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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.

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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/or odor.
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.

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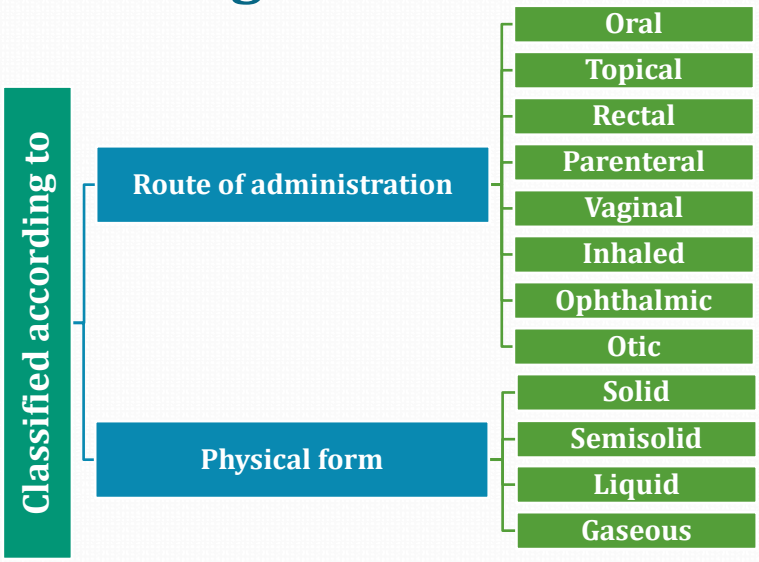
Types Of Dosage Forms



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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

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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

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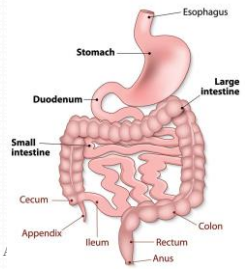
Steps of Drug Delivery to the Systemic Circulation

Oral administration of tablets

Initial transport of the drug through the gastrointestinal (GI) membrane



Drug is brought into solution in the GI fluids

- the drug should be capable of crossing the intestinal membrane into the systemic circulation

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.

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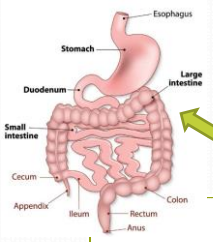
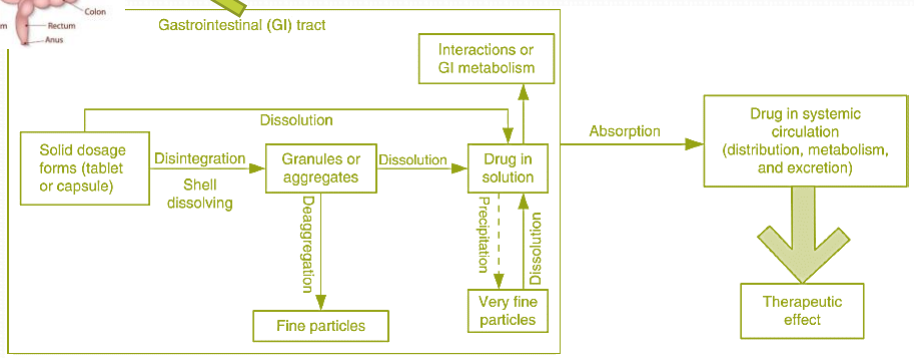
Fate of Solid Dosage Form Following Oral Administration



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



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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**.*

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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***.

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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.*

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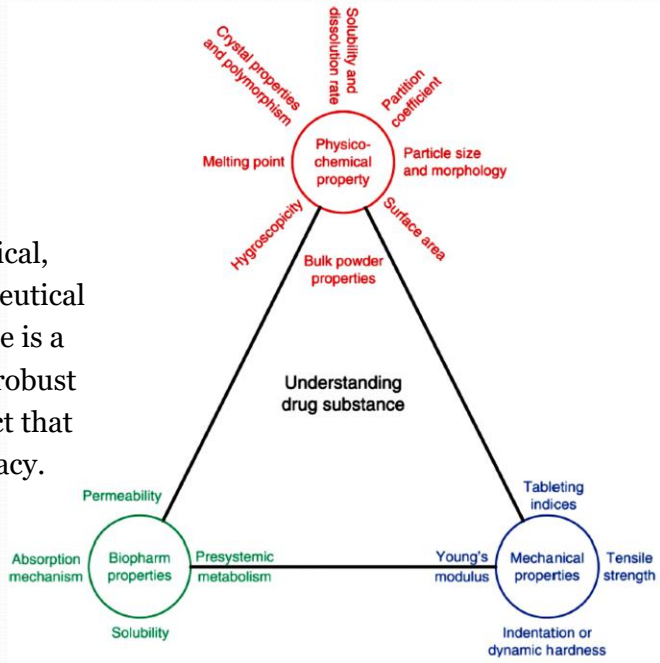
Understanding Drug Substance Properties

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.



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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

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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**"

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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.*

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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

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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.).

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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:

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

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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.

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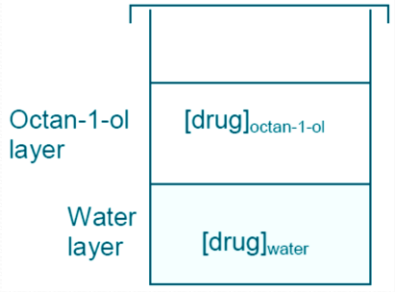
Physicochemical Properties

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

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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.

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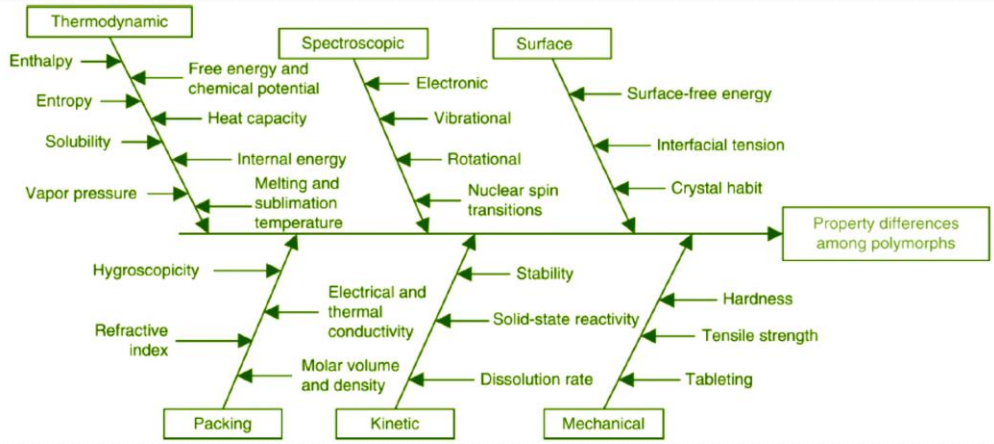
Physicochemical Properties

Crystal Properties & Polymorphism



Fishbone Schematic of Physical Property Differences among Polymorphs

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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.

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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

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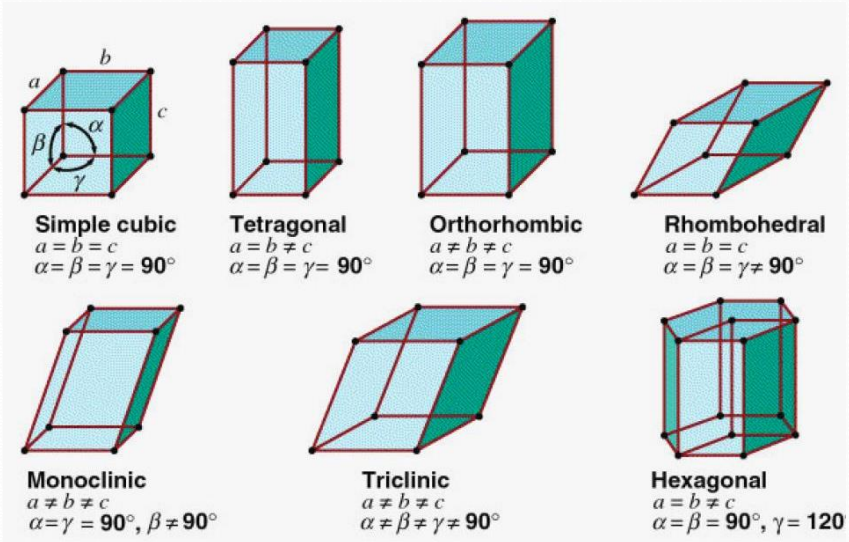
The Seven Crystal Systems



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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

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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.

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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.

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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.

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

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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

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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.

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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.

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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.

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

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

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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

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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.

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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**.

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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.

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Biopharmaceutical Properties

- Generating formulations with relevant oral bioavailability depends on a number of factors:

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

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.

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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.

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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.

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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.

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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"

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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

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