Chemical Engineering in the Pharmaceutical Industry

Topic 1 - Introduction

Reference: Chemical Engineering in the Pharmaceutical Industry: R&D to Manufacturing; Edited by D. J. am Ende, Chapter 1 & 2, Wiley, 2011.

What are Pharmaceuticals?

Pharmaceuticals in general are

drug delivery systems in which

drug-containing products are

designed and manufactured

to *deliver precise therapeutic response*.

API and Drug Product

- The Drug

  == Active Pharmaceutical Ingredient

  == API

- The *formulated final product*

  == Drug Product

Food and Drug Administration

- Food and Drug Administration == FDA
  - Responsible for protecting the public health by assuring the
    safety
    efficacy
    security
    of human and veterinary drugs, biological products, medical devices, and cosmetics.

- ***What are the roles and responsibilities of Jordan FDA?***

Drug Research & Development

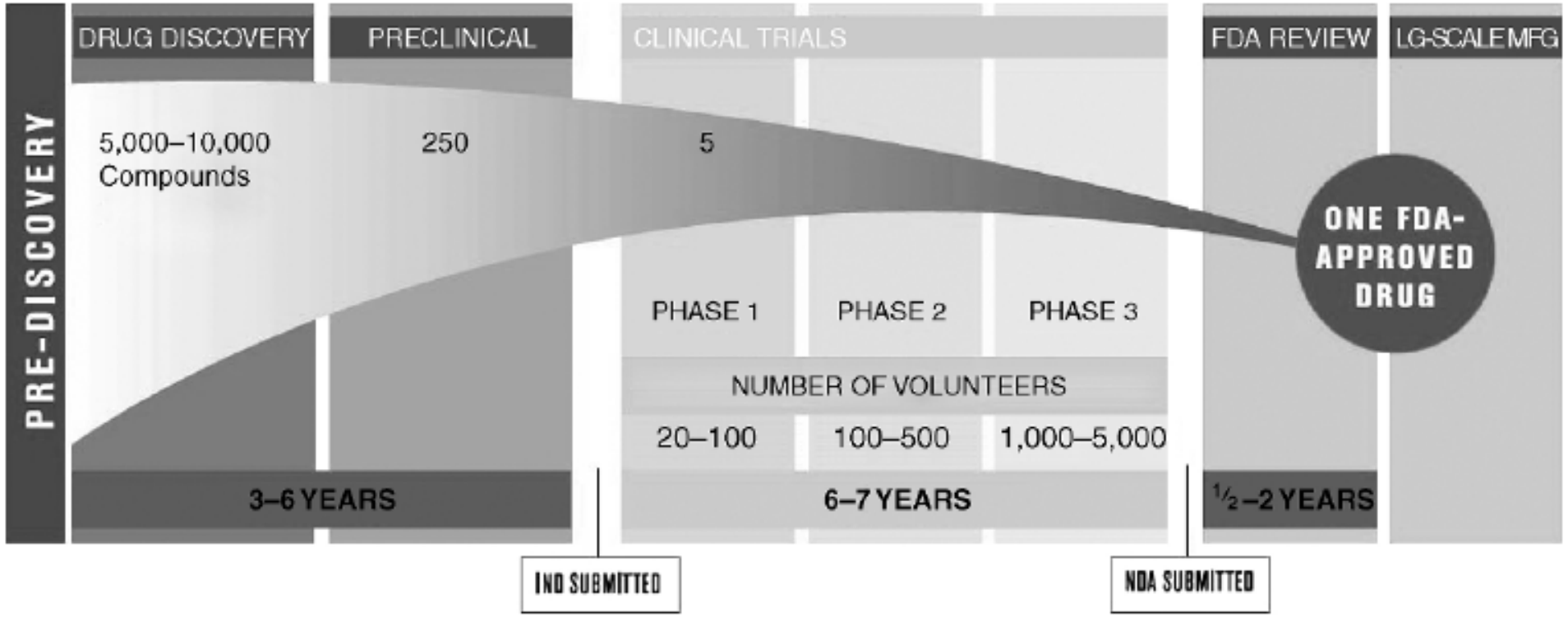


FIGURE 1.3 Drug research and development can take 10–15 years with one approval from 5 to 10,000 compounds in discovery. IND: investigational new drug; NDA: new drug application. *Source*: *Pharmaceutical Industry Profile 2009*, Pharmaceutical Research and Manufacturers of America (PhRMA) (www.phrma.org).

Drug Research & Development

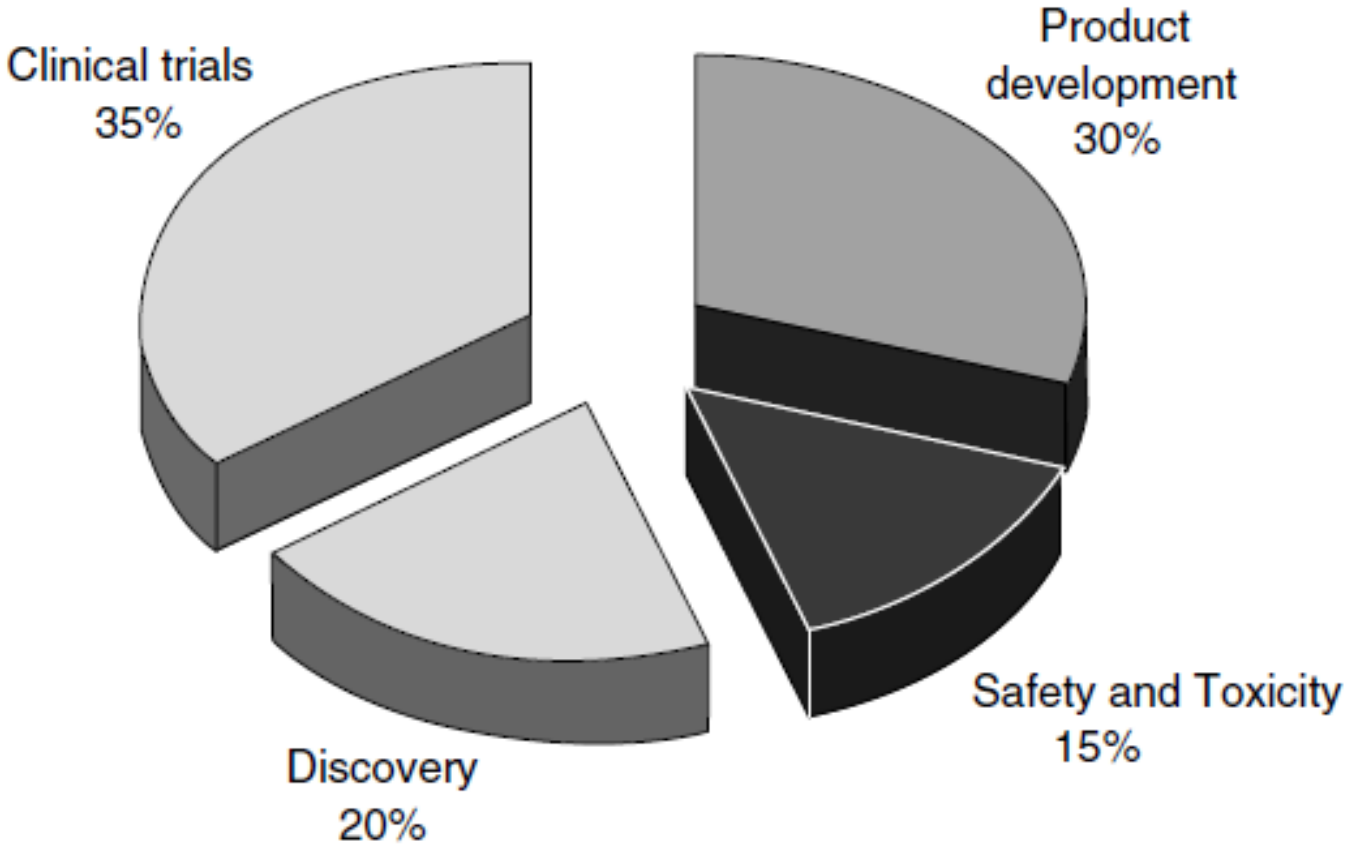


FIGURE 1.4 Estimated distribution of product development costs within R&D with the total cost to bring a new chemical entity to market in the range of $1–3.5 billion. *Source*: Ref. 16.

Drug Research & Development

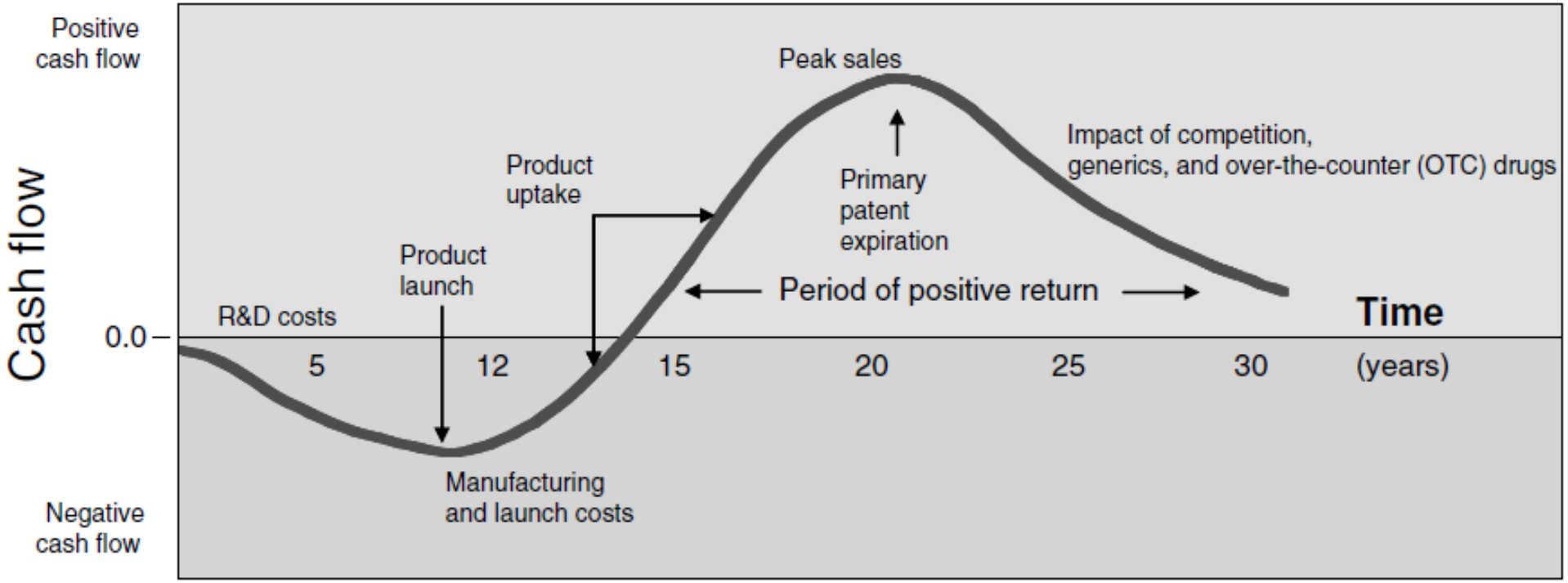


FIGURE 1.2 A hypothetical cash flow curve for a pharmaceutical product includes 10–15 years of negative cash flows of typically $1–3 billion. Reasonably high margins are needed, once the drug is on the market, if it is to recoup and provide a positive return on investment (ROI) over its life cycle.

Chemical Engineering in the Pharmaceutical Industry

Opportunities for Chemical Engineers

- Challenges faced by the pharmaceutical industry create several opportunities for its members, including chemical engineers.
  1. Pressures to reduce costs →economies of scale and application of efficient technology.
  2. Technological innovation and engineering analysis enhance products to create meaningful differentiation for patients, which provide values in the face of revenue constraints.
  3. Strategic management of technology used to meet industry challenges by chemical engineers is an additional opportunity.

Reducing Costs with Engineering Principles

Reducing Costs with Engineering Principles

- Across many industries, chemical engineers are employed to use process modeling and physical/chemical properties estimation to:
  - maximize yield and
  - minimize energy consumption and waste production

  associated with desired products.
- In the pharmaceutical industry, engineers
  - use computational tools to optimize distillation and solvent recovery,
  - apply thermodynamic solubility modeling to optimize crystallization, etc.

Reducing Costs with Engineering Principles

- The use of sound fundamental chemical engineering science can:
  - eliminate bottlenecks,
  - improve production,
  - unlock the full potential of biological, chemical, and formulation processes used to make medicine.
- Chemical engineers can also help reduce costs.

Reducing Costs with Engineering Principles

- In the R&D area, the use of high-throughput screening tools and multi-reactor laboratory systems efficiently promotes the generation of data at faster rates.
- When modeling and estimation technology cannot provide complete picture, engineers can get the data they need quickly with high-efficiency technology.

Reducing Costs with Engineering Principles

- Not all of the advanced laboratory technology works universally well in all situations:
  - A reactor system suitable for homogeneous reactions may have insufficient mixing for heterogeneous.
- Selection of the appropriate laboratory technology and proper interpretation of results produced by these laboratory tools benefit from the perspective of chemical engineering principles (mass transfer, heat transfer, reaction kinetics, fluid mechanics, etc.)

Reducing Costs with Engineering Principles

- With appropriate equipment in hand, engineers can utilize a statistically driven design of experiments to maximize the value of data generated via the experimental methodology.
- Process understanding that comes from combining models and experimental data is a key opportunity for chemical engineers.
  - Quality by Design (QbD)

Improving Product Value

Improving Product Value

- Chemical engineers have opportunity to meet market demands for pharmaceutical products that deliver greater value to patient, payer, and physician.
- They don't care about manufacturing process, but they do care about product convenience, safety, and compliance.
- Two examples of engineers contribution to product value: drug delivery, and diagnostics.

Improving Product Value

Drug Delivery

- **Inhalers:**
  - The application of particles engineering and convection modeling to inhalers can improve the consistency with which a dose is administered via the respiratory system independent of the strength of the patient's breathe.
  - Greater consistency of delivery increases the associated compliance.

Improving Product Value

Drug Delivery

- **Orally administered capsules and tablets:**
  - Engineers can manipulate polymer properties and transport driving forces to afford a consistent extended release of an API.
  - A steady slow release of medicine from a single delivery vehicle can reduce the frequency with which the medicine need to be taken and potential side effects, which in turn improve conveniences for the patient, and compliance with the dosing regimen.
  - Controlled release requires consistent API particle size distribution ➔ engineering effort applied to maintain control of crystal sizes during crystallization, filtration, and drying unit operations for drug substance.

Improving Product Value

Diagnostics

- Engineering principles can be used to improve diagnostic tools used to treat diseases.
- A diagnostic tool that enables physicians to initially assign the best treatment without trial and error approach reduces the cost charged to the payers through the preemptive elimination of ineffective options.
- Chemical engineering skills contribute to improvements in making diagnostic technology.
  - Advances in polymer technology and manufacturing processes can lead to devices that are lighter, smaller, and more resilient to being dropped.

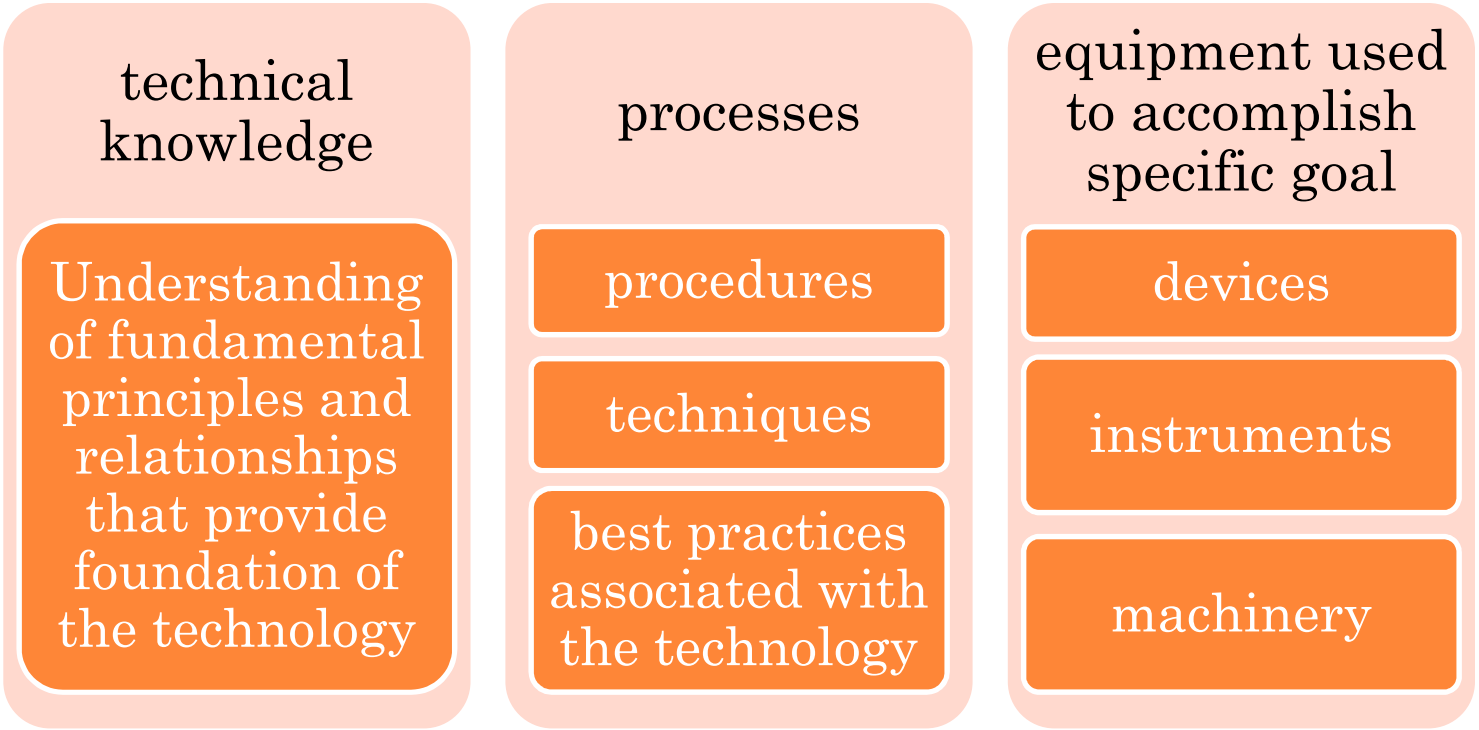
Strategic Technology Management

Strategic Technology Management

- Engineers have the opportunity to help direct strategic investments in technology.
- The availability of global development and supply options creates relatively new decisions for the pharmaceutical industry.
- Technology investment must be managed through a careful balance of internal capabilities, strategic partnerships, and reliance on eternal vendors.

Strategic Technology Management

- In the context of strategic management, technology can be defined as a system comprising

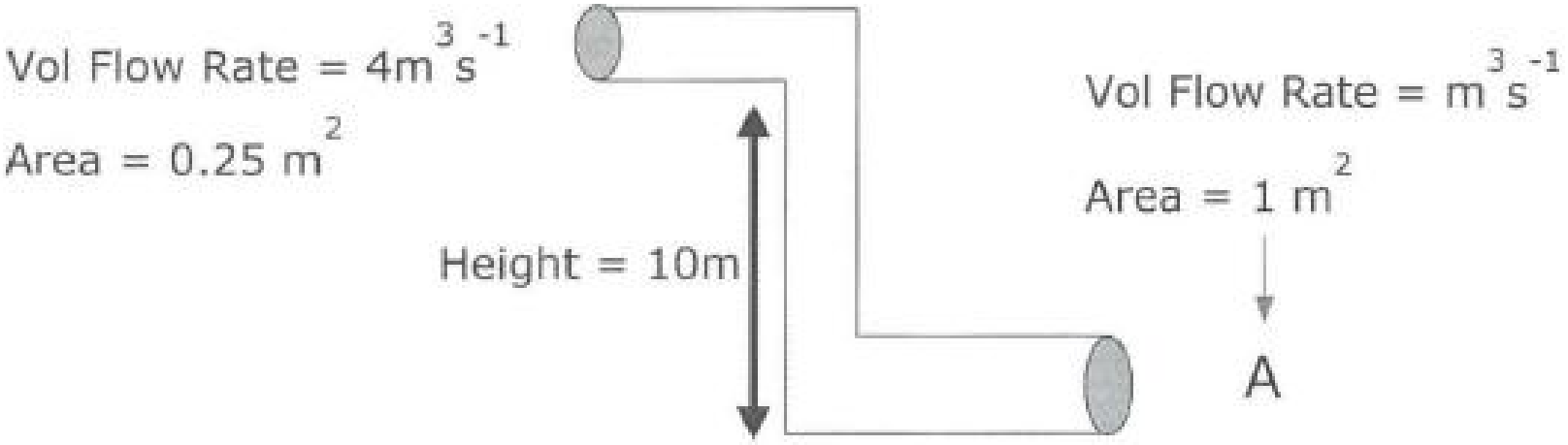


Strategic Technology Management

- Strategic technology management goal:
  - To make value–driven decisions around investments in the advancement, capacity, and capability with each of the technology components.
- Engineers can contribute to investment choices among various emerging technology with technical assessments of probability of success and potential applicability across a company's portfolio of products.

What is the energy loss due to pressure? Use Bernoulli's equation

$$\frac{u_A^2}{2g} + \frac{P_A}{\rho g} + z_A = \frac{u_B^2}{2g} + \frac{P_B}{\rho g} + z_B + \frac{E}{g}$$



Topic 2 - Design of Solid Dosage Formulations

Reference: Chemical Engineering in the Pharmaceutical Industry; Edited by M. T. am Ende & D. J. am Ende, 2nd edition, Chapter 2, Wiley, 2019.

Dosage Forms

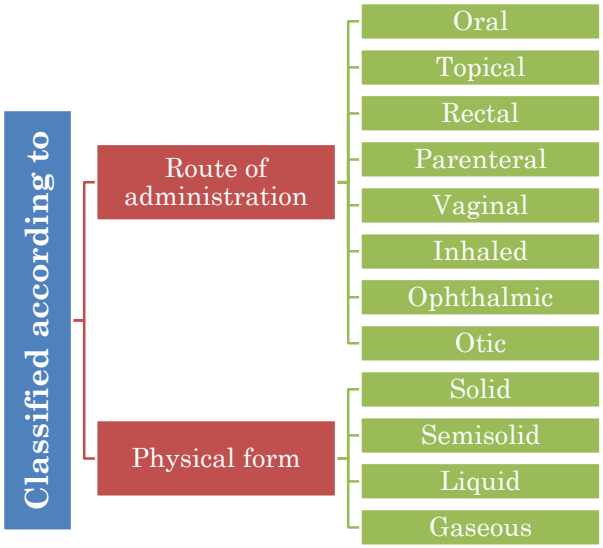
- **Definition**

  Dosage forms are the means (or the form) by which drug molecules are delivered to sites of action within the body.

- **The need for dosage forms:**

1. Accurate dose.
2. Protection e.g. coated tablets, sealed ampules.
3. Protection from gastric juice.
4. Masking taste and odour.
5. Placement of drugs within body tissues.
6. Optimal drug action.
7. Sustained release medication.
8. Controlled release medication.
9. Insertion of drugs into body cavities (rectal, vaginal)
10. Use of desired vehicle for insoluble drugs.

Types Of Dosage Forms



Oral Route

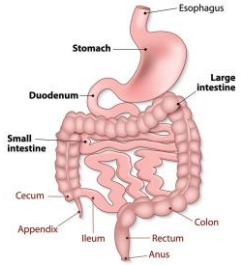
- The oral route is the most common way of administering drugs.
  - Convenient (self-administered)
  - Safe way of drug administration
  - More profitable to manufacture than the parenteral dosage forms that must be administered, in most cases, by trained personnel.
- This is reflected by the fact that well over 80% of the drugs that are formulated to produce systematic effects are marketed as oral dosage forms.
- Among the oral dosage forms, tablets of various different types are the most common because of their
  - low cost of manufacture (including packaging and shipping)
  - increased stability
  - virtual temper resistance

Types of Solid Oral Dosage Forms

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

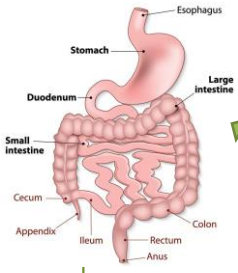
Steps of Drug Delivery to the Systemic Circulation

1. Oral administration of tablets
2. Initial transport of the drug through the gastrointestinal (GI) membrane

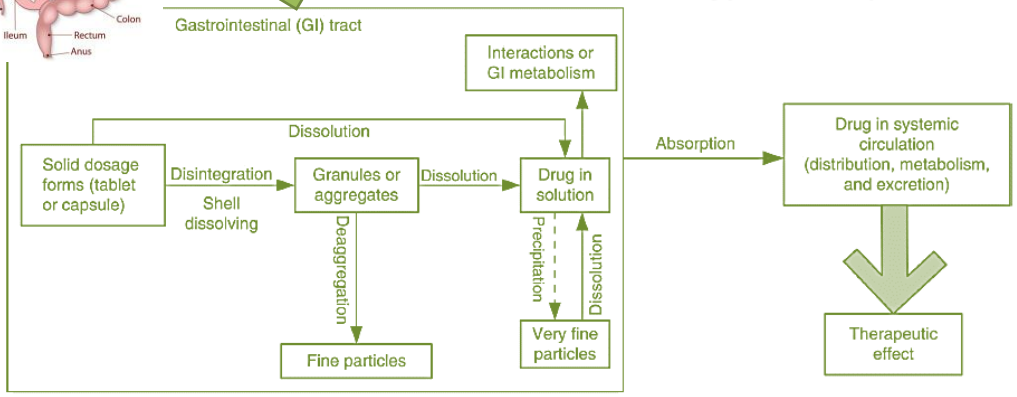


3. Drug is brought into solution in the GI fluids
   - the drug should be capable of crossing the intestinal membrane into the systemic circulation
4. Drug absorption from the GI tract
   - the rate of dissolution of the drug in the GI lumen (التجويف المعوي) can be a rate-limiting step in the absorption of drugs given orally.

Fate of Solid Dosage Form Following Oral Administration



The slowest of these events (dissolution and/or absorption) determines the rate of availability of the drug from tablet formulation.



Drug Bioavailability

- Bioavailability refers to the extent and rate at which the active moiety (drug or metabolite) enters systemic circulation, thereby accessing the site of action.
- Factors affecting the bioavailability of the drug:
  - Physical properties
  - Chemical properties
  - Biopharmaceutical properties
  - Design and production of the tablet

Complexity of tablet formulation transferred ***tablet formulation design*** *from an art to a* ***well-defined science****.*

Good Formulation and TPP

- A good formulation must be
  - bioavailable
  - manufacturable
  - chemically and physically **stable** from manufacturing through the end of shelf life
  - meeting many quality standards and special requirements to ensure the **efficacy** and **safety** of the product.
- 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***.

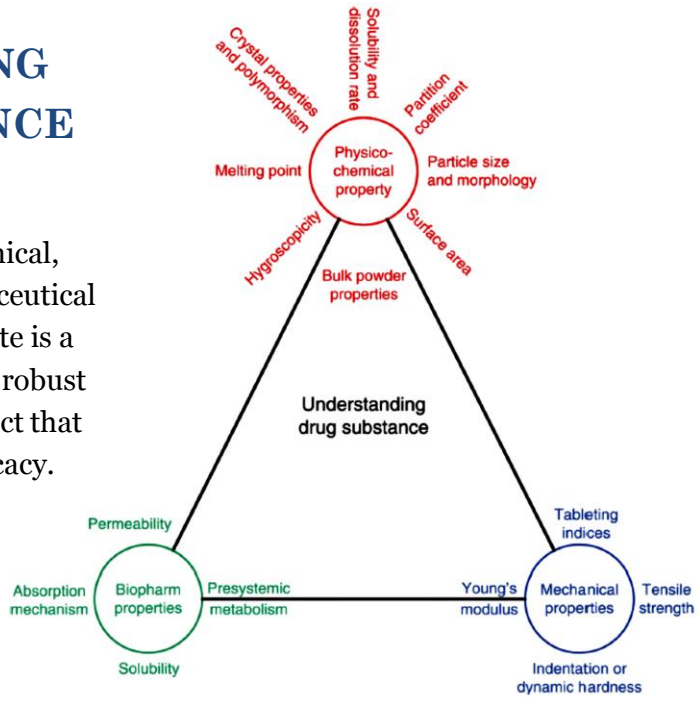
Typical Target Product Profile (TPP) for an Immediate Release (IR) Tablet

TPP	How Used by a Formulator	Typical for IR Tablet
Indications and usage	Examine other products in the same class: examine improvements	Once a day (QD) Twice a day (BID) Three times a day (TID)
Dosage and administration	Good to know what is expected before one starts formulating	Oral tablet
Dosage forms and strengths	Multiple strengths may be needed depending on the population being targeted (adults vs. children)	Dependent on drug Typically 10–500 mg
Overdosage	Useful if designing an extended release dosage, in which overdose (dose dumping) is a possibility	Dependent on drug
Description	This is up to the formulator and marketing: shape, size, and color of the tablet	A tablet with markings and color
Clinical pharmacology	Helps determine where the drug is absorbed and how fast the drug must get into solution	Dependent on drug
How supplied/ stored/handled	Important as most people do not like refrigerated dosage forms	Two-year room temperature shelf life

Other potential inputs a formulator may or may not need: *Warnings and Precautions, Adverse Reactions, Drug Interactions, Use in Specific Populations, Drug Abuse and Dependence, Clinical Studies, and Patient Counseling Information.*

Understanding Drug Substance Properties

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.



Physicochemical Properties

- Solubility and Drug Dissolution
- Partition Coefficient
- Crystal Properties and Polymorphism
- Particle Size, Particle Morphology, and Surface Area
- Bulk Powder Properties
- Melting Point and Hygroscopicity

Physicochemical Properties

Solubility and Drug Dissolution

- Aqueous solubility dictates the amount of compound that dissolves ➡ 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:*** the dynamic process by which a material is dissolved in a solvent
  - Characterized by a rate (amount dissolved per time unit)
- *Solubility:* the amount of material dissolved per unit volume of a certain solvent
  - Characterized as a concentration.
  - Solubility is often used as a short form for "**saturation solubility**"

Physicochemical Properties

Solubility and Drug Dissolution

- **Saturation solubility:** the maximum amount of drug dissolved at equilibrium conditions.
- ***Intrinsic solubility:*** 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 <u>immediate release dosage form</u> of poorly soluble drug, to increase the drug-dissolution rate *by increasing the surface area of a drug through particle size reduction.*

Physicochemical Properties

Solubility and Drug Dissolution

- The dissolution rate of a solute from a solution is described by the Noyes–Whitney equation:

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

  - ***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
  - C_t is the drug concentration in the bulk solution at a given time

Physicochemical Properties

Solubility and Drug Dissolution

- 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)
  - evaluations of 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**, or as a dispersed powder in a **beaker with agitation** (as detailed in pharmacopeias such as United States Pharmacopeia, etc.).

Physicochemical Properties

Partition Coefficient

- Partition coefficient is the relationship between chemical structure, lipophilicity, and its disposition *in vivo*.
- The lipophilicity of an organic compound is described in terms of a partition coefficient, log *P*
- The partition coefficient is defined as the ratio of the concentration of the unionized compound, at equilibrium, between organic and aqueous phases:

$$\log P = \frac{[A]_{organic}}{[A]_{aqueous}}$$

Physicochemical Properties

Partition Coefficient

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

$$\text{Acids}: \log D = \log P - \log\left[1 + 10^{(pH - pKa)}\right]$$

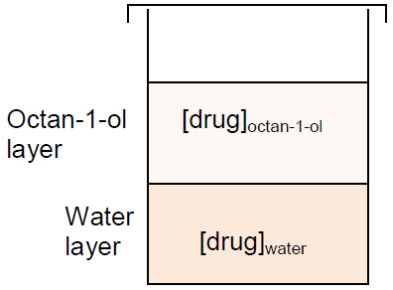
$$\text{Bases}: \log D = \log P - \log\left[1 + 10^{(pKa - pH)}\right]$$

  - **pKa** is the dissociation constant.
- The most widely used model of the lipid phase in pharmaceutical studies is the octanol/water system.

Physicochemical Properties

Partition Coefficient

- Compounds with log *P* values between 3 and 6 show good passive absorption
- Compounds with log *P* values of less than 3 or greater than 6 often have poor passive transport characteristics



log p values for selection of drug substance

Compound	Log P
Oxytetracycline	-1.12
Sulfadiazine	0.12
Aspirin	1.19
Benzylpenicillin	1.83
Temazepam	2.19
Lidocaine	2.26
Atrazine	2.75
Oxadizon	4.09
Permethrin	6.50

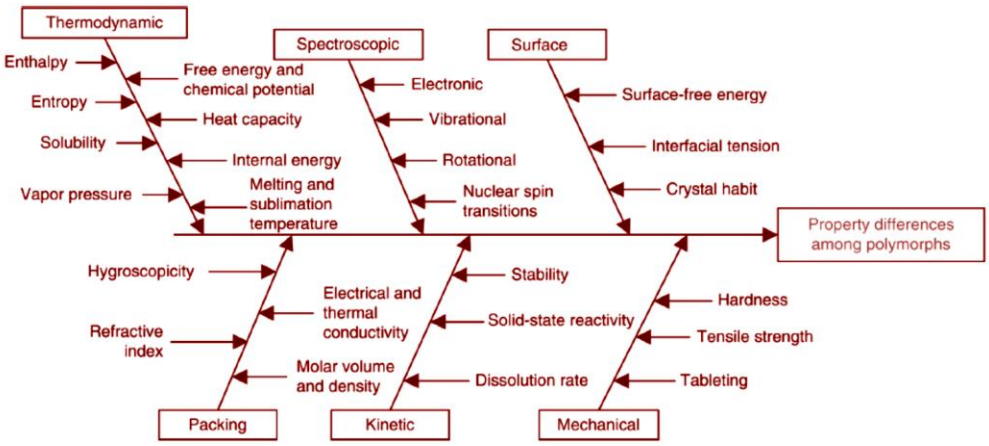
Physicochemical Properties

Crystal Properties & Polymorphism

- Most drug substances appear in more than one polymorphic form.
- **Polymorphs** differ in molecular packing (*crystal structure*), but share the same *chemical composition*.
- Polymorphs may exhibit significantly different solubility, dissolution rate, compactibility, hygroscopicity, physical stability, and chemical stability
  - ➡ Polymorphism has a profound implication on formulation development and biopharmaceutical properties.

Physicochemical Properties

Crystal Properties & Polymorphism



Fishbone Schematic of Physical Property Differences among Polymorphs

Physicochemical Properties

Crystal Properties & Polymorphism

- Higher solubility and faster dissolution rates of the metastable polymorph (i.e. a higher energy form) may lead to significantly better oral bioavailability.
  - Metastable polymorph 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 ➡ 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.**

Physicochemical Properties

Crystal Properties & Polymorphism

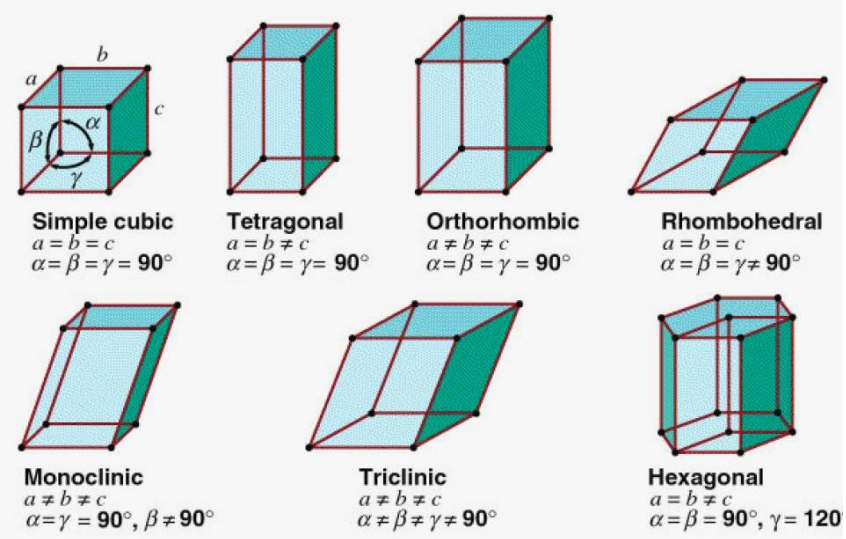
- Polymorphic form conversion from the most stable form may still occur, **even when a stable crystal form is chosen for development**.
- Polymorphic transformations can take place during pharmaceutical processing, such as *particle size reduction*, *wet granulation*, *drying*, and even during the *compaction process* and *compression process* as each of these processes may add the energy required to move the drug to the unstable form.

Physicochemical Properties

Crystal Properties & Polymorphism

- Seven specific categories of crystal system:
  1. Cubic
  2. Monoclinic
  3. Triclinic
  4. Hexagonal
  5. Trigonal (or Rhombohedral)
  6. Orthorhombic
  7. Tetragonal

The Seven Crystal Systems



Physicochemical Properties

Particle Size, Particle Morphology, and Surface Area

- Drug/API size
- Drug/API shape
- Drug/API surface morphology

Affected by

Dissolution and Chemical Reactivity

control

- Bulk flow
- Compactability
- Formulation homogeneity
- Surface-area

Physicochemical Properties

Particle Size, Particle Morphology, and Surface Area

- ***Spherical*** particles have the least contact surface area and exhibit **good flow**
- ***Acicular*** particles tend to have **poor flow**
- Milling of long acicular (or needle) crystals can enhance flow properties
  - Excessively small particles tend to be cohesive and aggravate flow problems.

Physicochemical Properties

Particle Size, Particle Morphology, and Surface Area

- **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
- *Kaerger* 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
  - **Compactibility** increased with a decrease in particle size.

Physicochemical Properties

Particle Size, Particle Morphology, and Surface Area

- **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.
- For example, *Zhang and Johnson* 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.

Physicochemical Properties

Particle Size, Particle Morphology, and Surface Area

- **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.
  - Example: Micronization enhanced the bioavailability of felodipine when administered as an extended release tablet.

Physicochemical Properties

Particle Size, Particle Morphology, and Surface Area

- Methods to determine **particle size and shape** include
  - Light microscopy
  - Scanning Electron Microscopy (SEM)
  - Sieve analysis
  - Various electronic sensing-zone particle counters
- Methods available for **surface area measurement** include
  - Air permeability
  - Various gas adsorption techniques

Physicochemical Properties

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 porosity.
- Generally, porous granules dissolve faster than dense granules, since pores allow water to penetrate more readily.

Physicochemical Properties

Bulk Powder Properties

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

$$\text{Intraparticle porosity} = 1 - \frac{\text{apparent particle density}}{\text{true particle density}}$$

$$\text{Total porosity} = 1 - \frac{\text{bulk density}}{\text{true particle density}}$$

- 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.

Physicochemical Properties

Bulk Powder Properties

- ***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.

$$\text{Hausner ratio} = \frac{\text{tapped density}}{\text{bulk density}}$$

$$\text{Compressibility (Carr Index)} = \frac{100 \times (\text{tapped density} - \text{bulk density})}{\text{bulk density}}$$

Physicochemical Properties

Bulk Powder Properties

Compressibility index (per cent)	Flow character	Hausner ratio
1–10	Excellent	1.00–1.11
11–15	Good	1.12–1.18
16–20	Fair	1.19–1.25
21–25	Passable	1.26–1.34
26–31	Poor	1.35–1.45
32–37	Very poor	1.46–1.59
> 38	Very, very poor	> 1.60

Physicochemical Properties

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.

PHYSICOCHEMICAL PROPERTIES

MELTING POINT AND HYGROSCOPICITY

- **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***.
- 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**.

BIOPHARMACEUTICAL PROPERTIES

- **Biopharmaceutics:** 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**.
  - 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.

Biopharmaceutical Properties

- Generating formulations with relevant oral bioavailability depends on a number of factors:
  1. **Solubility**
  2. **Permeability**

     determines the ability of drug to move across the lipophilic intestinal membrane in gastrointestinal tract (GIT).
  3. **Metabolic stability**

     refers to ability of a drug to withstand metabolism or degradation in the gut wall and the liver.

Absorbability is related to the first two factors: **Solubility** and **Permeability**

Biopharmaceutical Properties

Drugs and drug candidates are classified into four categories based on their solubility and permeability properties:

Solubility / Permeability	High	Low
High	**Class I:** No major challenges for immediate-release dosage form. Controlled-release dosage forms may be needed to limit rapid absorption	**Class II:** Formulation are designed to overcome solubility Salt formation, Precipitation inhibitors Metastable forms, Solid dispersions Lipid technologies, Particle size reduction
Low	**Class III:** Prodrugs Permeation enhancers Ion pairing Bioadhesives	**Class IV:** Formulation would have to use a combination of the approaches identified in Class II and III. Strategies for oral administration are not really viable. Often use alternative delivery methods such as intravenous administration.

Mechanical Properties

- Material mechanical properties play a role in manufacturing drug product.
- Particle properties influence the true areas of contact between particles and can affect unit operations, such as **compression**, **milling**, and **granulation**.
- Characterization of mechanical properties of drug substance is important in three areas:
  - Choosing a processing method, such as granulation or DC
  - Selecting excipients with properties that mask the poor properties of the drug
  - Helping to document what went wrong, i.e. when a tableting process is being scaled-up or when a new bulk drug process is being tested.

➡ It is to the formulator's advantage to quantify and understand the mechanical properties of the active and inactive ingredients.

Mechanical Properties

- Pharmaceutical materials are like metals, plastics, or wood:

Elastic | Plastic | Viscoelastic | Hard | Tough | Brittle

- The same concepts that materials/mechanical engineers use to explain/characterize **tensile**, **compressive**, or **shear strength** are relevant to pharmaceutical materials.
- A number of characterization tools are available for understanding the mechanical properties of the material.

Mechanical Properties

Characterization Tools

	Quasi-Static Testing	Dynamic Testing
API required	1–100 g	2–10 g
Advantages	"Independently" dissect out and investigate various mechanical properties	Understand the mechanics of materials at speeds representative of production tablet compaction
Limitations	Cannot determine properties at representative production scales	Difficult to factor out the individual mechanical property "component"

Mechanical Properties

Characterization Tests

Quasi-Static Testing

- Tensile strength
- Indentation/dynamic hardness
- Young's modulus
- Tableting indices

Dynamic Testing

- Force–displacement profiles
- Tablet volume–applied pressure profiles
- Heckel equation
  - Tablet porosity–applied pressure function

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	solubility enhancer	stability enhancer	taste masker

Excipients

- **Excipients** are selected based on their

Chemical / Physical compatibility with drugs	Regulatory acceptance	Processability

- 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.

EXCIPIENTS

- 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%**.

Types & Functions of Excipients for Tablet Production

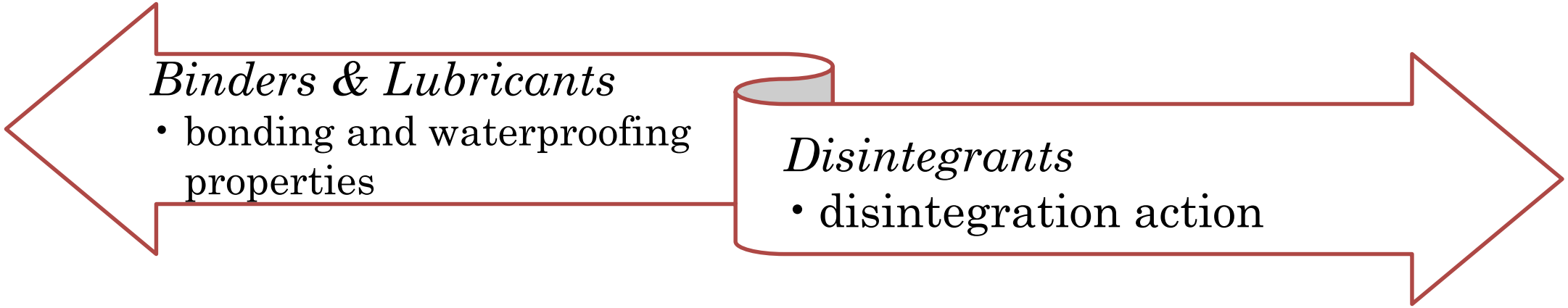
Excipient	Function	Some Examples of Excipients
Diluents	Act as bulking/filling material	Sugars, lactose, mannitol, sorbitol, sucrose, calcium salts, microcrystalline celluloses
Binders and adhesives	Holds powder together	Sugars, glucose, polymers, starch, gelatin
Disintegrants	To facilitate the breakup of the tablet in the gastrointestinal tract	Croscarmellose sodium (CCS), sodium starch glycolate (SSG), crospovidone
Glidants	Improve the flow of granules, needed for compression	Silica, magnesium stearate (MgSt), talc

Types & Functions of Excipients for Tablet Production

Excipient	Function	Some Examples of Excipients
Lubricants	Reduces friction between granules and the compression equipment	MgSt, stearic acid, talc, sodium lauryl sulfate (SLS)
Antiadherents	To minimize the problems if sticking to the tablet punch head	Talc, cornstarch, SLS, MgSt
Colorants	For identification and marketing	Natural pigments and synthetic dyes
Flavors and sweeteners	To improve the taste of chewable tablets	Mannitol, aspartame

EXCIPIENTS

- Some of the tableting excipients may exert effects in opposition to each other.



- In addition, some of these tableting 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.

EXCIPIENTS

- The sequence of adding the excipients during tablet production depends on the function of the excipient.
  - *Diluents* and *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**.

Drug–Excipient Compatibility Study

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.

Drug–Excipient Compatibility Study

- 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.

Drug–Excipient Compatibility Study

- 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.

Typical Excipients Selected for a Model Formulation Study

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

Drug–Excipient Compatibility Study

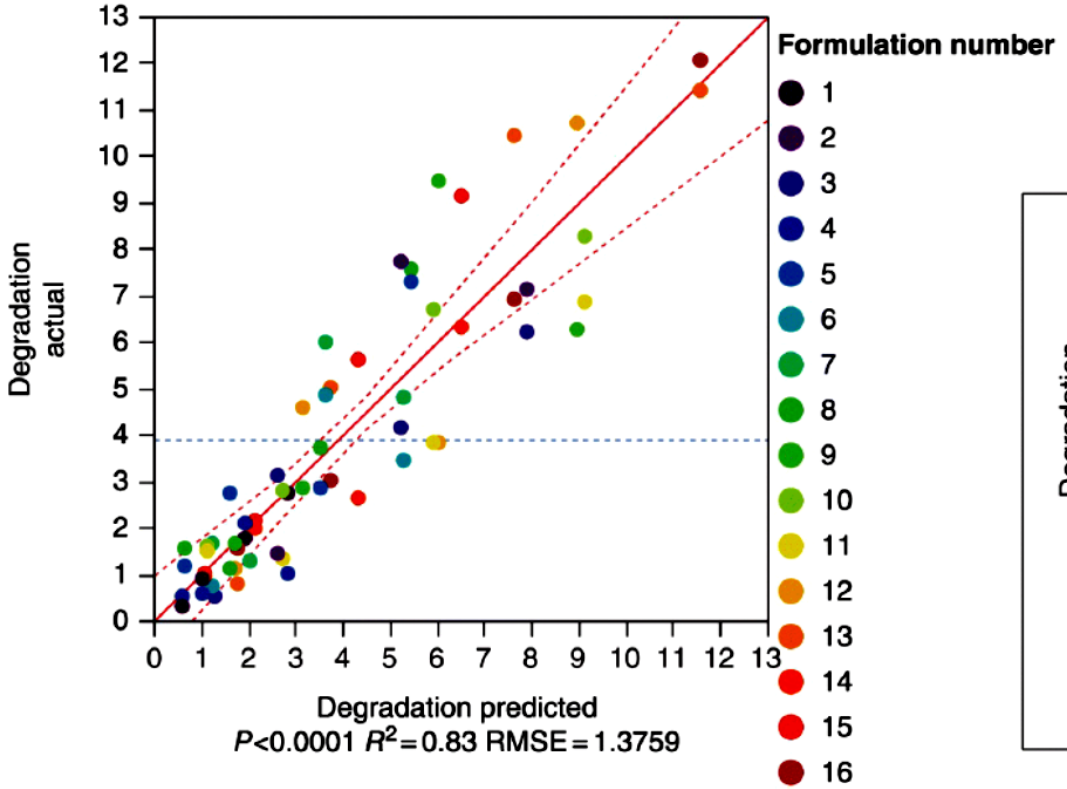
- Powders are physically mixed and may be granulated or compacted to accelerate any possible interaction.
- Samples may be exposed in open pans or sealed in bottles/vials to mimic product packaging.
- The storage conditions used vary widely in terms of temperature and humidity, but a temperature of 40 °C for storage of compatibility samples is considered appropriate.
- Some compounds may require higher temperatures to make reactions proceed at a rate that is measured over a convenient time period.
- Methods of analysis also vary widely, ranging from thermal techniques (DSC) to chromatographic techniques (TLC and HPLC) to microcalorimetry.

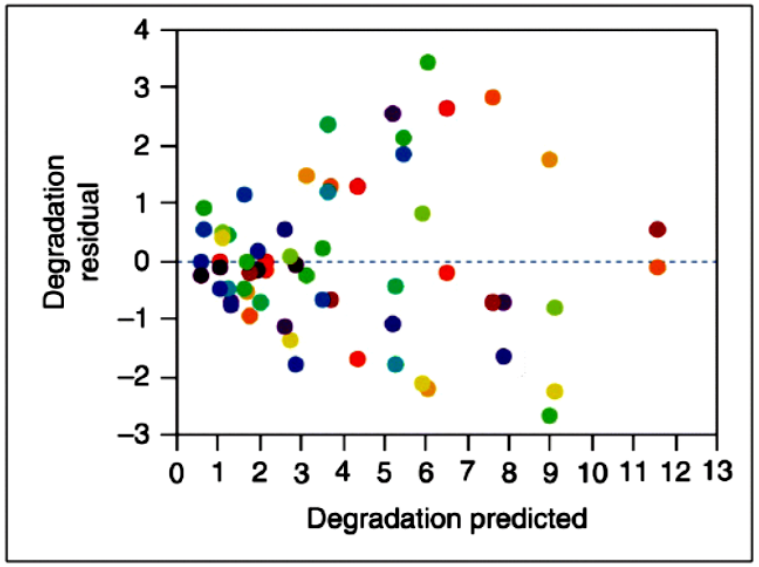
Formulation Composition for Excipient Compatibility Study utilizing Partial Factorial Design

Formulation Composition and Numbers	10%	38–40%	38–40%	0–4%	4%	1%	5%	20% (w/w) Water
1	API	MCC	ATab	None	PVP	MgSt	SSG	Dry (no)
2	API	MCC	ATab	None	HPC	MgSt	CCS	Wet
3	API	MCC	ATab	SLS	PVP	SSF	CCS	Wet
4	API	MCC	ATab	SLS	HPC	SSF	SSG	Dry (no)
5	API	MCC	Lactose	None	PVP	SSF	CCS	Dry (no)
6	API	MCC	Lactose	None	HPC	SSF	SSG	Wet
7	API	MCC	Lactose	SLS	PVP	MgSt	SSG	Wet
8	API	MCC	Lactose	SLS	HPC	MgSt	CCS	Dry (no)
9	API	Mannitol	ATab	None	PVP	SSF	SSG	Wet
10	API	Mannitol	ATab	None	HPC	SSF	CCS	Dry (no)
11	API	Mannitol	ATab	SLS	PVP	MgSt	CCS	Dry (no)
12	API	Mannitol	ATab	SLS	HPC	MgSt	SSG	Wet
13	API	Mannitol	Lactose	None	PVP	MgSt	CCS	Wet
14	API	Mannitol	Lactose	None	HPC	MgSt	SSG	Dry (no)
15	API	Mannitol	Lactose	SLS	PVP	SSF	SSG	Dry (no)
16	API	Mannitol	Lactose	SLS	HPC	SSF	CCS	Wet

Drug–Excipient Compatibility Study

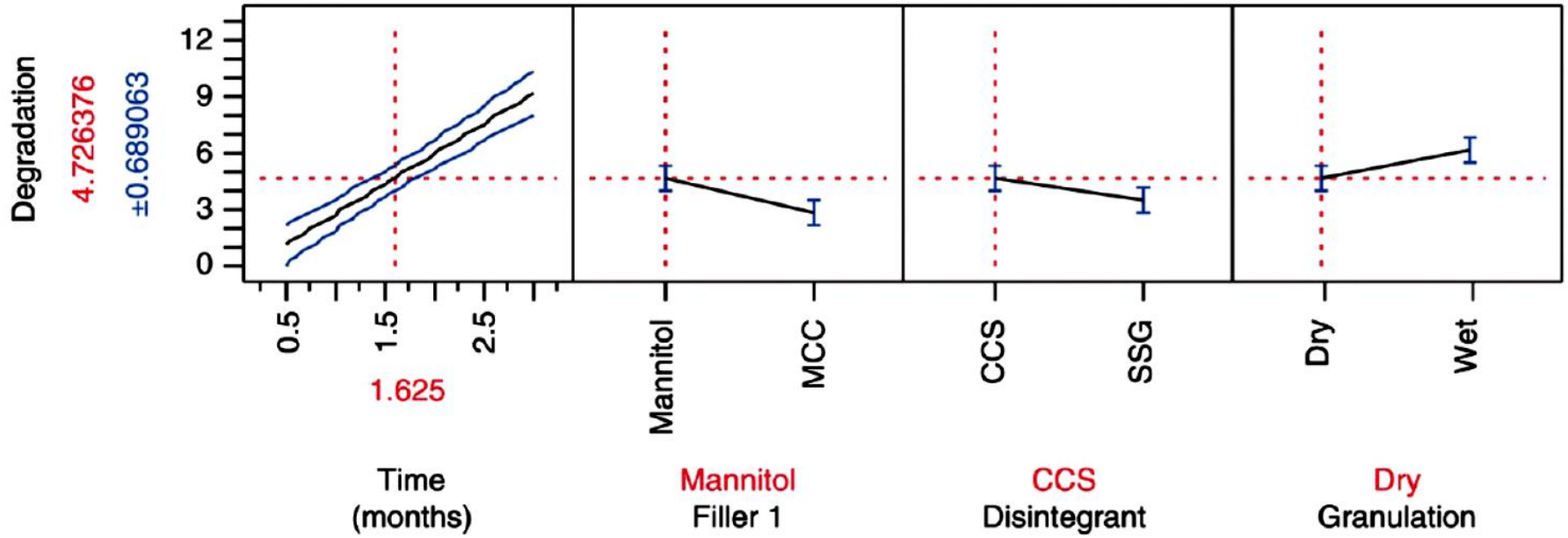
- Regression model defined for assessing the effect of formulation and time on degradation growth at a storage condition of 40 °C / 75% RH.





Drug–Excipient Compatibility Study

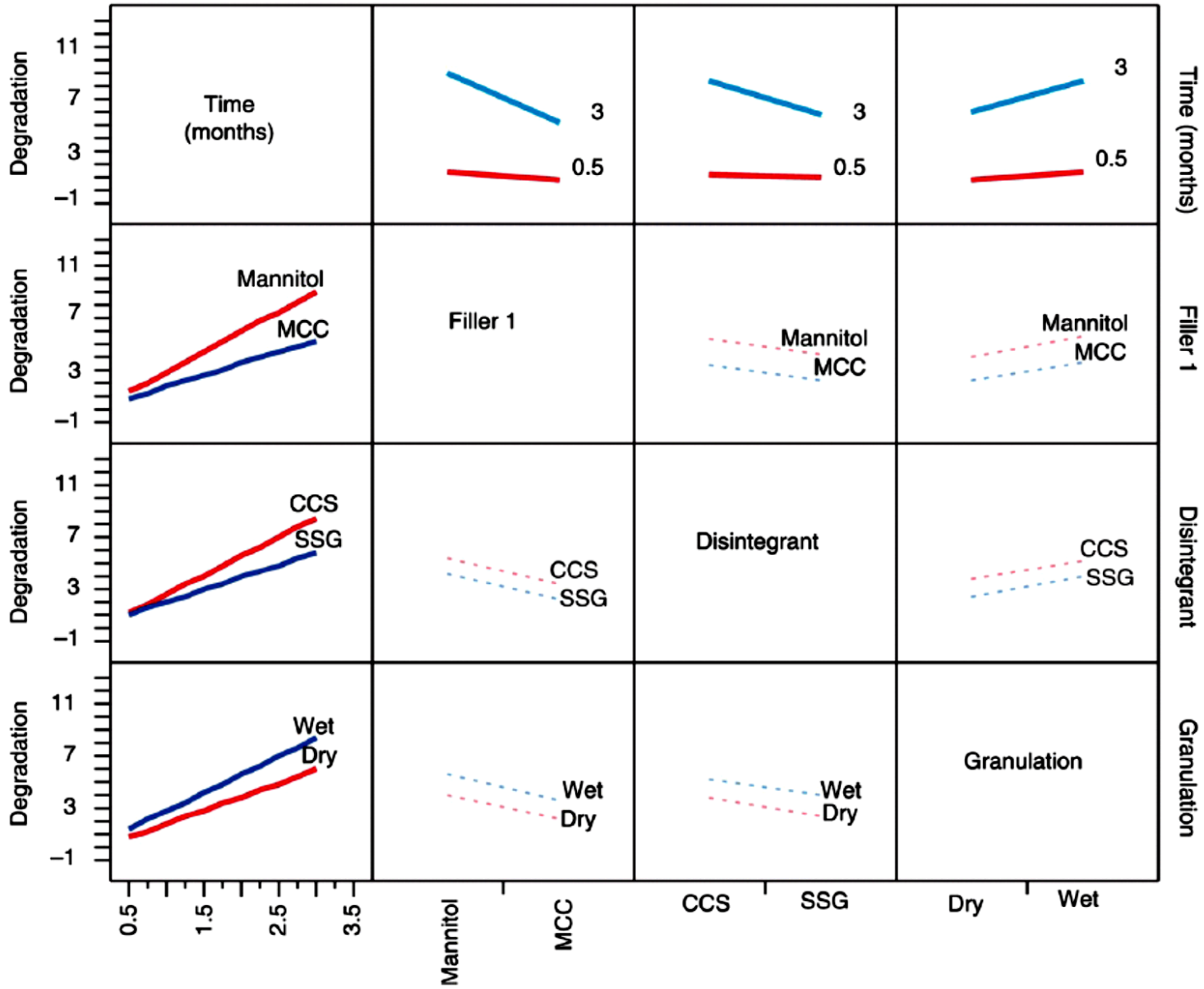
- Filler 2, Surfactant, Binder, and Lubricant did not show significance
- **Prediction profiler**



- Within Filler 1 mannitol causes more degradation as compared to MCC.
- SSG is better than CCS among disintegrant.
- Dry blend is better than wet granulation as the latter causes more degradation.

Drug–Excipient Compatibility Study

- **Interaction profiles**
  - Both mannitol and CCS could be detrimental for the stability of the API and are not being assessed for formulation development.
  - Wet granulation is to be avoided to increase the shelf life.



PROCESSING OF FORMULATIONS

Processing Of Formulations

The properties of a drug substance dictate the design of formulation composition and the choice of formulation–processing platform technology.

Most commonly used processing platforms for solid oral dosage form:	Direct Compression (DC)	Powder blends of the drug substance and excipients are compressed on a tablet machine.
		No mechanical treatment of the powder apart from a mixing process.
	Granulation (wet and dry)	A generic term for particle enlargement
		Powders are formed into permanent aggregates.
		Purpose: to improve the flow and compaction properties prior to compression.

Processing Of Formulations

Methods used to achieve the agglomeration

Wet granulation: a liquid is used to aid the agglomeration process

Dry granulation:

no liquid is used

DRY GRANULATION

The primary powder particles are aggregated under high pressure.

Two main processes:

- **Slugging**: A large tablet (known as a "slug") is produced in a heavy-duty tableting press
- **Roller compaction:** Powder is squeezed between two rollers to produce a sheet of material

Intermediate products are broken using a suitable milling technique to produce granular material, which is usually sieved to separate the desired size fraction.

- Unused fine material may be reworked to avoid waste.

Dry method may be used for

- Drugs that do not compress well after wet granulation, or
- Drugs which are sensitive to moisture.

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

- 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.

WET GRANULATION

Three main methods of producing pharmaceutical granulates

- Low-shear granulation
- High-shear granulation
- Fluid-bed granulation

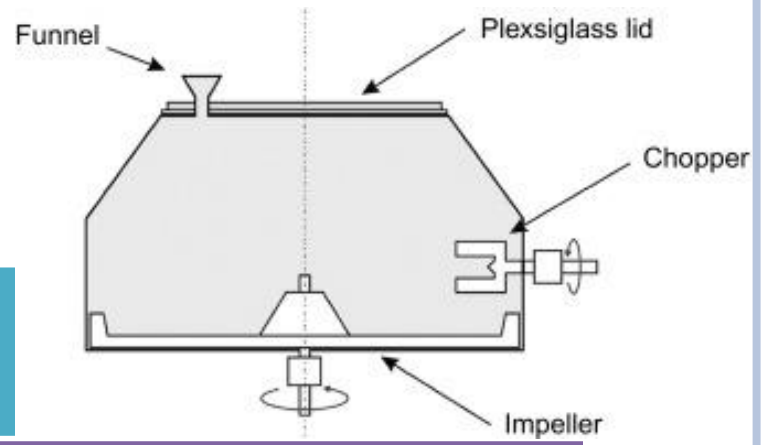
Low-shear Mixers

Encompass machines which impart relatively low shear stresses onto the granulate.

- Z-blade mixers

- Planetary mixers

WET GRANULATION



High-shear Granulators

Closed vessels that normally have two agitators

- an impeller which normally covers the diameter of the mixing vessel
- a small chopper positioned perpendicular to the impeller.

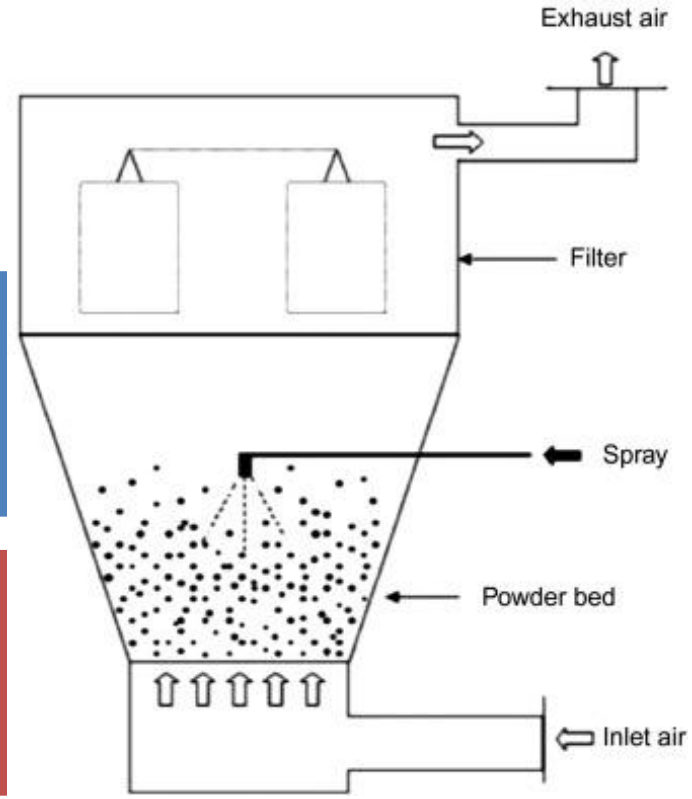
The powders are dry-mixed using the impeller, and then the granulating fluid is added.

Wet massing takes place using the impeller and the chopper, and granulation is usually completed in a number of minutes.

WET GRANULATION

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.

INFLUENCE OF MANUFACTURING METHOD ON TABLETING PERFORMANCE

- **Drug substance of study:**
  - Paracetamol granulated with hydrolyzed gelatin.
- The main difference in the granules produced by different methods is their final density
  - High-shear mixers produced 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.

Processing Platforms
Advantages and Disadvantages

Processing Platform	Advantages	Disadvantages
Direct Compression	• Simple, cheap process • Suitable for heat and moisture-labile drugs • Prime particle dissolution	• Generally limited to low-dose compounds • Potential to segregation • Expensive excipients
Dry granulation (Slugging)	• Imparts flowability to formulation • Suitable for heat and moisture-labile drugs	• Dusty process • Not suitable for all compounds • Slow process
Dry granulation (Roller compaction)	• Imparts flowability to formulation • Suitable for heat and moisture-labile drugs	• Slow process • Loss of compactibility for tableting • No hydrophilization of surfaces

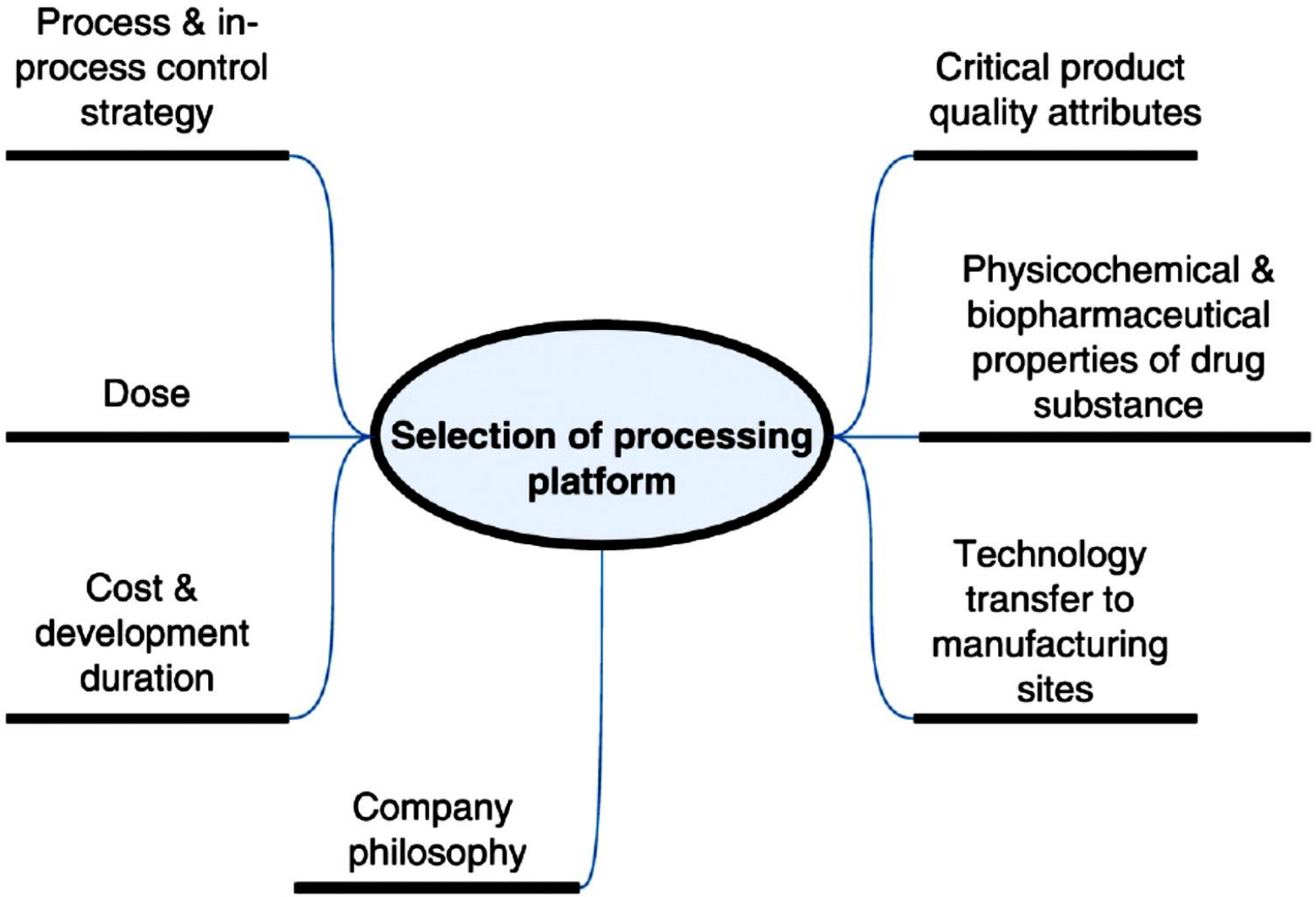
Processing Platforms
Advantages and Disadvantages

Processing Platform	Advantages	Disadvantages
Wet granulation (Aqueous)	• Robust process • Improves flowability • Can reduce elasticity problems • Can improve wettability • Reduces segregation potential	• Expensive • Specialized equipment • Stability concerns for moisture sensitive, thermolabile, and metastable drugs with aqueous granulation
Wet granulation (Nonaqueous)	• Suitable for moisture-sensitive drugs • Vacuum drying techniques can reduce/remove need for heat	• Expensive equipment • Explosion proof • Solvent recovery

Unit Operations Required for Manufacturing IR Tablet using Various Processing Platforms

Unit Operation	Direct Compression	Dry Granulation	Wet Granulation
Raw materials (weighing and sieving)	✓	✓	✓
Blending	✓	✓	✓
Compaction		✓	
Wet granulation			✓
Wet screening			✓
Drying			✓
Milling		✓	✓
Tablet compression	✓	✓	✓

Factors Affecting the Selection of Processing Platform



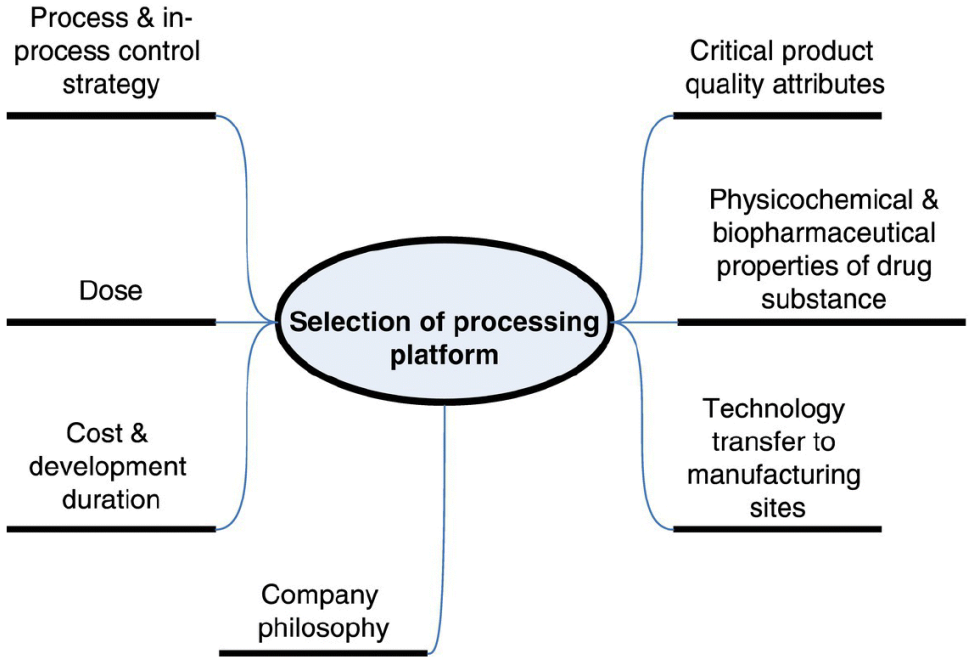
TABLET FORMULATION DESIGN

Tablet Formulation Design

Formulation design strategy is decided

The process of preparing and screening initial formulation possibilities begins

- **The Goal**:
  to develop a "robust" formulation
  - This objective facilitates identification of the factors that influence the selection of a design process



TABLET FORMULATION DESIGN

- First major design criterion: **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**.

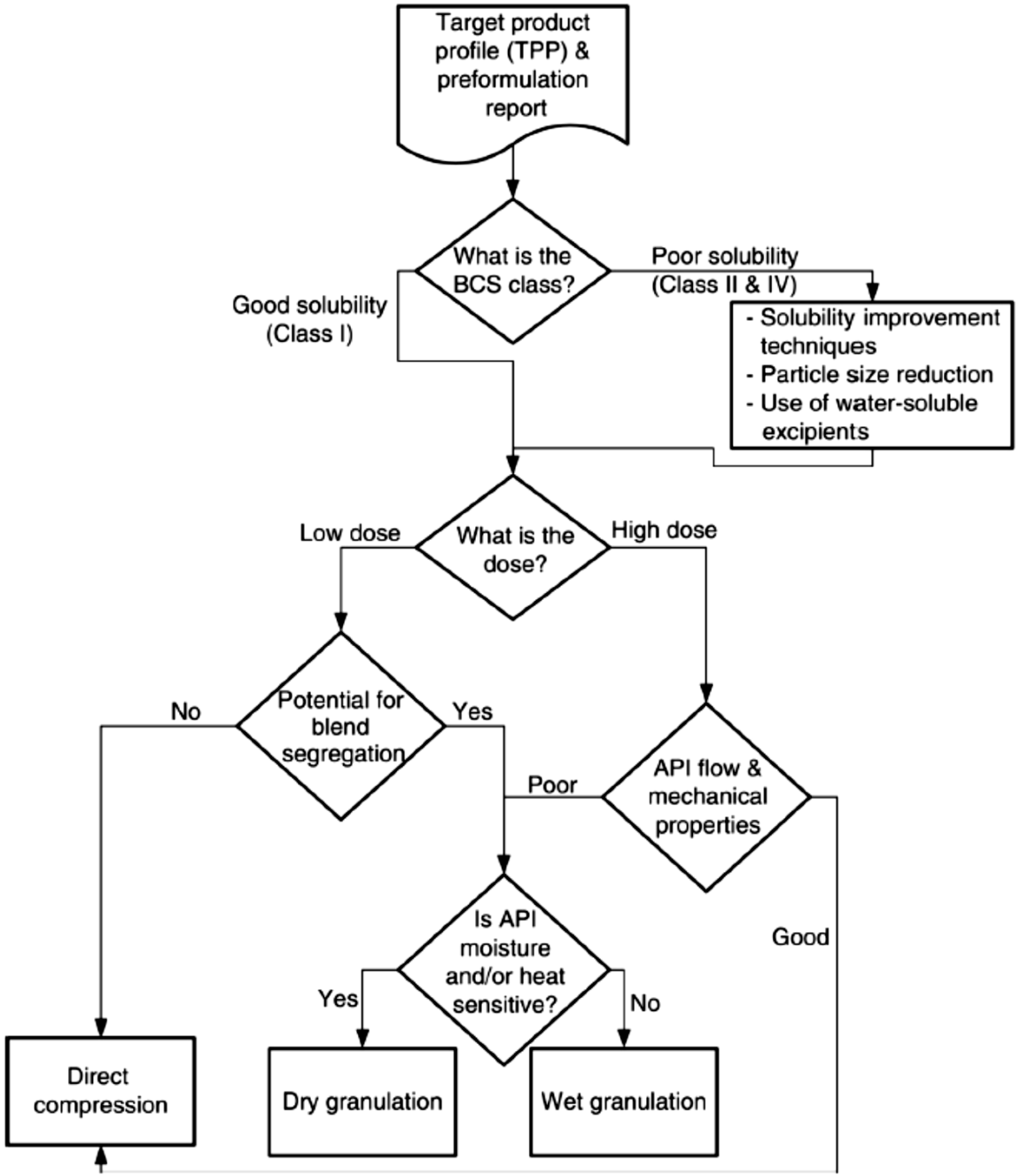
Tablet Formulation Design

- **Processing methods** may also significantly impact *dosage-form performance*.
- **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.

Tablet Formulation Design

- Another major consideration: **the anticipated dosage level**.
- 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**.

Decision Guiding Flowchart for Selection of Adequate Processing Platform



TABLET CHARACTERISTICS

Tablet Characteristics

- **There are two important classes of tablet characteristics.**
  1. The first set examines the tablet **immediately after manufacturing**;
  2. 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.

Release Profile: Factors Affecting In-Vivo Performance

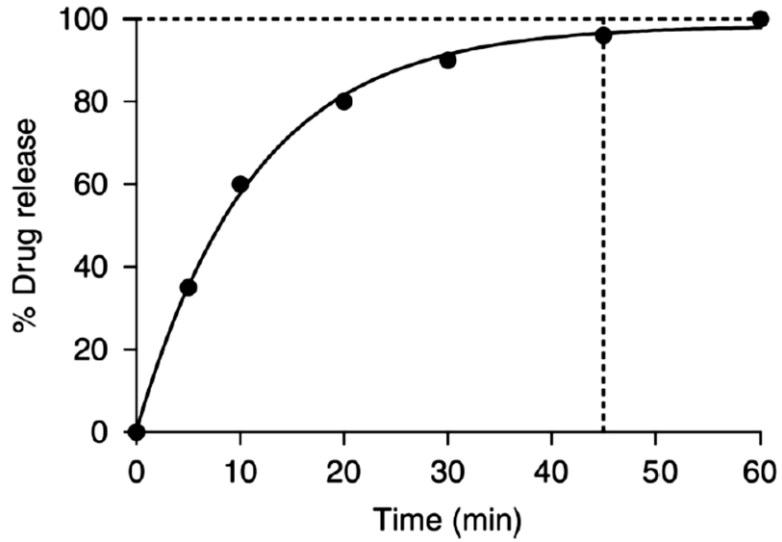
- Release Profile of a tablet can affect in-vivo drug performance, as this is the case it is important to measure this characteristic during development.
- The FDA guidance, ***Dissolution of Immediate Release Solid Oral Dosage Forms***, states the dissolution requirements for an immediate-release drug.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

What is a dissolution test?

RELEASE PROFILE: FACTORS AFFECTING 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.



Typical drug-release profile; very fast initial release with a leveling off.

WHAT AFFECTS DISSOLUTION

- 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**

USING DISSOLUTION TO DETERMINE CQAs

Using Dissolution to Determine CQAs

Dissolution can help determine

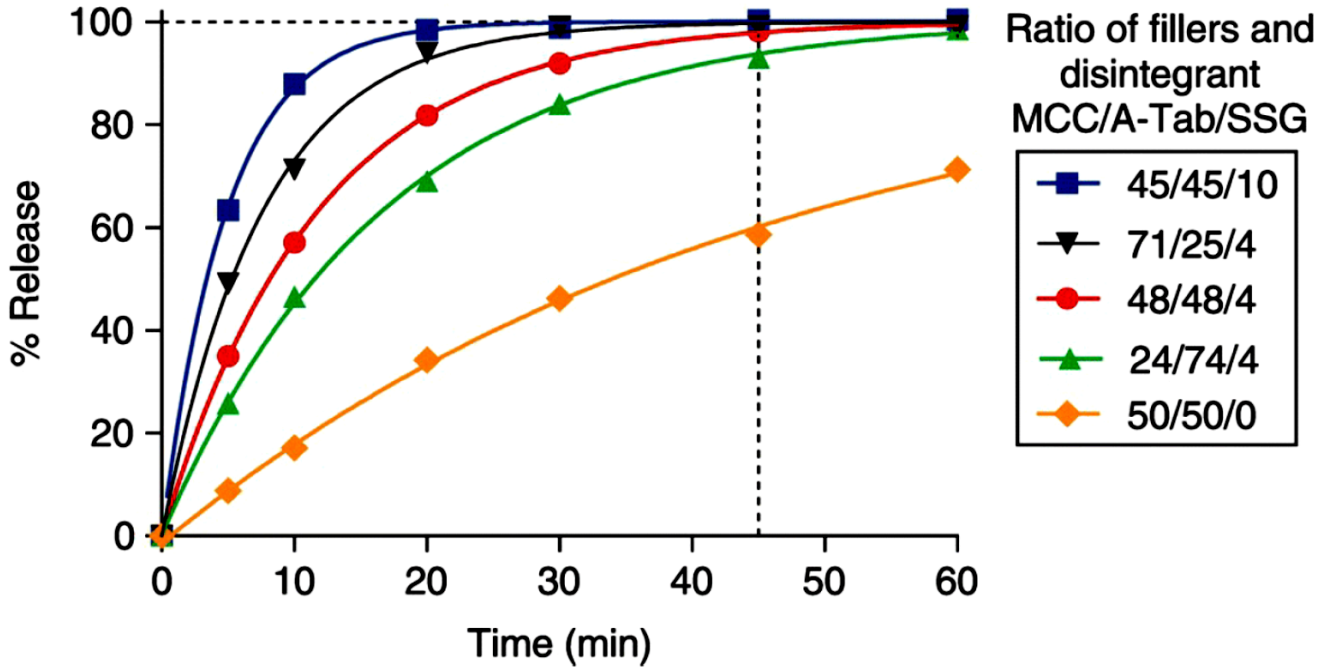
Maximum tablet hardness	Optimal drug substance particle size and/or density	Proper ratio or the amount of excipients

Ratio of Excipients

- 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

RATIO OF EXCIPIENTS

- **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.
  - **Fillers:** Micro Crystalline Cellulose (MCC) and Calcium Di-Basic Phosphate (A-Tab)
  - **Disintegrant:** Sodium Starch Glycolate (SSG)
- 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.



Using Dissolution to Determine CQAs

Optimal API Particle Size and Tablet Hardness

- **API particle size** has the potential to affect dissolution based on *different surface area* or *particle morphology*.
- **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:

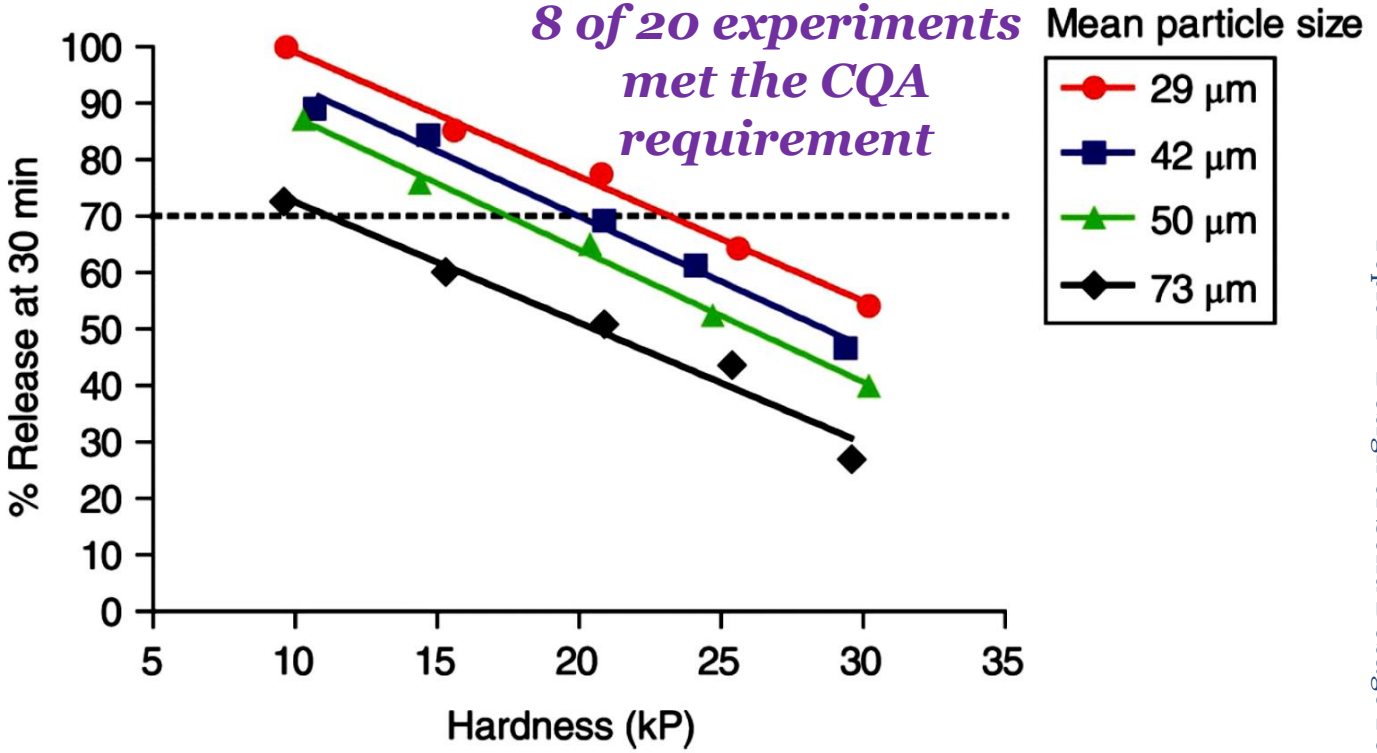
There is never an instance where bigger particles will improve the immediate release performance but there are many instances where it will not change the performance.

Using Dissolution to Determine CQAs
Optimal API Particle Size and Tablet Hardness

- **Example:** determining the optimal hardness and API particle size-range dissolution is chosen at the CQA of "not less than (NLT) 70% release at 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 (d50); 29, 42, 50, and 73 µm.

Using Dissolution to Determine CQAs

Optimal API Particle Size and Tablet Hardness



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

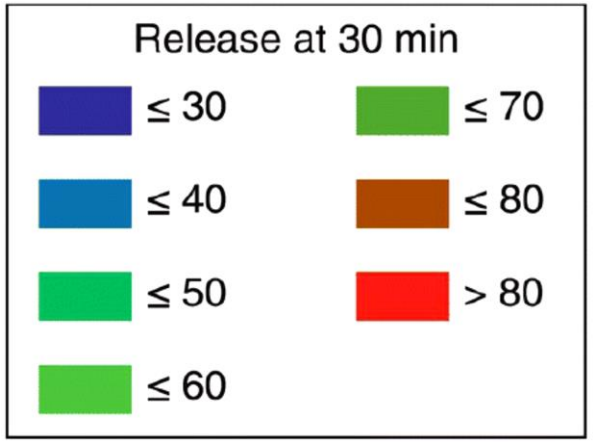
$$\%R_{at30min} = 139.2 - 0.59 \cdot D50 - 2.25 \cdot hardness$$

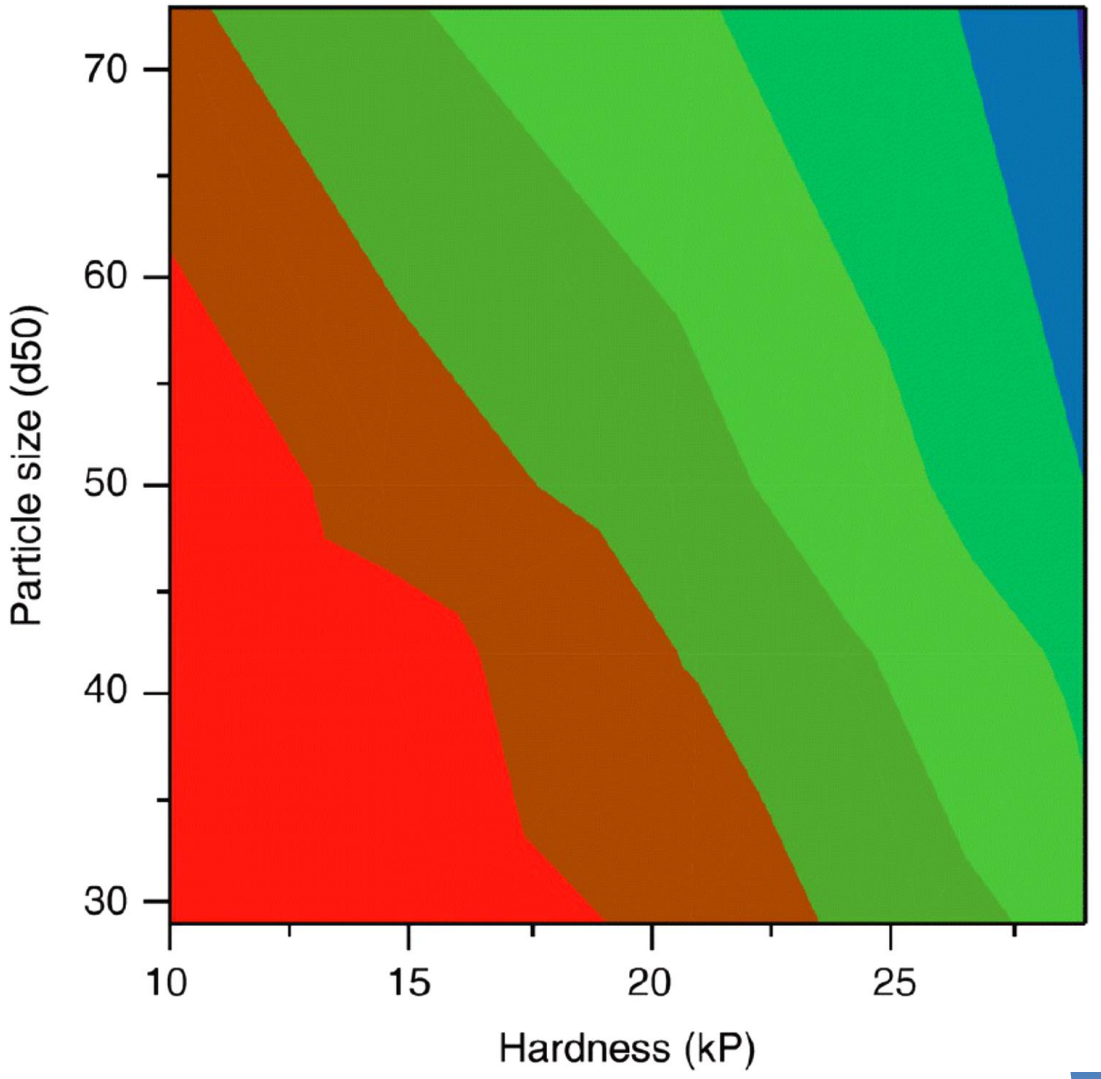
- And to maintain the CQA of NLT 70% Release at 30 minutes

$$69.3 \geq 0.59 \cdot D50 + 2.25 \cdot hardness$$

Using Dissolution to Determine CQAs
Optimal API Particle Size and Tablet Hardness

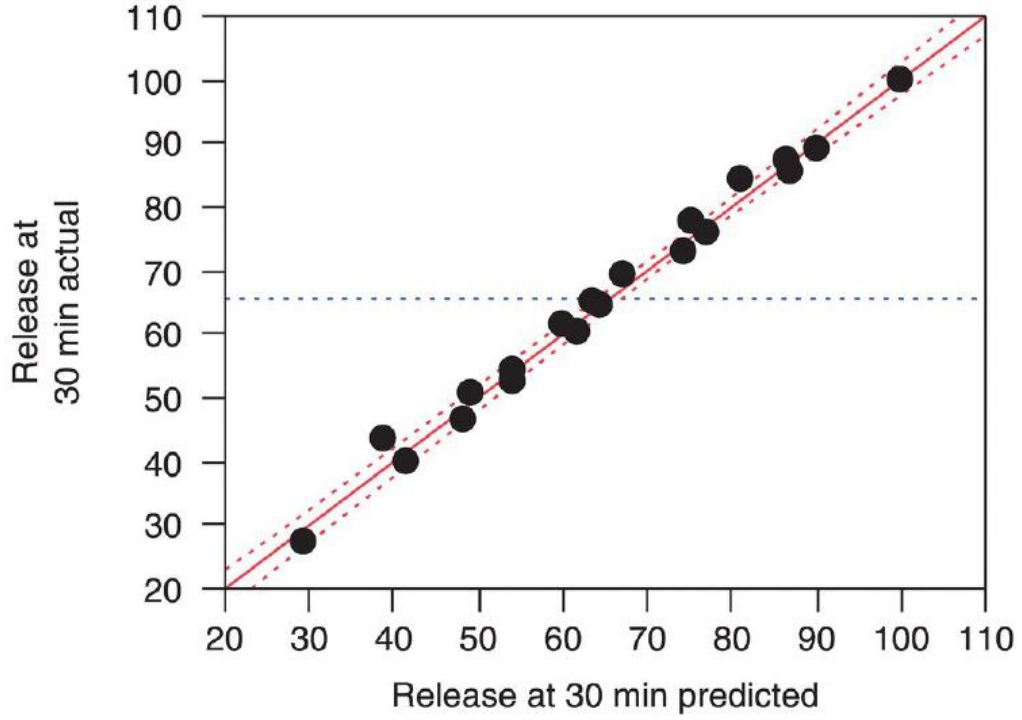
- Contour plot showing dissolution as a function of particle size and hardness.

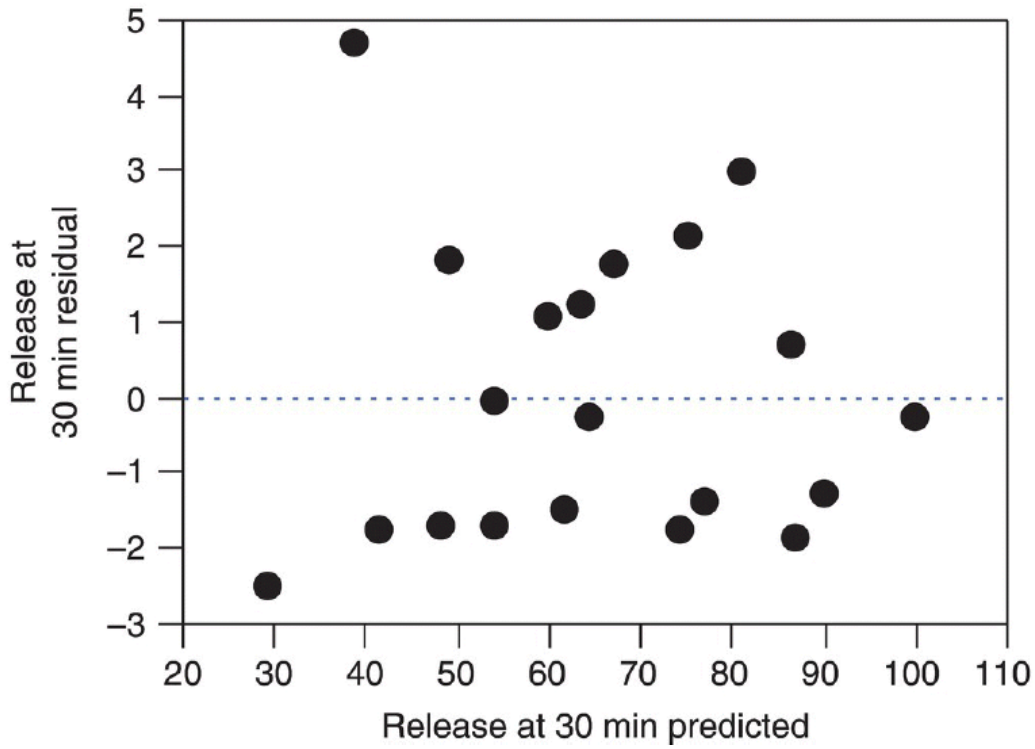




Using Dissolution to Determine CQAs

Optimal API Particle Size and Tablet Hardness





- Last check: Examine the residuals to ensure there is not a systematic error.
  - *The data shown in the figure are randomly distributed, indicating the regression does not have a systematic error.*

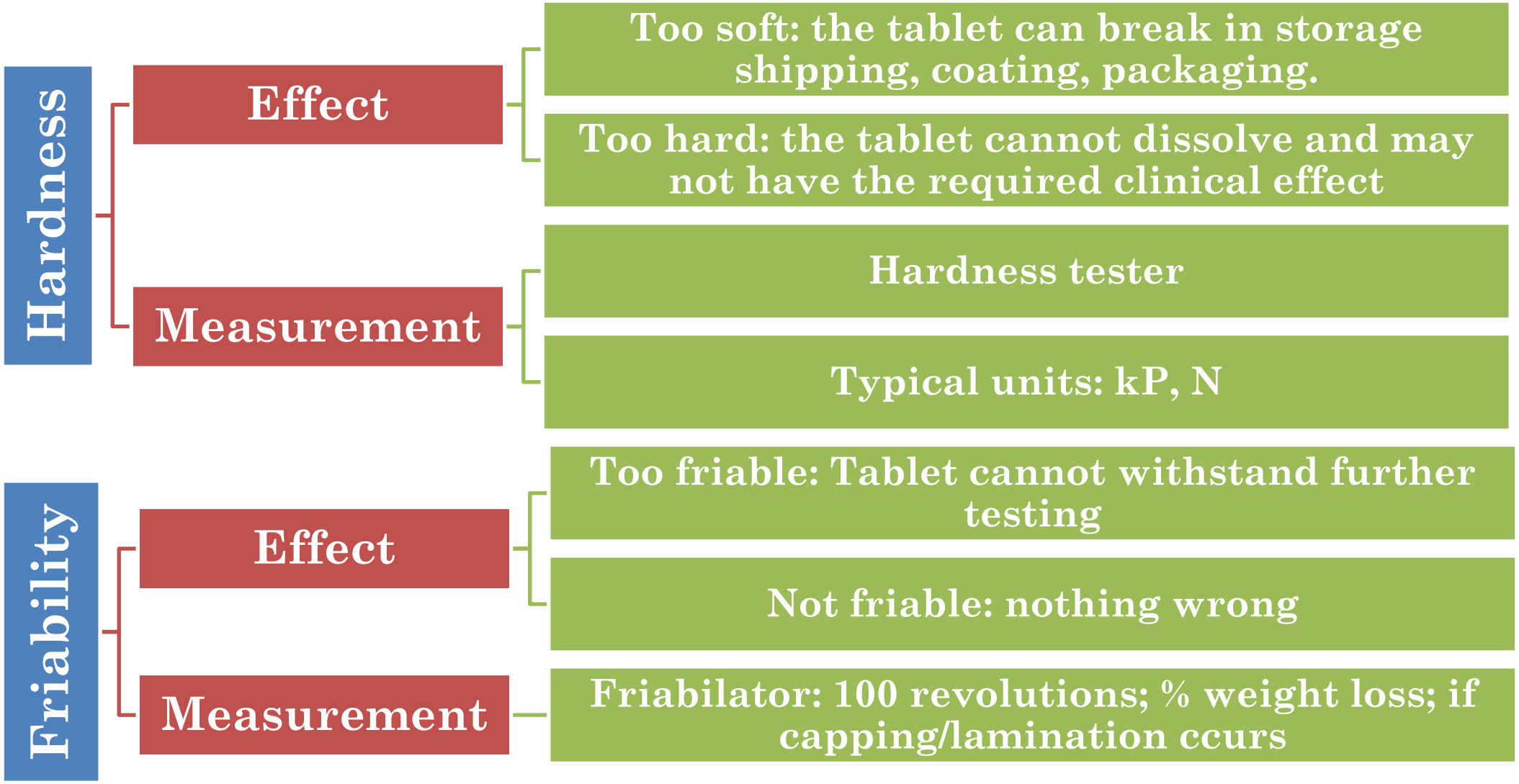
Physical Tablet Characteristics

- Physical attributes of the tablet are important for processing and to ensure a consistent quality drug product is delivered to the customer.

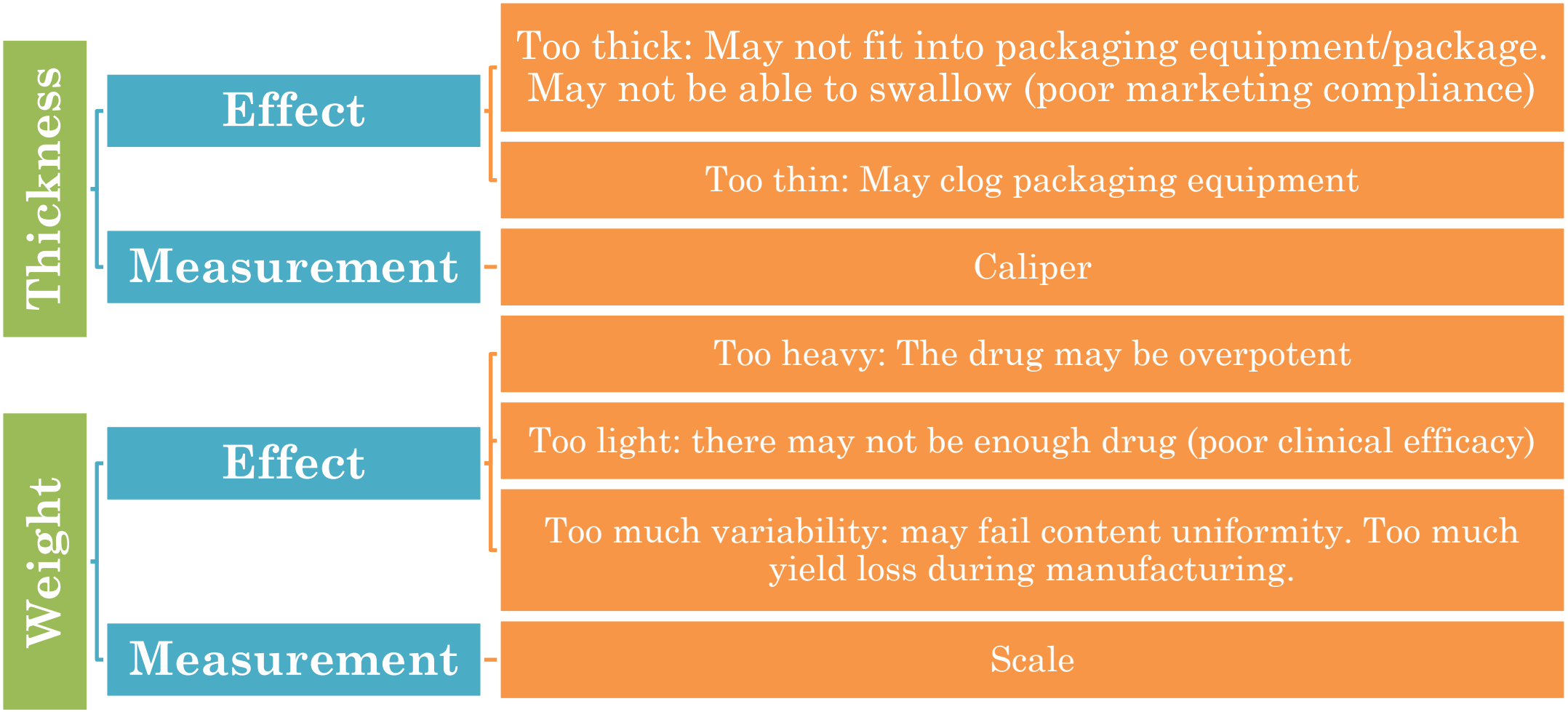
Tablet Hardness	Tablet Thickness	Tablet Friability	Tablet Disintegration	Tablet Weight

- When determining tablet characteristics, consider how the material is to be handled after compression.

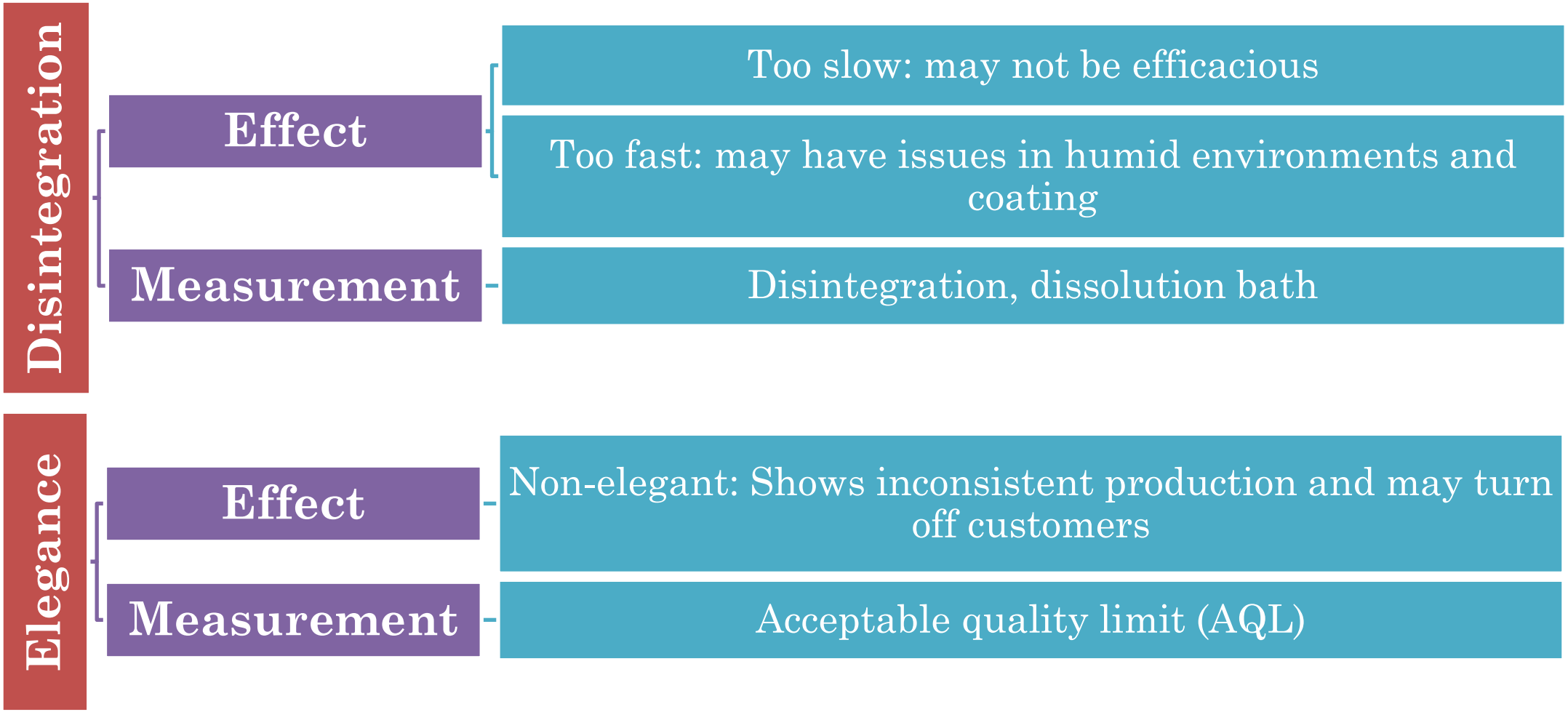
Physical Tablet Characteristics



Physical Tablet Characteristics



Physical Tablet Characteristics



PROCESS OPERATIONS AND SCALABILITY OF DOSAGE FORM

Process Operations and Scalability of Dosage Form

- There are many considerations in scaling-up unit operations that manufacture solid dosage forms.
- Scaling-up through **Preclinical** ➔ **Early Clinical (Phase I and Phase II)** ➔ **Late Clinical (Phase IIb and Phase III)** ➔ **Registration** ➔ **Engineering/Validation** batches has many challenges.
- Scale-up usually takes the course of laboratory experiments, pilot-scale tests, and then commercial-scale operation and continuous improvement.

Typical Scale-Up

Stage	Typical Material Required	REASON
Preclinical	0.05–1 kg	Early toxicology testing
Phase I and II	0.2–50 kg	Healthy volunteers and early proof of concept
Phase IIb and III	10–1000 kg	Proof of concept and verification trials
Registration	>100 kg and >100 000 unit dosages and minimum 1/10th commercial batch size	From FDA guidance
Engineering/ validation	Based on registration and expected product demand	Final process testing and process confirmation runs

Process Operations and Scalability of Dosage Form

- Beyond development, scale-up or scale-down also occurs **after approval**, in which changes are governed by Post-Approval Changes guidelines.
- Also, **Tech Transfer (TT)** is needed if multiple plants or CMOs (Contract Manufacturing Organizations) are required.
- Pharmaceutical process scale-up shall consider **formulation, process development, and marketing needs**.
- **Risk-based approach** is used to examine how the TPP of the drug is affected by CQAs of the final dosage form and the DS of the process.
- **Quality by Design (QbD) principles** are used to ensure a safe and efficacious product. DS, controls, and specifications are continuously improved through continuous learning.
- Another useful tool during scale-up is process **Failure Modes Effects Analysis (pFMEA)**, which is used to understand the failure modes of the CQAs to help mitigate risks in unit operations.

PROCESS FAILURE MODES EFFECTS ANALYSIS (PFMEA)

- pFMEA is done by understanding the **severity**, **occurrence**, and **detection** of any or all potential failure modes.
- pFMEA is different from Root Cause Analysis (RCA) as a RCA is performed after deviations have already occurred.
- **Risk Prioritization Numbers (RPNs**; scores from 1 to 1000) are calculated using pFMEA

  RPN = severity [1–10] × occurrence [1–10] × detection [1–10]

- RPNs point the engineer toward corrections that are implemented to **reduce risk** to the drug product.
  - Usually, an engineer starts to look to ameliorate problems with high RPN numbers.

Process Operations and Scalability of Dosage Form

- In addition to CQAs, **Critical Business Attributes (CBAs)** are also considered.
  - Business decisions that involve scale-up can relate to choice of CMO, batch size, operators needed, equipment purchases, use of PAT (process analytical technology) tools, etc.
- It is imperative to learn the **CPPs (Critical Process Parameters)** of the unit operation at hand.
  - This is done through an evolution of understanding the engineering principals and the processing knobs at the engineer's disposal.
  - These CPPs affect any or all of the CQAs of the DP

CQAs and CPPs for Some Unit Operations

Unit Operation	CQAs	CPPs	Potential Failure Mode
Roller Compaction	Ribbon density Degradants Downstream dissolution	Roll speed Feed screw speeds Roll force/pressure Roll separation/gap Room temperature/humidity	Ribbon density variation High degradation
Slugging	Hardness Dissolution	Slugging force	Too little or too much
Wet granulation	Particle size Powder density Degradants Downstream dissolution	*Granulation fluid mixing time, mixing speed, amount, addition rate, and temperature* Spray nozzle air volume Dry mixing time, Wet mixing time Impeller speed, Chopper speed Power consumption	Too little or too much

CQAs and CPPs for Some Unit Operations

Unit Operation	CQAs	CPPs	Potential Failure Mode
Fluid bed granulation	Particle size Powder density Powder wetness Degradants Downstream dissolution	*Granulation fluid mixing time, mixing speed, amount, addition rate, and temperature* Spray nozzle air volume Bed mixing time Supply air flow rate, temperature, dew point Product bed temperature Exhaust air temperature, dew point Filter shaking intervals	Loss of yield, Powder degradation
Milling	Particle size Degradants	Impeller speed, Feed rate Room temperature, Humidity	Undesired particle size, Degradation
Lyophilization	Degradants Physical form Product wetness	Pretreatment, freezing, drying temperature, Cycle times, Chamber pressure	Degradation, Loss of stability, Yield loss

CQAs and CPPs for Some Unit Operations

Unit Operation	CQAs	CPPs	Potential Failure Mode
Blending	Blend uniformity Content uniformity	Blend time (pre- and post-lube) Rotation rate Agitator speed Room temperature, humidity	Under-blending may lead to bad CU. Over-blending may lead to poor compressibility
Encapsulation	Powder density Downstream dissolution Weight	Speed, dosing	Improper weight, broken capsules, too dense powder in capsule
Tableting	Hardness Thickness Weight Dissolution Degradants Content uniformity	Tablet weight Press (turret) speed Main compression force Pre-compression force Feeder speed Upper punch entry Room temperature, humidity	Capping if dwell time is too low Low weights or high weight variability if powder flow is bad

CQAs and CPPs for Some Unit Operations

Unit Operation	CQAs	CPPs	Potential Failure Mode
Tablet coating	Appearance Dissolution	*Coating suspension mixing time, mixing speed, solids' load* Atomization pressure Preheat time Jog time #, number of guns, type of guns Gun to bed distance	Twinning if tablet shape is not round Spray drying of coating suspension if temperature is too high Nonuniform coating if pan speed is too slow Tablet defects if pan speed is too fast
Tablet printing	Appearance Degradants	Ink dosage amount, force, location	Ink degrades product

BLENDING, COMPRESSION, AND COATING SCALE-UP

Blending Scale-Up

- Blending is a critical operation that determines how well the product is to perform in the next phases.
- Achieving and maintaining homogenous mixing of powders is critical, especially in formulations involving small amounts of high-potency components.
- ***Lack of blend uniformity at the blending stage may result in lack of CU in the finished product dosage forms.***
- **Tumbling blenders** are typically used. The most common types of blenders are **In-Bin** and **V-shell** blenders.
  - **In-Bin blenders** are typically used for high drug-load blends and are good for storage of said blend.
  - **V-shell blenders** are used in intermediate drug-load blends.
- The main difference in these blenders is the geometry

Blending Scale-Up

In-Bin blender

V-shell blender

Blending Mechanisms

Convection

- causes large groups of particles to move in the direction of flow (orthogonal to the axis of rotation), the result of vessel rotation.

Dispersion

- is the random motion of particles as a result of collisions or inter-particle motion, usually orthogonal to the direction of flow (parallel to the axis of rotation).

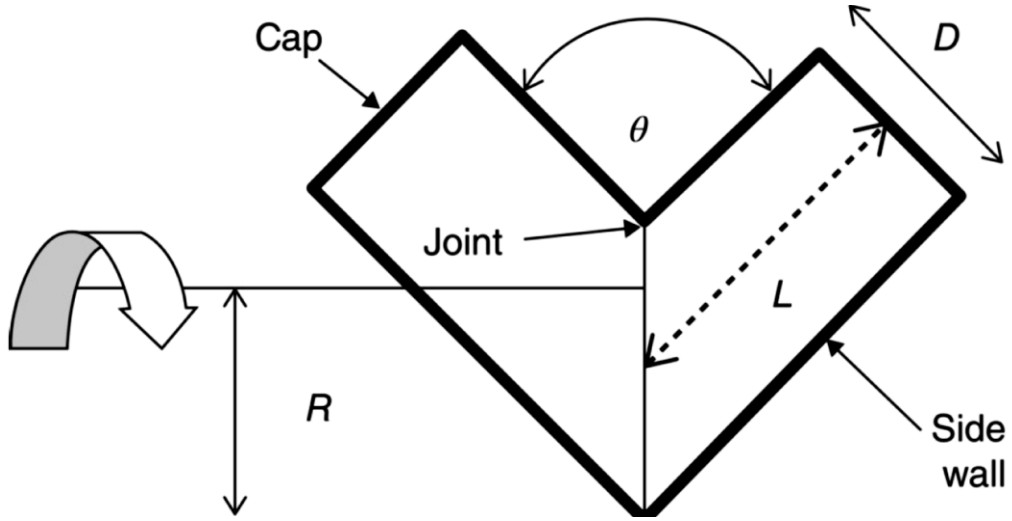
Shearing

- separates particles that have joined due to agglomeration or cohesion and requires high forces.

https://youtu.be/VS1fLNOLfyM?t=16

Blending Scale-Up

- There are three mechanisms of particle mixing: **convection**, **dispersion**, and **shearing**.
- In tumbling blenders (e.g. V-shell), convective and dispersive mixing are dominant, unless intensifier bars or chopper blades are added to cause shear mixing.
  - For example, within a V-shell blender, **convective** blending occurs within each shell side during tumbling, and **dispersive** mixing happens between shells.



- Blending in a DC case consists of a pre-lubricant and a post-lubricant blend ahead of compression. Lubricants such as Sodium Starch Fumarate (SSF) and Magnesium Stearate (MgSt) are normally used.

Blending Scale-Up

Important Parameters

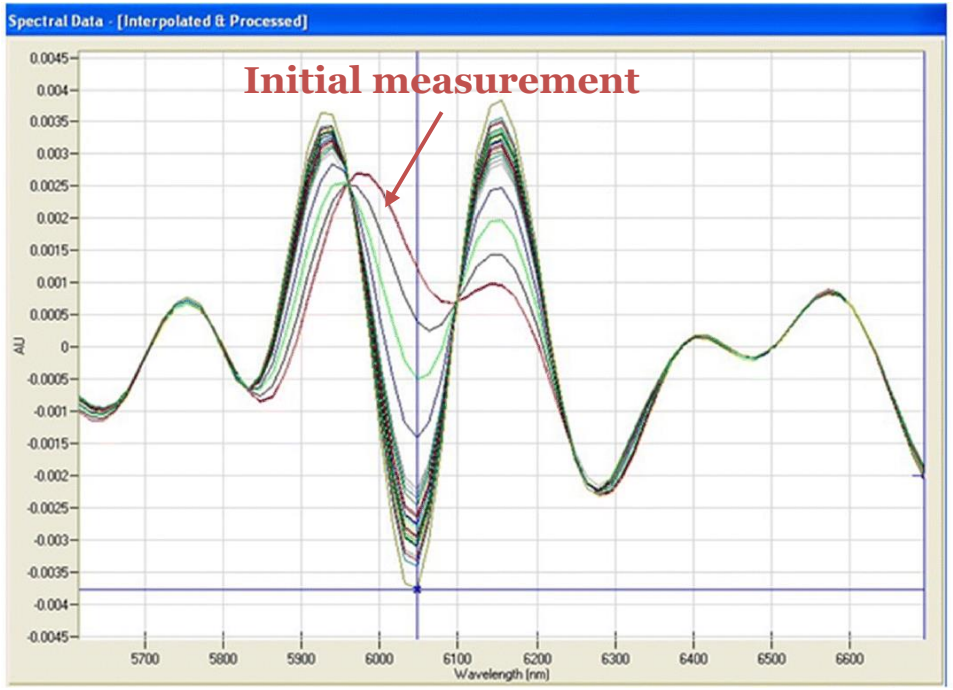
CMA/CPP	CPP/CQA/CBA It Can Affect
Particle shape and size	Blend uniformity, content uniformity, compressibility
Powder density	Blend uniformity, content uniformity, compressibility
Fill level	Blend uniformity, content uniformity
Loading procedure	Blend uniformity, content uniformity
Number of rotations (pre- and post-lube addition)	Blend uniformity, content uniformity
Rotation speed	Blend uniformity, content uniformity
Blender size	Throughput
Room humidity	Degradants, compressibility

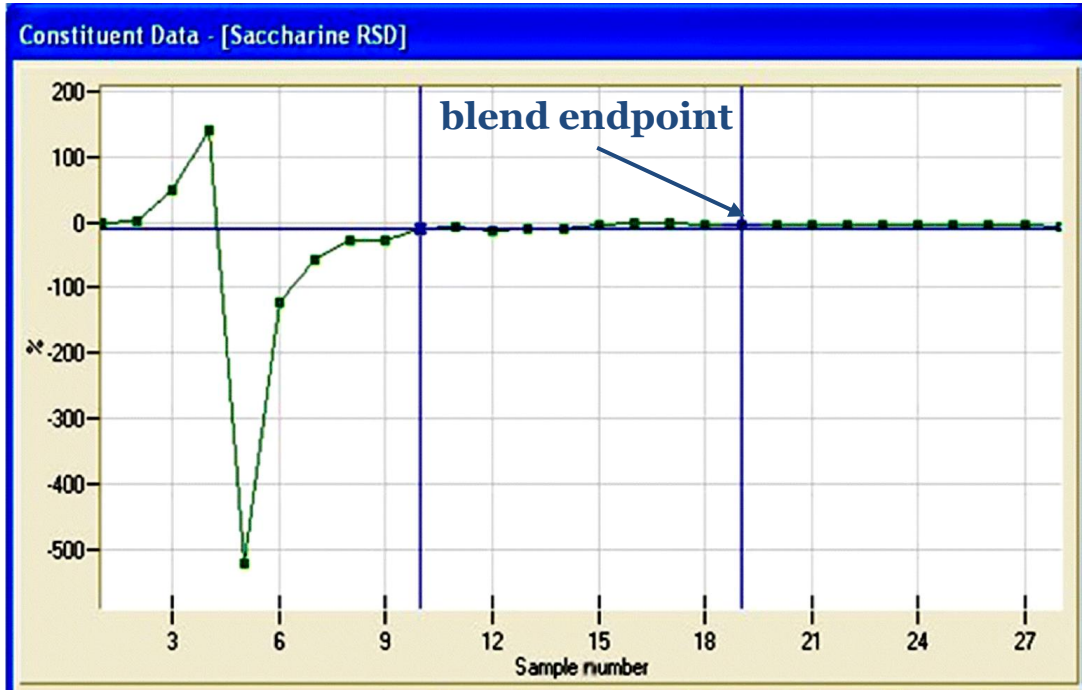
Blending Scale-Up

- There are many ways to determine if a blend is well mixed.
- Three simple ways are to
  1. Use online Process Analytical Technology (PAT) such of as Near Infrared (NIR) technology
  2. Sample blend using a thief over time and testing potency
  3. Simply compress the blend material and assess compressibility and CU

Blending Scale-Up

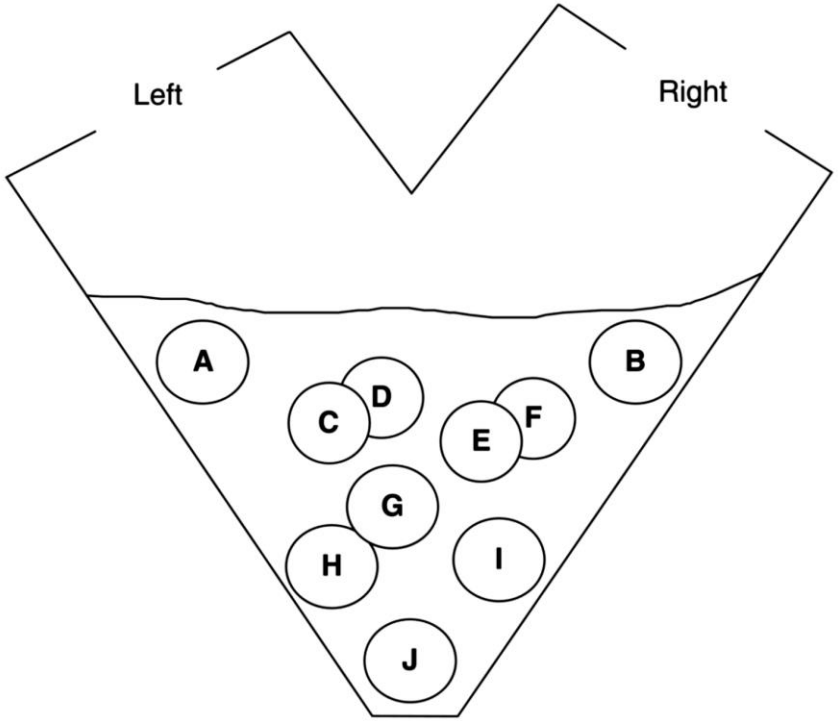
- The **NIR region** spans the wavelength range 780–2526 nm, in which absorption bands correspond mainly to overtones and combinations of fundamental vibrations.
- NIR spectroscopy is a fast and nondestructive technique that provides multi-constituent analysis of virtually any matrix.

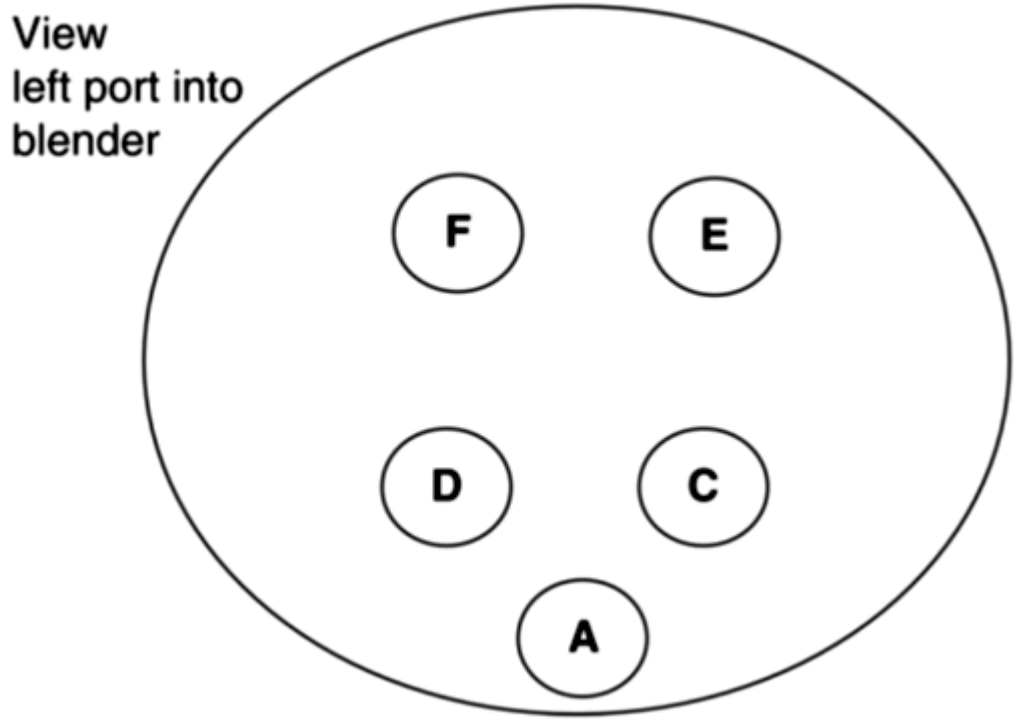




Blending Scale-Up

- If PAT tools cannot be used, a more traditional sample method is used.
- Samples are commonly pulled from many locations within the V-shell blender in order to understand if there is any location bias versus blend uniformity.





Blending Scale-Up

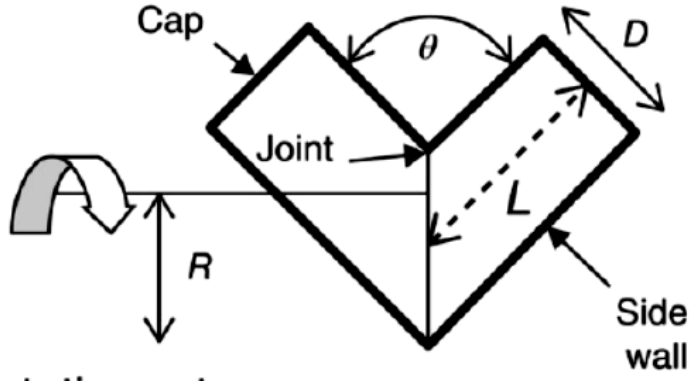
- Usually blenders are scaled from V-shell (laboratory, pilot scale, and commercial scales).
- However, depending on the product and manufacturing needs the blending operation may be transferred to an In-Bin Blender (pilot, commercial scales).
- Change in geometric characteristics of tumbling blenders may lead to different mixing behaviors; therefore, a straightforward transition cannot be accomplished unless engineering principles are used.
- Some scale-up approaches are matching **Froude (Fr) number**, matching **tangential/wall speed**, or scaling **particle surface velocities**.

COMMON SCALE-UP TECHNIQUES

1. Matching of froude number (Fr), $Fr = [\Omega^2 R]/g$
2. Matching of tangential speed (wall speed) of blender, $2\pi\Omega R$
3. Scaling of particle surface velocities,

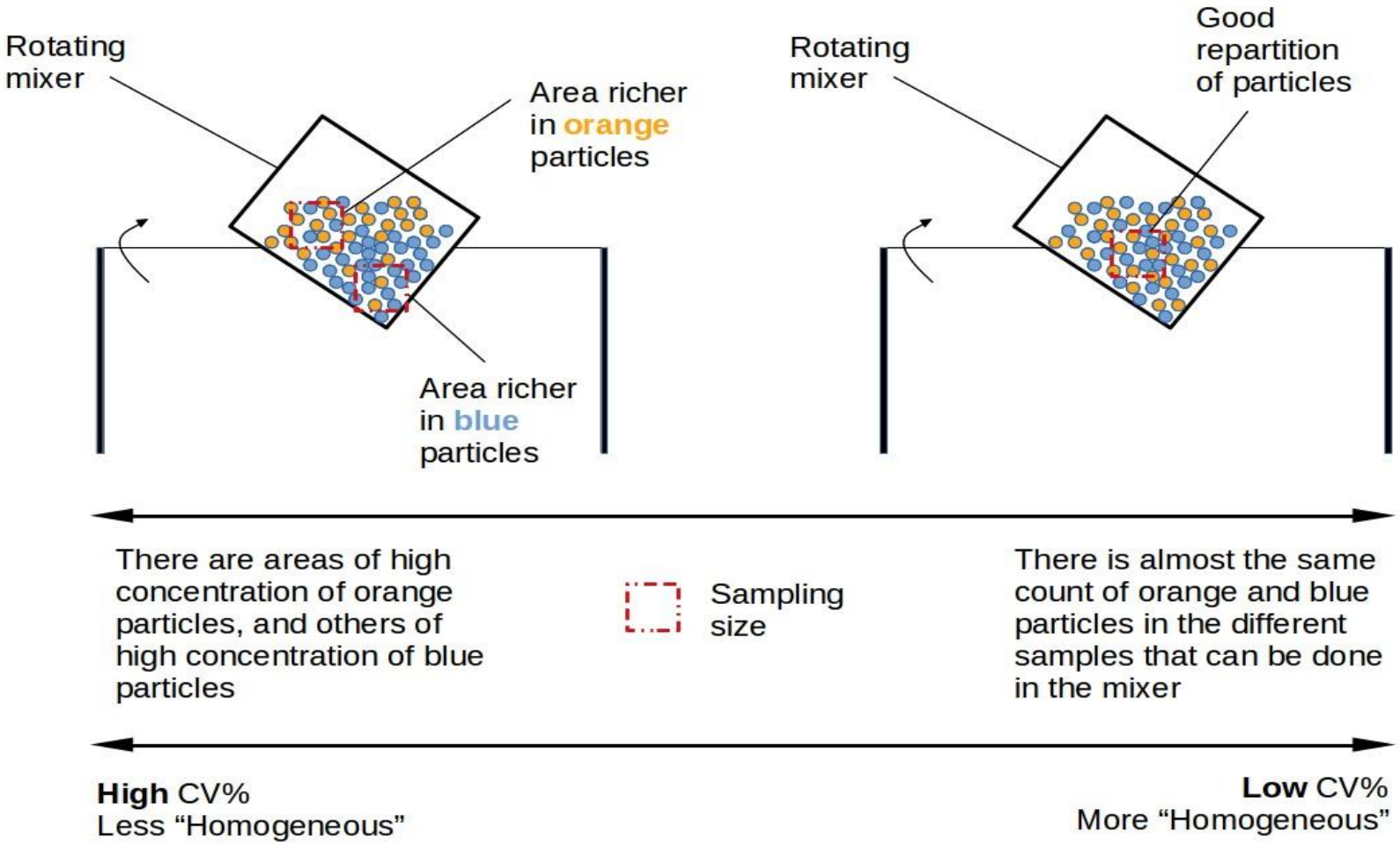
$$V = kR\,\Omega^{2/3}\left(\frac{g}{d}\right)^{1/6} \quad \text{for } \Omega \leq 30 \text{ rpm}$$

$$V = kR\,\Omega^{1/2}\left(\frac{g}{d}\right)^{1/4} \quad \text{for } \Omega > 30 \text{ rpm}$$



Ω - rotation rate
d - vessel diameter
k, K - dimensionless constants
V - particle velocity
d - particle diameter

HOMOGENEITY AND DEGREE OF MIXING



CV% = Coefficient of Variation of the mixture $= \frac{S}{\mu} \times 100\%$

where S **= samples standard deviation,** μ **= arithemic average of the samples concentration**

Compression Scale-Up

- Compression is important to make robust tablets.
  - Tablets that are too soft cannot withstand the downstream coating or packaging processes without chipping or breaking and losing tablet weight/active component.
  - Tablets that are too hard cannot dissolve effectively and therefore also cannot be efficacious when considering the TPP.
- Compression is typically used to make solid oral dosage forms of core tablets. Many types of equipment are manufactured; some include single station, rotary presses.
  - Typical manufacturers are Korsch, Elizabeth Hata, SMI, GEA Courtoy, and Manesty.

Compression Scale-Up
Parameters Critical in Tablet Production

CPP	CQA It Affects
Incoming blend	Tablet weight (flowability), compressibility in general
Feeder speed	Tablet weight
Fill depth	Tablet weight
Press speed (Dwell time)	Appearance (defects via capping or lamination)
Pre-compression	Tablet hardness
Main compression	Tablet hardness
Upper punch entry	Tablet hardness
Room humidity	Compressibility in general, degradants, tablet water content
Press temperature over time	Tablet hardness, degradants, possible change in physical form

Compression Scale-Up

- Tablet dies and tooling may be the same from laboratory to pilot to commercial scale; the change is in tooling dwell time.

$$\text{Dwell time} = \frac{60\,000 \times \text{punch head flat diameter}}{\pi \times \text{pitch circle diameter} \times \text{press speed}}$$

- Different dwell times can cause problems such as tablet capping or lamination.

Coating Scale-Up

- Tablet coating is the unit operation consisting of spray coating functional or nonfunctional/aesthetic coating onto the surface of the already compressed tablets.
- There are various sizes of tablet coaters, ranging up to 60″ + coating pans.
- Coating pans are either perforated or nonperforated.
- PAT tools may be implemented, for example, NIR for water content.

Coating Scale-Up
Important Parameters

CPP	CQA It Affects	Potential Problems
Pan load	Appearance, tablet water content	Improper pan loading for the scale being used
Spray gun to bed distance	Appearance	Improper spray to tablet bed
Number of spray guns	Appearance	
Exhaust temperature	Degradants, tablet water content	Spray drying of coating suspension
Atomization air flow rate	Appearance, tablet water content	Improper spray
Pattern air flow rate	Appearance, tablet water content	Improper spray
Spray rate	Appearance, tablet water content	Improper spray

Coating Scale-Up
Important Parameters

CPP	CQA It Affects	Potential Problems
Spray formulation	Appearance, dissolution	May impede tablet dissolution
Weight gain	Appearance, dissolution	Too high may impede tablet dissolution, too low may not cover tablets/appearance
Pan speed	Appearance	Too high of pan speed
Jogging	Appearance	Too much or too little jogging of the tablet bed
Incoming tablets	Appearance, dissolution	Too soft tablets Too much disintegrant, especially on the surface of the tablets

GRANULATION

Granulation

- Granulation is a term given to a number of processes used to produce materials in the form of coarse particles.
- Granulation (*Aggregation*) is a process whereby powder materials are made into larger particles (*agglomerates* or *granules*).
- In pharmacy, it is closely associated with the preparation of compressed tablets.
- Ideally, granulation yields coarse isodiametric particles with a very narrow size distribution.

What are the advantages of this form?

ADVANTAGES OF GRANULES FORM

1. Granules flow well.
2. They will feed evenly from chutes and hoppers.
3. They will pack into small volumes without great variation of weight.
4. Segregation in a mixture of powders is prevented if the mixture of powders is granulated.
5. Each granule contains the correct proportions of the components so that segregation of granules cannot cause inhomogeneity in the mixture.
6. The hazards of dust are eliminated, and granules are less susceptible to lumping and caking.
7. Finally, granular materials fluidize well and a material may be granulated to gain the advantages of this process.

Granulation

- The starting materials for granulation vary from fine powders to solutions.
- Methods can be classified as either *wet* or *dry* granulation.
- In **dry granulation**, a very coarse material is comminuted and classified.
  - If the basic material is a fine powder, it is first aggregated by pressure with punches and dies to give tablets or briquettes, or by passage through rollers to give a sheet that is then broken.

Granulation

- In **wet methods**, a liquid binder is added to a fine powder.
  - If the proportion added converts the powder to a crumbly, adhesive mass, it can be granulated by forcing it through a screen with an impeller. The wet granules are then dried and classified.
  - If a wetter mass is made, it can be granulated by extrusion.
  - Alternatively, the powder can be rotated in a pan and granulating fluid is added until agglomeration occurs.
  - *Granule growth* depends critically on the amount of fluid added, and other variables, such as particle size, pan speed, and the surface tension of the granulating fluid, must be closely controlled.
- Granular materials are also prepared by *spray drying* and by *crystallization*.

Granulation Methods

	Wet Granulation	Dry Granulation
Method Description	The powder formulation is mixed with water to cause particle adhesion, the resulting granules are then dried in the oven; binders may also be included to facilitate particle adhesion.	The powder formulation is compressed into pellets, slugs, or sheets that are milled, or broken down, to the appropriate particle size.
Method Disadvantages	cannot use water or heat sensitive powders	the granules are "weak" and have a wide size distribution that can be uneven.

Fluidization

FLUIDIZATION

- It occurs by moving fluid through a bed of particles.
- If the fluid velocity is low, the same situation is found when fluid is driven upward through a loose particulate (fixed) bed.
- At higher velocities, however, frictional drag causes the particles to move into a more expanded packing, which offers less resistance to flow.
- At some critical velocity, the particles are just touching and the pressure drop across the bed just balances its weight.
- This is the point of incipient fluidization, and beyond it true fluidization occurs, the bed acquiring the properties of surface leveling and flow.

FLUIDIZATION

- If the fluid is a **liquid**,
  - increase in velocity causes the quiescent bed to rock and break, allowing individual particles to move randomly in all directions.
  - increase in velocity causes progressive thinning of this system.

FLUIDIZATION

- In fluidization by **gases**, the behavior of the bed is quite different.
  - Although much of the gas passes between individual particles in the manner already described, the remainder passes in the form of bubbles so that the bed looks like a boiling liquid.
  - Bubbles rise through the bed, producing an extensive wake from which material is continually lost and gained, and breaking at the surface distributes powder widely.
  - This is an effective mixing mechanism, and any nonhomogeneity in the bed is quickly destroyed.
  - Rates of heat and mass transfer in the bed are therefore high.

Fluidization

- **Bubble size** and **movement** vary in different systems.
- In general, both decrease as the particle size decreases.
- As the size decreases and the powder becomes more cohesive, fluidization becomes more difficult.
- Eventually, bubbles do not form and very fine powders cannot be fluidized in this way.
- The final stage of fluidization occurs at very high velocities when, in both liquid and gaseous systems, the particles become entrained in the fluid and are carried along with it.
- These conditions are used to **convey** particulate solids from one place to another.

Mixing and Blending

Mixing and Blending

- **Blending** is *mixing* two or more powders until uniform.
- Mixing and blending may be achieved by rotating or shearing the powder bed.
- Mixing two or more components that may differ in composition, particle size, or some other physicochemical property is brought about through a sequence of events.
- Most powders at rest occupy a small volume such that it would be difficult to force two static powder beds to mix.

Mixing and Blending

- **Mixing** Process Steps:

  1. The first is to **dilate** the powder bed.
  2. The second step, which may be concurrent with the first, is to **shear** the powder bed.

  - Ideally, shearing occurs at the level of planes separated by individual particles.
  - The introduction of large interparticulate spaces is achieved by rotating the bed.

Batch Mixers

- A *V-blender* or *barrel roller* are classical examples of systems which, by rotating through 360°, dilate the powder bed while, through the influence of gravity, shear planes of particles.

Batch Mixers

- A *planetary mixer* uses blades to mechanically dilate and shear the powder.

Continuous Mixer

- A *ribbon blender* uses a screw action to rotate and shear the bed from one location to another in a continuous process.

Mixing and Blending

- Since the shearing of particles in a bed to achieve a uniform mix of blend is a statistical process, it must be monitored for efficiency.
- Sample thieves are employed to probe the powder bed, with minimal disturbance, and draw samples for analysis.
- These samples are then analyzed for the relevant dimension for mixing, for example, particle size, drug, or excipient content.
- Statistical mixing parameters have been derived based on the mean and standard deviation of samples taken from various locations in a blend at various times during processing.

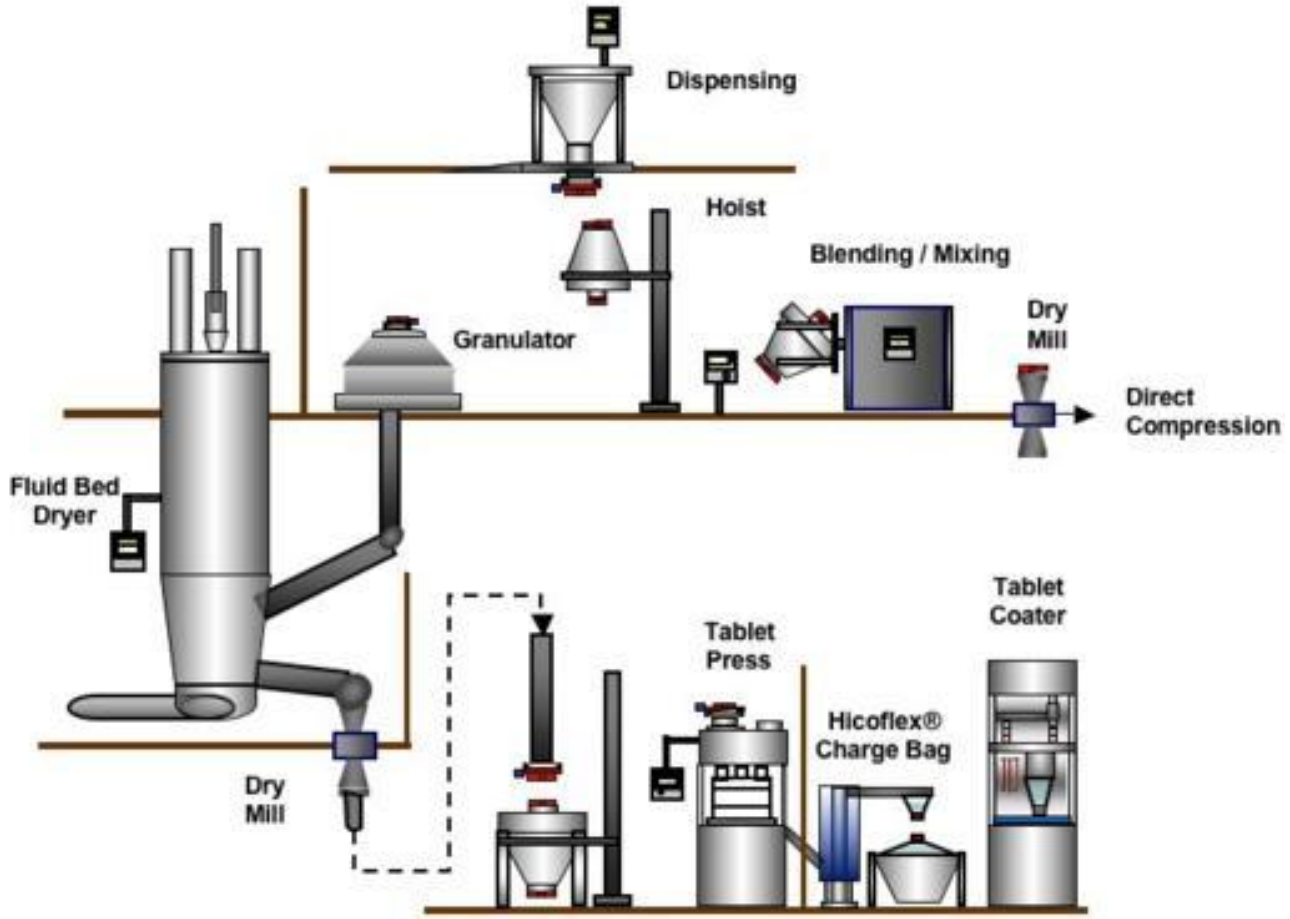
Mixing and Blending

- In large-scale mixers random number tables may be employed to dictate sample sites.
- There is a considerable science of sampling that can be brought to bear on this problem.
- The sample size for pharmaceutical products is ideally of the scale of the unit dose.
- This is relevant as it relates to the likely variability in the dose that in turn relates to the therapeutic effect.
- In the case of small unit doses, the goal should be to sample at a size within the resolution of the sample thief.

Solid Dosage Forms
Tablets

TABLETS

- **Tablet Manufacturing Process Video**
  - Part A
  - Part B

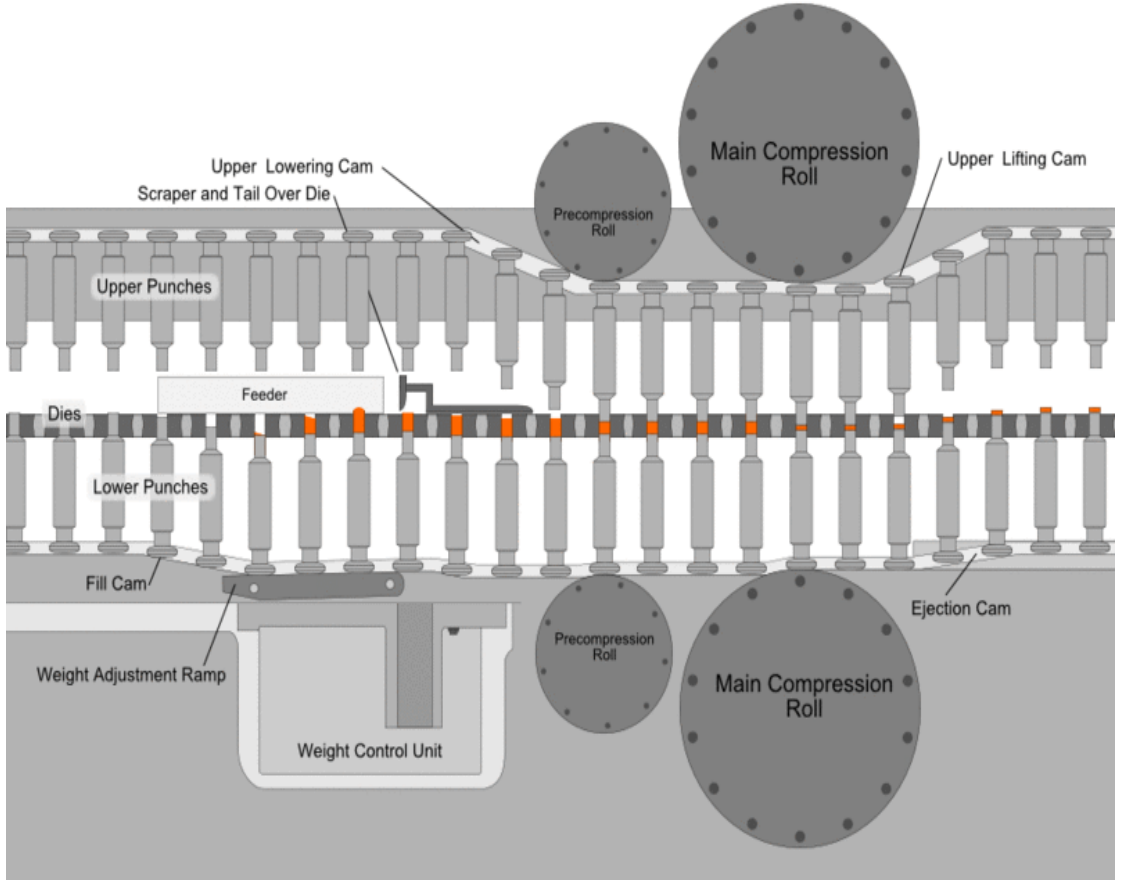


Tablets

- Additional processes are required for tablet production beyond those described previously.
- Compressed solids, tablets, or caplets are prepared by placing the blend of component additives in a cylinder or die, above a movable piston or punch.
- An upper punch is brought into the top of the piston, and pressure applied to the distal ends of the punches forces the powder into a compact.

TABLETS

- Tablet manufacture depicting the three steps of filling, compression, and ejection



Tablets

- **Product quality** depends on the *cohesive forces* acting on the powder under compression.
- These cohesive forces are influenced by the *selection of additives* in the dosage formulation.
- One method of evaluating tablet manufacture considers the effect of applied pressure on porosity of the compressed powder.
- Data may be plotted as the *negative natural logarithm of porosity against applied pressure* in the form of a **Heckel plot**.

HECKEL PLOT

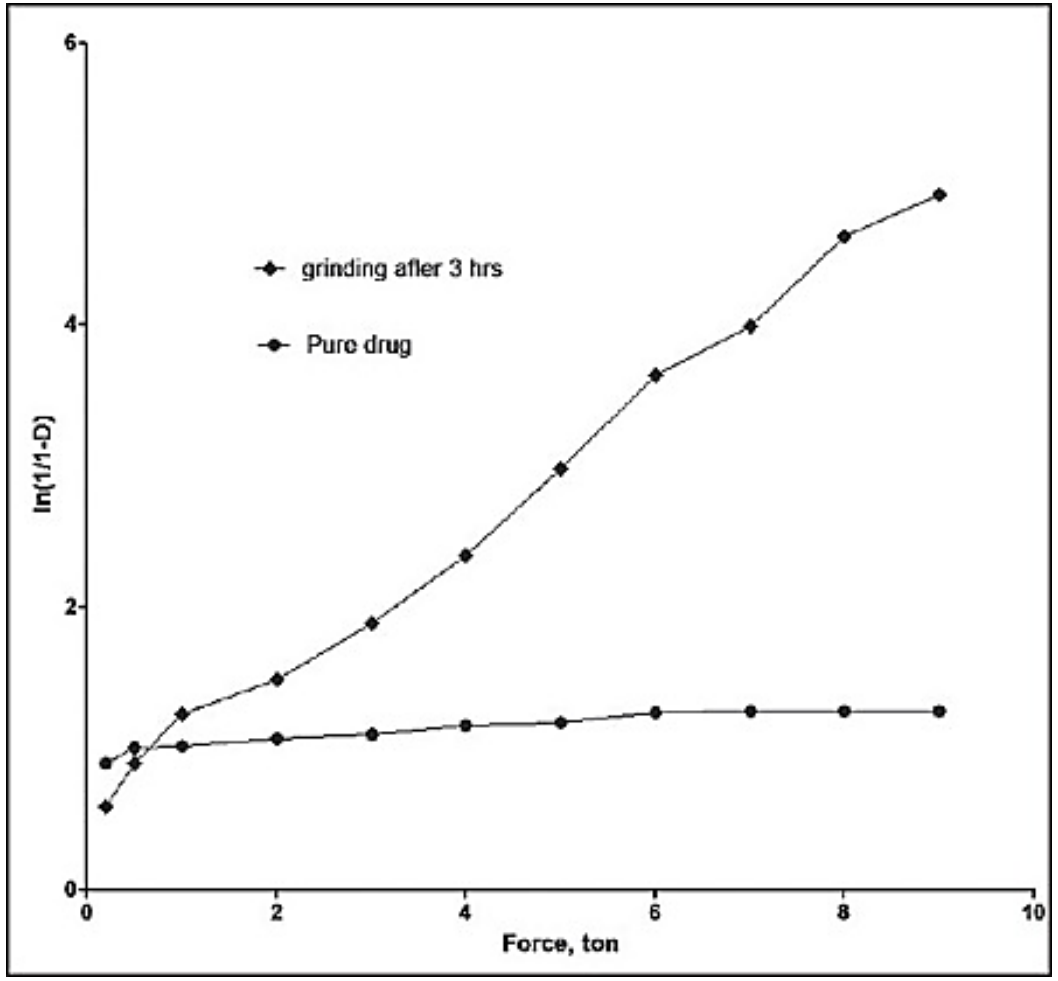
$$\ln \frac{1}{1-D} = KP + A$$

D = relative density of compacts
(ratio of compact density
to true density of powder)

P = applied pressure

K = slope of Heckel plot; $K = 1/P_y$
(P_y is the mean yield pressure)

A = densification at low pressure
(constant)



TABLETS

- The tooling of a tablet press varies according to the tablet design.
- Consideration must be given to the distribution of forces across the faces of the tablet punches as they are brought together to compress the tablet in the die.
- As more unusually shaped tablets are produced and more elaborate embossing tools are required, the forces are not distributed evenly across the punches, and care must be taken if they are to have a reasonable, useful life span.

TABLETS

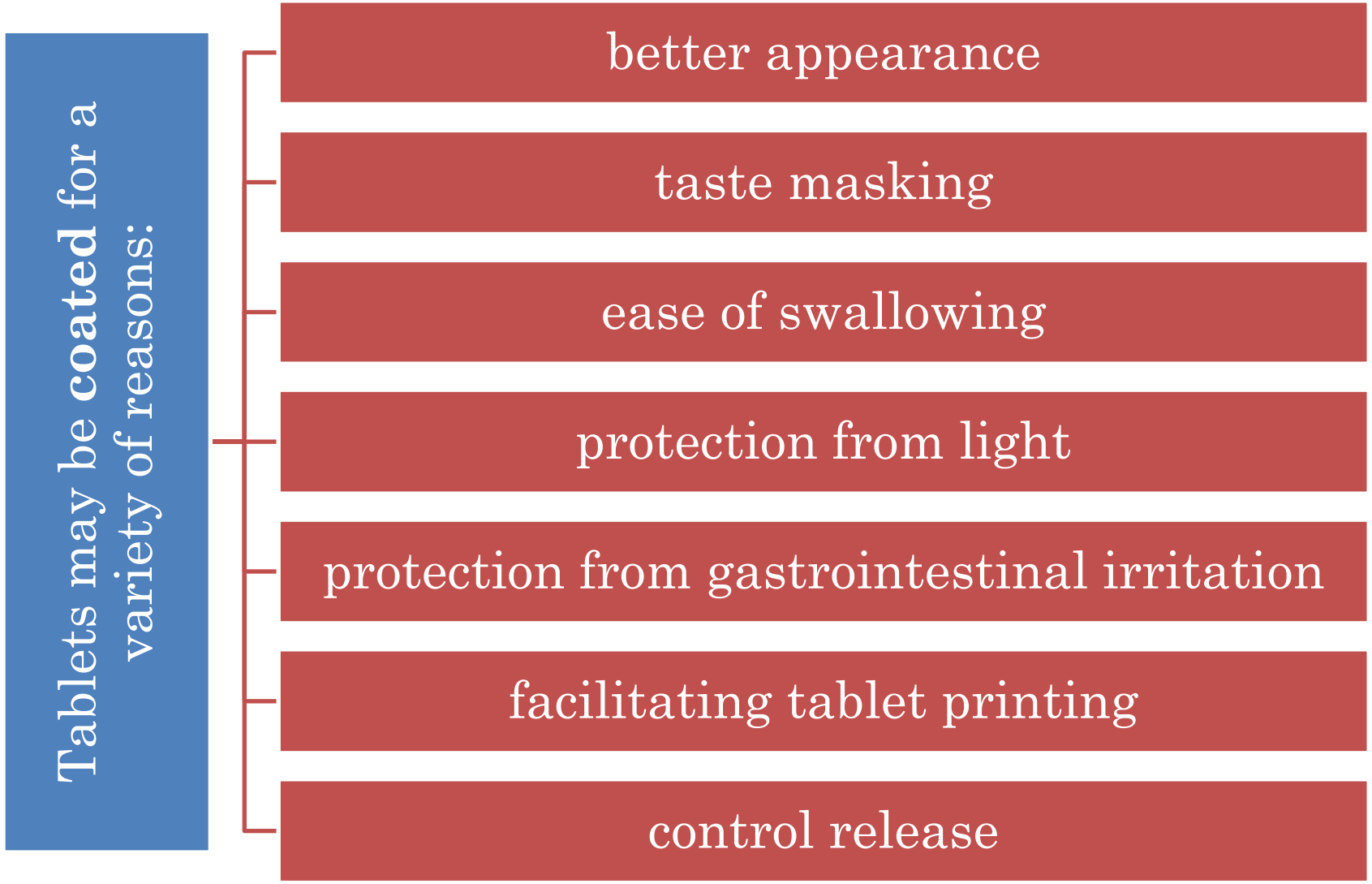
- Tablets have been prepared with different characteristics and for different purposes.
- The most common tablets are **uncoated**, **coated**, **chewable**, or **effervescent**.
- Some specialized dosage forms have been developed for *sublingual* and *buccal* delivery.
- Examples of uncoated conventional tablet include generic aspirin and Valium.
  - These tablets are designed for *rapid dissolution*.

UNCOATED TABLETS

- A typical **uncoated conventional tablet** might have the following composition:

Purpose	Examples
Drug	Generic aspirin, Valium
Filler	Lactose, sucrose, phosphates
Binder	Starch, polyvinylpyrrolidone, cellulosics
Glidant	Talc, silicon dioxide
Lubricant	Magnesium stearate
Disintegrant	Starch, sodium starch glycolate
Colorant	Various

COATED TABLETS



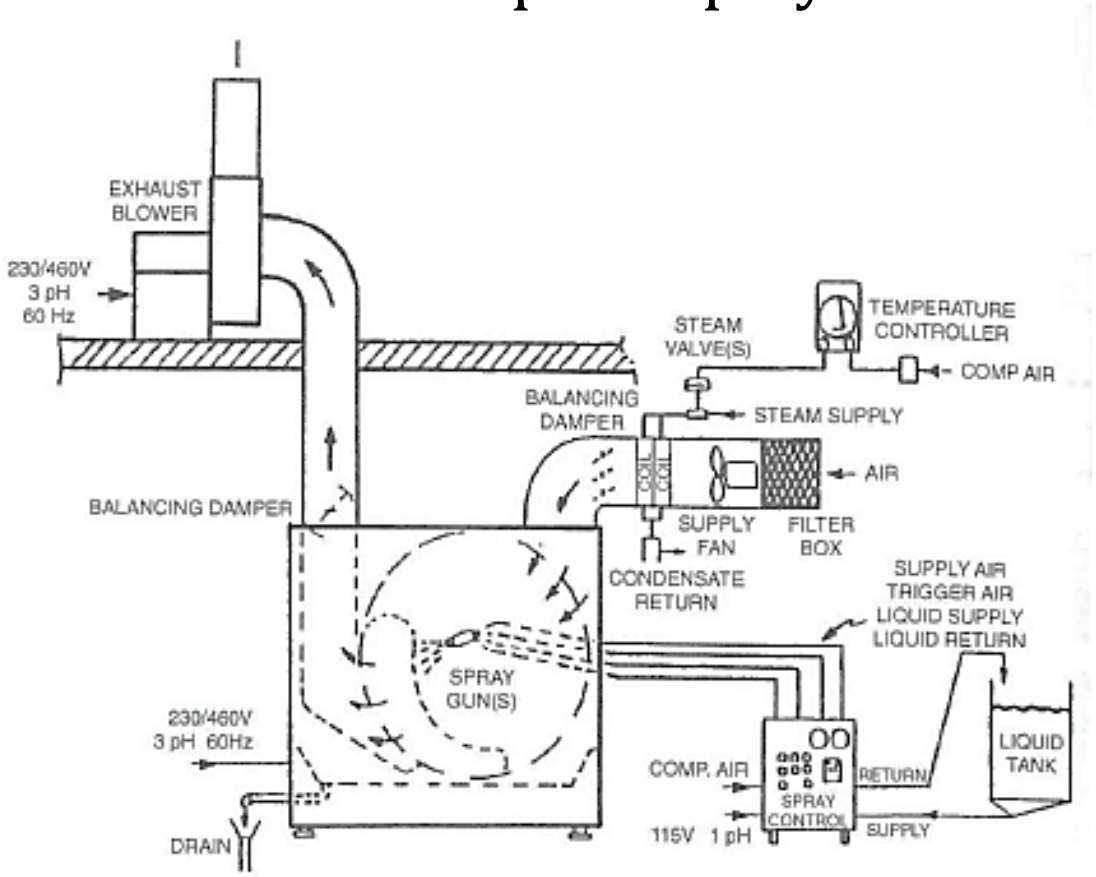
Coated Tablets

- The formulation of a coated tablet is similar to that of an uncoated tablet.
- Usually, it is coated from a solution of polymer, for example, methylcellulose, enteric polymer.
- Bayer aspirin or erythromycin products are examples of **coated tablets**.

TABLETS

- **Coating** is achieved by placing a batch of tablets in a coating pan and spraying or coating from solution with the required polymer.

- **Accela-Cota** is one of the more common coating systems.



CHEWABLE TABLETS

- **Chewable tablets** are usually flavored and contain additives that contribute to a smooth texture, including glycerin and sugars such as mannitol and sorbitol.
  - An example is *Tylenol* chewable tablets.

EFFERVESCENT TABLETS

- **Effervescent tablets** are formulated so that an acid-base reaction occurs when they are combined with water. This is achieved by using weak acids (e.g., citric, malic, tartaric, or fumeric acids) or bases (e.g., sodium or potassium carbonates) in the product.
  - The best known of these products is *Alka-Seltzer*.

Sublingual Tablets

- **Sublingual tablets** are designed to disintegrate and dissolve instantly.
- Hence, they must have structural integrity sufficient for storage, transport, and administration but capable of dissolution on the oral mucosa under the tongue.
- Nitroglycerin tablets designed for treating angina are prepared in a compositionally simple formulation of lactose massed with 60% ethanol.
- This route of administration is intended to avoid first-pass liver metabolism.

TABLETS

- Testosterone tablets have been prepared for **buccal** delivery by slow dissolution.
- The tablet does not contain a disintegrant and is intended to have an extended residence time in the buccal cavity at the rear of the mouth.
- Since release is not immediate, drug dosage may be significantly reduced by this route.