Physical Pharmacy II

2nd stage

College of Pharmacy

Lec: 1

Complexation

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Ph.D in Pharmaceutics

2025 -2026

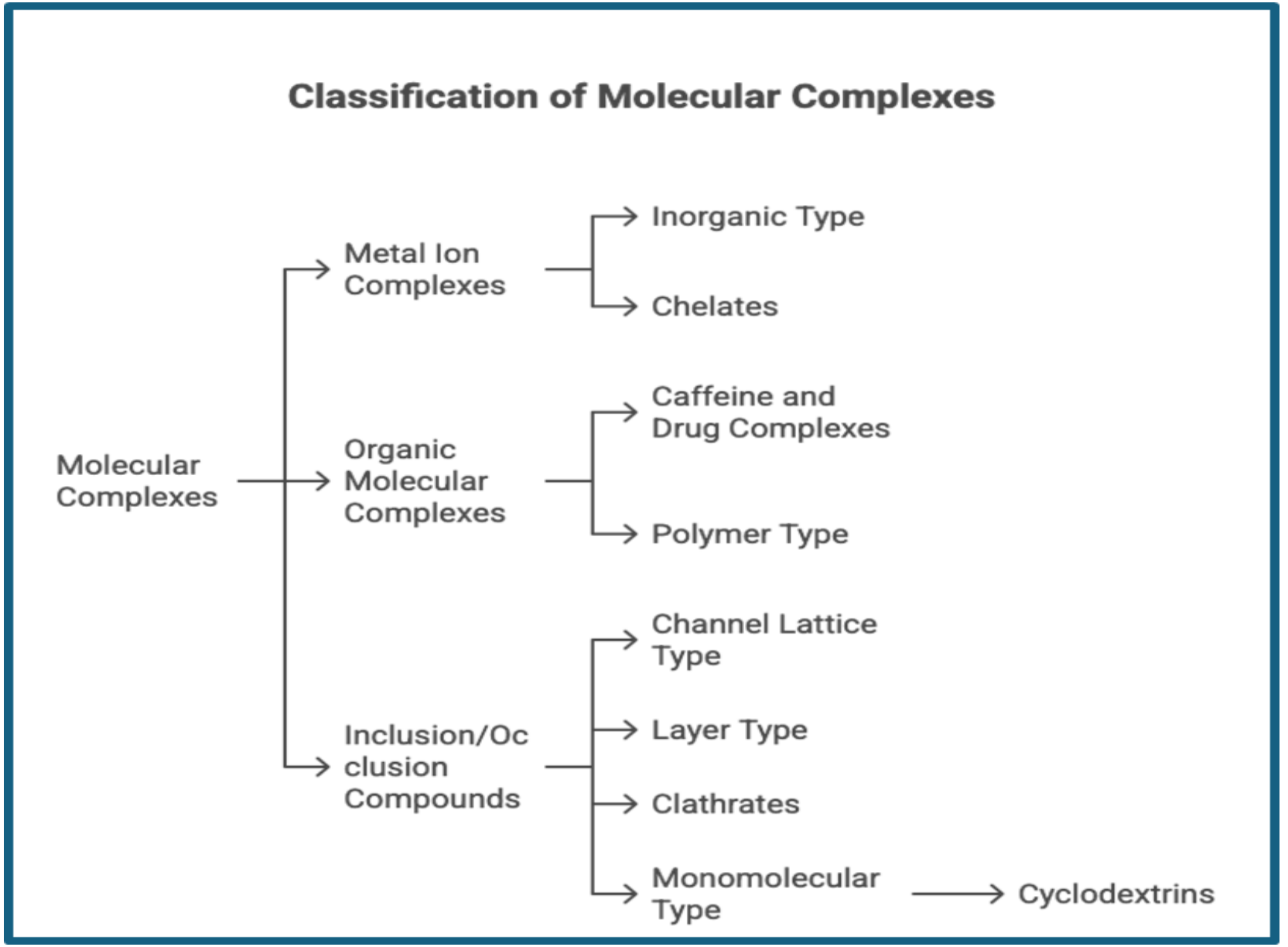
Semester: 2nd

- **Complexation** means **the association of two or more different chemical species** to form a **complex**.
- This association occurs through **weak or strong interactions**, not always through full chemical bonds.
- In pharmacy, complexation is very important because it can:
  - Increase **drug solubility**
  - Improve **drug stability**
  - Reduce **toxicity**
  - Modify **drug absorption and activity**
  - Sometimes cause **incompatibilities** in formulations

Basic Concept: Donor and Acceptor

- Complexes form by a **donor–acceptor mechanism** (Lewis acid–base concept):
  - **Donor**: A molecule or ion that donates an **electron pair**
    - Usually non-metal atoms like oxygen, nitrogen, sulfur
  - **Acceptor**: A molecule or ion that accepts the electron pair
    - Often a **metal ion** (e.g., Cu^{2+}, Fe^{3+}, Co^{3+})
- The forces involved may include:
  - Coordinate covalent bonds
  - Hydrogen bonding
  - Dipole–dipole forces
  - van der Waals forces

Complexes are classified according to arrangement in table 10-1



I. METAL COMPLEXES

Inorganic Complexes

- These involve a **central metal ion** surrounded by molecules or ions called **ligands**.

Terms:

- **Ligand**: Molecule that donates electrons (e.g., NH_3, H_2O, CN^-)
- **Coordination number**: Number of ligands attached to the metal

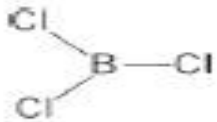
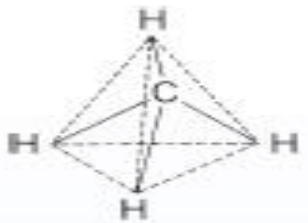
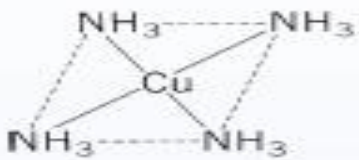
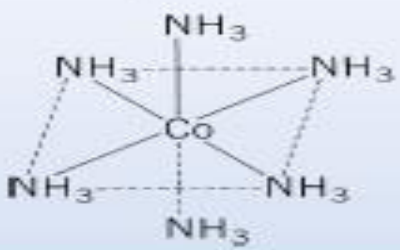
Example:

$$Co^{3+} + 6\ddot{N}H_3 = [Co(NH_3)_6]^{3+}$$

- Cobalt is the metal
- Six ammonia molecules are ligands
- Coordination number = 6
- Geometry = octahedral
- Each ligand donates a pair of electrons to form a coordinate covalent link between itself and the central ion having an incomplete electron shell

- Other complex ions belonging to the inorganic group include $[Ag(NH3\ )2]^+$, $[Fe(CN)6]^{4-}$, and $[Cr(H2O)6]^{3+}$

TABLE 10-2 Bond Types of Representative Compounds

Coordination Number	Orbital Configuration	Bond Geometry	Example	
			Formula	Structure
2	sp	Linear	O_2	O—O
3	sp^2	Trigonal	BCl_3	
4	sp^3	Tetrahedral	CH_4	
4	dsp^2	Square planar	$Cu(NH_3)_4^{2}$	
5	dsp^3	Bipyramidal	PF_5	
6	d^2sp^3	Octahedral	$Co(NH_3)_6^{3}$	

Chelates

- **A substance containing two or more donor groups may combine with a metal ion in a ring structure to form a special type of complex known as a chelate**
- Chelates are **special metal complexes** where:
  - One ligand binds the metal at **two or more sites**
  - Forms a **ring structure**
  - Much **more stable** than simple complexes
  - Steric Effects: A chelating agent can only easily replace ligands that are neighbors.
    - Ions such as Cu(II) and Ni(II), which form square planar complexes, and Fe(III) and Co(III), which form octahedral complexes, can exist in either of two geometric forms.
    - only cis-coordinated ligands-ligands adjacent on a molecule-will be readily replaced by reaction with a chelating agent

Examples on Natural Chelates:

- **Hemoglobin** → iron chelate (***carries O2 via Fe) and Chlorophyll (captures light via Mg***
- **Chlorophyll** → magnesium chelate (photosynthesis :captures light via Mg)
- **Albumin** → a major carrier protein. It tightly binds metal ions like Cu^{2+} and Ni^{2+}. Different species (human vs. dog) bind with different affinity!

II. ORGANIC MOLECULAR COMPLEXES

- An **organic coordination compound** or molecular complex *consists of constituents held together by weak forces of the donor-acceptor type or by hydrogen bonds*.
- These are **non-metal complexes** formed by **weak forces**, such as:
  - Hydrogen bonding
  - Dipole–dipole interactions

Drug Complexes:

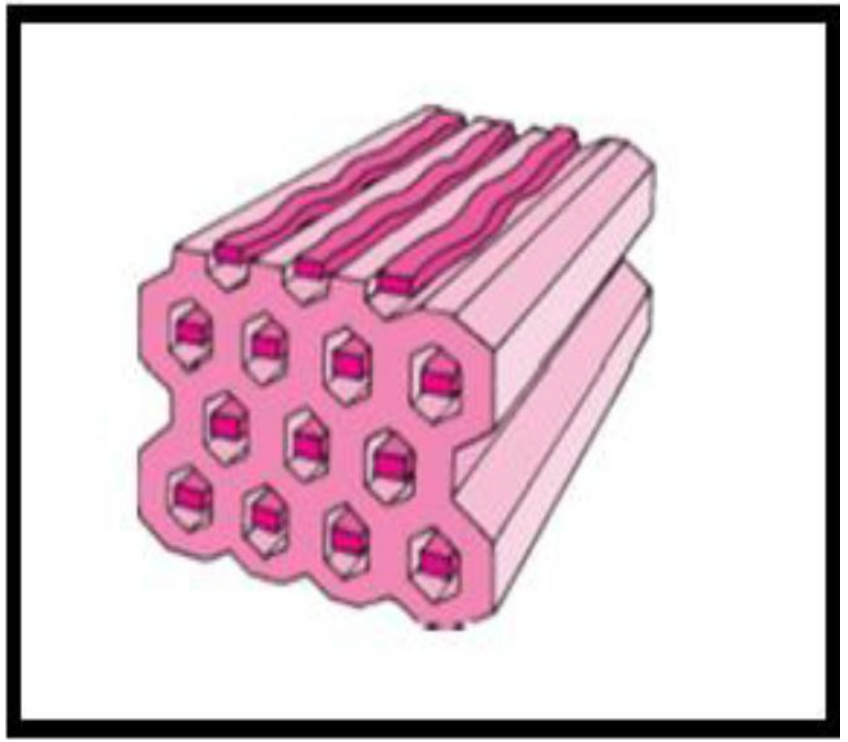
- **Example:**
  - **Caffeine + acidic drugs** (e.g., barbiturates, sulfonamides)
  - Interaction occurs through carbonyl groups of caffeine and the hydrogen atom of the acid.
  - **Importance in Pharmacy:**
    - Can affect drug solubility
    - Can change drug absorption
    - Can cause incompatibility in formulation

Polymer Complexes:

- Excipients like **PEGs, CMC, or polystyrene aren't inert!**
- The incompatibilities of certain polyethers, such as the Carbowaxes, Pluronics, and Tweens with tannic acid, salicylic acid, and phenol, can be attributed to these interactions.
- **The incompatibility** may be manifested as a precipitate, flocculate, delayed biologic absorption, loss of preservative action, or other
  - May be beneficial (controlled release)

III. INCLUSION COMPOUNDS - The "Molecular Hotel"

- In these complexes, one molecule (**guest**) is physically trapped inside another (**host**).
- **Types:**
  1. **Channel Lattice Compounds**
     - Example: **Deoxycholic acid (bile acids)**
       - Forms channels that trap (guest) other molecules such as paraffins, organic acids, esters, ketones, and aromatic compounds and with solvents such as ether, alcohol, and dioxane
       - No chemical bond, only size fitting
  2. **Clathrates**
     - Guest molecule is trapped in a **cage-like structure**
     - **Example:**
       - **Warfarin Sodium USP** is an official clathrate with water and isopropyl alcohol, which stabilizes it.

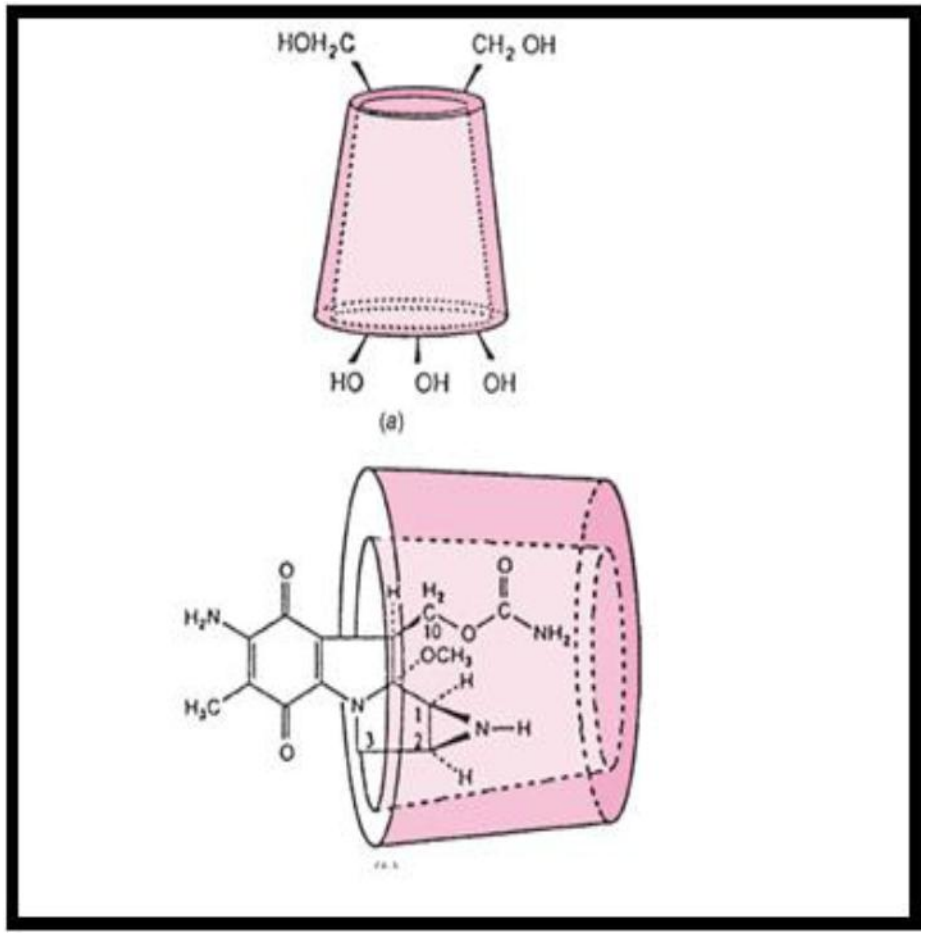


INCLUSION COMPOUNDS - The "Molecular Hotel"

- In these complexes, one molecule (**guest**) is physically trapped inside another (**host**).
- **Types:**

  3. Cyclodextrins (Monomolecular Inclusion Compounds)

  - Cyclic sugar molecules
  - Have a **hydrophobic cavity**
  - Trap poorly soluble drugs
  - **Types:**
    - α-CD (6 glucose units)
    - β-CD (7 glucose units)
    - γ-CD (8 glucose units)



INCLUSION COMPOUNDS - The "Molecular Hotel"

- **Pharmaceutical Benefits of Cyclodextrins:**

1. **Solubilization:** Retinoic acid solubility jumps **320-fold (0.5 to 160 mg/liter)** with β-CD.
    - Lach and associates used cyclodextrins to trap, stabilize, and solubilize sulfonamides, tetracyclines, morphine, aspirin, benzocaine, ephedrine, reserpine, and testosterone
2. **Stabilization:** Protects drugs like morphine or aspirin from degradation.
3. **Enhanced Activity:** Increased bioavailability for drugs like famotidine and tolbutamide by complexation with β -cyclodextrin

Methods of Studying Complexation

- One important method is:
  - ❑ **Method of Continuous Variation (Job's Method)**
    - Used to determine:
      - Stoichiometric ratio (drug : ligand)
      - Stability of the complex
    - A property (e.g., dielectric constant) is measured
- **Explain the Graph (Figure 10-7):**
  - if the dielectric constant, is plotted against the mole fraction from 0 to 1 for one of the components of a mixture
    - **Dashed Line (No Interaction):** Properties change smoothly when you mix A and B.
  - **Solid Line (Deviation from linearity**)indicates *complex formation*
    - The **peak or trough** tells you the *preferred ratio* (e.g., 1:1, 2:1) of the complex.
- **Stability Constant (K):** this number quantifies the strength of the complex. A high K means a very stable complex

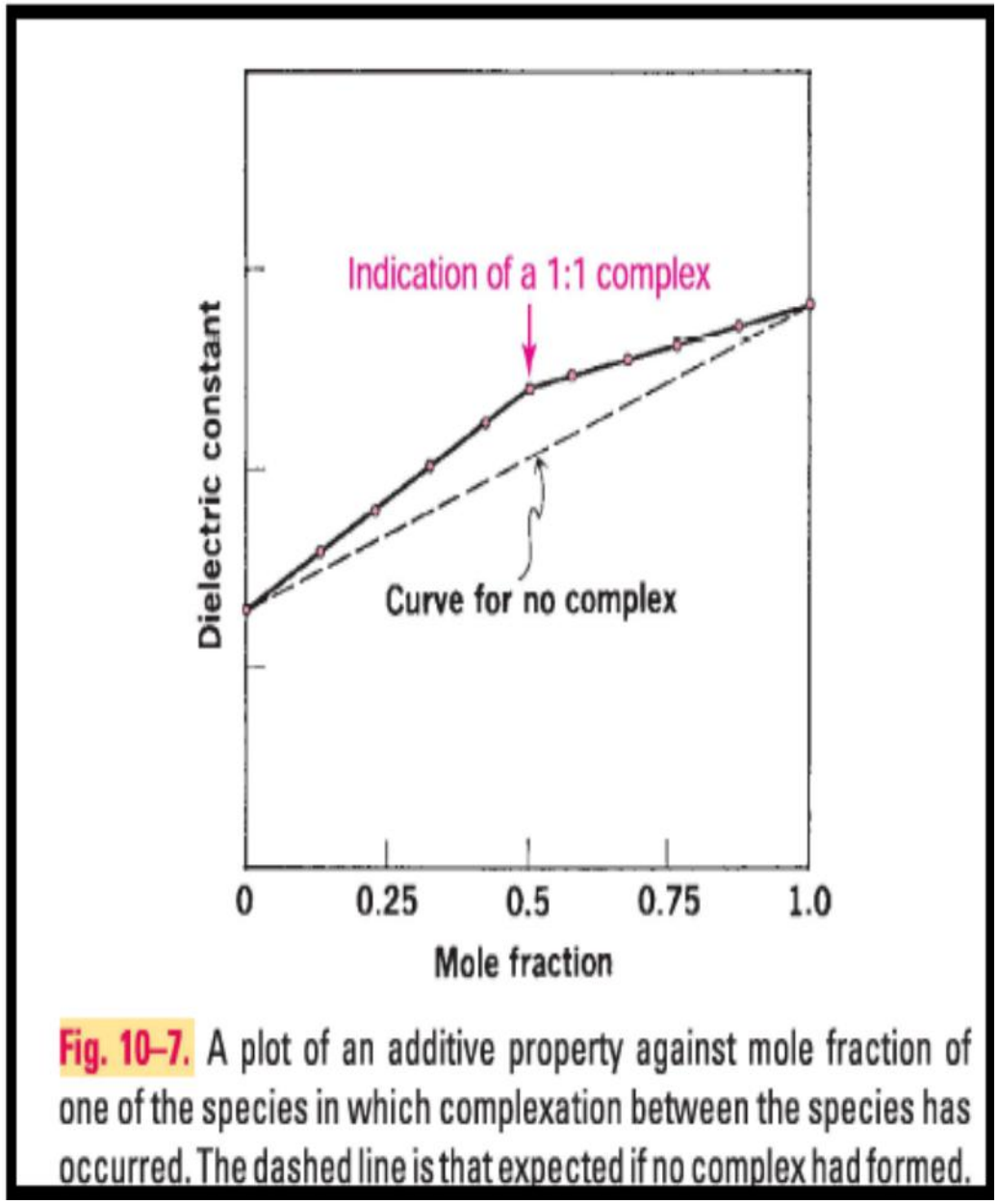


Fig. 10–7. A plot of an additive property against mole fraction of one of the species in which complexation between the species has occurred. The dashed line is that expected if no complex had formed.

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PHARMACEUTICAL POLYMERS

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PHARMACEUTICAL POLYMERS

History of Polymers

- Polymers are more commonly referred to as "plastics" since people are more familiar with plastic products that they encounter around the house than any other type of polymeric product.
- **Plastics** have the ability to be molded, cast, extruded into a final product such as plastic parts, films, and filaments.
- The **first semisynthetic polymer** ever made was *guncotton (cellulose nitrate) by Christian F. Schonbein in 1845*.
- the key difference between early polymers and pharmaceutical polymers is biocompatibility.

Polymers in generals

- The word "**polymer**" means "many parts." A polymer is a large molecule made up of many small repeating units.
- **A monomer** is a small molecule that combines with other molecules of the same or different types to form a polymer.
- If two, three, four, or five monomers are attached to each other, the product is known as a dimer, trimer, tetramer, or pentamer, respectively.
- An **oligomer** contains from 30 to 100 monomeric units.
- Products containing more than 200 monomers are simply called a polymer

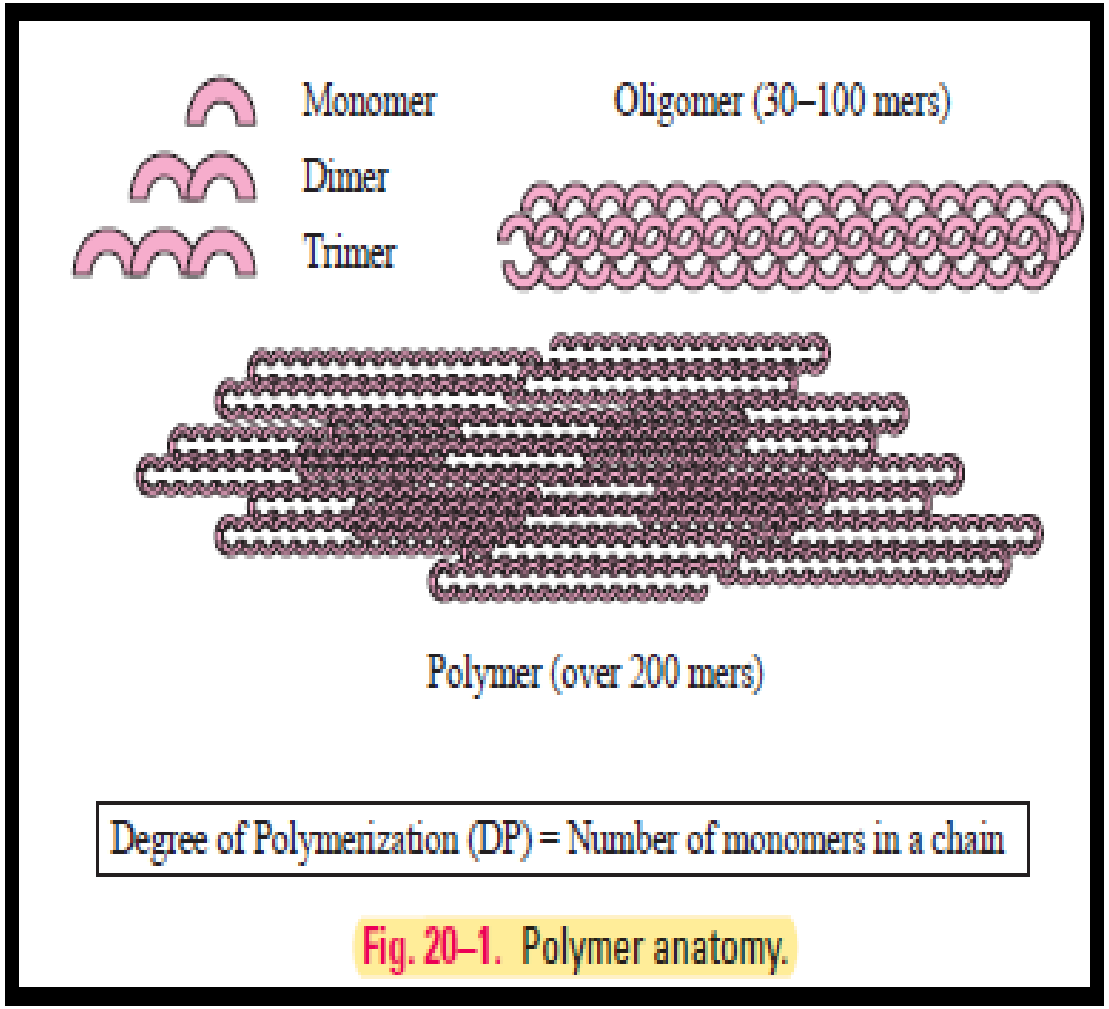

Fig. 20–1. Polymer anatomy.

Polymer Synthesis (polymerization)

- To make polymers, monomers must react with each other in a process called **polymerization**.
- There are **two main types of polymerization**:

1. Addition (chain) Polymerization (Free-radical polymerization)

- this like a **chain reaction**.
- The reaction starts with a special molecule called an **initiator** that creates a **free radical** (a very reactive particle).
- This radical attacks a monomer and starts a **rapid chain reaction**.
- Monomers keep adding one by one very quickly → forming a **long chain polymer**.
  - Reaction is **fast**
  - **Long polymer chains form early**

2. Condensation Polymerization (Step polymerization)

- Monomers must have **two different reactive groups**.
- two or more monomers carrying different reactive functional groups interact with each other.
- These small chains then join together slowly to make **long chains**.
  - Reaction is **slow and stepwise**
  - **Small molecules form first**, then bigger ones later (**higher-molecular-weight species formed later**)

Copolymerization and polymer blends

- **Copolymers** are formed when **more than one type of monomer** is used in the polymerization reaction.
  - **Types of polymers based on monomers**
    - If the polymer is made from **only one monomer**, it is called a **homopolymer**.
    - If the polymer is made from **two different monomers**, it is called a **copolymer**.
  - **Types of copolymers**
    - If the two monomers react **equally (no preference)** during polymerization (**reactivity's of two monomers are similar**) → the product is a **Random Copolymer**.
    - If the monomers are added in an **alternating pattern (When one monomer is preferentially added to another monomer)** → the product is an **Alternating Copolymer**.

- **Polymer blends** are **physical mixtures of two different polymers** (No chemical reaction)
  - They are mixed either:
    - In the **molten (melted) state**, or
    - In a **solution**.
  - **What happens after mixing?**
    - If blended by melting → the mixture **solidifies when cooled**.
    - If blended in solution → the mixture is **recovered at higher temperature** after solvent removal.

Thermoplastic vs Thermoset Polymers

Thermoplastic Polymers

- These polymers have **linear or branched chains**.
- They **soften and melt when heated** and **harden again when cooled**.
- This heating and cooling process can be **repeated many times** (thermomelting and solidification can be repeated indefinitely)

- **Why are they useful?**
- Because they can be easily shaped using:
  - Compression molding
  - Injection molding
  - Thermoforming
- **Examples:**
  - Polystyrene (PS)
  - Polyethylene (PE)
  - Polyvinyl chloride (PVC)

☞ Think of thermoplastics like **wax** — melt when heated, solid when cooled.

Thermoplastic vs Thermoset Polymers

Thermosetting Polymers

- Thermosetting polymers are cross-linked polymers
- formed upon:
  - ➢ combined application of a cross-linker and heat or
  - ➢ combined application of heat and reaction of internal functional groups
  - Heat causes a **permanent chemical reaction**.
- Once formed, they **cannot melt again**.
- **What happens if reheated?**
  - ➢ They **do not soften**. Instead, they **decompose or burn** with further application of heat.

☞ Think of thermosets like a **boiled egg** — once cooked, it cannot return to liquid.

- **Solubility of polymers (Dissolving) is entropy-favoured)**
  - **Linear/branched polymers** can usually **dissolve in suitable solvents**.
  - **Cross-linked polymers** (thermosets) **do not dissolve**, because their chains are tightly connected (cross-linking hinder chain movement)

Polymer Properties: Crystalline vs Amorphous Polymers

- Polymers can behave very differently depending on **how their chains are arranged**.
- The two main structures are:
  - **Crystalline polymers**
  - **Amorphous polymers**
- **Polymers have different thermal, mechanical, and physical properties**
- Polymer properties depend on:
  - Structure of the chains
  - Molecular weight
  - Shape of chains (linear or branched)
  - Interactions between chains

Polymer Properties: Crystalline vs Amorphous Polymers

❑ Crystalline polymers

- If polymer chains are **straight and regular (linear)**, they can **pack closely together** in an orderly way.
- This ordered packing forms **crystals (crystallites)**.

- **when heated:**
  - When temperature increases:
    - Crystals begin to melt.
    - At a specific temperature (melting temperature, Tm), the polymer suddenly melts.
  - Above the melting temperature:
    - Chains move freely
    - Molecules slide past each other → material becomes liquid.
  - Polymer strength and stiffness increases with crystallinity as a result of increased intermolecular interactions
- Examples:
  - Polybutylene terephthalate (PBT) sharp melting range of 220◦C
  - Polyethylene terephthalate (PET) sharp melting range of 250◦C to 260◦C

Polymer Properties: Crystalline vs Amorphous Polymers

❑ Amorphous polymers

- Sometimes polymer chains are **too irregular** that crystal formation is thermodynamically infeasible.
- So Such polymers instead of crystals, they form a glass-like structure.
- This structure is called amorphous.

- **How are amorphous polymers formed?**
  - Amorphous structure is formed due to either rapid cooling of a polymer melt in which crystallization is prevented by quenching or
  - The structure is **too irregular** to crystallize.
- Amorphous polymers **do NOT have a sharp melting point.** Instead, they:
  - Soften gradually Over a **wide temperature range**
  - This temperature region is called the **glass transition region (Tg)**.
- Example
  - Polystyrene melting range of 35◦C to 85◦C
  - poly (vinyl acetate) melting range of 70◦C to 115◦C

Polymer Properties – Thermal Transitions

- **Thermal Transitions in Polymers** are changes in physical state or structure that happen when the polymer is heated or cooled.
- Because the polymer chains in the crystalline state are tightly packed, melting causes them to spread out. As a result:
  - The volume of the polymer increases significantly.
  - The density decreases.

Melting Temperature (Tm)

- **Tm** is the temperature at which the **crystalline part** of a polymer melts. At Tm, the polymer changes from a **solid** to a **liquid**.
- This change happens suddenly.
- in experiments, Tm appears as a **sharp peak** in **DSC (Differential Scanning Calorimetry)**.
- *Tm relates to movement in crystalline regions.*

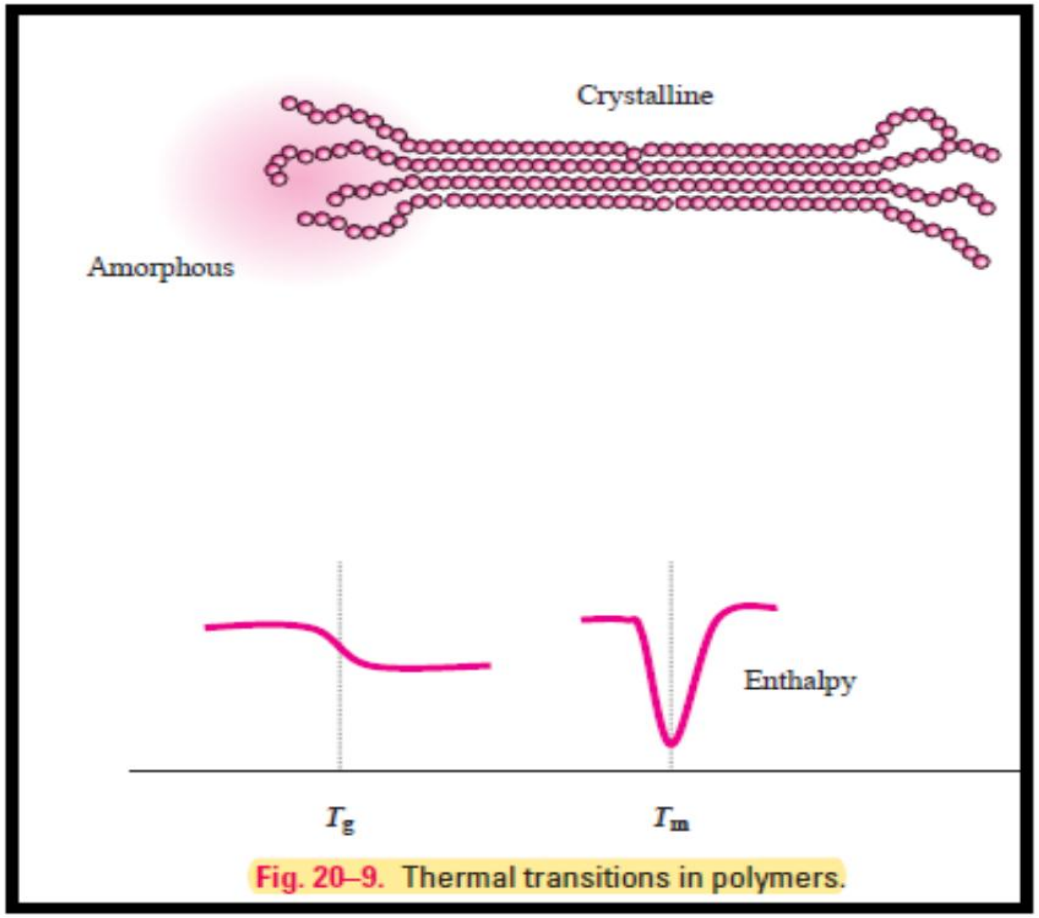

Fig. 20–9. Thermal transitions in polymers.

Figure 20–9, **Tm and Tg** of a given polymer can be detected by differential scanning calorimetry (DSC) as an **endothermic peak and a baseline shift**, respectively.

Polymer Properties – Thermal Transitions

Glass Transition Temperature (Tg)

- **Tg** occurs in the **amorphous (non-crystalline)** parts of a polymer.
- There is **no melting** at Tg. Instead, the polymer slowly changes from: **Hard and glassy → soft and rubbery**
- Tg happens over a **range of temperatures**, not at one exact point.
  - Tg is not a fixed value for a polymer.
- In DSC, Tg appears as a **change in the baseline**, not a peak.
- Tg measures molecular motion of **amorphous** polymer chains.
- It depends on factors like: Chain flexibility, Molecular weight and Additives (like plasticizers)
- **Polymer behavior:**
  - **Below Tg**: Polymer is **hard, stiff, and glassy**
  - **Above Tg**: Polymer becomes **soft, rubbery, and flexible**
    - It may even start to flow

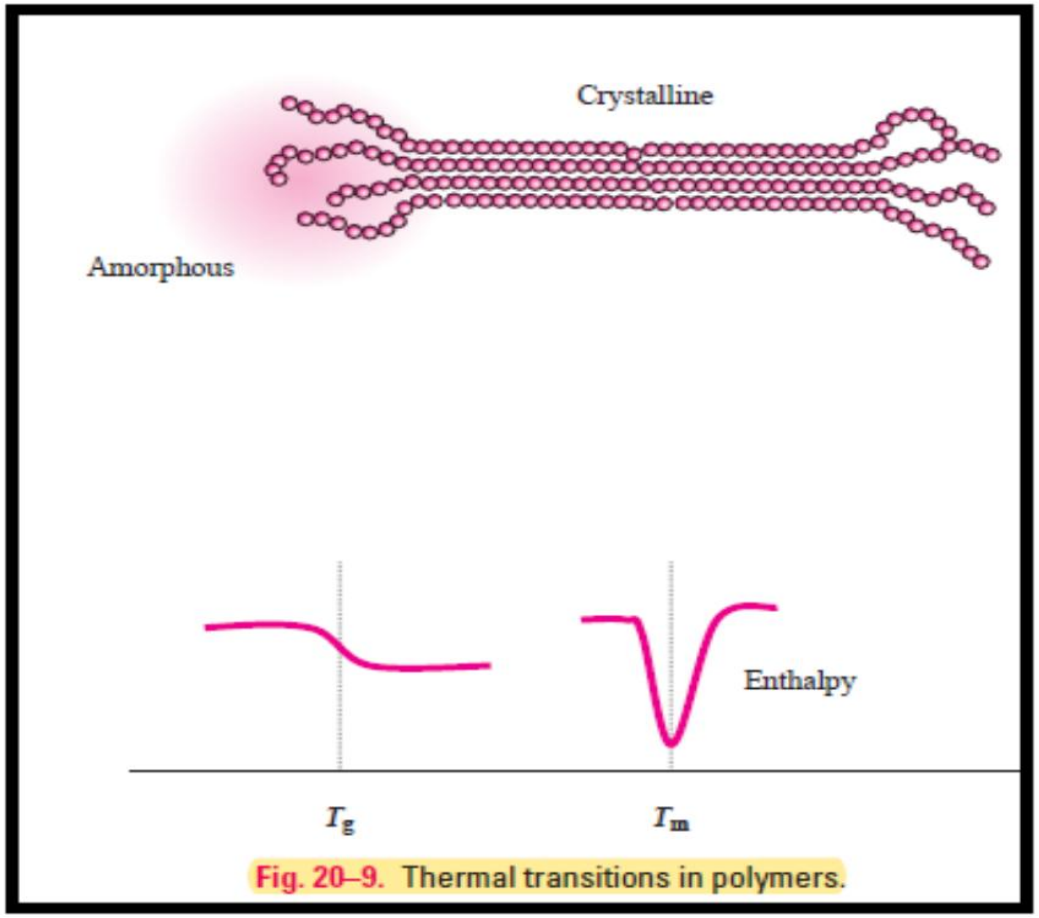

Fig. 20–9. Thermal transitions in polymers.

Figure 20–9, **Tm and Tg** of a given polymer can be detected by differential scanning calorimetry (DSC) as an **endothermic peak and a baseline shift**, respectively.

Plasticized Polymers

- A **plasticizer** is a substance added to a polymer to:
  - Increase **flexibility**
  - Improve **processing**
- It works by allowing polymer chains to **move more easily**.
- **Effects of Plasticizers**
  - **Lower the glass transition temperature (Tg)**
  - Make polymers:
    - **Softer**
    - **More flexible**
  - Increase **molecular movement**
  - Allow **drug molecules** to diffuse faster through the polymer (important in pharmaceuticals)

Polymer Properties – Molecular Weight of Polymers

Why polymer molecular weight is different

- Polymers are made by joining **many monomers**.
- During polymerization, chains **do not all grow to the same length** (Monomers may or may not be added equally)
- As a result, a polymer batch may contain polymer chains with different lengths (molecular weights)
- This is called **molecular weight distribution**.

Why we use average molecular weight

- A polymer **cannot be described as a molecule with a specific molecular weight**
- **Since chains are different, the molecular weight of all chains should be considered and must be averaged to have a more realistic figure for molecular weight of a given polymer**
- We use **average values** to describe it realistically.
- A **narrow molecular weight distribution** is preferred when high **mechanical strength** is needed.

Types of Average Molecular Weight

- There are different ways that molecular weights of a polymer can be expressed; by the number of the chains, by the weight of the chains (the chain size), or by viscosity.
- Polymer samples contain **many chains of different lengths**, not a single molecular weight.
  So we describe the molecular weight using **averages**:
  - **Number average molecular weight (Mn)** → based on **how many chains** there are
  - **Weight average molecular weight (Mw)** → based on **how heavy the chains are**
  - If all polymer chains are similar in size, then the number and weight average values will be equivalent (**Mn ≈ Mw**).
- If chains are of different sizes, then weight average is distancing itself from the number average value (Mw > Mn).

Polymer Properties – Mechanical Properties of Polymers

- The mechanical behavior of polymers depends on:
  - **Structure**
  - **Molecular weight**
  - **Intermolecular forces**
- **Types of Mechanical Resistance**
  - Polymers can resist different kinds of stress:
    - **Stretching** → Tensile strength
    - **Compression** → Compressive strength
    - **Bending** → Flexural strength
    - **Sudden force** → Impact strength
    - **Repeated loading** → Fatigue

➢ **Effect of Molecular Weight**

- As **molecular weight increases**:
  - Chain entanglement increases
  - Intermolecular forces increase
  - Mechanical strength **improves**

➢ **Effect of Polymer Structure**

- **Flexible polymers**: Perform better under **stretching**
- **Rigid polymers**: Perform better under **compression**

Polymers for pharmaceutical applications

➢ **Role of polymers in tablets**

- In traditional tablet manufacturing, polymers are used as **excipients** (inactive ingredients)

➢ **Polymers in liquid dosage forms**

- In liquids (like syrups or suspensions), polymers act as **rheology modifiers**.
  That means they:
  - Control **viscosity**
  - Help **stabilize suspensions**, so particles don't settle quickly

➢ **Classification based on solubility**

- Pharmaceutical polymers are often classified as:
  - **Water-soluble**
  - **Water-insoluble** (oil soluble or organic soluble).
- **Cellulose-based polymers**
  - **Water-soluble cellulose ethers**
    - Methyl cellulose
    - Hydroxypropyl cellulose
  - **Water-insoluble cellulose derivatives**
    - Ethyl cellulose
    - Cellulose acetate, phthalate, butyrate
      - These are widely used in tablets and capsules, especially when controlled or delayed drug release is needed.

Polymers for pharmaceutical applications

Synthetic water-soluble polymers

- Some commonly used synthetic polymers include:
  - Polyethylene glycol (PEG)
  - polyethylene glycol vinyl alcohol polymers
  - Polyvinyl pyrrolidone (PVP)
  - Polyethylene oxide
  - Polymethacrylates esters
- These polymers may carry **ionic charges** (anionic or cationic), which affects how they interact with drugs.

Natural gums

- **Gum arabic (gum acacia)**
  - Known for its **emulsifying properties**
  - Produces high viscosity at high concentrations

Polymers in drug delivery

- Pharmaceutical Polymers are widely used to achieve:
  - taste masking
  - enhanced stability
  - improved bioavailability.
- **Synthetic polymers in drug delivery**
  - Polymers made from **acrylic or methacrylic acids** are widely used in the drug delivery area to protect the drug
  - They are classified as **Cationic** , **Anionic** and **Neutral (non-ionic)**
  - Their charge affects where and how the drug is released.

❑ **Methacrylate-based polymers :**Examples include:

- Butyl methacrylate
- Methyl methacrylate
- Dimethyl aminoethyl methacrylate

- These polymers are used to:
  - Protect sensitive drugs
  - Mask unpleasant taste or odor
  - Protect drugs from moisture
  - Improve drug storage stability

Polymers in drug delivery

- **Example: Eudragit® E 100**
  - Supplied as granules
  - Commonly used for **taste masking**
  - Dissolves in acidic conditions (like the stomach)

➢ **Biodegradable polymers**

- These polymers break down naturally in the body and are very important for modern drug delivery.
- They can be:
  - **Natural** (polysaccharides, protein-based polymers)
  - **Synthetic**
    - **Most common synthetic biodegradable polymers**
      - Polyesters of **lactic acid** and **glycolic acid** (e.g., PLGA)
      - which are used for variety of pharmaceutical applications