPa = 1.01325 × 10^5 \frac{dynes}{cm^2} = 1.033 \frac{kgf}{cm^2}</td>
</tr>
<tr>
<td></td>
<td>= 760 mm Hg at 0 °C (torr) = 10.333 m H₂O at 4 °C</td>
</tr>
<tr>
<td></td>
<td>= 14.696 \frac{lbf}{in^2} (psi) = 33.9 ft H₂O at 4 °C = 2116 \frac{lbf}{ft^2}</td>
</tr>
<tr>
<td></td>
<td>= 29.921 in Hg at 0 °C</td>
</tr>
<tr>
<td>1 MPa</td>
<td>9.869 atm = 10 bar = 145.04 psi</td>
</tr>
<tr>
<td>1 psi</td>
<td>2.31 ft H₂O = 0.0680 atm</td>
</tr>
<tr>
<td></td>
<td>= 703.1 \frac{kgf}{m^2} = 0.07031 \frac{kgf}{cm^2} = 51.71 mm Hg</td>
</tr>
</tbody>
</table>

**Note:** \( P_{\text{absolute}} = P_{\text{gauge}} + P_{\text{atmospheric}} \)

For example, if a pressure gauge reads 30 psig, then the absolute pressure is 44.7 psia,

**i.e.** \( P_{\text{absolute}} = P_{\text{gauge}} + P_{\text{atmospheric}} = 30 + 14.7 = 44.7 \text{ psia} \)
<table>
<thead>
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<tr>
<td><strong>Pressure (continued)</strong></td>
<td>Vacuum: A vacuum gauge may have range from 0 to −30 in Hg. So if the vacuum gauge is reading −25.0 in Hg then the absolute pressure is $P_{\text{absolute}} = P_{\text{gauge}} + P_{\text{atmospheric}} = −25.0 + 29.921 = +4.921$ in Hg = 0.16 atm = 2.42 psia (assuming that the atmospheric pressure is taken at sea level equivalent to 1.0 atm = 29.921 in Hg)</td>
</tr>
<tr>
<td><strong>Temperature</strong></td>
<td>°C = 5/9 (*F − 32) *F = 9/5 °C + 32 K = °C + 273.15 = 5/9 °R °R = °F + 459.67 Freezing point H₂O = 0 °C or 32 °F or 273.15 K Boiling point H₂O = 100 °C or 212 °F or 373.15 K</td>
</tr>
</tbody>
</table>
| **Density (ρ)** | \[
\begin{align*}
1 \text{ g/cm}^3 &= 1 \text{ g/ml} = 1 \text{ kg/L} = 62.43 \text{ lbm/ft}^3 = 1000 \text{ kg/m}^3 = 8.345 \text{ lbm/U.S.gal} \\
100 \text{ lbm/ft}^3 &= 1601.85 \text{ kg/m}^3 = 1.602 \text{ g/cm}^3 \\
\rho(\text{H}_2\text{O}, 20 ^\circ\text{C}) &= 998.2 \text{ kg/m}^3 = 0.9982 \text{ g/cm}^3 \\
\rho(\text{H}_2\text{SO}_4, 25 ^\circ\text{C}, 95 \text{ wt %}) &= 1.84 \text{ g/cm}^3
\end{align*}
\]
| **Force** | \[
\begin{align*}
1 \text{ N} &= 1 \text{ kg} \cdot \text{m/sec}^2 = 10^5 \text{ dynes} = 10^8 \text{ g} \cdot \text{cm/sec}^2 = 0.22481 \text{ lbf} = 0.102 \text{ kgf} \\
1 \text{ lbf} &= 32.174 \text{ lbm} \cdot \text{ft/sec}^2 = 4.4482 \text{ N} = 4.4482 \times 10^5 \text{ dynes} \\
1 \text{ kgf} &= 1 \text{ kg} \cdot 9.80665 \text{ m/sec}^2 = 9.80665 \text{ kg} \cdot \text{m/sec}^2 = 9.80665 \text{ N} = 2.205 \text{ lbf}
\end{align*}
\]
| **Energy** | \[
\begin{align*}
1 \text{ W} &= \text{J/sec} \\
1 \text{ calorie} &= 4.184 \text{ J} \text{ (thermochemical)} \\
1 \text{ J} &= 1 \text{ N} \cdot \text{m} = 1 \text{ W} \cdot \text{sec} = 0.23901 \text{ cal} = 10^7 \text{ ergs} = 10^7 \text{ dyne-cm} \\
1 \text{ J} &= 2.778 \times 10^{-7} \text{ kW} \cdot \text{hr} = 0.7376 \text{ ft-lbf} = 0.00094845 \text{ Btu} \\
1 \text{ Btu} &= 1054.35 \text{ J} = 1.054 \text{ kJ} = 251.996 \text{ cal} = 0.2929 \text{ W} \cdot \text{hr} = 1054.35 \text{ N} \cdot \text{m} \\
1 \text{ kWh} &= 3.6 \text{ MJ}
\end{align*}
\]
| **Heat generation rate** | \[
\begin{align*}
1 \text{ Btu/\text{lbm-\text{hr}}} &= 0.64612 \text{ W/\text{kg}}
\end{align*}
\]
| **Heat transfer coefficient (U_o, h_o)** | \[
\begin{align*}
1 \text{ W/ (m}^2\text{K)} &= 0.1761 \text{ Btu/ (hr} \cdot \text{ft}^2\text{\circ F}) \\
1 \text{ Btu/ (hr} \cdot \text{ft}^2\text{\circ F)} &= 5.678 \text{ W/ (m}^2\text{K)} = 4.882 \text{ kcal/ (hr m}^2\text{\circ C)}
\end{align*}
\]
| **Nusselt Number (Nu)** | \[
\text{Nu} = \frac{hD}{k} \equiv \frac{\text{conduction + convection}}{\text{conduction}}
\]

where $h$ is the heat transfer coefficient, $D$ is the pipe diameter, and $k$ is thermal conductivity. For purely laminar and fully developed pipe flow (conduction dominates) limiting cases:

- **Case of uniform heat flux or constant temperature difference:**
  \[
  \text{Nu}_\infty = \frac{h_\infty D}{k} \approx 4.364
  \]

- **Case of constant wall temperature:**
  \[
  \text{Nu}_\infty = \frac{h_\infty D}{k} \approx 3.656
  \]
### Quantity Equivalent Values

**Nusselt Number (\(\text{Nu}\)) (continued)**

For *turbulent* pipe flow:  

*Dittus-Boelter Equation:*

\[
\text{Nu} \equiv \frac{hD}{k} = 0.023 \text{Re}^{0.8} \text{Pr}^n
\]

\[
n = \begin{cases} 
0.4 & \text{for heating} \\
0.3 & \text{for cooling}
\end{cases}
\]

Dittus-Boelter valid for: \(10\,000 < \text{Re} < 120\,000, 0.7 < \text{Pr} < 120, \frac{L}{D} > 60\) (ie fully developed) and *when the pipe temperature is within 10 °F for liquids and 100 °F for gases.*  

*Sieder-Tate Equation:*

\[
\text{Nu} \equiv \frac{hD}{k} = 0.023 \text{Re}^{0.8} \text{Pr}^{1/3} \left(\frac{\mu_b}{\mu_{\text{wall}}}\right)^{0.14}
\]

Valid for \(\text{Re} > 10\,000, \frac{L}{D} > 60,\) higher Prandtl numbers \(0.7 < \text{Pr} < 16\,700,\) and larger temperature differences between bulk and wall. Properties evaluated at bulk temperature except for \(\mu_{\text{wall}}\) which is evaluated at the wall temperature.  

*Source:* From Pitts and Sissom [1].

### Prandtl Number (\(\text{Pr}\))

\[
\text{Pr} = \frac{C_p \mu}{k} = \frac{\text{viscous diffusion rate}}{\text{heat conduction rate}}
\]

Prandtl number is a characteristic of the fluid. Liquids in general have high Prandtl numbers.  

- Ethylene glycol \(0 °C = 615\)
- Water at \(20 °C = 7.02\)
- Water at \(80 °C = 2.22\)
- Steam \(107 °C \approx 1.06\)
- Gases \(\approx 0.7\)

### Latent heat

- \(1\) Btu \(\text{lb}_m = 2.326\) kJ/kg
- \(1\) J \(\text{g} = 0.23901\) cal/g  

\(\Delta H_{\text{fus}}\) \(\text{H}_2\text{O} = 6.01\) kJ/mol or \(334\) J/g  

\(\Delta H_{\text{vap}}\) \(\text{H}_2\text{O} = 2230\) J/g \(= 40.65\) kJ/mol

### Power

- \(1\) W \(= \frac{1}{\text{sec}} = \frac{1}{\text{sec}} = \frac{1}{\text{sec}} = \frac{0.23901}{\text{cal}} = 0.7376 \frac{\text{ft}-\text{lb}}{\text{sec}} = 0.0009485 \frac{\text{Btu}}{\text{sec}} = 3.414 \frac{\text{Btu}}{\text{hr}} = 0.001341 \text{hp}\)

### Power/volume

- \(1\) W \(L = \frac{\text{kw}}{\text{m}^3} = 0.03798 \frac{\text{hp}}{\text{ft}^3} = 96.67 \frac{\text{Btu}}{\text{hr} - \text{ft}^3} = 12.9235 \frac{\text{Btu}}{\text{hr} - \text{gal}}\)

### Specific heat \((C_p)\)

- \(1\) kJ \((\text{kg} \cdot \text{K}) = \frac{1}{\text{kg} \cdot \text{K}} = 0.239 \) kCal \((\text{kg} \cdot \text{C}) = 0.239 \) kcal \((\text{kg} \cdot \text{C}) = 0.239 \) J
- \(1\) Btu \((\text{lb}_m \cdot °\text{F}) = \frac{1}{(\text{lb}_m \cdot °\text{F})} = 4184 \) cal \((\text{kg} \cdot \text{K}) = 4184 \) kg \cdot \text{K}
### Quantity Equivalent Values

#### Specific heat \((C_p)\) (continued)

- For water \((20^\circ C)\): \(C_p = 4184 \) \(\frac{J}{kg \cdot K} = 1 \) \(\frac{cal}{gm \cdot ^\circ C} = 1 \) \(\frac{Btu}{lb \cdot ^\circ F}\)
- For air \((20^\circ C)\): \(C_p = 1013 \) \(\frac{J}{kg \cdot K} = 29.29 \) \(\frac{J}{mol \cdot K}\)

\[
= 0.24 \frac{cal}{gm \cdot ^\circ C} = 7 \frac{cal}{mol \cdot ^\circ C}
\]

#### Thermal conductivity \((k)\)

\[
1 \frac{Btu}{(hr \cdot ft \cdot ^\circ F)} = 1.7307 \frac{W}{(m \cdot K)} = 0.00413 \frac{cal}{(sec \cdot cm \cdot K)}
\]

\[
1 \frac{W}{(m \cdot K)} = 0.5799 \frac{Btu}{(hr \cdot ft \cdot ^\circ F)} = 0.85984 \frac{kcal}{(hr \cdot m \cdot ^\circ C)}
\]

\[
1 \frac{W}{(m \cdot K)} = 0.00239 \frac{cal}{sec \cdot cm \cdot ^\circ C} = 0.578 \frac{Btu}{hr \cdot ft \cdot ^\circ F}
\]

Thermal conductivity \(k\) is independent of pressure

- For water \((20^\circ C)\): \(k = 0.597 \) \(\frac{W}{m \cdot K}\)
- For air \((20^\circ C)\): \(k = 0.0257 \) \(\frac{W}{m \cdot K}\)
- For ethanol \((20^\circ C)\): \(k = 0.17 \) \(\frac{W}{m \cdot K}\)

#### Throughput (continuous at 365 days/yr)

- \(1\) yr = 365 days = 8760 hr = 5.256 \(\times 10^7\) min
- \(1\) kg/hr = 16.67 g/min = 24 kg/day = 8760 kg/yr = 8.76 MT/yr
- \(10\) MT/yr = 10 000 kg/yr = 27.4 kg/day = 1.14 kg/hr = 19.03 g/min

- \(1\) Billion tablets/year = \(2.74 \times 10^6\) tablets/day

\[
= 114,155 \frac{tablets}{hr} = 31.7 \frac{tablets}{sec}
\]

- \(10\) MTAPI/yr = 10 000 kg/API/yr of API formulated as a 10 mg dose / tablet

\[
= 1.0\) Billion tablets/yr
\]

#### Thermal diffusivity

\[
\alpha = \frac{k}{\rho C_p} = \left[\frac{m^2}{s}\right]
\]

\[
1 \frac{m^2}{sec} = 10.76 \frac{ft^2}{sec} = 387.49 \frac{ft^2}{hr}
\]

\[
1 \frac{ft^2}{sec} = 929.03 \frac{cm^2}{sec} = 0.092903 \frac{m^2}{sec}
\]

For air \((20^\circ C)\): \(\alpha = 2.12 \times 10^{-5} \frac{m^2}{s}\)

For water \((20^\circ C)\): \(\alpha = 1.43 \times 10^{-7} \frac{m^2}{s}\)

#### Viscosity

Dynamic viscosity \((\mu)\)

\[
(1 \text{ Pa} \cdot \text{sec}) = \frac{1 \text{ N} \cdot \text{sec}}{m^2} = \frac{-1 \text{ kg}}{m \cdot \text{sec}} = 1000 \text{ cP (centipoise)}
\]

\[
1 \text{ cP} = 0.01 \text{ poise} = 0.01 \frac{g}{(cm \cdot \text{sec})} = 0.001 \text{ Pa} \cdot \text{sec} = 1 \text{ mPa sec (milliPascal sec)}
\]
<table>
<thead>
<tr>
<th>Quantity</th>
<th>Equivalent Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viscosity (continued)</td>
<td>1 cP = 3.6 kg/(m·hr) = 0.001 kg/(m·sec) = 2.419 lbm/(ft·hr)</td>
</tr>
<tr>
<td></td>
<td>1 poise = 1 g/(cm·sec) = 100 cP</td>
</tr>
<tr>
<td></td>
<td>For liquid water (20 °C): μ = 1.002 × 10^{-3} Pa·sec = 1.002 cP</td>
</tr>
<tr>
<td></td>
<td>For gases (20 °C): μ ≈ 10^{-5} kg/msec = 0.01 cP</td>
</tr>
<tr>
<td></td>
<td>For air (20 °C): μ ≈ 1.8 × 10^{-5} kg/msec = 0.018 cP</td>
</tr>
<tr>
<td></td>
<td>Kinematic viscosity (ν):</td>
</tr>
<tr>
<td></td>
<td>ν = μ/ρ = kg/msec · m^3/kg = [m^2/s]</td>
</tr>
<tr>
<td></td>
<td>Stoke = 1 cm^2/sec = 1 St</td>
</tr>
<tr>
<td></td>
<td>Centistoke = 1 × 10^{-6} m^2/sec = 0.01 stoke = 0.01 cm^2/sec = 1 cSt</td>
</tr>
<tr>
<td></td>
<td>= 0.0036 m^2/hr = 0.0388 ft^2/hr</td>
</tr>
<tr>
<td></td>
<td>1 m^2/s = 10^4 cm^2/s = 10^4 stoke = 10^6 centistoke</td>
</tr>
<tr>
<td></td>
<td>ν(H_2O 20 °C) = 1.004 × 10^{-6} m^2/sec = 1.004 cSt</td>
</tr>
<tr>
<td></td>
<td>Gravitational force</td>
</tr>
<tr>
<td></td>
<td>g = 9.8066 m/sec^2 = 32.174 ft/sec</td>
</tr>
<tr>
<td></td>
<td>Ideal Gas Law</td>
</tr>
<tr>
<td></td>
<td>PV = nRT and R = PV/nT</td>
</tr>
<tr>
<td></td>
<td>R = 8.314 J/mol·K = 8.314 m^3·Pa/mol·K = 82.06 × 10^{-3} m^3·atm/mol·K</td>
</tr>
<tr>
<td></td>
<td>R = 0.08206 L·atm/mol·K = 1.987 cal/mol·K</td>
</tr>
<tr>
<td></td>
<td>R = 1.987 Btu/ft^3·atm/lb·mol·R = 0.729 lb·mol·R/ft^3·atm</td>
</tr>
<tr>
<td></td>
<td>R = 82.057 atm·cm^3/(mol·K) = 10.73 psi·ft^3/lb·mol·R</td>
</tr>
<tr>
<td></td>
<td>At STP (Standard Temperature and Pressure), temperature is equal to 0 °C and pressure is equal to 1 atm. At STP, 1 mol of an ideal gas occupies 22.415 L.</td>
</tr>
<tr>
<td></td>
<td>Raoult’s Law</td>
</tr>
<tr>
<td></td>
<td>(approximation and generally valid for concentrated solutions when x_A is close to 1)</td>
</tr>
<tr>
<td></td>
<td>Raoult’s Law:</td>
</tr>
<tr>
<td></td>
<td>( p_A = y_A P_T = x_A p_A^*(T) )</td>
</tr>
<tr>
<td></td>
<td>where ( x_A ) is the mol fraction of A, ( y_A ) is the mol fraction in the vapor phase, ( P_T ) is the total pressure, ( p_A^*(T) ) is the vapor pressure of A, and ( p_A ) is the partial pressure of A.</td>
</tr>
<tr>
<td></td>
<td>As ( x_A ) approaches 1, the partial pressure ( p_A \approx p_A(T) ) approaches the vapor pressure of liquid A.</td>
</tr>
<tr>
<td></td>
<td>Example: Drying 2-propanol (IPA) from a wet-cake using a nitrogen stream (single-pass through the cake).</td>
</tr>
<tr>
<td></td>
<td>How long will it take to remove 100 g of IPA from a wet-cake using nitrogen blow-through (the cake) at 1 L/min at 30 °C? Assume the drying cake remains isothermal at 30 °C and the nitrogen remains saturated and the system total pressure is 1 atm = 760 mmHg absolute.</td>
</tr>
<tr>
<td></td>
<td>Solution:</td>
</tr>
<tr>
<td></td>
<td>1. Vapor pressure of IPA (30 °C) = 58.3 mmHg</td>
</tr>
<tr>
<td></td>
<td>2. Assume ( x_A \approx 1 ) for IPA</td>
</tr>
<tr>
<td></td>
<td>3. Ignoring solids and any mass transfer limitations, simply calculate the saturation condition for IPA in ( N_T ).</td>
</tr>
<tr>
<td></td>
<td>Mol fraction of saturated 2-PrOH in nitrogen:</td>
</tr>
<tr>
<td></td>
<td>( y_{IPA} = \frac{p_{IPA}(T)}{P_T} = \frac{58.3 \text{ mmHg}}{760 \text{ mmHg}} = 0.0767 \text{ mol frac IPA} )</td>
</tr>
</tbody>
</table>
Mol fraction of nitrogen:

\[ y_{N_2} = 1 - 0.0767 = 0.9233 \text{ mol frac N}_2 \]

5. Calculate mass of nitrogen per gram of IPA required to become fully saturated with 2PrOH (30 °C):

\[
\frac{0.9233 \times 28 \text{ g/mol}}{0.0767 \times 58.3 \text{ g/mol}} = 5.78 \text{ g of N}_2/(\text{g of 2PrOH})
\]

6. Flow of 1 L/min (N\(_2\)) at 30 °C:

\[
\frac{1 \text{ L}}{273 \text{ K}} \times \frac{22.4 \text{ mol}}{1 \text{ mol}} = 1.13 \text{ g N}_2/\text{min}
\]

7. To saturate and remove 100 g of IPA using nitrogen at 30 °C and 1 L/min:

\[
100 \text{ g of 2PrOH} \left( \frac{5.78 \text{ g N}_2}{1 \text{ g 2PrOH}} \right) = 511.5 \text{ min} = 8.5 \text{ hr}
\]

Note: This is only a rough estimate (order of magnitude). The assumptions are idealized since there is typically a significant drop in temperature due to evaporative cooling which will lower the vapor pressure and slow the rate of drying. For a comprehensive treatment of mass transfer during flow-through drying see Treybal [2].

Henry’s Law (generally valid for dilute solutions when \(x_A\) is close to 0; and commonly applied to solutions of noncondensible gases)

Henry’s Law:

At a constant temperature, the amount of a gas dissolved in a specific type and volume of liquid is directly proportional to the partial pressure of that gas in equilibrium with that liquid.

\[ p_A = y_A P_T = x_A H_A(T) \]

where \(H_A\) is the Henry’s Law constant with units of (pressure/mol fraction), \(x_A\) is the mol fraction of gas dissolved in liquid, \(y_A\) is the mol fraction in the vapor, \(P_T\) is the total pressure, \(p_A\) is the partial pressure of \(A\).

Commonly used variation for pure gas (\(y_A \approx 1\)) over liquid: (such as a hydrogenation)

\[ p_A = y_A P_T \approx (1.0)P_{sat} = C_{sat} \cdot H_A(T) \]

where \(H_A\) is the Henry’s Law constant with units of (pressure/(mol/L)), \(C_{sat}\) is the gas solubility in mol/L at saturation pressure \(P_{sat}\).

Example:

Calculate the solubility of H\(_2\) in methanol at 25 °C and 3.5 bar (absolute pressure of pure H\(_2\)):

Solution: The Henry’s constant for hydrogen in methanol at 25 °C:

\[ H_{H_2} = 268 \text{ bar L/mol H}_2 \]

\[
\text{Solubility} = C_{sat} = \frac{P_{sat}}{H_{H_2}} = \frac{3.5 \text{ bar mol H}_2}{268 \text{ bar L}} = 0.0131 \text{ mol H}_2/L \text{ at 3.5 bar and 25 °C}
\]

Other commonly used forms of Henry’s Law:

\[ p_A = y_A P_T = \frac{C_A}{k_H} \]

where \(k_H\) is the Henry’s Law constant, with units of \(\text{mol/L atm}\).

Example:

a. Calculate the solubility of pure oxygen in equilibrium with water at 25 °C at 1 atm (absolute pressure of oxygen):

Henry’s constant, \(k_H\) for O\(_2\) in water at 25 °C: \(1.3 \times 10^{-3} \text{ mol/L atm}\) (see table below)
Quantity Equivalent Values

Henry’s Law (continued)

\[ C_{\text{sat,O}_2} = p_{\text{O}_2} \cdot k_{H,O_2} = \frac{1.0 \text{ atm} \cdot 0.0013 \text{ mol L} \cdot \text{atm}}{L} = \frac{0.0013 \text{ mol L} \cdot \text{atm}}{L} = 0.0013 \text{ M}_{\text{O}_2} \]

b. Instead of pure oxygen, calculate the solubility of oxygen in water while in equilibrium with air at 25 °C and 1 atm.

Recognize the mol fractions in the gas phase: \( y_{\text{N}_2} = 0.79 \) and \( y_{\text{O}_2} = 0.21 \)

\[ p_T = 1 \text{ atm} \text{ so } p_{\text{O}_2} = y_{\text{O}_2} \cdot p_T = (0.21)(1 \text{ atm}) = 0.21 \text{ atm} \]

\[ C_{\text{sat,O}_2} = p_{\text{O}_2} \cdot k_{H,O_2} = \frac{0.21 \text{ atm} \cdot 0.0013 \text{ mol L} \cdot \text{atm}}{L} = \frac{2.73 \times 10^{-4} \text{ mol O}_2}{L} \]

Forms of Henry’s Law and Constants (Gases in Water at 298 K)

<table>
<thead>
<tr>
<th>Equation</th>
<th>( k_H = \frac{p_{\text{gas}}}{C_{\text{aq}}} )</th>
<th>( k_H = \frac{C_{\text{aq}}}{p_{\text{gas}}} )</th>
<th>( k_H = \frac{p_{\text{gas}}}{x_{\text{aq}}} )</th>
<th>( k_H = \frac{C_{\text{aq}}}{C_{\text{gas}}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Units</td>
<td>L_{\text{soln atm}} mol_{\text{gas}}</td>
<td>mol_{\text{gas}} L_{\text{soln atm}}</td>
<td>atm mol_{\text{soln}} mol_{\text{gas}}</td>
<td>Dimensionless</td>
</tr>
<tr>
<td>\text{O}_2</td>
<td>769.23</td>
<td>0.001 3</td>
<td>42 590</td>
<td>0.031 80</td>
</tr>
<tr>
<td>\text{H}_2</td>
<td>1282.05</td>
<td>0.000 78</td>
<td>70 990</td>
<td>0.019 07</td>
</tr>
<tr>
<td>\text{CO}_2</td>
<td>29.41</td>
<td>0.034 0</td>
<td>1 630</td>
<td>0.831 7</td>
</tr>
<tr>
<td>\text{N}_2</td>
<td>1639.34</td>
<td>0.000 61</td>
<td>90 770</td>
<td>0.014 92</td>
</tr>
<tr>
<td>He</td>
<td>2702.7</td>
<td>0.000 37</td>
<td>149 700</td>
<td>0.009 051</td>
</tr>
<tr>
<td>Ne</td>
<td>2222.22</td>
<td>0.000 45</td>
<td>123 000</td>
<td>0.011 01</td>
</tr>
<tr>
<td>Ar</td>
<td>714.28</td>
<td>0.001 4</td>
<td>39 550</td>
<td>0.034 25</td>
</tr>
<tr>
<td>CO</td>
<td>1052.63</td>
<td>0.000 95</td>
<td>58 280</td>
<td>0.023 24</td>
</tr>
</tbody>
</table>

where:
\( C_{\text{aq}} \) = moles of gas per Liter of solution
\( p_{\text{gas}} \) = partial pressure of gas above the solution in atmospheres
\( x_{\text{aq}} \) = mole fraction of gas in solution
https://chemengineering.wikispaces.com/Henry%27s+Law

Reynolds Number for stirred vessel:

\[ \text{Re} = \frac{\rho ND^2}{\mu} \]

where \( \rho \) = density, \( N \) = stir speed, \( D \) = impeller diameter, and \( \mu \) = viscosity

For pipe or tube:

\[ \text{Re} = \frac{\rho u D_{\text{pipe}}}{\mu} \]

where \( u \) = fluid velocity, \( \rho \) = density, \( D \) = pipe inside diameter, and \( \mu \) = viscosity

Example (Stirred Tank):
Calculate Re for a lab reactor containing water using the following parameters:
Impeller diameter: \( D = 5 \text{ cm} = 0.05 \text{ m} \)
<table>
<thead>
<tr>
<th>Quantity</th>
<th>Equivalent Values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reynold's Number (Re)</strong></td>
<td>Stirrer speed: $N = 600 \text{ rpm} / (60 \text{ sec/min}) = 10 \text{ rotations/sec}$</td>
</tr>
<tr>
<td></td>
<td>$\rho = 1 \text{ g/cm}^3 = 1000 \text{ kg/m}^3$</td>
</tr>
<tr>
<td></td>
<td>Viscosity of water: $\mu = 1 \text{ cp} = 0.001 \text{ kg/(m s)}$</td>
</tr>
<tr>
<td></td>
<td>$Re = \frac{1000 \text{ kg/m}^3 \times 10 \text{ rps} \times (0.05 \text{ m})^2}{0.001 \text{ kg/(m s)}} = 25000$</td>
</tr>
<tr>
<td></td>
<td>Example (pipe flow):</td>
</tr>
<tr>
<td></td>
<td>What flow rate of water inside a $\frac{1}{4}''$ OD tube would provide a Reynolds number of 25 000:</td>
</tr>
<tr>
<td></td>
<td>Assume inside diameter of tube, ID = 0.23 in = 0.584 cm</td>
</tr>
<tr>
<td></td>
<td>Tube: cross-sectional area: $(3.14 \times (0.584)^2)/4 = 0.268 \text{ cm}^2$</td>
</tr>
<tr>
<td></td>
<td>$\rho = 1 \text{ g/cm}^3 = 1000 \text{ kg/m}^3$</td>
</tr>
<tr>
<td></td>
<td>Viscosity of water: $\mu = 1 \text{ cp} = 0.001 \text{ kg/(m s)}$</td>
</tr>
<tr>
<td></td>
<td>$Re = \frac{(1000 \text{ kg/m}^3) \cdot u \cdot (0.00584 \text{ m})}{0.001 \text{ kg/(m s)}} = 25000$</td>
</tr>
<tr>
<td></td>
<td>$u = \frac{(25000) (0.001 \text{ kg/m s})}{(1000 \text{ kg/m}^3) (0.00584 \text{ m})} = 4.28 \text{ m/s}$</td>
</tr>
<tr>
<td></td>
<td>Volumetric flow rate = $u \cdot \text{area} = 428 \text{ cm/sec} \times 0.268 \text{ cm}^2 = 114.7 \text{ cm}^3/\text{sec} = 6.88 \text{ L/min}$</td>
</tr>
<tr>
<td><strong>Power Number (Np)</strong></td>
<td>$Np = \frac{P}{\rho N^3 D^5}$</td>
</tr>
<tr>
<td></td>
<td>where $P = \text{power, } \rho = \text{density, } N = \text{stir speed, } D = \text{impeller diameter}$</td>
</tr>
<tr>
<td></td>
<td>For a given reactor + agitator configuration the mixing power of an impeller can be uniquely characterized by the power number:</td>
</tr>
<tr>
<td></td>
<td>• Turbulent flow where $Re &gt; 2000$:</td>
</tr>
<tr>
<td></td>
<td>$Np_{\text{turbulent}} = \text{constant} \geq \text{Power} \propto \rho N^3 D^5$</td>
</tr>
<tr>
<td></td>
<td>Example: If the measured power required to agitate a tank of liquid at 600 rpm with a 5 cm ID impeller is 1.0 W then what is the power at 1000 rpm (16.7 rps) in water?</td>
</tr>
<tr>
<td></td>
<td>Solution: Check Reynolds number ($Re = 25 000$; see above for calculation);</td>
</tr>
<tr>
<td></td>
<td><em>Power Number</em>, $Np$, will be a constant for this reactor + impeller when $Re &gt; 2000$</td>
</tr>
<tr>
<td></td>
<td>$Np = \frac{P}{\rho N^3 D^5}$</td>
</tr>
<tr>
<td></td>
<td>Calculate $Np$:</td>
</tr>
<tr>
<td></td>
<td>Note that 1.0 W = 1.0 $\frac{\text{kg m}^2}{\text{s}^3}$</td>
</tr>
<tr>
<td></td>
<td>Power Number, $Np = \frac{1.0 \text{ kg m}^2/\text{s}^3}{1000 \text{ kg/m}^3 \times (10 \text{ rps})^3 \times (0.05 \text{ m})^5} = 3.2$ will be constant for $Re &gt; 2000$</td>
</tr>
<tr>
<td></td>
<td>Calculate the Power required for the higher stir speed of 1000 rpm</td>
</tr>
<tr>
<td></td>
<td>$P = Np \rho N^3 D^5 = 3.2$</td>
</tr>
<tr>
<td></td>
<td>$P = 3.2 \times 1000 \text{ kg/m}^3 \times (16.7 \text{ rps})^3 \times (0.05 \text{ m})^5$</td>
</tr>
<tr>
<td></td>
<td>$P = 4.7 \text{ W}$</td>
</tr>
<tr>
<td></td>
<td>Note the ~5x increase in power draw to increase stirring from 600 to 1000 rpm.</td>
</tr>
<tr>
<td><strong>Surface tension ($\gamma$)</strong></td>
<td>$[\text{dyne/}\text{cm}]$</td>
</tr>
<tr>
<td></td>
<td>Water–air interface: $\gamma_{\text{H2O-AIR}} (20 ^\circ\text{C}) = 72.75 \text{ dynes/cm}$ CRC HB 62nd edition</td>
</tr>
<tr>
<td></td>
<td>$1 \frac{\text{dyne}}{\text{cm}} = 0.001 \frac{\text{N}}{\text{m}} = 1 \frac{\text{erg}}{\text{cm}^2}$</td>
</tr>
</tbody>
</table>
### Quantity Equivalent Values

<table>
<thead>
<tr>
<th>ppm</th>
<th>Equivalent Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0001</td>
<td>1 ppm</td>
</tr>
<tr>
<td>0.001</td>
<td>10 ppm</td>
</tr>
<tr>
<td>0.01</td>
<td>100 ppm</td>
</tr>
<tr>
<td>0.1</td>
<td>1000 ppm</td>
</tr>
</tbody>
</table>

### Moisture content

- **Moisture content (wet basis)** Range = 0–100%

\[
\% M_{\text{wet}} = 100 \frac{\text{mass}_{\text{solvent}}}{\text{mass}_{\text{solvent}} + \text{mass}_{\text{dry solids}}} = 100 \frac{\text{mass}_{\text{solvent}}}{\text{mass}_{\text{Total}}}
\]

Note wet basis is the same as % Loss on drying (%LoD) where:

\[
\% \text{LoD} = 100 \frac{\text{mass}_{\text{loss on drying}}}{\text{mass}_{\text{initial wet cake}}}
\]

- **Moisture content (dry basis)** range = 0 to >100%

\[
\% M_{\text{dry}} = 100 \frac{\text{mass}_{\text{solvent}}}{\text{mass}_{\text{dry solids}}}
\]

To convert wet basis to dry basis: wt\%\( M_{\text{dry}} = 100 \frac{\% M_{\text{wet}} - \% M_{\text{wet}}}{100 + \% M_{\text{dry}}}
\]

To convert dry basis to wet basis: wt\%\( M_{\text{wet}} = 100 \frac{\% M_{\text{dry}}}{100 + \% M_{\text{dry}}}
\]

Example: 100 g of wetcake contains 40 g of water and 60 g of dry API, compare the moisture contents (wet vs dry basis):

\[
\% M_{\text{wet}} = \% \text{LoD} = 100 \frac{40 \text{ g}}{40 \text{ g} + 60 \text{ g}} = 40\%
\]

\[
\% M_{\text{dry}} = 100 \frac{40 \text{ g}}{60 \text{ g}} = 67\%
\]

### Humidity

- **Absolute humidity for water in air**: \( h = \frac{\text{kg}_{\text{water}}}{\text{kg}_{\text{dry air}}} \)

Example: Calculate the absolute humidity of air saturated with water at 30 °C at 1 atm pressure.

Solution:
- The vapor pressure of water at 30 °C, is 31.8 torr = 0.0418 atm
- Calculate the mole fraction water:

\[
y_{\text{water}} = \frac{P_{\text{water}}(T)}{P_{T}} = \frac{0.0418 \text{ atm}}{1 \text{ atm}} = 0.0418 \text{ mol frac water}
\]

- Mole fraction of air

\[
y_{\text{air}} = 1 - 0.0418 = 0.9582 \text{ mol frac air}
\]

- Calculate mass ratio of water to air to find the absolute humidity:

\[
\frac{0.0418 \times 18.02 \text{ g/mol}}{0.9582 \times 29 \text{ g/mol}} = 0.0271 \frac{\text{kg}_{\text{water}}}{\text{kg}_{\text{dry air}}}
\]

- This value can also be obtained be read from a pyschometric chart for water/air;
- Because the air is saturated, in this example, the relative humidity is 100%. 
Example: Determine the number of pressure purges required to reduce the oxygen concentration in a reactor from 21 to 0.1 vol % $\text{O}_2$ using nitrogen. A nitrogen source is used to pressurize the reactor to 50 psig and is vented down to 5 psig, in several cycles. Calculate the approximate number of cycles required.

$$
\ln \left( \frac{0.001}{0.21} \right) \approx -5.347
\ln \left( \frac{5 \text{psig} + 14.7 \text{psig}}{50 \text{psig} + 14.7 \text{psig}} \right) \approx 1.189
$$

$$
k = \frac{-5.347}{1.189} \approx 4.5 \approx 5 \text{ cycles}
$$

Source: Adapted from Kinsley [3].

Polymath (6.10) program for Semi-Batch (i.e. Fed-Batch) with 1 hour Feed-Time. $A$ is being Fed to $B$.

Assume Isothermal Kinetics

Feed stream $A$:
1 L fed over 60 minutes
($C_{ao} = 1 \text{ mol A/L}$)

![Diagram showing the reactor](image)

at $t=0 \ V = 1 \text{ L}$

$C_{b}(0) = 1.0 \text{ mol B/L}$

\[ A + B \xrightarrow{k} C \]

rate $= -kC_AC_B$ where $k = \left( \frac{L}{\text{mol min}} \right)$

$\Delta H = -30 \text{ kcal/mol}$

Initial conditions at $t = 0$

- Volume in the reactor, $V_0 = 1 \text{ L}$
- Concentration of $B$ in the reactor, $C_{b}(0) = 1 \text{ M}$
- Concentration of $A$ and $C$ in the reactor = 0

### # A + B → C
# A is fed to B

d(Ca)/dt = if (t > dose) then ra else ra + Cao * vo/V - Ca * Vo/V # mols/(l.min)

d(Cb)/dt = if (t > dose) then ra else ra - vo * Cb/V #

d(Cc)/dt = if (t > dose) then -ra else -ra - vo * Cc/V #

Dose = 60 # minutes

$V = if \ (t > dose) \ then \ Vo + vo * dose \ else \ Vo + vo * t #
molsAfed = if (t > dose) then Cao * vo * dose else Cao * vo * t #
molsB = Cb * V
Vo = 1 # liter (initial volume of the reactor)
vo = 1/60 # L/min (volumetric flow rate of the feed)
k = 0.1 # rate constant
Cao = 1 # mol/L (concentration of A in the feed stream)
Cbo = 1 # mol/L (initial concentration of B in the reactor)
ra = -k * Ca * Cb # reaction rate expression
rate = -ra #

#Heat of Reaction
DeltaH = 30 × 1000/0.23901 # Exothermic heat of reaction, (30 kcal/mol) × (1000 cal/kcal) × (J/0.23901 cal)
Q = DeltaH × rate × V/60# (J/mol) × (mol/(L-min)) × (L) × (min/60 sec) = J/sec = W
WL = Q/V # W/L

#Yields
YC = if (t > 0) then (Cc * V)/(Cbo * Vo) else 0 #Yield of C
XB = if (t > 0) then (Cbo * Vo – Cb * V)/(Cbo * Vo) else 0 #Conversion of B

#Initial Conditions
Ca(0) = 0 #There is no A initially in the reactor
Cb(0) = 1 # initial concentration of B (mol/L) initially in the reactor
Cc(0) = 0

The plots below simulate concentration, heat, and yield profiles for rate constants of 0, 0.01, 0.05, 0.1, and 1 (L/(mol-min)) under Isothermal conditions.
REFERENCES


PART I

INTRODUCTION
CHEMICAL ENGINEERING IN THE PHARMACEUTICAL INDUSTRY: AN INTRODUCTION

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Process Modeling & Engineering Technology Group, Pfizer, Inc., Groton, CT, USA

Across the pharmaceutical industry chemical engineers are employed throughout research and development (R&D) to full-scale manufacturing and packaging in technical and managerial capacities. The chapters in these two volumes provide an emphasis on the application of chemical engineering science to process design, development, and scale-up for active pharmaceutical ingredients (APIs), drug products (DPs), and biologicals including sections on regulatory considerations such as design space, control strategies, process analytical technology (PAT), and quality by design (QbD). The focus of this introduction is to provide a high-level overview of bringing a drug to market and highlight industry trends, current challenges, and how chemical engineering skills are an exquisite match to address those challenges.

In general pharmaceuticals are drug delivery systems in which drug-containing products are designed and manufactured to deliver precise therapeutic responses [1]. The drug is considered the “active,” i.e. active pharmaceutical ingredient (API) or “drug substance,” and the formulated final dosage form is simply referred to as the drug product (DP).

This book focuses on API in volume 1 and DP in volume 2. The API and DP are designed and developed in R&D and then transferred to the commercial manufacturing sites by teams of organic chemists, analytical chemists, pharmaceutical scientists, and chemical engineers. Prior to the transition to the commercial site, co-development teams are formed with members from R&D and manufacturing working together to define the computational and experimental studies to conduct based on risk and scientific considerations. The outcome of this multidisciplinary team effort forms the regulatory filing strategy for the API and drug products.

Once the commercial API and DP have been established, the co-development teams support three major regulatory submissions for a global product. A New Drug Application (NDA) is submitted to the US Food and Drug Administration (FDA), whereas in the欧洲 Union a Marketing Authorization Application (MAA) is submitted to the European Medicines Agency (EMA), and in Japan a Japan New Drug Application (JNDA) is submitted to the Pharmaceuticals and Medical Devices Agency (PMDA). Subsequently, the rest of world regulatory filings are led by the commercial division with no significant involvement by R&D since more commercial experience is available at the site by that time.

In the United States, federal and state laws exist to control the manufacture and distribution of pharmaceuticals. Specifically, the FDA exists by the mandate of the US Congress with the Food, Drug, and Cosmetics Act as the principal law to enforce and constitutes the basis of the drug approval process [1]. Specifically in the United States, “The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation’s food supply, cosmetics, and products that emit radiation. The FDA is also responsible for advancing the public health where possible by speeding innovations that make medicines and foods

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more effective, safer, and more affordable. They also serve the public by ensuring accurate, science-based information on medicines and foods to maintain and improve their health.\(^4\) On 28 March 2018 the FDA announced organizational changes available on their website. Janet Woodcock remains the director of the small molecule division, referred to as Center for Drug Evaluation and Research (CDER).\(^2\) Peter W. Marks is the director of the large molecule division, referred to as Center for Biologics Evaluation and Research (CBER).\(^3\) Further information can also be easily obtained from the FDA website, including the overall drug review process, current good manufacturing practices (cGMP), International Council on Harmonization (ICH), and mechanisms to comment on draft guidances, recalls, safety alerts, and warning letters that have been issued to companies.\(^4\)

EMA is a decentralized body of the European Union with headquarters in London whose main responsibility is the protection and promotion of public and animal health, through the evaluation and supervision of medicines for human and veterinary use.\(^5\)

The Japan Pharmaceutical Affairs Law (JPAL) is a law intended to control and regulate the manufacturing, importation, sale of drugs, and medical devices.\(^6\) It exists to assure the quality, efficacy and safety of drugs, cosmetics, and medical devices while improving public health and hygiene. The JPAL also provides guidance to pharmaceutical companies on how to translate their QbD control strategy, which was found to align well with the three levels of criticality initially used in early QbD filings for noncritical, key, and critical process parameters. Japan’s Ministry of Health, Labour and Welfare (MHLW) has issued clear guidance in English for three key ministerial ordinances to assure compliance requirements for manufacturers.

Japan, Europe, and United States collaborate as the International Council on Harmonization – Quality (ICH) to establish greater expectations for science and risk-based approaches to transform the pharmaceutical industry over the past decade. Critical to that transformation were the QbD guidances, Q8, Q9, and Q10 [2–4]. The final versions of the guidances are readily available on the CDER website, including the more recent QbD guidance for drug substance composed in Q11.\(^7\)

1http://www.fda.gov/AboutFDA/WhatWeDo/default.htm
2http://www.fda.gov/AboutFDA/CentersOffices/OrganizationCharts/ucm350895.htm
3http://www.fda.gov/AboutFDA/CentersOffices/OrganizationCharts/ucm350556.htm
4http://www.fda.gov/default.htm
5http://www.ema.europa.eu/htms/aboutus/emeaoverview.htm
6http://www.jouhoukoukai.com/repositories/source/pal.htm
7https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm065005.htm

1.1 GLOBAL IMPACT OF THE INDUSTRY

The value of the pharmaceutical industry to the American economy is substantial. In 2016, the industry employed over 854 000 people with each job indirectly supporting an additional 4 jobs. Thus as an aggregate, the industry supported 4.4 million jobs and generated nearly $1.2 trillion in annual economic output when direct, indirect, and induced effects were considered for 2016.\(^8\)

As an industry sector, the pharmaceutical industry is considered profitable, in spite of the high attrition rate for new chemical entities (NCEs).\(^9\) For example, Forbes estimated the profit margin for the health-care technology industry in 2015 to be approximately 21%, clearly placing near the top for profitable industries.\(^10\) The companies that are most profitable in this sector were major pharmaceutical and generics companies. As far as total revenues in pharmaceutical sales, the top 20 pharmaceutical companies are listed in Table 1.1.

Based on revenue, the pharmaceutical and biopharmaceutical companies are based in the following countries: 9 (United States), 2 (Switzerland), 2 (United Kingdom), 1 (France), 3 (Germany), 1 (Israel), 1 (Denmark), and 1 (Republic of Ireland). Only 1 company in the top 20 revenue producing is privately held.

Global prescription drug sales are on the order of $800 billion in 2017. These drug sales are forecasted to grow at 6.3% compound annual growth rate (CAGR) between 2016 and 2022 to nearly $1.2 trillion (as shown in Figure 1.1),\(^11\) while generic drugs account for approximately 10% of those sales figures.

There is considerable value in being the first company to deliver a new medicine that treats a new indication (e.g. breakthrough therapy designation from regulators) or uses a new mechanism of action to benefit patients. Therefore, new developments in pharmaceutical R&D that speed quality drug candidates to the market are important investments for the future.

1.2 INVESTMENTS IN PHARMACEUTICAL R&D

R&D is the engine that drives innovation of new drugs and therapies. Significant investment is required to discover and advance potential NCEs and new molecular entities

8http://phrma.org/industryprofile
11http://info.evaluategroup.com/rs/607-YGS-364/images/wp16.pdf; some estimates are even higher, with 2017 global revenue of $1.05 trillion (see, for example, https://www.fool.com/investing/2016/07/31/12-big-pharma-stats-that-will-blow-you-away.aspx).
(NMEs). For example, the pharmaceutical industry invested approximately $150 billion into R&D in 2015. Worldwide pharmaceutical R&D spending is expected to grow by 2.8% (CAGR) to $182 billion in 2022 (Figure 1.2).\textsuperscript{12} The cost of advancing drug candidates and entire pharmaceutical portfolios in R&D is significant. In 2001 the average cost for an approved medicine was estimated to be $802 million, and by the end of 2014, the average cost escalated to $2.6 billion as reported by Tufts Center for the Study of Drug Development.\textsuperscript{13} Although these figures clearly depend on the drug type, therapeutic area, and speed of development, the bottom


\textsuperscript{13}Based on estimated average pre-tax industry cost per new prescription drug approval (inclusive of failures and capital costs: source, DiMasi et al. [5]).
line is that the up-front investments required to reach the market are massive especially when considering the uncertainty whether the up-front investment will payback.

Given there might be 10 or more years of R&D costs without any revenue generated on a NCE or NME, the gross margins of a successful drug need to cover prior R&D investments and candidate attrition and to cover the continuing marketing and production costs. Figure 1.3 shows the classic cash flow profile for a new drug developed and marketed. First there is a period of negative cash flow during the R&D phase. When the drug is approved and launched, only then are revenues generated, which have to be priced high enough to recoup the extensive R&D investment and provide a return on the investment.
The net present value (NPV) calculation is one way to assess return on investment with a discount rate of 10–12% generally chosen in the pharmaceutical industry as the rate to value products or programs for investment decisions [6]. The highest revenues for a new drug are achieved during the period of market exclusivity (where no competitors can sell the same drug). So it is in the company’s best interest to ensure the best patent protection strategy is in place to maximize the length of market exclusivity. Patents typically have a validity of 20 years from the earliest application grant date base on applications filed after 1995. In some cases the time of market exclusivity can be extended through new indications, new formulations, and devices, which may themselves be patent protected (see Table 1.2).

Once market exclusivity ends, generic competition is poised to immediately introduce an alternative cheaper option that will erode sales for the patent owner. A dramatic example of patent cliff can be seen in the sales of Lipitor (Figure 1.4). Peak sales occurred in 2006 with sales nearing $13 billion in revenue, but at the end of patent exclusivity in 2011, sales dropped off precipitously to less than $4 billion in 2012. The trend continued to drop off through 2017 to less than $2 billion.

It now takes 10–15 years for a new medicine to go from the discovery laboratory to the pharmacy. Figure 1.5 shows the typical development activity timeline from discovery to launch. From thousands of compounds evaluated for potential therapeutic effect, very few will clear all the safety, efficacy, and clinical hurdles to make it to approval. Figure 1.5 also shows how a general range of volunteers, and clinical supplies, increases through phases I–III of clinical trials with clinical development typically lasting six years or more.

Before entering human clinical studies, the drug candidate is tested for safety and efficacy in preclinical studies. When the candidate looks promising for a targeted indication or potential therapeutic effect, the company files an Investigational New Drug Application (IND) for regulatory agency and clinical site approval. At this time, referred to as phase I, the drug candidate will be tested in a few healthy volunteers \( (n \sim 10^3) \) in single and multiple dose studies to test for safety and understand human pharmacokinetics. If the phase I evaluations are positive, then the candidate can progress to a larger population of healthy volunteers \( (n \sim 100^3) \) pending approval by the regulatory agency on study design, i.e. doses, route of administration, detection of efficacy, and side effects. If the candidate passes the phases I and II hurdles ensuring safety and efficacy, then the clinical teams will design incrementally larger, broader, and worldwide clinical studies in test patients (phase III, \( n \sim 1000^3 \)).

The two common exceptions to conducting phase II studies in healthy volunteers are for oncology or biological candidates. These candidates proceed directly into the patient population, referred to as phase III, to test treatment of the

![FIGURE 1.3](image.png) A hypothetical cash flow curve for a pharmaceutical product includes 10–15 years of negative cash flows of typically $1–3 billion. Reasonably high margins are needed, once the drug is on the market, if it is to recuperate and provide a positive return on investment (ROI) over its lifecycle.

![TABLE 1.2](image.png) Periods of Exclusivity Granted by the FDA

<table>
<thead>
<tr>
<th>Specific FDA Applications</th>
<th>Period of Exclusivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Chemical Entity Exclusivity (NCE)</td>
<td>5 years</td>
</tr>
<tr>
<td>Orphan Drug Exclusivity (ODE)</td>
<td>7 years</td>
</tr>
<tr>
<td>Generating Antibiotic Incentives Now (GAIN) exclusivities</td>
<td>5 years added to certain</td>
</tr>
<tr>
<td>New Clinical Investigation Exclusivity</td>
<td>3 years</td>
</tr>
<tr>
<td>Pediatric Exclusivity (PED)</td>
<td>6 months added to existing patents/exclusivity</td>
</tr>
</tbody>
</table>

Source: Form https://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079031.htm#What_is_the_difference_between_patents_a
indicated cancer or to progress the known safe and efficacious candidate derived from human antibodies or viruses, respectively.

After several years of careful study, the drug candidate may be submitted to the regulatory agency (e.g. FDA, EMA, PMDA) for approval. Depending on the type of API, the regulatory submission may need to be filed differently. For example, in the United States, a small molecule is submitted as an NDA, while a biologic is submitted as a Biologics Licensing Application (BLA).
$1–3.5 billion. Source: Adapted from Suresh and Basu [7].

As mentioned, the 2014 cost to advance a NCE or NME to market was estimated at $2.6 billion. The cost of product development that includes the cost to manufacture clinical supplies is estimated to be in the range of 30–35% of the total cost of bringing a NCE/NME to market with the following other cost contributors: discovery 20–25%, safety and toxicology 15–20%, and clinical trials 35–40% [7]. The distribution is graphically displayed in Figure 1.6. Clearly the distribution will depend on the specific drug, its therapeutic area, dose, and specific company.

Chemical engineers, chemists, biologists, pharmaceutical scientists, and others make up the diverse scientific disciplines of product development that include API and formulation development including API and DP manufacture of clinical supplies.

1.3 BEST SELLERS

The top 20 drugs in sales are shown in Table 1.3 with Humira, topping the list with 2017 global sales of $18.43 billion. Interestingly 11 of these top drugs are biologics, 1 is a vaccine, and the remaining 8 are small molecule drugs. The top 20 selling drugs in that year total nearly $135 billion. This has changed significantly since the publication of the original version of this book in 2010 when the majority of top-selling drugs at that time were small molecules.

The majority of the 20 top sellers have remained in similar positions over the past 2 years; however a few have made significant moves in this short time. For instance, Harvoni was the second place with $9.08 billion in sales in 2016 and dropped to seventeenth place in 2017 with $4.37 billion sales. Another interesting move was Eylea from eleventh to second place from 2016 to 2017 increasing sales from $5.05 to 8.23 billion. It is also noteworthy that 9 of the top 20 products are partnerships, which further illustrates the significant cost to develop DPs are often sharing the risk.

In Table 1.4 the top-selling drugs of all time were analyzed by Forbes, utilizing the lifetime sales of branded drugs between 1996 and 2012 and company reported sales data between 2013 and 2016. It is noteworthy that the number one in sales, Lipitor, at $148.7 billion is not even on the top 20 drug sales list for 2017 in Table 1.3. While there is a large gap between the top two selling drugs, amounting to $53 billion for Lipitor above Humira, if Humira annual sales continue at $18 billion, it will outperform Lipitor as the all-time best-selling drug in just under 3 years. However, the patent expiry for Humira was in 2016, and therefore sales may drop rapidly in the coming years if generics or biosimilars are able to penetrate the market.

1.4 PHARMACEUTICAL RESEARCH AND DEVELOPMENT EXPENDITURES

1.4.1 Pharmaceutical Development

In general, pharmaceutical product development is different than most other research intensive industries. Specifically in the pharmaceutical industry, there is the consistent need to ensure that clinical supplies are manufactured and delivered in a timely manner regardless of the current state of development or efficiency of the process. In other words, delivering clinical supplies when they are needed requires using technology that is good enough at the time even if it is not a fully optimized process. However, this is a regulated industry for clinical supplies as well as for commercial.

Further, process development, optimization, and scale-up historically tends to be an iterative approach [8] – clinical supply demands are met by scale-ups to kilo lab or pilot plant through phase I, phase II, and phase III, and it is through this period that R&D teams (including analysts/chemist/engineers, referred to as the ACE model) refine, optimize, and understand the API and DP processes to enable them to be eventually transferred to manufacturing. Manufacturing of clinical supplies in kilo lab, pilot plant, and solid dosage plants occurs under the constraints of cGMP conditions, which is discussed further in the chapter on kilo lab and pilot plant. The pilot plant and kilo lab are also sometimes used to “test” the scalability of a process. In this way, pilot plants serve a dual purpose, which make them unique as compared with non-pharmaceutical pilot plants. In terms of cost, however, large-scale experimentation in kilo lab or pilot plant can be significant – so there has been a shift toward greater predictability at lab scale to offset the need for pilot plant-scale “technology demonstration” experiments. Engineers through their training are well suited to scale-up and scale-down processes and can effectively model the chemical and physical
behaviors in the lab to ensure success on scale. Many chapters in these two volumes discuss how scale-up/scale-down of various unit operations is performed. Chemical engineers are well trained in process modeling and optimization that support the reduction of experimentation and rehearsal batches prior to commercialization. This helps to reduce the number of larger-scale “experiments,” thereby lowering costs during R&D. In this way, with the recent trend toward increasing efficiency and continuous improvement, the pilot plant and kilo labs are preferentially utilized to manufacture

<table>
<thead>
<tr>
<th>Rank</th>
<th>Brand Name</th>
<th>API</th>
<th>Marketer</th>
<th>Indication</th>
<th>2017 Sales ($ Billion)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 biologic</td>
<td>Humira</td>
<td>Adalimumab</td>
<td>AbbVie</td>
<td>Autoimmune diseases and rheumatoid arthritis</td>
<td>18.43</td>
</tr>
<tr>
<td>2 biologic</td>
<td>Eylea</td>
<td>Aflibercept</td>
<td>Regeneron Pharmaceuticals and Bayer</td>
<td>Macular degeneration</td>
<td>8.23</td>
</tr>
<tr>
<td>3</td>
<td>Revlimid</td>
<td>Lenalidomide</td>
<td>Celgene</td>
<td>Multiple myeloma</td>
<td>8.19</td>
</tr>
<tr>
<td>4 biologic</td>
<td>Rituxan</td>
<td>Rituximab (MabThera)</td>
<td>Roche and Biogen</td>
<td>Treatment of cancer</td>
<td>8.11</td>
</tr>
<tr>
<td>5</td>
<td>Enbrel</td>
<td>Etanercept</td>
<td>Amgen and Pfizer</td>
<td>Autoimmune diseases including rheumatoid arthritis, psoriasis, and other inflammatory conditions</td>
<td>7.98</td>
</tr>
<tr>
<td>6 biologic</td>
<td>Herceptin</td>
<td>Trastuzumab</td>
<td>Roche and Biogen</td>
<td>Treatment of cancer, mainly breast and gastric</td>
<td>7.55</td>
</tr>
<tr>
<td>7</td>
<td>Eliquis</td>
<td>Apixaban</td>
<td>BMS and Pfizer</td>
<td>Anticoagulant, mainly used to treat atrial fibrillation and deep vein thrombosis</td>
<td>7.40</td>
</tr>
<tr>
<td>8 biologic</td>
<td>Avastin</td>
<td>Bevacizumab</td>
<td>Roche and Biogen</td>
<td>Advanced colorectal, breast, lung, kidney, cervical, and ovarian cancer and relapsed glioblastoma</td>
<td>7.21</td>
</tr>
<tr>
<td>9 biologic</td>
<td>Remicade</td>
<td>Infliximab</td>
<td>Johnson &amp; Johnson and Mc rk</td>
<td>Autoimmune diseases</td>
<td>7.16</td>
</tr>
<tr>
<td>10</td>
<td>Xarelto</td>
<td>Rivaroxaban</td>
<td>Bayer and Johnson &amp; Johnson</td>
<td>Anticoagulant</td>
<td>6.54</td>
</tr>
<tr>
<td>11</td>
<td>Januvia/ Janumet</td>
<td>Sitagliptin</td>
<td>Merck</td>
<td>Treatment of type 2 diabetes</td>
<td>5.90</td>
</tr>
<tr>
<td>12 biologic</td>
<td>Lantus</td>
<td>Insulin glargine</td>
<td>Sanofi</td>
<td>Long-acting human insulin analog for the treatment of diabetes</td>
<td>5.65</td>
</tr>
<tr>
<td>13 vaccine</td>
<td>Prevnar 13/ Prevener</td>
<td>Pneumococcal 13-valent conjugate vaccine</td>
<td>Pfizer</td>
<td>Pneumococcal vaccine</td>
<td>5.60</td>
</tr>
<tr>
<td>14</td>
<td>Opdivo</td>
<td>Nivolumab</td>
<td>BMS</td>
<td>Melanoma</td>
<td>4.95</td>
</tr>
<tr>
<td>15 biologic</td>
<td>Neulasta/ Peglasta/ Neupogen</td>
<td>(Pegfilgrastim and Filgrastim)</td>
<td>Amgen and Kyowa Hakko Kirin</td>
<td>Neutropenia; decreases the incidence of infection during cancer treatment</td>
<td>4.56</td>
</tr>
<tr>
<td>16</td>
<td>Lyrica</td>
<td>Pregabalin</td>
<td>Pfizer</td>
<td>Anti-epileptic and neuropathic pain</td>
<td>4.51</td>
</tr>
<tr>
<td>17</td>
<td>Harvoni</td>
<td>Ledipasvir (sofosbuvir)</td>
<td>Gilead Sciences</td>
<td>HCV/HIV-1 infection</td>
<td>4.37</td>
</tr>
<tr>
<td>18</td>
<td>Advair</td>
<td>Fluticasone and Salmeterol</td>
<td>GlaxoSmithKline</td>
<td>Asthma</td>
<td>4.36</td>
</tr>
<tr>
<td>19</td>
<td>Tecfidera</td>
<td>Dimethyl fumarate</td>
<td>Biogen</td>
<td>Multiple sclerosis</td>
<td>4.21</td>
</tr>
<tr>
<td>20 biologic</td>
<td>Stelara</td>
<td>Ustekinumab</td>
<td>Johnson &amp; Johnson</td>
<td>Plaque psoriasis</td>
<td>4.01</td>
</tr>
</tbody>
</table>

Shaded row indicates API is a new chemical entity; non-shaded row indicates API is a biologic.

TABLE 1.3 Top 20 Global Pharmaceutical Products (2017 Sales)
### TABLE 1.4 Fifteen Top-Selling Drugs (2013–2016) for Cumulative Sales Through 2016

<table>
<thead>
<tr>
<th>Rank</th>
<th>Drug/Drug Product Typea</th>
<th>API</th>
<th>Marketer</th>
<th>Approval</th>
<th>$ Billion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lipitor Atorvastatin/film-coated tablet</td>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>Pfizer</td>
<td>1996</td>
<td>148.7</td>
</tr>
<tr>
<td>2</td>
<td>Humira Adalimumab/solution for injection</td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>AbbVie</td>
<td>2003</td>
<td>95.6</td>
</tr>
<tr>
<td>3</td>
<td>Advair (United States) Seretide(EU) fluticasone + salmeterol/dry powder inhaler</td>
<td><img src="image3" alt="Chemical Structure" /></td>
<td>GlaxoSmithKline</td>
<td>2001</td>
<td>92.5</td>
</tr>
<tr>
<td>4</td>
<td>Remicade/lyophilized powder for constitution, solution injection</td>
<td><img src="image4" alt="Chemical Structure" /></td>
<td>Janssen</td>
<td>1998</td>
<td>85.5</td>
</tr>
<tr>
<td>5</td>
<td>Plavix clopidogrel/film-coated tablet</td>
<td><img src="image5" alt="Chemical Structure" /></td>
<td>Bristol-Myers Squibb</td>
<td>1997</td>
<td>82.3</td>
</tr>
<tr>
<td>6</td>
<td>Enbrel Etanercept/subcutaneous injection</td>
<td><img src="image6" alt="Chemical Structure" /></td>
<td>Amgen/Pfizer</td>
<td>1998</td>
<td>77.2</td>
</tr>
<tr>
<td>7</td>
<td>Rituxan Rhuabx (solution injection)</td>
<td><img src="image7" alt="Chemical Structure" /></td>
<td>Roche Genentech</td>
<td>1997</td>
<td>75.9</td>
</tr>
<tr>
<td>8</td>
<td>Herceptin Trastuzumab/intravenous (IV) infusion</td>
<td><img src="image8" alt="Chemical Structure" /></td>
<td>Roche Genentech</td>
<td>1999</td>
<td>65.2</td>
</tr>
<tr>
<td>9</td>
<td>Avastin Bevacizumab/IV infusion</td>
<td><img src="image9" alt="Chemical Structure" /></td>
<td>Roche Genentech</td>
<td>2004</td>
<td>62.3</td>
</tr>
<tr>
<td>10</td>
<td>Nexium Esomeprazole/delayed release capsule; IV injection</td>
<td><img src="image10" alt="Chemical Structure" /></td>
<td>AstraZeneca</td>
<td>2001</td>
<td>60.2</td>
</tr>
</tbody>
</table>

(continued)
supplies for toxicological and clinical supplies rather than being used to “test” or verify that the chemistry or process will work on scale.

A primary focus of process development is to drive down the cost contribution of the API to the final formulated pharmaceutical product cost while at the same time optimizing to ensure quality and process robustness. The impact of API costs on overall manufacturing costs is approximated in Figure 1.7. The cost contribution of API is expected to increase with increasing complexity of molecular structures of APIs, e.g. biologics. It is interesting to note that API molecular complexity can often impact API cost more than formulation or packaging costs. As Federsel points out that, “Given the importance of ‘time to market’ which remains one of the highest priorities of pharmaceutical companies, the need to meet increasingly stretched targets for speed to best route has come to the forefront in process R&D” [9]. In the not too distant past it was considered satisfactory to have a good-enough synthetic route that was fit for purpose (i.e. could support the quantities of material needed) but not one considered best or lowest cost ($/kg of API). The prevailing view was that the market would bear higher product pricing as compensation for higher cost of goods (COGs). Further cost reduction through new routes could be and were pursued post-launch with savings realized later in the life cycle. According to Federsel, and evidenced frequently in contemporary R&D organizations, this approach is no longer viable, at least not as a default position. Instead the best

<table>
<thead>
<tr>
<th>Drug/Drug Product Type</th>
<th>API</th>
<th>Marketer</th>
<th>Approval</th>
<th>$ Billion</th>
</tr>
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<tbody>
<tr>
<td>Zyprexa</td>
<td><a href="#">Chemical Structure</a></td>
<td>Eli Lilly</td>
<td>1996</td>
<td>60.2</td>
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<tr>
<td>Olanzapine/oral disintegrating tablets; injections</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diovan</td>
<td><a href="#">Chemical Structure</a></td>
<td>Novartis</td>
<td>1997</td>
<td>60.1</td>
</tr>
<tr>
<td>Valsartan/film-coated tablet</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Lantus</td>
<td><a href="#">Chemical Structure</a></td>
<td>Sanofi-Aventis</td>
<td>2001</td>
<td>58.3</td>
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<tr>
<td>Insulin glargine/Subcutaneous Injection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crestor</td>
<td><a href="#">Chemical Structure</a></td>
<td>AstraZeneca</td>
<td>2003</td>
<td>55.2</td>
</tr>
<tr>
<td>Rosuvastatin/film-coated tablet</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Singulair</td>
<td><a href="#">Chemical Structure</a></td>
<td>Merck</td>
<td>1998</td>
<td>47.4</td>
</tr>
<tr>
<td>Montelukast/chewable tablet</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


www.drugs.com source of dosage form type for originator drug.

supplies for toxicological and clinical supplies rather than being used to “test” or verify that the chemistry or process will work on scale.

A primary focus of process development is to drive down the cost contribution of the API to the final formulated pharmaceutical product cost while at the same time optimizing to ensure quality and process robustness. The impact of API costs on overall manufacturing costs is approximated in Figure 1.7. The cost contribution of API is expected to increase with increasing complexity of molecular structures of APIs, e.g. biologics. It is interesting to note that API molecular complexity can often impact API cost more than formulation or packaging costs. As Federsel points out that, “Given the importance of ‘time to market’ which remains one of the highest priorities of pharmaceutical companies, the need to meet increasingly stretched targets for speed to best route has come to the forefront in process R&D” [9]. In the not too distant past it was considered satisfactory to have a good-enough synthetic route that was fit for purpose (i.e. could support the quantities of material needed) but not one considered best or lowest cost ($/kg of API). The prevailing view was that the market would bear higher product pricing as compensation for higher cost of goods (COGs). Further cost reduction through new routes could be and were pursued post-launch with savings realized later in the life cycle. According to Federsel, and evidenced frequently in contemporary R&D organizations, this approach is no longer viable, at least not as a default position. Instead the best
synthetic route to API (i.e. route with ultimate lowest cost materials) coupled with best process design and engineering (process with lowest processing costs) must be worked out as early as possible in API process development [9]. The optimal API process developed by the time of launch is necessary to extract additional revenues and respond to reduced COG margins. Achieving this requires continuous improvement in scientific and technical tools as well as multidisciplinary skill sets in the R&D labs, including chemical engineering science. The implementation of process design principles, drawing on the right skill sets, both from chemistry and engineering perspectives during clinical phase II, is considered such an important step toward leaner more cost-effective processes readied for launch that several portions of this book will expand on this concept.

1.5 RECENT TRENDS FOR PHARMACEUTICAL DRUG AND MANUFACTURING

During the past decade, the pharmaceutical field has evolved to a science and risk-based industry. It is now commonplace for the regulatory dossier to contain scientifically rigorous information and descriptions of the risk management approach used for decision making. Now, the industry is undergoing significant changes in the API (from small molecule to biologics), manufacturing (from batch toward continuous), medicinal approach (generalized to personalized), and complexity of manufacturing (from simple dosage forms toward additive manufacturing or 3D printing).

1.5.1 Drug Substances Trend Toward Biologics

Biologic medicines are revolutionizing the treatment of cancer, autoimmune disorders, and rare illnesses and are therefore critical to the future of the pharmaceutical industry. Cancer immunotherapy includes monoclonal antibodies, checkpoint inhibitors, antibody-drug conjugates (ADCs), and kinase inhibitors, to name a few.

From the 2017 top-selling drugs shown in Table 1.3, there is a strong trend toward drugs derived from biological origins dominating the market than small molecules. In fact, the majority of best sellers are biologics, often monoclonal antibodies, which treat new diseases such as Crohn’s and ulcerative colitis previously unmet medical needs by small molecule APIs. It is also evident that the biologics retain their value even after patent exclusivity expires, e.g. Humira sales continue to grow post-patent expiry in 2016. The current generic industry is skilled in small molecule development but appears to be challenged to rapidly erode sales for biologics. In fact, in the coming years, it appears the first biologic medicine may take over as the all-time best seller from Lipitor.

Biological drug candidates include many different types of molecules including monoclonal antibodies, vaccines, therapeutic proteins, blood and blood components, and tissues. In contrast to chemically synthesized drugs, which have a well-defined structure and can be thoroughly verified, biologics are derived from living material (human, animal, microorganism, or plant) and are vastly larger and more complex in structure. Biosimilars are versions of biologic products that reference the originator product in applications submitted for marketing approval to a regulatory body and are not exactly generic equivalents. However, biosimilar DPs are far more complex to gain regulatory approval in developed markets than for chemical generics and may involve costly clinical trials. Those that succeed will also have to compete with the originator companies who are unlikely to exit the market considering their expertise and investments. The biosimilars market is expected to increase significantly with the first FDA approval for Sandoz ZARXIO subcutaneous IV injection product in 2015 that helped establish a clear pathway for gaining regulatory approval [10]. Recently, Hospira, a Pfizer company, received FDA approval of their epoetin alfa biosimilar, Retacrit, in May 2018 [11].

Biologic and biosimilar medicines are treating illnesses, with unmet needs while retaining value even after post-exclusivity period. These are clear advantages for the originator, biopharmaceutical company developing biologic medicines, and are expected to continue to increase in the coming

14www.blog.crohnology.com
15https://www.selectusa.gov/pharmaceutical-and-biotech-industries-united-states
years. While the major disciplines making advancements in this area are biologists and chemists, there is a role for chemical and biochemical engineers in the design and development of the processing and purification steps. Chemical engineers are skilled at developing predictive models, and scale-up/scale-down principles, which make them a key contributor to this growing field. In fact, for biologics, scale-down predictive models of process steps were established and helped pave the way for biological products to use them for validation [12].

Chemical engineers that include biochemical engineering are well trained to impact the biotech industry, which utilizes cellular and biomolecular processes for new medicines [13]. Chemical engineers can also support the design of protein recovery, purification, and scaling up from lab to commercial production of the therapeutic proteins.

1.5.2 Lean Manufacturing

Pharmaceutical production of APIs and DPs can be generally characterized as primarily batch-operated multipurpose manufacturing plants. At these facilities commercial supplies of API intermediates, APIs, and DPs are manufactured before being packaged, labeled, and distributed to customers. Pharmaceutical production plants were typically designed to be flexible to allow a number of different products to be run in separate equipment trains, depending on the demand. Further, these facilities have various degrees of automation, relatively high levels of documentation, and change control to manage configurations, with relatively long downtimes for cleanup and turnover of the plant between product changes [14]. These considerations are in part to meet regulatory requirements for commercial manufacturing. Manufacturing costs or COGs often account for approximately one-third of the total costs with expenses exceeding that of R&D [15]. For this reason COG’s have received considerable focus as an area of opportunity for potential savings [7, 16].

It has been claimed that through adopting QbD principles and principles of lean manufacturing, pharmaceutical companies, as an aggregate, could save in the range of $20–50 billion/year by eliminating inefficiencies in current manufacturing [16]. This translates to 10–25% reduction in current COGs. An early QbD product approval of Chantix afforded an opportune chance to prove the benefits of these lean manufacturing and QbD principles. Chantix (varenicline tablet) was approved as an immediate release tablet commercially manufactured in the Pfizer Illertissen, Germany site. The OEB classification of this product required containment, available at small scale in this facility. Product demand increased dramatically in 1 year by 430%. The site employed lean manufacturing to eliminate process inefficiencies and wastes to increase production from 1 batch/day to 3 batches/day, delivering the desired 900 batches/year in the small-scale facility [17]. The lean manufacturing was indeed proven when the manufacturing maintained an inventory of only approximately one week lead ahead of demand.

The principles of lean manufacturing are often cited as an approach to reduce COGs in pharmaceutical development and manufacturing. Lean manufacturing describes a management philosophy concerned with improving profitability through the systematic elimination of activities that contribute to waste – thus the central theme to lean manufacturing is the elimination of waste where waste is considered the opposite of value. Based on the work of Taiichi Ohno, creator of the Toyota Production System, wastes are considered based on the following [18]:

- Overproduction
- Waiting
- Transportation
- Unnecessary processing
- Unnecessary inventory
- Unnecessary motion
- Defects

All of these wastes have the effect of increasing the proportion of non-value-added activities. Lean thinking is obviously applicable to many industries including pharmaceutical manufacturing as well as pharmaceutical development. Continuous processing, for pharmaceutical APIs and DPs, is one application of lean thinking applied to pharmaceutical manufacturing. The challenge is that batch processing inherently leads to overproduction and specifically the buildup of excess inventory of intermediates and DPs to supply the market. This leads to longer cycle times and is addressed through the concepts of continuous manufacturing (CM).

According to Ohno, “The greatest waste of all is excess inventory” where in simplest terms, excess inventory incurs cost associated with managing, transporting, and storing inventories adding to the waste. Large inventories also tie up large amounts of capital. Excess inventory represents an opportunity cost where capital is held up in the form of work in process (WIP), API finished goods, and formulated finished goods versus what could be invested elsewhere or back into R&D. Implementation of lean manufacturing principles can be used to develop workflows and infrastructures to reduce inventories. One way to reduce inventories is through continuous processing. Several chapters discuss the technical benefits of CM. A reliable steady delivery of product API and DP through small product-specific continuous plants could potentially reduce the level of inventory required in a dramatic way if the workflows were designed to ensure consistent delivery of product to packaging and distribution. The facilities of continuous production trains tend to be significantly smaller.

The costs of inventory holdings are significant and include both the carrying cost and the cash value of the inventory.
The carrying costs of inventory include two main contributions—(i) weighted average cost of capital (WACC) and (ii) overhead [19].

Estimates for the combined carrying cost of WACC and overhead range from 14 to 25% that translates to approximately 20% return for every dollar of inventory eliminated [20]. Technology platforms and new workflows designed to minimize the need for stockpiling API and DP inventories across the industry therefore would seem to offer very rapid payback.

### 1.5.3 Continuous Manufacturing

For a large pharmaceutical company carrying $5 billion in inventories, the holding cost based on the combined WACC and overhead of 20% is approximately $1 billion/year. Considered another way, technologies that ensure a reliable and steady distribution of product with the result of eliminating the need to build and store massive inventories can return the company cost savings equivalent to a blockbuster drug (generating $1 billion/year). Indeed one of the three factors having the largest impact on the profitability of a manufacturing organization is inventory with the other two being throughput and operating expense according to Goldratt and Cox [21]. Continuous processing if designed for reliable operations essentially year-round or in other cases simply “on demand” could potentially eliminate the need to accumulate significant inventories above and beyond two to four weeks of critical safety stocks of finished goods.

CM across API and DP integrated under one roof as a platform technology is one long-term approach to transforming the way the industry manages their commercial supply chain.

As one reference cites, “Even for very small processes, continuous processes will prove to be less expensive in terms of equipment and operating costs. Dedicated continuous processes often put batch processes out of business” [22]. The real point here is that continuous is one approach to lean manufacturing and to reducing inventories and costs but certainly not the only approach. Other lean systems can be devised that utilize the existing batch facilities as well. Since the publication of the first edition of this book in 2010, there has been a significant wave of interest in considering continuous processing for pharmaceutical API and DP.

In July 2015 FDA granted Vertex Pharmaceuticals approval of the first DP, Orkambi, a cystic fibrosis (CF) drug, to be produced using a CM process. Vertex’s second drug, Symdeko, for treating the underlying cause of CF occurred in February 2018. Janssen aims to manufacture 70% of their “highest volume” products using CM within eight years.16 In addition, they intend to increase yield by reducing waste by 33% and reduce manufacturing and testing cycle times by 80% through the use of CM. Their claim is that CM can reduce operating costs by as much as 50%, gain higher throughputs, and significantly reduce waste [23]. Janssen’s HIV drug Prezista is also manufactured via a continuous process after obtaining approval to convert from batch to continuous.17 Pfizer and Eli Lilly have made investments in CM and recently submitted an NDA or gained approval for a product, respectively. Merck states that CM will help achieve their goals of well-controlled processes with flexible sizes to handle small-to-large volume products localized closer to the customer.18

Merck Manufacturing Division targets a total lead time of 90 days formulation to the patient, reducing the current timing by one-quarter. Multiple companies are teaming together to leverage CM, e.g. Novartis-MIT Center for Continuous Manufacturing. A critical component of CM is that PAT is embedded into the overall plan for monitoring and control of the process. As stated by Kevin Nepveux, “one of the best ways to go about implementing CM processes is to develop the analytics in-line with the application.”19 In summary, CM requires significant focus by chemical engineers as there is more attention on cost savings and cost efficiencies.20

### 1.5.4 Personalized Medicine

“One size doesn’t fit all is a tenet of personalized medicine, also called precision medicine,” states Lisa Esposito in a recent report [24]. In her article, she highlights the long-standing personalized medicine approach taken to treat cancer based on the individual patient’s disease state and conditions. There is a growing expectation that the pharmaceutical industry should deliver DPs targeted to the individual, tailoring the amount of drug based on their mass, metabolism, genetic factors, and disease state. In this section, we discuss two approaches for manufacturing personalized/precision medicine through a pharm-on-demand concept for military personnel and for complex dosage forms using additive manufacturing (referred to as 3D printing).

The Defense Advanced Research Projects Agency (DARPA) Battlefield Medicine program is keenly interested in miniaturized, flexible platforms for end-to-end manufacturing of pharmaceuticals to support the troops on location. As discussed in other chapters within this book, advances in continuous flow synthesis, chemistry, biological engineering, and downstream processing, coupled with online analytics, automation, and enhanced process control measures, are

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18ibid.
proving that such capabilities are ready for implementation. The desire is to have a mobile, on-demand pharmacy located at the battlefield that could ensure readiness to treat threats of chemical, biological, radiological, and nuclear weapons [25].

1.5.5 Additive Manufacturing

Additive manufacturing, also referred to as three-dimensional (3D) printing, is an automated process of building layer by layer a complex dosage form personalized and manufactured on demand. FDA approved the first 3D printed DP in August 2015 for Aprecia Pharmaceuticals SPRITAM product as a disintegrating tablet [26]. The 3D printing in this case binds the powders while maintaining a porous structure (without the typical compression of a tablet press), providing a fast dissolving tablet. For example, 1000 mg of levetiracetam dissolves within seconds [27]. Extensions of 3D printing include printing extremely low dose APIs or highly potent APIs, but encapsulated with excipients, thus reducing potential exposure. Norman et al. [27] provide a thorough review of the different modalities of 3D printing for pharmaceutical manufacturing, which includes an analysis of the potential benefits of such products.

1.6 CHEMICAL ENGINEERS SKILLED TO IMPACT FUTURE OF PHARMACEUTICAL INDUSTRY

The fundamental principles taught in the chemical engineering curriculum ensure the chemical engineer is well poised to apply them to solve the coming challenging issues in the pharmaceutical industry. Chemical engineers are uniquely positioned to help address these needs in part derived from their ability to predict using mathematical models and their understanding of equipment and manufacturability. As Wu et al. highlighted, chemical engineers can help transform pharmaceuticals from an industry focusing on inventing and testing to a process and product design industry [28]. Significant pressure exists on what used to be a historically high-margin nature of the pharmaceutical industry to deliver safe, environmentally friendly, and economic processes in increasingly shorter timelines. This means fewer scale-ups at kilo and pilot plant scale, with expectation that a synthesis or formulation can be designed in the lab to perform as expected (and right the first time) at the desired manufacturing scale.

Chemical engineers are also uniquely positioned to influence regulators by incorporating advancements such as continuous processing coupled with PAT into a highly regulated industry. From R&D through manufacturing within the pharmaceutical industry, chemical engineering can be leveraged to bring competitive advantage to their respective organizations through process and predictive modeling that lead to process understanding, improving speed of development, and developing new technology platforms and leaner manufacturing methods. The chapters in these two volumes are intended to provide examples of chemical engineering principles specifically applied toward relevant problems faced in the pharmaceutical sciences and manufacturing areas. Further the broader goal of this work is to promote the role of chemical engineering within our industry, to promote the breadth of skill sets therein, and to showcase the critical synergy between this discipline and the many scientific disciplines that combine to bring pharmaceutical drugs and therapies to patients in need around the world.

REFERENCES

PART II

DRUG PRODUCT DESIGN, DEVELOPMENT, AND MODELING
DESIGN OF SOLID DOSAGE FORMULATIONS

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Formulation Development, Vertex Pharmaceuticals, Cambridge, MA, USA

2.1 INTRODUCTION

The oral route is the most common way of administering drugs. It not only represents a convenient (self-administered) and safe way of drug administration but is also more profitable to manufacture than the parenteral dosage forms that must be administered, in most cases, by trained personnel. This is reflected by the fact that well over 80% of the drugs in the United States that are formulated to produce systematic effects are marketed as oral dosage forms. Among the oral dosage forms (Table 2.1), tablets of various different types are the most common because of their low cost of manufacture (including packaging and shipping), increased stability, and virtual temper resistance.

Following oral administration of tablets, the delivery of the drug to the systemic circulation requires initial transport through the gastrointestinal (GI) membrane. The drug absorption from the GI tract requires that the drug is brought into solution in the GI fluids and that it is capable of crossing the intestinal membrane into the systemic circulation; therefore, the rate of dissolution of the drug in the GI lumen can be a rate-limiting step in the absorption of drugs given orally. Particles of drugs, e.g. insoluble crystalline forms or specific delivery systems such as liposomes, are generally found to be absorbed to a very small extent. The cascade of events from release of the drug from tablet, i.e. disintegration of tablet into granules or aggregates followed by dissolution of the drug in the gut lumen, interactions, and/or degradation within the lumen and the absorption of the drug across the intestinal membrane into the systemic circulation, is schematically shown in Figure 2.1. The slowest of these events (dissolution and/or absorption) determines the rate of availability of the drug from tablet formulation. Many factors in each step influence the rate and extent of availability of the drug. Physical, chemical, and biopharmaceutical properties of the drug, as well as the design and production of the tablet, play a very important role in its bioavailability after oral administration. These considerations make the seemingly simple tablet formulation approach complex to formulate in reality. These realizations have resulted in a change in philosophy of tablet formulation design in last decade or more, wherein it is no longer considered an art but well-defined science.

The single greatest challenge to the tablet formulator is in the definition of the purpose of the formulation and the identification of the suitable materials to meet development objectives. A good formulation must not only be bioavailable but also be manufacturable, and be chemically and physically stable from manufacturing through the end of shelf life. In addition, many quality standards and special requirements must be met to ensure the efficacy and safety of the product.

All of these formulation goals can be described as the target product profile (TPP). A TPP is a summary of characteristics that, if achieved, will provide optimal efficacy, patient compliance, and marketability. A TPP (Table 2.2) often includes attributes like pharmacokinetic information (e.g. immediate release vs. extended release), dosage form (e.g. tablet vs. injectable), and shelf-life information (e.g. two years at 25 °C/60% Relative Humidity (RH)). There are also many other potential inputs for drug development that a formulator may or may not need, such as: Warnings and Precautions, Adverse Reactions, Drug Interactions, Use in Specific Populations, Drug Abuse and Dependence, Clinical Studies, and Patient Counseling Information.

It is important to establish the TPP so that the formulation effort will be effective and focused. When the formulation

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TABLE 2.1 Types of Solid Oral Dosage Forms

<table>
<thead>
<tr>
<th>Type of Oral Dosage Form</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate release tablets</td>
<td>Disintegrate in stomach after taken orally</td>
</tr>
<tr>
<td>Delayed release tablets</td>
<td>Enteric-coated tablets to keep tablets intact in stomach and disintegrate in intestine for absorption</td>
</tr>
<tr>
<td>Sustained/controlled release tablets</td>
<td>Release drug slowly over a period of time to decrease the frequency of administration</td>
</tr>
<tr>
<td>Chewable tablets</td>
<td>Tablets are broken by chewing before swallowing with water</td>
</tr>
<tr>
<td>Orally disintegrating tablets</td>
<td>Disintegrate in oral cavity without drinking water to form a suspension for ease of swallowing</td>
</tr>
<tr>
<td>Hard gelatin capsules</td>
<td>Two-piece capsule shells filled with granules, powders, pellets, sprinkles, semisolids, and oils</td>
</tr>
<tr>
<td>Soft gelatin capsules</td>
<td>One-piece capsule filled with oily liquid</td>
</tr>
<tr>
<td>Sachets</td>
<td>Single-dose unit bag containing granules</td>
</tr>
</tbody>
</table>

This chapter examines tablet-formulation design and development of an immediate release oral solid dosage form using a mix of Pharmaceutical Science, Statistical, and Engineering approaches. The chapter is aimed toward providing engineers an overview of the key physicochemical, mechanical, and biopharmaceutical properties of the drug and their requirements are defined by the TPP, a strategy must be established to facilitate effective formulation development. To formulate a formulation strategy, one must consider the physical, chemical, and biopharmaceutical characteristics of the drug; optimal technologies to achieve formulation goals; and the manufacturing capabilities to support the product.

TABLE 2.2 Typical Target Product Profile (TPP) for an Immediate Release (IR) Tablet

<table>
<thead>
<tr>
<th>TPP</th>
<th>How Used by a Formulator</th>
<th>Typical for IR Tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indications and usage</td>
<td>Examine other products in the same class: examine improvements</td>
<td>Once a day (QD)</td>
</tr>
<tr>
<td></td>
<td>Good to know what is expected before one starts formulating</td>
<td>Twice a day (BID)</td>
</tr>
<tr>
<td>Dosage and administration</td>
<td>Multiple strengths may be needed depending on the population being targeted (adults vs. children)</td>
<td>Three times a day (TID)</td>
</tr>
<tr>
<td>Dosage forms and strengths</td>
<td>Useful if designing an extended release dosage, in which overdose (dose dumping) is a possibility</td>
<td>Dependent on drug typically 10–500 mg</td>
</tr>
<tr>
<td>Overdosage</td>
<td>This is up to the formulator and marketing: shape, size, and color of the tablet helps determine where the drug is absorbed and how fast the drug must get into solution</td>
<td>Dependent on drug</td>
</tr>
<tr>
<td>Description</td>
<td>A tablet with markings and color</td>
<td>Two-year room temperature shelf life</td>
</tr>
<tr>
<td>Clinical pharmacology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>How supplied/stored/handled</td>
<td>Important as most people do not like refrigerated dosage forms</td>
<td></td>
</tr>
</tbody>
</table>
influence on the selection of formulation process platform. Subsequently, critical tablet characteristics that affect the stability and bioavailability of the drug product are discussed. Finally, strategy for tablet-process optimization and scale-up is defined to select proper equipment and to define operational design space (DS). A systematic scientific approach to tablet formulation and process development along with practical examples is discussed to expedite the drug product development.

2.2 UNDERSTANDING DRUG SUBSTANCE

Integrating the physicochemical, mechanical, and biopharmaceutical properties of a drug candidate is a prerequisite in developing a robust and bioavailable drug product that has optimal therapeutic efficacy. The measurement of physical, mechanical, and chemical properties helps guide not only the selection of dosage form but also provides an insight into their processability and storage to ensure optimal drug product quality. Figure 2.2 lists the critical physicochemical, mechanical, and biopharmaceutical properties that need to be understood to aid in the design of tablet formulation.

2.2.1 Physicochemical Properties

Prior to the development of tablet dosage form, it is essential to understand to determine certain fundamental physical and chemical properties of the drug molecule along with other derived properties. This information dictates many of the subsequent approaches in tablet formulation development and is known as preformulation. It should be kept in mind that many of these properties are dependent on the solid form, and complete characterization of each of the most relevant solid forms is needed to provide a complete physicochemical picture.

2.2.1.1 Solubility and Drug Dissolution Solubility of a drug candidate may be the critical factor determining its

![FIGURE 2.2 Understanding drug substance properties.](image-url)
usefulness, since aqueous solubility dictates the amount of compound that dissolves; therefore, the amount available for absorption. A compound with low aqueous solubility could be subject to dissolution rate-limited absorption within the GI residence time.

**Dissolution** is the dynamic process by which a material is dissolved in a solvent that is characterized by a rate (amount dissolved per unit time), while **solubility** is the amount of material dissolved per unit volume of a certain solvent that is characterized as a concentration. Solubility is often used as a short form for “saturation solubility,” which is the maximum amount of drug dissolved at equilibrium conditions. Finally, **intrinsic solubility** is the solubility of the neutral form of an ionizable drug.

Dissolution rate is directly proportional to the aqueous solubility, $C_s$, and the surface area, $A$, of drug exposed to the dissolution medium. It is common, when developing an immediate release dosage form of poorly soluble drug, to increase the drug-dissolution rate by increasing the surface area of a drug through particle size reduction.

The dissolution rate of a solute from a solution is described by the Noyes–Whitney equation as follows [1]:

$$\frac{dC}{dt} = \left(\frac{D \times A}{h}\right) \times (C_s - C_t) \quad (2.1)$$

$D$ is the diffusion coefficient of the drug substance (in a stagnant water layer around each drug particle with a thickness $h$, $A$ is the drug particle surface area, $C_s$ is the saturation solubility, and $C_t$ is the drug concentration in the bulk solution at a given time.

The dissolution rate, rather than the saturation solubility, is most often the primary determinant in the absorption process of a sparingly low-soluble drug. Determining the dissolution rate is critical. The main area for dissolution-rate studies are evaluations of different solid forms of a drug (e.g. salts, solvates, polymorphs, amorphous, and stereoisomers) or different particle sizes of the drug. The dissolution rate can either be determined for a constant surface area of the drug in a rotating disc apparatus [2] or as a dispersed powder in a beaker with agitation (as detailed in pharmacopeias such as United States Pharmacopeia, etc.).

The impact of solubility and dissolution rate on formulation selection is discussed later in the chapter.

### 2.2.1.2 Partition Coefficient

Partition coefficient is the relationship between chemical structure, lipophilicity, and its disposition in vivo and has been reviewed by a number of authors [3]. The lipophilicity of an organic compound is described in terms of a partition coefficient, $log P$, which is defined as the ratio of the concentration of the unionized compound, at equilibrium, between organic and aqueous phases:

$$logP = \frac{[A]_{\text{organic}}}{[A]_{\text{aqueous}}} \quad (2.2)$$

For ionizable drugs, the ionized species does not partition into the organic phase, the apparent partition coefficient, $D$, is calculated from the following:

Acids: $logD = logP - log\left[1 + 10^{(pH - pKa)}\right] \quad (2.3)$

Bases: $logD = logP - log\left[1 + 10^{(pKa - pH)}\right] \quad (2.4)$

$pKa$ is the dissociation constant.

Since it is virtually impossible to determine $log P$ in a realistic biological medium, the octanol/water system has been widely adopted as a model of the lipid phase [4]. There has been much debate about the suitability of this system [5], but it remains the most widely used in pharmaceutical studies.

Generally, compounds with $log P$ values between 3 and 6 show good passive absorption, whereas those with $log Ps$ of less than 3 or greater than 6 often have poor passive transport characteristics. The role of $log P$ in absorption processes occurring after oral administration has been discussed by Navia and Chaturvedi [6].

#### 2.2.1.3 Crystal Properties and Polymorphism

Most drug substances appear in more than one polymorphic form. Polymorphs differ in molecular packing (crystal structure), but share the same chemical composition [7]. Hydrates or solvates are often called “pseudo-polymorphs” because, in addition to containing the same given drug molecule, hydrates or solvates also contain molecules of solvents that are incorporated into the crystal lattice. Amorphous forms are characterized by the absence of long-range order.

Polymorphism has a profound implication on formulation development and biopharmaceutical properties, because polymorphs may exhibit significantly different solubility, dissolution rate, compactibility, hygroscopicity, physical stability, and chemical stability [7]. Figure 2.3 provides a detailed list (Ishikawa or Fishbone diagram) of physical properties that can differ among the polymorphs.

Higher solubility and faster dissolution rates of the metastable polymorph may lead to significantly better oral bioavailability. Chloramphenicol palmitate [9] (bacteriostatic antimicrobial) and ampicillin [10] (antibiotic example of this is, such as is the case with) are examples of the anhydrous form which gave higher blood serum levels than the less-soluble trihydrate form.

Although use of a faster-dissolving polymorph may have clinical benefit, it is important to keep in mind that a polymorph with a higher solubility or faster dissolution rate is also metastable (i.e. a higher energy form) and tends to convert to
a thermodynamically more stable form over time. Conversion from a metastable form to a stable form could lower a drug’s oral bioavailability, and lead to inconsistent product quality. From a formulating perspective, it is desirable to use the thermodynamically stable form of the API; however, biopharmaceutical and processability considerations may dictate the deliberate selections of a metastable form for processing.

It is important to keep in mind that polymorphic form conversion from the most stable form may still occur, even when a stable crystal form is chosen for development. Polymorphic transformations can take place during pharmaceutical processing, such as particle size reduction, wet granulation, drying, and even during the compaction process and compression process [11, 12] as each of these processes may add the energy required to move the drug to the unstable form.

2.2.1.4 Particle Size, Particle Morphology, and Surface Area

Bulk flow, compactability, formulation homogeneity, and surface-area control dissolution and chemical reactivity, which are directly affected by size, shape, and surface morphology of the Drug/Active Pharmaceutical Ingredient (API).

Spherical particles have the least contact surface area and exhibit good flow, whereas acicular particles tend to have poor flow [13]. Milling of long acicular (or needle) crystals can enhance flow properties; however, excessively small particles tend to be cohesive and aggravate flow problems.

In addition to the flow properties, crystal shape and size have been demonstrated to impact mixing and tabletability. L-lysine monohydrate with plate-shaped crystals exhibited greater tabletability than the prism-shaped crystals [14]. Kaerger et al. [15] studied the effect of paracetamol particle size and shape on the compactibility of binary mixture with microcrystalline cellulose, showing that compressibility increased with particle size and irregular crystals, whereas compactibility increased with a decrease in particle size.

Particle size affects drug content uniformity (CU). For low-dose direct compression (DC) formulations, where drug CU is of particular concern, the particle size of the drug substance has to be small enough to meet the US Pharmacopeia requirement on CU [16]. For example, Zhang and Johnson [17] showed that low-dose blends containing a larger drug particle size (18.5 μm) failed to meet the USP requirement, whereas a blend containing smaller particle sizes (6.5 μm) passed.

Surface areas of drug particles are important because dissolution is a function of this parameter (as predicted by the Noyes–Whitney equation). This is particularly true in those cases where the drug is poorly soluble. Such drugs are likely to exhibit dissolution rate-limited absorption. For such drugs, particle size reduction (e.g. micronization) is often utilized to increase the surface area which enhances the dissolution rate; e.g. micronization enhanced the bioavailability of felodipine when administered as an extended release tablet [18].

Methods to determine particle size and shape include light microscopy, scanning electron microscopy (SEM), sieve analysis, and various electronic sensing-zone particle counters. Methods available for surface area measurement include air permeability and various gas adsorption techniques.

2.2.1.5 Bulk Powder Properties

Density and porosity are two important pharmaceutical properties that are derived from the information on particle size, particle shape, and surface area. A comparison of true particle density, apparent particle density, and bulk density can provide information on total porosity, interparticle porosity, and intraparticle

![Diagram of physical property differences among polymorphs](image-url)
porosity. Generally, porous granules dissolve faster than dense granules, since pores allow water to penetrate more readily.

Interparticle (interspace) porosity = 1 – \( \frac{\text{bulk density}}{\text{apparent particle density}} \) (2.5)

Intraparticle porosity = 1 – \( \frac{\text{apparent particle density}}{\text{true particle density}} \) (2.6)

Total porosity = 1 – \( \frac{\text{bulk density}}{\text{true particle density}} \) (2.7)

The increase in bulk density of a powder is related to the cohesivity of a powder. Bulk density and tapped density are used to calculate compressibility index and Hausner ratio, which are measures of the propensity of a powder to flow and be compressed. A rule of thumb: a compressibility index of higher than 30% indicates poor powder flow. The Hausner ratio varies from about 1.2 for a free-flowing powder to 1.6 for cohesive powders.

Hausner ratio = \( \frac{\text{tapped density}}{\text{bulk density}} \) (2.8)

Compressibility (Carr index) = \( 100 \times \frac{\text{tapped density} – \text{bulk density}}{\text{bulk density}} \) (2.9)

2.2.1.6 Melting Point and Hygroscopicity Low melting materials tend to be more difficult to manufacture and handle in conventional solid dosage forms. A rule of thumb: melting points below about 60 °C are considered to be problematic. Temperatures in conventional manufacturing equipment, such as fluid-bed dryers and tablet presses, can exceed 50 °C. During the milling process, hot spots in the milling chamber may have much higher temperatures.

Moisture uptake is a concern for pharmaceutical powders and is known to affect a wide range of properties, such as powder flow, compactibility, and stability [8, 17, 46]. On the other hand, moisture may improve powder flow and uniformity of the bulk density as well as an appropriate amount of moisture may act as a binder to aid compaction. Thus, knowledge of the type and level of moisture is critical for understanding its impact not only on deformation behavior but also on the attributes of the final product.

2.2.2 Biopharmaceutical Properties

Biopharmaceutics is defined as the study of the relationships between the physicochemical properties, dosage forms, and routes of administration of drugs, and its effect on the rate and extent of absorption in the living body. Complete oral absorption occurs when the drug has a maximum permeability coefficient and maximum solubility at the site of absorption, which results in rapid and uniform pharmacological response. Based upon this premise, a key objective in designing a rational oral dosage form is having sound understanding of multitude of factors including physicochemical properties of the drug and dosage-form components, and physiological aspects of GI tract.

Generating formulations with relevant oral bioavailability depends on a number of factors including solubility, permeability, and metabolic stability. Absorbability is related to the first two factors whose importance has been recognized in the guise of the biopharmaceutics classification system (BCS) [19, 20]. This approach classifies drugs and drug candidates into four categories based on their solubility and permeability properties. The Food and Drug Administration (FDA) has issued guidelines to define low and high solubility and permeability [21].

The primary objective of the BCS is to guide decisions with respect to in vivo and in vitro correlations and need for bioequivalence studies; it is also used to identify dosage-form strategies that are designed at overcoming absorption barriers presented by solubility and/or permeability-related challenges as depicted in Table 2.3.

The BCS nomenclature is centered on the premise that most orally administered drugs are absorbed via passive diffusion process through the small intestine and excludes other important factors such as the drug absorption mechanism (carrier-mediated, P-glycoprotein efflux, etc.) and pre-systemic degradation or complexation that may enhance or limit oral bioavailability.

1Permeability determines the ability of drug to move across the lipophilic intestinal membrane in gastrointestinal tract (GIT). Permeability of a drug may be predicted using computational (in silico) models or measured using both physicochemical and biological methods (in vitro, in situ, or in vivo).
2Metabolic stability refers to ability of a drug to withstand metabolism or degradation in the gut wall and the liver.
3Biopharmaceutics classification system (BCS) is guidance for predicting the intestinal drug absorption using solubility and permeability provided by the U.S. Food and Drug Administration.
4Passive diffusion is a transport process, wherein drug molecules pass across the lipoidal intestinal membrane from a region of high concentration in the lumen (GIT) to a region of lower concentration in the blood (systemic circulation). Mathematically, it is described by Fick’s first law of diffusion.
5Carrier-mediated transport may be subdivided into active transport and facilitated diffusion or transport. Active transport is a process whereby drug is bound to a carrier or membrane transporter and is transported against the concentration gradient across a cell membrane. Facilitated diffusion differs from active transport in that it cannot transport a substance against a concentration gradient of that substance.
6P-glycoprotein is one of the key counter-transport efflux proteins that expel specific drugs back into the lumen of the GIT after they have been absorbed.
TABLE 2.3 Dosage-form Options Based on Biopharmaceutical Classification System

<table>
<thead>
<tr>
<th>Class I: High solubility, high permeability</th>
<th>Class II: Low solubility, high permeability</th>
</tr>
</thead>
<tbody>
<tr>
<td>No major challenges for immediate-release dosage form</td>
<td>Formulation are designed to overcome solubility</td>
</tr>
<tr>
<td>Controlled-release dosage forms may be needed to limit rapid absorption</td>
<td>Salt formation</td>
</tr>
<tr>
<td>Prodrugs</td>
<td>Precipitation inhibitors</td>
</tr>
<tr>
<td>Permeation enhancers</td>
<td>Metastable forms</td>
</tr>
<tr>
<td>Ion pairing</td>
<td>Solid dispersions</td>
</tr>
<tr>
<td>Bioadhesives</td>
<td>Lipid technologies</td>
</tr>
</tbody>
</table>

The accompanying section discusses excipient, their types, and the selection procedure based upon their effect on the drug substance properties.

2.3 EXCIPIENTS

Excipients facilitate formulation design to perform a wide range of functions to obtain the desired properties for the finished drug product. Historically, pharmaceutical excipients have been regarded as inert additives, but this is no longer the case. Each additive must have a clear justification for inclusion in the formulation and must perform a defined function in the presence of the active and any other excipients included in the formulation. Excipients may function, for example, as an antimicrobial preservative, a solubility enhancer, a stability enhancer, or a taste masker, to name a few.

Excipients are selected based on their chemical/physical compatibility with drugs, regulatory acceptance, and processability. First, excipients shall be chemically compatible with drug substances. Second, in the time of globalization, excipients are to meet the requirements of not only the FDA or EMEA but also the regulatory agencies of other potential marketing countries. Third, excipients impact the properties of a powder mixture, such as flowability, density, compactibility, and adhesiveness. For example, different fillers are selected carefully to balance the plasticity, elasticity, and brittleness of the pre-compaction powder mixture, in order to make large-scale production feasible.

For tablets, excipients are needed both for the facilitation of the tableting process (e.g. glidants) and for the formulation (e.g. disintegrants). Except for diluents, which may be present in large quantity, the level of excipient use is usually limited to only a few percent and some lubricants are required at less than 1%. Details of the types, uses, and mechanisms of action of various excipients for tablet production have been discussed at length in several articles and books. The types and functions of excipients for tablet production are summarized in Table 2.5.

It is worth noting that some of these tabletting excipients may exert effects in opposition to each other. For example, binders and lubricants, because of their respective bonding and waterproofing properties, may hinder the disintegration action of the disintegrants. In addition, some of these tabletting excipients may possess more than one function that may be similar (e.g. talc as lubricant and glidant) or opposite (e.g. starch as binder and disintegrant) to each other.

Furthermore, the sequence of adding the excipients during tablet production depends on the function of the excipient. Whereas the diluents and the binders are to be mixed with the active ingredient early on for making granules, disintegrants may be added before granulation (i.e. inside the granules), and/or during the lubrication step (i.e. outside the granules) before tablet compression.
### TABLE 2.4 Characterization Tools for Understanding the Mechanical Properties of Materials

<table>
<thead>
<tr>
<th>Characterization Tests</th>
<th>Quasi-Static Testing</th>
<th>Dynamic Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>API required</strong></td>
<td>1–100 g</td>
<td>2–10 g</td>
</tr>
<tr>
<td><strong>Advantages</strong></td>
<td>“Independently” dissect out and investigate various mechanical properties</td>
<td>Understand the mechanics of materials at speeds representative of production tablet compaction</td>
</tr>
<tr>
<td><strong>Limitations</strong></td>
<td>Cannot determine properties at representative production scales</td>
<td>Difficult to factor out the individual mechanical property “component”</td>
</tr>
</tbody>
</table>
| **Tensile strength**   | • describes the global strength of the material  
                          • measured using traditional tablet hardness tester [22] or transverse compression in tensile tester [23]  
                          • Typical desired value >1 MPa | Force–displacement profiles  
                          • indicator of tablet-forming ability of powder  
                          • assessment of the elastic properties  
                          • thermodynamic analysis of the process of compact formation |
| **Indentation/dynamic hardness** | • describes the “local” plasticity of the material  
                          • measured using pendulum impact device or free-falling indenter [23, 24] | Tablet volume–applied pressure profiles  
                          • measured using hydraulic press, rotary press, compaction simulator, compaction emulator |
| **Young’s modulus**    | • describes stiffness and toughness of the material  
                          • measured using both four- and three-point beam bending, flexure testing [25] | Heckel equation  
                          • tablet porosity–applied pressure function |
| **Tableting indices**  | • dimensionless numbers that integrates above described tests |       |
| Bonding index (BI)     | • defines the tendency of the material to remain intact after compression  
                          • desired value >0.01 |       |
| Brittle fracture index (BFI) | • measure of brittleness of a material  
                          • BFI = 1 represents very brittle material and BFI < 0.3 is relatively non-brittle material |       |
| Strain index (SI)      | • indirect measure of elastic strain |       |

### TABLE 2.5 Types and Functions of Tableting Excipients

<table>
<thead>
<tr>
<th>Excipient</th>
<th>Function</th>
<th>Some Examples of Excipients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diluents</td>
<td>Act as bulking/filling material</td>
<td>Sugars, lactose, mannitol, sorbitol, sucrose, calcium salts, microcrystalline celluloses</td>
</tr>
<tr>
<td>Binders and adhesives</td>
<td>Holds powder together</td>
<td>Sugars, glucose, polymers, starch, gelatin</td>
</tr>
<tr>
<td>Disintegrants</td>
<td>To facilitate the breakup of the tablet in the gastrointestinal tract</td>
<td>Croscarmellose sodium (CCS), sodium starch glycolate (SSG), crospovidone</td>
</tr>
<tr>
<td>Glidants</td>
<td>Improve the flow of granules, needed for compression</td>
<td>Silica, magnesium stearate, talc</td>
</tr>
<tr>
<td>Lubricants</td>
<td>Reduces friction between granules and the compression equipment</td>
<td>Magnesium stearate (MgSt), stearic acid, talc, sodium lauryl sulfate (SLS)</td>
</tr>
<tr>
<td>Antiadherents</td>
<td>To minimize the problems if sticking to the tablet punch head</td>
<td>Talc, cornstarch, SLS, MgSt</td>
</tr>
<tr>
<td>Colorants</td>
<td>For identification and marketing</td>
<td>Natural pigments and synthetic dyes</td>
</tr>
<tr>
<td>Flavors and sweeteners</td>
<td>To improve the taste of chewable tablets</td>
<td>Mannitol, aspartame</td>
</tr>
</tbody>
</table>
2.4 DRUG–EXCIPIENT COMPATIBILITY STUDY

Excipient compatibility testing provides a preliminary evaluation of the physical and chemical interactions that can occur. Testing is carried under stressed temperature and humidity conditions, between a drug and potential excipients. This helps excipient selection, particularly for tablet formulations in order to minimize unexpected formulation stability problems during product development.

Traditionally, a binary mixture of drug with the excipient being investigated is intimately mixed, and the ratio of drug to excipient is often 1:1; however, other mixtures may also be investigated. These blends were stored at various temperatures and humidity, and analyzed for potential degradation products.

More recently, the use of a model formulation approach to excipient screening has become much more widespread across the industry. Model formulations include commonly used excipients in each functional category such as fillers, binders, disintegrants, and lubricants, and those with different chemical structures viz. celluloses, starches, and sugars. Both wet and dry model formulations may be prepared for stability testing. It is recommended that a Design of Experiment (DOE) be used to assist in the development and interpretation of results for these types of studies. Table 2.6 contains an example of the model formulation approach. It lists excipients and their approximate composition that would be found in a typical tablet formulation.

Table 2.6 Typical Excipients Selected for a Model Formulation Study

<table>
<thead>
<tr>
<th>Excipient Type</th>
<th>% Composition</th>
<th>Level 1</th>
<th>Level 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>API</td>
<td>10</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Filler 1</td>
<td>38–40</td>
<td>MCC</td>
<td>Mannitol</td>
</tr>
<tr>
<td>Filler 2</td>
<td>38–40</td>
<td>Dicalcium phosphate</td>
<td>Spray-dried lactose</td>
</tr>
<tr>
<td>Surfactant</td>
<td>0–4</td>
<td>None</td>
<td>Sodium lauryl sulfate</td>
</tr>
<tr>
<td>Binder</td>
<td>4</td>
<td>PVP</td>
<td>HPC</td>
</tr>
<tr>
<td>Disintegrant</td>
<td>5</td>
<td>Sodium starch glycolate</td>
<td>Croscarmellose sodium</td>
</tr>
<tr>
<td>Lubricant</td>
<td>1</td>
<td>Magnesium stearate</td>
<td>Sodium stearyl fumarate</td>
</tr>
<tr>
<td>Wet granulation</td>
<td>20% (w/w) water</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Table 2.7 Formulation Composition for Excipient Compatibility Study

<table>
<thead>
<tr>
<th>Formulation Composition and Numbers</th>
<th>10%</th>
<th>38–40%</th>
<th>38–40%</th>
<th>0–4%</th>
<th>4%</th>
<th>1%</th>
<th>5%</th>
<th>20% (w/w) Water</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>API</td>
<td>MCC</td>
<td>ATab</td>
<td>None</td>
<td>PVP</td>
<td>MgSt</td>
<td>SSG</td>
<td>Dry (no)</td>
</tr>
<tr>
<td>2</td>
<td>API</td>
<td>MCC</td>
<td>ATab</td>
<td>None</td>
<td>HPC</td>
<td>MgSt</td>
<td>CCS</td>
<td>Wet</td>
</tr>
<tr>
<td>3</td>
<td>API</td>
<td>MCC</td>
<td>ATab</td>
<td>SLS</td>
<td>PVP</td>
<td>SSF</td>
<td>CCS</td>
<td>Wet</td>
</tr>
<tr>
<td>4</td>
<td>API</td>
<td>MCC</td>
<td>ATab</td>
<td>SLS</td>
<td>HPC</td>
<td>SSF</td>
<td>SSG</td>
<td>Dry (no)</td>
</tr>
<tr>
<td>5</td>
<td>API</td>
<td>MCC</td>
<td>Lactose</td>
<td>None</td>
<td>PVP</td>
<td>SSF</td>
<td>CCS</td>
<td>Dry (no)</td>
</tr>
<tr>
<td>6</td>
<td>API</td>
<td>MCC</td>
<td>Lactose</td>
<td>None</td>
<td>HPC</td>
<td>SSF</td>
<td>SSG</td>
<td>Wet</td>
</tr>
<tr>
<td>7</td>
<td>API</td>
<td>MCC</td>
<td>Lactose</td>
<td>SLS</td>
<td>PVP</td>
<td>MgSt</td>
<td>SSG</td>
<td>Wet</td>
</tr>
<tr>
<td>8</td>
<td>API</td>
<td>MCC</td>
<td>Lactose</td>
<td>SLS</td>
<td>HPC</td>
<td>MgSt</td>
<td>CCS</td>
<td>Dry (no)</td>
</tr>
<tr>
<td>9</td>
<td>API</td>
<td>Mannitol</td>
<td>ATab</td>
<td>None</td>
<td>PVP</td>
<td>SSF</td>
<td>SSG</td>
<td>Wet</td>
</tr>
<tr>
<td>10</td>
<td>API</td>
<td>Mannitol</td>
<td>ATab</td>
<td>None</td>
<td>HPC</td>
<td>SSF</td>
<td>CCS</td>
<td>Dry (no)</td>
</tr>
<tr>
<td>11</td>
<td>API</td>
<td>Mannitol</td>
<td>ATab</td>
<td>SLS</td>
<td>PVP</td>
<td>MgSt</td>
<td>CCS</td>
<td>Dry (no)</td>
</tr>
<tr>
<td>12</td>
<td>API</td>
<td>Mannitol</td>
<td>ATab</td>
<td>SLS</td>
<td>HPC</td>
<td>MgSt</td>
<td>SSG</td>
<td>Wet</td>
</tr>
<tr>
<td>13</td>
<td>API</td>
<td>Mannitol</td>
<td>Lactose</td>
<td>None</td>
<td>PVP</td>
<td>MgSt</td>
<td>CCS</td>
<td>Wet</td>
</tr>
<tr>
<td>14</td>
<td>API</td>
<td>Mannitol</td>
<td>Lactose</td>
<td>None</td>
<td>HPC</td>
<td>MgSt</td>
<td>SSG</td>
<td>Dry (no)</td>
</tr>
<tr>
<td>15</td>
<td>API</td>
<td>Mannitol</td>
<td>Lactose</td>
<td>SLS</td>
<td>PVP</td>
<td>SSF</td>
<td>SSG</td>
<td>Dry (no)</td>
</tr>
<tr>
<td>16</td>
<td>API</td>
<td>Mannitol</td>
<td>Lactose</td>
<td>SLS</td>
<td>HPC</td>
<td>SSF</td>
<td>CCS</td>
<td>Wet</td>
</tr>
</tbody>
</table>
on open dish stability at 25 °C/60%RH, 40 °C dry, and 40 °C/75%RH. The study duration is three months which is analyzed for physical and chemical stability.

Figure 2.4 shows a regression model that is defined for assessing the effect of formulation and time on degradation growth at a storage condition of 40 °C/75%RH. A regression analysis is completed for data at 40 °C/75%RH to determine which excipient affects the growth of degradation products. From the analysis (Table 2.8), Time, Filler 1, Disintegrant, and Granulation have effect on degradation as well there are some interactions between Time and Filler 1, Time and Disintegrant, and Time and Granulation (borderline as $p$-value $≈ 0.05$).

The prediction profiler and the interaction profiles (Figure 2.5) provide information on the specific excipient within a significant class (from Table 2.7) and the sensitivity of each of the variables on the degradation growth. As seen from the prediction profiler, within Filler 1 mannitol causes more degradation as compared to MCC. Similarly, SSG is better than CCS among disintegrant and dry blend is better than wet granulation as the latter causes more degradation.

These results suggest that both mannitol and CCS could be detrimental for the stability of the API and are not being assessed for formulation development. In addition, wet granulation is to be avoided to increase the shelf life.

### 2.5 PROCESSING OF FORMULATIONS

The properties of a drug substance dictate the design of formulation composition and the choice of formulation-processing platform technology. The most commonly used

![Figure 2.4](image-url) Degradation actual versus predicted plot and degradation residuals versus degradation predicted plot. The residuals are evenly distributed indicating there is no bias in the model. The formulation number refers to those listed in Table 2.7.

<table>
<thead>
<tr>
<th>Term</th>
<th>Estimate</th>
<th>Std Error</th>
<th>$t$ Ratio</th>
<th>Prob &gt; $t$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>-0.029267</td>
<td>0.338094</td>
<td>-0.09</td>
<td>0.9313</td>
</tr>
<tr>
<td>Time (months)</td>
<td>2.4060773</td>
<td>0.179126</td>
<td>13.43</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Filler 1 [mannitol]</td>
<td>0.9593669</td>
<td>0.171987</td>
<td>5.58</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Disintegrant [CCS]</td>
<td>0.6043247</td>
<td>0.171987</td>
<td>3.51</td>
<td>0.0009*</td>
</tr>
<tr>
<td>Granulation [dry]</td>
<td>-0.717924</td>
<td>0.171987</td>
<td>-4.17</td>
<td>0.0001*</td>
</tr>
<tr>
<td>(Time (months) $- 1.625$) $\times$ Filler 1 [mannitol]</td>
<td>0.640884</td>
<td>0.179126</td>
<td>3.58</td>
<td>0.0007*</td>
</tr>
<tr>
<td>(Time (months) $- 1.625$) $\times$ disintegrant [CCS]</td>
<td>0.5068487</td>
<td>0.179126</td>
<td>2.83</td>
<td>0.0065*</td>
</tr>
<tr>
<td>(Time (months) $- 1.625$) $\times$ granulation [dry]</td>
<td>-0.358106</td>
<td>0.179126</td>
<td>-2.00</td>
<td>0.0505</td>
</tr>
</tbody>
</table>

**TABLE 2.8** Regression Results from the Excipient Compatibility Experiments

All parameters shown are significant. The parameters analyzed that did not show significance were Filler 2, Surfactant, Binder, and Lubricant and were subsequently removed from the model during stepwise regression.

*Means that the term is statistically significant to a $p < 0.05$ value.
processing platforms for solid oral dosage form include DC and granulation (wet and dry).

DC is the term used to define the process where powder blends of the drug substance and excipients are compressed on a tablet machine. There is no mechanical treatment of the powder apart from a mixing process.

Granulation is a generic term for particle enlargement, whereby powders are formed into permanent aggregates.
The purpose of granulating tablet formulations is to improve the flow and compaction properties prior to compression. A number of methods are used to achieve the agglomeration; these are normally classified as either wet granulation, where a liquid is used to aid the agglomeration process, or dry granulation, where no liquid is used.

### 2.5.1 Dry Granulation

In the dry methods of granulation the primary powder particles are aggregated under high pressure. There are two main processes. Either a large tablet (known as a “slug”) is produced in a heavy-duty tableting press (a process known as “slugging”) or the powder is squeezed between two rollers to produce a sheet of material (“roller compaction”). In both cases, these intermediate products are broken using a suitable milling technique to produce granular material, which is usually sieved to separate the desired size fraction. The unused fine material may be reworked to avoid waste. This dry method may be used for drugs that do not compress well after wet granulation, or those which are sensitive to moisture.

### 2.5.2 Wet Granulation

Wet granulation involves the massing of a mix of dry primary powder particles using a granulating fluid. The fluid contains a solvent which must be volatile so that it is removed by drying, and be nontoxic. Typical liquids include water, ethanol, and isopropanol, either alone or in combination. The granulation liquid may be used alone or, more usually, as a solvent containing a dissolved adhesive (also referred to as a binder or binding agent) which is used to ensure particle adhesion once the granule is dry.

The three main methods of producing pharmaceutical granulates are low-shear granulation, high-shear granulation, and fluid-bed granulation. Low-shear mixers encompass machines such as Z-blade mixers and planetary mixers which, as their name suggests, impart relatively low-shear stresses onto the granulate.

High-shear granulators are closed vessels that normally have two agitators; an impeller which normally covers the diameter of the mixing vessel and a small chopper positioned perpendicular to the impeller. The powders are dry-mixed using the impeller, and then the granulating fluid is added. Wet massing takes place using the impeller and the chopper, and granulation is usually completed in a number of minutes.

Fluid-bed granulation involves spraying the dry powder with a granulating fluid inside a fluid-bed drier. The powder is fluidized in heated air and then sprayed with the granulating fluid. When all the granulating liquid has been added, the fluidization of the powder continues until the granules are dry.

Seager et al. [26] produced a detailed analysis on the influence of the manufacturing method on the tableting performance of paracetamol granulated with hydrolyzed gelatin. The main difference in the granules produced by different methods is their final density, high-shear mixers producing denser granules than low-shear granulators, which in turn produced denser granules than fluid-bed granulations. Disintegration times were greater for tablets produced from the denser granulates. A detailed description of granulation process development and scale-up is found in the literature [27]. The advantages and disadvantages of each process are detailed in Table 2.9.

#### TABLE 2.9 Processing Platforms – Advantages and Disadvantages

<table>
<thead>
<tr>
<th>Processing Platform</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct compression</td>
<td>• Simple, cheap process</td>
<td>• Generally limited to low-dose compounds</td>
</tr>
<tr>
<td></td>
<td>• Suitable for heat and moisture-labile drugs</td>
<td>• Potential to segregation</td>
</tr>
<tr>
<td></td>
<td>• Prime particle dissolution</td>
<td>• Expensive excipients</td>
</tr>
<tr>
<td>Dry granulation (slugging)</td>
<td>Imparts flowability to formulation</td>
<td>Dusty process</td>
</tr>
<tr>
<td></td>
<td>Suitable for heat and moisture-labile drugs</td>
<td>Not suitable for all compounds</td>
</tr>
<tr>
<td>Dry granulation (roller compaction)</td>
<td>• Imparts flowability</td>
<td>Slow process</td>
</tr>
<tr>
<td></td>
<td>• Suitable for heat and moisture-labile drugs</td>
<td>Loss of compactibility for tableting</td>
</tr>
<tr>
<td></td>
<td>• Limits segregation tendency</td>
<td>No hydrophilization of surfaces</td>
</tr>
<tr>
<td></td>
<td>Robust process</td>
<td>Expensive</td>
</tr>
<tr>
<td>Wet granulation (aqueous)</td>
<td>Improves flowability</td>
<td>Specialized equipment</td>
</tr>
<tr>
<td></td>
<td>Can reduce elasticity problems</td>
<td>Stability concerns for moisture sensitive,</td>
</tr>
<tr>
<td></td>
<td>Can improve wettability</td>
<td>thermolabile, and metastable drugs with aqueous granulation</td>
</tr>
<tr>
<td></td>
<td>Reduces segregation potential</td>
<td></td>
</tr>
<tr>
<td>Wet granulation (nonaqueous)</td>
<td>Suitable for moisture-sensitive drugs</td>
<td>Expensive equipment</td>
</tr>
<tr>
<td></td>
<td>Vacuum drying techniques can reduce/remove need for heat</td>
<td>Explosion proof</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Solvent recovery</td>
</tr>
</tbody>
</table>
Each processing platform has unique characteristics and complexity in terms of unit operations. Table 2.10 lists the unit operations required for manufacturing immediate release tablet using the processing platform discussed earlier.

Since more than one platform technology may be used to manufacture a drug product, selection of the most appropriate processing platform is affected by many factors as shown in Figure 2.6.

### 2.6 TABLET FORMULATION DESIGN

Having decided on a formulation design strategy, the process of preparing and screening initial formulation possibilities begins. It is important to appreciate that the goal is to develop a “robust” formulation and this objective facilitates identification of the factors that influence the selection of a design process as depicted in Figure 2.6. The first major design criterion is the nature of the API and in particular the possible dosage level (described in Preformulation report and TPP). The knowledge of biopharmaceutical class to which the API belongs helps in deciding the formulation rationale. In particular, the implications of low permeability and low solubility must be carefully considered prior to the selection of the processing platform. For example, a poorly soluble drug often tends to be poorly wettable, too. If the objective is to obtain a fast-dissolving and dispersing dosage form, inclusion of a wetting agent such as sodium lauryl sulfate or polysorbate 80 may be appropriate or even necessary.

Processing methods may also significantly impact dosage-form performance. For example, it may not be appropriate to wet-granulate amorphous drug because water may lower the glass-transition temperature and facilitate recrystallization during or after processing. In other situations, wet granulation can be used to avoid potential segregation and CU problems where there is a significant difference in particle size or bulk density between the drug and excipients.

Another major consideration must be the anticipated dosage level. It is worth emphasizing that in the case of a high dose active, a major proportion of the processing difficulties are traced to the physicochemical and mechanical properties of the API. Unfortunately, the key properties of the API may change during scale-up of the synthetic API process, or from lot to lot when outsourced. It follows that continuous monitoring of critical quality attributes (CQAs) of API that affect the process is an essential policy. Figure 2.7 depicts a decision-guiding flowchart for selection of the processing platform.

### 2.7 TABLET CHARACTERISTICS

There are two important classes of tablet characteristics. The first set examines the tablet immediately after manufacturing:

---

**TABLE 2.10** Unit Operations Required for Various Processing Platforms

<table>
<thead>
<tr>
<th>Unit Operation</th>
<th>Direct Compression</th>
<th>Dry Granulation</th>
<th>Wet Granulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raw materials</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>(weighing and sieving)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blending</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Compaction</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Wet granulation</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Wet screening</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drying</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Milling</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Tablet compression</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

---

**FIGURE 2.6** Factors affecting selection of processing platform.
the second class examines what happens to the tablet over time.

Immediately after manufacturing and during the formulation process of a tablet, the release of the tablet is of utmost importance. If the tablet does not disintegrate or dissolve in the body, then the efficacious effect desired is likely not going to happen. There are many factors that can affect this from excipient choice to manufacturing.

After manufacturing, a tablet must maintain consistency over time. Similarly to drug release, excipients and processing can affect the shelf life of a tablet.

2.7.1 Release Profile: The Factors that Affect In-Vivo Performance

Release Profile of a tablet can affect in-vivo drug performance, as this is the case it is important to measure this characteristic during development. The FDA guidance, Dissolution of Immediate Release Solid Oral Dosage Forms, states the dissolution requirements for an immediate-release drug. Dissolution testing is useful in development to determine how processing and formulations can potentially affect in-vivo performance. What is a dissolution test?

Dissolution is a test that provides some assurance of tablet performance by an indication of the mass transfer the drug into solution.

There are many stages in the development of a dissolution method. The final Quality Control (QC) form of the method is used in day-to-day production to ensure consistency of the tablets produced. In early development, dissolution testing is useful in screening formulations but this dissolution test may not be or even resemble the final QC test used when the drug has been approved. The development of a dissolution method

---

**FIGURE 2.7** Flowchart for selection of adequate processing platform.
at each stage of development is the responsibility the analytical development (AD) group in a company. Figure 2.8 shows a “typical” immediate-release dissolution profile.

Even though it is generally the responsibility of the AD group to develop the dissolution method, it is critical for the drug developer to understand the final QC requirements from a regulation perspective as to aide in developing a final drug product. A final QC dissolution method is carried out according to the guidance is defined as:

Dissolution testing should be carried out under mild test conditions, basket method at 50/100 rpm or paddle method at 50/75 rpm, at 15-minute intervals, to generate a dissolution profile. For rapidly dissolving products, generation of an adequate profile sampling at 5- or 10-minute intervals may be necessary. For highly soluble and rapidly dissolving drug products (BCS classes 1 and 3), a single-point dissolution test specification of NLT 85% (Q = 80%) in 60 minutes or less is sufficient as a routine quality control test for batch-to-batch uniformity. For slowly dissolving or poorly water-soluble drugs (BCS class 2), a two-point dissolution specification, one at 15 minutes to include a dissolution range (a dissolution window) and the other at a later point (30, 45, or 60 minutes) to ensure 85% dissolution, is recommended to characterize the quality of the product. The product is expected to comply with dissolution specifications throughout its shelf life. If the dissolution characteristics of the drug product change with time, whether or not the specifications should be altered will depend on demonstrating bioequivalence of the changed product to the original biobatch or pivotal batch. To ensure continuous batch-to-batch equivalence of the product after scale-up and post-approval changes in the marketplace, dissolution profiles should remain comparable to those of the approved biobatch or pivotal clinical trial batch(es) [28].

This is important knowledge to ensure compliance when developing and changing formulations. The QC method described above is not always the best method to use during development to assess potential impact on bioavailability; alternate media or methods may provide additional insight.

### 2.7.2 What Affects Dissolution: Problems and Trouble Shooting with Dissolution Testing

Beyond compliance dissolution is used to determine the performance of the tablet. Assuming a well-developed dissolution method, there are many things that can affect the dissolution of the tablet:

- Processing conditions: compressing the tablet too hard, overblending the lubricant
- Excipients: amount and choice
- API physical properties
- Storage: over time the tablet dissolution may slow down due to excipient interactions with the drug and excipient reaction with each other

A discriminating dissolution method is useful in developing a tablet formula and manufacturing process; however, a proper method may take time for the AD group to develop, just as it takes a while to develop a reliable process.

#### 2.7.2.1 Problems with Dissolution: Non-Engineered Mixing Vessels and Trouble Shooting

Assuming a good dissolution method may not be the best assumption. Dissolution is a QC test required for regulatory compliance; however, there are many problems with the dissolution test.

Dissolution Apparatus 1 is a paddle mixer in a cylindrical vessel; from an engineering standpoint this does not provide good mixing. If an engineer is designing this, he/she would have put a baffle or two in there to promote top to bottom mixing. As is imagined, there may be problems with bottom settling and coning with tablets that disintegrate into large particles, which have a high density. In this case the dissolution results have significant variation as how the drug settles and the percentage of the drug settling has an effect on the results.

Apparatus 2 is a basket mixer in a cylindrical vessel; again from an engineering standpoint, this does not provide good mixing. There is little mixing power associated with the method, if the powder flows out of the basket the powder either settles, floats, or suspends depending on the powder’s buoyancy. If the powder stays in the basket, the method has a high probability to be reliable (Figure 2.9).

When examining dissolution-results method there are five considerations to determine if results are method-biased.

1. What is the media used in the dissolution bath? What is the solubility of the drug in the media? This determines the mass transfer-driving force for the drug to go into solution.
2. Does my drug change forms in the dissolution media? If it does the form it changes into may not have the...
same solubility. Form conversion is a stochastic event and affects the consistency of the results.

3. Are the particles suspended and flowing? This also affects the mass transfer of the drug into the media.

4. Is the tablet submerged in the media? Often a floating tablet provides many problems and inconsistent results.

5. What is the dissolution median comprised of? The media may react with the API or excipients used in the tablet.

When analyzing a change in dissolution profiles ensures that the changes are due to changes made to the process and formula versus problems with the method. It is always a good idea to observe the dissolution testing so to see what is actually occurring.

### 2.8 USING DISSOLUTION TO DETERMINE CQAS

Assuming an acceptable dissolution method has been developed, dissolution is a useful tool to determine CQAs for the tablet. Dissolution can help determine the maximum tablet hardness, the optimal drug substance particle size and/or density, and the proper ratio or the amount of excipients.

#### 2.8.1 Using Dissolution to Determine the Ratio of Excipients

A tablet formulation can affect the dissolution profile. A tablet often contains a mixture of water-soluble and insoluble fillers/binders, and disintegrants that all have the potential to affect the dissolution profile. Determining the optimal loading of excipients is a difficult task even after the compatible excipients have been chosen.

Examining excipient optimization of a BCS class II tablet based on dissolution performance. For example, compressing a tablet consisting of 20% API with a particle size of 29 μm at a hardness of approximately 10 kP with remaining 80% of the tablet has different ratios of filler, binder, and disintegrant. Two commonly used fillers are Micro Crystalline Cellulose (MCC) and Calcium Di-Basic Phosphate (A-Tab), and a commonly used disintegrant Sodium Starch Glycolate (SSG), which are used based upon excipient-compatibility example. These are compressed into five different ratios; dissolution results are shown in Figure 2.10.

As is seen in Figure 2.10, different excipient ratios can affect tablet performance. For this example it looks like 71/25/4 MCC/A-Tab/SSG has the most optimal performance without putting an excess amount of disintegrant in the tablet (Table 2.11).

#### 2.8.2 Using Dissolution to Determine the Optimal API Particle Size and Tablet Hardness

The next properties that can affect dissolution are API particle size and tablet hardness. API particle size has the potential to affect dissolution based on different surface area or particle morphology and the tablet hardness can affect how fast the tablet disintegrates into primary particles enabling the API to dissolve. As a rule of thumb about particle size:

There is never an instance where bigger particles will improve the immediate release performance but there are many instances where it will not change the performance.

![Dissolution Comparison](http://www.dissoaccess.htm)
In optimizing the release of the drug, first a target CQA must be defined which is determined from IVIVC or good scientific reasoning. A hypothetical CQA could be NLT (not less than) 70% release at 30 minutes, to ensure proper absorbance in the body; 30 minutes is chosen as it is the approximate gastric emptying time of an empty stomach [29].

Continuing with the example, determining the optimal hardness and API particle size-range dissolution is chosen at the CQA at $t = 30$ minutes. Starting with the “optimal” formulation from the example (71/25/4 MCC/A-Tab/SSG), the material is compressed at five hardness, ranging from approximately 10 to 30 kP, and four different API average particles sizes ($d_{50}$s), ranging from 29 to 73 μm. Table 2.12 indicates the results attained and from observation there is an effect of both hardness and API particle size.

In examining Figure 2.11, the data have a linear relationship between % release and hardness; as well, there is a relationship between release and particle sizes. It is noted that 8 of 20 experiments met the CQA requirement of NLT 70% release at 30 minutes. From this point a design equation is developed to mathematically describe the DS.

Regression is completed providing an expression for the relationship of acceptable hardness and API particle-size combinations. The expression is used to describe the DS (Tables 2.13 and 2.14).

Based on this information the relationship between hardness, particle size, and % Release at 30 is:

$$R_{30\text{min}} = 139.2 - 0.592 d_{50} - 2.25 \text{ hardness} \quad (2.10)$$

This is not an ideal form of the equation as greater than 100% is predicted; however, it is used to determine the maximum range of hardness and particle size to attain release greater than 80%. The model is further developed to attain the curvature but more data above 30 kP and smaller particle sizes are required. For determining tablet and API properties, there is sufficient information for control.

To determine the acceptable combinations of hardness and particle size to maintain the CQA of NLT 70% Release at 30 minutes, Eq. (2.10) is rearranged.

### TABLE 2.12 Effect of API Particle Size and Tablet Hardness on the 30 Minute-Dissolution Time Point

<table>
<thead>
<tr>
<th>T30 min</th>
<th>$d_{50}$</th>
<th>Hardness</th>
<th>T30 min</th>
<th>$d_{50}$</th>
<th>Hardness (kP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>99.1</td>
<td>29</td>
<td>9.7</td>
<td>87.18</td>
<td>50</td>
<td>10.3</td>
</tr>
<tr>
<td>85.17</td>
<td>29</td>
<td>15.6</td>
<td>75.91</td>
<td>50</td>
<td>14.4</td>
</tr>
<tr>
<td>77.45</td>
<td>29</td>
<td>20.8</td>
<td>65.03</td>
<td>50</td>
<td>20.4</td>
</tr>
<tr>
<td>64.3</td>
<td>29</td>
<td>25.6</td>
<td>52.42</td>
<td>50</td>
<td>24.7</td>
</tr>
<tr>
<td>54.15</td>
<td>29</td>
<td>30.2</td>
<td>40</td>
<td>50</td>
<td>30.2</td>
</tr>
<tr>
<td>89.04</td>
<td>42</td>
<td>10.7</td>
<td>72.65</td>
<td>73</td>
<td>9.6</td>
</tr>
<tr>
<td>84.35</td>
<td>42</td>
<td>14.7</td>
<td>60.13</td>
<td>73</td>
<td>15.3</td>
</tr>
<tr>
<td>69.17</td>
<td>42</td>
<td>20.9</td>
<td>50.84</td>
<td>73</td>
<td>20.9</td>
</tr>
<tr>
<td>61.31</td>
<td>42</td>
<td>24.1</td>
<td>43.62</td>
<td>73</td>
<td>25.4</td>
</tr>
<tr>
<td>46.61</td>
<td>42</td>
<td>29.4</td>
<td>26.97</td>
<td>73</td>
<td>29.6</td>
</tr>
</tbody>
</table>

### TABLE 2.13 Results from the Linear Regression (Completed Using JMP8.0)

| Term                 | Estimate | Std Error | t Ratio | Prob > |t| |
|----------------------|----------|-----------|---------|---------|---|
| Intercept            | 139.2    | 1.99      | 69.9    | <0.0001<sup>a</sup>|
| $d_{50}$             | -0.592   | 0.0289    | -20.5   | <0.0001<sup>a</sup>|
| Hardness             | -2.247   | 0.0659    | -34.0   | <0.0001<sup>a</sup>|

<sup>a</sup>Indicates the variable is significant.

### TABLE 2.14 Summary of Fit of the Regression

<table>
<thead>
<tr>
<th>Term</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R^2$</td>
<td>0.989</td>
</tr>
<tr>
<td>$R^2$ Adj</td>
<td>0.988</td>
</tr>
<tr>
<td>Root mean square error</td>
<td>2.070</td>
</tr>
<tr>
<td>Mean of response</td>
<td>65.31</td>
</tr>
<tr>
<td>Observations</td>
<td>20</td>
</tr>
</tbody>
</table>

<sup>7</sup>IVIVC: In-Vitro In-Vivo Correlation, but which benchtop data accurately correlates with human bioavailability.